9-18-2014

Development of experiments involving pharmaceutical manufacturing principles

Alexander Struck Jannini

DEVELOPMENT OF EXPERIMENTS INVOLVING PHARMACEUTICAL MANUFACTURING PRINCIPLES

by
Alexander V. Struck Jannini

A Thesis

Submitted to the
Department of Chemical Engineering
College of Engineering
In partial fulfillment of the requirement
For the degree of
Master of Science in Engineering
at
Rowan University
August 20, 2014

Thesis Chair: C. Stewart Slater, Ph.D.

Acknowledgements

This project was funded by a grant from the National Science Foundation, #ECC0540855. I would like to take this time to thank God for this opportunity and giving me the courage and perseverance to continue my work. I would like to acknowledge the assistance of David Krause, Heather Malino, Kevin Sweeney, and Matthew van der Wielen with the laboratory experiments. Their creativity and drive helped shape this project into what has been presented today. I would also like to thank Dr.'s C.S. Slater and Mariano J. Savelski for their insight and ceaseless dedication to this project. Lastly, I would like to thank my family, and my Rowan University family, for their support.

Abstract

Alexander V. Struck Jannini
DEVELOPMENT OF EXPERIMENTS INVOLVING PHARMACEUTICAL MANUFACTURING PRINCIPLES
2014
C. Stewart Slater, Ph.D.
Master of Science in Chemical Engineering

Laboratory experiments were developed to incorporate pharmaceutical engineering concepts into Freshman-level engineering courses. The goal is to increase the interest of pharmaceutical engineering in students and provide the necessary background for more advanced courses in the field. The experiments can be used on an individual basis, or to be grouped into themes for more focused learning objectives. The laboratory experiments are available at the pharmaceutical knowledge and training website www.PharmaHUB.org under the Teaching Resources tab.

Table of Contents

List of Figures

List of Tables

Chapter 1

Introduction and Background

Pharmacy itself originates from the ancient art of apothecary. The earliest evidence of apothecary can be found in ancient Mesopotamia, where medical texts were found on clay tablets. These texts described symptoms of illnesses, instructions for making “drug" compounds, and even invocations to gods [1]. This practice can also be seen throughout all ancient cultures, including: Egyptian, Indian, Chinese, Persian, Greek, and Roman [2]. This practice was observed in monasteries during the Middle Ages, and taken into private practice as apothecary shops in the 13th century [1, 2]. Apothecary shops did not change significantly until the 19th century, when the term pharmacy was used instead of the traditional apothecary [1].

It was in 1821 when the first United States pharmaceutical board was created in Philadelphia. The Philadelphia College of Medicine was formed on March 13, which encompassed not only a school of pharmacy, but a self-policing board of pharmacists to make sure that frauds and “snake-oil” salesmen were not inflicting damage on the public through improper pharmaceutical practices in Philadelphia [1]. The educational institution opened November 9 of the same year. Pharmaceutical education soon spread throughout America, and the University of Michigan also opened a college of pharmacy in 1868. What was novel about this program is that the course did not require pregraduation apprenticeship, which was convention at the time [1, 2].

Pharmacy was again changed in the years of 1890 to 1930. During this time, the pharmaceutical industry evolved twice; once from small shops to family-name

companies, and then once again to large-scale manufacturing corporations that are prevalent today [3]. In this period of time, several aspects of culture and technology caused these changes in the pharmaceutical industry. Four early instances include; innovations in the methods of drug preparation using machinery, the growth in popularity of standardized preparations, changes in therapeutic agents, and the influence of medical research [4]. This, in addition with the Federal Regulatory Act of 1906, paved the way for the large-scale manufacturers to dominate the pharmaceutical industry [3].

Since then, the pharmaceutical industry has been steadily growing as one of the most profitable major manufacturing sectors [3]. This is not to say that the industry has not had drawbacks. Since the 1950's pharmaceutical corporations have been faced with several crises that have harmed their image. Market manipulation, price fixing, dumping, and scores of unethical medical and business practices have destroyed certain firms [3]. This has not stopped the industry from advancing, however, and the pharmaceutical sector continues to grow.

The year of 2010 marked one of the highest points of the pharmaceutical industry, where it had the second largest earnings of all industries [5]. The pharmaceutical industry also increased its worldwide profit growth of 4.2% to approximately 800 billion USD that year [6]. This is substantial growth, considering that in the year 2007, the pharmaceutical industry amassed revenue of 315 billion USD [7]. These economic factors are coupled with shifting paradigms of the industry, such as a move towards shorter drug development times and an increased openness to change existing processes, which will increase the need for chemical engineers with pharmaceutical training [8]. In 2010, 5% of employed chemical engineers and 14% of all biomedical engineers in the United States

worked in pharmaceutical and medicinal manufacturing [9, 10]. One engineer reported that there was an observable increase in chemical engineering emphasis in active pharmaceutical ingredient process development within Pfizer from the years 1995 to 2010 [11]. From 2004 to 2014, roughly 76 thousand jobs are to be created in the pharmaceutical and medicine manufacturing sector, while basic chemical manufacturing jobs are to decrease by roughly 46 thousand in that same time span [12].

As the demand for engineers has increased in the pharmaceutical industry, universities have found a need to provide engineers with education in the field of pharmaceutical engineering. Pharmaceutical engineering is defined as the design of pharmaceutical and diagnostic products and the associated manufacturing processes [13]. Several universities have incorporated pharmaceutical engineering education into advanced degree studies. Some examples of universities that have introduced pharmaceutical engineering programs on the graduate level are Rutgers University, the University of Michigan, and the New Jersey Institute of Technology. All three of these universities offer a master's degree program in pharmaceutical engineering, while Rutgers University also offers a pharmaceutical engineering option for Ph.D. students in chemical and biochemical engineering. This pharmaceutical engineering option requires 5 courses which focus on the different aspects of pharmaceutical engineering [14].

Stevens Institute of Technology offers a master's degree program in pharmaceutical manufacturing. The goal of this program is to provide students with a strong background in Good Manufacturing Practices, project management, and pharmaceutical facilities. This is considered an interdisciplinary program, administered by the mechanical engineering department [15]. In addition, Purdue University offers graduate scholarships

from the Department of Education's Graduate Assistance in Areas of National Need program for students to continue research in the field of pharmaceutical engineering. The graduate student also has the ability to be a part of an international exchange program, gain industry experience through internship opportunities, and conduct supervised teaching to prepare them for a career in academia [16].

Due to the expanding interest in pharmaceutical engineering training, the National Science Foundation funded an Engineering Virtual Organization to facilitate the creation and sharing of pharmaceutical engineering educational information [17]. The result was the website pharmaHUB.org. The objective of this website was to facilitate collaborations with the Engineering Research Center for Structured Organic Particulate Systems (ERC SOPS) and the National Institute for Pharmaceutical Technology and Education (NIPTE) [17]. PharmaHUB.org is named based on the middleware that was used in its creation. This middleware, known as HUBzero, has several features that were useful for the design of the website; including the ability for online simulation, making it possible to deliver simulation tools via the web; content management capabilities that make it possible for online presentations to combine voice and images; community-building capabilities such as content uploading, a question/answer forum, and a user support area [17, 18].

With this increased interest in pharmaceutical engineering at the graduate level, there has been some diffusion into undergraduate curricula. A majority of the universities that have developed undergraduate pharmaceutical engineering programs are found in Europe. In 2003, the University of Basel, in Switzerland, introduced a bachelor's program in pharmaceutical engineering [19]. For the most part, however, colleges and

universities tend to offer pharmaceutical specializations within traditional bachelor's degree programs. This is especially true in the engineering colleges of the United Kingdom and Scandinavia. In these countries, the pharmaceutical industry is a major contributor to the country's economy. For example, 40 percent of all exports from the Republic of Ireland are pharmaceuticals [20]. In the United States, the University of Iowa offers a pharmaceutical specialization for undergraduates. This specialization can be obtained through higher-level electives that focus on different aspects of pharmaceutical sciences, such as drug delivery systems and basic pharmacology [21]. Stevens Institute of Technology also offers a pharmaceutical manufacturing concentration for students of mechanical engineering. This specialization is obtained through courses that incorporate pharmaceutical facility design, validation, and hands-on projects in the field of pharmaceutical manufacturing [22].

Within these specializations, a majority of emphasis is on upper-level undergraduate courses, such as creating special topic courses that focus on pharmaceutical sciences. At the New Jersey Institute of Technology, a class focusing on drug transport and pharmacokinetics was implemented as a specialty topic course for students wishing to obtain a specialization in pharmaceutical engineering [23]. The Georgia Institute of Technology has a course for senior and graduate level students in the field of pharmaceutical engineering; specifically drug design, development, and delivery [24]. Rutgers University has a Pharmaceutical Engineering Training Program, which allows both graduates and undergraduates to work on projects based on realistic problems found in the pharmaceutical industry. These projects deal mainly with product manufacturing or process research and development [25].

Although new upper-level elective courses can be developed to include pharmaceutical engineering concepts with relative ease, there is a level of difficulty when trying to incorporate concepts into lower-level undergraduate courses. In particular, the concepts have to be appropriate for students who are just beginning their undergraduate study. In addition, these concepts might have to be presented in ways that can be applicable to different engineering majors. There is also the complexity of adding new courses into an already saturated curriculum. One approach is to modify pre-existing courses so that they have a focus in pharmaceutical engineering and at the same time, meet student learning outcomes. For example, problem sets developed at Rowan University for the use in lower-level undergraduate courses contain material and energy balances that incorporate different aspects of pharmaceutical engineering [26, 27]. In addition to using problem sets, incorporating pharmaceutical concepts into laboratory experiments can be used to reinforce the course's existing educational objectives. One of the initial efforts in this was the development of a first-year laboratory experiment that focused on an investigation of the controlled release principles of drug delivery methods through the dissolution of a lozenge [28].

Chapter 2

Experimental Methods

Experiments that have been developed for the use in a lower-level, laboratory-based course will be described. Experimental methods as they pertain to the individual laboratory experiments will be described in the relevant sections. These experiments were designed to not only introduce pharmaceutical concepts, but also to reinforce basic engineering educational objectives such as; understand and apply core science and mathematics principles; work individually and in teams to identify and solve engineering problems; design and conduct experiments as well as analyze and interpret data [29]. Only the most novel of these works will be described. The experiments to be discussed are the Tablet Statistical Analysis Lab, the Fluidization of Pharmaceutical Excipients Lab, the Asthma Drug Delivery Lab, the Degradation of Dissolvable Strips Lab, the Effervescence Reaction Lab, the Dextromethorphan Crystallization Lab, and the Creation of Dissolvable Strips Lab. Other experimental write-ups are available on www.PharmaHUB.org, the resource described previously.

The experiments were designed to meet the safety standards of a typical undergraduate laboratory and be performed by the students in approximately 2 hours. The cost of these experiments was also considered so they did not rely on highly specialized equipment and the operating costs are reasonable. Another point that was considered when developing these experiments was the ease of the setup.

Two versions of these experiments are available; a student version and an instructor version, both of which can be found on the website www.PharmaHUB.org in the

Teaching Materials section. The pharmaceutical and engineering concepts that the experiment would incorporate are discussed in a brief introduction, which the students would read before beginning the experiment. The instructor's version includes a more detailed procedure, equipment and supplies list, additional pictures of correct setups for the laboratory experiments, concepts to reinforce, and a solutions section. In order to obtain access to the instructor versions, faculty members must register to the PharmaHUB website.

Chapter 3

Experiments Developed

3.1 Tablet Statistical Analysis Lab

Tablets have a long history in the pharmaceutical industry. The earliest sign of pills being used can be seen in the 17th and 18th century, when apothecaries were used pill jars as their necessary equipment [2]. Tablets are often considered the best option for drug delivery by drug corporations, as they easy and inexpensive to manufacture and are relatively stable to package, ship, and store. From a patient perspective, tablets are easy to swallow, have little issues with odor and taste, and are easy to administer [30].

Tablets grew in popularity with the advances in pharmaceutical chemistry. The progresses in medicine of the 17th to 19th century caused pharmacists and apothecaries to shift from prescribing whole plants to offering powdered leaves and roots. By the 19th century, several active pharmaceutical ingredients were being identified from plants and reproduced via chemical reactions [31]. To mask the often bitter tastes, additives were added to mask the flavor, which caused the invention of the tablet.

Tablets can be considered one of the products that caused the change in the pharmaceutical sectors from small shops to large-scale manufacturing corporations. In the late 19th and early 20th century, pharmaceutical companies gained reputations for their ability to standardize tablets and used this ability as a selling point. In these terms, standardization means the process of making a drug or other pharmaceutical product so that it conforms to a standard, such as a certain amount of active ingredient within a certain range. Since this laboratory experiment involves statistical analyses on tablets, a review of standardization practices in the pharmaceutical industry are presented.

The H.K. Mulford Company was one of the companies that began the practice of standardization. The H.K. Mulford Company began in 1891 as a small manufacturing pharmacy, but grew due to its reputation of high quality products [3, 32]. While the company specialized in lozenges, elixirs, antiseptics, syrups, and other preparations that were similar to its competitors, what set the Mulford Company apart were its efficient tableting machines [33, 34]. These patented tableting machines allowed the company to make tablets in a highly standardized fashion, ensuring that the tablets were relatively similar to each other [34]. This standardization was found to appeal highly to physicians, and became one of the selling points of the Mulford Company [3]. Indeed, this early standardization allowed the Mulford Company to survive the wave of standardization that would occur in later years.

In the early ages of pharmacy, standards were published in pharmacopeias. The earliest of these date back to the Medical Edict of 1240 by Frederick II of Sicily, which ordered that apothecaries prepare remedies always in a similar fashion [35]. Another known act of drug regulation occurred in 1540, when England enacted the Apothecaries Wares, Drugs, and Stuffs Act. This act caused inspection and supervision of medicinal manufacturing of the common medicines of the time [35].

The regulation of drug products via government and laws did not occur in the United States until the early 20th century. In 1902, the United States government passed a bill that controlled the production and sales of biologicals after an outbreak of tetanus occurred in Camden and St. Louis. These outbreaks were thought to be linked to smallpox vaccines [3]. The act specified that manufacturers of vaccines had to be licensed in order to sell their products, that the packages be properly labelled and dated,

and gave the Treasury Department the rite to inspect company policies at any time [36]. This was considered the first act in which pharmaceutical companies had to meet drug regulation in its modern form [3].

In 1906, another law was passed to regulate the adulteration of foods and drug manufacturing. After the publication of Upton Sinclair's *The Jungle*, in which the atrocities of the food industry were made public, outcry reached an apex, and the people demanded better regulation of their goods. From this, the Pure Food and Drug Act was formed [3]. Through this law, main ingredients had to be identified in foods, drugs, medicines, and liquors. Chemical examinations were required, and the Department of Agriculture was given authority over the examinations and regulations of the food and drug industries [37].

These two acts helped shape the pharmaceutical industry into what it is today. The regulatory sections of these two acts ensured that pharmaceutical providers had to have standardized products. This proved to be a feat that was only capable of large-scale companies, who had the capital to spend on the necessary labs and technicians required for standardization [3]. The Mulford Corporation provides a great example of this. In the first few years, the company did not have the equipment needed to test their diphtheria antitoxins, and so had to use the Laboratory of Hygiene at the University of Pennsylvania in order to ensure that their antitoxins met specifications [3]. Later, they managed to obtain their own standardization labs.

Other large-scale manufacturers were hardly affected by the passing of these laws. Parke Davis, for example, changed very little, as they had been using standardization

techniques long before legislation [38]. Smith, Kline, and French also had analytical methods that they used to ensure that they met the standards of the Food and Drug Act. Indeed, company personnel such as Mahlon Kline were actually in full support of the law [3]. Wyeth Company was similarly affected, using advanced tableting machines to make sure they met the standards of the Food and Drug Act [3].

Unfortunately, cataclysmic events once again occurred in 1937 when over 100 people died of diethylene glycol poisoning in the United States. These victims were poisoned after taking a sulfanilamide elixir laced with diethylene glycol. These elixirs were manufactured using diethylene glycol as a solvent, and were sent to the market without any safety testing. This disaster was one of the catalysts behind the passing of the Federal Food, Drug, and Cosmetic Act of 1938 [35]. Other factors that caused the passing of the 1938 Act include Banbar, an ineffective cure for diabetes; Lash-Lure, an eyelash dye that caused eye injuries; Radithor, a radium containing tonic that caused painful deaths; and Wilhide Exhaler, a falsified tuberculosis medication [39]. This law required that drugs be labeled with directions for safe usage, and that approval of all new drugs be obtained by the Food and Drug Administration (FDA) before being put on the market. The law also required factory inspections, and gave the FDA several enforcements tools to ensure compliance [39].

A second tragedy which influenced the development of pharmaceutical regulation occurred in Western Germany in 1956. At this time, a sedative known as thalidomide went on sale. Over the next few years, it was linked in over 10,000 birth defects from the years 1958 to 1960 [35]. Due to this, the United States Government passed the Drug Amendments Act of 1962. This act, also known as the Kefauver-Harris Amendments,

allowed the FDA to set good manufacturing practices (GMP's) and gave the FDA the authority to enforce these practices. The FDA was also given control over drug advertising and the marketing of generic drugs [40].

GMP's are manufacturing requirements that need to be met by corporations. If they are not met, the product is considered adulterated, which can lead to regulatory actions [41]. GMP's cover many areas of pharmaceutical manufacturing, including personnel training and hygiene, building/ facility requirements, packaging, and process control [41, 42]. Several of these GMP's can be compared to the World Health Organization's (WHO) quality assurance measures and the European Medicines Agency's similar standards, which call for such things as an acceptable API variances and excipient quality testing [43, 44].

Since GMP's deal with acceptable variances and excipient quality testing, statistics play a vital role in the pharmaceutical industry. This area is of such importance to the industry, that it has its own journal article, Pharmaceutical Statistics; in which discussions on the current statistical work done in the pharmaceutical industry is presented. Discussions on higher-level statistics, such as how to design clinical trials, appropriate sample sizes, and ethical dilemmas for statisticians are common [45]. The changes in pharmaceutical statistical practices since the 1980's have also been an important topic of discussion [46]. In terms of novel approaches to statistics in the pharmaceutical industry is the use of Bayesian methods, statistical methods and calculations that uses databases of records to construct probability networks [47]. This has been extensively studied for use in product development and safety trials [48, 49].

Engineers who will enter into the pharmaceutical industry should have knowledge of GMP's and statistical work [43]. For this reason, engineers should receive a foundation in GMP's and statistics if they are to enter into the pharmaceutical industry. The Tablet Statistical Analysis Lab was designed with this in mind. The objective of this experiment was to conduct a statistical analysis on the mass of analgesics; in this case, ibuprofen tablets. From an educational perspective, the intended outcome of the experiment was that the students would gain experience interpreting data and using some basic statistical analysis methods. Statistics is an important aspect of the pharmaceutical industry, used to determine the reliability and accuracy of data taken from drug samples, monitor and detect the adversities of a process, and assess the capability and reliability of a process [50].

For this experiment, students take mass measurement of two types of ibuprofen tablets; Advil® brand and a generic brand. Table 1 shows example raw data of these mass measurements. Students are given ten samples of each brand, and then take mass measurements using an analytical scale. The first calculations performed are mean ($\bar{x}$), standard deviation (σ), and variance (s) of both brands. Students then determine if the mass of the two brands are significantly different from each other through an F-test. The equation for the F-test, along with the calculations used based on the raw data is shown as Equation 1.

$$F_{exp} = \frac{s_1^2}{s_2^2} = \frac{(9.726 * 10^{-5})^2}{(1.526 * 10^{-5})^2} = 40.63 \qquad (1)$$

For this experiment, the F-critical value was given as 3.18, based on the F-critical value table found in the Montgomery et al statistics text [51]. Since the experimental F-value is greater than the critical F-value, the two brands are considered statistically different. A T-test is then used to compare the two sets of data to a known mass of an ibuprofen tablet (μ_0), obtained from the Handbook of Pharmaceutical Manufacturing Formulations [52]. The T-test equation, along with a sample calculation of the t-test for the generic brand is shown in Equation 2.

$$t_{exp} = \left| \frac{\overline{x} - \mu_o}{\frac{\sigma}{\sqrt{n}}} \right| = \left| \frac{0.3320 - 0.4800}{\frac{0.00391}{\sqrt{10}}} \right| = 119.8 \qquad (2)$$

The critical t-value, or t-critical, was determined to be 2.262 using a generic t-table in the Montgomery et al text [51]. Since the experimental t-value was larger than the t-critical value, it can be concluded that the generic brand is statistically different than the theoretical value. When the T-test is conducted for the name brand, it was found that the experimental t-value was smaller than the critical t-value. This leads to the conclusion that the name brand was not statistically different than the theoretical value. The calculation for this is shown in Equation 3.

$$t_{exp} = \left| \frac{\overline{x} - \mu_o}{\frac{\sigma}{\sqrt{n}}} \right| = \left| \frac{0.4867 - 0.4800}{\frac{0.00986}{\sqrt{10}}} \right| = 2.136 \qquad (3)$$

Table 1. Raw data of mass measurements for the Tablet Statistical Analysis Lab.

Trial Number	Advil® Brand Mass (grams)	Generic Brand Mass (grams)
1	0.4784	0.3354
2	0.4837	0.3300
3	0.4715	0.3296
4	0.5019	0.3280
5	0.4840	0.3383
6	0.4842	0.3284
7	0.5050	0.3307
8	0.4930	0.3365
9	0.4804	0.3272
10	0.4845	0.3362
Average	0.4870	0.3320
Std. Dev.	0.010	0.004
Variance	9.72 · 10-5	1.52 · 10-5

From these calculations, students can see that there is a difference between the two brands. In fact, the data shows that the standard deviation for the generic brand was lower than the name brand. The reason is that the generic brand did not have a sugar coating or a polishing coat like the Advil® brand. These coatings are much less regulated than the active pharmaceutical ingredient (API) content of the tablet, and as such, adds more variance to the population. The students also see that the generic brand does not correlate well with the literature value, which is also due to the lack of coatings. As such, the values may change depending on the generic brand used for this experiment.

Students also perform an outlier test, taking a portion of their data analysis for a Box-Whisker plot to determine any outliers. Students should not find any outliers in their experimental data, since the tablets are subjected to the high standards of pharmaceutical manufacturing [53]. Students also complete an exercise where they are given a table of mass measurements from a hypothetical batch of tablets, and must determine whether or not an outlier exists. This data is shown in Table 2.

Table 2. Example data from the outlier testing problem in the Tablet Statistical Analysis Lab.

Data Provided	Sorted Data (Low→High)	Quartiles
0.4850	0.4217	Q_1
0.5198	0.4448	
0.5048	0.4465	0.4665
0.4857	0.4481	
0.4786	0.4662	
0.5435	0.4668	Q_2
0.4448	0.4686	
0.4668	0.4786	
0.4465	0.4835	0.4844
0.4835	0.4837	
0.4686	0.4850	
0.5211	0.4857	
0.4863	0.4863	Q_3
0.4217	0.5048	
0.4481	0.5101	
0.4837	0.5198	
0.5895	0.5211	0.5150
0.5227	0.5227	
0.4662	0.5435	
0.5101	0.5895	

Once the data has been sorted from highest to lowest, the students calculate the three quartiles (Q). The first quartile (Q_1) is the median of the lower half of the data, while the third quartile (Q_3) is the median of the higher half of the data. The second quartile (Q_2) is the median of the entire data set. Q_1 and Q_3 are then used to determine the low and high outlier cut-off points (O_L and O_H, respectively). The equations for determining O_L and O_H are shown in Equations 4 and 5.

$$O_L = Q_1 - 1.5\,(Q_3 - Q_1) = 0.4665g - 1.5 * (0.5150g - 0.4665g) = 0.3989g \quad (4)$$

$$O_H = Q_3 + 1.5\,(Q_3 - Q_1) = 0.5150 + 1.5 * (0.5150g - 0.4665g) = 0.5876g \quad (5)$$

A box-and-whisker plot can then be used to show the outlier (Figure 1).

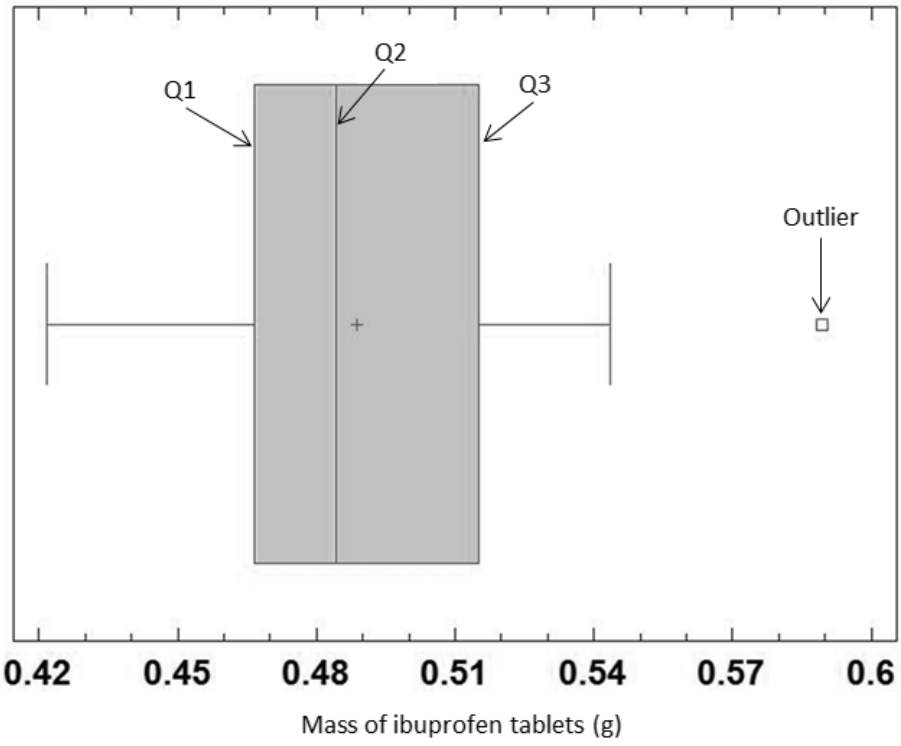


Figure 1. The Box-and-Whisker plot for the exercise found in the Tablet Statistical Analysis Lab. One outlier is clearly visible in this plot.

As an introductory experiment, this lab presents important pharmaceutical terminology.

Students learn about the different pharmaceutical substances, such as API and the

different types of excipients (fillers, binders, glidants, etc.). These technical terms were reinforced through an exercise where students determine the API and look up the first three inactive ingredients or excipients; and their functions. In addition, students learn about batch manufacturing processes and receive an introduction to process flow diagrams through an exercise. Students are given a manufacturing procedure from the Handbook of Pharmaceutical Manufacturing Formulations on how to make coated ibuprofen tablets, read it, and then convert their readings into a flow diagram of this process [52], shown in Figure 2. The Student and Instructor's Version of this laboratory experiment can be found in Appendix A.1 and B.1, respectively.

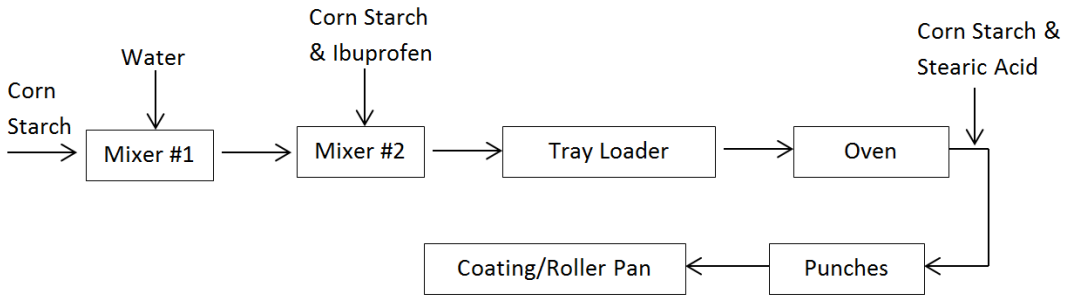


Figure 2. The solution to the flow diagram exercise found in the Tablet Statistical Analysis Lab. Above, the powder is corn starch, and mix #1 is ibuprofen and corn starch.

3.2 Fluidization of Pharmaceutical Excipients Lab

Fluidization is defined as a technique or phenomenon where the internal frictional forces in a bed of solid particles are reduced so that the bed flows like a fluid. Counter forces, such as drag, also exist in a fluidized bed [54]. The first investigations into fluidization

began in the late 1940's with Richard H. Wilhelm and Mooson Kwauk, who investigated the different phases of fluidization [55]. Fluidization then began a period of extensive research through the 1950's and well into the 1970's, when Kunii and Levenspiel published their book entitled 'Fluidization Engineering' [54]. The book laid out extensive details on the previous research done; including equations, heuristics, and graphs of fluidization data [56]. After the 1970's, fluidization research began to decrease, only to grow again in the late 90's. One example is a group of researchers from Beijing that began an in-depth study on how to fluidize fine particles in 1998 [57].

The pharmaceutical industry has used fluidization technology for several years. Early investigations of fluidization in the pharmaceutical industry can be seen in a three-part series of articles by Davies and Gloor [58, 59, 60]. Pharmaceutical manufacturers can use fluidized beds for granulation, and has been used for this purpose for several decades. Granulation is defined as a process where small powder particles are gathered and turned into larger particles [61]. This is done to improve the powder properties for downstream processing [62]. A two-phase process is usually used for granulation, which includes spraying, drying, and the addition of a binding liquid [62, 63]. In cases where there are heat- or moisture-sensitive drugs, granulation can occur with compaction.

In the early days of this unit process, granulation was considered more of an art than a science. After extensive investigations by a few researchers, models were developed for granulation phenomenon, and can be seen in several review articles [64, 65]. A highlight of some of these theoretical developments include: Determining the drop penetration time based on capillary pressure; determining deformation through a Stokes deformation number; a multidimensional model that follows distributions in granule size, porosity,

and liquid content [66, 67, 68, 69]. From a manufacturing perspective, there have been several studies on granulation. Controls and scale-up work that has been done has been compiled by Faure, York, and Rowe [70]. This compilation includes an extensive list of process parameters that affect wet granulation. Techniques used for controlling the distribution and shape of granules were also discussed. Some of these techniques include fuzzy logic, neural networks, and image processing [71, 72, 73].

Fluidization can also be used for coating operations. The appeal of using a fluidized bed apparatus for coating processes is due to high energy and mass transfer rates that are available through the system [74]. Coating is often used for taste masking and drug release control in pharmaceutical products [75]. A patent was filed in 2014 by the New Jersey Institute of Technology that used fluidized bed coating for drug release control [76]. Coating can also be used to improve product flowability [77]. One study investigated the improvement in flow properties of ibuprofen after a thin-coating with a fluidized bed apparatus [78].

Coating in fluidized beds is mostly used for dry solid particles, powders, or pellets. In this setup, particles are fluidized by hot air, and then the coating solution is sprayed over top of the particles. The hot air causes solvents to evaporate, leaving a coating on the surface of the fluidized particles [79]. In most of the cases in the pharmaceutical industry, the Wurster process is used. The Wurster process was patented in 1966, and uses a spray coater that sprays up from the bottom, which allows for higher coating quality and homogeneity [80, 81]. This process has been shown to be the most useful equipment setup for small-particle coating [82].

Fluidized beds are also used for drying. Due to its rapid heat and mass transfer abilities, large capabilities, and relatively low capital cost, fluidized beds are often utilized for the drying of wet granules [83, 84, 85]. This type of drying can be done either in batch or continuous processes. Usually, batch operation is used in small-scale productions and continuous operation is used in large scale productions. Batch operations may also be used for heat-sensitive materials [86].

There has been extensive research on drying using fluidized beds. Chandran, Subba Rao, and Varma published their work on developing a kinetic model for this phenomenon in 1990 [87]. Thomas and Varma investigated several factors on fluidized bed drying, including temperatures, flow rates of the heating medium, and the mass of solids in the fluidized bed [88]. Circulating fluidized beds are used for drying, and have been investigated by Balasubramanian and Srinivasakannan [86]. A model has also been developed for fluidized bed drying of granular material [89]. Mixtures of solids have also been investigated for their drying behavior in fluidized bed systems [90].

From the literature review, it is obvious that fluidization is now an important unit operation in the pharmaceutical industry. The Fluidization of Pharmaceutical Ingredients Lab was designed so that students would be introduced to the fluidization equipment and the phenomenon of fluidization. This experiment is based on a polymer coating lab for freshmen developed by Rowan engineering faculty [91]. The objectives of the lab are to analyze the fluidization of a pharmaceutical ingredient, such as an excipient, and measure basic fluid/particle properties. In order to do this, students first determine three properties; bulk density, particle density, and bed porosity. This is done through a gravimetric analysis, where the students use a graduated cylinder and water to determine

the bulk and particle densities, and then calculate the porosity of the substance using these two parameters. Students compare these to literature values and learn how to use particulate data bases. The second part of the experiment focuses on fluidization phenomena. The objective of this part is to determine fluidization regimes and the effect of process parameters related to fluidization. The setup of the fluidized bed is shown in Figure 3, in which the excipient is fluidized in air.

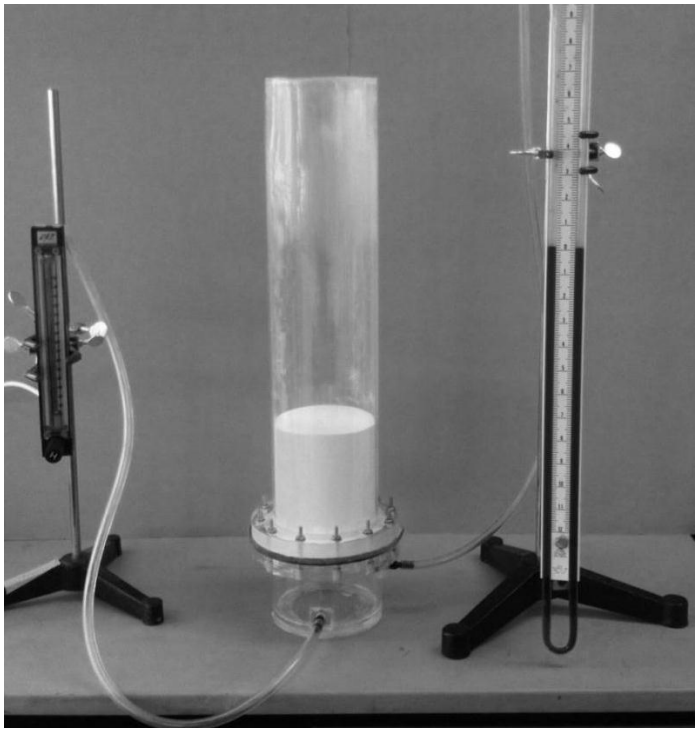
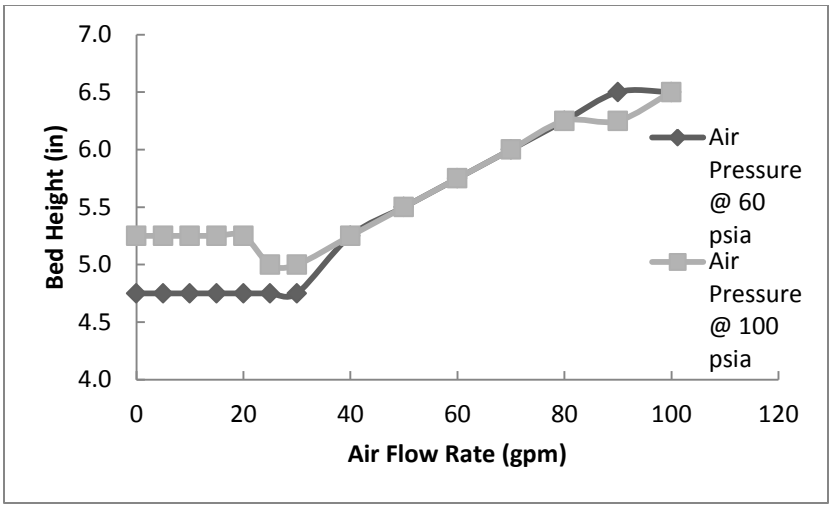


Figure 3. The fluidized bed apparatus used in the Fluidization of Excipients Lab.

Students conduct an experiment to measure the bed height as a function of air flow rate. They notice through this exercise that as bed height starts to increase, fluidization has also started. Pressure drop readings across the column are also taken during this study.

Through graphs of these variables, as seen in Figure 4, students observe where the slope of the lines change, denoting transformation from packed bed to fluidized bed behavior. In addition, students receive an exercise in using online reference tools. This exercise asks the students to find an article through library electronic search tools that discusses fluidized beds in the pharmaceutical manufacturing. The students are to print out the article of their choosing and discuss it in the next class.

a)



b)

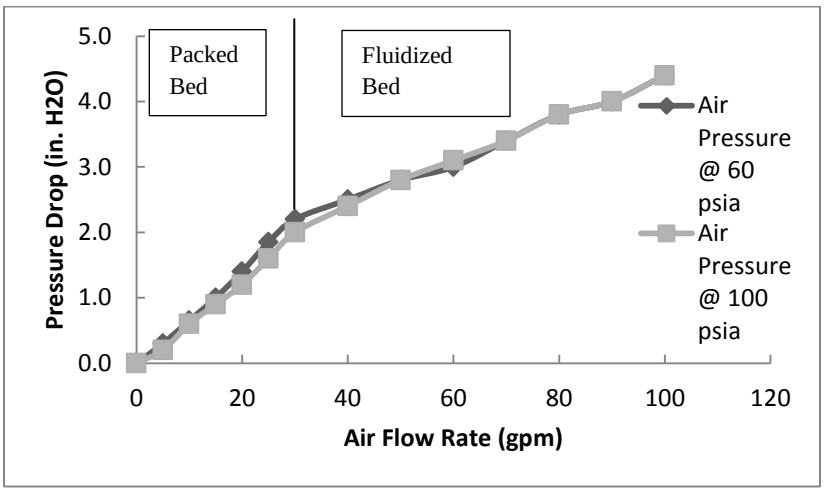


Figure 4. Sample data from the Fluidization of Pharmaceutical Ingredients Lab. a) Air flow rate versus bed height is shown. b) Air flow rate versus pressure drop. Studies used Avicel® Ph200 at 20 °C.

The pharmaceutical objective of this experiment is to show equipment used in transportation, granulation, coating, and drying of solids [58]. Since the solid particles act like a fluid, they become much easier to transport through conventional conveying equipment. Students also see how excipient properties affect the fluidization process. The students gain this experience through an exercise that has them compare the

Reynolds Number at minimum fluidization, Re_{mf}, of two different substances; Avicel® (microcrystalline cellulose powder) and kaolin (white clay powder). The main difference between these two studies is the average particle size (1.4 µm for kaolin and 180 µm for Avicel®), which is the primary reason the Reynolds Number calculations at minimum fluidization are different. The Reynolds Number (Re) calculation gives students experience in units and conversions, requiring them to convert to one system of units and prove that Re is dimensionless. Students are also introduced to fluid flow in calculations and conversion of volumetric flow rates to a fluid velocity in the bed. Finally, they use a design equation to predict what the Re_{mf} should be and compare that to their experimentally determined value [92]. This equation, along with supplemental governing equations, is shown in Equations 6 through 9.

$$Re_{mf} = \sqrt{(C_1^2 + C_2 * Ar)} - C_1 \quad (6)$$

With:

$$Ar = \frac{Dp^3 \, \rho_g \left(\rho_s - \rho_g\right) g}{\mu^2} \quad (7)$$

$$C_1 = \frac{300\left(1 - \varepsilon_{mf}\right)}{7} \quad (8)$$

$$C_2 = \frac{\varepsilon_{mf}^3}{1.75} \quad (9)$$

Where ε_{mf} is the void fraction at minimum fluidization; D_p is the diameter of the particle; ρ_g is the density of the fluid; ρ_s is the particle density of the solid; and μ is the viscosity of the fluid. In the Avicel® experiment, the design equation predicted a

Reynolds number of 19.36, while experimental data determined a Reynolds number of 19.10, which is within 1.4% difference. The Student and Instructor's version of this lab can be found in Appendix A.2 and B.2, respectively.

3.3 Asthma Drug Delivery Lab

Asthma is one of the most chronic illnesses diagnosed in children. The illness has been reported throughout most of human history, being recorded in ancient Chinese, Indian, Egyptian, and Greek writings [93]. Cures from these writings include special teas, vapors, honey, mustard oil, turmeric, and garlic. Asthma's current definition wasn't established until 1698 by John Floyer, an English physician. Floyer defined asthma as "laborious respiration with lifting of the shoulders and wheezing" and also understood that the illness was intermittent and episodic, which requires rescue and controller therapy [94].

It wasn't until 1896 that the approach to asthma treatment took on its current form of acute rescue treatment, controller treatment, and prevention of long-term complications [95]. Sir Thomas Granger Stewart and George Alexander Gibson noted that environmental allergens can affect asthma at this time, and offered some advice for removing offending allergens from the environment [96]. From then on, asthma was treated pharmacologically. The first treatment prescribed for asthma treatment was anticholinergic belladonna-related alkaloids [95]. It was Stewart and Gibson who suggested smoking stramonium, a dried leaf and flower of the plant *Datura stramonium*, with tobacco (or preferably pure stramonium) to reduce the symptoms of asthma [96]. In 1914, hypodermic injections of pilocarpine, a drug derived from plants of the genus

Pilocarpus, were noted to be effective, and added to the common treatments for asthma [97].

In 1940, theophylline, a non-anti-cholinergic bronchodilator, was reported for the first time as a method for treating asthma [98]. This sparked the use of non-anti-cholinergic bronchodilators for asthma treatments, leading the way to the prescription of ephedrine, adrenaline, salbutamol, remiterol, and fenoterol [99]. Unfortunately, these drugs did not go through specific safety regulations, and were unrestrictedly supplied in over-the-counter medications. It was this that caused an epidemic of asthma related deaths in the United States, Australia, United Kingdom and New Zealand from the 1960's to 1980's [100]. These epidemics lead to the prescribing and careful regulation of asthma medications.

While cigarettes and injections were used early in asthma treatments, inhalers were used in the first third of the twentieth century [95]. Atomizers and inhalers can be seen in early 1900's and through the 1950's [93]. In the year 1956, the metering valve was first invented, and so, the first pressurized meter dose inhaler (pMDI) came into being [101]. A pMDI delivers a dose of pharmaceutical medication that has been suspended through a chlorofluorocarbon (CFC) [102]. A pMDI consists of three major components: A reservoir, in which the raw drug is suspended; a metering valve, which delivers a specified amount of the medication when depressed; and a spray actuator, which delivers the drug to the body.

The pMDI is arguably the most famous version of an asthma inhaler, with most respiratory drugs being offered in this form of delivery [102]. The advantages of this

drug delivery method are that it is efficient when used correctly, they are portable, and they are relatively easy to use. In most cases, pMDI's have a deposition efficiency of 6.5% to 24%, which is better than previous methods of drug delivery [103]. However, there are some drawbacks to this method. The major problem with MDI's is that if not used correctly, the drug will deposit itself on the tongue, causing fungal infections in the mouth [104]. Also, the use of CFC's has become under fire, since they lead to ozone depletion. As such, new excipients are used, which cause a decrease in efficiency. These new propellants also have to be rigorously tested for any possible toxicological effects [102].

Another form of asthma medication delivery is known as the dry powder inhaler (DPI). Although DPI's are not as widely known as pMDI's, this method of delivery has been investigated since the 1930's. The first patent to be given for a powder inhalation method was awarded in 1940 for the inhalation of aluminum powder [105]. The first pharmaceutical dry powder inhaler can be seen in a patent from 1949 [106]. These dry powder inhalers do not use a propellant agent in order to deliver the medication. Rather, the mechanism of delivery is solely based on the size of the particles and their inhalation from the device [102, 107].

This lack of needing a propellant is considered a great advantage, since one does not have to worry about using ozone depleting propellants. Some other advantages for using a DPI are that it is easy to use and causes less irritation in patients [108]. In addition, the DPI is just as portable and compact as a pMDI. Thus, several companies have produced DPI's for asthmatic therapeutics [93, 102].

DPI's are not without their setbacks, however. One of the main problems with DPI's is paradoxically caused by their greatest asset; they do not use propellants. As such, patients who use DPI's must inhale at a suitable flow rate in order to obtain the correct dosage of the drug [109]. This is a problem specifically for young children [110]. Some of the lesser DPI disadvantages include that they are more expensive than MDI's and also need to be stored in cool and dry areas [111].

As asthma medications have several different modes of drug delivery, this was thought to be an opportune moment for introducing differences in drug delivery mechanisms. The Asthma Drug Delivery Lab compares three different drug delivery systems for asthma medicines. The first objective of the experiment is to have the students reverse engineer the three systems; a dry powder inhaler, a metered dose "rescue" inhaler, and a nasal spray. Secondly, the students determine the quality control measures of the inhalers and how they deliver a specific dosage each time used.

The dry powder inhaler, an ADVAIR Diskus®, is also known as a diskhaler. The students compare the production design of the Diskus® with a metered dose "rescue" inhaler and a nasal spray through a reverse engineering exercise. Only the ADVAIR Diskus® reverse engineering process is described in this paper, as it was the most technically complex device. First, the students brainstorm the drug delivery mechanism of the diskhaler, using the patient insert as the source of information. Most students will guess that there is some sort of puncture device that allows the medicine to enter the main chamber of the diskhaler, as it is described in the pamphlet as blisters being punctured open. Seeing the inner mechanisms gives the student insight into how the inhaler actually works, using a tearing mechanism to open the blister packets. Since the design

utilizes blisters, the device ensures that only a certain amount of active pharmaceutical substance is released for each use, keeping the rest of the powder fresh inside the individual blisters for subsequent doses, as shown in Figure 5. Students also have to discuss the ergonomics and aesthetics of each of the products, so that they also understand the importance of these two factors on product design in drug delivery.

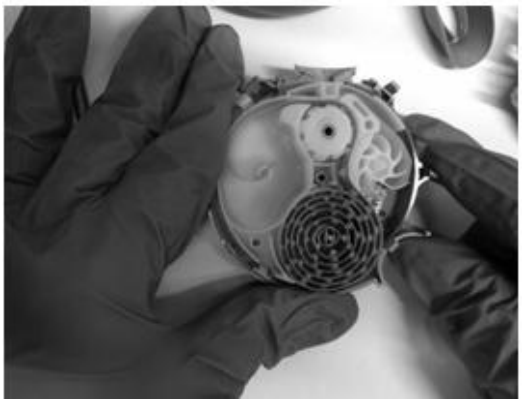


Figure 5. The inner mechanisms of an ADVAIR Diskus®.

The second half of this experiment has the students review the quality control aspect of the three devices by taking mass measurements of the doses being delivered and calculating the mean and standard deviation (Table 3). From this data, the students compare the standard deviations, and what that implies about the function of the devices. Students observe that the diskhaler has the lowest standard deviation of the three devices, which is due to the design of the device. Similar results are not obtained with the metered dose inhaler and the nasal spray because the metered dose inhaler involves a fluid that easily evaporates and the precision of the nasal spray depends on how well the apparatus is primed. These product designs enter into the discussion of why the standard

deviations for those two designs have an order of magnitude difference from that of the diskhaler. Students are also tasked with looking up typical standard deviations for therapeutic dosage delivery. The Student and Instructor's version of this lab can be found in Appendix A.3 and B.3, respectively.

Table 3. Sample data and results from the Asthma Drug Delivery Lab.

Trial Number	Mass of Diskhaler Powder(g)	Mass of Metered Dose Inhaler (g)	Mass of Nasal Spray (g)
1	0.0130	0.0130	0.0867
2	0.0130	0.0128	0.0979
3	0.0127	0.0088	0.0989
4	0.0132	0.0107	0.0854
5	0.0126	0.0130	0.1004
6	0.0123	0.0140	0.0983
7	0.0130	0.0140	0.1022
8	0.0129	0.0148	0.1000
9	0.0124	0.0120	0.0991
10	0.0130	0.0121	0.0986
Average	0.0128	0.0125	0.0968
Std. Dev.	$2.81 \cdot 10^{-04}$	$1.66 \cdot 10^{-03}$	$5.48 \cdot 10^{-03}$

3.4 Degradation of Dissolvable Strips Lab

Drug delivery has become a widely popular area of study for chemical engineers. Indeed, this topic is also of great importance to the pharmaceutical industry as well. From a pharmaceutical perspective, the purpose of developing novel methods of drug delivery systems is to improve patient compliance and optimize dosage regiment while not compromising the therapeutic efficacy [112]. From an economical perspective, drug

delivery systems also cost less and take about half the time as it does for a pharmaceutical company to develop as opposed to new drug discovery [113].

Although tablets are the most common form of drug delivery, other methods exist. Transdermal patches, inserts, and implants are all examples of these other methods. Implants were first discovered as possible methods for drug delivery in the 1960's through the experimentation of Judah Folkman of the National Naval Medical Center. His experiments found that sealed segments of silicon tubing containing drugs could be planted within the body as a constant rate drug delivery device [114]. An early form of insert was offered by the Alza Corporation in the 1970's, which would deliver glaucoma medication to the eye through an ocular insert [115]. This insert was found to be more effective than the commonly prescribed ophthalmic solutions that were available at the time [116]. Inserts are now becoming popular as modes of contraception. The Alza Corporation was again early providers of this kind of insert, which was inserted vaginally to release a contraceptive drug [115]. These rings, and other versions of vaginal inserts, are still popular forms of contraception.

Another innovation that occurred in the 1970's was the transdermal skin patch. Once again, the Alza Corporation was a pioneer in this form of drug delivery, being one of the first corporations to obtain a patent for transdermal skin patches [117]. This type of transdermal patch was advertised as a bandage that would administer anti-motion sickness medication [115]. In the early to middle 1980's transdermal delivery systems began to be a popular area of research [118]. Transdermal patches are currently popular for nicotine delivery for use as smoking cessation aids [119]. More recent research has investigated transdermal patches for uses in wound and scar treatment [120, 121].

While the 1970's drug delivery research was focused on the macroscopic level, the middle to late 1980's was the moment when investigations began to focus on the microscopic level. This is not to say that investigations in the microscopic level did not occur previously. The earliest patent based on microparticles was dated in 1973 [122]. Microparticles were prioritized during this middle to late 1980's period [115]. A revolution of microparticle research occurred in the early 1990's, when a group of researchers invented a process for fabricating uniform sized microparticles [123]. This area of research still continues in this century.

In the late 1970's, the concept of nano-therapeutics were beginning to form and rise in interest. Three key technologies developed in the 1980's stimulated and ensured the success of the field: Polyethylene glycol drugs and drug carriers; active targeting of the drug conjugate via cell membrane receptor antibodies; and discovering the enhanced permeation and retention (EPR) effect. The conjugation of polyethylene glycol was the first of these technological jumps, and was first reported by researchers at Rutgers University in the 1960's [124]. It was effectively used to deliver cancer fighting proteins [115]. In 1975, the first example of drug conjugate targeting was published [125]. This research led to another cancer fighting breakthrough, in which drug conjugates were actively targeted by ligands which were imperative for liver cancer treatment [115, 126]. The EPR effect was the last of the developments to be discovered. This discovery was made in 1984 by Hiroshi Maeda of Kumamoto University after carrying out animal studies with a novel drug conjugate [115]. Further investigation lead to a publication on the effect, and helped shape the research done in nanoparticles to this day [127].

Surface-controlled drug release has been a clinically successful area of research since the 1960's, and can be one of, or a combination of, macroscopic, microscopic, and nanoscopic technologies [115]. One of the first successful investigations into surface controlled drug delivery began with the polysaccharide heparin, which was used to coat surfaces of polymers to prevent coagulation of blood on polymers. This area of research was heavily investigated since the 1960's [128]. More recent investigations look at using drug eluting stents, which have been investigated by Johnson & Johnson and Boston Scientific [129]. There have also been insights into surface coatings for enhanced drug delivery for mucosal tissues. Gastric retention formulations have been one of the key areas of study for mucoadhesive systems [130].

While the drug delivery development of the past century might seem impressive, scientists and engineers conclude that development has been quite poor for this time period. One worker of SmithKline Beecham Pharmaceuticals stated in 1999 that the developments of the century would score no more than a 2 or 3 on a 1-10 scale [131]. There is speculation, however, that development will increase in this current century. More emphasis will be placed on creating "smart tablets" that can be used for both immediate and controlled release [131]. These smart tablets are to be more beneficial to patients by maximizing drug efficacy by using a smarter drug delivery selection system. With this in mind, regulatory requirements are also hypothesized to change [131]. With this in mind, it is imperative that those seeking employment in the pharmaceutical industry be well-versed in the drug delivery process.

Drug delivery education is not always a difficult concept to incorporate into engineering curriculums. One of the benefits of this area is that it contains aspects of important

engineering topics. Drug delivery itself relies heavily on transport phenomenon, a staple in the chemical engineering curriculum [118]. Others have already made significant progress integrating drug delivery into engineering education. Farrell and Hesketh of Rowan University developed an introduction to drug delivery for chemical engineers in 2002 [28]. A drug delivery experiment was also developed that could be used for the Freshman Engineering Clinic class offered at Rowan University by Farrell and Vernengo [132]. At the National University of Singapore, a group of educators used a design project to discuss controlled-release drug delivery devices [133]. Simon, Kanneganti, and Kim of the New Jersey Institute of Technology introduced a laboratory on drug transport and pharmacokinetics, as mentioned previously [23]. As also mentioned in a previous section, the Georgia Institute of Technology offers an interdisciplinary course on drug design, development, and delivery [24]. The Georgia Institute of Technology developed a laboratory module around the same time focusing on skin diffusion, an important aspect of transdermal drug delivery [134].

Following this trend, the Degradation of Dissolvable Strips Lab is an investigation into the drug delivery aspects of dissolvable strips. In this experiment, students are tasked with investigating the dissolution rate of ingredients in dissolvable strips. Strip films have become an area of interest in the past few years as an alternative to conventional tablets and capsules, especially for patients suffering from dysphagia [135]. Some examples of consumer products formulated into orally administered strips include breath fresheners, energy supplements, and analgesics for flu and sinus symptoms [136]. In this lab, students work with Sheets™ brand energy strips, containing caffeine and blue food dye. Blue food dye in the product is used to model the release of a pharmaceutical

ingredient. The students are to investigate the effect of temperature on the dissolution rate by placing one strip in water kept at room temperature (~ 22 °C), and placing another in water at body temperature (~ 37 °C). To simulate the mouth, a shallow petri dish is filled with 25 mL of water, in which a strip is placed; absorbance measurements are taken at regular intervals, generating graphs as seen in Figure 6. The absorbance values are related to the concentration of the ingredients released by using a standardization curved developed at the beginning of the experiment.

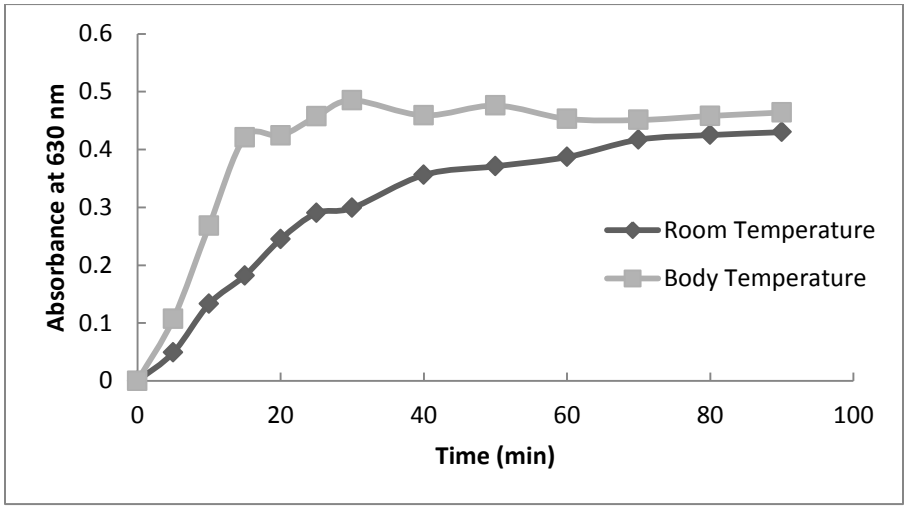


Figure 6. Sample data from the Dissolvable Strip Lab, using one strip film for each.

The experiment introduces the students to spectrophotometry, and the principles related to the methodology used to measure solution concentration. This is done by having the students apply the Beer-Lambert law to determine the molar absorptivity coefficient of the blue food dye at both temperatures at the time of 80 minutes, which is considered a

point where the strip has fully dissolved in the water. The equation and a sample calculation are shown in Equation 10.

$$\epsilon_{22} = \frac{A}{\ell c} = \frac{0.425}{(1\ cm)(3.03 \cdot 10^{-7} M)} = 1.40 \cdot 10^{-6}\ M^{-1} cm^{-1} \qquad (10)$$

Where A is the absorbance (unitless), ℓ is the measurement cell width, and c is the molar concentration of the sample. The students should notice that the coefficients are identical between the two cases (ε_{22} and ε_{37} are $1.401 \cdot 10^{6}$ M^{-1} cm^{-1}), which determines that for the ranges used in this experiment, the temperature does not significantly affect the molar absorptivity coefficient. The students are then charged with determining how the Beer-Lambert law and molar absorptivity coefficients can be applied in other engineering applications. Some of the common answers will be waste water treatment, product synthesis, and algae growth.

The pharmaceutical relevance of this experiment is that students are introduced to a novel drug delivery system. The students also see how the strip film quickly dissolves in water, indicating that the polymer used in the strips breaks down when it comes in contact with water. The concept of higher temperatures affecting the dissolution rate of the strip is also reinforced through an example involving rate laws. In this example, the students use absorbance readings and determine the rate law coefficient, k, for both experimental conditions. Upon calculating, the students see that the rate coefficient is higher for the body temperature experimental run than the room temperature study.

Some additional parts of this experiment have been developed based on advanced instrumentation and the available time. If a broader range spectrophotometer is available, absorbance data can be taken for caffeine at a wavelength of 273 nm. An agitated system can also be used to examine the convective effects on dissolution rate of the strip. The Student and Instructor's version of this lab can be found in Appendix A.4 and B.4, respectively.

3.5 Effervescence Reaction Lab

An effervescence reaction is one in which an organic acid and a carbonate substance which will release carbon dioxide upon reaction with the organic acid [137]. Effervescent reactions can be seen in several different areas of chemical research. Recently, investigations have been made in using effervescent reactions for the extraction of solids. The effervescence reactions help to improve the extraction yield, with absolute recoveries in the range of 61 to 85 % [138]. Another study also looked at using effervescent reactions and nanoparticles to increase the extraction yields in dispersive liquid-liquid microextraction [139].

Effervescence reactions are also important in the food industries, specifically the champagne and sparkling wine industry. Carbon dioxide plays an important role in the champagne and sparkling wine; as it affects the frequency of bubbles, the growth rate of bubbles, the oral feelings, and the aromatic perception [140]. Carbonation is also an important aspect in beer, seltzers, and sodas. In beer production, carbonation helps to release aroma compounds, improving the smell of beers [141]. This process is also used highly in coffee production [142].

Effervescence itself has been used for over 250 years in the pharmaceutical industry [143]. The most famous pharmaceutical product that makes use of effervescence is Alka-Seltzer®. Alka-Seltzer® was developed in 1930's as a cure for a hangover [144]. Since then, the tablets have been used as cures for heartburn, headaches, seasickness, and flu/cold-like symptoms. Due to the success of Alka-Seltzer®, other manufacturers began to produce their own form of effervescent tablets. This has led to several patents being awarded for the production of effervescent tablets, including a novel process for making tablets in 1978, granules in 1986, and a modification of the effervescent compositions in 1987 [137, 145, 146].

Currently, effervescent tablets are still an area of research. Ranitidine, an API often used for ulcers, acid reflux, and Zollinger-Ellison syndrome, is currently being investigated for possible inclusion in effervescent tablets [147]. Prochlorperazine maleate, an API for nausea treatment, is also investigated for use in effervescent tablets for improved patient compliance [148]. In the field of prostate cancer research, the API flutamide was incorporated into effervescent tablets in order to increase its bioavailability with considerable success [149]. The effervescent powders themselves are also an area of study. Effervescent powders are currently being investigated for their use in respiratory drug delivery to incorporate an active release mechanism, increasing the release efficiency [150].

Since effervescence is an interesting and innovative area of the pharmaceutical industry, it was decided that an experiment should be developed to introduce this type of reaction. This experiment, the Effervescence Reaction Lab, evaluates the effect of tablet manufacturing process on the rate of this effervescence reaction. Students compare the

effervescent reaction of a whole tablet of Alka-Seltzer® to the initial raw ingredients. These are allowed to react with water, while students take residual mass measurements as time progresses. Students must determine why the whole tablet reacts faster. Upon a review of the manufacturing procedure, it is determined that there is a milling step to reduce the active ingredient particle size. Therefore, with greater surface area and a more uniform composition, the reaction proceeds faster than the un-milled raw materials.

By having students measure the amount of mass that left the system, they determine the amount of carbon dioxide (CO_2) gas produced via the effervescence reaction. Using stoichiometry, the students also determine the amount of CO_2 they should have theoretically generated during the reaction. The stoichiometric equation is shown in Equation 14.

$$C_6H_8O_7(aq) + 3NaHCO_3(aq) \rightarrow 3H_2O(l) + 3CO_2(g) + Na_3C_6H_5O_7(aq) \quad (14)$$

Using these two values, the students determine the percent difference between their theoretical and experimentally observed values, as shown in Figure 7. They see that the longer the reaction continues the difference between theoretical values and experimental values starts to decrease. Students use this information in an exercise to obtain an equilibrium constant for the effervescent reaction. The Student and Instructor's version of this lab can be found in Appendix A.5 and B.5, respectively.

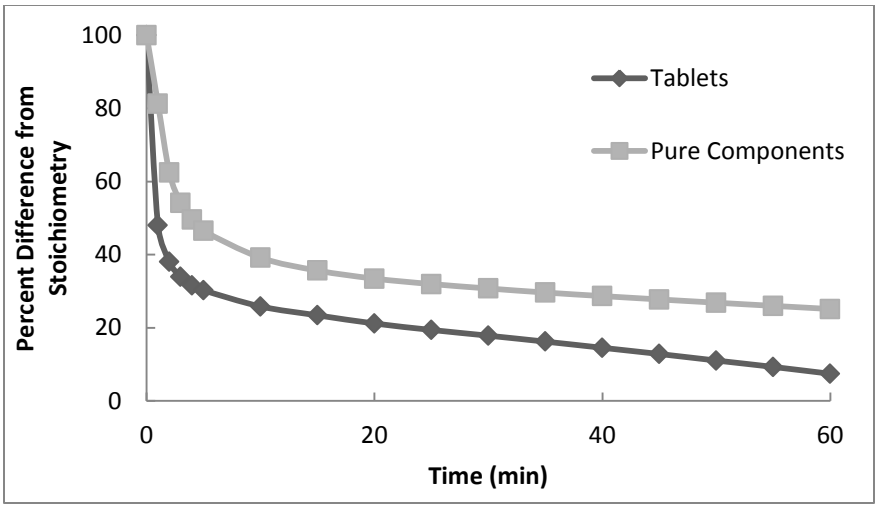


Figure 7. The differences from stoichiometry between the tablet and the pure components, students see that as the time increases, the percent error decreases.

3.6 Dextromethorphan Crystallization Laboratory

Crystallization is an important aspect of several different industries. In chemical engineering, crystallization is an important process for solid-liquid separation, and is often incorporated into separation texts [151, 152, 153]. Crystallization is a process in which solid particles are formed from a homogenous mixture. In crystallization, a mixture is concentrated, usually to saturation, and is then cooled until the solute concentration becomes greater than the solubility of the mixture at that temperature. This causes the solute to form crystals and precipitate out of solution [153]. Crystallization is often employed as a separation process for two reasons. Crystallization has a large separation factor, and as such, creates crystals of high purities; crystallization also produces crystals of uniform sizes and shapes [152]. The latter characteristic is a highly regarded aspect for the pharmaceutical and food industry.

In crystallization theory, there are four important parameters of the crystal; saturation, purity, nucleation rate, and single crystal growth rate. Saturation is the maximum

concentration of a solute which is thermodynamically stable [151]. In several cases, however, a solution can contain more solute than the saturation limit. In this case, the system is considered supersaturated, and is often metastable, meaning that the solution, while unstable, can remain unaltered for long periods of time [151]. Purity is the relative purity of crystals created, which is important if several different substances can be formed from one reaction. Factors such as crystal size and shape can affect the purity of the solids precipitating out [154].

Nucleation rate concerns the rate of crystal production, and occurs in four specific mechanisms; homogeneous, heterogeneous, secondary, and attritive [151]. Homogeneous nucleation is the formation of crystals due to supersaturation only, while heterogeneous results from the presence of other insoluble materials. Secondary nucleation is somewhat of a catch-all, and includes nucleation caused by the contact between different crystals. Attrition is the breakup of existing crystals that then grow into larger crystalline structures [151]. Single crystal growth defines the rate at which existing crystals grow in size. Factors such as agitation of the system, crystal size, and geometry of crystal all affect single crystal growth [151].

The solubility of a solute, and its dependence on temperature, is an important aspect of the designing of crystallization equipment. To visualize this dependence, solubility curves are often employed. Solubility curves, or solubility diagrams, can also be used with Miers diagrams, which graph the metastable, stable, and unstable regions of solutions [152]. Through these diagrams, calculation of yields for crystallizers can be easily completed. Particle sizes and nucleation rates can be determined theoretically [153].

Crystallization, as stated before, is an important unit operation in the pharmaceutical industry. API's often are synthesized and purified using crystallization processes [155]. The areas of crystallization; including theory, empirical formulas, appendices of data, and scale-up considerations have been well documented [156, 157, 158]. Crystallization is also an important aspect of pharmaceutical research and development, with numerous papers being published on novel approaches in this field.

Crystallization is being investigated for possible uses in changing crystal characteristics. For example, acetaminophen can have its thermodynamic stability and other properties change by adding other molecules before the crystallization process [159]. Indeed, cocrystallization is often used to change the properties of one or two molecules so that they may be optimized for use in a pharmaceutical product [160]. This has recently been investigated to increase the solubility of nitrofurantoin, an API used in treating urinary tract infections [161]. The melting point of a crystal can be changed in this manner as well. Researchers found that using cocrystals of hexamethylenebisacetamide A, an anticancer drug, helped increase the solubility and melting point of the API [162]. Compressibility and flowability can also be improved by using cocrystals, as was discussed in an article on carbamazepine cocrystals published in 2007 [163].

One of the unit operations that have been researched for crystal engineering and cocrystallization is supercritical fluid processes. Several studies have been completed that focus on supercritical fluids and their use in crystal engineering. Researchers have found that using supercritical fluids not only reduces solvent waste, but also reduces the necessary volumes for API crystal formation [164]. Others have found that using supercritical fluid crystallization can also be used to change particle size to alter the

particle dispersion of the final product [165]. Feasibility studies are included, such as an investigation into the feasibility of creating indomethacin-saccharin cocrystals to use in anti-inflammatory medications via supercritical fluid technology [166]. Another study found that cocrystals of indomethacin, theophylline, caffeine, sulfamethazine, aspirin, and carbamazepine could all be produced viably using supercritical CO_2 [167].

In addition to using supercritical fluids, others are looking at developing other methods, such as high-throughput crystallization technologies. These technologies combine design of experiments, experimental protocols, and data analysis, and consist of both hardware and software components [168]. This technology can be used to determine a selection for specific salts. For example, a study used several salt forms of the antibacterial sulfathiozole to determine the use of high-throughput systems. The results of this found that the high-throughput machine rapidly identified 10 salt forms and could characterize them based on melting point ranges [169]. Another study found that high-throughput was effective in determining which cocrystals of caffeine-oxalic acid and theophylline-oxalic acid had proper solubilities and solid/solution stability properties [170]. Others have looked at including Raman microscopy in the high-throughput process to gain even more information, such as equilibrium of cocrystal formation and polymorphic transformation [171].

While crystallization is a relevant topic in pharmaceutical manufacturing, many engineers in the industry find that the unit operation is de-emphasized in most engineering curriculums. Most newly employed engineers learn what they do about crystallization from on the job training [155]. The Dextromethorphan Crystallization Lab is designed specifically to provide background in crystallization for undergraduates. Objectives for

this experiment are to develop a solubility curve for dextromethorphan hydrobromide (DXM), and to also learn the underlying theory of crystallization, such as the thermal energy transfer that occurs in the crystallization process. Students are tasked with determining the temperature at which saturation occurs for several concentrations of DXM in water. Students complete this by heating up solutions of DXM and water and recording the point of recrystallization. The experiment involves the students taking a specific mass of DXM and adding it to 5 mL of water in a test tube. DXM is known for being an insoluble molecule in water [172]. As such, students will observe that the particles simply sink to the bottom of the test tube. To obtain solubility data, the students are to heat this mixture in a hot water bath, kept at around 90 °C, which can be seen in Figure 8.

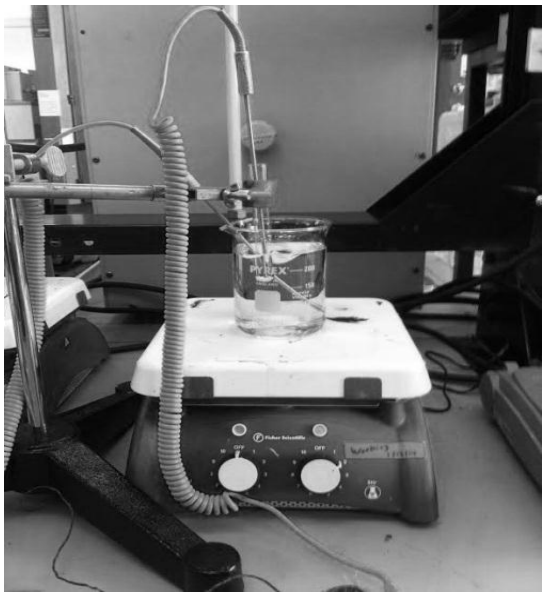


Figure 8. The hot water bath setup used for the Dextromethorphan Crystallization Lab. Two thermocouples are used to regulate the temperature of the hot water bath and the water in the test sample.

The mixture is heated until the students see all the crystals dissolve in the water. Using a thermocouple, the students will record the point at which crystals start to reform in the test tube. A sample of what this looks like can be seen in Figure 9. This is considered the temperature of saturation for that concentration. This is done for several concentrations, including one which is chosen by the students. A sample solubility curve that would have been produced can be seen in Figure 10.

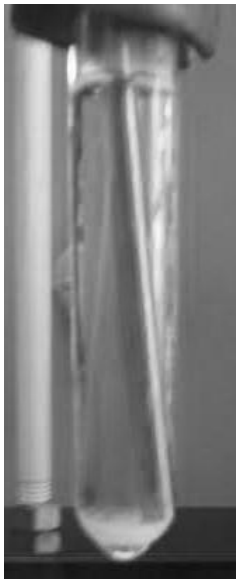


Figure 9. The DXM and water solution once recrystallization has begun. Notice the white substance at the bottom of the tube.

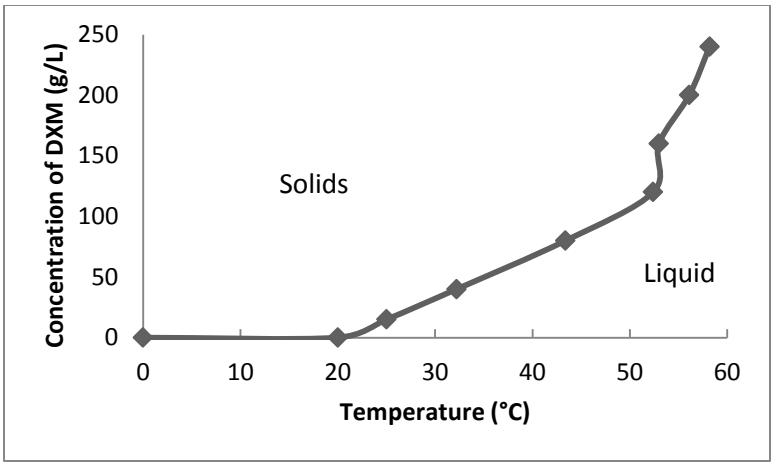


Figure 10. An example of a solubility curve developed for the Dextromethorphan Crystallization Lab.

By recording the saturation temperatures, students are given the task of creating a solubility curve for DXM in water. The random concentration that the students chose is used for two purposes; to allow students to determine the reliability of their solubility curve; and to gain experience using interpolation. Interpolation is an important tool for engineers, as it can be used to determine new values that lay inside existing data points. Students are to determine the saturation temperature that corresponds to their chosen concentration. Calculating the percent difference from their interpolated value to that which they found experimentally will determine how well their solubility curve can predict the point of saturation for a given temperature. For example, for a random concentration of 150 grams per liter, the temperature was determined via interpolation to be 53 °C. This is 0.95% different than the 52.5 °C temperature found via experimentation. A sample of this interpolation is shown in Equations 15 and 16.

$$\frac{(higher\ tick - lower\ tick)}{length\ between\ ticks} = \frac{(temperture - lower\ tick)}{length\ between\ line\ and\ tick} \quad (15)$$

$$\frac{100\ g/L}{4.3\ cm} = \frac{50\ g/L}{length\ between} \rightarrow length\ between = 2.2\ cm$$

$$\frac{(higher\ tick - lower\ tick)}{length\ between\ ticks} = \frac{(temperture - lower\ tick)}{length\ between\ line\ and\ tick} \quad (16)$$

$$\frac{(60 - 50)°C}{4\ cm} = \frac{(x - 50)°C}{1.1\ cm} \rightarrow x = 53\ °C$$

Interpolation is also reinforced through exercises. In these exercises, a solubility curve adapted from Dalman is given to the students [173]. Students are given a scenario in which they need to determine a temperature for a solution in which a specific mass of crystals will precipitate out. The interpolation necessary for this solution is shown in Figure 11. Another exercise is also given that uses interpolation; this time using the DXM solubility curve that the students generated. This exercise has them determine a saturation concentration at a certain temperature. The interpolation necessary in this exercise is shown in Figure 12.

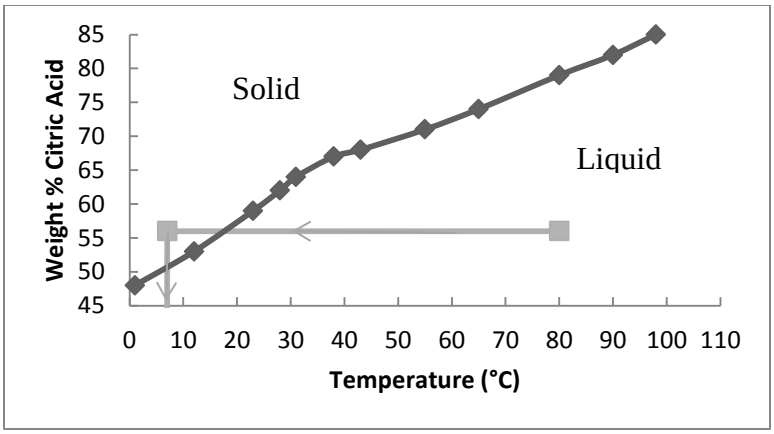


Figure 11. The interpolation used for the citric acid exercise. Here, the dark line is the solubility curve, and the lighter line is the interpolation steps to determine the temperature.

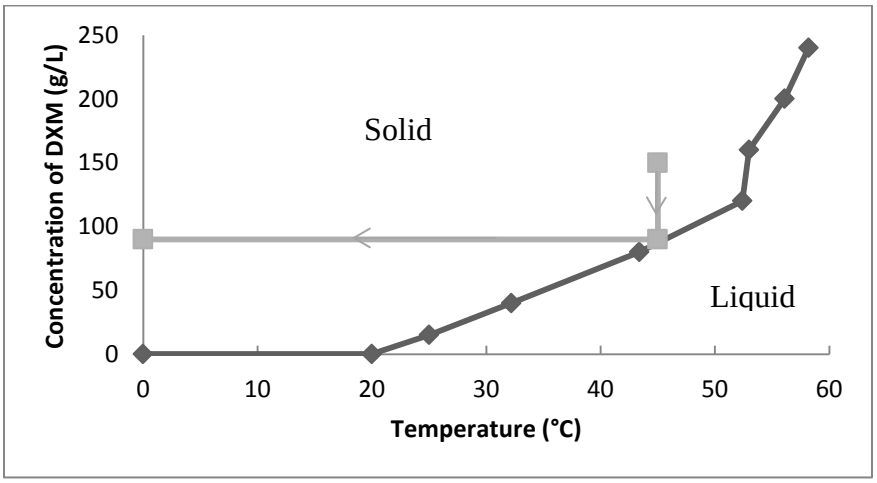


Figure 12. The interpolation necessary for the DXM exercise. Once again, the dark line represents the solubility curve (provided by sample data), while the lighter line represents the interpolation steps.

This was used as part of an exercise that introduced some topics that would be in a principles of chemical processes course. This problem was developed from an example

problem found in the Felder and Rousseau text [174]. In this problem, a simplified crystallization process is described using a cooler/crystallizer, a filter, and a dryer. A box diagram of this process is shown in Figure 13. The interpolation shown in Figure 12 is used to determine the solids produced in the crystallizer. Once this is done, the mass of liquid that leaves with the filter cake can be determined, given that the filter is 100% effective at removing crystals and that the cake is 80% crystals by mass. The mass % equation is used for this calculation, which can be seen in Equation 17. Lastly, the yield is determined by finding the mass of crystals removed via the process and comparing it to the mass of crystals in the starting solution. The mass of crystals and yield were calculated using Equations 18 and 19, respectively.

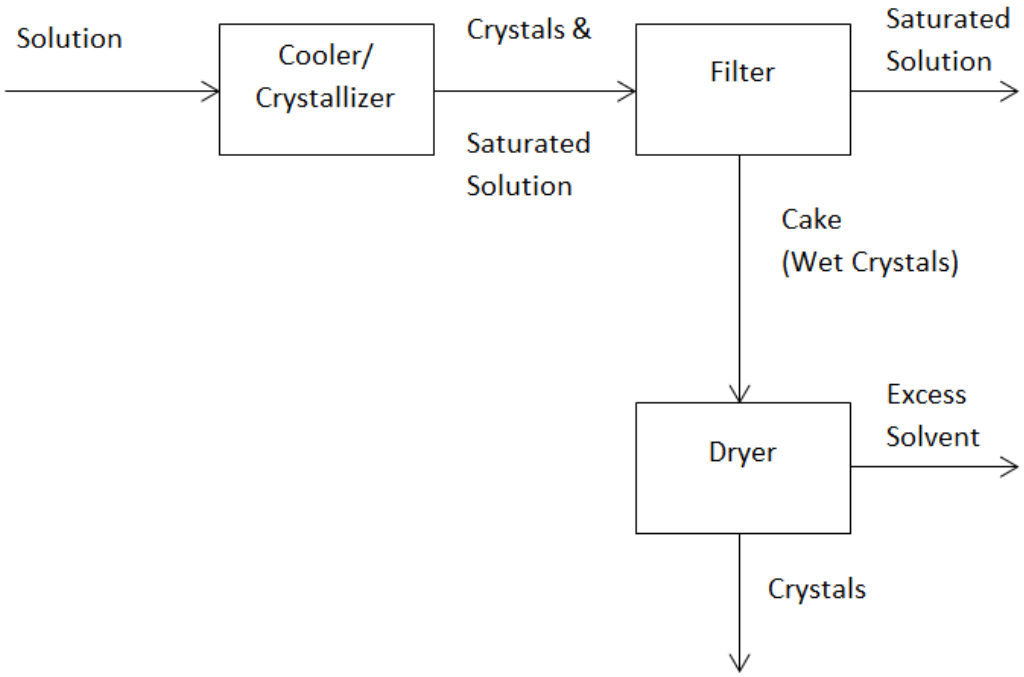


Figure 13. The box diagram for the industrial crystallization exercise given in the Dextromethorphan Crystallization Lab.

$$mass\ \% = 80\% = \frac{m_{crystals}}{m_{crystals} + m_{liquid}} * 100\% \quad (17)$$
$$= \frac{4\ kg}{4\ kg + m_{liquid}} * 100\%$$
$$m_{liquid} = 1\ kg$$

$$m_{crystals-total} \quad (18)$$
$$= m_{crystals-cake}$$
$$+ m_{crystals-solution}$$
$$= 4.0\ kg + 0.09\ kg = 4.09\ kg$$

$$Yield = \frac{m_{crystals-total}}{m_{crystals-start}} = \frac{4.09\ kg}{15\ kg} = 0.273 \quad (19)$$

The solubility curves are the focus of this experiment, as they are a useful tool for engineers when designing crystallization equipment [152, 153]. Another focus of this experiment is to discuss a separate aspect of crystallization; thermal energy transfer. The flow of heat is an important concept for crystallization theory, since heat will need to be transferred to or from the solution in the process. And with this flow of heat there is also the transfer of energy. For transferring energy, a scenario is given to students in which they determine the energy required to heat the water bath used in the experiment, and also a theoretical 200 gallon tank of water. The equation they use, and a sample calculation for the 200 gallon tank of water, is shown Equation 20.

$$Q = mC_p\Delta T = 7.57 \cdot 10^5 g * 4.18\ \frac{J}{g * °C} * (90 - 20)\ °C \quad (20)$$
$$Q = 1.90 \cdot 10^5 J = 190\ kJ$$

Where Q is the energy in the form of heat added to the system, m is the mass of the water, C_p is the specific heat of water, and ΔT is the temperature change for the water. This introduces the students to the differences in values from lab-bench to industrial scale. In terms of heat transfer, two exercises are given. The first example has students determine the thermal diffusivity (α) of a substance. The thermal diffusivity of a substance is the ratio of a substance's ability to conduct thermal energy in relation to its ability to store thermal energy [175]. Students are tasked with calculating the thermal diffusivity for aluminum and water. They are also tasked with determining the temperature dependence of the thermal diffusivity of aluminum by calculating this ratio for several temperatures. The theoretical equation and a sample calculation for the thermal diffusivity of water at 25 °C are shown in Equation 21.

$$\alpha = \frac{k}{\rho C_p} = \frac{0.6100\ {}^{J}/_{s\ m\ K}}{0.9974\ {}^{kg}/_{m^3} * 4180\ {}^{J}/_{kg\ K}} = 1.46 \cdot 10^{-4}\ \frac{m^2}{s} \qquad (21)$$

Where k is the thermal conductivity, ρ is the density, and C_p is the specific heat of the substance. The calculation for aluminum at the same temperature yields an α value of $9.77 \cdot 10^{-5}\ \frac{m^2}{s}$, showing that water has a higher thermal diffusivity, and thus a higher conduction to storage of thermal energy ratio than aluminum at this temperature. When comparing α values for aluminum at different temperatures, students see that the thermal diffusivity decreases with increasing temperature. The sample values can be seen in

Table 4. This reinforces the notion that pure metals show a decrease in thermal conductivity and thermal diffusivity with increasing temperature [175].

Table 4. Sample thermal diffusivity values of aluminum at varying temperatures. As shown, thermal diffusivity values decrease as temperature increases.

Temperature (K)	α (m^2/s)
200	$1.09 \cdot 10^{-4}$
400	$9.43 \cdot 10^{-5}$
800	$7.34 \cdot 10^{-5}$

The second exercise has the students model the rate of heat transfer for a test tube. Students are to model the flow of heat from the center of the water in the test tube to the top of the water in the test tube (Figure 14). In this exercise, a simplistic model is given to the students in which three assumptions are made: That heat flows at a steady state; that all the sides, except for the open end of the tube are perfectly insulated; that free convection on the top surface of the water is negligible. While these assumptions are simplistic, they are necessary to provide appropriate content for lower level undergraduates.

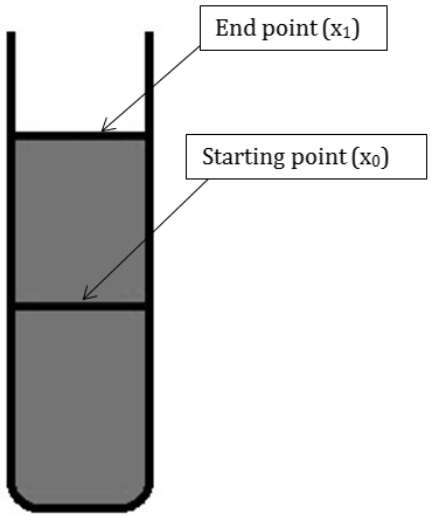


Figure 14. A representation of the one-dimensional, steady-state conduction model for the test tube in the Dextromethorphan Crystallization Lab.

With these assumptions, a heat flow equation that models heat flow in one direction can be used (Equation 22).

$$\frac{q_x \Delta x}{A} = -k\,\Delta T \qquad (22)$$

With q_x being the heat transfer rate, Δx the length at which the heat transfer is taking place $(x_1 - x_0)$, A the surface area of the heat transfer, k the thermal conductivity of the substance, and ΔT the difference in temperature from the end point to the start point $(T_1 - T_0)$. This exercise has the students use different values for k; one assuming the substance is pure water, and the other via an approximation for salt solutions (Equation 23) [176].

$$k = 0.29411 - 0.174 * C + 0.000879 * T - 2 \cdot 10^{-6} * T^2 \quad (23)$$

$$= 0.29411 - 0.174 * \left(\frac{0.2g}{(0.2+5)g}\right) + 0.000879$$

$$* 78.98°F - 2 * 10^{-6} * (78.98\,°F)^2$$

$$= 0.969\ \frac{BTU}{fthr°F} * \frac{{}^{W}/_{mK}}{1.5\ {}^{BTU}/_{fthr°F}} = 0.56\ \frac{W}{mK}$$

With k being the thermal conductivity, C being the concentration of the salt in the solution, and T being the temperature of the system. In both instances, the students use their test tube #1 data to determine the heat flow. The percent difference between the two heat transfer rates is then calculated. Since the solution is dilute, percent difference will be minimal between the two. The Student and Instructor's version of this lab can be found in Appendix A.6 and B.6, respectively.

3.7 Creation of Dissolvable Strips Laboratory

In the field of drug delivery, there has been a focus on finding different sites of administration for therapeutics. While the oral route remains the most popular, it does have its drawbacks. These include hepatic first pass metabolism or first pass effect, and degradation of the drug in the gastrointestinal tract [177]. In addition, tablets are known to be problematic for patients that suffer from dysphagia, the medical term for difficulty swallowing [135]. As a consequence, researchers have investigated transmucosal drug delivery methods. One of the promising subsets of these methods is oral transmucosal drug delivery. Oral transmucosal drug delivery systems deliver the drug through the

buccal region of the mouth. The buccal region is the area of the mouth that corresponds to the inner cheeks. The rough texture of the buccal mucosa (mucous membrane) makes it suitable for drug delivery [178]. Buccal drug delivery offers three advantages; direct entry into systematic circulation, ease of administration, and the ability to terminate delivery when required [179].

This buccal region is becoming especially popular for pediatrics and pediatric medications. Oral transmucosal delivery has been investigated for pediatric medications in order to increase patient compliance in this subset [180, 181]. There has been a new focus on pediatrics in the pharmaceutical industry, especially in Europe. The European Union began a tighter regulation of pediatric medicines beginning in 2007, after the concern of unlicensed and off-label medicines for pediatric use reached an apex [182]. Since then, there have been several studies on the challenges faced by the pharmaceutical industry to provide effective products for child patients [181, 183, 184]. Investigations from this have led to several systems that have been developed for oral transmucosal drug delivery; including liquids, solids, semisolids, and even sprays [177].

Of all the delivery systems that have been developed, one of the most recent is orally dissolving thin films, or strips [185]. Thin films, or buccal patches, improve patient compliance in those with difficulty swallowing due to their small size and thickness [186]. Thin films have an area similar to a postage stamp and a thickness between 50 and 200 millimeters [135, 187]. In addition, thin films are usually designed so that they dissolve without the patient needing to administer water [187]. Fast dissolving films were first developed for the confection and oral care markets, used as breath strips and/or delivering vitamins and personal care products [188]. It was only in the past few years

that thin films have been used to deliver API's found in several over the counter products; including dextromethorphan HBr, found in cold medications; simethicone, an anti-foaming agent found in anti-gas medications; and benzocaine, an anesthetic used in oral pain relief [189]. This delivery method is currently being investigated for prescription drugs [187].

While thin films do have great advantages, there are some drawbacks to the delivery method. For example, due to the instability of the films, specifically their hygroscopic nature, they need to be packaged and stored in dry areas [188]. To combat degradation, film products are often stored individually in flexible plastics that act as moisture barriers [189]. This can lead to some additional costs in manufacturing, but there are methods to reduce these costs. A recent invention has been developed to form a pharmaceutical product directly onto packaging surfaces, reducing wasted material and the associated costs [190]. In addition, dosage uniformity can be a technical challenge for these films [188, 191]. The last setback for thin films is that high dosages cannot be incorporated into them [135, 188]. These limitations of thin films also put constraints on the drugs that can be incorporated into them. API's and drug formulations that can be delivered via this method must meet certain criteria: They must have a dosage lower than 20 mg; they must be of a small to moderate molecular weight; they must have good stability in water and saliva; they must be able to diffuse and partition into the epithelium of the upper gastrointestinal tract; they must be able to permeate oral mucosal tissue. When used for pediatric medicine, it is also beneficial to use a drug with no bitter tastes [188]. Of course, this last criterion is not as important, as it is possible to use excipients to mask bitter tastes.

These setbacks have not stifled investigations of this method. One of the earliest research investigations into thin films was in using patches of miconazole nitrate, an anti-fungal agent. Researchers found that the patches were able to deliver a potent dosage over a longer period of time than the commonly used gel delivery method [192]. Another early study looked at optimizing mucoadhesive patches that contained cetylpyridinium chloride, a common antiseptic used to kill bacteria in the mouth [193]. Immunization was also investigated early in thin film research. The idea that vaccination could be conducted without needles provided advantages in both cost and safety. Animal research studies have been conducted to show that immunization via mucosal thin films is achievable [194]. Contraception is also an area of study for dissolvable strips. Jain, Jain, Gupta, and Kharya investigated polyvinylpyrrolidone (PVP) films for the buccal administration of the contraceptive drug progesterone [195].

Others have explored using other types of plastics for making dissolvable strips, such as hydroxypropylmethylcellulose and pullulan, and their qualities when made into thin films dissolvable strips [196, 197]. Maltodextrins, a polymer that is formulated from natural sugars is also under investigation as a possible polymer for making dissolvable strips. Maltodextrins have several characteristics that make them good candidates for thin film; such as solubility in water, an inherent sweetness, and favorable hygrscopicity [198]. One research team investigated the effect dextrose equivalents have on the physical characteristics of the maltodextrin films [199]. Another study used nicotine to further test the sweetness of the maltodextrin films, since nicotine is known for having a bitter taste [198]. Lastly, some researchers have investigated loading thin films with nanoparticles.

This has been studied for enhancing the dissolution rate of poorly water soluble drugs [200].

Dissolvable strips are also being considered for use in cancer therapies. In this case, dissolvable strips are loaded with antiemetic drugs to cancer patients, to reduce the effects of nausea and vomiting that can occur when they are given potent opioid analgesics [201]. The use of thin films in this type of therapy is regarded for reducing the time it takes for the drug to take effect. This was first seen in 2009, when a group of researchers published their work on using disintegrating films containing prochlorperazine and found the films to deliver the drug in rats within 2 minutes [202]. This was soon followed by a study that focused on using thin films loaded with dexamethasone for reducing nausea in chemotherapy patients [203]. This latter work was soon tested in a clinical trial, which produced favorable results. This led the researchers to conclude that these oral thin films are effective at reducing nausea and vomiting in chemotherapy patients [204].

With the advances in thin film research, and with several dissolvable strip products on the market, the need for engineers to have an understanding of this drug delivery technique, from its manufacture to end use is important. The Creation of Dissolvable Strips Lab is designed to introduce students to the manufacturing and quality testing of dissolvable strips. In this lab, students are introduced to the different ingredients that make up dissolvable strips; these being polymers, plasticizers, sweeteners, and other flavoring agents [135]. The students are then tasked with creating these thin films and conducting quality control measurements on their final products.

To create these films, students are given a "recipe" for making these strips which was developed based on literature [135, 188]. This includes the polymer carboxymethylcellulose (CMC), the plasticizer glycerol, citric acid for saliva stimulation, sucrose as a sweetening agent, and sodium lauryl sulfate as a surfactant. Included for flavor and color were peppermint oil and blue food dye, respectively. All of these items are added to water kept just below the boiling point (approximately 80 to 90 °C) and at a vigorous stir. Since this process is open to the atmosphere, air bubbles do form in solution. To remove these, students create an apparatus involving two Buchner flasks and some tubing. The mixture is placed in this apparatus, seen in Figure 15, and allowed to sit under vacuum for approximately 30 minutes.

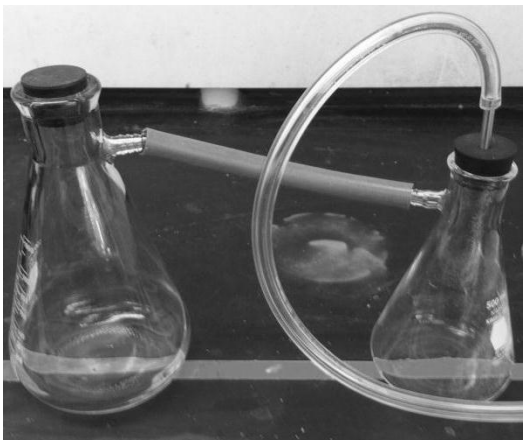


Figure 15. The vacuum apparatus used for removing air bubbles from the thin film mixture.

Once this is complete, the students place their mixture in a petri dish and also a special casting tray developed for this lab (Figure 16). Students pour 400 mL of their thin film solution into the cast using a graduated cylinder, while students determine the amount

added to the petri dish using a bench scale. The thin films solutions are allowed to sit for 1 to 4 days, allowing the solution to dry and form dissolvable strips.

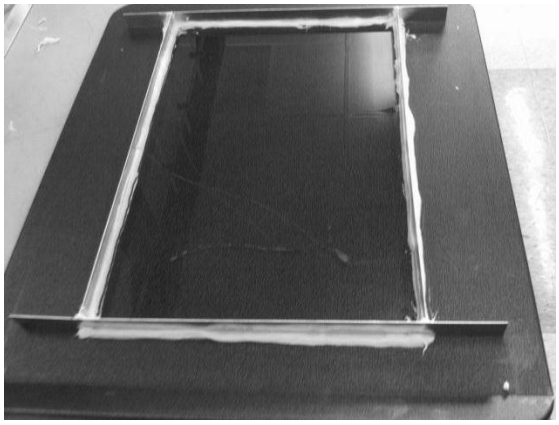


Figure 16. The casting tray used to create dissolvable strips. The surface is a Teflon® baking sheet, and the guides are aluminum strips. The guides are reinforced using silicone caulk.

Once the films are dried, students perform different analyses on their strips. Using the dried solution in the cast, students cut 4 samples with dimension of 1 in. by 1.5 in. These samples are then used for quality analysis. The tests used in this section of the lab were chosen from literature based on their ease of setup and lack of specialty or expensive equipment [135, 188]. The three tests chosen were thickness measurements, folding endurance, and surface pH. Thickness measurements are taken using a caliper and measuring the thickness of each side of the samples. The folding endurance is calculated by folding a strip in half repeatedly until the strip breaks in two. Surface pH is found by placing one drop of water unto the surface of a sample. Litmus paper is then placed on the watered surface to collect the pH of the sample. The mean and range is calculated for

each of these quality tests. Students are then asked to comment on their findings; such as if the surface pH was acceptable for human ingestion, how the folding endurance compares to a commercial brand strip, and what dangers there are for large variances in strip thickness. Quality measurements can be seen in Figure 17. Sample data can be seen in Table 5.

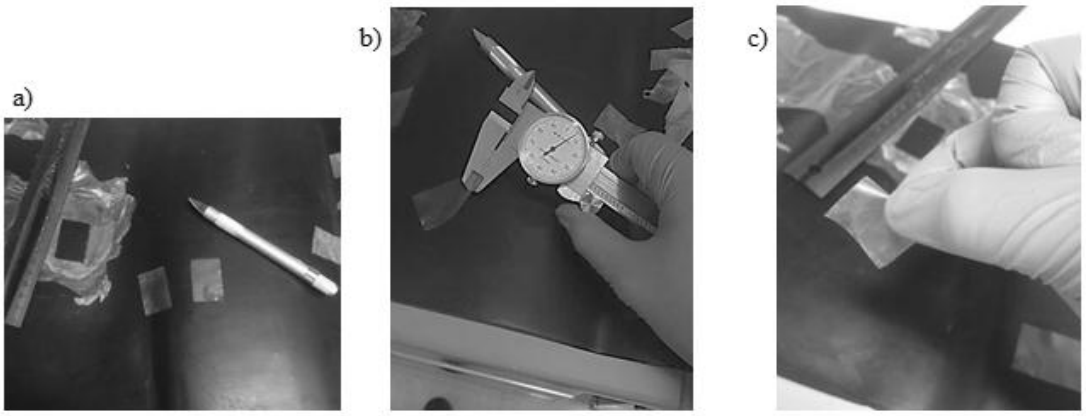


Figure 17. Sample quality measurements for the Creation of Dissolvable Strips Lab. a) Creation of sample strips for quality testing. b) Measuring the thickness using a caliper. c) Pinching the strip sample before conducting a folding endurance test, ensuring a good fold.

Table 5. Sample data for the Creation of Dissolvable Strips Lab quality analysis section.

Sample	Thickness (mm)	Folds endured	Surface pH
1	0.08	32	5.0
2	0.10	28	5.5
3	0.12	39	5.5
4	0.07	23	6.0
Average	0.09	30.5	5.5

Using the petri dish sample, students conduct a moisture content analysis. By weighing the sample before and after drying, and assuming the mass that evaporated was strictly water, students can determine the mass of water that left the sample. The moisture content equation, and a sample calculation, is shown in Equation 24. In this equation, m_1 is the final mass of the sample and m_0 is the initial mass of the sample. Using this, students can also determine the amount of energy that was needed to evaporate the water. This calculation is seen in Equation 25, with Q being the energy required to dry the sample, m_{vap} being the mass of the water vaporized, and $L_{vap}^{H_2O}$ being the latent heat of vaporization for water. Lastly, students determine where this energy came from. Since the sample was allowed to sit in an open area, the energy was transferred from natural convection in the air. In addition, students might cite solar energy if they left their sample in a sunny area of the lab.

$$\%_{moisture} = \left[1 - \left(\frac{m_1 - m_0}{m_0}\right)\right] * 100 \quad (24)$$

$$\%_{moisture} = \left[1 - \left(\frac{20.315\ g}{20.65\ g}\right)\right] * 100 = 1.63\%$$

$$Q = m_{vap} * L_{vap}^{H_2O} \quad (25)$$

$$Q = \frac{(20.95\ g - 0.635\ g)}{1000\ g/kg} * 2260\frac{kJ}{kg} = 45.91\ kJ$$

The manufacturing aspects of thin films are also discussed throughout the lab. Students are first given an introduction to the two processes that are usually used in industry to produce dissolvable strips; solvent-casting and hot melt extrusion [187]. Students are

given a comparison of the two processes, including the unit operations used and when it is preferred to use one process over the other. To reinforce this, students are given a scenario in which the specifications of a thin film product are given and are tasked with determining which unit operation would best suit their product. Students also research different API's that are placed in thin films, and what kinds of treatments they are used in. Students are then tasked with determining what kind of thin film polymer, hydrophilic or hydrophobic, would be best to use for these API's. The Student and Instructor's version of this lab can be found in Appendix A.7 and B.7, respectively.

Chapter 4

Assessment

Initial assessment efforts show that the experiments convey both desired pharmaceutical concepts and core engineering objectives. Preliminary assessment of the laboratory experiments was completed and assessment of broader pharmaceutical engineering educational activities in underway. Some of the results relevant to the experiments developed will be shown. Other results from course development, problem sets, and laboratory activities are planned for later. Representative results using the Tablet Statistical Analysis Lab are provided, which involved three student groups. The students were individually given a pre-lab test to measure their knowledge of several pharmaceutical and statistical aspects that were covered in the laboratory experiment. Multiple choice questions included several pharmaceutical concepts such as definition of an API and function of excipients, along with questions about appropriate use of F- and T-tests. A representative question about excipients would be "The substance used in a tablet to take up space in a pharmaceutical product is…" and a representative question about the F-test would be: "The purpose of an F-test is to …". The correct answer to the excipient question and the F-test question is "filler" and "to compare two sets of data to one another", respectively. After the experiment was completed, a post-lab test was performed and the average of the correct responses of the students is shown in Figure 18. This indicates that the students have a better understanding of pharmaceutical concepts and the purpose of statistical tests after conducting the experiment. The test can be seen in Appendix C.

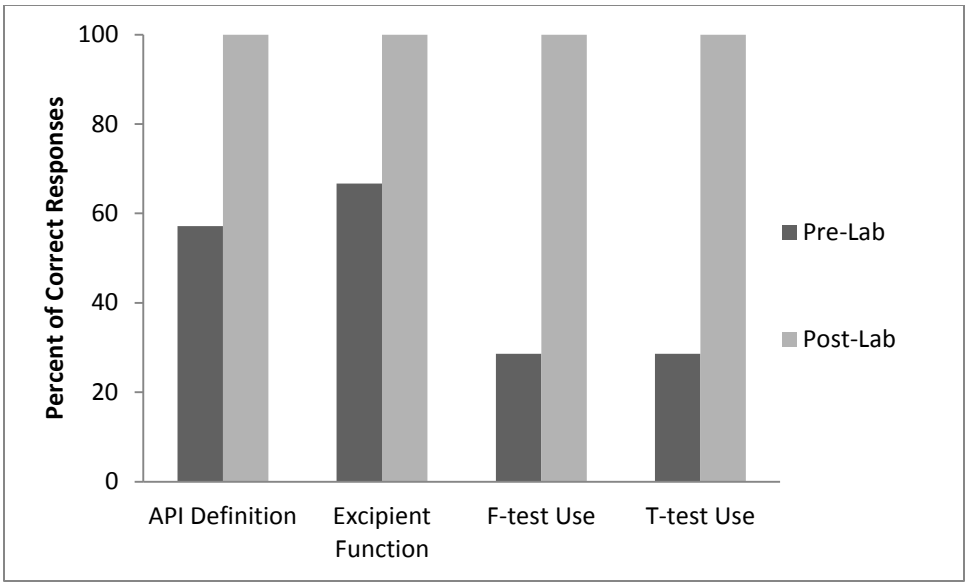


Figure 18. Pre-lab and post-lab concept test results for the assessment of the Tablet Statistical Analysis Lab.

Students were given a post-lab survey to determine if the experiment helped to advance the broader educational objectives of increasing pharmaceutical interest and experimental methods. The survey asked the students to agree or disagree with a statement about their experience with the laboratory using a Likert scale (1 being a strong disagreement and 5 being a strong agreement with the statement). The statements used in the survey relate to the student's interest in pharmaceutical engineering (*I wish to pursue more studies in the field of pharmaceutical engineering*), the pharmaceutical aspect of the laboratory (*The experiment introduced a concept of pharmaceutical engineering*), the utility of the statistical tests (*I can apply the statistical principles I learned in this lab to other engineering problems*), and the educational objectives of the experiment (*I had to appropriately use laboratory equipment (scales, etc.) for data collection*). The survey in its entirety can be found in Appendix C. The average responses showed that most

students gave a response of 4 for all categories of statements (Figure 19). We have also solicited input from current employers about the industrial relevance of the experiments. Representative feedback from one of our pharmaceutical professionals indicates, "These experiments are valuable in exposing engineering students to principles of pharmaceutical engineering." Raw assessment data can be found in Appendix D.

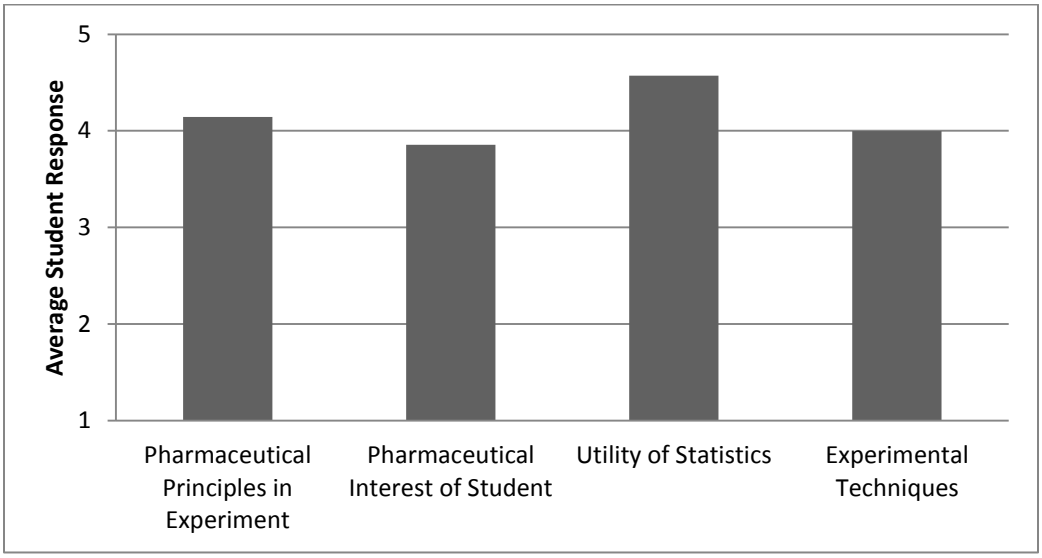


Figure 19. Post-lab student survey results from the Tablet Statistical Analysis Lab.

Chapter 5

Future Work

With the current laboratory experiments, it is possible that a course could be adapted to include these experiments for a semester. With this, a more thorough assessment plan should be implemented. While some assessment has been shown, this was only for a small population and for one laboratory experiment. The goal would be to gain a population of a whole class (approximately 24 students) and receive input for more experiments. The implementation would be similar to the assessment shown previously, where students are given a pre- and post-lab quiz and a post-lab survey. These will be developed to target specific goals of the intended laboratory experiments.

In addition, more experiments should be developed. This will not only give more options to faculty as far as which experiments they will have the students conduct for one semester, but may also rise to a second semester of experiments. Experiments could also be developed for other classes, such as a thermodynamics or mass transfer course. These experiments would be more complex than the experiments shown in this work, and would be more targeted to the specific field of engineering.

For future laboratory experiments on the freshman level, emphasis will be placed on taking existing experiments and expanding on those concepts. An example would be an expansion of the Tablet Statistical Analysis and the Creation of Dissolvable Strips Labs. For the Tablet Statistical Analysis Lab, an expansion would be on using different tablets or other forms of drug delivery. With these different forms of drug delivery, different statistical analysis techniques could be used. Using analysis of variance, control charts,

and design of experiment techniques, students could gain an in-depth assessment of statistics and experimental design. Emphasis could also be put on Bayesian methodology.

The Creation of Dissolvable Strips Lab could be expanded to using advanced mathematical equations to model certain parameters of the thin film. For example, students may use advanced heat transfer equations to determine drying times for different polymer matrices. This could be used for the students to design different dryers. In addition, a semester long project could be developed specifically with dissolvable strips. The semester long project would investigate starting volumes versus final volumes using a fixed volume cast. The students could then develop a mathematical model to determine the final volume of a thin film when it is cast in a certain initial volume. In addition, design of experiments could be implemented to investigate this. Students would start with a simple 2^2 factorial model and move to more rigorous models, such as a 2^3 factorials.

Chapter 6

Conclusions

The experiments developed can be easily integrated into Freshman-level engineering courses. These experiments illustrate basic engineering and science principles, while acquainting students with fundamentals of pharmaceutical engineering. The experiments convey concepts in pharmaceutical fundamentals, drug manufacture, drug formulation/delivery, and pharmacokinetics/pharmacodynamics. Experiments developed to date include: Tablet Statistical Analysis Lab; Asthma Drug Delivery Lab; Antacid Comparison Lab; Effervescence Reaction Lab; Fluidization of Pharmaceutical Substances Lab; Degradation of Dissolvable Strips Lab; Bandage Comparison Lab; Dextromethorphan Crystallization Lab; and Creation of Dissolvable Strips Lab. The experiments can be used individually to meet specific educational objectives, such as applying statistical methods to manufacturing quality control, or grouped into a theme for more in-depth learning. The experiments have multiple parts that allow faculty to add more complexity or accomplish other learning objectives. These experiments can peak student interest in pharmaceutical engineering and provide background needed for advanced courses or laboratories. Complete laboratory procedures, both students and instructor versions, are available through the pharmaceutical knowledge and training website, www.PharmaHUB.org.

List of References

[1] G. A. Bender, Great Moments in Pharmacy, Midland: Northwood Institute Press, 1966.

[2] P. Boussel, H. Bonnemain and F. Bove, History of Pharmacy and Pharmaceutical Industry, Paris: Asklepios Press, 1982.

[3] J. Liebenau, Medical Science and Medical Industry: The Formation of the American Pharmaceutical Industry, Baltimore: Johns Hopkins University Press, 1987.

[4] W. Becker, *Wholesalers of Hardware and Drugs, 1870-1900,* Baltimore: Johns Hopkins University Press, 1969.

[5] United States Census Bureau, *2010 Earnings by Industry,* Washington: United States Census Bureau, 2010.

[6] J. Cacciotti and P. Clinton, "The Lull Between Two Storms," *Pharmaceutical Executive,* vol. 31, no. 5, pp. 3-13, 2011.

[7] Report Linker, "US Pharmaceutical Industry Report, 2008-2009," Research in China, April 2009. [Online]. Available: http://www.reportlinker.com/p0118600-summary/US-Pharmaceutical-Industry-Report.html. [Accessed 28 August 2013].

[8] M. Rosenzweig, "Where are Chemical Engineers Headed," *Chemical Processing Magazine,* pp. 22-27, 5 August 2004.

[9] Bureau of Labor Statistics, "Biomedical Engineers," in *Occupational Outlook Handbook, 2012-2013 Edition*, Washington, DC, U.S. Department of Labor, 2013.

[10] Bureau of Labor Statistics, "Chemical Engineers," in *Occupational Outlook Handbook, 2012-2013 Edition*, Washington, DC, U.S. Department of Labor, 2013.

[11] D. J. am Ende, "Preface," in *Chemical Engineering in the Pharmaceutical Industry*, Hoboken, John Wiley and Sons, Inc., 2010, pp. ix-x.

[12] J. M. Berman, "Industry Output and Employment Projections to 2014," *Monthly Labor Review,* pp. 45-69, November 2005.

[13] C. Rosas, "Process Development," in *Active Pharmaceutical Ingredients: Development, Manufacturing, and Regulation*, New York, Taylor and Francis, 2005, pp. 9-90.

[14] Rutgers University, "PhD in Chemical and Biochemical Engineering with an Option in Pharmaceutical Engineering," Rutgers University Department of Pharmaceutical Engineering, [Online]. Available: http://pharmeng.rutgers.edu/acadPhd.html. [Accessed 24 July 2013].

[15] Stevens Institute of Technology, "Pharmaceutical Manufacturing," Stevens Institute of Technology, 2014. [Online]. Available: http://www.stevens.edu/ses/me/pharmaceutical-manufacturing. [Accessed April 24 2014].

[16] Purdue University, "GAANN Fellowship in Pharmaceutical Engineering," Purdue University, 2014. [Online]. Available: https://engineering.purdue.edu/ChE/GAANNpharma/main.html. [Accessed 19 Febraury 2014].

[17] K. Kuriyan, A. C. Catlin and G. V. Reklaitis, "PharmaHUB: Builing a Virtual Organization for Pharmaceutical Engineering and Science," *Journal of Pharmaceutical Innovation*, vol. 4, no. 2, pp. 81-89, 2009.

[18] J. Fortes, R. Figueiredo and M. Lundstrom, "Virual Computing Infrastructures for Nanoelectronics Simulation," *Proceedings of the IEEE*, vol. 93, no. 10, pp. 1839-1847, 2005.

[19] H. Leuenberger, N. Menshutina, G. Betz and M. N. Puchkov, "E-Learning and Development of New Courses and Scientific Work in the Field of Pharmaceutical Technology," *Chimia*, no. 60, pp. 80-82, 2006.

[20] E. Byrne, "The Role of Specialization in the Chemical Engineering Curriculum," *Education for Chemical Engineers*, vol. 1, pp. 3-15, 2006.

[21] The University of Iowa, "Chemical Engineering - Pharmaceuticals (Major Org)," August 2012. [Online]. Available: https://www.engineering.uiowa.edu/sites/default/files/cbe/CBE%20Pharmaceuticals%20Maj%20Org%20Seq%202012-08.pdf. [Accessed 19 February 2014].

[22] Stevens Institute of Technology, "Areas of Concentration," Department of Mechanical Engineering, 2014. [Online]. Available: http://www.stevens.edu/ses/me/undergrad/concentrations. [Accessed 24 April 2014].

[23] L. Simon, K. Kanneganti and K. S. Kim, "Drug Transport and Pharmacokinetics for Chemical Engineers," *Chemical Engineering Education,* vol. 44, no. 4, pp. 262-266, 2010.

[24] M. R. Prausnitz and A. S. Bommarius, "Drug Design, Development, and Delivery: An Interdisciplinary Course on Pharmaceuticals," *Chemical Engineering Education,* vol. 45, no. 1, pp. 47-52, 2011.

[25] B. J. Glasser, J. Cole and F. J. Muzzio, "A Comprehensive Approach to Pharmaceutical Engineering Training," *Pharmaceutical Technology,* vol. 25, no. 12, pp. 34-36, 2001.

[26] K. McIver, K. Whitaker, V. Dedelva, S. Farrell, M. J. Savelski and C. S. Slater, "Introductory Level Problems Illustrating Concepts in Pharmaceutical Engineering," *Advances in Engineering Education,* vol. 3, no. 1, 2012.

[27] M. J. Savelski, C. S. Slater, C. A. Del Vecchio, A. J. Kosteleski and S. A. Wilson, "Development of Problem Sets for K-12 and Engineering on Pharmaceutical Particulate Systems," *Chemical Engineering Education,* vol. 44, no. 1, pp. 50-57, 2010.

[28] S. Farrell and R. P. Hesketh, "An Introduction to Drug Delivery for Chemical Engineers," *Chemical Engineering Education,* vol. 36, no. 3, pp. 198-203, 2002.

[29] Accreditation Board for Engineering and Technology, "Criteria for Accrediting Engineering Programs," Rowan University, 27 October 2013. [Online]. Available: http://www.abet.org/uploadedFiles/Accreditation/Accreditation_Step_by_Step/Accreditation_Documents/Current/2013_-_2014/eac-criteria-2013-2014.pdf. [Accessed 24 January 2014].

[30] K. Harbir, "Processing Technologies for Pharmaceutical Tablets: A Review," *International Research Journal of Pharmacy,* vol. 3, no. 7, pp. 20-23, 2012.

[31] Royal Pharmaceutical Society, *Capsules and Tablets,* London: Royal Pharmaceutical Society, 2002.

[32] F. E. Stewart, "Twenty Years, 1891-1911. Mulford Company Records," Mulford, West Point, 1911.

[33] H.K. Mulford Company, *Price List*, Philadelphia: The H.K. Mulford Company, 1893.

[34] O. Smith and H. Mulford, "Machine for Manufacturing Compressed Pills". United States of America Patent 413,310, 22 October 1889.

[35] L. Rägo and B. Santoso, "Drug Regulation: History, Present, and Future," in *Drug Benefits and Risks: International Textbook of Clionical Pharmacology*, Clifton, IOS Press, 2008, pp. 65-77.

[36] Department of the Treasury, *Miscellaneous Publication No. 22,* Washington: The Department of the Treasury, 1903.

[37] U.S. Food and Drug Administration, "Federal Food and Drugs Act of 1906," U.S. Department of Health and Human Services, 20 May 2009. [Online]. Available: http://www.fda.gov/regulatoryinformation/legislation/ucm148690.htm. [Accessed 10 June 2014].

[38] Parke Davis and Company, *Complete Catalogue of the Laboratories of Parke, Davis, and Company,* Detroit: Parke Davis and Company, 1898.

[39] U.S. Food and Drug Administration, "The 1938 Food, Drug, and Cosmetic Act," The U.S. Department of Health and Human Services, 24 September 2012. [Online]. Available: http://www.fda.gov/aboutFDA/WhatWeDo/History/origin/ucm054826.htm. [Accessed 10 June 2014].

[40] U.S. Food and Drug Administration, "Kefauver-Harris Amendments Revolutionized Drug Development," *Consumer Health Information,* pp. 1-2, 10 October 2012.

[41] U.S. Food and Drug Administration, "Facts About Current Good Manufacturing Practices (cGMPs)," U.S. Department of Health and Human Services, 2 May 2013. [Online]. Available: http://www.fda.gov/drugs/developmentapprovalprocess/manufacturing/ucm169105.htm. [Accessed 11 June 2014].

[42] M. Sujith Kumar, N. Vishal Gupta, V. Balamuralidhara, B. Srirupa, T. Pramod Kumar and I. Naga Krishna Teja, "Compilation of Key GMP Requirements in US and Japan for Tablet Manufacturing," *International Journal of Drug Development and Research,* vol. 3, no. 4, pp. 45-54, 2011.

[43] The European Medicines Agency, "Specifications and Control Tests on the Finished Product," The European Medicines Agency, London, 1992.

[44] The World Health Organization, "Quality Assurance of Pharmaceuticals: A Compendium of Guidelines and Related Materials," World Health Organization, Geneva, 2007.

[45] Cooper University Hospital, "Literature Reviews," *Pharmaceutical Statistics,* vol. 1, no. 1, pp. 61-66, 2002.

[46] S. Day, "Changing Times in Pharmaceutical Statistics: 1980-2000," *Pharmaceutical Statistics,* vol. 1, no. 1, pp. 9-16, 2002.

[47] G. F. Cooper and E. Herskovits, "A Bayesian Method for the Induction of Probabilistic Networks from Data," *Machine Learnin,* vol. 9, no. 4, pp. 309-347, 1992.

[48] F. Natanegara, B. Neuenschwander, J. W. Seaman Jr., N. Kinnersley, C. R. Heilmann, D. Ohlssen and G. Rochester, "The Current State of Bayesian Methods in Medical Product Development: Survey Results and Recommendations from the DIA Bayesian Scientific Working Group," *Pharmaceutical Statistics,* vol. 13, no. 1, pp. 3-12, 2014.

[49] K. L. Price, H. A. Xia, M. Lakshminarayana, D. Madigan, D. Manner, J. Scott, J. D. Stamey and L. Thompson, "Bayesian Methods for Design and Analysis of Safety Trials," *Pharmaceutical Statistics,* vol. 13, no. 1, pp. 13-24, 2014.

[50] National Science Foundation, "Mathematics & Statistics (QLP Module 6)," The National Science Foundation Database Administration, 2012. [Online]. Available: http://nsf-dba.com/courses/387/mathematics-statistics-for-the-pharmaceutical-industry. [Accessed 30 August 2013].

[51] D. C. Montgomery, G. C. Runger and N. F. Hubele, Engineering Statistics, Hoboken: John Wiley and Sons, Inc., 2011.

[52] S. Niazi, "Ibuprofen Tablets," in *Handbook of Pharmaceutical Manufacturing Formulations; Compressed Solid Products*, New York, Informa Healthcare USA, 2009, pp. 317-319.

[53] The United States Food and Drug Administration, "Code of Federal Regulations: Title 21, Volume 4, Part 211, Subpart F," Office of the Federal Register National Archives and Redords Administration, Washington, 2013.

[54] M. Horio, "Fluidization Science, its Development and Future," *Particuology,* vol. 8, no. 6, pp. 514-524, 2010.

[55] R. Wilhelm and M. Kwauk, "Fluidization of Solid Particles," *Chemical Engineering Progress*, vol. 44, no. 3, pp. 201-218, 1948.

[56] D. Kunii and O. Levenspiel, Fluidization Engineering, New York: Wiley, 1969.

[57] Z. Wang, M. Kwauk and H. Li, "Fluidization of Fine Particles," *Chemical Engineering Science,* vol. 53, no. 3, pp. 377-395, 1998.

[58] W. L. Davies and W. J. Gloor, "Batch Production of Pharmaceutical Granulations in a Fluidized Bed I: Effects of Process Variables on Physical Properties of Final Granulation," *Journal of Pharmaceutical Sciences,* vol. 60, no. 12, pp. 1869-1874, 1971.

[59] W. L. Davies and W. T. Gloor, "Batch Production of Pharmaceutical Granulations in a Fluidized Bed II: Effects of Various Binders and their Concentrations on Granulations and Compressed Tablet," *Journal of Pharmaceutical Sciences*, vol. 61, no. 4, pp. 618-622, 1972.

[60] W. L. Davies and W. T. Gloor, "Batch Production of Pharmaceutical Granulations in a Fluidized Bed III: Binder Dilution Effects on Granulation," *Journal of Pharmaceutical Sciences,* vol. 62, no. 1, pp. 170-171, 1973.

[61] B. Ennis and J. Litster, "Paticle Size Enlargment," in *Perry's Chemical Engineer's Handbook*, New York, McGraw-Hill, 1997, pp. 20:56-20:85.

[62] A. Burggraevem, T. Van Der Kerkhof, M. Hellingsm, J. Remon, C. Vervaet and T. De Beer, "Understanding Fluidized-Bed Granulation," *Pharmaceutical Technology,* vol. 35, no. 8, pp. 63-67, 2011.

[63] A. Burggraeve, T. Monteyne, C. Vervaet, J. P. Remon and T. De Beer, "Process Analytical Tools for Monitoring, Understanding, and Control of Pharmaceutical Fluidized Bed Granulation: A Review," *European Journal of Pharmaceutics and Biopharmaceutics,* vol. 83, no. 1, pp. 2-15, 2013.

[64] J. Litster, "Scaleup of Wet Granulation Processes: Science not Art," *Powder Technology,* vol. 130, no. 1-3, pp. 35-40, 2003.

[65] S. M. Iveson, J. D. Litster, K. Hapgood and B. J. Ennis, "Nucleation, Growth, and Breakage Phenomena in Agitated Wet Granulation Processes: A Review," *Powder Technology,* vol. 117, no. 1-2, pp. 3-39, 2001.

[66] K. Hapgood, J. Litster, S. Biggs and T. Howes, "Drop Penetration into Loose Packed Powder Beds," *Journal of Colloidal Interface Science,* vol. 253, no. 1, pp. 353-366, 2002.

[67] S. Iveson and J. Litster, "Grwoth Regime Map for Liquid-Bound Granules," *AIChE Journal,* vol. 44, no. 7, pp. 1510-1518, 1998.

[68] S. Iveson, P. Wauters, S. Forrest, J. Litster, G. Meesters and B. Scarlett, "Growth Regime Map for Liquid-Bound Granules: Further Development and Experimental Validation," *Powder Technology,* vol. 117, no. 1-2, pp. 83-97, 2001.

[69] P. Wauters, *Modelling and Mechanisms of Granulation, PhD Thesis,* Delft: Delft University of Technology, 2001.

[70] A. Faure, P. York and R. Rowe, "Process Control and Scale-up of Pharmaceutical Wet Granulation Processes: A Review," *European Journal of Pharmaceutics and Biopharmaceutics,* vol. 52, no. 3, pp. 269-277, 2001.

[71] S. Watano, Y. Sato and K. Miyanami, "Control of Granule Growth in Fluidized Bed Granulation by and Image Processing System," *Chemical and Pharmaceutical Bulletin,* vol. 44, no. 8, pp. 1556-1560, 1996.

[72] S. Watano, H. Takashima and K. Miyanami, "Scale-up of Agitation Fluidized Bed Granulation by Neural Network," *Chemical and Pharmaceutical Bulletin,* vol. 45, no. 7, pp. 1193-1197, 1997.

[73] S. Watano and K. Miyanami, "Image Processing for On-line Monitoring of Granule Size Distribution and Shape in Fluidized Bed Granulation," *Powder Technology,* vol. 83, no. 1, pp. 55-60, 1995.

[74] J. Chauhan and P. Yadav, "Study of Scale-up Parameters of Fluidized Bed Coating," *Der Pharmacia Sinica*, vol. 2, no. 1, pp. 228-238, 2011.

[75] H. Stahl, "Precision Coating Technology for Improved Yield, Enhanced Product Quality, Reduced Process Time and Easier Scale-up," GEA Pharma Systems, 2014. [Online]. Available: http://www.gea-ps.com/NPSPORTAL/cmsdoc.nsf/webdoc/webb7j3eja. [Accessed 18 June 2014].

[76] D. To and R. N. Dave, "Taste Masked Active Pharmaceutical Powder Compositions and Processes for Making Them". United States Patent US 2014/0106058 Al , 17 April 2014.

[77] S. Srivastava and G. Mishra, "Fluid Bed Technology: Overview and Parameters for Process Selection," *International Journal of Pharmaceutical Sciences and Drug Research*, vol. 2, no. 4, pp. 236-246, 2010.

[78] H. Ehlers, H. Räikkönen, O. Antikainen, J. Heinämäki and J. Yliruusi, "Improving Flow Properties of Ibuprofen by Fluidized Bed Particle Thin-coating," *International Journal of Pharmaceutics*, vol. 368, no. 1-2, pp. 165-170, 2009.

[79] L. Gomes de Souza, M. Nitz and O. Taranto, "Film Coating of nifedipine Extended Release Pellets in a Fluid Bed Coater with a Wurster Insert," *Biomedical Research International*, vol. 2014, no. 1, pp. 1-11, 2014.

[80] D. Wurster, "Particle Coating Process". United States of America Patent 3,253,944, 31 May 1966.

[81] E. Teunou and D. Poncelet, "Batch and Continuous Fluid Bed Coating - Review and State of the Art," *Journal of Food Engineering* , vol. 53, no. 4, pp. 325-340, 2002.

[82] K. KuShaari, P. Pandey, Y. Song and R. Turton, "Monte Carlo Simulations to Determine Coating Uniformity in a Wurster Fluidized Bed Coatinf Process," *Powder Technology*, vol. 166, no. 2, pp. 81-90, 2006.

[83] E. Räsänen, J. Rantanen, J. Mannerma, J. Yliruusi and H. Vuorela, "Dehydration Studies Using a Novel Multichamber Microscale Fluid Bed Dryer with In-line Near-infared Measurement," *Journal of Pharmaceutical Sciences*, vol. 92, no. 10, pp. 2074-2081, 2003.

[84] S. Syahrul, F. Hamdullahpur and I. Dincer, "Energy Analysis in Fluidized-bed Drying of Large Wet Particles," *International Journal of Energy Resources,* vol. 26, no. 6, pp. 507-527, 2002.

[85] L. Briens and M. Bojarra, "Monitoring Fluidized Bed Drying in Pharmaceutical Granules," *Pharmaceutical Science and Technology,* vol. 11, no. 4, pp. 1612-1618, 2010.

[86] N. Balasurbramanian and C. Srinivasakannan, "Drying of Granular Materials in Circulating Fluidized Beds," *Advanced Powder Technology,* vol. 18, no. 2, pp. 135-142, 2007.

[87] A. Chandran, S. Subba Rao and Y. Varma, "Fluidized Bed Drying of Solids," *AIChE Journal,* vol. 36, no. 1, pp. 29-38, 1990.

[88] P. Thomas and Y. Varma, "Fluidized Bed Drying of Granular Food Materials," *Powder Technology,* vol. 69, no. 3, pp. 213-222, 1992.

[89] C. Srinivasakannan and N. Balasubramanian, "An Analysis of Modeling of Fluidized Bed Drying of Granular Material," *Advanced Powder Technology,* vol. 19, no. 1, pp. 73-82, 2008.

[90] G. Srinivas and Y. Pydi Setty, "Drying Behavior of Uniform and Binary Mixture of Solids in a Batch Fluidized Bed Dryer," *Powder Technology,* vol. 241, no. 1, pp. 181-187, 2013.

[91] R. P. Hesketh, C. S. Slater, S. Farrell and M. Carney, "Fluidized Bed Polymer Coating Experiment," *Chemical Engineering Education,* vol. 36, no. 2, pp. 138-143, 2002.

[92] D. Kunil and O. Levenspiel, Fluidization Engineering, Boston: Butterworth Heinemann, 1993.

[93] Royal Pharmaceutical Society, *Devloping Treatments - Asthma,* London: Museum of the Royal Pharmaceutical Society, 2006.

[94] J. Floyer, *A Treatise of the Asthma,* London: Richard Wilkin, 1698.

[95] E. K. Chu and J. M. Drazen, "Asthma: One Hundred Years of Treatment and Onward," *American Journal of Respiratory and Critical Care Medicine* , vol. 171, no. 11, pp. 1202-1208, 2005.

[96] T. Stewart and G. Gibson, "Asthma," in *Twentieth Century Practice: An International ncyclopedia of Modern Medical Science by Leading Authorities of Europe and America*, New York, William Wood and Company, 1896, pp. 585-617.

[97] W. Osler and T. McCrae, "Bronchial Asthma," in *The Principles and Practice of Medicine*, New York and London, Appleton and Company, 1914, pp. 627-631.

[98] F. Rachemann, "Asthma," in *Textbook of Medicine*, Philadelphia, W.B. Saunders, 1940, pp. 549-558.

[99] S. T. Holgate, "A Brief History of Asthma and Its Mechanisms to Modern," *Asthma, Allergy, and Immunology Research*, vol. 2, no. 3, pp. 165-171, 2010.

[100] N. Pearce, "The Use of Beta Agonists and the Risk of Death and Near Death from Asthma," *Journal for Clinical Epidemiology*, vol. 62, no. 6, pp. 582-587, 2009.

[101] P. Meshburg, "Aerosol Containers and Valves Therefor". United States of America Patent 2,721,010, 18 October 1955.

[102] A. Clark, "Medical Aerosol Inhalers: Past, Present, and Future," *Aerosol Science and Technology*, vol. 22, no. 4, pp. 374-391, 2007.

[103] M. Dolovich, "Lung Dose, Distribution, and Clinical Response to Therapeutic Aerosols," *Aerosol Science and Technology*, vol. 18, no. 3, pp. 230-240, 1993.

[104] G. Salzman and D. Pyszcynski, "Oropharyngeal Candidiasis in Patients Treated with Beclomethasone Diproprionate Delivered by Metered-Dose Inhaler Alone and with Aerochamber," *Journal of Allergy and Clinical Immunology*, vol. 81, no. 2, pp. 424-428, 1988.

[105] W. Stewart, "Apparatus for Administering Powdered Aluminum". United States of America Patent 2,214,032, 10 September 1940.

[106] M. Fields, "Inhalator". United States of America Patent 2,470,296, 17 May 1949.

[107] L. Gradon and T. R. Sosnowski, "Formation of Particles for Dry Powder Inhalers," *Advanced Powder Technology*, vol. 25, no. 1, pp. 43-55, 2014.

[108] P. Rachna, R. A C, S. Nimrata and B. Rajni, "Process Validation of Dry Powder Inhalers (Generalized Approach, Theory, and Practices): A Reivew," *International Research Journal of Pharmacy*, vol. 2, no. 12, pp. 114-116, 2011.

[109] S. P. Newman, F. Morén, E. Trofast, N. Talaee and S. T. Clarke, "Terbutaline Sulphate Turbuhaler: Effect of Inhaled Flow Rate on Drug Deposition and Efficacy," *International Journal of Pharmaceutics*, vol. 74, no. 2-3, pp. 209-213, 1991.

[110] D. E. Geller, "Comparing Clinical Features of the Nebulizer, Metered-Dose Inhaler, and Dry Powder Inhaler," *Respiratory Care*, vol. 50, no. 10, pp. 1313-1322, 2005.

[111] H. Chrystyn and D. Price, "Not All Asthma Inhalers are the Same: Factors to Consider When Prescribing an Inhaler," *Primary Care Respiratory Journal*, vol. 18, no. 4, pp. 243-249, 2009.

[112] O. Pillai, A. B. Dhanikula and R. Panchagnula, "Drug Delivery: An Odyssey of 100 Years," *Current Opinion in Chemical Biology*, vol. 5, no. 4, pp. 439-446, 2001.

[113] M. Speers, "Economic Aspects of Controlled Drug Delivery," in *Encyclopedia of Controlled Drug Delivery*, New York, John Wiley and Sons, 1999, pp. 341-347.

[114] J. Folkman and D. Long, "The Use of Silicone Rubber as a Carrier for Prolonged Drug Therapy," *Journal of Surgical Research*, vol. 4, no. 3, pp. 139-142, 1964.

[115] A. Hoffman, "The Origins and Evolution of "Controlled" Drug Delivery Systems," *Journal of Controlled Release*, vol. 132, no. 3, pp. 153-163, 2008.

[116] M. Armaly and K. Rao, "The Effect of Pilocarpine Ocusert with Different Release Rates on Ocular Pressure," *Investigative Ophthalmology*, vol. 12, no. 7, pp. 491-496, 1973.

[117] A. Zaffaroni, "Bandage for Administering Drugs". United States of America Patent 3,598,122, 10 August 1971.

[118] N. Peppas, "Historical Perspective on Advanced Drug Delivery: How Engineering Design and Mathematical Modeling Helped the Field Mature," *Advanced Drug Delivery*, vol. 65, no. 1, pp. 5-9, 2013.

[119] A. M. Deveaugh-Geiss, L. H. Chen, M. L. Kotler, L. R. Ramsay and M. J. Durcan, "Pharmacokinetic Comparison of Two Nicotine Transdermal Systems, a 21-mg/24 Hour Patch and a 25-mg/16 Hour Patch: A Randomized, Open-Label, Single-Dose, Two-Way Crossover Study in Adult Smokers," *Clinical Therapeutics,* vol. 32, no. 6, pp. 1140-1148, 2010.

[120] K. Kataria, A. Gupta, R. B. Mathur and S. R. Dhakate, "In Vivo Wound Healing Performance of Drug Loaded Electrospun Composite Nanofibers Transdermal Patch," *International Journal of Pharmaceutics,* vol. 469, no. 1, pp. 102-110, 2014.

[121] R. Zhao, Q. Yan, H. Huang, J. Lv and W. Ma, "Transdermal siRNA-TGFβ1-337 Patch for Hypertrophic Scar Treatment," *Matrix Biology,* vol. 32, no. 5, pp. 265-276, 2013.

[122] G. A. Boswell and R. M. Scribner, "Polyactide Drug Mixtures". United States of America Patent 3,773,919, 20 November 1973.

[123] W. R. Gombotz, M. S. Healy and L. R. Brown, "Very Low Temperature Casting of Controlled Release Microspheres". United States of America Patent 5,019,400, 28 May 1991.

[124] F. F. Davis, "The Origin of PEGnology," *Advanced Drug Delivery,* vol. 54, no. 4, pp. 457-458, 2002.

[125] H. Ringsdorf, "Structure and Properties of Pharmacologically Active Polymers," *Journal of Polymer Science: Polymer Symposia,* vol. 51, no. 1, pp. 135-153, 1975.

[126] J. Kopeček, "Reactive Copolymers of N-(2-hydroxypropyl)methacrylamide with N-methacryloylated Derivatives of L-leucine and L-phenylalanine, 1. Preparation, Characterization, and Reactions with Diamines," *Die Makromolekulare Chemie,* vol. 178, no. 8, pp. 2169-2183, 1977.

[127] K. Iwai, H. Maeda and T. Konno, "Use of Oily Contrast Medium for Selective Drug Targeting to Tumor: Enhanced Therapeutic Effect and X-Ray Image," *Cancer Research,* vol. 44, no. 5, pp. 2115-2121, 1984.

[128] N. Plate and I. Valuev, "Heparin-Containing Polymeric Materials," *Advanced Polymer Science,* vol. 79, no. 1, pp. 95-137, 1986.

[129] U. Westedt, M. Wittmar, M. Hellwig, P. Hanefield, A. Grenier, A. K. Schaper and T. Kissel, "Paclitaxel releasing films consisting of Poly(vinyl alcohol)-graft-poly(lactide-co-glycolide) and their Potential as Biodegradable Stent Coatings," *Journal of Control Release,* vol. 111, no. 1-2, pp. 235-246, 2006.

[130] E. Mathiowitz, D. E. Chickering III and C. Lehr, Bioadhesive Drug Delivery Systems; Fundamentals, Novel Approaches, and Development, Boca Raton: CRC Press, 1999.

[131] A. Smith, "Drug Delivery Systems in the 20th Century: Merely Scratching the Surface," *Pharmaceutical Science and Technology Today,* vol. 2, no. 6, pp. 225-227, 1999.

[132] S. Farrell and J. Vernengo, "A Controlled Drug-Delivery Experiment Using Alginate Beads," *Chemical Engineering Education,* vol. 46, no. 2, pp. 97-109, 2012.

[133] Q. Xu, Y. Liang, Y. W. Tong and C. Wang, "Design Project on Controlled-Release Drug Delivery Devices: Implementation, Management, and Learning Experiences," *Chemical Engineering Education,* vol. 44, no. 4, pp. 289-298, 2010.

[134] J. A. Norman, S. N. Andrews and M. R. Prausnitz, "Undergraduate Laboratory Module on Skin Diffusion," *Chemical Engineering Education,* vol. 45, no. 4, pp. 276-282, 2011.

[135] K. Mandeep, A. Rana and S. Nimrata, "Fast Dissolving Films: An Innovative Drug Delivery System," *International Journal of Pharmaceutical Research and Allied Sciences,* vol. 2, no. 1, pp. 14-24, 2013.

[136] Particle Sciences Drug Development Services, *Dissolving Films: A Technical Brief,* vol. 3, Bethlehem: Particle Sciences Drug Development Services, 2010.

[137] G. Gergely, T. Gergely and I. Gergely, "Effervescent Composition and Method of Making Same". United States of America Patent 4,678,661, 7 June 1987.

[138] G. Lasarte-Aragonés, R. Lucena, S. Cárdenas and M. Valcárcel, "Effervescence-Assisted Dispersive Micro-Solid Phase Extraction," *Journal of Chromotography A,* vol. 1218, no. 51, pp. 9128-9134, 2011.

[139] G. Lasarte-Aragonés, R. Lucena, S. Cárdenas and M. Valcárcel, "Effervescent Assisted Dispersive Liquid-Liquid Microextraction with Extractant Removal by Magnetic Nanoparticles," *Analytica Chimica Acta*, vol. 807, no. 1, pp. 61-66, 2014.

[140] G. Liger-Belair, G. Poldori and V. Zéninari, "Analytica Chimica Acta," *Unraveling the Evolving Nature of Gaseous and Dissolved Carbon Dioxide in Champagne Wines: A State-of-the-Art Review, from the Bottle to the Tasting Glass*, vol. 732, no. 1, pp. 1-15, 2012.

[141] R. Clark, R. Linforth, F. Bealin-Kelly and J. Hort, "Effects of Ethanol, Carbonation, and Hopacids on Volatile Delivery in a Model Beer System," *Journal of the Institute of Brewing*, vol. 117, no. 1, pp. 74-81, 2011.

[142] T. Yu, B. Macnaughtan, M. Boyer, R. Linforth, K. Dinsdale and I. D. Fisk, "Aroma Deliver from Spray Dired Coffee Containing Pressurised Internalized Gas," *Food Research International*, vol. 49, no. 2, pp. 702-709, 2012.

[143] N.-O. Lindberg and H. Hansson, "Effervescent Pharmaceuticals," in *Encyclopedia of Pharmaceutical Technology*, New York, Marcel Dekker, Inc., 2002, pp. 1037-1049.

[144] J. Acton, T. Adams and M. Packer, Origin of Everyday Things, New York: Sterling Publishing Incorporated, 2006.

[145] F. Witzel and K. W. Clark, "Effervescent Tablet and Method". United States of America Patent 4,127,645, 28 November 1978.

[146] J. Bru, "Process for Manufacturing Effervescent Granules and Tablets". United States of America Patent 4,614,648, 30 September 1986.

[147] A. Aslani and H. Jahangiri, "Formulation, Characterization, and Physicochemical Evaluation of Ranitidine Effervescent Tablets," *Advanced Pharmaceutical Bulletin*, vol. 3, no. 2, pp. 315-322, 2013.

[148] S. B. Shirsand, S. Suresh, M. S. Para and P. V. Swamy, "Design of Fast Disintergrating Tablets of Prochlorperazine Maleate by Effervescent Method," *Indian Journal of Pharmaceutical Sciences*, vol. 71, no. 4, pp. 447-451, 2009.

[149] K. A. Elkhodairy, M. A. Hassan and S. A. Afifi, "Formulation and Optimization of Orodispersible Tablets of Flutamide," *Saudi Pharmaceutical Journal,* vol. 22, no. 1, pp. 53-61, 2014.

[150] L. Ely, W. Roa, W. H. Finlay and R. Lobenberg, "Effervescent Dry Powder for Respiratory Drug Delivery," *European Journal of Pharmaceutics and Biopharmaceutics,* vol. 65, no. 3, pp. 346-353, 2007.

[151] P. A. Belter, E. L. Cussler and W.-S. Hu, Bioseparations: Downstream Processing for Biotechnology, New York: John Wiley and Sons, 1988.

[152] P. C. Wankat, Rate-Controlled Separations, New York: Elselvier, 1990.

[153] C. J. Geankoplis, Transport Processes and Separation Process Principles, Upper Saddle River: Prentice Hall, 2003.

[154] A. Mersmann, "Physical and Chemical Properties of Crystalline Systems," in *Crystallization Technology Handbook,* Boca Raton, CRC Press, 2001, pp. 1-44.

[155] R. R. McKeon, J. T. Wertman and P. C. Dell'Orco, "Crystallization Design and Scale-Up," in *Chemical Engineering in the Pharmaceutical Industry,* New York, John Wiley and Sons, 2011, pp. 213-247.

[156] J. W. Mullin, Crystallization, Oxford: Butterworth-Heinemann, 2001.

[157] A. S. Myerson, Handbook of Industrial Crystallization, Oxford: Butterworth-Heinemann, 2002.

[158] H. Hung, E. L. Paul, M. Midler and J. A. McCauley, Crystallization of Organic Compounds: An Industrial Perspective, Hoboken: Wiley, 2009.

[159] I. D. H. Oswald, D. R. Allan, P. A. McGregor, W. D. Samuel Motherwell, S. Parsons and C. R. Pulham, "The Formation of Paracetamol (Acetaminophen) Adducts with Hydrogen-Bond Acceptors," *Acta Crystallographica Section B,* vol. B58, no. 6, pp. 1057-1066, 2002.

[160] S. Aitipamula, P. S. Chow and R. B. H. Tan, "Dimorphs of a 1:1 Cocrsytal of Ethenzamide and Saccharin: Solid-State Grinding Methods Result in Metastable Polymorph," *CrystEngComm,* vol. 11, no. 5, pp. 889-895, 2009.

[161] A. Alhalaweh, S. George, S. Basavoju, S. L. Childs, S. A. A. Rizvi and S. P. Velaga, "Pharmaceutical Cocrystals of Nitrofurantoin: Screening, Characterization, and Crystal Structure Analysis," *CrystEngComm*, vol. 14, no. 15, pp. 5078-5088, 2012.

[162] C. B. Aakeröy, S. Forbes and J. Desper, "Using Cocrystals to Systematicall Modulate Aqueous Solubility and Melting Behavior of an Anticancer Drug," *Journal of the American Chemical Society*, vol. 131, no. 47, pp. 17048-17049, 2009.

[163] M. B. Hickey, M. L. Peterson, L. A. Scoppettuolo, S. L. Morrisette, A. Vetter, H. Guzmán, J. F. Remenar, Z. Zhang, M. D. Tawa, S. Haley, M. J. Zaworotko and Ö. Almarsson, "Performance Comparison of a Cocrystal of Carbamazepine with Marketed Product," *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 67, no. 1, pp. 112-119, 2007.

[164] M. A. Rodrigues, L. Padrela, V. Geraldes, J. Santos, H. A. Matos and E. G. Azevedo, "Theophylline Polymorphs by Atomization of Supercritical Antisolvent Induced Suspensions," *The Journal of Supercritical Fluids*, vol. 58, no. 2, pp. 303-312, 2011.

[165] M. Rossmann, A. Brauer and E. Schluecker, "Supercritical Antisolvent Micronization of PVP and Ibuprofen Sodium Towards Tailored Solid Dispersions," *The Journal of Supercritical Fluids*, vol. 89, no. 1, pp. 16-27, 2014.

[166] L. Padrela, M. A. Rodrigues, S. P. Velaga, H. A. Matos and E. G. de Azevedo, "Formation of Indomethacin-Saccharin Cocrystals Using Supercritical Fluid Technology," *European Journal of Pharmaceutical Sciences*, vol. 38, no. 1, pp. 9-17, 2009.

[167] L. Padrela, M. A. Rodrigues, S. P. Velaga, A. C. Fernandes, H. A. Matos and E. G. de Azevedo, "Screening for Pharmaceutical Cocrystals Using the Supercritical Fluid Enhanced Atomization Process," *The Journal of Supercritical Fluids*, vol. 53, no. 1-3, pp. 156-164, 2010.

[168] S. L. Morissette, O. Almarsson, M. L. Peterson, J. F. Remenar, M. J. Read, A. V. Lemmo, S. Ellis, M. J. Cima and C. R. Gardner, "High-Throughput Crystallization: Polymorphs, Salts, Co-Crystals, and Solvates of Pharmaceutical Solids," *Advanced Drug Delivery Reviews*, vol. 56, no. 3, pp. 275-300, 2004.

[169] C. R. Gardner, O. Almarsson, H. Chen, S. L. Morisette, M. L. Peterson, Z. Zhang, S. Whang, A. V. Lemmo, J. Gonzales-Zugasti, J. Monagle, J. Marchionna, S. J. Ellis, C. McNulty, A. Johnson, D. Levinson and M. J. Cima, "Application of High-Throughput Technologies to Drug Substance and Drug Product Development," *Computers and Chemical Engineering,* vol. 28, no. 6-7, pp. 943-953, 2004.

[170] V. Luu, J. Jona, M. K. Stanton, M. L. Peterson, H. G. Morrison, K. Nagapudi and H. Tan, "High-Throughput 96-Well Solvent Mediated Sonic Blending Synthesis and On-Plate Solid/Solution Stability Characterization of Pharmaceutical Cocrystals," *International Journal of Pharmaceutics,* vol. 441, no. 1-2, pp. 356-364, 2013.

[171] T. Kojima, S. Tsutsumi, K. Yamamoto, Y. Ikeda and T. Moriwaka, "High-Throughput Cocrystal Slurry Screening by Use of In Situ Raman Microscopy and Multi-Well Plate," *International Journal of Pharmaceutics,* vol. 399, no. 1-2, pp. 52-59, 2010.

[172] J. Margarey, "Dextromethorphan," August 1997. [Online]. Available: http://www.inchem.org/documents/pims/pharm/pim179.htm. [Accessed 7 July 2014].

[173] L. H. Dalman, "The Solubility of Citric and Tartaric Acids in Water," *Journal of the American Chemical Society,* vol. 59, no. 12, pp. 2547-2549, 1937.

[174] R. M. Felder and R. W. Rousseay, Elementary Principles of Chemical Processes, New York: John Wiley and Sons, 1986.

[175] F. P. Incropera, D. P. Dewitt and T. L. L. A. S. Bergman, Introduction to Heat Transfer, Hoboken: John Wiley and Sons, 2007.

[176] J. V. Wilson, "Approximations for Physical Properties of Sea Salt Solutions," Office of Saline Water, Washington DC, 1973.

[177] V. F. Patel, F. Liu and M. B. Brown, "Advances in Oral Transmucosal Drug Delivery," *Journal of Controlled Release,* vol. 153, no. 2, pp. 106-116, 2011.

[178] M. J. Rathbone, G. Ponchel and F. A. Ghazali, "Systemic and Oral Mucosal Drug Delivery and Delivery Systems," in *Oral Mucosal Drug Delivery,* New York, Marcel Dekker Inc., 1996, pp. 241-284.

[179] M. J. Rathbone, B. K. Drummond and I. G. Tucker, "The Oral Cavity as a Site for Systematic Drug Delivery," *Advanced Drug Delivery Reviews,* vol. 13, no. 1-2, pp. 1-22, 1994.

[180] A. T. Florence, "Neglected Diseases, Neglected Technologies, Neglected Patients," *International Journal of Pharmaceutics,* vol. 350, no. 1-2, pp. 1-2, 2008.

[181] A. Cram, J. Breitkreutz, S. Desset-Brèthes, T. Nunn and C. Tuleu, "Challenges of Developing Palatable Oral Paediatric Formulations," *International Journal of Pharmaceutics,* vol. 365, no. 1-2, pp. 1-3, 2009.

[182] European Medicines Agency, "The European Paediatric Initiative: History of Paediatric Regulation," 11 July 2007. [Online]. Available: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/09/WC500003693.pdf. [Accessed 14 July 2014].

[183] J. Breitkreutz, "European Perspectives on Pediatric Formulations," *Clinical Therapeutics,* vol. 30, no. 11, pp. 2146-2154, 2008.

[184] A. Bowles, J. Keane, T. Ernest and D. T. C. Clapham, "Specific Aspects of Gastro-Intestinal Transit in Children for Drug Delivery," *International Journal of Pharmaceutics,* vol. 395, no. 1-2, pp. 37-43, 2010.

[185] M. Harihan and A. Bogue, "Orally Dissolving Film Strips: The Final Evolution of Orally Dissolving Dosage Forms," *Drug Delivery Technology,* vol. 9, no. 2, pp. 24-29, 2009.

[186] C. Li, P. P. Bhatt and T. P. Johnston, "Evaluation of a mucoadhesive buccal patch for delivery of peptides," *Drug Development and Industrial Pharmacy,* vol. 24, no. 10, pp. 919-926, 1998.

[187] A. Jyoti, S. Gurpreet, S. Seema, A. C and Rana, "Fast Dissolving Films: A Novel Approach to Oral Drug Delivery," *International Research Journal of Pharmacy,* vol. 2, no. 12, pp. 69-74, 2011.

[188] T. kaIra, M. Madhra, K. Gandhi, A. Dahiya and Khushboo, "Fast Dissolving Film: A Review," *International Journal of Research and Pharmaceutical Sciences,* vol. 3, no. 4, pp. 542-551, 2012.

[189] S. D. Barnhart, "Thin Film Oral Dosage Forms," in *Modified-Release Drug Delivery Technology*, New York, Informa Healthcare, 2008, pp. 209-216.

[190] G. L. Myers, B. A. Bogue, G. Slominski, K. Davidson and L. Miloshoff, "Method and System for Forming a Pharmaceutical Product Directly Onto a Packaging Surface". United States of America Patent US20120076921A1, 12 March 2012.

[191] B. Bhyan, S. Jangra, M. Kaur and H. Singh, "Orally Fast Dissolving Films: Innovations in Formulation and Technology," *International Journal of Pharmaceutical Sciences Review and Research,* vol. 9, no. 2, pp. 50-57, 2011.

[192] N. A. Nafee, F. A. Ismail, N. A. Boraie and L. M. Mortada, "Mucoadhesive Buccal Patches of Miconazole Nitrate: in vitro/in vivo Performance and Effect of Ageing," *International Journal of Pharmaceutics*, vol. 264, no. 1-2, pp. 1-14, 2003.

[193] N. A. Nafee, M. A. Boraie, F. A. Ismail and L. M. Mortada, "Design and Characterization of Mucoadhesive Buccal Patches Containing Cetylpyridinium Chloride," *Acta Pharmaceutica,* vol. 53, no. 3, pp. 199-212, 2003.

[194] Z. Cui and R. J. Mumper, "Bilayer Films for Mucosal (Genetic) Immunization via the Buccal Route in Rabbits," *Pharmaceutical Research,* vol. 19, no. 7, pp. 947-953, 2002.

[195] S. K. Jain, A. Jain, Y. Gupta and A. Kharya, "Design and Development of a Mucoadhesive Buccal Film Bearing Progesterone," *Pharmazie,* vol. 63, no. 2, pp. 129-135, 2008.

[196] S. M. Shehata, *Formulation and Evaluation of Naproxen Mucoadhesive Buccal Patches for Local Effect,* Riyadh: King Saud University, 2002.

[197] V. I. Garsuch, *Preparation and Characterization of Fast-Dissolving Oral Films for Pediatric Use,* Düsseldorf: Heinrich Heine University of Düsseldorf, 2009.

[198] F. Cilurzo, I. E. Cupone, P. Minghetti, S. Buratti, F. Selmin, C. G. M. Gennari and L. Montanari, "Nicotine Fast Dissolving Films Made of Maltodextrins: A Feasability Study," *AAPS PharmSciTech,* vol. 11, no. 4, pp. 1511-1517, 2010.

[199] F. Cilurzo, I. E. Cupone, P. Minghetti, F. Selmin and L. Montari, "Fast Dissolving Films Made of Maltodextrins," *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 70, no. 3, pp. 895-900, 2008.

[200] L. Sievens-Figueroa, A. Bhakay, J. I. Jerez-Rozo, N. Pandya, R. J. Romanach, B. Michniak-Kohn, Z. Iqbal, E. Bigili and R. N. Davé, "Preparation and Characterization of Hydroxylpropyl Methyl Cellulose Films Containin Stable BCS Class II Drug Nanoparticles for Pharmaceutical Applications," *International Journal of Pharmaceutics,* vol. 423, no. 2, pp. 496-508, 2012.

[201] E. McNicol, N. Horowicz-Mehler, R. A. Fisk, K. Bennett, M. Gialeli-Goudas, P. W. Chew, J. Lau and D. Carr, "Management of Opioid Side Effects in Cancer-Related and Chronic Noncancer Pain: A Systematic Review," *The Journal of Pain,* vol. 4, no. 5, pp. 231-256, 2003.

[202] M. Nishimura, K. Matsuura, T. Tsukioka, H. Yamashita, N. Inagaki, T. Sugiyama and Y. Itoh, "In Vitro and In Vivo Characteristics of Prochlorperazine Oral Disintegrating Film," *International Journal of Pharmaceutics,* vol. 368, no. 1-2, pp. 98-102, 2009.

[203] H. Shimoda, K. Taniguchi, M. Nishimura, K. Matsuura, T. Tsukioka, H. Yamashita, N. Inagaki, K. Hirano, M. Yamamoto, Y. Kinosada and Y. Itoh, "Preparation of a Fast Dissolving Oral Thin Film Containing Dexamethasone: A Possible Application to Antiemesis During Cancer Chemotherapy," *European Journal of Pharmaceutics and Biopharmaceutics,* vol. 73, no. 3, pp. 361-365, 2009.

[204] M. Nishigaki, K. Kawahara, M. Nawa, M. Futamura, M. Nishimura, K. Matsuura, K. Kitaichi, Y. Kawaguchi, T. Tsukioka, K. Yoshida and Y. Itoh, "Development of Fast Dissolving Oral Film Containing Dexamethasone as an Antiemetic Medication: Clinical Usefulness," *International Journal of Pharmaceutics,* vol. 424, no. 1-2, pp. 12-17, 2012.

Appendix A

Student Versions of Laboratory Experiments

A.1 Tablet Statistical Analysis Lab

Tablet Statistical Analysis Lab
Developed by: Alex Jannini, David Krause, Heather Malino and Kevin Sweeney, Rowan University, Department of Chemical Engineering
Edited by: C. Stewart Slater and Mariano Savelski, Rowan University, Department of Chemical Engineering
Date of Experiment:

OBJECTIVES

- Students will perform a basic statistical analysis applied to an over-the-counter drug
- Students will learn about pharmaceutical engineering, including key terms and concepts

INTRODUCTION

In the pharmaceutical industry, drugs are manufactured, produced, and marketed for therapeutic use. The industry has been one of the highest earning industries of the last decade, with 791 billion dollars in worldwide sales in 2010. The majority of these sales were in North American companies, totaling 335 billion dollars[1].

A pharmaceutical product is not just one specific chemical, but many chemicals combined together to make a final product. Tablets, which the students will be working with in this lab, are composed of a few chemicals mixed together and then compressed. The therapeutic ingredient is known as the active pharmaceutical ingredient (API). The API is what causes the desired effect of the drug. The rest of the ingredients that remain inert are known as the excipients.

Excipients can have different functions, which is why there are sub-categories of excipients found in pharmaceuticals. For example, a filler is a type of excipient used to make up the volume of a medicine so that it can be taken in the form of a pill. In some cases, excipients known as binders are used to act as glue and make sure the ingredients stick together. Lubricants and glidants are used in combination since they reduce wall friction and interparticle friction, respectively. This prevents the tablet from clumping and sticking to equipment. Excipients

may also be flavors or colors, which will mask any unpleasant tastes that the other ingredients have and improve the appearance of the product.

In any engineering field, statistical analysis is an important tool. In the pharmaceutical industry, statistics can be used in various ways. For example, statisticians use statistics to create trials for experimental drugs. A chemical engineer might use statistics in order to figure out a new process that creates more product for less. In these cases, statistics play an important role in analyzing data in order to come to a conclusion.

In this lab, the students will be looking at two different over the counter medications that contain the API ibuprofen, a known pain reliever and fever reducer. The rest of the inactive ingredients in the tablets are binders, fillers, or any other kind of excipient. This lab will consist of a statistical analysis on the difference in mass between the ibuprofen tablets, and also the difference in the mass of a generic brand and the trademarked brand Advil®. An introduction to creating a flow diagram will also be incorporated into this experiment.

MATERIALS NEEDED

- Container of Advil® tablets (minimum of 10 tablets)
- Container of generic ibuprofen tablets (minimum of 10 tablets)
- Weigh boat
- Tweezers
- Bench scale (accurate up to 1/1,000 g).

SAFETY CONSIDERATIONS

Always wear laboratory safety glasses when working in the lab.

PROCEDURE

1. Make sure that the bench scale is turned on, and that the scale is set to measure weight in grams.

2. Take the Advil package and note where they list the active and inactive ingredients. Record all of the ingredients that are listed as non-active ingredients.

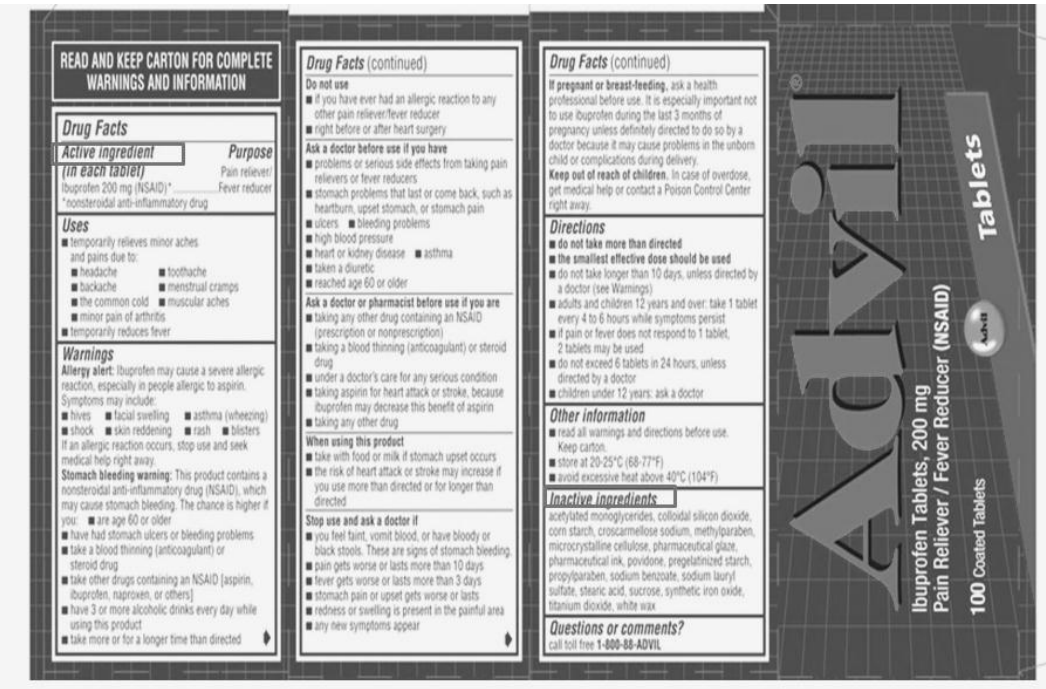


Figure 1. Where to find the active and inactive ingredients

3. Place the weigh boat on the bench scale. Record the weight, and then tare the instrument. The bench scale should now read 0 grams.
4. Open the box of Advil®, and with tweezers, place one tablet in the weigh boat. You may use the table provided below, but you should also record your findings in your lab notebook.
5. Once the mass has been recorded, tare the scale again.
6. Repeat the two previous steps until you have weighed ten Advil tablets. Empty your weigh boat, place it back on the bench scale, and tare the instrument. You should now have the Advil® portion of the data table filled out.
7. Now, look at your generic brand. Record all the non-active ingredients.
8. Open the container, and using the tweezers, place one tablet in the weigh boat. Once again, tare the instrument after recording the mass.
9. Repeat until you have collected ten measurements of the generic brand. You should now have the generic brand portion of the data table filled out.
10. Once all measurements have been completed, dispose of the measured tablets and the weigh boats. Return the containers to their respective boxes.

Table 1. Empty table for recording the mass of the tablets

Trial Number	Name Brand Mass (grams)	Generic Brand Mass (grams)
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		

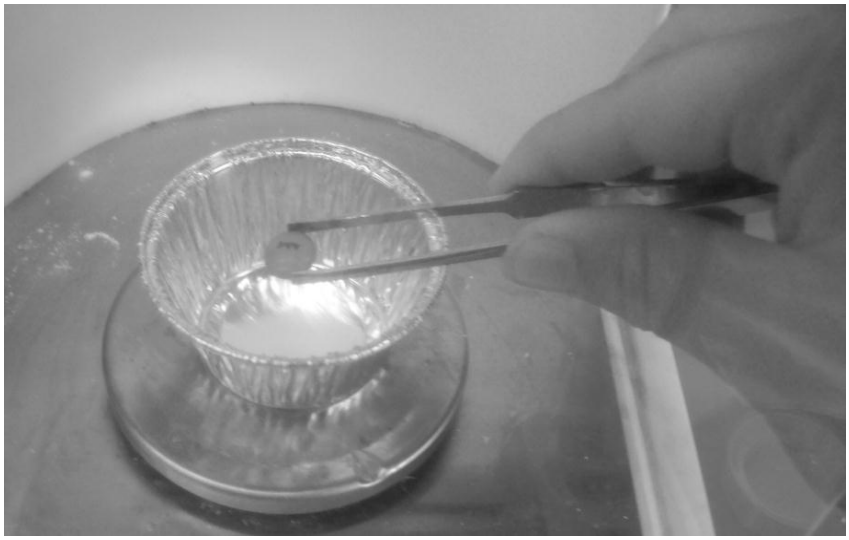


Figure 2. Proper technique for weighing tablets

STATISTICAL ANALYSIS

You will need your calculator to do the following calculations. You must show all work to receive credit.

1. First, take the average of each set of data. Use the equation below, with *i* being the trial number (given in the data table), *n* being the total number of trials (10), and *x* being the mass recorded for the specific trial number. Record this in your lab notebook and include in your results.

$$\bar{x} = \frac{\sum_{i=1}^{10} x_i}{n} \qquad (1)$$

2. Standard deviation is defined as the variation from the average. In other words, it is the average of the difference between each value obtained and the average value obtained. So, in this case, it would be important to know the standard deviation of the mass of the tablets for the trademarked brand and also the generic brand. To calculate the standard deviation, use the equation below, with *i* once again being the trial number, *n* being the total number of trials, and *x* being the mass recorded.

$$\sigma = \sqrt{\frac{\sum_{i=1}^{10}(|x_i - \bar{x}|^2)}{n}} \quad (2)$$

3. Now, we will look for any outliers in our data. An outlier can be defined as a data point significantly different than the mean of the data. In other words, an outlier is a datum point that significantly distant from other points. To do this, find the median data point in both sets of data. To find the median, list the data in order from lowest value to highest value, and find the point that resides in the middle. If you have an even number of data points, the median is found by averaging the two middle data points. From now on, this median (the median of the entire data set) is known as **overall median**. From here, find the first and third quartiles. These values are found by splitting the list of data in half. In this case, we now have two sets of five data points; one with the lower data points, and the other with the higher data points. The **first quartile** can be found by taking the median of the lower data points. The **third quartile** is the median of the higher data points. Lastly, we state that the overall median is the **second quartile**. Using the equations below, calculate if any of your data points are *outliers.*

$$O_L = Q_1 - 1.5(Q_3 - Q_1) \quad (3)$$

Where, O_L is the low-value outlier cutoff, Q_1 is the first quartile, and Q_3 is the third quartile.

$$O_H = Q_3 + 1.5(Q_3 - Q_1) \quad (4)$$

Where, O_H is the high-value outlier cutoff, Q_3 is the third quartile, and Q_1 is the first quartile.

Are any weights you measured above O_H or below O_L? If so, they are outliers. Arrange your findings in a box-and-whisker plot as described in the diagram below.

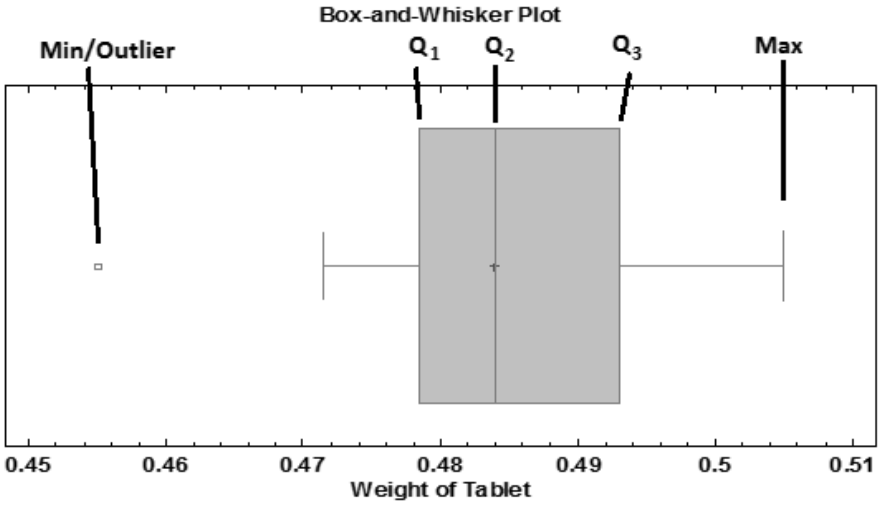


Figure 3: A typical box-and-whisker plot.

RESULTS

Be sure to record all findings for this lab. Answer any questions that might have been asked in the procedure section of the lab.

QUESTIONS

1. During the statistical analysis section, you were asked to find the standard deviation of the trademarked and the generic brand. Explain what this value tells you. Compare the two standard deviations you calculated, and determine what this means.

2. Now, you will determine whether or not these two brands are different from each other. To do this, you will use a statistical analysis technique known as an F-test. An F-test is used to compare two samples. This test can become difficult if the samples are not done in a similar manner. In this case, the number of measurements taken in each sample is similar, so this makes the F-test much simpler. To conduct an F-test, do the following:

a. Find the variance of the two samples. The variance of a sample is defined as the average of the squared difference of the means. An equation of what this would look like is shown below:

$$Variance = s = \frac{sum\ of\ the\ squared\ differences\ from\ the\ average\ value}{number\ of\ measurements\ taken} \quad (5)$$

$$s = \frac{\sum(x_i - \bar{x})^2}{n} \quad (6)$$

Another way of looking at the variance is it's relation to the standard deviation of a sample. The relation of the variance of a sample to the standard deviation of a sample is shown below:

$$s = \sigma^2 \quad (7)$$

If you compare the equation of variance to the equation of standard deviation, you can see how this is true. Use the relation between standard deviation and variance to find a value of variance for the two samples.

b. Now, find the F-value for your experiment. To find your F-value, use the following equation:

$$F_{exp} = \frac{s_1^2}{s_2^2} \quad (8)$$

For this equation, the variance in the numerator "s_1" has to be the larger of the two variances.

c. Now, compare this value to a critical value. This is known as the F-critical value. The F-critical value is dependent on the number of measurements taken in each sample, and the percent confidence that is desired. The percent confidence is another way of saying how accurate one wishes to be in their experiments. The higher the percent confidence, the more certain one is in their experiments. In this case, you will use a standard percent confidence of 95%. So, you will need an F-critical value which corresponds to a 95% percent confidence, a variance based on 10 measurements in the numerator, and a variance based on 10

measurements in the denominator. Usually, these would be looked up in tables, as seen in appendix A Figure 1. However, below you will find an critical F value for your calculations[3]:

$$F_{crit} = 3.18$$

If the F value you calculated in part b of this problem is larger than the critical value given, then the two samples are significantly different. If the F value you calculated in part c of this problem is smaller than the critical value given, then the two samples are not significantly different. State whether or not there is significant difference between the two samples .

3. Research suggests that one ibuprofen tablet should have a mass of 480 mg.[2] Do you think there is significant difference between the values you obtained and this literature value for a typical formulation? To answer this, you will use another statistical test known as the t-test. There are several different types of t-tests used in statistics. In this case, you will be using a one-sample t-test, which compares a single mean to a fixed value. So for this test, the fixed value will be the 480 mg. You will conduct a t-test on both samples. In order to conduct this analysis, do the following:

   a. For a t-test, you will need to find a t-value. The t-value for an experiment relates the average, standard deviation, and number of measurements to a given value. Using the symbols found previously in this experiment, the equation for the t-value is as follows:

$$t_{exp} = \left| \frac{\overline{x} - \mu_o}{\frac{\sigma}{\sqrt{n}}} \right| \quad (9)$$

   In this case, μ_o will be the mass found in research (480 mg).

   b. You will now compare this value to a critical value. This is known as the critical t-value. Like the F-critical value, the critical t-value is dependent on the percent confidence that is desired and the number of measurements taken in the sample. Again, you will use a percent confidence of 95%. The critical t-value you will be using is given below[3]:

$$t_{crit} = 2.262$$

Just like with the F-test, if the critical t-value is higher than the value obtained earlier, then there is no difference between your sample and the value from literature. If the t-value calculated earlier is higher than the critical t-value, then there is a significant difference between the sample and the value obtained from literature. State whether or not there is significant difference between the value obtained from experiments and the value obtained from literature.

c. Repeat this process for whichever sample you did not already conduct the analysis on.

4. It has been estimated that the world production of ibuprofen is in the vicinity of 15,000 tons per year.[4] It has also been estimated that the average price for one ibuprofen tablet is roughly 0.12 USD.[5] Using this information, calculate the total price of ibuprofen production for a year.

5. Remember that you listed the inactive ingredients from each of the brands. Research the first three ingredients from both brands and state what type of excipient you believe them to be (i.e. filler, preservative, lubricant, etc.).

6. It is your first day on the job working for Pfizer and you are told to do an experiment on the Advil production line. A new tablet press has been installed and your boss wants to know if it is producing tablets with consistent weight. To start your experiment, you pull a sample of 20 tablets off of the line and weigh them. The data is arranged in a table below. Your boss tells you that each pill must be 90% to 110% of the mean tablet size, which is 0.485 g. Do any pills in your sample fall outside of these bounds? Furthermore, did you find any outliers in your sample? What does this say about the consistency of the new pill press?

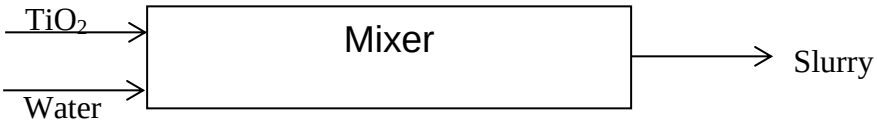
Table 2: Experimental data from production line

Advil Sample - 20 Tablet weights (g)			
0.4850	0.5435	0.4686	0.4837
0.5198	0.4448	0.5211	0.5895
0.5048	0.4668	0.4863	0.5227
0.4857	0.4465	0.4217	0.4662
0.4786	0.4835	0.4481	0.5101

7. You will now have an introduction to creating process flow diagrams. These diagrams are an important part of engineering, as they are used in most plants. A process flow diagram indicates the major equipment used in a process. In this case, a box with a label will be acceptable as a piece of equipment. An example is shown below:

   A heater heats water from 10°C to 50°C:

   If you have more than one stream entering or exiting a process, multiple lines can be drawn. For example, if a mixer blends water and titanium dioxide to make a slurry the process flow diagram would look like:



   a. Make a process flow diagram for the creation of the ibuprofen tablets as described by the steps below:

      i. Mix the powder (maize starch) for 15 minutes at high speed. Add 10.67 g of cold water and check weight (theoretical weight, 58.00g). If required adjust with hot water. Record the quantity of extra water added.

      ii. Mix this binding solution with Mixture 1 (Ibuprofen and maize starch).

      iii. Collect and spread the granules onto the trays, one third the thickness of the tray.

      iv. Load the trolley into the oven and dry the granules in the trays and change the position of the trays for uniform drying.

      v. Mix stearic acid and corn starch separately and add to the granules before sending them to a compressor. Compress into 330-mg tablets, using 10-mm convex punches at 4 to 9 kPa.

      vi. Put the tablets into the coating and rolling pan.

   b. Make another process flow diagram that shows the coating of the ibuprofen tablets as described by the steps below:
      i. Make sugar coating:

1. Heat 72.0 g of item 6 (purified water) in mixer to boiling.
2. Dissolve 168.0g of item 4 (sucrose) and then cool to 25°C.
3. Filter the syrup through a 180-µm stainless steel sieve.
4. Dispense item 5 (titanium dioxide) into the sugar syrup from the previous step and homogenize.
5. Check for evenness of the dispersion.

ii. Apply Sugar Coating to tablets in coating pan by rolling tablets and slowly adding the sugar solution over 30 minutes.

iii. Make gloss solution

1. Melt items 1 - 3 (bee's wax, polyethylene glycol, carnauba wax) in a steam-heated vessel by gentle heating to 70°C or in a stainless steel container on a hotplate heater.
2. Mix thoroughly.
3. Pass the mixture through a homogenizer.
4. Store the polishing emulsion in a closed container at room temperature.

iv. Apply gloss solution to tablets in coating pan by rolling tablets. Once the desired polish appears, stop rolling the pan.

v. Dry the tablets in the pan at 30°C for 30 minutes. Final tablet weight should be 480 mg.

REFERENCES

1. Cacciotti, J. and Clinton, P. "The Lull between Two Storms." Pharmaceutical Executive. 2010.
2. Niazi, S. K. Handbook of Pharmaceutical Manufacturing Formulations; Compressed Solid Products. New York: Informa Healthcare USA, 2009.
3. Montgomery, D. C. Introduction to Statistical Quality Control. John Wiley and Sons, Inc. 2013.

4. Myers, R.L. The 100 Most Important Chemical Compounds: A Reference Guide. ABC-CLIO, 2007.
5. Volume Discounts. http://www.drmichael.com/volume_discounts.htm

A.2 Fluidization of Pharmaceutical Excipients Lab

Fluidization of Pharmaceutical Substances

Developed by: Alex Jannini, David Krause, Heather Malino and Kevin Sweeney, Rowan University, Department of Chemical Engineering
Edited by: C. Stewart Slater and Mariano Savelski, Rowan University, Department of Chemical Engineering

Date of Experiment:

OBJECTIVES

- Students will fluidize a pharmaceutical excipient, and learn about the variables affecting fluid-particle transport
- Students will construct and interpret fluidization graphs using experimental data
- Students will gain experience using the online literary search engines

INTRODUCTION

A fluidized bed occurs when solid particulate matter is put under specific conditions that allow it to behave as a fluid. This is usually performed in some sort of vessel and achieved through the use of a pressurized fluid, such as air. Some of the properties that the particulate matter has in its fluidized state include the ability to be transported in a manner that is similar to other fluids. This phenomenon is called fluidization. Fluidization and fluidized beds are used in several different industries for several different purposes.

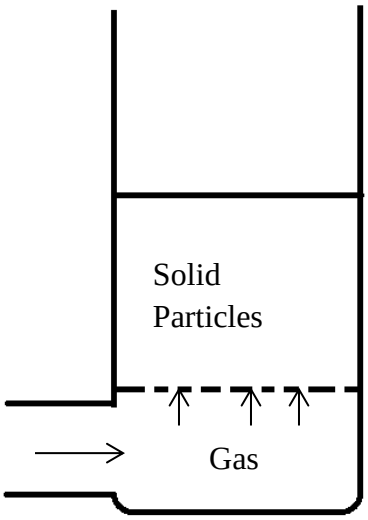


Figure 1: Simple schematic of a fluidized bed

In fluidization, there are many different variables that need to be considered. If one was to design a fluidized bed, equipment parameters such as the pressure of the incoming fluid, the flow rate of the incoming fluid, and the temperature of the system would need to be part of the design process. In addition, the material that is to be fluidized will also need to be investigated. Material properties such as particle size, density, and porosity (also known as the void fraction, or the fraction of empty space in a packed vessel) are important when designing a fluidized bed.

As the solids are fluidized, they behave as common fluids. As such, flow variables can be investigated with the moving particles. One such variable is

called pressure drop. Pressure drop is the difference in pressure between two points along the path of fluid movement in the process. Pressure drop is caused by frictional forces, resistances to the flow, as the fluid flows through the vessel.

In the pharmaceutical industry, fluidized beds have many different applications. Initially, fluidized beds were mainly used for the drying and coating of solids[1]. Granulation, the act of forming or crystallizing substances into grains or granules in fluidized beds, was later investigated for pharmaceutical purposes.[1] Fluidization can also be used for the transportation of solids, as the fluidized solids can be transported via pipes rather than conveyer belts or in discrete amounts[1].

In this experiment, you will be investigating four different variables of a fluidized bed; air flowrate, air pressure, pressure drop, and bed height. You will then use the data you collected to perform some fluidized bed calculations. By the end of this experiment, you should have a better understanding on how fluidization occurs, and why it is an important aspect of pharmaceutical manufacturing.

MATERIALS NEEDED

PART I

- 250 mL plastic graduated cylinder
- 1000 mL plastic graduated cylinder
- Bench scale capable of reading at least 1 kg
- Avicel® PH 200
- Kaolin powder
- DI water
- Stirrer

PARTS II & III

- Fluidized bed filled with Avicel® PH 200
- Ruler

SAFETY CONSIDERATIONS

Laboratory goggles must be worn at all times when in the laboratory. Laboratory gloves and a dust mask must be worn if handling pharmaceutical powders. Obtain and read the MSDS on Avicel® PH 200 and kaolin.

PROCEDURE

PART I – DETERMINING BULK AND PARTICLE DENSITIES

1. Begin by placing the empty 250 mL graduated cylinder on the bench scale. Tare the instrument.
2. Place approximately 50 to 60 grams worth of one of the powders into the graduated cylinder. If you are a little over or under, that is fine, as long as the powder does not surpass a measureable level on the graduated cylinder. You may have to use a scoop or a beaker to do this.

3. Record both the mass of the powder you added to the cylinder, and how much volume it takes up. Use these values to calculate the bulk density by dividing the mass added by the volume it takes up. Set aside this graduated cylinder.
4. Now, fill the 1000 mL graduated cylinder with DI water to around the 700 to 800 mL mark. Again, this does not need to be precise. Record the volume of water you added.
5. Place the graduated cylinder filled with water on the bench scale, and once again tare the instrument.
6. Slowly, add the powder from the small graduated cylinder into the large one. You may need to stir the solution at intervals of the pouring process so that all the particles are suspended. Remember that you do not want to surpass the readable levels of the graduated cylinder.
7. Once the particles have been poured in, stir the mixture thoroughly, but carefully. You do not want to lose any of the water. Once stirred, place back on the scale bench and record the mass of the powder you added to the water. Also, record the new volume of the water and powder mixture.
8. Now, find the particle density. The particle density is the mass of the powder added to the water and the volume taken up by the particles. You can determine the volume taken up by the particles by subtracting the volume of water from the volume of the mixture.
9. Do this for the other powder. Make sure that you clean and dry the graduated cylinders thoroughly, and use new cylinders before starting to work with the new powder. You may use the following table to record your findings, but you should copy this table into your lab notebook.

Table1. Empty table for recording data during the fluidization lab.

Measurement	Kaolin	Avicel PH 200
Mass of substance (g)		
Volume of substance (mL)		
Bulk density (g/cm^3)		
Volume of water (mL)		
Volume of mixture (mL)		
Volume of particles (mL)		
Mass of substance (g)		
Particle density (g/cm^3)		

PART II – THE FLUIDIZED BED

1. The first step in running these experiments is to become acquainted with the equipment. First, briefly look over the equipment and the station in front of you. Note where your pressurized air is coming from.
2. After investigating your system, measure the inner diameter of the fluidized bed. You will need this for calculations later.

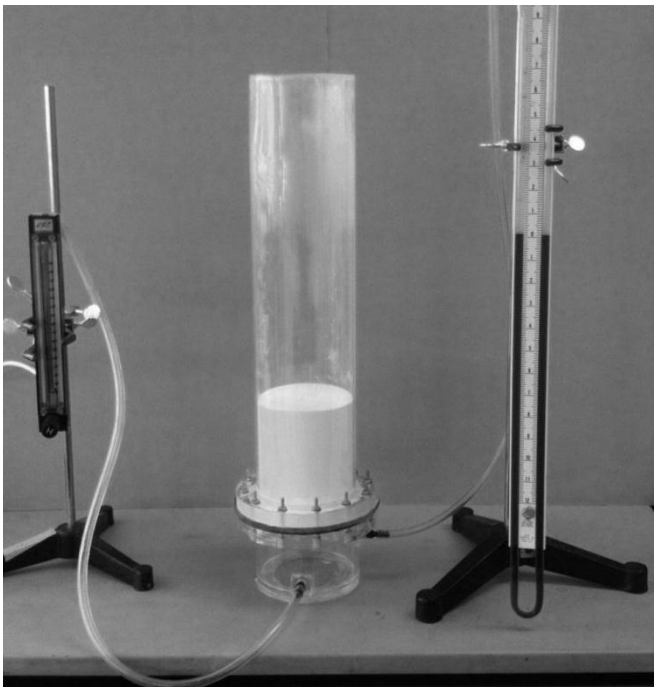
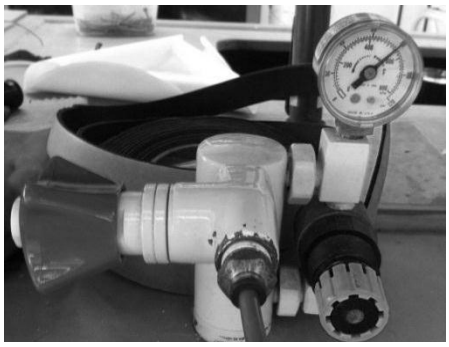


Figure 2. Laboratory scale fluidized bed.

PART III – SUBSTANCE INVESTIGATIONS

1. After becoming familiarized with your equipment, you may begin testing. Begin by measuring the height of the fixed bed.
2. Set the incoming air at a pressure of 60 pounds per square inch (psi). Make sure that the flowmeter is closed, but the air valve is open (make sure you know which is which!).
3. With the inlet air pressure at 60 psi, open the flowmeter and slowly raise the flow rate of the incoming air to 5 gallons per minute (gpm). At this reading, take a pressure drop measurement and a bed height measurement.
4. Once the measurements have been recorded, increase the air flow rate by 5 gpm. Again, measure the pressure drop and the bed height.



Figures 3 and 4. From left to right; the inlet air valve and the flow meter used in the fluidized bed setup.

5. Repeat this until you reach 30 gpm. Now, increase the intervals to 10 gpm. If you notice plug flow, bubbling, or channeling in the fluidized bed, record the flow rate and pressure drop, but make a note of the phenomenon that occurred. Also, it might be necessary to check on the air pressure periodically during the experiment. You should make sure this is done before taking any measurements.
6. Once you have taken the pressure drop and bed height at the maximum flow rate of air, bring the flow rate back down to zero.
7. Complete the same steps as above, but now using an air pressure of 100 psi. You may use the tables below to record your data, but you should also copy your data into your lab notebook.

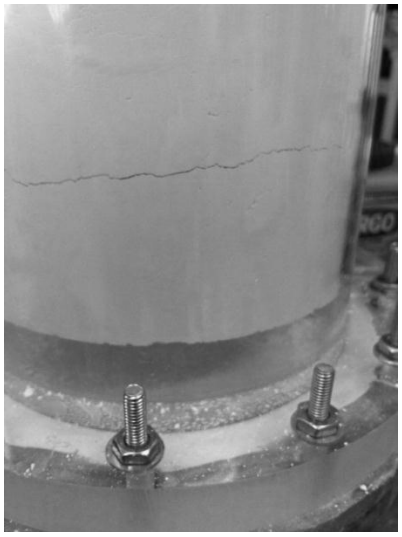


Figure 5. Plug flow occurring in the fluidized bed.

Table 2. Empty data table for recording pressure drop at an air pressure of 60 psi and bed expansion in the fluidization lab

Air Pressure of 60 psi		
Flow Meter Reading (gpm)	Pressure Drop (in H_2O)	Bed Expansion (inches)
0		
5		
10		
15		
20		
25		
30		
40		
50		
60		
70		
80		
90		
100		

Table 3. Empty data table for recording pressure drop at an air pressure of 60 psi and bed expansion in the fluidization lab

Air Pressure of 100 psi		
Flow Meter Reading (gpm)	Pressure Drop (in H_2O)	Bed Expansion (inches)
0		
5		
10		
15		
20		
25		
30		
40		
50		
60		
70		
80		
90		
100		

RESULTS

Record all results in your lab notebook.

QUESTIONS

1. Based on your results, what was the point of minimum fluidization (the point where fluidization was first noticed) for both of the data sets? What does this tell you about air pressure when it comes to minimum fluidization? Does this mean that air pressure is a negligible variable when it comes to fluidization? Why or why not?

2. You will make a graph of the air flow rate versus the bed height (this means that the air flow rate is on the x-axis and the bed height is on the y-axis) for both of the air pressures. Using the graph, determine when the bed goes from behaving as a packed bed to a fluidized bed.

3. Prepare a fluidization graph. A fluidization graph is obtained by plotting the air flow rate versus the pressure drop. When you make these graphs, there will be a change in the slope at a certain point. This point is known as the point of minimum fluidization. At this point, the bed of solids changes from behaving like a packed bed to behaving like a fluidized bed. Label where you believe this point is on the graphs you made. Also label what sections of the graph model the packed bed behavior and fluidized bed behavior.

4. For this experiment, we have delved into some of the properties of fluid mechanics, a branch of science that deals with the properties of fluids and some of the phenomenon that occurs when they are placed under certain conditions. One of the first variables you will learn in fluid mechanics is known as the Reynolds Number, a dimensionless quantity that is used to determine a flow regime. Today you will determine the Reynolds number of the system at minimum fluidization. To do this, you will use the following formula:

$$Re = \frac{D_p v_{mf} \rho_g}{\mu} \quad (1)$$

   a. The Reynolds Number is considered a dimensionless quantity. This means that there are no units attached. Prove this with the following information:

      D_p = Average diameter of the particle (m)
      v_{mf} = Velocity of minimum fluidization (m/s)
      ρ_g = Density of the gas (kg/m^3)
      μ = Dynamic viscosity of the gas (Pa*s)

b. Find the Reynolds number for the minimum fluidization point for both of your experimental runs. To help you in the calculation of this number, use the following values[2,3,4]:

$$D_p = 180\ \mu m\ (micrometers)$$
$$\rho_g @\ 60\ psi = 0.328\ {}^{lb}/_{ft^3}$$

$$\rho_g @\ 100\ psi = 0.582\ {}^{lb}/_{ft^3}$$
$$\mu = 1.716 * 10^{-5}\ Pa * s$$

In addition, determine which of the fluidization regimes the fluidized bed was in at minimum fluidization based on the figure below.

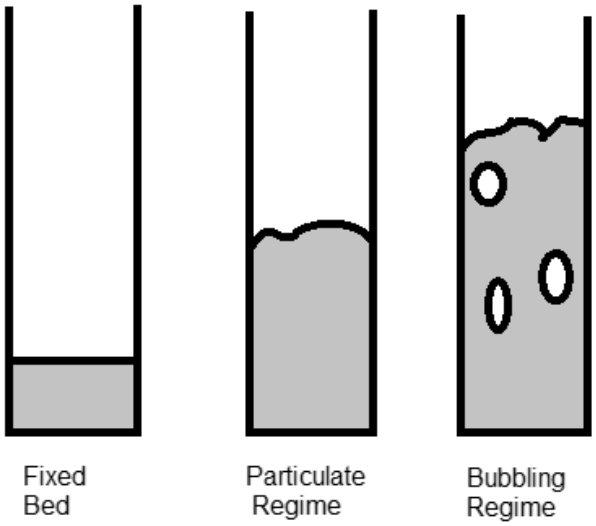


Figure 6. A few fluid regimes of fluidized beds. Adapted from Perry's Chemical Engineering Handbook.[5]

5. The following fluidization data was collected using kaolin powder with the same apparatus (same dimensions) at an air pressure of 60 psi:

Table 4. Fluidization data using kaolin powder at an air pressure of 60 psi

GPM	Bed Height (in.)	ΔP (psi)
0	5.00	0.0
5	5.00	0.5
10	5.00	1.8
15	5.50	1.8
20	5.75	2.4
25	5.75	2.4
30	6.00	2.5
40	6.00	2.8
50	6.50	3.2
60	6.50	3.6
70	6.50	3.8
80	6.75	4.1
90	6.75	4.2
100	6.50	4.6

a. Create a flow rate versus bed height graph and a flow rate versus pressure drop graph.
b. Determine if there is a point of minimum fluidization using the graphs.
c. If you could determine a point of minimum fluidization, determine the Reynolds number at that point. If not, find the Reynolds number at the same point you used for Question 4. Use an average particle diameter of 1.4 μm for this problem.[6]

6. Now, we will go over another important tool for engineers; design equations. Design equations are used by engineers to determine information about a process without having to do extensive experimentation. These equations are usually based on data obtained by research. For example, the following equation can be used to determine the Reynolds number at minimum fluidization[7]:

$$Re_{mf} = \sqrt{(C_1^2 + C_2 * Ar)} - C_1 \qquad (2)$$

Where Ar (Archimedes Number), C_1, C_2, are shown below:

$$Ar = \frac{Dp^3 \, \rho_g \left(\rho_s - \rho_g\right) g}{\mu^2} \qquad (3)$$

$$C_1 = \frac{300(1-\varepsilon_{mf})}{7} \quad (4)$$

$$C_2 = \frac{\varepsilon_{mf}^3}{1.75} \quad (5)$$

Where:

D_p = Average diameter of the particle (m)
ρ_g = Density of the gas (kg/m^3)
ρ_s = Particle density of the excipient (kg/m^3)
g = Acceleration due to gravity (9.81 m/s^2)
μ = Dynamic viscosity of the gas (Pa*s)

In order to use the equations above, you will need to determine the porosity at minimum fluidization (ε_{mf}). This can be a difficult characteristic to determine, which is why many researchers have come up with different constants to approximate the porosity.[8] However, we have enough information to determine ε_{mf}, so we will solve for C_1 and C_2.

To determine ε_{mf}, we first need to know the normal porosity, ε. This can be determined by using the bulk density (ρ_b) and the particle density (ρ_s):

$$\varepsilon = 1 - \frac{\rho_b}{\rho_s} \quad (6)$$

We also have to determine the total volume (V_{tot}). For this, use the bed height at the 0 gpm air flowrate, and multiply by the cross-sectional area of the bed. Now, we can determine the void volume (V_v) using the following equation:

$$\varepsilon = \frac{V_v}{V_{tot}} \quad (7)$$

Now, to determine the volume occupied by the particles (V_p):

$$V_p = V_{tot} - V_v \quad (8)$$

From here, we now need to use the point of minimum fluidization to determine the volume (V_{mf}). This can be done by using the bed height at the point of minimum fluidization and the cross-sectional area. Using V_{mf}, you can determine the void volume at minimum fluidization (V_{vmf}):

$$V_p = V_{mf} - V_{vmf} \quad (9)$$

Finally, determine ε_{mf}:

$$\varepsilon_{mf} = \frac{V_{vmf}}{V_{mf}} \qquad (10)$$

a) Determine ε_{mf} for the Avicel® trial at the air pressure of 60 psi.
b) Determine the Re_{mf} using Equation (2) for the same conditions as part a).
c) Calculate the percent difference between your answer for part b) and the answer you obtained in Question 4.

$$\%\ Difference = \frac{|Re - Re_{mf}|}{\left(\frac{Re + Re_{mf}}{2}\right)} * 100\% \qquad (11)$$

d) You should notice a considerable (>10%) difference in part c). This is because you are using superficial velocity, as opposed to interstitial velocity. Superficial velocity is defined as the theoretical flow through the bed based on the flow rate of the liquid divided by the cross sectional area of the tube. Interstitial velocity takes into account how the flow is affected by the volume occupied by particles. Interstitial velocity is the flow velocity post a particle, and is the "correct" velocity to use in the Re_{mf} equation. To determine the interstitial velocity (v_i):

$$v_i = \frac{Q_{mf}}{A_s * \varepsilon_{mf}} \qquad (12)$$

Where:
Q_{mf} = volumetric flow rate at minimum fluidization (m^3)
A_s = cross sectional area (m^2)
ε_{mf} = porosity at minimum fluidization (dimensionless)

Determine v_i, calculate a new Re as in Question 4, and then compare as in part c).

7. It is important to learn how to use the online library tools that you have available. These online tools have thousands of scientific papers and articles in databases that you have free access to. Using one of the scientific online resources (i.e. Science Direct, SciFinder, etc.) available, you and your lab partners will find an article online about pharmaceutical manufacturing practices. Try to find an article that also discusses either fluidization or fluidized beds. Print out the article, and as a group, be

prepared to discuss the article in class. NOTE: It is all right if you do not understand all of the technical details of the paper, but you should have a good understanding of the overall concept being discussed.

In addition, use the MSDS's that you obtained as part of your pre-lab and any other literature to compare the bulk densities that you found in part I of the experiment.

REFERENCES

1. Davies, W.L. and Gloor, W.T. Jr. Batch Production of Pharmaceutical Granulates in a Fluidized Bed I: Effects of Process Variables on Physical Properties of Final Granulation. Journal of Pharmaceutical Sciences. Vol. 60 no. 12. pp. 1869 – 1874. 1971.
2. The FMC Biopolymer Company. Avicel® for Solid Dosage Forms. 2012. Accessed 9 September 2013. http://www.fmcbiopolymer.com/Pharmaceutical/Products/Avicelforsoliddoseforms.aspx
3. Engineering Toolbox. Air – Temperature, Pressure, and Density. Accessed 9 September 2013. http://www.engineeringtoolbox.com/air-temperature-pressure-density-d_771.html
4. Engineering Toolbox. Air – Absolute and Kinematic Viscosity. Accessed 9 September 2013. http://www.engineeringtoolbox.com/air-absolute-kinematic-viscosity-d_601.html
5. Perry, R.H. and Green, D.W. Perry's Chemical Engineer's Handbook. 7th edition. 1997. McGraw-Hill.
6. Fisher Scientific. "Kaolin, pure, Acros Organics." 2013. Accessed 4 December 2013. http://www.fishersci.com/ecomm/servlet/fsproductdetail_10652_16067959__-1_0
7. Kunil, D. and Levenspiel, O. Fluidization Engineering. 2nd edition. Butterworth Heinemann. Boston. 1993
8. Subramanian, R.S. Flow through Packed Beds and Fluidized Beds. Clarkson University. http://web2.clarkson.edu/projects/subramanian/ch301/notes/packfluidbed.pdf

A.3 Asthma Drug Delivery Lab

Asthma Drug Delivery Laboratory Experiment

Developed by: Alex Jannini, David Krause, Heather Malino and Kevin Sweeney, Rowan University, Department of Chemical Engineering

Edited by: C. Stewart Slater and Mariano Savelski, Rowan University, Department of Chemical Engineering

Date of Experiment:

OBJECTIVES

- Students will learn about intrusive laboratory experiments
- Students will gain experience in reverse engineering strategies and project designs
- Students will conduct a basic quality control analysis operation

Figure 1: Diagram of the dry powder inhaler

INTRODUCTION

ADVAIR® is a dry powder inhaler prescribed to patients with asthma and chronic obstructive pulmonary disease that uses two active pharmaceutical ingredients. Fluticasone propionate, one of the two, is a corticosteroid, which is used to reduce the inflammation of the lungs. Salmeterol xinofoate, the second, is a bronchodilator, which relaxes the muscles in the airways to help improve breathing.[1]

ADVAIR® is not only used as an option for people with asthma, but also can be used as a maintenance treatment for chronic obstructive pulmonary disease.[1] Chronic obstructive pulmonary disease (COPD) is a disease that makes it difficult to breathe. It also takes the form of chronic bronchitis, causing a long-term cough with mucus, and emphysema, which destroys the lungs over time. Most sufferers of COPD have a combination of the two symptoms.[2] Asthma occurs when the airways of the lungs tighten and narrow, which leads to wheezing, shortness of breath, coughing, and a tightening in the chest.[3]

ADVAIR® comes in three varieties: ADVAIR DISKUS® 100/50; ADVAIR DISKUS® 250/50; ADVAIR DISKUS® 500/50. The three varieties of ADVAIR® have different amounts of fluticasone propionate in the powder. For example, in an ADVAIR DISKUS® 100/50, there will be 100 µg (micrograms) of fluticasone

propionate and 50 µg of salmeterol. The 250/50 prescription of ADVAIR® is used for COPD treatment.[1]

In this lab, the teams will be examining an ADVAIR DISKUS®, and conduct an invasive reverse engineering experiment on the diskus. They will then compare the dry powder inhaler to two other types of inhaled medication transport systems; a nasal spray and a traditional metered dose inhaler. The goal is to see the difference in the transport process that each system uses, and to also see if there is any way to improve the design of the diskus. A quality control study on the packaging of powder in the ADVAIR DISKUS® is also provided. This will include an average and a standard deviation of the powder packages.

MATERIALS NEEDED

- ADVAIR DISKUS®
- Small flathead screwdriver
- Analytical scale (able to read at least 1/10,000g)
- Albuterol metered dose inhaler (or suitable substitute)
- Fluticasone propionate nasal spray (or suitable substitute)
- Narrow-headed spatula
- KimWipes
- Weigh boats

SAFETY CONSIDERATIONS

All students should know that laboratory gloves and eyewear must be worn at all times to protect from sharp edges and medicines.

Figure 2: Removal of outer shell

PROCEDURE

PART I - REVERSE ENGINEERING

1. Open up the diskus box and remove the information packets. Make general observations on the diagrams and information included.
2. Remove the inhaler from the tinfoil package. Based on its outside appearance, how do you think it works? Sketch the diskus.
3. With the flathead screwdriver, proceed to remove the outer shell of

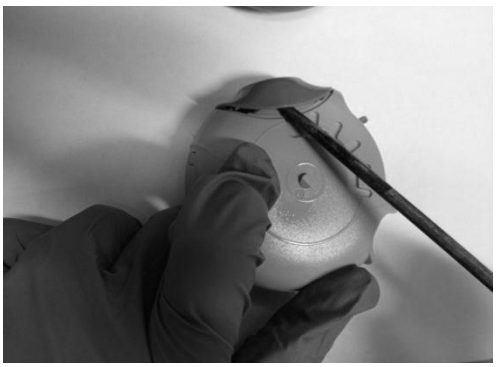


Figure 3: Proper removal of mouthpiece

the inhaler. Be careful to not break or shatter any plastic.

4. Insert the screwdriver under the mouthpiece and use it as a lever to dislodge the mouthpiece.

5. Along the outside circumference of the diskus you will notice several slots and tabs that hold each half of the inhaler together. One by one, carefully depress each tab and pry the inhaler open.

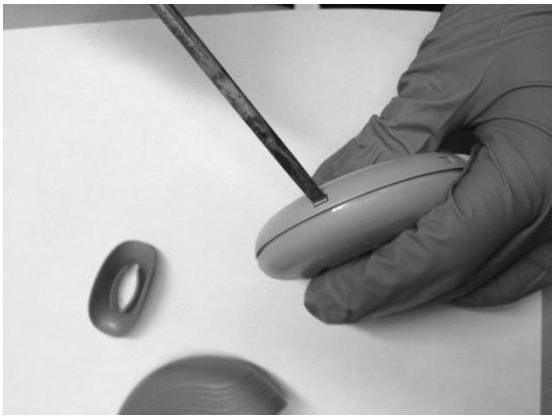


Figure 4: Proper depression of the tabs

6. This should expose the inside of the inhaler. Make observations on its appearance and the gears. Sketch the inside of the diskus.

7. Pull the lever down and reset it a few times. Discard the powder inside the blisters. Note how the gears move. Based on this, do you have any other ideas as to how the inhaler works?

8. Remove the foil strip. It will be stuck at one part after the foil has been split in half. Cut this section away to fully remove the rest of the foil strip.

9. The large white plastic mold that the foil fits into can be removed. Look for white tabs interlocking with the purple exterior shell by the mouthpiece. Push these tabs in to remove the white mold.

10. At this point, the gears should be fully exposed. Move the lever up and down. Was your hypothesis as to how the diskus worked correct? If not, what is actually happening?

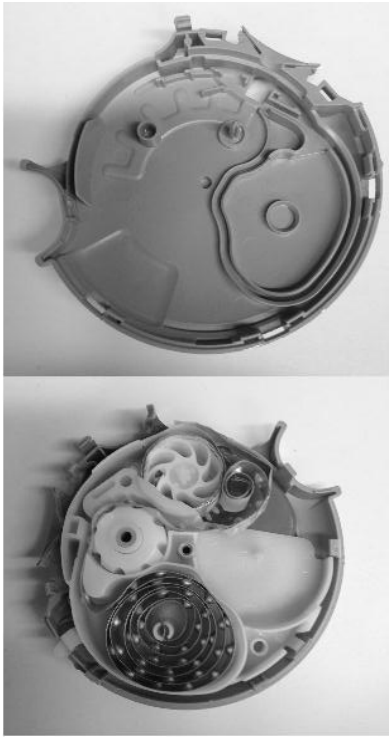


Figure 5: Inside the Diskus

11. Set the diskus aside and look at the aerosol inhaler and nasal spray. Compare and contrast these methods of asthma drug delivery to the diskus. (i.e. size, complexity, ergonomics, visual appeal, etc.)

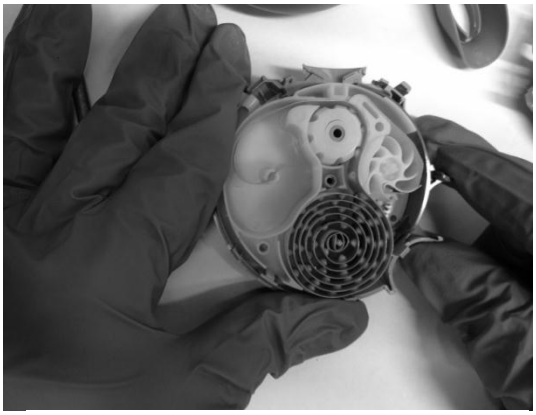


Figure 6: Operating the open Diskus

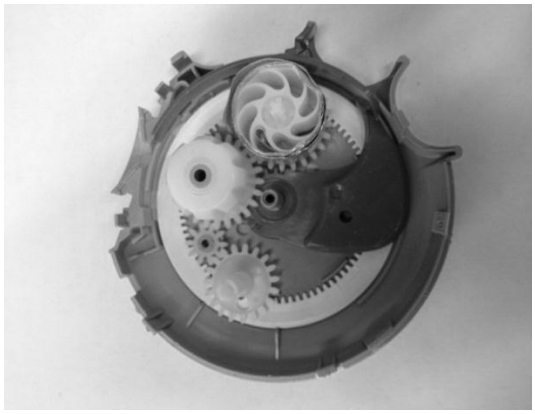


Figure 7: Removal of the inner plastic layer

PART II - QUALITY CONTROL/MEASUREMENT

You may wish to place your findings in the table found in the RESULTS section of this experiment, but you should also record them in your laboratory notebook.

ADVAIR® Quality Control

1. Take the foil strip that was previously removed over to a weighing station that has a precise analytical scale.
2. Place a weigh boat on the scale and tare the instrument.
3. Remove the boat and pull back the foil strip exposing the powdered drug in one blister. Carefully empty its contents into the weigh boat using a spatula to scrape off any remaining powder.
4. Place the boat back on the scale and record the result. Tare the scale once again so the powder does not have to constantly be thrown out in between measurements. Repeat this nine more times so that the weights of ten blister packs have been recorded.
5. After all measurements have been taken, dispose of the boat and powder in the trash.
6. Reassemble the diskus and place it back in the box along with included pamphlets.

Figure 8: Proper removal of medicine from blister pack

Metered Dose Inhaler Quality Control (See Figure 9 for proper techniques for this section)

1. First, take a weight boat, and place it on the analytical scale.
2. Now, take a KimWipe and fold it until you have a small rectangle that will fit over the end of the metered dose inhaler. Place this folded KimWipe in the weigh boat, and then zero the analytical scale.
3. Take the metered dose inhaler, and shake well. Remove the KimWipe from the weigh boat, and place on the end of the inhaler where the propellant will exit.
4. With the KimWipe on the end of the inhaler, press down on the canister section of the inhaler, allowing the propellant to exit the inhaler and the KimWipe to capture it.
5. Quickly place the Kimwipe back on the weigh boat and take a mass measurement. (This may be difficult as the excipient, which acts as a propellant, will evaporate.) Take the measurement once the scale stays on the same value for at least a second.
6. Dispose of the KimWipe. Repeat steps 2 to 5 with fresh KimWipes until you have ten mass measurements.

Nasal Spray Quality Control (See Figure 9 for proper techniques for this section)

1. Once again, take a weight boat, and place it on the analytical scale.
2. Now, take a KimWipe and fold it. Place this folded KimWipe in the weigh boat so that it covers the bottom and most of the sides of the weigh boat. Once this is done, place the weigh boat back on the scale, and then zero the instrument.

3. Take another KimWipe or a paper towel and fold several times. Take the nasal spray and shake. Prime the device by spraying it a few times into this second wipe.
4. With the spray primed, take the weigh boat off the scale, and place on a slightly downward angle. Spray the propellant into the weigh boat once.
5. Place the weigh boat back on the scale and take a mass measurement.
6. Dispose of the KimWipe. Repeat steps 2 to 5 until you have ten mass measurements. (Step 3 may not need to be repeated every time, but once every 2 to 3 measurements.)

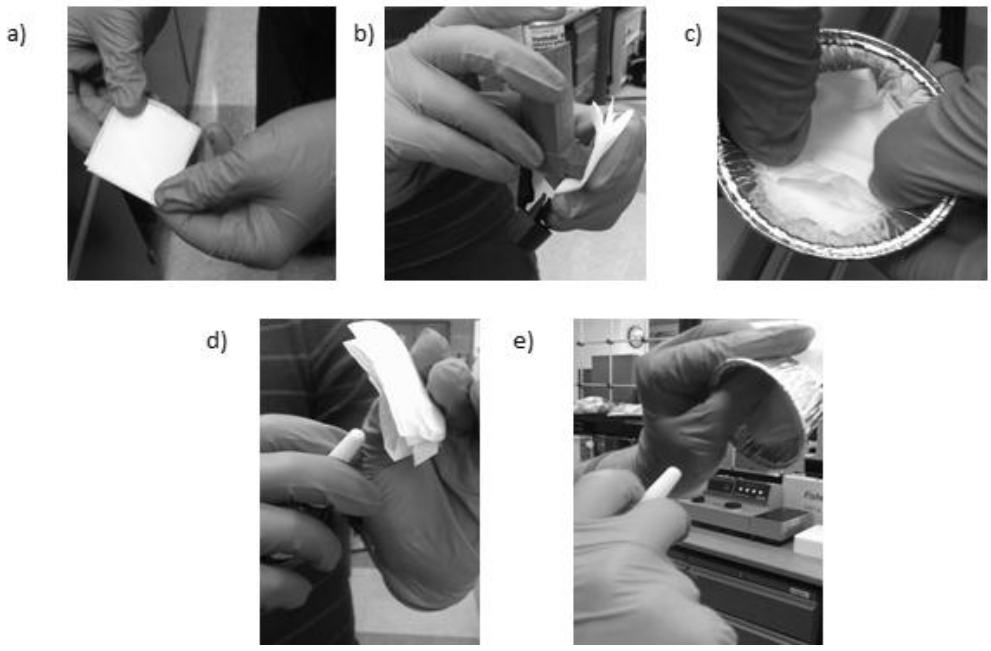


Figure 9: Different examples of the correct technique for metered dose inhaler (MDI) and nasal spray quality control measurements. a) The folding of the KimWipe before taking a mass sample of the MDI. b) The MDI cartridge being pushed down so that the medicine will be ejected into the KimWipe, and a mass measurement taken. c) The lining of a KimWipe on the bottom of a weigh boat far nasal spray mass measurements. d) Priming the nasal spray apparatus before taking a mass measurement. e) Taking a mass measurement using the nasal spray.

RESULTS

Make sure that the students record all results in a lab notebook, and that all members of the teams receive the data. These results can be placed in the table below and turned in along with solutions to the questions below. Questions were also asked throughout the procedure, and should be answered as well.

Table 1. Empty data table for collecting data in the Asthma Drug Delivery laboratory experiment

Diskhaler Trial	Mass (g)	MDI Trial	Mass (g)	Nasal Spray Trial	Mass (g)
1		1		1	
2		2		2	
3		3		3	
4		4		4	
5		5		5	
6		6		6	
7		7		7	
8		8		8	
9		9		9	
10		10		10	
Average					
Std. Dev.					

QUESTIONS

1. Compare and contrast the different styles of drug delivery that you examined in part I. Which of these systems did you think had the most appeal? Which do you think will work the best?

2. When comparing the MDI and the nasal spray, which of the two has a higher standard deviation? Compare all three standard deviations. Determine the highest and the lowest standard deviation. Explain what these results imply about the quality control measures of the three devices.

3. What were some sources of error in part II? How do you think you could fix some of these problems?

4. Based on the average weight of the blisters, what percentage of the powder are active pharmaceutical ingredients (API's) and what percentage is inactive? Assume that the amount of active ingredient from each sample is equal to the amount stated in the prescription dosage.

   The formula for finding the percentage of inactive ingredients is as follows:

$$\%_{Inactive} = \left(\frac{M_{total}^{avg} - \sum M_{API}}{M_{total}^{avg}}\right) x\ 100 \quad (1)$$

M_{API} *can be found on the package. Watch the units*!

From this, find the percentage of active ingredients.

5. Do you think that the assumption made for problem 4 was a valid assumption to make? Why or why not?

6. The Advair dry powder inhaler, as described in the introduction section, contains two active ingredients, fluticasone propionate and salmeterol powder. There is one other ingredient listed on the label, lactose.
    a. What is lactose? Where else is lactose commonly found?
    b. Why would lactose be used in the inhaler? What type of excipient should it be considered?
    c. What are some negatives of using lactose?

    Be sure to site all references.

7. All metered dose inhalers (MDIs) need a propellant. A propellant makes up almost 99% of the dose of an inhaler. The propellant must have specific properties. Some of these include the boiling point, solubility of the API, toxicity and others. The API is suspended in the propellant and when the medication is dispensed the propellant creates an aerosol cloud, that the medication can be inhaled by the patient.[4]
    a. What is a CFC?
    b. Why are CFCs no longer used as propellants in inhalers?
    c. What type of propellant is used in the Ventolin inhaler? Which type of propellant did it replace?
    d. Compare the two propellants. Why do you think they replaced the propellant?

    Be sure to cite all references.

REFERENCES

1. GlaxoSmithKline. "Highlights and Full Prescribing Information for ADVAIR DISKUS." January 2011. http://us.gsk.com/products/assets/us_advair.pdf
2. United States National Library of Medicine. "Chronic Obstructive Pulmonary Disease." May 2011. http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001153/
3. United States National Library of Medicine. "Asthma." July 2012. http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001196/
4. Noakes, T. Medical aerosol propellants. The Journal of Fluorine Chemistry. Vol. 118, pp. 35-45. 2002.

A.4 Degradation of Dissolvable Strips Lab

Degradation of Dissolvable Strips
Developed by: Alex Jannini, David Krause, Heather Malino and Kevin Sweeney, Rowan University, Department of Chemical Engineering
Edited by: C. Stewart Slater and Mariano Savelski, Rowan University, Department of Chemical Engineering
Date of Experiment:

OBJECTIVES

- Students will learn about mass transfer and degradation rates of drug delivery films
- Students will learn how to properly operate a spectrophotometer
- Students will determine the effect of temperature on this process

INTRODUCTION

In 2000, the pharmaceutical company Pfizer introduced a new over-the-counter product for the treatment of bad breath. This product came in a novel form that was not seen before; a small, orally dissolvable strip. This product revolutionized the industry, generating roughly 250 million dollars in sales. By 2002, many other brands of dissolvable strips were also on the shelves.[1] In 2011, the energy supplement industry also saw the potential profits of sheets. One company, known as Sheets, introduced a caffeine based strip which they claim has zero calories, zero sugar, and has the same caffeine as one cup of coffee, shown in Figure 1. The brand also states that negative side effects, such as a "crash," are not common when taking the product. Although the company has faced controversy, especially with the endorsement of LeBron James, Sheets continues to make energy supplement strips.[2]

Figure 1. The energy strips you will be using in class.

While the use of dissolvable strips is a relatively new delivery method, it has become a popular method of drug delivery. In fact, many other fields of over-the-counter pharmaceutical products have introduced dissolvable strip products. Dissolvable strips that contain medicines for flu and sinus infection symptoms can now be found in most pharmacies.[3]

With dissolvable strips, the delivery vehicle is a thin, flexible sheet of polymer. The active pharmaceutical ingredient (API) is incorporated into this polymer to form the final product. Depending on the nature of the medicine, the API can be incorporated in one of two ways; either through liquid dissolution or solid suspension in the polymer. The size and thickness of these strips is dependent on the dosage of API that needs to be delivered.[3]

In this experiment, you will investigate the dissolution and degradation rate of a dissolvable strip that contains menthol. You will be using a spectrophotometer to take absorbance readings. These absorbance readings will then be used to find the amount of menthol that was released from the strips. You will also be comparing these rates for two different temperatures; ambient, otherwise known as room (roughly 20°C), and body (37°C).

MATERIALS NEEDED

- 2 Sheets™ brand Mint Boost dissolvable strips
- 2 petri dishes
- 2 timers
- Incubator or oven capable of reaching and maintaining 37°C
- Pair of tweezers
- Deionized water
- 500 µL to 5000 µL pipette
- Spectrophotometer capable of measuring absorbance at 630 nm
- Cuvettes
- Thermometer/thermocouple

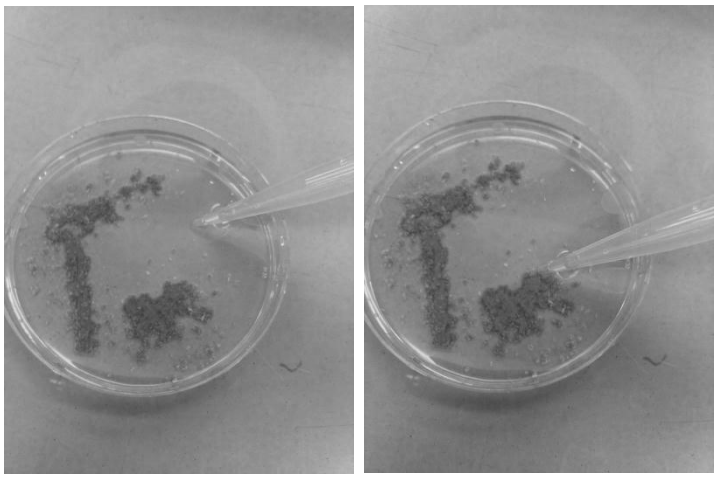
SAFETY CONDITIONS

Laboratory gloves and eyewear must be worn at all times inside the lab. Be sure to keep water away from the spectrophotometer.

PROCEDURE

1. Start by turning on the spectrophotometer and setting it to take absorbance readings at 630 nm.
2. While the spectrophotometer warms up, place 2.5 mL of deionized water into each of the petri dishes.
3. Place one of the petri dishes into the oven/incubator that is set at 37°C.
4. Allow 20 minutes to pass so that the water may reach 37°C and the spectrophotometer may warm up.

5. After the 20 minutes have passed, fill a cuvette with deionized water and zero the spectrophotometer.
6. Now that the spectrophotometer has been zeroed, use the tweezers to place a strip into one of the petri dishes. Once the strip has been placed in the petri dish, cover and start the timer.



Figures 2 and 3. From left to right, the proper (l) and improper (r) way to take a sample.

7. Place the other strip in the other petri dish using the tweezers. Once placed, close the petri dish and start a secondary timer. NOTE: It is a good idea to stagger the starting times so that you do not find yourself rushing to take two measurements. It may also be a good idea if you are working in teams to split the team so that one section of the group is in charge of one specific temperature study.
8. After five minutes have elapsed, take a sample of your water into a cuvette. Make sure that this sample is relatively far from the dissolvable strip so that you do not accidentally pick up any large portions of the dissolvable strip, as in Figures 2 and 3.
9. Take an absorbance reading then return the sample to the corresponding petri dish.
10. Take absorbance readings every five minutes for the first thirty minutes. After that, take absorbance readings every ten minutes until you have reached 90 minutes. You may use Table 1, but you should also record your results in your laboratory notebook.

Table 1. Empty data table to record absorbance at 630 nm data for the dissolvable strips laboratory.

Time (min)	Absorbance readings at 630 nm	
	Room Temperature (20°C)	Body Temperature (37°C)
0	0	0
5		
10		
15		
20		
25		
30		
40		
50		
60		
70		
80		
90		

11. Once you have taken all the necessary measurements, make sure to turn off the spectrophotometer and the incubator/oven.
12. Dispose of all equipment used in this lab, and make sure that any water spills were cleaned up before exiting the laboratory.

RESULTS

Be sure to record all the data you collected in this experiment into your laboratory notebook. If you split into two groups to complete this experiment, be sure that you share the data sets.

DATA ANALYSIS

To analyze the data, the best method is to create a graph of the time versus absorbance reading. In this case, the x-axis will be the time axis and the y-axis will be the absorbance axis. Create one of these graphs using Excel or another program and turn it in along with the rest of your laboratory report.

QUESTIONS

1. Now, you will take your absorbance readings and figure out the concentration of menthol in your solutions. You will do this using the following graph, which correlates absorbance at 630 nm to concentration in mg/mL. Once you have the concentrations, create another graph of concentration versus time for both temperature sets. In addition, fill in

Table 2. Make a copy of this table and turn in along with the rest of the deliverables for this experiment.

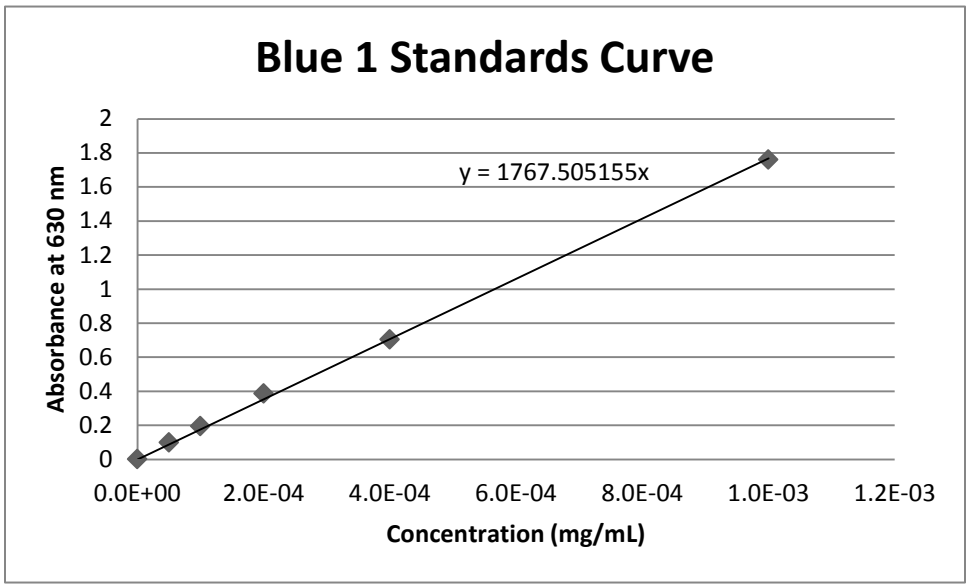


Table 2. Empty data table for recording concentrations in the dissolvable strips laboratory.

Time (min)	Concentration (mg/mL)	
	Room Temperature (20°C)	Body Temperature (37°C)
0	0	0
5		
10		
15		
20		
25		
30		
40		
50		
60		
70		
80		
90		

2. Now that you have found the concentration of the solution over time, you will need to use concentration and absorbance readings to determine the molar absorptivity of the blue food dye. The molar absorptivity, or the

molar absorption coefficient, is defined as how strongly a substance absorbs light at a particular wavelength[4]. This coefficient is seen in the Beer-Lambert Law, an important law that governs the absorbance of light. This law is shown below:

$$A = \varepsilon \ell c \tag{1}$$

With:

$$A = absorbance\ (dimensionless)$$
$$\varepsilon = molar\ absorption\ coefficient$$
$$\ell = length\ the\ light\ has\ to\ travel\ through\ the\ solution\ (cm)$$
$$c = concentration\ of\ solution\ in\ moles\ per\ liter\ (M)$$

a) Use one of the higher time points (70 to 90 minutes) of both the room temperature and body temperature experimental runs to determine the molar absorption coefficients of both runs. Use the following constants to help you in this calculation.

$$\ell = 1\ cm$$
$$molar\ mass\ of\ Blue\ 1 = 793\ \frac{g}{mol}$$

b) Based on the values, do you think that the temperature affects the molar absorption coefficient?

3. Determine how well the molar absorption coefficients can determine the concentration of the solution based on absorbance readings. Use the molar coefficients you previously found and determine the concentration that the solution should be at based on the Beer-Lambert Law. Use a time point between 30 and 50 minutes in both cases. Determine how different these two numbers are by using percent difference. The equation for percent difference is shown below. In this case, the "E" terms are the molar concentrations. It should be noted that percent difference is a dimensionless number. Make sure you do all the necessary unit conversions before calculating the percent difference.

$$Percent\ Difference = \frac{|E_1 - E_2|}{\left(\frac{E_1 + E_2}{2}\right)} * 100\% \tag{2}$$

4. It is known that the molar absorptivity coefficient of the blue food dye used in these sheets is $1.3 \times 10^6\ M^{-1}cm^{-1}$.[5]

a) How different is the molar absorptivity coefficient that you found using your experimental data from this known value? Use experimental error to determine this difference. The equation for percent error is shown below.

$$Percent\ Error = \frac{|E - A|}{A} * 100\% \quad (3)$$

Here, the "E" term is the molar absorptivity coefficient obtained through the experimental data, while the "A" term is the molar absorptivity coefficient given to you above. It should be noted that when using this equation, the two terms need to be in the same units. It should be noted that percent error is also a dimensionless number.

b) Now, use the same time point that you used in Question 6 and determine the concentration based on the given molar absorptivity coefficient. Again, compare using percent error. Do this for both experimental runs. Here, the "E" term will be the concentration that you obtained during experimentation, while the "A" term will be the concentration that you obtained using the given molar absorptivity coefficient.

5. The Beer-Lambert Law is one of the most important laws used in spectroscopy (the interactions between light and matter). How could you use this law in an engineering aspect?

6. Now, we will discuss a rate law. A rate law, or rate equation, is an equation that governs the rate of a process as a function of a variable, such as time. These laws are used by engineers to determine the design of a chemical process. Rate laws applied to this experiment relate absorbance with time. For example, an important variable of a rate law, the rate coefficient/constant (k), can be determined using absorbance data. This can be done using the following equation:

$$\ln \frac{(A - A_\infty)}{(A_0 - A_\infty)} = -k * t \quad (4)$$

Where:

t	Time
A	Absorbance at time t
A_0	Absorbance at t=0
A_∞	Absorbance at t=∞
k	Rate coefficient

a) Determine the rate coefficient from your absorbance data. To do this, you will need to determine A_∞ based on your data. Use a point earlier in your experiment, and determine a rate coefficient for both sets of data.
b) Based on these results, does temperature affect the dissolution rate? Use the rate constant values you obtained to verify your answer.

REFERENCES

1. InnovateUs, Inc. “What are Breath Strips?” http://www.innovateus.net/health/what-are-breath-strips.
2. Donaldson James, Susan. “Sheets Give Caffeine Jolt, Potential for Abuse.” ABC News. 10 June, 2011. http://abcnews.go.com/Health/lebron-james-shills-sheets-caffeine-strips-bad-idea/story?id=13805037#.UeWj2m1nA6e.
3. Particle Sciences Drug Development Services. “Dissolving Films.” 2010. Volume 3.
4. Biology Online. Molar Extinction Coefficient. Biology Online.org. 22 June 2008. Accessed 11 September 2013. http://www.biology-online.org/dictionary/Molar_extinction_coefficient.
5. Reeves, J. Beer’s Law. Laboratory for science majors at The University of North Carolina Wilmington. Accessed 12 September 2013. http://uncw.edu/chem/Courses/Reeves/OnLineLabs/scienceMajors/BeersLaw_PH.pdf

A.5 Effervescence Reaction Lab

Effervescence Laboratory Experiment

Developed by: Alex Jannini, David Krause, Heather Malino and Kevin Sweeney, Rowan University, Department of Chemical Engineering

Edited by: C. Stewart Slater and Mariano Savelski, Rowan University, Department of Chemical Engineering

Date of Experiment:

OBJECTIVES

- Students will perform a basic mass balance on an effervescence reaction in pharmacology
- Students will conduct theoretical stoichiometric calculations and compare to experimental results
- Students will learn about the equilibrium constants and other fundamental aspects of reactions

Figure 1. Standard original strength packet

INTRODUCTION

Alka-Seltzer® is an effervescent antacid ($NaCO_3$, KCO_3 plus anhydrous citric acid) containing acetylsalicylic acid (aspirin), which is an analgesic, antipyretic, and anti-inflammatory drug. Simply put, Alka-Seltzer® relieves upset stomach, provides pain relief, breaks fevers, and reduces inflammation.

The effervescence allows for a faster rate of drug dissolution into a liquid medium (water in this case) by increasing the surface area of the drug exposed to solution and by "bubbling" the mixture, causing a stirring effect. The effervescence reaction is:

$$C6H8O7(aq) + NaHCO3(aq) \rightarrow H2O(l) + CO2(g) + Na3C6H5O7(aq) \quad (1)$$

Figure 2. Weighing the tablets

In this lab you will determine how much CO2 is generated and released to the atmosphere by taking the initial and final weights of an Alka-Seltzer® solution. This is an introduction to mass balances, an important concept for engineers. This experimental value will then be compared to the theoretical amount of CO2 mass generated, found through stoichiometry.

MATERIALS NEEDED

- 2 Alka-Seltzer® tablets (1 packet)
- Analytical scale (+/- 0.0001 g)
- Weigh boat
- Graduated cylinder
- 200 mL plastic beaker
- Timer

Figure 3. Creating the solution

PROCEDURE

1. Make sure safety glasses and examination gloves are on before entering the lab.
2. Remove both Alka-Seltzer® tablets from the packet. If the tablets are broken, be careful to not lose any pieces. How do you think a broken tablet will affect the rate of the tablets dissolving?
3. Place a weigh boat on the scale. Tare the instrument so it calibrates to zero with the added weight of the boat.
4. Weigh the Alka-Seltzer® tablets and record in your notebook.
5. Alka-Seltzer® is supposed to be dissolved in 4 oz. (118.3 mL) of water according to the manufacturer's directions. Using deionized water, measure out this volume of water with a graduated cylinder and add it to the beaker.
6. Weigh the beaker plus the added water and record it in your notebook. This weight plus the weight of the Alka-Seltzer® tablets is your initial weight.
7. Drop both tablets into the beaker.
8. For the first five minutes, take a weight every 60 seconds. After five minutes have passed, measure the weight every five minutes until an hour has elapsed. Tap the bubbles off of the sides of the beaker as they form.
9. Dispose of the solution down the sink.

PART II

10. Fill the beaker back up with the same amount of deionized water and weigh the water and the beaker.

11. On a weigh boat, measure out 2.0 g citric acid and 3.832 g sodium bicarbonate.
12. Drop the powder into the beaker and record weights at the same time intervals as Part I.
13. Dispose of the solution down the sink and clean up the lab area.

QUESTIONS

1. Fill in the tables:

Tablet	**Weight**	**Time**
Initial:		0 m
		1 m
		2 m
		3 m
		4 m
		5 m
		10 m
		15 m
		20 m
		25 m
		30 m
		35 m
		40 m
		45 m
		50 m
		55 m
Final:		60 m

Raw	**Weight**	**Time**
Initial:		0 m
		1 m
		2 m
		3 m
		4 m
		5 m
		10 m
		15 m
		20 m
		25 m
		30 m
		35 m
		40 m
		45 m
		50 m
		55 m
Final:		60 m

1. You should notice that the initial weights of the two solutions are different.
   a. What may cause this?
   b. To fix this, take the difference between the two sets, find the difference between the two initial points. This difference will need to be subtracted from the solution with the higher weights. Find the new weights and record them in the table below.

Adjusted	**Weight**	**Time**
Initial:		0 m
		1 m
		2 m
		3 m
		4 m
		5 m
		10 m
		15 m
		20 m
		25 m
		30 m
		35 m
		40 m
		45 m
		50 m
		55 m
Final:		60 m

c. Please graph the revised data set along with the other set that was not changed.

2. Determine the experimental amount of CO_2 generated and released to the atmosphere by subtracting the initial weight from the final weight.

3. Balance the reaction given in the beginning of the laboratory.

4. According to the manufacturer's website, each tablet contains 1000 mg of citric acid and 1916 mg of sodium bicarbonate. Determine the moles of each reactant.

5. Determine which reactant is the limiting reactant. What is the percent excess? Why do you think there is extra added?

6. Using the effervescence reaction given in the beginning of the lab, determine the moles produced of CO_2 gas.

7. How many milligrams of CO_2 were made in both reactions?

8. What is the theoretical final weight of each solution? Use the weight of the beaker and water measured in the lab.

9. Determine your percent error at each point with the given equation:

$$\%_{Error} = \left(\frac{\left(M_{theoretically\ lost} - \left(M_{experimental}^{inital} - M_{experimental}^{point\ in\ time} \right) \right)}{M_{theoretically\ lost}} \right) x\ 100 \qquad (3)$$

10. What were some sources of error in this lab?

11. Was there if a difference in the way the pure components dissolved versus the tablets? Why do you think they behaved the same/differently? It is known that Alka-Seltzer tablets use a milling process to reduce the size of their powder.[1] Do you think that the use of milling the powders when forming the tablets adds into the difference in behavior?

12. What is a different way that this experiment can be designed so that the gas released could be directly measured?

13. In reaction engineering, it is important to understand the mathematics behind chemical reactions. One of the important concepts is the reaction rate of a chemical reaction. This reaction rate determines how many moles of a reactant are being converted to a product over a period of time. The rate of reaction is commonly symbolized by r_A. The basic equation of the r_A is:

$$r_A = k\,[C_A]^x \qquad (4)$$

Where k is the rate constant and CA is the concentration of the limiting reactant in a chemical reaction. This is also known as a rate law. A rate law can be linear or nonlinear in regards to the concentration. In most cases, rate laws are zero-order (x=0), first-order (x=1), or second-order

(x=2). Now, you will determine the rate constant and order of the rate law for a sub-reaction that takes place in the effervescent reaction.

This sub-reaction is the formation of bicarbonate to carbon dioxide:

$$HCO_3^- + H_3O^+ \rightarrow CO_2 + 2H_2O \qquad (5)$$

In this reaction, the limiting reactant is the bicarbonate ion. To determine the concentration of the bicarbonate ion (C_{HCO_3}), we can use the following equation.

$$C_{HCO_3} = \frac{initial\ mol\ HCO_3^- - mol\ CO_2}{Volume_{Water}} \qquad (6)$$

We can assume that all the sodium bicarbonate breaks down to sodium ions and bicarbonate ions, giving us the initial moles of bicarbonate ions.

a. Using the data you collected, determine the moles of CO_2 generated at each time point, and use that to determine the concentration of bicarbonate ions at each time point. Once this is done, make graphs of the following: C_{HCO_3} vs. time, ln(C_{HCO_3}) vs. time, and 1/C_{HCO_3} vs. time. Determine which one is a linear relationship, and print out that graph. Do this for both sets of data.
b. The rate constant can be found by determining the slope of the linear relationship. Find the k for both sets of data.
c. Now, determine the order of both sets of data. As a reminder; a zero-order reaction will be linear for concentration vs. time; a first-order reaction will be linear for ln(concentration vs. time; a second-order reaction will be linear for 1/concentration vs. time.
d. Do the orders match for the tablet and raw ingredients? What about the k values?

REFERENCES

1. H. Phykitt, "Analgesic Composition and Method of Making the Same". United States of America Patent 8,580,853, 13 June 2011.

A.6 Dextromethorphan Crystallization Lab

Dextromethorphan Crystallization Laboratory
Developed by: Alex Jannini, David Krause, Heather Malino and Matthew Van der Wielen, Rowan University, Department of Chemical Engineering
Edited by: C. Stewart Slater and Mariano J. Savelski, Rowan University, Department of Chemical Engineering
Date of Experiment:

OBJECTIVES

- Students will develop a solubility curve for dextromethorphan.
- Students will gain an understanding of the techniques of crystallization and how it is used in the pharmaceutical industry.
- Students will learn the fundamentals of energy balances and heat transfer.

INTRODUCTION

A crystal is defined as a solid material whose atoms, molecules, or ions are arranged in an ordered pattern in three dimensions. Crystallization is the process by which solid crystals precipitate out of a solution. After the precipitation occurs, there will be a solid phase and a liquid phase in the solution. Then, the solution will be filtered to separate the two phases. Sometimes the solid phase is the desirable phase while other times the liquid phase is desired. Crystallization is a commonly used method of separating solid-liquid solutions in industry. Crystallization has been utilized in many different processes for decades. For example, many commodity chemicals like xylene and inorganic salts such as sodium chloride are formed using crystallization[1].

In more recent years, crystallization is used in the pharmaceutical industry. The most common reason for using crystallization in the pharmaceutical industry is to obtain a high purity active pharmaceutical ingredient (API). In the case of vitamin C purification, crystals are formed in either an aqueous or alcohol based media and then filtered out of solution[2].

One of the tools used in designing crystallization processes is the solubility curve. A solubility curve can be used to determine the saturated concentration of a solution of solids in a liquid. An example solubility curve is shown on the next page. The solubility curve is usually based on the concentration of solid in the solution and the temperature of the solution. In most cases, solubility curves are made with a solute in a solvent. In this lab, you will be making a solubility curve for the salt form of dextromethorphan in water.

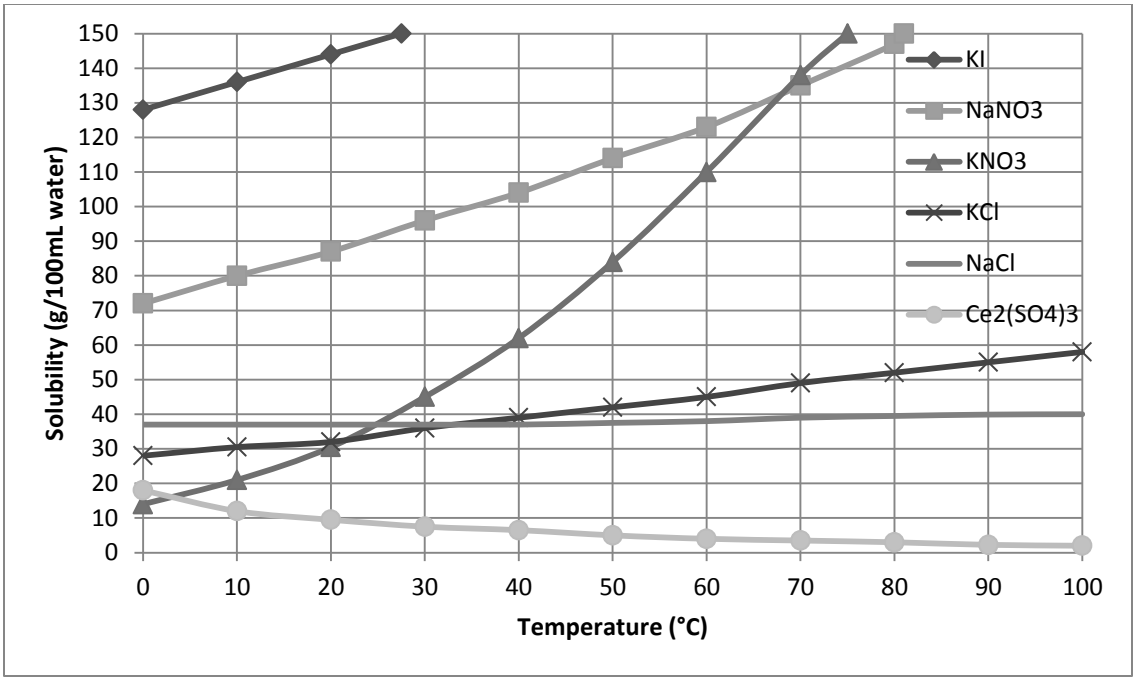


Figure 1. A sample solubility curve for several different salts. Adapted from the Halifax Regional School Board.[3]

Dextromethorphan (DXM) is the active pharmaceutical ingredient (API) in several cough syrups. Dextromethorphan is a strong antitussive agent.[4] It is often found as a monohydrated hydrobromated salt. This means that one molecule of HBr is attached to the dextromethorphan crystal. It belongs to the morphine group of alkaloids. A typical amount of dextromethorphan in one dose of cough medicine is approximately 15 mg.

SAFETY AND CONSIDERATIONS

Safety googles must be worn at all times in the lab. Gloves should also be worn during this experiment. When working with the powder, a dust mask should be worn. The chemical is of USP grade.

MATERIALS NEEDED

- Dextromethorphan HBr (one lab that contains 6 groups of students will need approximately 30 grams)
- Citric Acid, Anhydrous (one lab that contain 6 groups of students will need approximately 180 grams)
- Analytical scale (capable of reading 10^{-3} grams)
- Weigh boats
- 14 test tubes
- Test tube rack
- 1 large (approximately 800 mL or higher) beaker
- Heat/stir plate
- Stir bar
- 2 thermocouples with rod attachments
- Large graduated cylinder (1000 mL)
- 5mL micropipette
- Sharpie® or marking pencil
- Ring stand with test tube clamp

PROCEDURE

PART 1: DXM

For time limitations, divide the lab up so that half the team completes steps 1-2 while the other half of the group completes step 3-6.

1. Using the marking pencil or Sharpie®, number 7 test tubes and place them into a test tube rack.
2. Using the analytical scale, measure the dextromethorphan and prepare the test tubes as indicated below:

Test tube #	Milligrams (mg) of DXM
1	200
2	400
3	600
4	800
5	1000
6	1200
7	450-750

   Tube #7 is a choice. You may choose any value (other than 600 mg) to place in this vial. Make sure to record this number.
3. Note the maximum volume of the large beaker. You will need to fill the beaker ¾ of the way full. Use the large graduated cylinder in order to precisely measure the amount of water you add to the beaker. Record the volume of water that you added to the beaker.
4. The beaker that you filled with water will be used as a hot water bath. Place the water bath on the hot/stir plate, and place a stir bar in the

beaker. Place the heat control setting somewhere in the middle, and set the stir setting to the lowest possible setting.

5. Place one of the thermocouple rods in the water. The water bath needs to stay within 80 to 90 °C, which is the temperature suitable for dissolving all the DXM. This will require supervision and maintenance.
6. Now, setup the test tube clamp on the ring stand so that the clamp is just above the beaker.
7. Once you have measured out the masses of DXM necessary, use the micropipette and place 5 mL of water in each of the test tubes.
8. Now, secure test tube #1 in the tube clamp, and place the second thermocouple rod in the tube. Lower the clamp so that the test tube is as submerged as possible in the water bath.
9. Stir the test tube with the rod of the thermocouple. Keep stirring the solution until you see the DXM completely dissolve in the water. Loosen the clamp and remove the tube. Use a test tube holder if the tube is too hot.
10. Now hold the thermocouple in the solution. You may also need to wipe off the tube if there is excess condensation on the tube. Hold the test tube up to the light and examine the solution for the first signs of crystallization. Record the temperature immediately as crystallization begins in the data table.
11. Repeat steps 8 through 10 for the other test tubes. Record all data. You may use the table below, but you should also record all results in your lab notebook.

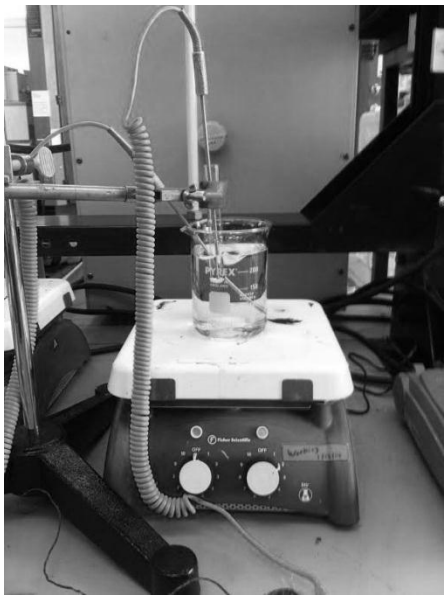


Figure 2. Proper setup of a test tube in the hot water bath.

Figure 3. The DXM and water solution once completely dissolved.

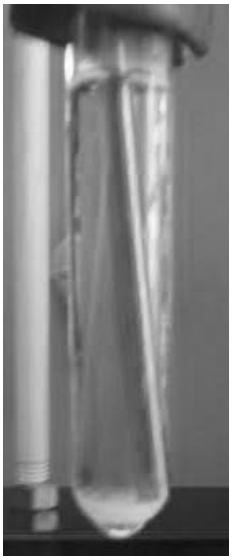


Figure 4. The DXM and water solution once crystallization has begun. Notice the white substance at the bottom of the tube.

RESULTS

You may use the table below to record your data. However, it is encouraged to also write your results down in your lab notebook.

Test Tube Number	Temperature of Recrystallization (°C)
1	
2	
3	
4	
5	
6	
7	

DATA ANALYSIS

For this section, you will be using Microsoft Excel. Once you have completed the lab and collected all the data, open up a new Excel file and place the data in a spreadsheet. Now, the concentration that we have right now is in mg/5mL. Change this to g/L. Remember that there are 1000 mg per g and 1000 mL per L.

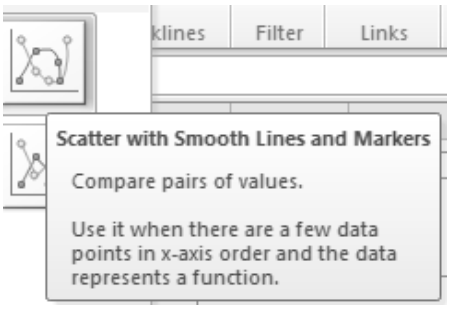


Figure 5. A screenshot of the graph you will need in Excel.

Once this is done, we need to create a solubility curve. To do this, we will be using the chart wizard. In excel, go to the insert tab and chose to insert a scatter graph. Look specifically for the "scatter with smooth lines and markers" option. Create a scatterplot that has temperature on the X-axis and concentration on the Y-axis for the first six points of the data collected. In addition, please use the following data points when creating your graph of the DXM data:

Table 1. Additional points for the solubility curve for DXM. Obtained from DrugBank and INCHEM.[5,6]

Concentration (g/L)	Temperature (°C)
0.00851	0
0.0747	20
15.0	25

Once this is done, change the chart layout so that you have titles for the x- and y-axis. This should be the first option in the chart layout section. Once you have titles for the axes, label them accordingly. Label the chart with your group number or the last names of your group members, and then delete the "Series 1" label.

Once you have a chart, you will need to edit the x-axis. To do this, click on the values on the x-axis. You should see these values boxed. Once done, right click, and click on the "Format Axis" option. You should now see the Axis Option menu. In this menu, look for "Major tick mark type." In the dropdown menu, select the inside option. Once this is done, print out your graph. Do the same thing for the citric acid data. Make sure to print out that graph as well. You will need these later.

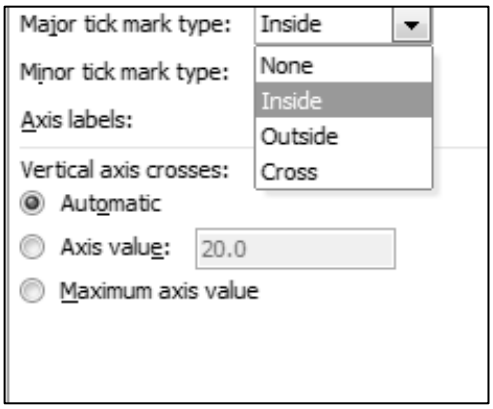


Figure 6. A screenshot of the "Major tick mark" option.

QUESTIONS

1. Now that we have a graph, we can check the accuracy of it. We will do this by using the random point that you collected during the procedure.
    a. We will check the accuracy of the graph through a process known as interpolation. In interpolation, you determine a new data point that lies within data that has already been collected. To do this, you will need a ruler. First, determine the concentration of your unknown in grams/L. Once you know that value, locate it on your chart. If your concentration lies within two tick marks, you will need to use the ruler. First, determine the length between the two tick marks. Next, solve the following equation:

$$\frac{(higher\ tick\ mark - lower\ tick\ mark)}{length\ between\ tick\ marks} = \frac{(random\ point\ - lower\ tick\ mark)}{length\ between} \quad (1)$$

Once you have found the length between the concentration and the lower tick, mark that on your graph. Once that is done, draw a straight line from this point to the line generated. Then, draw a straight line down to the x-axis. Now, you will have to determine the temperature this corresponds to. Here, you will have to do the same thing that you did previously. Determine the length between the tick marks on the x-axis, and then determine the length between the lower tick mark and the line you drew down. Using the equation below, determine the temperature:

$$\frac{(higher\ tick - lower\ tick)}{length\ between\ ticks} = \frac{(temperture - lower\ tick)}{length\ between\ line\ and\ tick} \qquad (2)$$

b. Now that we have the temperature obtained from interpolation, we will determine the percent error between the temperature obtained through part a. and the temperature obtained experimentally. Use the following equation:

$$\%\ Error = \frac{|value\ obtained - value\ observed|}{value\ observed} * 100\% \qquad (3)$$

What does this tell you about the possible shape of the solubility curve?

2. Energy is required to heat the water bath to 90°C. The most basic equation that models the energy required to heat the water from room temperature to 90°C is:

$$Q = mC_p\Delta T \qquad (4)$$

Where "Q" is the energy required in J/g, "m" is the mass of water and "Cp" is the specific heat capacity of water.

a. Using the specific heat as 4.18 J/(g * °C) and the density of water as 1.00 g/mL, determine the amount of energy required to heat the water to 90°C. You may assume that the water was at room temperature (20 °C) before heating.
b. If a tank in an industrial process needs to heat 200 gallons of water to 90°C, how much energy would be needed?

3. Whenever there is a flow of heat from one source to another, there is an exchange of energy. This flow of energy is studied in the field of heat transfer. We will now discuss one of the basic conventions of heat

transfer; conduction. Conduction can be defined as the transfer of energy from more energetic particles to less energetic particles due to their interactions.[7] One important term in conduction is the thermal diffusivity of a substance. The thermal diffusivity (represented from now on by the variable, α) measures the ability of a material to conduct thermal energy in relation to its ability to store thermal energy.[7] To find α, we can use the following equation:

$$\alpha = \frac{k}{\rho C_p} \qquad (5)$$

With:

$$k = thermal\ conductivity\ \left[\frac{W}{m * K}\right]$$

$$\rho = density\ \left[\frac{kg}{m^3}\right]$$

$$C_p = specific\ heat\ at\ constant\ pressure\ \left[\frac{J}{kg * K}\right]$$

a. The term α is considered a dimensionless constant. With the units provided, prove that this is so.
b. Determine the thermal diffusivity of water at 25 °C and aluminum at 25 °C. Which is higher? What does this tell you about the two substances in regards to the conduction and storage of thermal energy? To do this, you will need to use the following table:

Table 2. Thermophysical properties for water and aluminum at varying temperatures. Adapted from Incropera et al and Thermal Fluids Central.[7,8]

Temperature (K)	Water			Aluminum		
	$k\ \left[\frac{W}{m * K}\right]$	$\rho\ \left[\frac{kg}{m^3}\right]$	$C_p\ \left[\frac{kJ}{kg * K}\right]$	$k\ \left[\frac{W}{m * K}\right]$	$\rho\ \left[\frac{kg}{m^3}\right]$	$C_p\ \left[\frac{kJ}{kg * K}\right]$
290	0.598	0.999	4.184	235	2708	0.868
300	0.613	0.997	4.179	237	2702	0.903

Obviously, you will need to use interpolation in order to obtain the correct data points. Use a similar method as used in Question 1.

c. Now, determine the thermal diffusivity for aluminum at 200 and 400 K. Use the following data below. What does this tell you about the thermal diffusivity of aluminum in regards to temperature? Do you think this is true for all temperature ranges? Try with 400 and 800. Does this provide more insight into the thermal diffusivity of aluminum with respect to temperature?

Table 3. Thermophysical data for aluminum at varying temperatures. Adapted from Incropera et al and Thermal Fluids Central.[7,8]

Temperature (K)	$\rho \left[\frac{kg}{m^3}\right]$	$\frac{k}{C_p}\left[\frac{W/_{m*K}}{J/_{kg*K}}\right]$
200	2719	237
400	2681	240
800	2591	218

4. In simple heat transfer, we can model the flow of heat using one-dimensional, steady-state conduction. What this means is that we model the flow of energy as though it were in one direction at an unvarying rate. This allows us to model the flow of heat over a certain distance. We will do this for the case of the test tubes we used in this experiment.

   First, we must show how to properly model this flow of heat. Picture the test tubes used in this. We will say that in the direct middle of the water will be the starting point. Then, we will say that top of the water level (where water meets air) is the ending point. So with these start and end points, we will be modeling the flow of heat from the middle of the test tube water level to the top of the test tube water level.

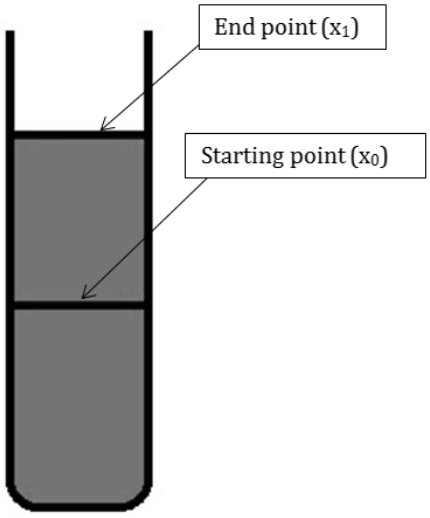


Figure 7. A representation of the one-dimensional, steady-state conduction model for the test tube.

In order to model this, we need to make two assumptions: 1) that the heat flows at a steady-state (does not fluctuate over time) and 2) that all the sides except for the end point are perfectly insulated. (NOTE: The other assumption that is made in order to use this model is that the surface temperature of the water is the same as the air temperature. If this assumption is not made, the flow of heat from the surface via natural convection, or the natural flow of air on the surface of the water, needs to be taken into account. This makes the model much more difficult; and as such, is eliminated from the model.)
With these assumptions made, we can use the following equation to model the flow of heat from the starting point to the end point. To do this, we can use the following equation to solve for the heat flow[7]:

$$\frac{q_x \Delta x}{A} = -k\,\Delta T \qquad (6)$$

With:

$$q_x = heat\ transfer\ rate\ in\ the\ x-direction\ [W]$$
$$\Delta x = length\ from\ x_0\ to\ x_1 = x_1 - x_0\ [m]$$
$$A = surface\ area\ of\ the\ heat\ transfer\ [m^2]$$
$$k = thermal\ conductivity\ \left[\frac{W}{m*K}\right]$$
$$\Delta T = difference\ in\ temperatures\ from\ end\ point\ to\ start\ point = T_1 - T_0\ [K]$$

Now, we will also say that half the volume of the water added to the test tube is in this specific space used for the model (2.5 mL). Assuming that the water is a perfect cylinder, and that the test tube has an inner diameter of 0.55 in, you find all the information necessary to model this flow of heat.

a. First, we will model this as though it were pure water. Take the temperature of recrystallization you found for test tube #1 in your DXM experiments, and state that this is T_o. T_1 will be the temperature of the air (20 °C). Determine the heat transfer rate if the thermal conductivity of water is at a weighted average of 0.58 W/m*K.
b. Now, we are going to find the thermal conductivity (k) for a mixture of the salts used in this experiment. To do this, we will use a thermal conductivity approximation for salt solutions. This is shown below[9]:

$$k = 0.29411 - 0.174 * C + 0.0008791 * T - 2 * 10^{-6} * T^2$$

Where:

$$C = concentration\ of\ salt\ (wt.fraction)$$
$$T = temperature\ of\ the\ system\ (°F)$$

$$k = \frac{BTU}{hrft°F} = {}^{W}/_{mK} \Big/ 1.5 \; {}^{BTU}/_{hrft°F}$$

Make sure to use these units when using the calculation. Again, use data obtained from test tube #1 for this. For the temperature, determine the average between the air and the temperature of crystallization. Determine the k value for DXM using this equation, then find q_x using the equation from part a.

c. Determine the percent difference between parts a and b. Is there a considerable difference? Which do you think is more accurate? Keep in mind that the thermal conductivity approximation you were given was developed using sea salt.
d. In order to calculate this, we made two assumptions about the heat flow. Can these assumptions be made for our experiment? Why or why not?

5. Citric acid is often used as a flavoring agent in pharmaceuticals. The saturation point for citric acid in water is provided. This is another way of showing the solubility of a substance, but with different units. Instead of concentration in mass solute per volume solution, we give the concentration in mass solute per mass solution.

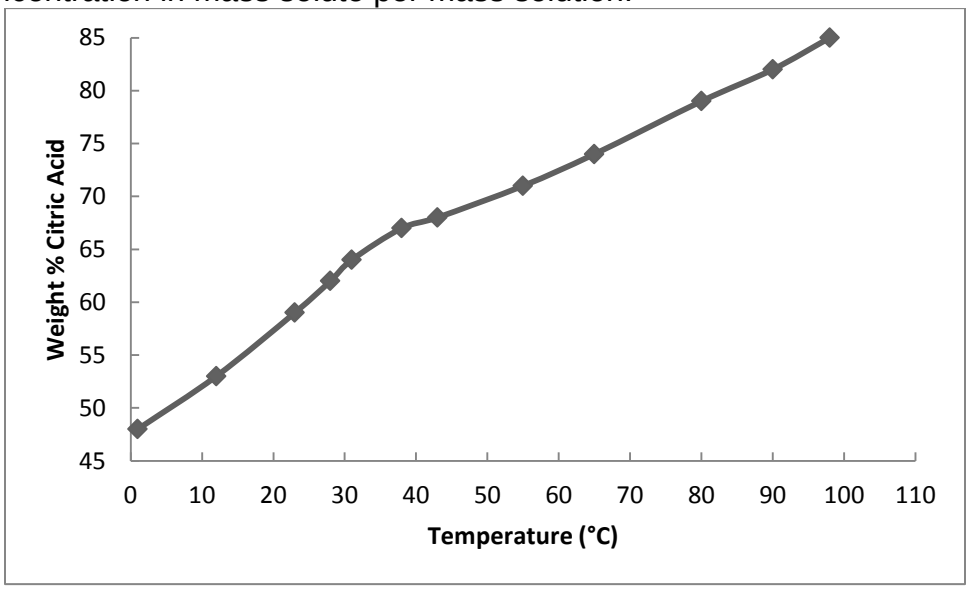


Figure 8. The saturated weight percent of citric acid in water with respect to temperature. Adapted from Dalman.[10]

a. Now, we have discussed solubility curves in great detail. In the introduction of this experiment, we discussed how a solubility curve tells you the point where a solution of solid crystals will completely dissolve into a solvent. Using the graph above, describe what would happen if you picked a point above the solubility curve

(example, 60 wt% and 10 °C) and what would happen if you picked below the solubility curve (example, 50 wt% and 60°C).

b. During the production of the new pharmaceutical tablet, 75 kg of citric acid is placed in a mixer with 100 kg water at 40 °C. The operators on duty notice that not all of the powder is dissolving into the water. Using the solubility curve, explain why this occurs. If we needed to fully dissolve the citric acid in the water, what would you recommend doing?

c. In another operation that uses citric acid, 78 pounds of citric acid is dissolved in 60 pounds of water and is heated to 80 °C. The solution needs to be cooled so that 18 pounds of crystals can be collected. To what temperature should this solution be cooled to?

6. In the previous question, you were given a scenario in which a solution of crystals and solvent were cooled past the solubility point. Indeed, this is what is commonly done in industry in order to separate crystals from liquids. Usually, the solution is sent to a cooler, a type of machine that drops the temperature of the solution. This allows crystals and saturated solution to form. This mixture is sent to a filter, which physically separates the liquid from the solid. Then, the solid (known as "cake") is sent to a dryer, so that more liquid can be removed from the crystals. An example of this can be seen below:

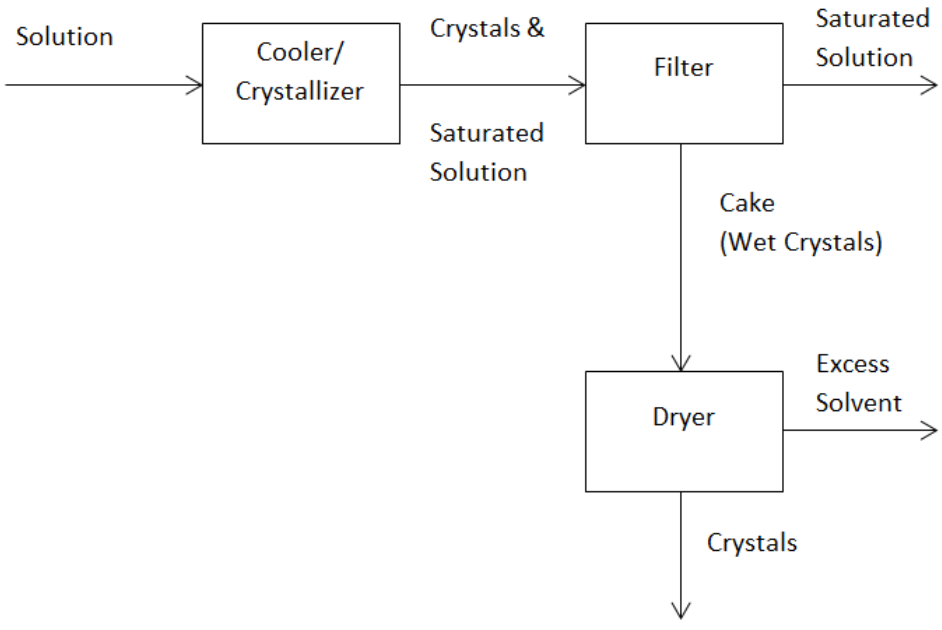


Figure 9. A simplified version of the setup used to separate crystals from solution. Adapted from Felder and Rousseau.[11]

a. 100 kg of a solution with a concentration of 150 grams of DXM per liter of water is sent through this process. The temperature of the solution is initially 75 °C, and is cooled down to 45 °C. Using your DXM data, determine the mass of crystals that would precipitate out. Assume that the solution has the same density as water.
b. Now, say this cooled solution is sent to a filter. The filter is considered 100% effective at removing the crystals. If the composition of the cake is 80% crystal by mass, calculate the mass of saturated solution that has been separated with the crystals.
c. If the dryer only allows the water to evaporate, what is the overall mass of crystals that was collected? If compared to the original amount of crystals in solution, what is the overall yield of this process?

REFERENCES

1. C. Wibowo, "Solid-Liquid Equilibruim: The Foundation of Crystallization Process Design," Chemical Engineering Progress, pp. 38-45, March 2014.
2. I. Le Fur, J.-P. Richard and G. Wolff, "Process for preparing ascorbic acid". United States of America Patent 5391770, 21 February 1995.
3. Halifax Regional School Board. “Solubility Curves (ANSWERS).” Halifax Regional School Board Staff. Accessed 19 May 2014. Available: http://hrsbstaff.ednet.ns.ca/benoitn/chem12/solutions/exercises/ans_solubility_curves.htm
4. G. Y. S. K. Swamy, K. Ravikumar and A. Bhujanga Rao, "Dextromethorphan, an antitussive agent." Acta Crystallographica Online, Sanathnagar, India, 2003.
5. J. Magarey. International Program on Chemical Safety. “Dextromethorphan.” INCHEM. Available: http://www.inchem.org/documents/pims/pharm/pim179.htm. August 1997. Accessed: 21 May 2014.
6. The Metabolomics Innovation Center. “Dextromethorphan.” Available: http://www.drugbank.ca/drugs/DB00514. 22 November 2014. Accessed: 21 May 2014.
7. F.P. Incropera, D.P. Dewitt, T.L. Bergman, and A.S. Lavine. “Introduction to Heat Transfer.” 5th ed. John Wiley and Sons. Hoboken. 2007.
8. Thermal-Fluids Central. “Thermophysical Properties: Aluminum and Aluminum Alloy.” Available: https://www.thermalfluidscentral.org/encyclopedia/index.php/Thermophysical_Properties:_Aluminum_and_Aluminum_Alloy. 14 July 2010. Accessed: 22 May 2014.
9. J.V. Wilson. Approximations for Physical Properties of Sea Salt Solutions. Office of Saline Water. March 1973.

10. L.H. Dalman, “The Solubility of Citric and Tartaric Acids in Water.” Journal of the American Chemical Society, vol. 59, no. 12, pp. 2547-2549. December 1937.
11. R.M. Felder and R.W. Rousseau. *Elementary Principles of Chemical Processes*. 2nd Edition. New York. John Wiley and Sons. 1986.

A.7 Creation of Dissolvable Strips Lab

Creation of Dissolvable Strips
Developed by: Alex Jannini, David Krause, Heather Malino, and Matthew van der Wielen, Rowan University, Department of Chemical Engineering
Edited by: C. Stewart Slater and Mariano J. Savelski, Rowan University, Department of Chemical Engineering
Date of Experiment:

OBJECTIVES

- Students will learn about the commonly used processes for industrial thin film production
- Students will learn and use basic quality control testing methods
- Students will gain insight into energy requirements for drying thin films

INTRODUCTION

Dissolvable strips have become an important mechanism for drug delivery. Orginially created as candy, dissolvable strips fill a niche role, providing rapid-release drug delivery. Due to the drug being dissolved directly into the blood stream through the tounge, it bypasses the metabolism of the body, which can cause drugs to lose some of their bioavaliability (the amount of drug that will circulate through the body). Other advantages of using thin films include not having to take the drug with water, no risk of choking, and reduced dose size because the drug is more bioavailable sublingually (tissues under the tounge).[1]

The ingredients of a dissolvable strip will vary, depending on the desired drug release rate, the sensitivity of the drug, and several other factors. However, all strips will contain the following ingredients; an active pharmaceutical ingredient (API), polymers, placticzers, and sweetners/flavoring.[2] A polymer is often determined based on its reactions with water. The more hydrophilic (attraction to water) the polymer is, the faster the film will dissolve and release the API. The plasticzer helps improve flexibilty and prevent brittleness in the strip, while the sweetners and flavorings help to improve palatability and increases patient compliance.

On an industrial level, dissolvable strips are primarily made with either a solvent-casting film system or a film extrustion system. Solvent-casting systems are the most common process, as they do not require heat, which could damage an API, and are relatively inexpensive to construct. A typical setup for a solvent-casting system can be seen on the next page.[3] The drawbacks to solvent-casting techniques can include variances in film thickness and non-uniform drying.

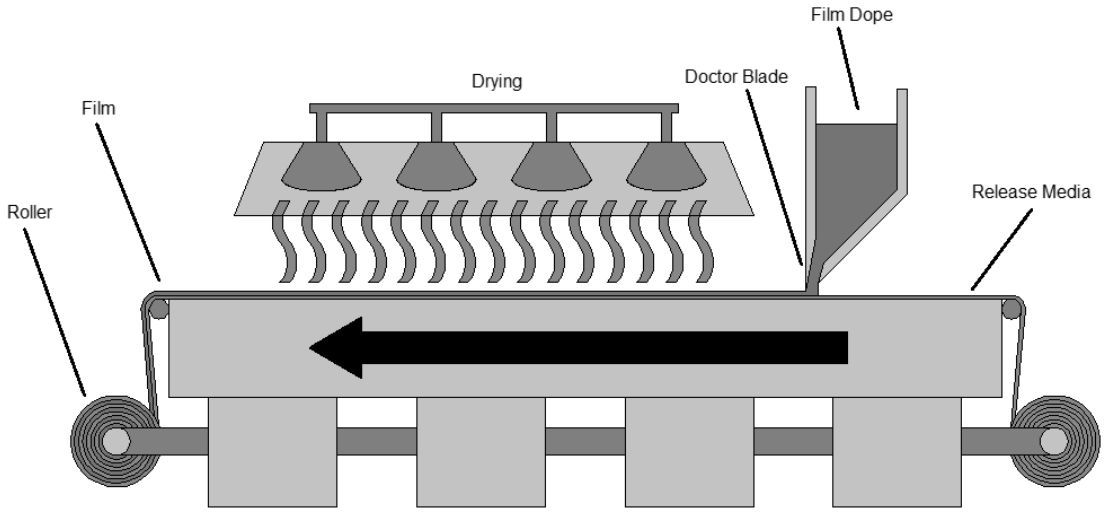


Figure 1. A diagram of a solvent-casting system as adapted from Particle Sciences.[3]

Alternatively, hot melt extrusion is also used to create strips. The advantages to extrusion are a simpler design and the lack of water needed to run the process, but the materials used in the dissolvable strip must be heat resistant and be able to flow as a dry powder. A sample of both of these systems can be seen in Figures 1 and 2.

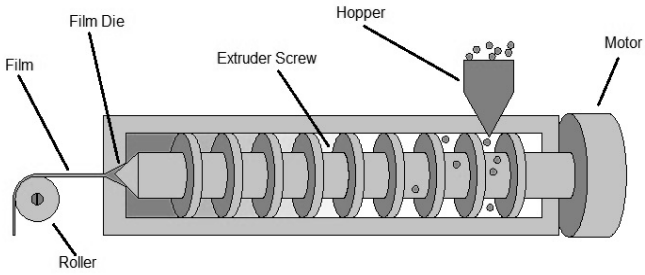


Figure 2. Screw-forced extrusion of dry feedstock as adapted from Particle Sciences.[3]

In this lab, you will be creating your own dissolvable strips. This procedure is based on the solvent casting method described above. Through this lab, you will have a better understanding of the way that dissolvable strips are created, and some of the engineering principles behind the process.

SAFETY CONSIDERATIONS

Make sure to wear safety goggles at all time. Laboratory safety gloves should also be worn.

MATERIALS NEEDED

- 1000 mL beaker
- Hot plate and mixer
- Magnetic stir bar
- CMC (carboxymethylcellulose)
- Pectin
- Xanthan gum
- Sodium lauryl sulfate
- Citric acid (anhydrous)
- Glycerol
- Sucrose
- Blue Food Dye (Blue #40)
- 3 drops of Peppermint oil
- Dropper
- Deionized water
- 3 mL syringe
- 2 Buchner (vacuum) flasks
- Funnel
- Fine mesh screen
- Vacuum tubing
- Vacuum source
- Spatula
- Petri Dish
- Teflon-lined sheet/plate apparatus with thickness guiding bars
- Analytical scale
- Tubing and stopper

PROCEDURE

CMC Method

Table 1: CMC preparation

Species	Weight (g)	Weight %
CMC	7.7	1.6
Glycerol	2.6	0.6
Peppermint oil	0.5	0.1
Citric acid	1.0	0.2
Sodium lauryl sulfate	1.0	0.2
Sucrose	1.5	0.3
Water	500	97
TOTAL	514.3	100

1. Weigh out the appropriate amounts of all powdered ingredients.
2. Add the required amount of deionized water to the large beaker. Reminder: density of water = 1 g/mL.
3. Place the beaker on the hot plate and add the stir bar. Set the heat to the lowest setting and set the stir to a low-medium rate (4 out of 10).
4. Add the CMC to the water at a very slow rate, dusting the powder over the surface of the water and waiting for it to be absorbed. Once most of it is mixed in, the solution will become very viscous and trap air bubbles.

Once the viscosity increases, you will need to increase the stirring intensity. Do this slowly.

5. Add the glycerol to the solution with the 3 mL syringe. You will need approximately 2 mL of glycerol to correspond to the weight shown in Table 1.
6. Add the remaining components to the solution similarly to how the CMC was added. At this point, the solution should be extremely viscous and appear opaque white.
7. Add three drops of peppermint oil to the solution.
8. Add one drop of blue food dye. The mixture should now be a light blue color.
9. Transfer the solution into the vacuum flask with the mesh and funnel, pouring through the mesh, to catch any large clumps of solidified product and the stir bar. Discard the solidified product.
10. We will now make a vacuum filtration system. The purpose of this is to de-aerate the mixture. This minimizes the bubbles in the solution. Hook the vacuum flask up to a tube and place a rubber stopper in the top of the flask. Then, connect the tube to the other vacuum flask. Next, place a stopper with an attachment into the top of the other flask and connect this to the vacuum source. See Figure 4 for the appropriate setup. This second beaker will stop any foam from entering the vacuum.
11. Turn on the vacuum and wait approximately 30 minutes for the gas to leave the solution. The solution should slowly turn clear and may get frothy. The froth will subside.
12. Turn off the vacuum and disconnect the tubing from the vacuum source. Then, remove the beaker with solution from the setup.
13. Carefully pour some of the solution into a 500 mL graduated cylinder. This will make it easier to transfer the solution to the Teflon sheet or petri dish.

Figure 3. Funnel and screen setup for pouring into flask.

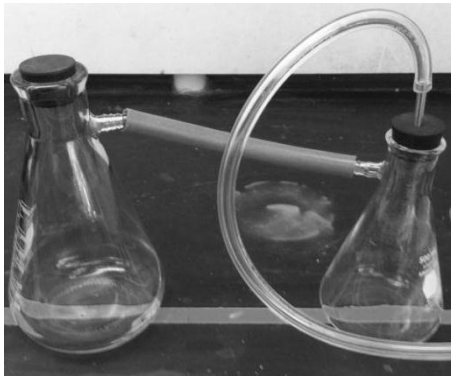


Figure 4: The setup that should be used when using the vacuum.

14. Take a petri dish and weigh it. Record this weight.
15. Prepare a sample of the film in the petri dish by adding 10 mL to the dish. Do this by using a small graduated cylinder (10 to 25 mL). If any bubbles remain on top of the solution, be sure to draw solution from under the surface.
16. Weigh the wet petri dish and record this weight.
17. Pour out 400 mL of the remaining solution onto the sheet using the 500 mL graduated cylinder.
18. Allow 1-2 days for the samples to dry. The batch should appear much thinner and have a glossy finish on its surface. Take a final weight of the petri dish sample and record its weight.

QUALITY ANALYSIS

How uniform is your batch? In industry, this is done by sampling a batch and testing it in several ways to ensure that specifications are met. Several samples are taken and their results are averaged. Quality analysis is critical to the success of a company, so that deviations can be caught and fixed before they become a costly problem.

Figure 5. Strips being cut

Sample Creation

1. Carefully peel the strip out of the mold with a spatula.
2. Take a ruler and measure 4 samples with dimensions of 1” x 1.5”. Try to find room for samples from each of the four corners so that the samples are representative of the entire batch.
3. Using a scalpel carefully cut out the four samples.

Figure 6. How to use the calipers to determine thickness

Thickness Measurements

1. Using a caliper, take each sample and place it in the jaws of the caliper.
2. Adjust the jaws so that the sample fits snugly between them. Do not over tighten the caliper so that the sample tears. The sample should

be pinched, but also be able to slide out from between the jaws when a small force is applied to it.

3. Record your results and repeat for all samples.

Folding endurance

1. Take a sample and fold it in half along the 1.5" face (At the 0.75" mark). Pinch the folding point with your fingers so that a distinct crease is formed.
2. Unfold the strip and flip it over. Carefully fold the strip in the opposite direction, along the same crease and pinch. This has now been 2 folds.
3. Repeat steps 1 and 2, counting the number of folds that you perform.
4. Record the final number of folds, and repeat for the rest of the samples.

Surface pH

1. Using one of the halves from each sample, use a pipette to drop a small quantity of DI water on the strip.
2. Place a broad-range litmus paper strip in the drop.
3. Compare the color of the strip to the package to determine the pH of the sample.
4. Record your results and repeat for the rest of the samples. Again, you only need to measure the pH from one half of each sample.

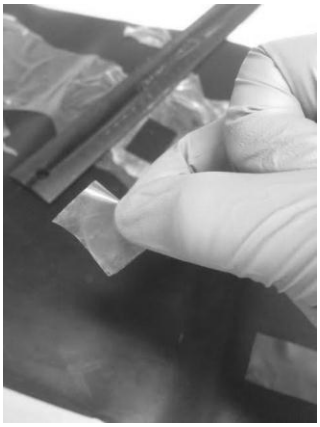


Figure 7. Ensure a good fold by pinching the strip

Analysis

1. Average the results from each test.
2. Find the range of results for all tests. Was there significant variance in the data you collected?
3. Do you think that the average pH of the samples would be dangerous to ingest? What about the highest/lowest pH sample?
4. The average number of folds it takes to break a Sheets® brand strip was found to be in the range of 15-20 folds. Does your average fall in this range? If not, why do you think it didn't?
5. What could be a dangerous consequence from a lot of variance in the thickness of each sample? Would you sell the strips you made to pharmacies?

Moisture Content Analysis

In this section, you will use the initial and final weights of the petri dish sample, as well as an introductory energy balance, to find the energy required to dry the sample and the amount of water remaining in the sample.

1. Find the change in mass of the sample. Assume that the mass that evaporated was 100% water.
2. Find the moisture content with the following equation:

$$\%_{moisture} = \left[1 - \left(\frac{m_1 - m_0}{m_0}\right)\right] * 100$$

Where,
m_1 = final weight of the sample
m_0 = initial weight of the sample

3. You will now calculate the amount of energy required to evaporate all of the water that was lost. This energy was transferred into the sample from its surroundings, so the balance of energy transferred appears as such:

$$Q = m_{vap} * L_{vap}^{H_2O}$$

Where,
Q = energy required to dry the sample
m_{vap} = mass of water vaporized, $(m_1 - m_0)$
$L_{vap}^{H_2O}$ = Latent heat of vaporization for water, 2260 kJ/kg
Make sure to watch your units!

4. Where do you think this energy came from?

QUESTIONS

1. For the following APIs, research the drug's therapeutic value and determine if a hydrophilic or hydrophobic polymer matrix would be best suited for drug delivery:
    a) Salbutamol
    b) Zolpidem tartrate
    c) Ondansetron
    d) Fentanyl citrate
2. Your boss approaches you with a new design project. The pharmaceutical company you work for has recently signed a contract with a client, requiring that you produce 800,000 dissolvable strips/year of a new API designed to treat the common cold. The API, referred to as DK-12, is potent in very small doses, but degrades rapidly when it hits stomach acid. Therefore, a dissolvable strip is the perfect method for introducing the drug into the body. The film must be fast-dissolving.
    a) Before any equipment can be decided upon, you must create the formulation. The required ingredients are:

- DK-12 (10% w/w)
- Water soluble polymer (40-50% w/w)
- Plasticizers (0-20% w/w)
- Sweetening agent (3-6% w/w)
- Saliva stimulating agent (2-6% w/w)
- Colors and flavors (1-10% w/w)

Find a suitable chemical for each of these components and compile a list for your boss.

b) Now that you've selected the ingredients for the strip film, you have to select whether you are going to use a hot-melt extruder or a solvent casting system. The material dissolves easily in water and polar solvents, and is not friable (does not degrade from heat). It must be noted that since DK-12 is new, it is very expensive, and therefore it is important to minimize wasted API. Explain your reasoning.

REFERENCES

1. K. Mandeep, A. C. Rana and S. Nimrata, "Fast Dissolving Films: An Innovative Drug Delivery System," *International Journal of Pharmaceutical Research & Allied Sciences,* vol. 2, no. 1, pp. 14-24, 2013.
2. T. Kalra, M. Madhra, K. Gandhi, A. Dahiya and Khushboo, "Fast dissolving film: A review," *International Journal of Research in Pharmaceutical Sciences,* vol. 3, no. 4, pp. 542-551, 2012.
3. Particle Sciences, "Dissolving Films," *Particle Sciences,* vol. 3, 2010.

Appendix B

Instructor's Versions of Laboratory Experiments

B.1 Tablet Statistical Analysis Lab

Tablet Statistical Analysis Lab – Instructor's Version
Developed by: Alex Jannini, David Krause, Heather Malino and Kevin Sweeney, Rowan University, Department of Chemical Engineering
Edited by: C. Stewart Slater and Mariano Savelski, Rowan University, Department of Chemical Engineering
Date of Experiment:

OBJECTIVES

- Students will perform a basic statistical analysis applied to an over-the-counter drug
- Students will learn about pharmaceutical engineering, including key terms and concepts

INTRODUCTION

In the pharmaceutical industry, drugs are manufactured, produced, and marketed for therapeutic use. The industry has been one of the highest earning industries of the last decade, with 791 billion dollars in worldwide sales in 2010. The majority of these sales were in North American companies, totaling 335 billion dollars[1].

A pharmaceutical product is not just one specific chemical, but many chemicals combined together to make a final product. Tablets, which the students will be working with in this lab, are composed of a few chemicals mixed together and then compressed. The therapeutic ingredient is known as the active pharmaceutical ingredient (API). The API is what causes the desired effect of the drug. The rest of the ingredients that remain inert are known as the excipients.

Excipients can have different functions, which is why there are sub-categories of excipients found in pharmaceuticals. For example, a filler is a type of excipient used to make up the volume of a medicine so that it can be taken in the form of a pill. In some cases, excipients known as binders are used to act as glue and make sure the ingredients stick together. Lubricants and glidants are used in combination since they reduce wall friction and interparticle friction, respectively. This prevents the tablet from clumping and sticking to equipment. Excipients may also be flavors or colors, which will mask any unpleasant tastes that the other ingredients have and improve the appearance of the product.

In any engineering field, statistical analysis is an important tool. In the pharmaceutical industry, statistics can be used in various ways. For example, statisticians use statistics to create trials for experimental drugs. A chemical engineer might use statistics in order to figure out a new process that creates more product for less. In these cases, statistics play an important role in analyzing data in order to come to a conclusion.

In this lab, the students will be looking at two different over the counter medications that contain the API ibuprofen, a known pain reliever and fever reducer. The rest of the inactive ingredients in the tablets are binders, fillers, or any other kind of excipient. This lab will consist of a statistical analysis on the difference in mass between the ibuprofen tablets, and also the difference in the mass of a generic brand and the trademarked brand Advil®. An introduction to creating a flow diagram will also be incorporated into this experiment.

MATERIALS NEEDED

- Container of Advil® tablets (minimum of 10 tablets)
- Container of generic ibuprofen tablets (minimum of 10 tablets)
- Weigh boat
- Tweezers
- Bench scale (accurate up to 1/1,000 g).

SAFETY CONSIDERATIONS

Always wear laboratory safety glasses when working in the lab.

PROCEDURE

1. Make sure that the bench scale is turned on, and that the scale is set to measure weight in grams.
2. Take the Advil package and note where they list the active and inactive ingredients. Record all of the ingredients that are listed as non-active ingredients.

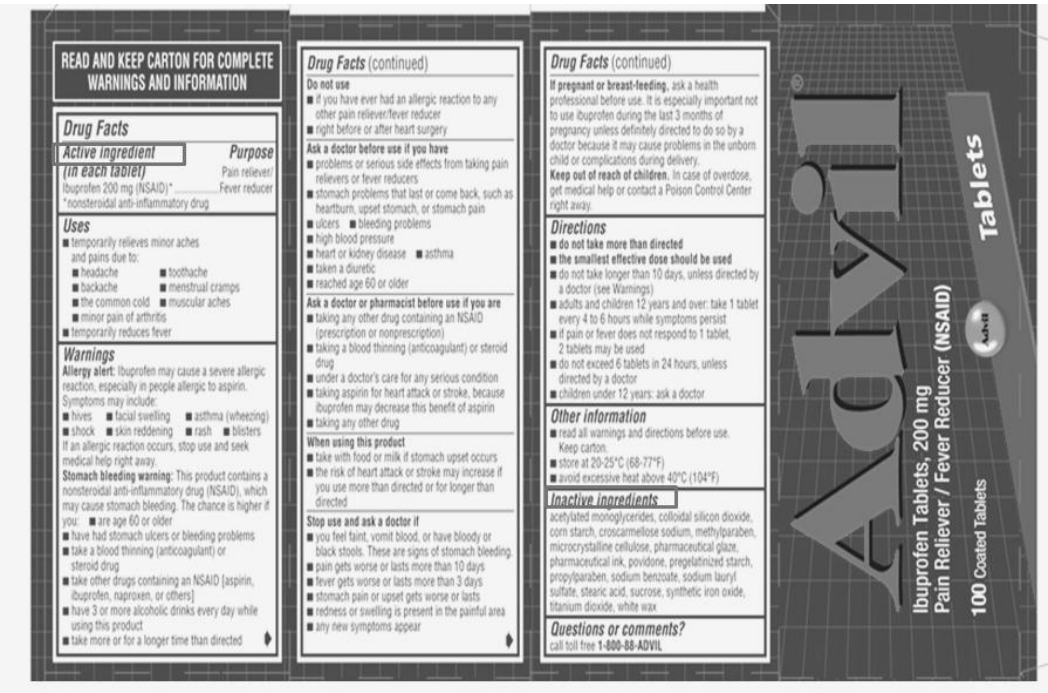


Figure 1. Where to find the active and inactive ingredients

3. Place the weigh boat on the bench scale. Record the weight, and then tare the instrument. The bench scale should now read 0 grams.
4. Open the box of Advil®, and with tweezers, place one tablet in the weigh boat. You may use the table provided below, but you should also record your findings in your lab notebook.
5. Once the mass has been recorded, tare the scale again.
6. Repeat the two previous steps until you have weighed ten Advil tablets. Empty your weigh boat, place it back on the bench scale, and tare the instrument. You should now have the Advil® portion of the data table filled out.
7. Now, look at your generic brand. Record all the non-active ingredients.
8. Open the container, and using the tweezers, place one tablet in the weigh boat. Once again, tare the instrument after recording the mass.
9. Repeat until you have collected ten measurements of the generic brand. You should now have the generic brand portion of the data table filled out.
10. Once all measurements have been completed, dispose of the measured tablets and the weigh boats. Return the containers to their respective boxes.

Table 1. Empty table for recording the mass of the tablets

Trial Number	Name Brand Mass (grams)	Generic Brand Mass (grams)
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		

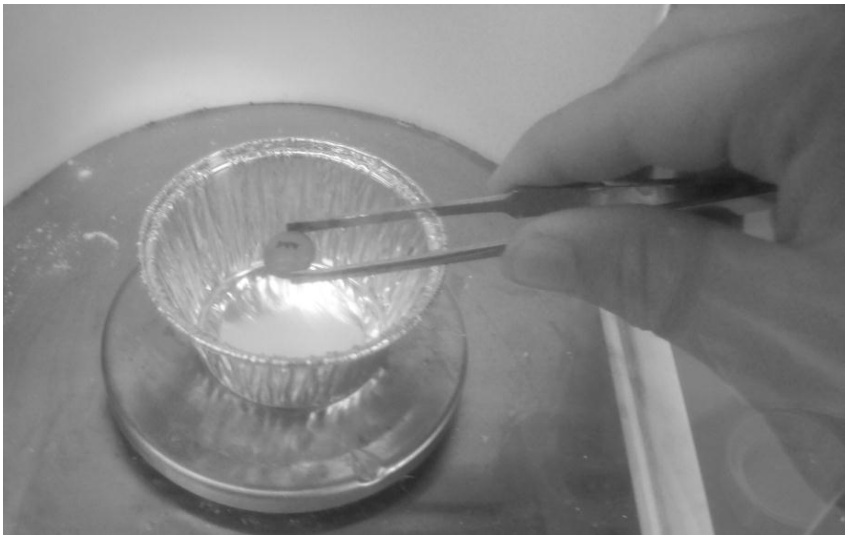


Figure 2. Proper technique for weighing tablets

STATISTICAL ANALYSIS

You will need your calculator to do the following calculations. You must show all work to receive credit.

1. First, take the average of each set of data. Use the equation below, with *i* being the trial number (given in the data table), *n* being the total number of trials (10), and *x* being the mass recorded for the specific trial number. Record this in your lab notebook and include in your results.

$$\bar{x} = \frac{\sum_{i=1}^{10} x_i}{n} \quad (1)$$

2. Standard deviation is defined as the variation from the average. In other words, it is the average of the difference between each value obtained and the average value obtained. So, in this case, it would be important to know the standard deviation of the mass of the tablets for the trademarked brand and also the generic brand. To calculate the standard deviation, use the equation below, with *i* once again being the trial number, *n* being the total number of trials, and *x* being the mass recorded.

$$\sigma = \sqrt{\frac{\sum_{i=1}^{10}(|x_i - \bar{x}|^2)}{n}} \quad (2)$$

3. Now, we will look for any outliers in our data. An outlier can be defined as a data point significantly different than the mean of the data. In other words, an outlier is a datum point that significantly distant from other points. To do this, find the median data point in both sets of data. To find the median, list the data in order from lowest value to highest value, and find the point that resides in the middle. If you have an even number of data points, the median is found by averaging the two middle data points. From now on, this median (the median of the entire data set) is known as **overall median**. From here, find the first and third quartiles. These values are found by splitting the list of data in half. In this case, we now have two sets of five data points; one with the lower data points, and the other with the higher data points. The **first quartile** can be found by taking the median of the lower data points. The **third quartile** is the median of the higher data points. Lastly, we state that the overall median is the **second quartile**. Using the equations below, calculate if any of your data points are *outliers.*

$$O_L = Q_1 - 1.5(Q_3 - Q_1) \quad (3)$$

Where, O_L is the low-value outlier cutoff, Q_1 is the first quartile, and Q_3 is the third quartile.

$$O_H = Q_3 + 1.5(Q_3 - Q_1) \quad (4)$$

Where, O_H is the high-value outlier cutoff, Q_3 is the third quartile, and Q_1 is the first quartile.

Are any weights you measured above O_H or below O_L? If so, they are outliers. Arrange your findings in a box-and-whisker plot as described in the diagram below.

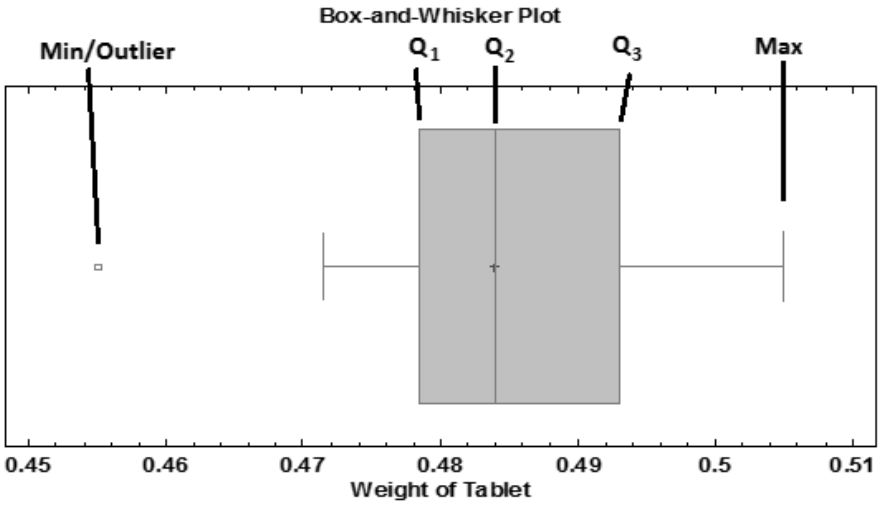


Figure 3: A typical box-and-whisker plot.

RESULTS

Be sure to record all findings for this lab. Answer any questions that might have been asked in the procedure section of the lab.

QUESTIONS

1. During the statistical analysis section, you were asked to find the standard deviation of the trademarked and the generic brand. Explain what this value tells you. Compare the two standard deviations you calculated, and determine what this means.

2. Now, you will determine whether or not these two brands are different from each other. To do this, you will use a statistical analysis technique known as an F-test. An F-test is used to compare two samples. This test can become difficult if the samples are not done in a similar manner. In this case, the number of measurements taken in each sample is similar,

so this makes the F-test much simpler. To conduct an F-test, do the following:

a. Find the variance of the two samples. The variance of a sample is defined as the average of the squared difference of the means. An equation of what this would look like is shown below:

$$Variance = s = \frac{sum\ of\ the\ squared\ differences\ from\ the\ average\ value}{number\ of\ measurements\ taken} \quad (5)$$

$$s = \frac{\sum(x_i - \bar{x})^2}{n} \quad (6)$$

Another way of looking at the variance is it's relation to the standard deviation of a sample. The relation of the variance of a sample to the standard deviation of a sample is shown below:

$$s = \sigma^2 \quad (7)$$

If you compare the equation of variance to the equation of standard deviation, you can see how this is true. Use the relation between standard deviation and variance to find a value of variance for the two samples.

b. Now, find the F-value for your experiment. To find your F-value, use the following equation:

$$F_{exp} = \frac{s_1^2}{s_2^2} \quad (8)$$

For this equation, the variance in the numerator "s_1" has to be the larger of the two variances.

c. Now, compare this value to a critical value. This is known as the F-critical value. The F-critical value is dependent on the number of measurements taken in each sample, and the percent confidence that is desired. The percent confidence is another way of saying how accurate one wishes to be in their experiments. The higher the percent confidence, the more certain one is in their

experiments. In this case, you will use a standard percent confidence of 95%. So, you will need an F-critical value which corresponds to a 95% percent confidence, a variance based on 10 measurements in the numerator, and a variance based on 10 measurements in the denominator. Usually, these would be looked up in tables, as seen in appendix A Figure 1. However, below you will find an critical F value for your calculations[3]:

$$F_{crit} = 3.18$$

If the F value you calculated in part b of this problem is larger than the critical value given, then the two samples are significantly different. If the F value you calculated in part c of this problem is smaller than the critical value given, then the two samples are not significantly different. State whether or not there is significant difference between the two samples .

3. Research suggests that one ibuprofen tablet should have a mass of 480 mg.[2] Do you think there is significant difference between the values you obtained and this literature value for a typical formulation? To answer this, you will use another statistical test known as the t-test. There are several different types of t-tests used in statistics. In this case, you will be using a one-sample t-test, which compares a single mean to a fixed value. So for this test, the fixed value will be the 480 mg. You will conduct a t-test on both samples. In order to conduct this analysis, do the following:

    a. For a t-test, you will need to find a t-value. The t-value for an experiment relates the average, standard deviation, and number of measurements to a given value. Using the symbols found previously in this experiment, the equation for the t-value is as follows:

$$t_{exp} = \left| \frac{\overline{x} - \mu_o}{\frac{\sigma}{\sqrt{n}}} \right| \quad (9)$$

In this case, μ_o will be the mass found in research (480 mg).

    b. You will now compare this value to a critical value. This is known as the critical t-value. Like the F-critical value, the critical t-value is

dependent on the percent confidence that is desired and the number of measurements taken in the sample. Again, you will use a percent confidence of 95%. For an example of a t-Table, see Appendix A Figure 2. The critical t-value you will be using is given below[3]:

$$t_{crit} = 2.262$$

Just like with the F-test, if the critical t-value is higher than the value obtained earlier, then there is no difference between your sample and the value from literature. If the t-value calculated earlier is higher than the critical t-value, then there is a significant difference between the sample and the value obtained from literature. State whether or not there is significant difference between the value obtained from experiments and the value obtained from literature.

c. Repeat this process for whichever sample you did not already conduct the analysis on.

4. It has been estimated that the world production of ibuprofen is in the vicinity of 15,000 tons per year.[4] It has also been estimated that the average price for one ibuprofen tablet is roughly 0.12 USD.[5] Using this information, calculate the total price of ibuprofen production for a year.

5. Remember that you listed the inactive ingredients from each of the brands. Research the first three ingredients from both brands and state what type of excipient you believe them to be (i.e. filler, preservative, lubricant, etc.).

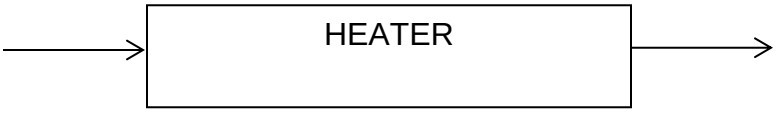
6. It is your first day on the job working for Pfizer and you are told to do an experiment on the Advil production line. A new tablet press has been installed and your boss wants to know if it is producing tablets with consistent weight. To start your experiment, you pull a sample of 20 tablets off of the line and weigh them. The data is arranged in a table below. Your boss tells you that each pill must be 90% to 110% of the mean tablet size, which is 0.485 g. Do any pills in your sample fall outside of these bounds? Furthermore, did you find any outliers in your sample? What does this say about the consistency of the new pill press?

Table 2: Experimental data from production line

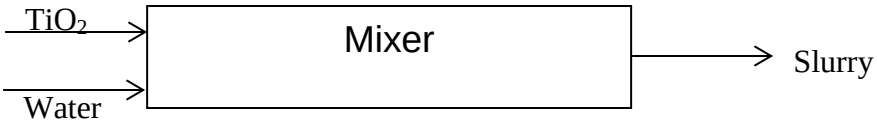
Advil Sample - 20 Tablet weights (g)			
0.4850	0.5435	0.4686	0.4837
0.5198	0.4448	0.5211	0.5895
0.5048	0.4668	0.4863	0.5227
0.4857	0.4465	0.4217	0.4662
0.4786	0.4835	0.4481	0.5101

7. You will now have an introduction to creating process flow diagrams. These diagrams are an important part of engineering, as they are used in most plants. A process flow diagram indicates the major equipment used in a process. In this case, a box with a label will be acceptable as a piece of equipment. An example is shown below:

A heater heats water from 10°C to 50°C:



If you have more than one stream entering or exiting a process, multiple lines can be drawn. For example, if a mixer blends water and titanium dioxide to make a slurry the process flow diagram would look like:



a. Make a process flow diagram for the creation of the ibuprofen tablets as described by the steps below:
    i. Mix the powder (maize starch) for 15 minutes at high speed. Add 10.67 g of cold water and check weight (theoretical weight, 58.00g). If required adjust with hot water. Record the quantity of extra water added.

    ii. Mix this binding solution with Mixture 1 (Ibuprofen and maize starch).

    iii. Collect and spread the granules onto the trays, one third the thickness of the tray.

iv. Load the trolley into the oven and dry the granules in the trays and change the position of the trays for uniform drying.

v. Mix stearic acid and corn starch separately and add to the granules before sending them to a compressor. Compress into 330-mg tablets, using 10-mm convex punches at 4 to 9 kPa.

vi. Put the tablets into the coating and rolling pan.

b. Make another process flow diagram that shows the coating of the ibuprofen tablets as described by the steps below:

i. Make sugar coating:

1. Heat 72.0 g of item 6 (purified water) in mixer to boiling.

2. Dissolve 168.0g of item 4 (sucrose) and then cool to 25°C.

3. Filter the syrup through a 180-µm stainless steel sieve.

4. Dispense item 5 (titanium dioxide) into the sugar syrup from the previous step and homogenize.

5. Check for evenness of the dispersion.

ii. Apply Sugar Coating to tablets in coating pan by rolling tablets and slowly adding the sugar solution over 30 minutes.

iii. Make gloss solution

1. Melt items 1 - 3 (bee's wax, polyethylene glycol, carnauba wax) in a steam-heated vessel by gentle heating to 70°C or in a stainless steel container on a hotplate heater.

2. Mix thoroughly.

3. Pass the mixture through a homogenizer.

4. Store the polishing emulsion in a closed container at room temperature.

iv. Apply gloss solution to tablets in coating pan by rolling tablets. Once the desired polish appears, stop rolling the pan.

v. Dry the tablets in the pan at 30°C for 30 minutes. Final tablet weight should be 480 mg.

ANSWER KEY

PROCEDURE

2. Take the Advil package and note where they list the active and inactive ingredients. Record all of the ingredients that are listed as non-active ingredients **Ans:** On the container of a bottle of Advil purchased November 2012, the inactive ingredients listed were acetylated monoglycerides, colloidal silicon dioxide, corn starch, croscarmellose sodium, methylparaben, microcrystalline cellulose, pharmaceutical glaze, pharmaceutical ink, povidone, pregelatinized starch, propylparaben, sodium benzoate, sodium lauryl sulfate, stearic acid, sucrose, synthetic iron oxide, titanium dioxide, and white wax.
7. Now, look at your generic brand. Record all the non-active ingredients.

Ans: This answer will vary depending on the generic brand that was purchased for this experiment. For a bottle of CVS Pharmacy® brand ibuprofen tablets purchased November 2012, the non-active ingredients are carnauba wax, corn starch, and fumed silica gel, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, polydextrose, polyethylene glycol, red iron oxide, sodium starch glycolate, stearic acid, and titanium oxide.

STATISTICAL ANALYSIS

These calculations were done using the following table of data.

Table 3. Sample data used for the answer key section of this guide.

Trial Number	Name Brand Mass (grams)	Generic Brand Mass (grams)
1	0.4784	0.3354
2	0.4837	0.3300
3	0.4715	0.3296
4	0.5019	0.3280
5	0.4840	0.3383
6	0.4842	0.3284
7	0.5050	0.3307
8	0.4930	0.3365
9	0.4804	0.3272
10	0.4845	0.3362

1. First, take the average of each set of data. Record this in your lab notebook and include in your results.

Ans: The average for the Advil data was found to be 0.487g. The average for the generic brand was found to be 0.332g.

2. Standard deviation is defined as the variation from the average. In other words, it is the average of the difference between each value obtained and the average value obtained. So, in this case, it would be important to know the standard deviation of the mass of the tablets for the trademarked brand and also the generic brand.

Ans: The standard deviation for the Advil data was found to be 0.010g. The standard deviation of the generic brand was found to be 0.004g.

3. Are any weights you measured above O_H or below O_L? If so, they are outliers. Arrange your findings in a box-and-whisker plot as described in the diagram below. (*Omitted from solutions, see above for diagram.)*

Ans: FOR THE ADVIL® BRAND:

$$Q_2 = \frac{(0.4840+0.4842)}{2} = 0.4841\ g\ ;\ Q_3 = 0.4930\ g\ ;\ Q_1 = 0.4804\ g$$

$$O_L = 0.4804 - 1.5(0.4930 - 0.4804) = 0.4615\ g$$

Since the minimum value in this data set is 0.4715 g, a low-value outlier does not exist.

$$O_H = \ 0.4930 + 1.5(0.4930 - 0.4804) = 0.5119\ g$$

Again, all data points are less than this number, so a high-value outlier does not exist. A Box-and-Whisker plot of this is shown below.

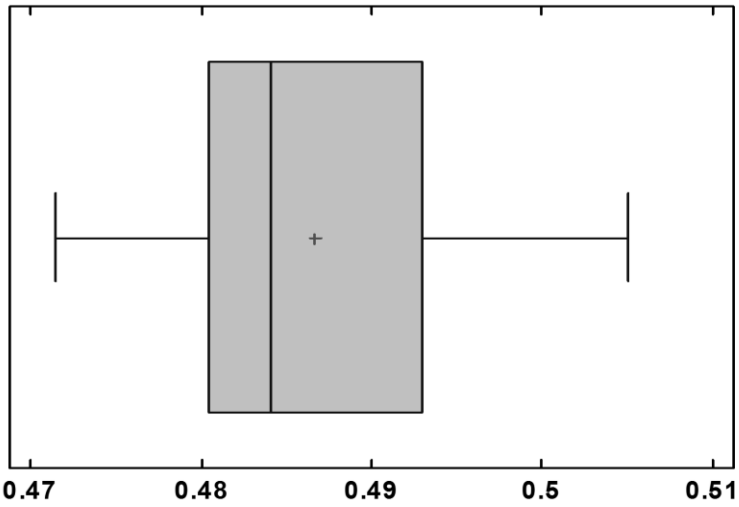


Figure 4. Box-and-Whisker plot for the Advil® brand. The x-axis here is the mass of the ibuprofen tablets in grams.

FOR THE GENERIC BRAND:

$$Q_2 = \frac{(0.3307+0.3300)}{2} = 0.3304\ g\ ;\ Q_3 = 0.3362\ g\ ;\ Q_1 = 0.3284\ g$$

$$O_L = 0.3284 - 1.5(0.3362 - 0.3284) = 0.3167\ g$$

Since the minimum value in this data set is 0.3272 g, a low-value outlier does not exist.

$$O_H = 0.3362 + 1.5(0.3362 - 0.3284) = 0.3479\ g$$

Again, all data points are less than this number, so a high-value outlier does not exist. The Box-and-Whisker plot is shown below.

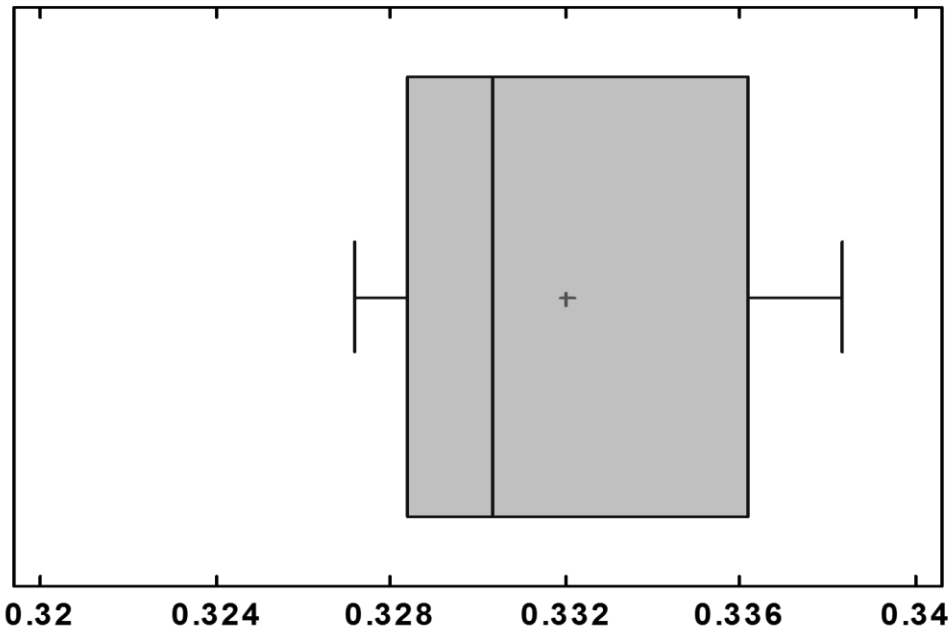


Figure 5. Box-and-Whisker plot for the generic brand. The x-axis here is the mass of the ibuprofen tablets in grams.

QUESTIONS

1. During the statistical analysis section, you were asked to find the standard deviation of the trademarked and the generic brand. Explain what this value tells you, and why it is important. Compare the two standard deviations you calculated, and determine what this means. **Ans:** As stated in this lab, the standard deviation of the variation from the average. This

shows the precision of each of the brands. If a brand has a lower standard deviation, then it is more precise. From the statistical analysis section, the generic brand had a smaller standard deviation. This means that the process used to make the generic brand is more precise.

2. Now, you will determine whether or not these two brands are different from each other. To do this, you will use a statistical analysis technique known as an F-test. **Ans:** The answers for each piece are as follows:
   a) The variance for the Advil® brand was found to be 9.72E-05, while the generic brand was found to have a variance of 1.52E-05.
   b) The F-value was found to be 40.63.
   c) Since the F-value calculated was higher than the F-critical value given, there is significant difference between the two brands at 95% confidence.

3. Research suggests that one ibuprofen tablet should have a mass of 480 mg.[2] Do you think there is significant difference between the values you obtained and this literature value for a typical formulation? To answer this, you will use another statistical test known as the t-test. **Ans:** The answer for each piece are as follows:
   a) For the Advil® brand, the experimental t-value was found to be 2.14.
   b) Since the critical t-value is higher than the experimental t-value, there is no significant difference between the literature value and the Advil® brand.
   c) For the generic brand, the experimental t-value was found to be 119.79. Since this value is considerably higher than the critical t-value, there is significant difference between the value obtained from literature and the generic brand value.

4. It has been estimated that the world production of ibuprofen is in the vicinity of 15,000 tons per year.[4] It has also been estimated that the average price for one ibuprofen tablet containing 200 mg of ibuprofen is roughly 0.12 USD.[5] Using this information, calculate the total price of ibuprofen production for a year. **Ans:** To determine the price of ibuprofen production, this was done:

$$15000\frac{tons}{year} * 0.12\ \frac{USD}{tablet} * \frac{tablet}{200\ mg} * 1000\ \frac{kg}{ton} * 1000\frac{g}{kg} * 1000\ \frac{mg}{g}$$

$$= 9.0 * 10^9\ \frac{USD}{year}$$

5. Remember that you listed the inactive ingredients from each of the brands. Research the first three ingredients from both brands and state what type of excipient you believe them to be (i.e. filler, preservative, lubricant, etc.).

Ans: The answer to each of the ingredients is as follows:

FOR THE ADVIL® BRAND:

1) The first listed inactive ingredient was acetylated monoglycerides. According to Lipid Technologies and Applications, this ingredient is often used as a coating ingredient.[6]
2) The second inactive ingredient, colloidal silicon dioxide, is also known as silicon dioxide or silica. In nature, it is also known as sand or quartz. According to Pharmaceutical Dosage Forms: Tablets, a compendium of information on tablets, colloidal silicon dioxide is often used as a glidant.[7]
3) The third inactive ingredient listed was corn starch. As described in the excipients catalog on PharmaHUB.org, corn starch consists of the starch granules separated from the mature grain of corn. This excipient can fit into many categories, including binders, diluents, and disintegrants.[8]

FOR THE GENERIC BRAND:

1) The first listed non-active ingredient listed on the CVS® brand was carnauba wax. Carnauba wax is also known as palm wax or Brazil wax, and comes from the leaves of a palm tree grown only in Brazil. According to About.com, carnauba wax is often used as a coating agent for candies and also for cars. Likewise, it is most likely used to coat the tablet.[9]
2) The second listed non-active ingredient was corn starch. As stated in number 3) of the Advil section of this answer, it is used as a disintegrant, binder, or diluent.[8]
3) The third non-active ingredient listed was fumed silica gel. What makes fumed silica gel unique is that it has a rather large surface area. Fumed silica gel has many applications, but in this case, it is probably used as a thickening agent, or a thickener.[10]

6. Do any pills in your sample fall outside of these bounds? Furthermore, did you find any outliers in your sample? What does this say about the consistency of the new pill press?

Ans: By taking the percent error of each data point from the average point of 0.4850 grams, we find that three tablets are out of the speculated range. The equation used and the percent error for each point is shown below.

$$\% \, Error = \frac{|Data \; Point - 0.4850 \; g|}{0.4850 \; g} * 100\%$$

Table 4. Percent error of each of the mass samples. The rows and columns correspond to the same points as seen in the questions section.

0.000	12.062	3.381	0.268
7.175	8.289	7.443	21.546
4.082	3.753	0.268	7.773
0.144	7.938	13.052	3.876
1.320	0.309	7.608	5.175

Through outlier testing, one outlier was found. Through the use of the quartiles, the following values were calculated:

Median	0.4844
First Quartile	0.4665
Third Quartile	0.5150
O_L	0.3938
O_H	0.5876

Through these values, we find one outlier. The data point 0.5895 is larger than the O_H value, and therefore an outlier to the series. A Box-and-Whisker plot was developed, and shown below.

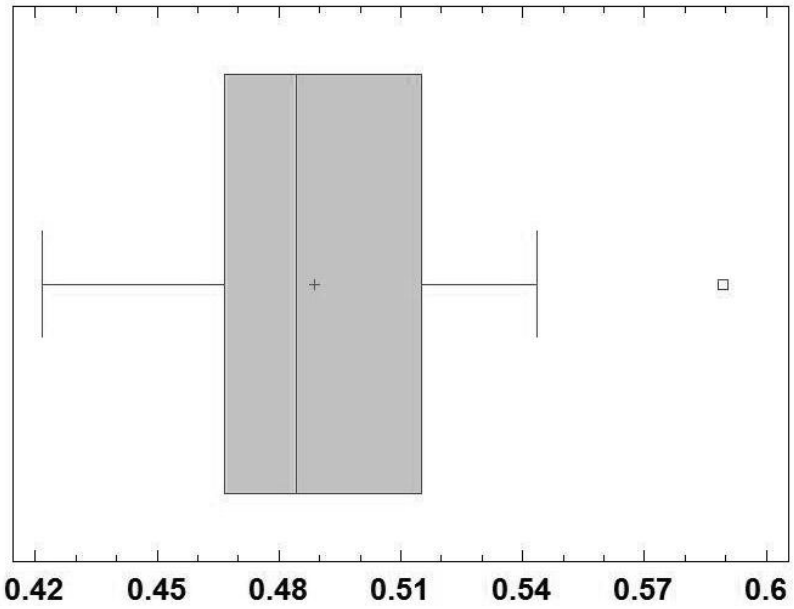


Figure 6. Box-and-Whisker plot for Problem 6. The x-axis here is the mass of the ibuprofen tablets in grams. One outlier is clearly visible in this plot.

This tells us that this pill press is not consistent enough for the product specifications and is not precise enough to produce no outliers.

7. For this exercise, read the following description on the creation of ibuprofen tablets, and then create a process flow diagram of the process.

Ans: After reading the description, the following flow diagrams were made:

a.

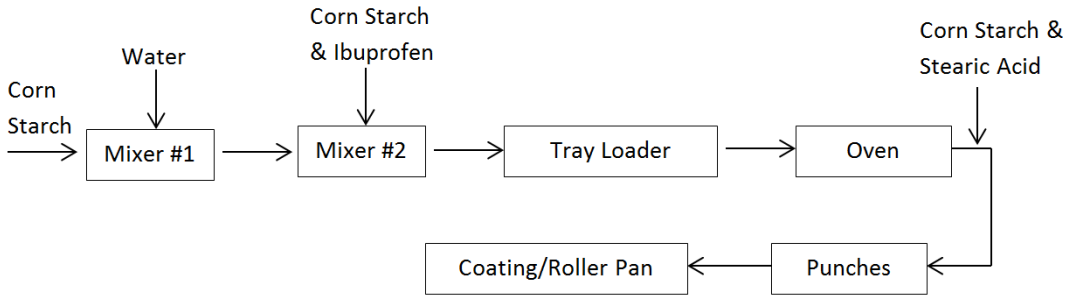


Figure 7. Solution to part a) of Question 7.

b.

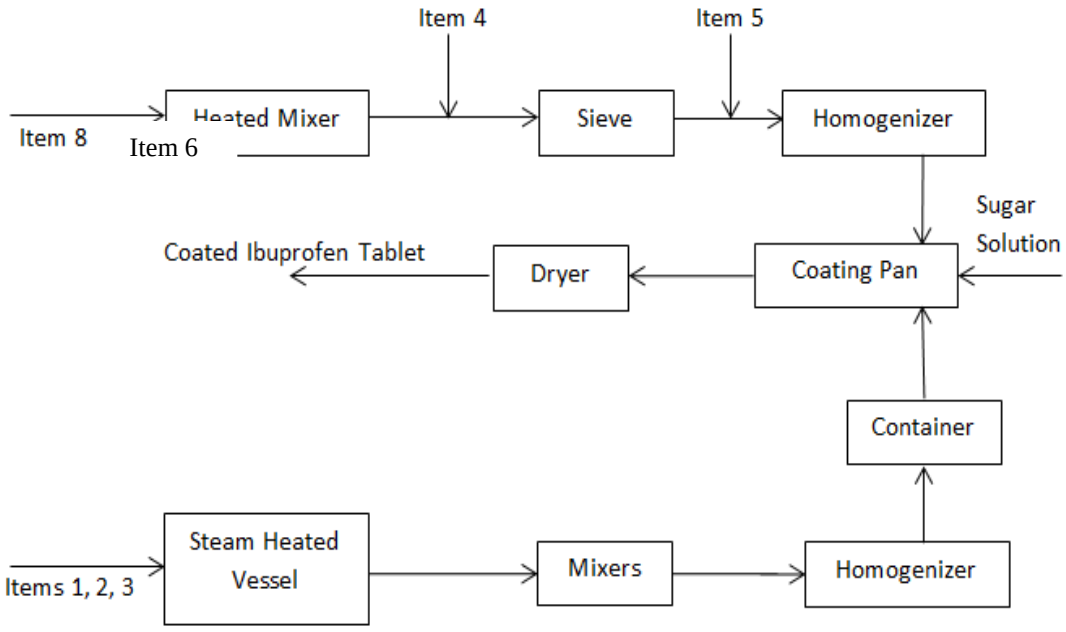


Figure 8. Solution to part b) of Question 7.

REFERENCES

1. Cacciotti, J. and Clinton, P. “The Lull between Two Storms.” Pharmaceutical Executive. 2010.
2. Niazi, S. K. Handbook of Pharmaceutical Manufacturing Formulations; Compressed Solid Products. New York: Informa Healthcare USA, 2009.
3. Montgomery, D. C. Introduction to Statistical Quality Control. John Wiley and Sons, Inc. 2013.
4. Myers, R.L. The 100 Most Important Chemical Compounds: A Reference Guide. ABC-CLIO, 2007.
5. Volume Discounts. http://www.drmichael.com/volume_discounts.htm
6. Gunstone, F. D. and Padley, F.B.. Lipid Technologies and Applications. Marcel Dekker. New York. 1997.
7. Augsberger, L. L. and Hoag, S. W. Pharmaceutical Dosage Forms: Tablets. InformaHealthcare. New York. 2008.
8. Hoag, S., Wassgren, C. Basu, P. and Khan, M. The Excipients Knowledge Base. PharmaHUB.org. http://pharmahub.org/excipientsexplore

9. Helmenstine, A.M. PhD. “What is Carnauba Wax?” About.com. 2012. http://chemistry.about.com/od/foodchemistryfaqs/f/carnauba-wax.htm
10. “Fumed Silica Powder.” READE Advanced Materials. 2012. http://www.reade.com/home/10039

B.2 Fluidization of Pharmaceutical Excipients Lab

Fluidization of Pharmaceutical Excipients – Instructor's Guide
Developed by: Alex Jannini, David Krause, Heather Malino and Kevin Sweeney, Rowan University, Department of Chemical Engineering
Edited by: C. Stewart Slater and Mariano Savelski, Rowan University, Department of Chemical Engineering

Date of Experiment:

OBJECTIVES

- Students will fluidize a pharmaceutical excipient, and learn about the variables affecting fluid-particle transport
- Students will construct and interpret fluidization graphs using experimental data
- Students will gain experience using the online literary search engines

INTRODUCTION

A fluidized bed occurs when solid particulate matter is put under specific conditions that allow it to behave as a fluid. This is usually performed in some sort of vessel and achieved through the use of a pressurized fluid, such as air. Some of the properties that the particulate matter has in its fluidized state include the ability to be transported in a manner that is similar to other fluids. This phenomenon is called fluidization. Fluidization and fluidized beds are used in several different industries for several different purposes.

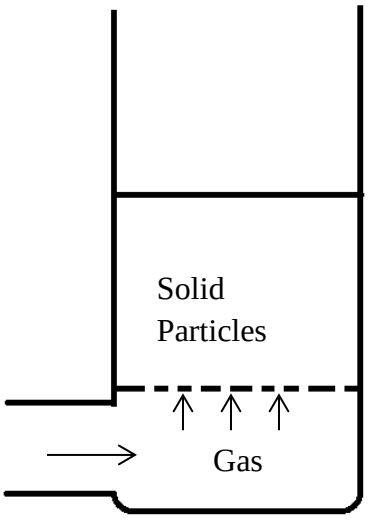


Figure 1: Simple schematic of a fluidized bed

In fluidization, there are many different variables that need to be considered. If one was to design a fluidized bed, equipment parameters such as the pressure of the incoming fluid, the flow rate of the incoming fluid, and the temperature of the system would need to be part of the design process. In addition, the material that is to be fluidized will also need to be investigated. Material properties such as particle size, density, and porosity (also known as the void fraction, or the fraction of empty space in a packed vessel) are important when designing a fluidized bed.

As the solids are fluidized, they behave as common fluids. As such, flow variables can be investigated with the moving particles. One such variable is called pressure drop. Pressure drop is the difference in pressure between two points along the path of fluid movement in the process. Pressure drop is caused by frictional forces, resistances to the flow, as the fluid flows through the vessel.

In the pharmaceutical industry, fluidized beds have many different applications. Initially, fluidized beds were mainly used for the drying and coating of solids[1]. Granulation, the act of forming or crystallizing substances into grains or granules in fluidized beds, was later investigated for pharmaceutical purposes.[1] Fluidization can also be used for the transportation of solids, as the fluidized solids can be transported via pipes rather than conveyer belts or in discrete amounts[1].

In this experiment, you will be investigating four different variables of a fluidized bed; air flowrate, air pressure, pressure drop, and bed height. You will then use the data you collected to perform some fluidized bed calculations. By the end of this experiment, you should have a better understanding on how fluidization occurs, and why it is an important aspect of pharmaceutical manufacturing.

MATERIALS NEEDED

PART I

- 250 mL plastic graduated cylinder
- 1000 mL plastic graduated cylinder
- Bench scale capable of reading at least 1 kg
- Avicel® PH 200
- Kaolin powder
- DI water
- Stirrer

PARTS II & III

- Fluidized bed filled with Avicel® PH 200
- Ruler

INSTRUCTOR'S NOTE

As part of a pre-lab assignment, have the students obtain a material safety data sheet (MSDS) for both kaolin and Avicel® PH 200. Any Avicel® may be accepted, but additional literature will be needed for future problems. This lab uses fluidized beds that are described in the Hesketh et al. article, "Fluidized Bed Polymer Coating Experiment."[2] This article describes how to create fluidized bed.

SAFETY CONSIDERATIONS

Laboratory goggles must be worn at all times when in the laboratory. Laboratory gloves and a dust mask must be worn if handling pharmaceutical powders. Obtain and read the MSDS on Avicel® PH 200 and kaolin.

PROCEDURE

PART I – DETERMINING BULK AND PARTICLE DENSITIES

1. Begin by placing the empty 250 mL graduated cylinder on the bench scale. Tare the instrument.
2. Place approximately 50 to 60 grams worth of one of the powders into the graduated cylinder. If you are a little over or under, that is fine, as long as the powder does not surpass a measureable level on the graduated cylinder. You may have to use a scoop or a beaker to do this.
3. Record both the mass of the powder you added to the cylinder, and how much volume it takes up. Use these values to calculate the bulk density by dividing the mass added by the volume it takes up. Set aside this graduated cylinder.
4. Now, fill the 1000 mL graduated cylinder with DI water to around the 700 to 800 mL mark. Again, this does not need to be precise. Record the volume of water you added.
5. Place the graduated cylinder filled with water on the bench scale, and once again tare the instrument.
6. Slowly, add the powder from the small graduated cylinder into the large one. You may need to stir the solution at intervals of the pouring process so that all the particles are suspended. Remember that you do not want to surpass the readable levels of the graduated cylinder.
7. Once the particles have been poured in, stir the mixture thoroughly, but carefully. You do not want to lose any of the water. Once stirred, place back on the scale bench and record the mass of the powder you added to the water. Also, record the new volume of the water and powder mixture.
8. Now, find the particle density. The particle density is the mass of the powder added to the water and the volume taken up by the particles. You can determine the volume taken up by the particles by subtracting the volume of water from the volume of the mixture.
9. Do this for the other powder. Make sure that you clean and dry the graduated cylinders thoroughly, and use new cylinders before starting to work with the new powder. You may use the following table to record your findings, but you should copy this table into your lab notebook.

Table1. Empty table for recording data during the fluidization lab.

Measurement	Kaolin	Avicel PH 200
Mass of substance (g)		
Volume of substance (mL)		
Bulk density (g/cm^3)		
Volume of water (mL)		
Volume of mixture (mL)		
Volume of particles (mL)		
Mass of substance (g)		
Particle density (g/cm^3)		

PART II – THE FLUIDIZED BED

1. The first step in running these experiments is to become acquainted with the equipment. First, briefly look over the equipment and the station in front of you. Note where your pressurized air is coming from.
2. After investigating your system, measure the inner diameter of the fluidized bed. You will need this for calculations later.

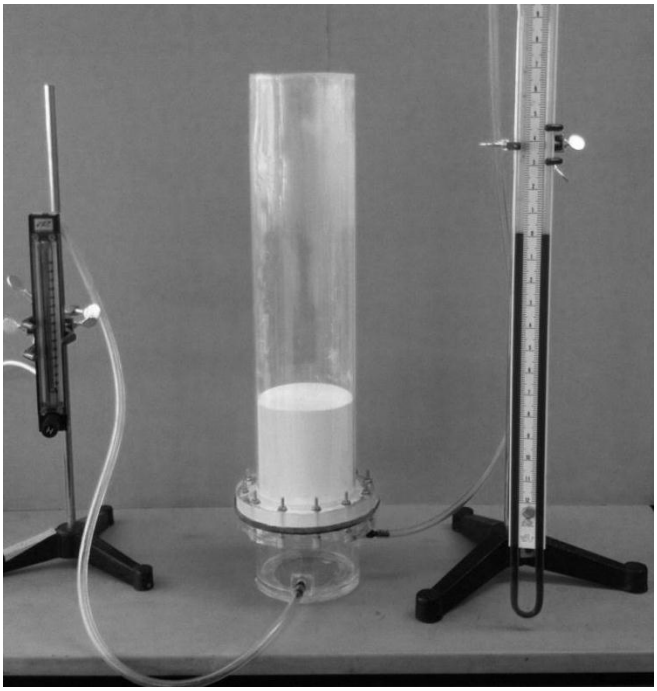
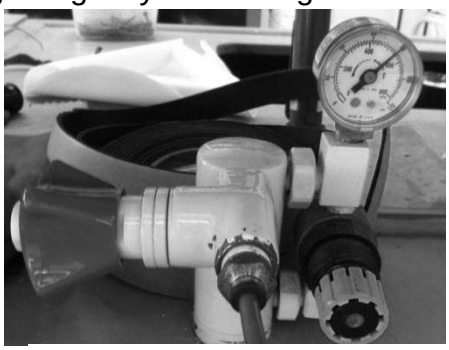


Figure 2. Laboratory scale fluidized bed.

PART III – SUBSTANCE INVESTIGATIONS

1. After becoming familiarized with your equipment, you may begin testing. Begin by measuring the height of the fixed bed.
2. Set the incoming air at a pressure of 60 pounds per square inch (psi). Make sure that the flowmeter is closed, but the air valve is open (make sure you know which is which!).



Figures 3 and 4. From left to right; the inlet air valve and the flow meter used in the fluidized bed setup.

3. With the inlet air pressure at 60 psi, open the flowmeter and slowly raise the flow rate of the

incoming air to 5 gallons per minute (gpm). At this reading, take a pressure drop measurement and a bed height measurement.

4. Once the measurements have been recorded, increase the air flow rate by 5 gpm. Again, measure the pressure drop and the bed height.
5. Repeat this until you reach 30 gpm. Now, increase the intervals to 10 gpm. If you notice plug flow, bubbling, or channeling in the fluidized bed, record the flow rate and pressure drop, but make a note of the phenomenon that occurred. Also, it might be necessary to check on the air pressure periodically during the experiment. You should make sure this is done before taking any measurements.
6. Once you have taken the pressure drop and bed height at the maximum flow rate of air, bring the flow rate back down to zero.
7. Complete the same steps as above, but now using an air pressure of 100 psi. You may use the tables below to record your data, but you should also copy your data into your lab notebook.

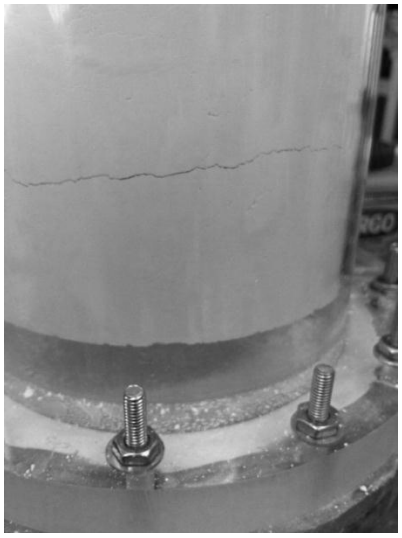


Figure 5. Plug flow occurring in the fluidized bed.

Table 2. Empty data table for recording pressure drop at an air pressure of 60 psi and bed expansion in the fluidization lab

Air Pressure of 60 psi		
Flow Meter Reading (gpm)	Pressure Drop (in H_2O)	Bed Expansion (inches)
0		
5		
10		
15		
20		
25		
30		
40		
50		
60		
70		
80		
90		
100		

Table 3. Empty data table for recording pressure drop at an air pressure of 60 psi and bed expansion in the fluidization lab

Air Pressure of 100 psi		
Flow Meter Reading (gpm)	Pressure Drop (in H_2O)	Bed Expansion (inches)
0		
5		
10		
15		
20		
25		
30		
40		
50		
60		
70		
80		
90		
100		

RESULTS

Record all results in your lab notebook.

QUESTIONS

1. Based on your results, what was the point of minimum fluidization (the point where fluidization was first noticed) for both of the data sets? What does this tell you about air pressure when it comes to minimum fluidization? Does this mean that air pressure is a negligible variable when it comes to fluidization? Why or why not?

2. You will make a graph of the air flow rate versus the bed height (this means that the air flow rate is on the x-axis and the bed height is on the y-axis) for both of the air pressures. Using the graph, determine when the bed goes from behaving as a packed bed to a fluidized bed.

3. Prepare a fluidization graph. A fluidization graph is obtained by plotting the air flow rate versus the pressure drop. When you make these graphs, there will be a change in the slope at a certain point. This point is known as the point of minimum fluidization. At this point, the bed of solids changes from behaving like a packed bed to behaving like a fluidized bed. Label where you believe this point is on the graphs you made. Also label what sections of the graph model the packed bed behavior and fluidized bed behavior.

4. For this experiment, we have delved into some of the properties of fluid mechanics, a branch of science that deals with the properties of fluids and some of the phenomenon that occurs when they are placed under certain conditions. One of the first variables you will learn in fluid mechanics is known as the Reynolds Number, a dimensionless quantity that is used to determine a flow regime. Today you will determine the Reynolds number of the system at minimum fluidization. To do this, you will use the following formula:

$$Re = \frac{D_p v_{mf} \rho_g}{\mu} \quad (1)$$

   a. The Reynolds Number is considered a dimensionless quantity. This means that there are no units attached. Prove this with the following information:

      D_p = Average diameter of the particle (m)
      v_{mf} = Velocity of minimum fluidization (m/s)
      ρ_g = Density of the gas (kg/m^3)
      μ = Dynamic viscosity of the gas (Pa*s)

b. Find the Reynolds number for the minimum fluidization point for both of your experimental runs. To help you in the calculation of this number, use the following values[3,4,5]:

$$D_p = 180\ \mu m\ (micrometers)$$
$$\rho_g @\ 60\ psi = 0.328\ {}^{lb}/_{ft^3}$$
$$\rho_g @\ 100\ psi = 0.582\ {}^{lb}/_{ft^3}$$
$$\mu = 1.716 * 10^{-5}\ Pa * s$$

In addition, determine which of the fluidization regimes the fluidized bed was in at minimum fluidization based on the figure below.

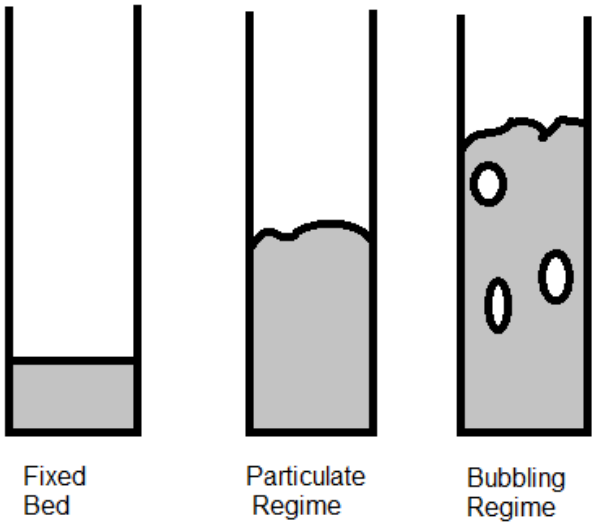


Figure 6. A few fluid regimes of fluidized beds. Adapted from Perry's Chemical Engineering Handbook.[6]

5. The following fluidization data was collected using kaolin powder with the same apparatus (same dimensions) at an air pressure of 60 psi:

Table 4. Fluidization data using kaolin powder at an air pressure of 60 psi

GPM	Bed Height (in.)	ΔP (psi)
0	5.00	0.0
5	5.00	0.5
10	5.00	1.8
15	5.50	1.8
20	5.75	2.4
25	5.75	2.4
30	6.00	2.5
40	6.00	2.8
50	6.50	3.2
60	6.50	3.6
70	6.50	3.8
80	6.75	4.1
90	6.75	4.2
100	6.50	4.6

a. Create a flow rate versus bed height graph and a flow rate versus pressure drop graph.
b. Determine if there is a point of minimum fluidization using the graphs.
c. If you could determine a point of minimum fluidization, determine the Reynolds number at that point. If not, find the Reynolds number at the same point you used for Question 4. Use an average particle diameter of 1.4 μm for this problem.[7]

6. Now, we will go over another important tool for engineers; design equations. Design equations are used by engineers to determine information about a process without having to do extensive experimentation. These equations are usually based on data obtained by research. For example, the following equation can be used to determine the Reynolds number at minimum fluidization[8]:

$$Re_{mf} = \sqrt{(C_1^2 + C_2 * Ar)} - C_1 \qquad (2)$$

Where Ar (Archimedes Number), C_1, C_2, are shown below:

$$Ar = \frac{Dp^3 \, \rho_g \left(\rho_s - \rho_g\right) g}{\mu^2} \qquad (3)$$

$$C_1 = \frac{300(1-\varepsilon_{mf})}{7} \quad (4)$$

$$C_2 = \frac{\varepsilon_{mf}^3}{1.75} \quad (5)$$

Where:

D_p = Average diameter of the particle (m)
ρ_g = Density of the gas (kg/m^3)
ρ_s = Particle density of the excipient (kg/m^3)
g = Acceleration due to gravity (9.81 m/s^2)
μ = Dynamic viscosity of the gas (Pa*s)

In order to use the equations above, you will need to determine the porosity at minimum fluidization (ε_{mf}). This can be a difficult characteristic to determine, which is why many researchers have come up with different constants to approximate the porosity.[9] However, we have enough information to determine ε_{mf}, so we will solve for C_1 and C_2.

To determine ε_{mf}, we first need to know the normal porosity, ε. This can be determined by using the bulk density (ρ_b) and the particle density (ρ_s):

$$\varepsilon = 1 - \frac{\rho_b}{\rho_s} \quad (6)$$

We also have to determine the total volume (V_{tot}). For this, use the bed height at the 0 gpm air flowrate, and multiply by the cross-sectional area of the bed. Now, we can determine the void volume (V_v) using the following equation:

$$\varepsilon = \frac{V_v}{V_{tot}} \quad (7)$$

Now, to determine the volume occupied by the particles (V_p):

$$V_p = V_{tot} - V_v \quad (8)$$

From here, we now need to use the point of minimum fluidization to determine the volume (V_{mf}). This can be done by using the bed height at the point of minimum fluidization and the cross-sectional area. Using V_{mf}, you can determine the void volume at minimum fluidization (V_{vmf}):

$$V_p = V_{mf} - V_{vmf} \quad (9)$$

Finally, determine ε_{mf}:

$$\varepsilon_{mf} = \frac{V_{vmf}}{V_{mf}} \qquad (10)$$

e) Determine ε_{mf} for the Avicel® trial at the air pressure of 60 psi.

f) Determine the Re_{mf} using Equation (2) for the same conditions as part a).

g) Calculate the percent difference between your answer for part b) and the answer you obtained in Question 4.

$$\%\ Difference = \frac{|Re - Re_{mf}|}{\left(\frac{Re + Re_{mf}}{2}\right)} * 100\% \qquad (11)$$

h) You should notice a considerable (>10%) difference in part c). This is because you are using superficial velocity, as opposed to interstitial velocity. Superficial velocity is defined as the theoretical flow through the bed based on the flow rate of the liquid divided by the cross sectional area of the tube. Interstitial velocity takes into account how the flow is affected by the volume occupied by particles. Interstitial velocity is the flow velocity post a particle, and is the "correct" velocity to use in the Re_{mf} equation. To determine the interstitial velocity (v_i):

$$v_i = \frac{Q_{mf}}{A_s * \varepsilon_{mf}} \qquad (12)$$

Where:

Q_{mf} = volumetric flow rate at minimum fluidization (m^3)

A_s = cross sectional area (m^2)

ε_{mf} = porosity at minimum fluidization (dimensionless)

Determine v_i, calculate a new Re as in Question 4, and then compare as in part c).

7. It is important to learn how to use the online library tools that you have available. These online tools have thousands of scientific papers and articles in databases that you have free access to. Using one of the scientific online resources (i.e. Science Direct, SciFinder, etc.) available, you and your lab partners will find an article online about pharmaceutical manufacturing practices. Try to find an article that also discusses either fluidization or fluidized beds. Print out the article, and as a group, be prepared to discuss the article in class. NOTE: It is all right if you do not

understand all of the technical details of the paper, but you should have a good understanding of the overall concept being discussed.

In addition, use the MSDS's that you obtained as part of your pre-lab and any other literature to compare the bulk densities that you found in part I of the experiment.

ANSWER KEY

The data below was used in answering the questions.

Table 5. Sample data collected to carry out calculations for the questions below.

Measurement	Kaolin	Avicel PH 200
Mass of substance (g)	61.5	63.67
Volume of substance (mL)	220	177
Bulk density (g/cm^3)	0.2795	0.3597
Volume of water (mL)	850	700
Volume of mixture (mL)	875	740
Volume of particles (mL)	25	40
Mass of substance (g)	61.25	63.40
Particle density (g/cm^3)	2.450	1.585

Table 6: Sample fluidization data at 60 psi used for calculations.

Air Pressure of 60 psi		
Flow Meter Reading (gpm)	Pressure Drop (in H_2O)	Bed Expansion (inches)
0	0.00	4.75
5	0.30	4.75
10	0.65	4.75
15	1.00	4.75
20	1.40	4.75
25	1.85	4.75
30	2.20	4.75
40	2.50	5.25
50	2.80	5.50
60	3.00	5.75
70	3.40	6.00
80	3.80	6.25
90	4.00	6.50
100	4.40	6.50

Table 7. Sample fluidization data at 100 psi used for calculations.

Air Pressure of 100 psi		
Flow Meter Reading (gpm)	Pressure Drop (in H_2O)	Bed Expansion (inches)
0	0.00	5.25
5	0.20	5.25
10	0.60	5.25
15	0.90	5.25
20	1.20	5.25
25	1.60	5.00
30	2.00	5.00
40	2.40	5.25
50	2.80	5.50
60	3.10	5.75
70	3.40	6.00
80	3.80	6.25
90	4.00	6.25
100	4.40	6.50

In both cases, channeling occurred after reaching 60 gpm, which could not be stopped. Increasing agitation of the bed was seen in the 70-100 gpm data points. The 60 air pressure could not move past the flow rate of 70 gpm.

1. Based on your data, what was the point of minimum fluidization (the point where fluidization was first noticed) for both of the data sets? What does this tell you about air pressure when it comes to minimum fluidization? Does this mean that air pressure is a negligible variable when it comes to fluidization? Why or why not? **Ans:** This may vary from group to group. Using the data above, the point of fluidization was at approximately 40 gpm for both sets of data. From the data, it would appear that air pressure doesn't affect the minimum fluidization requirement of the particles. This does not mean that the air pressure is a negligible variable when it comes to fluidization, however. As shown in the data, the air pressure does limit the flow rate of air through the system. The flow rate of air is known to affect the fluidization of the particles. Therefore, the air pressure does influence the fluidization of the particles.

2. The following graph was made. It is easy to see when fluidization occurs because it is at that point that the bed height starts to increase. When the air pressure was at 100 psi, the bed height was shown to decrease at 2 points, 25 and 30 gpm, before increasing. This could have been because the powder was channeling, and the students shook the column to disrupt

the channeling. This shaking also settled the particles, decreasing the bed height.

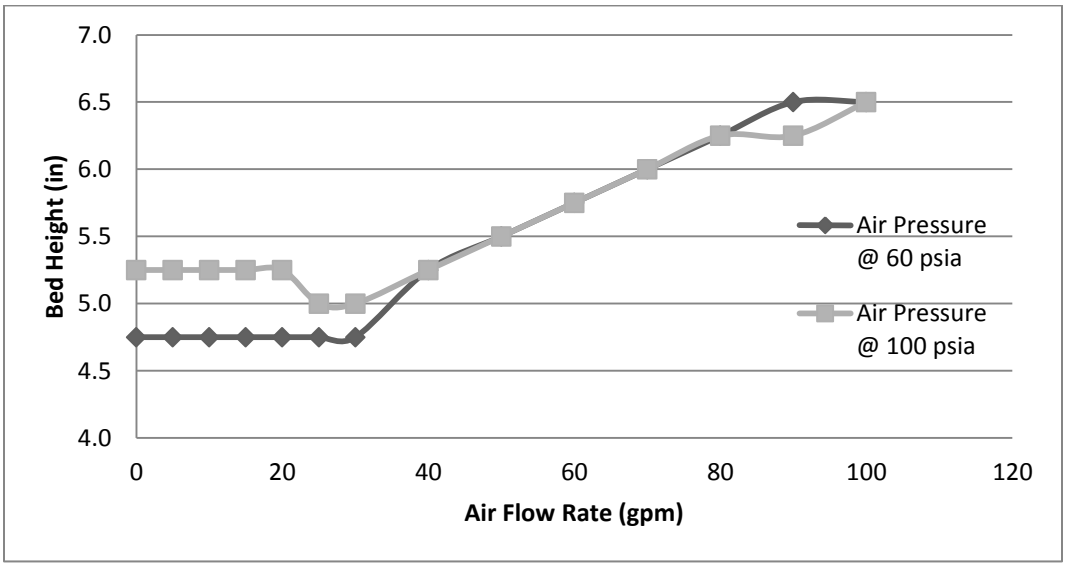


Figure 7. Air flow rate versus the height of the bed. Here, we can see that the bed fluidizes as the bed height increases.

3. You will need to make a fluidization graph. A fluidization graph is obtained by plotting the air flow rate versus the pressure drop (this means that the air flow rate is on the x-axis and the pressure drop is on the y-axis). Label the parts of the graph. **Ans:** From the data above, the following graph was made.

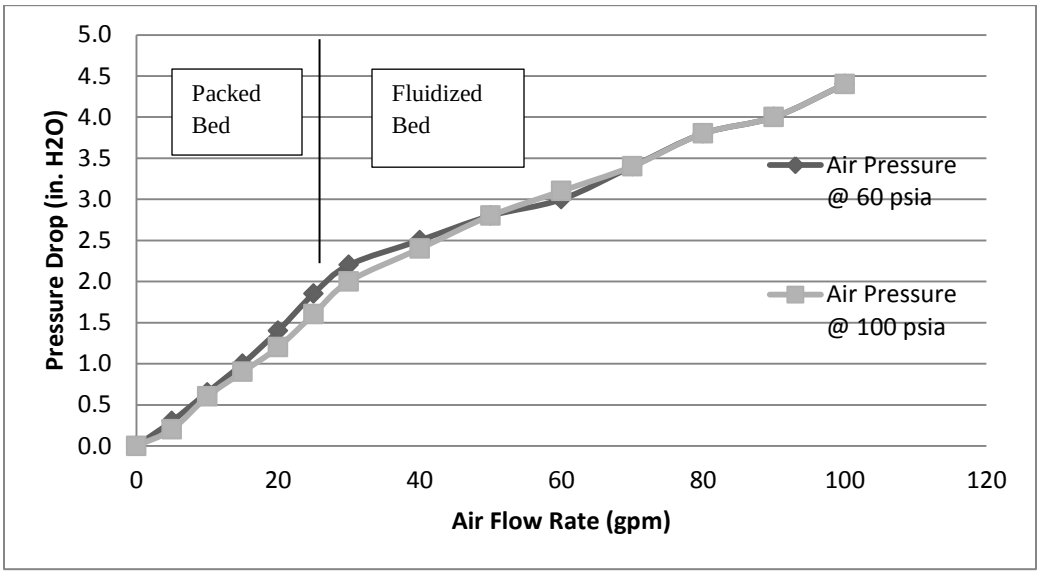


Figure 8. Air flow rate versus the pressure drop. The black line was added to show where the students thought that the packed bed starts to behave as a fluidized bed.

When we graph the data, it would appear that the two sets have the same point of minimum fluidization (around 35 gpm).

4. One of the first variables you will learn in fluid mechanics is known as the Reynolds Number, a dimensionless constant that is used to determine a flow regime.
    a. The Reynolds Number is considered a dimensionless quantity. This means that there are no units attached. Prove this. **Ans:** Using the table of information given, we plug in all the units for the different variable that determine the Reynolds Number:

$$Re = \frac{D_p v_{mf} \rho_g}{\mu} = \frac{m * \left(\frac{m}{s}\right) * \left(\frac{kg}{m^3}\right)}{Pa * s} = \frac{\left(\frac{kg}{s * m}\right)}{\left(\frac{N}{m^2}\right) * s} = \frac{\left(\frac{kg}{s * m}\right)}{\left(\frac{kg}{m * s^2}\right) * s}$$

$$= \frac{\left(\frac{kg}{s * m}\right)}{\left(\frac{kg}{m * s}\right)}$$

As shown, the unit will cancel out, making the Reynolds Number a dimensionless quantity.

    b. Find the Reynolds number for the minimum fluidization point for both of your experimental runs. **Ans:** Through the calculations, it was found that the Reynolds number for the two experimental runs was as follows.

Reynolds Number at 60 psi:	15
Reynolds Number at 100 psi:	27

The first, and not entirely correct, way to solve this is to use the cross-sectional area of the cylindrical bed. Taking the minimum fluidization flow rate and dividing that number by the cross-sectional area to obtain the minimum fluidization velocity, as shown below. It should be noted that this is based on superficial velocity, and is not necessarily an accurate model for what is happening in the system.

$$Diameter\ of\ Bed = D_b = 4.25\ in = 0.011\ m$$

$$Cross - Sectional\ Area = A_{cs} = \frac{\pi}{4} * D_b^2 = \frac{\pi}{4} * (0.011\ m)^2 = 9.15 * 10^{-3}\ m^2$$

$$v_{mf} = \frac{Q_{mf}}{A_{cs}} = \frac{2.52 * 10^{-3}\ {}^{m^3}/_{s}}{9.15 *\ 10^{-3}\ m^2} = 0.27\ \frac{m}{s}$$

The density of air is converted from pounds per cubic feet to kilograms per cubic meters, as shown below.

$$\rho_g at\ 60\ psi =\ 0.328\ \frac{lb}{ft^3} *\ 16.02\ \frac{{}^{kg}/_{m^3}}{{}^{lb}/_{ft^3}} = 5.25 \frac{kg}{m^3}$$

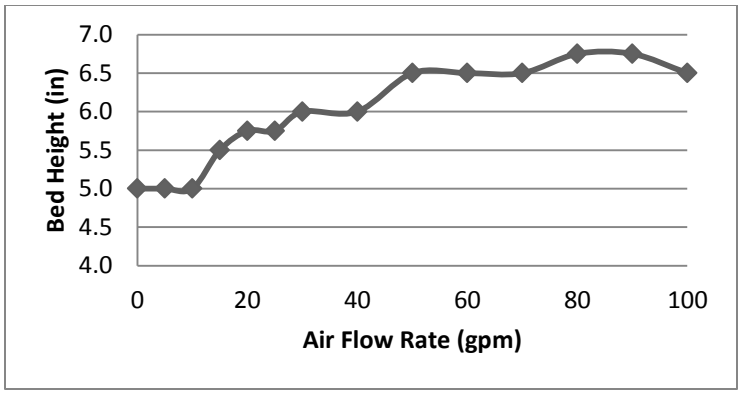
Now, to find the Reynolds number at 60 psi:

$$Re = \frac{D_p v_{mf} \rho_g}{\mu} = \frac{1.8 *\ 10^{-4} m * 0.27\ {}^{m}/_{s} * 5.25\ {}^{kg}/_{m^3}}{1.72 * 10^{-5} Pa * s} = 15$$

Based on the figure given, the minimum fluidization point is in the particulate fluidization regime in both instances.

5. Using the data provided, do the following:
   a. Create a flow rate versus bed height graph and a flow rate versus pressure drop graph.
   Ans: Using the data provided, the following graphs were created.

a)



b)

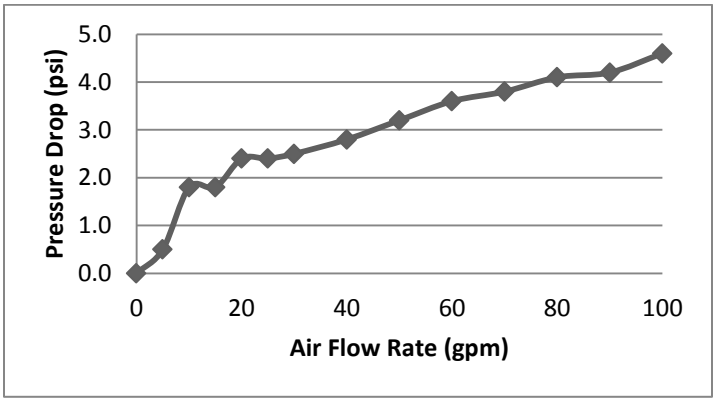


Figure 9. a) Air flow rate versus bed height for the kaolin powder. b) Air flow rate versus pressure drop for the kaolin powder.

b. Determine if there is a point of minimum fluidization using the graphs.

   Ans: From the graphs above, it is slightly difficult to determine when the particle starts to behave like a fluidized bed. Using the graph, it is estimated that the point of minimum fluidization occurs at 20 gpm.

c. If you could determine a point of minimum fluidization, determine the Reynolds number at that point. If not, find the Reynolds number at the same point you used for Question 4.

   Ans: Using the same equations as in Question 4, the Reynolds number was found. Again, this is not entirely correct because we are using a superficial velocity, so this may not be the most accurate model.

$$Re = \frac{D_p v_{mf} \rho_g}{\mu} = \frac{1.4 * 10^{-6} m * 0.138\ {}^{m}/_{s} * 5.25\ {}^{kg}/_{m^3}}{1.72 * 10^{-5} Pa * s} = 0.059$$

6. Now, we will go over another important tool for engineers; design equations. Design equations are used by engineers to determine information about a process when only limited information is given.
   a) Determine ε_{mf} for the Avicel® trial at the air pressure of 60 psi.
   Ans: First, use Equation (6):

$$\varepsilon = 1 - \frac{\rho_b}{\rho_s} = 1 - \frac{359.7\ \frac{kg}{m^3}}{1585\ \frac{kg}{m^3}} = 0.773$$

   Now, determine V_v using Equation (7):

$$V_{tot} = A_{cs} * bed\ height\ @\ 0\ gpm$$
$$= 9.15 * 10^{-3}\ m^2 * 4.75\ in * 0.0254\ \frac{m}{in}$$
$$= 1.104 * 10^{-3}\ m^3$$

$$\varepsilon = \frac{V_v}{V_{tot}} = 0.773 = \frac{V_v}{1.104 * 10^{-3}\ m^3}$$

$$V_v = 8.536 * 10^{-4}\ m^3$$

   To determine V_p, use Equation (8):

$$V_p = V_{tot} - V_v = 1.104 * 10^{-3}\ m^3 - 8.536 * 10^{-4}\ m^3 = 2.506 * 10^{-4}\ m^3$$

   Solving for V_{vmf} using Equation (9):

$$V_{mf} = A_{cs} * bed\ height\ @\ 40\ gpm$$
$$= 9.15 * 10^{-3}\ m^2 * 5.25\ in * 0.0254\ \frac{m}{in}$$
$$= 1.220 * 10^{-3}\ m^3$$

$$V_p = V_{mf} - V_{vmf} = 2.506 * 10^{-4}\ m^3 = 1.220 * 10^{-3}\ m^3 - V_{vmf}$$

$$V_{vmf} = 9.699 * 10^{-4}\ m^3$$

   Finally, determine ε_{mf} using Equation (10):

$$\varepsilon_{mf} = \frac{V_{vmf}}{V_{mf}} = \frac{9.699 * 10^{-4}\ m^3}{1.220 * 10^{-3}\ m^3} = 0.795$$

   b) Determine the Re_{mf} using Equation (2) for the same conditions as part a).

Ans: We begin by finding Ar, C_1, and C_2 using Equations (3), (4), and (5), respectively:

$$Ar = \frac{Dp^3\ \rho_g\ (\rho_s - \rho_g)\ g}{\mu^2}$$

$$= \frac{(1.8 * 10^{-4} m)^3 * 5.25\ {}^{kg}/_{m^3} * \left(1585\ {}^{kg}/_{m^3} - 5.25\ {}^{kg}/_{m^3}\right) * 9.81\ {}^{m}/_{s^2}}{(1.72 * 10^{-5} Pa * s)^2}$$

$$Ar = 2496$$

$$C_1 = \frac{300(1 - \varepsilon_{mf})}{7} = \frac{300 * (1 - 0.795)}{7} = 8.80$$

$$C_2 = \frac{\varepsilon_{mf}^3}{1.75} = \frac{0.795^3}{1.75} = 0.287$$

$$Re_{mf} = \sqrt{(C_1^2 + C_2 * Ar)} - C_1 = \sqrt{(8.80^2 + 0.287 * 2496)} - 8.80$$

$$Re_{mf} = 19.36$$

c) Calculate the percent difference between your answer for part b) and the answer you obtained in Question 4.
Ans: Using Equation (11):

$$\%\ Difference = \frac{|Re - Re_{mf}|}{\left(\frac{Re + Re_{mf}}{2}\right)} * 100\% = \frac{|15.17 - 19.36|}{\left(\frac{15.17 + 19.36}{2}\right)} * 100\%$$
$$= 24.25\%$$

This large difference is mainly because the Re_{mf} equation should use the interstitial velocity (v_i).

d) Determine v_i, calculate a new Re as in Question 4, and then compare as in part c).
Ans: Using Equation (12):

$$v_i = \frac{Q_{mf}}{A_{cs} * \varepsilon_{mf}} = \frac{2.52 * 10^{-3}\ \frac{m^3}{s}}{9.15 * 10^{-3}\ m^2 * 0.795} = 0.3465\ \frac{m}{s}$$

Determining the new Re from Equation (1):

$$Re = \frac{D_p v_i \rho_g}{\mu} = \frac{1.8 * 10^{-4} m * 0.3465\ {}^{m}/_{s} * 5.25\ {}^{kg}/_{m^3}}{1.72 * 10^{-5} Pa * s} = 19.10$$

Calculate the percent difference using Equation (11):

$$\%\ Difference = \frac{\left|Re - Re_{mf}\right|}{\left(\frac{Re + Re_{mf}}{2}\right)} * 100\% = \frac{|19.10 - 19.36|}{\left(\frac{19.10 + 19.36}{2}\right)} * 100\% = 1.38\%$$

Using the correct velocity, the percent error decreases significantly.

7. Using one of the scientific online resources (i.e. Science Direct, SciFinder, etc.) available, you and your lab partners will find an article online about pharmaceutical manufacturing practices. Try to find an article that also discusses either fluidization or fluidized beds. In addition, use the MSDS's that you obtained as part of your pre-lab and any other literature to compare the bulk densities that you found in part I of the experiment.
Ans: On August 1, 2013, a Science Direct search was made with the keywords pharmaceutical manufacturing and fluidization. A screenshot is shown below.

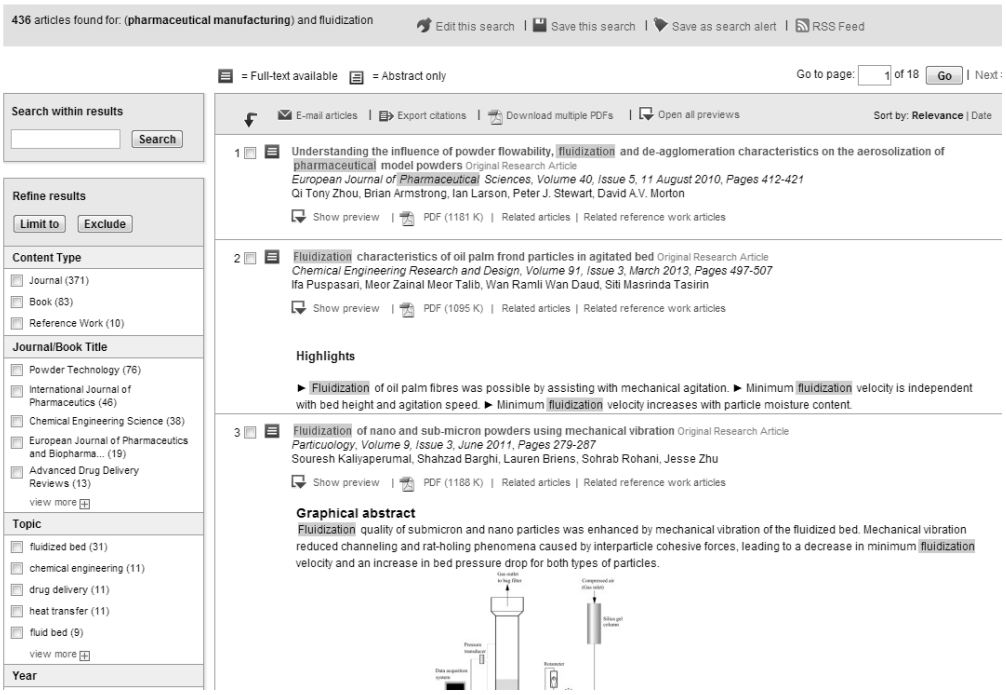


Figure 10. A screenshot of the Science Direct search.

The articles found by the groups of students should be discussed on the day that the laboratory report is turned in. Try to give each group of

students roughly five minutes to discuss their paper. You might find it helpful to have the students notify you in advance of their choice, so as to limit the amount of repeating reports.

Using other literature sources, it was determined that the density of kaolin was in the range of 1.8 to 2.6 grams per cubic centimeter (g/cc).[10] For Avicel® PH 200, the bulk density was found to be in the range of 0.29 to 0.36 g/cc.[11] While the kaolin value found in experimentation was smaller than specified by the literature, it could still be correct, as the density given was not specified as either bulk or particle density. If considered particle density, then the laboratory findings are still within range.

REFERENCES

1. Davies, W.L. and Gloor, W.T. Jr. Batch Production of Pharmaceutical Granulates in a Fluidized Bed I: Effects of Process Variables on Physical Properties of Final Granulation. Journal of Pharmaceutical Sciences. Vol. 60 no. 12. pp. 1869 – 1874. 1971.
2. Hesketh, R.P., Slater, C.S., Farrell, S., and Carney, M. "Fluidized Bed Polymer Coating Experiment." Chemical Engineering Education. Vol. 36 no. 2 pp. 138-143. 2002.
3. The FMC Biopolymer Company. Avicel® for Solid Dosage Forms. 2012. Accessed 9 September 2013. http://www.fmcbiopolymer.com/Pharmaceutical/Products/Avicelforsoliddoseforms.aspx
4. Engineering Toolbox. Air – Temperature, Pressure, and Density. Accessed 9 September 2013. http://www.engineeringtoolbox.com/air-temperature-pressure-density-d_771.html
5. Engineering Toolbox. Air – Absolute and Kinematic Viscosity. Accessed 9 September 2013. http://www.engineeringtoolbox.com/air-absolute-kinematic-viscosity-d_601.html
6. Perry, R.H. and Green, D.W. Perry's Chemical Engineer's Handbook. 7th edition. 1997. McGraw-Hill.
7. Fisher Scientific. "Kaolin, pure, Acros Organics." 2013. Accessed 4 December 2013. http://www.fishersci.com/ecomm/servlet/fsproductdetail_10652_16067959__-1_0
8. Kunil, D. and Levenspiel, O. Fluidization Engineering. 2nd edition. Butterworth Heinemann. Boston. 1993
9. Subramanian, R.S. Flow through Packed Beds and Fluidized Beds. Clarkson University. http://web2.clarkson.edu/projects/subramanian/ch301/notes/packfluidbed.pdf
10. Fischer Scientific. Kaolin, acid washed powder, Material Safety Data Sheet. Revised: 20 July 2009.

11. The FMC Biopolymer Company. Product Specification Bulletin: Avicel® PH-200. Revised: 01 April 2009.

B.3 Asthma Drug Delivery Lab

Asthma Drug Delivery Laboratory Experiment – Instructor's Guide

Developed by: Alex Jannini, David Krause, Heather Malino and Kevin Sweeney, Rowan University, Department of Chemical Engineering
Edited by: C. Stewart Slater and Mariano Savelski, Rowan University, Department of Chemical Engineering

Date of Experiment:

OBJECTIVES

- Students will learn about intrusive laboratory experiments
- Students will gain experience in reverse engineering strategies and project designs
- Students will conduct a basic quality control analysis operation

Figure 1: Diagram of the dry powder inhaler

INTRODUCTION

ADVAIR® is a dry powder inhaler prescribed to patients with asthma and chronic obstructive pulmonary disease that uses two active pharmaceutical ingredients. Fluticasone propionate, one of the two, is a corticosteroid, which is used to reduce the inflammation of the lungs. Salmeterol xinofoate, the second, is a bronchodilator, which relaxes the muscles in the airways to help improve breathing.[1]

ADVAIR® is not only used as an option for people with asthma, but also can be used as a maintenance treatment for chronic obstructive pulmonary disease.[1] Chronic obstructive pulmonary disease (COPD) is a disease that makes it difficult to breathe. It also takes the form of chronic bronchitis, causing a long-term cough with mucus, and emphysema, which destroys the lungs over time. Most sufferers of COPD have a combination of the two symptoms.[2] Asthma occurs when the airways of the lungs tighten and narrow, which leads to wheezing, shortness of breath, coughing, and a tightening in the chest.[3]

ADVAIR® comes in three varieties: ADVAIR DISKUS® 100/50; ADVAIR DISKUS® 250/50; ADVAIR DISKUS® 500/50. The three varieties of ADVAIR® have different amounts of fluticasone propionate in the powder. For example, in an ADVAIR DISKUS® 100/50, there will be 100 µg (micrograms) of fluticasone

propionate and 50 µg of salmeterol. The 250/50 prescription of ADVAIR® is used for COPD treatment.[1]

In this lab, the teams will be examining an ADVAIR DISKUS®, and conduct an invasive reverse engineering experiment on the diskus. They will then compare the dry powder inhaler to two other types of inhaled medication transport systems; a nasal spray and a traditional metered dose inhaler. The goal is to see the difference in the transport process that each system uses, and to also see if there is any way to improve the design of the diskus. A quality control study on the packaging of powder in the ADVAIR DISKUS® is also provided. This will include an average and a standard deviation of the powder packages.

INSTRUCTOR'S NOTE

All of these forms of drug delivery can be purchased online. It may also be possible to obtain these through the companies that make them. GlaxoSmithKline is the creator of the ADVAIR DISKUS®, and may be contacted for assistance. They may be contacted through the following website: https://www.contactus.gsk.com/callback.html.

Figure 2: Removal of outer shell

MATERIALS NEEDED

- ADVAIR DISKUS®
- Small flathead screwdriver
- Analytical scale (able to read at least 1/10,000g)
- Albuterol metered dose inhaler (or suitable substitute)
- Fluticasone propionate nasal spray (or suitable substitute)
- Narrow-headed spatula
- KimWipes
- Weigh boats

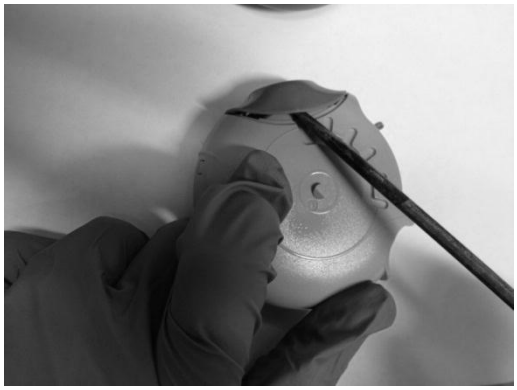


Figure 3: Proper removal of mouthpiece

SAFETY CONSIDERATIONS

All students should know that laboratory gloves and eyewear must be worn at all times to protect from sharp edges and medicines.

PROCEDURE

PART I - REVERSE ENGINEERING

1. Open up the diskus box and remove the information packets. Make general observations on the diagrams and information included.
2. Remove the inhaler from the tinfoil package. Based on its outside appearance, how do you think it works? Sketch the diskus.
3. With the flathead screwdriver, proceed to remove the outer shell of the inhaler. Be careful to not break or shatter any plastic.
4. Insert the screwdriver under the mouthpiece and use it as a lever to dislodge the mouthpiece.
5. Along the outside circumference of the diskus you will notice several slots and tabs that hold each half of the inhaler together. One by one, carefully depress each tab and pry the inhaler open.

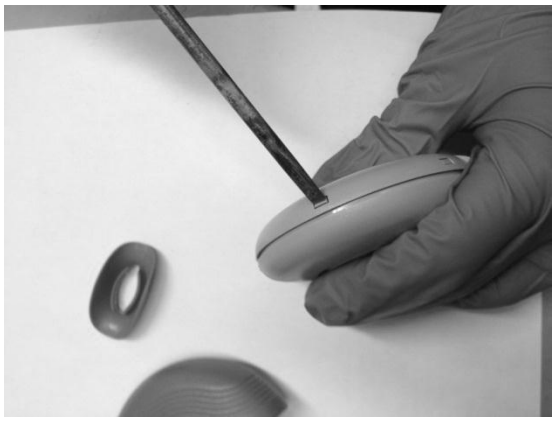


Figure 4: Proper depression of the tabs

6. This should expose the inside of the inhaler. Make observations on its appearance and the gears. Sketch the inside of the diskus.
7. Pull the lever down and reset it a few times. Discard the powder inside the blisters. Note how the gears move. Based on this, do you have any other ideas as to how the inhaler works?
8. Remove the foil strip. It will be stuck at one part after the foil has been split in half. Cut this section away to fully remove the rest of the foil strip.
9. The large white plastic mold that the foil fits into can be removed. Look for white tabs interlocking with the purple exterior shell by the mouthpiece. Push these tabs in to remove the white mold.

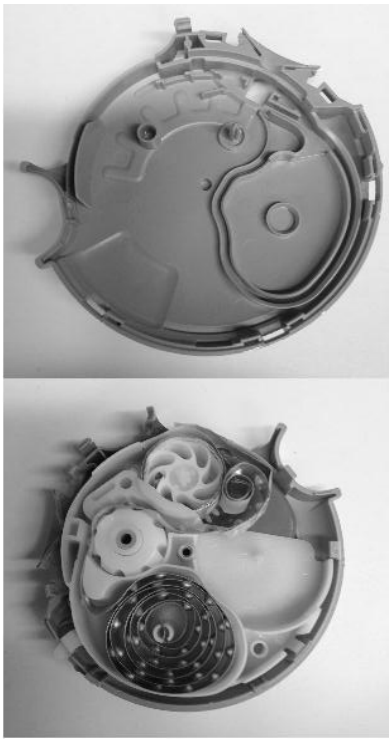


Figure 5: Inside the Diskus

10. At this point, the gears should be fully exposed. Move the lever up and down. Was your hypothesis as to how the diskus worked correct? If not, what is actually happening?

11. Set the diskus aside and look at the aerosol inhaler and nasal spray. Compare and contrast these methods of asthma drug delivery to the diskus. (i.e. size, complexity, ergonomics, visual appeal, etc.)

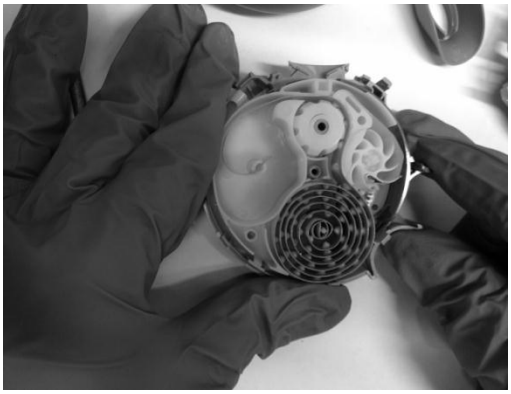


Figure 6: Operating the open Diskus

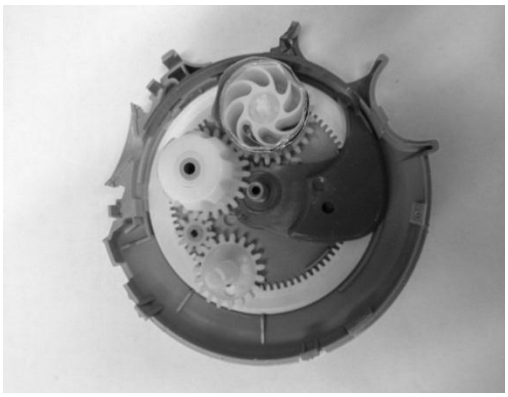


Figure 7: Removal of the inner plastic layer

PART II - QUALITY CONTROL/MEASUREMENT

You may wish to place your findings in the table found in the RESULTS section of this experiment, but you should also record them in your laboratory notebook.

ADVAIR® Quality Control

1. Take the foil strip that was previously removed over to a weighing station that has a precise analytical scale.
2. Place a weigh boat on the scale and tare the instrument.
3. Remove the boat and pull back the foil strip exposing the powdered drug in one blister. Carefully empty its contents into the weigh boat using a spatula to scrape off any remaining powder.
4. Place the boat back on the scale and record the result. Tare the scale once again so the powder does not have to constantly be thrown out in between measurements. Repeat this nine more times so that the weights of ten blister packs have been recorded.
5. After all measurements have been taken, dispose of the boat and powder in the trash.
6. Reassemble the diskus and place it back in the box along with included pamphlets.

Figure 8: Proper removal of medicine from blister pack

Metered Dose Inhaler Quality Control (See Figure 9 for proper techniques for this section)

1. First, take a weight boat, and place it on the analytical scale.
2. Now, take a KimWipe and fold it until you have a small rectangle that will fit over the end of the metered dose inhaler. Place this folded KimWipe in the weigh boat, and then zero the analytical scale.
3. Take the metered dose inhaler, and shake well. Remove the KimWipe from the weigh boat, and place on the end of the inhaler where the propellant will exit.
4. With the KimWipe on the end of the inhaler, press down on the canister section of the inhaler, allowing the propellant to exit the inhaler and the KimWipe to capture it.
5. Quickly place the Kimwipe back on the weigh boat and take a mass measurement. (This may be difficult as the excipient, which acts as a propellant, will evaporate.) Take the measurement once the scale stays on the same value for at least a second.
6. Dispose of the KimWipe. Repeat steps 2 to 5 with fresh KimWipes until you have ten mass measurements.

Nasal Spray Quality Control (See Figure 9 for proper techniques for this section)

1. Once again, take a weight boat, and place it on the analytical scale.
2. Now, take a KimWipe and fold it. Place this folded KimWipe in the weigh boat so that it covers the bottom and most of the sides of the weigh boat. Once this is done, place the weigh boat back on the scale, and then zero the instrument.

3. Take another KimWipe or a paper towel and fold several times. Take the nasal spray and shake. Prime the device by spraying it a few times into this second wipe.
4. With the spray primed, take the weigh boat off the scale, and place on a slightly downward angle. Spray the propellant into the weigh boat once.
5. Place the weigh boat back on the scale and take a mass measurement.
6. Dispose of the KimWipe. Repeat steps 2 to 5 until you have ten mass measurements. (Step 3 may not need to be repeated every time, but once every 2 to 3 measurements.)

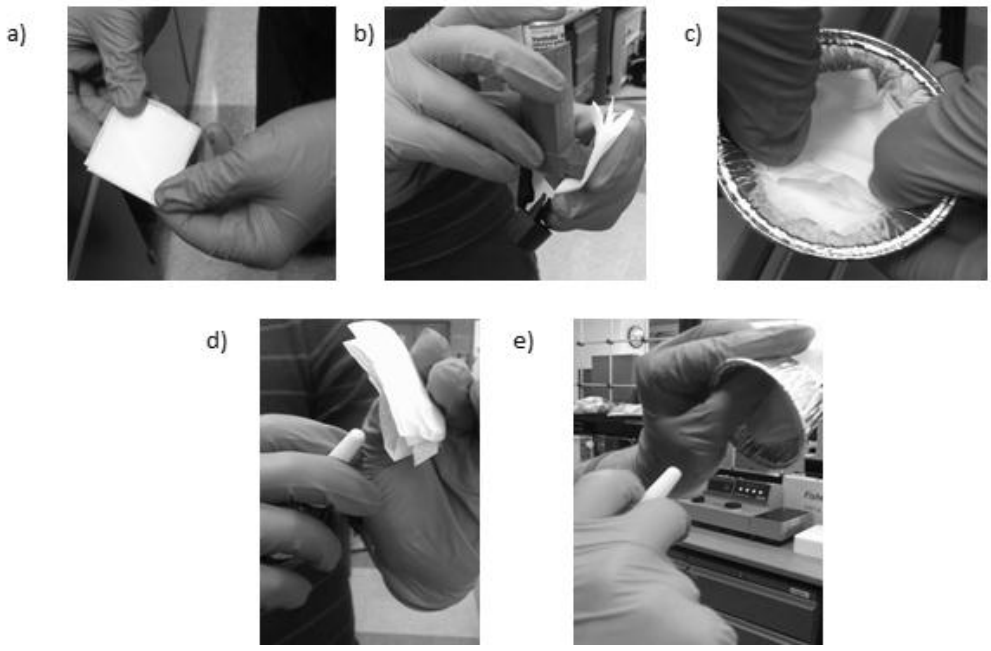


Figure 9: Different examples of the correct technique for metered dose inhaler (MDI) and nasal spray quality control measurements. a) The folding of the KimWipe before taking a mass sample of the MDI. b) The MDI cartridge being pushed down so that the medicine will be ejected into the KimWipe, and a mass measurement taken. c) The lining of a KimWipe on the bottom of a weigh boat far nasal spray mass measurements. d) Priming the nasal spray apparatus before taking a mass measurement. e) Taking a mass measurement using the nasal spray.

RESULTS

Make sure that the students record all results in a lab notebook, and that all members of the teams receive the data. These results can be placed in the table below and turned in along with solutions to the questions below. Questions were also asked throughout the procedure, and should be answered as well.

Table 1. Empty data table for collecting data in the Asthma Drug Delivery laboratory experiment

Diskhaler Trial	Mass (g)	MDI Trial	Mass (g)	Nasal Spray Trial	Mass (g)
1		1		1	
2		2		2	
3		3		3	
4		4		4	
5		5		5	
6		6		6	
7		7		7	
8		8		8	
9		9		9	
10		10		10	
Average					
Std. Dev.					

QUESTIONS

1. Compare and contrast the different styles of drug delivery that you examined in part I. Which of these systems did you think had the most appeal? Which do you think will work the best?

2. When comparing the MDI and the nasal spray, which of the two has a higher standard deviation? Compare all three standard deviations. Determine the highest and the lowest standard deviation. Explain what these results imply about the quality control measures of the three devices.

3. What were some sources of error in part II? How do you think you could fix some of these problems?

4. Based on the average weight of the blisters, what percentage of the powder are active pharmaceutical ingredients (API's) and what percentage is inactive? Assume that the amount of active ingredient from each sample is equal to the amount stated in the prescription dosage.

   The formula for finding the percentage of inactive ingredients is as follows:

$$\%_{Inactive} = \left(\frac{M_{total}^{avg} - \sum M_{API}}{M_{total}^{avg}}\right) x\ 100 \qquad (2)$$

M_{API} *can be found on the package. Watch the units*!

From this, find the percentage of active ingredients.

5. Do you think that the assumption made for problem 4 was a valid assumption to make? Why or why not?

6. The Advair dry powder inhaler, as described in the introduction section, contains two active ingredients, fluticasone propionate and salmeterol powder. There is one other ingredient listed on the label, lactose.
   a. What is lactose? Where else is lactose commonly found?
   b. Why would lactose be used in the inhaler? What type of excipient should it be considered?
   c. What are some negatives of using lactose?

   Be sure to site all references.

7. All metered dose inhalers (MDIs) need a propellant. A propellant makes up almost 99% of the dose of an inhaler. The propellant must have specific properties. Some of these include the boiling point, solubility of the API, toxicity and others. The API is suspended in the propellant and when the medication is dispensed the propellant creates an aerosol cloud, that the medication can be inhaled by the patient.[4]
   a. What is a CFC?
   b. Why are CFCs no longer used as propellants in inhalers?
   c. What type of propellant is used in the Ventolin inhaler? Which type of propellant did it replace?
   d. Compare the two propellants. Why do you think they replaced the propellant?

   Be sure to cite all references.

ANSWER KEY
PROCEDURE - PART I

8. Make general observations on the diagrams and data included.
   Ans: The handouts included with the diskus contained very detailed directions for the use of the diskus. Diagrams displaying how to use this diskus were also included in the handouts. Several sections of the handouts included legal issues, such as side effects, copyrights, warranties, and other information that is assumed to be included by legal regulation.

9. Based on its outside appearance, how do you think it works?
   Ans: The lever needs to be pressed down to release the medicine, and then the drug is inhaled from the mouthpiece.

6. Make observations on its appearance and the gears.
   Ans: The inside of the diskus is hollow, with several gears that work to release the drug from the folder.

7. Based on this, do you have any other ideas as to how the inhaler works?
   Ans: There is no device that punctures the blisters that hold the powder. Instead, the device rips the blister open using the lever.

10. Was your hypothesis as to how the diskus worked correct? If not, what is actually happening?
    Ans: If hypothesis is correct: Yes, the diskus works as hypothesized earlier in the experiment. If hypothesis is incorrect: No, the diskus works in a way that is different than hypothesized. In fact, the lever helps tear the blister pack open, which releases the powder so that it can be inhaled from the mouthpiece.
11. Sketch both of these and take observations as to how they deliver the drug.
    Ans: Both the aerosol inhaler and the nasal spray work by suspending the drug in fluid. This fluidized drug is then delivered to the body by the use of a propellant.

PROCEDURE - PART II

The table in the results section was filled out. Below are the results.

Table 2. Sample data collected in the Asthma Drug Delivery laboratory experiment.

Diskhaler Trial	Mass (g)	MDI Trial	Mass (g)	Nasal Spray Trial	Mass (g)
1	0.0130	1	0.0130	1	0.0867
2	0.0130	2	0.0128	2	0.0979
3	0.0127	3	0.0088	3	0.0989
4	0.0132	4	0.0107	4	0.0854
5	0.0126	5	0.0130	5	0.1004
6	0.0123	6	0.0140	6	0.0983
7	0.0130	7	0.0140	7	0.1022
8	0.0129	8	0.0148	8	0.1000
9	0.0124	9	0.0120	9	0.0991
10	0.0130	10	0.0121	10	0.0986
Average	0.0128		0.0125		0.0968
Std. Dev.	2.81E-04		1.66E-03		5.48E-03

QUESTIONS

1. Compare and contrast the different styles of drug delivery that you examined in part I. Which of these systems did you think had the most appeal? Which do you think will work the best?
   Ans: The ADVAIR DISKUS® releases the drug in the most controlled manner. However, some patients suffering from an asthma attack or unable to inhale deeply may find it difficult to generate enough force to inhale the entire dosage and therefore would prefer a metered dose inhaler. Due to the aesthetics of the ADVAIR DISKUS®, it is most likely the drug delivery system with the highest appeal.

2. When comparing the MDI and the nasal spray, which of the two has a higher standard deviation? Compare all three standard deviations. Determine the highest and the lowest standard deviation. Explain what these results imply about the quality control measures of the three devices
   Ans: When comparing the MDI and the nasal spray, the nasal spray has the higher standard deviation. Of the three sets of data, the one with the lowest standard deviation was the ADVAIR Diskus® while the nasal spray had the largest standard deviation. If we consider no error in the measurement taking process, it would appear that the Diskus® is the most precise when it comes to the delivery of medication, while the nasal spray is the least precise. It would appear that the Diskus® has the highest quality control measures in place for drug manufacturing and delivery.

3. What were some sources of error in part II? How do you think you could fix some of these problems? Which of these systems do you think had the smallest source of error? Why?
   Ans: Inconsistency in weights for the ADVAIR Diskus® can be attributed to powder remaining on the foil strip, the spatula, and not being caught in the weigh boat. A more accurate method would be to not use a spatula and tap each blister in with as little space between the weigh boat and foil strip as possible. Residue remaining on the foil strip could be washed off with water, collected in a separate beaker, and the water allowed to evaporate. The small quantity of the measurements can be a problem, as well. If there is a breeze and the wind guards are not shut on the scale then this will affect the scale's ability to make an accurate

measurement. A more accurate scale could be used, if one could be acquired (capable of reading 10^{-5} grams).
As far as the metered dose inhaler, error could be made in the measurement process. Since the propellant will evaporate off, there is difficulty in keeping an accurate measurement. With the nasal spray, error could be included if the mechanism is not primed, causing a variable amount of drug to be released each time. These problems with the metered dose inhaler and the nasal spray are design flaws. It is difficult to take an accurate mass measurement of the MDI because an excipient used as a propellant evaporates off of the KimWipe. If you wait until after the excipient evaporates, you will see little if any change in mass from when the analytical scale was zeroed. There is little you can do to change this, as it is part of the MDI design. To get more accurate results, a high-end spectrophotometer could be used to obtain more accurate results. The spectrophotometer could be set to the absorbance level of the API and then sample could be taken in water to find the amount of API release with each spray.[5] For the nasal spray, it depends on how well you prime the apparatus, and at what angle you place it while spraying. If the angle is too small, the apparatus will not spray the same amount as it would at a higher angle. However, you cannot spray at too high an angle, or else the KimWipe will fall out of the weigh boat.
In other words, these errors are based on the design of the apparatus and the inability to obtain quality measurements in a simple way, such as the ADVAIR Diskus.® The Diskus is obviously the system with the smallest source of error based on the design of the system. It is much easier to determine the mass of the blister packets because they are in a solid form, and do not require a gas propellant in order to be properly administered to the lungs. The Diskus also does not require priming or a proper angle in order to take mass measurements. With that being said, it can also be determined that the Diskus will have the best results when it comes to precisely administering a pharmaceutical substance.

4. Based on the average weight of the blisters, what percentage of the powder are active pharmaceutical ingredients (API's) and what percentage is inactive? Assume that the amount of active ingredient from each sample is equal to the amount stated in the prescription dosage.
Ans: This number will vary, but preliminary experimentation yields an average weight of around 12.62 mg per blister. Using the 250/50 mcg diskus, there should theoretically be 300 mcg of API, or 0.3 mg. Therefore

the %inactive will be roughly (12.32/12.62 * 100) = 97.62%. To find %active, subtract this number from 100%: 100-97.62 = 2.38%.

5. Do you think that the assumption made for problem 4 was a valid assumption to make? Why or why not?
   Ans: Technically, the assumption made to solve problem 4 cannot be made, since there is no way to tell whether or not the mass of API is exactly that which is prescribed for each dosage. Therefore, we cannot say for certain that there is exactly the same amount of API in each of the blister packs.

6. The Advair dry powder inhaler, as described in the introduction section, contains two active ingredients, fluticasone propionate and salmeterol powder. There is one other ingredient listed on the label, lactose.
   a. What is lactose? Where else is lactose commonly found?
      Ans: From the Elmhurst college website, Lactose is a disaccharide sugar derived from galactose and glucose and it is found in cow and human milk. It has a formula of $C_{12}H_{22}O_{11}$.[6]

   b. Why would lactose be used in the inhaler? What type of excipient would it be considered?
      Ans: Lactose is used as a powder excipient in the inhaler because it is inexpensive, tasteless (except for a mild sweetness), and harmless to humans, in most cases. In this type of product, lactose would be used to enhance the API aerosolisation and delivery to the lungs.[7]

   c. What are some negatives of using lactose?
      Ans: Lactose can cause some people to have an allergic reaction. This could prohibit people with severe lactose allergies from using this medication.[1]

7. All metered dose inhalers (MDIs) need a propellant. A propellant makes up almost 99% of the dose of an inhaler. The propellant must have specific properties. Some of these include the boiling point, solubility of the API, toxicity and others. The API is suspended in the propellant and when the medication is dispensed the propellant creates an aerosol cloud, that the medication can be inhaled by the patient.[4]
   a. What is a CFC?

Ans: CFC is a chlorofluorocarbon, a molecule that contains carbon, chlorine, and fluorine. They are often is in the manufacturing of aerosol sprays and as refrigerants.[8]

b. Why are CFC's no longer used as a propellant in inhalers?
Ans: CFC's were found to be harmful to the Earth's ozone layer, and so the use of CFCs have been heavily regulated and eventually eliminated by the Montreal Protocol to Reduce Substances that Deplete the Ozone Layer (along with the London Amendment).[8]

c. What type of propellant is used in the Ventolin inhaler? Which type of propellant did it replace?
Ans: The Ventolin inhaler uses propellant HFA-134a. This propellant is norflourane and it replaced the propellants CFC-11 and CFC 12, otherwise known as trichloromethane and dichlorodifluoromethane.[9]

d. Compare the two propellants. Why do you think they replaced the propellant?
Ans: The two compounds have similar properties and are both non-toxic to humans when used as directed by a physician. HFA-134a does not contain CFCs and is a much greener propellant than the previous propellants used.[9]

REFERENCES

1. GlaxoSmithKline. "Highlights and Full Prescribing Information for ADVAIR DISKUS." January 2011. http://us.gsk.com/products/assets/us_advair.pdf
2. United States National Library of Medicine. "Chronic Obstructive Pulmonary Disease." May 2011. http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001153/
3. United States National Library of Medicine. "Asthma." July 2012. http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001196/
4. Noakes, T. Medical aerosol propellants. The Journal of Fluorine Chemistry. Vol. 118, pp. 35-45. 2002.
5. Samir, A.; Salem, H.; Abdelkawy, M. New Developed Spectrophotometric Method for Simultaneous Determination of Salmeterol Xinafoate and Fluticasone Proprionate in Bulk Powder and Seritide® Diskus Inhalation. Bulletin of Faculty of Pharmacy, Cairo University. Volume 50. Issue 2. pp 121-126. 2012.
6. Ophardt, C. E. "Lactose." The Elmhurst College Virtual Chembook. 2003. http://www.elmhurst.edu/~chm/vchembook/546lactose.html
7. Mills, S. "Pharmaceutical Excipients – an Overview Including Consideration for Paediatric Dosing." The World Health Organization. 2010.

8. Elknis, J. W. “Chloroflourocarbons.” National Oceanic and Atmospheric Administration (NOAA), Climate Monitoring and Diagnostics Laboratory (CMDL). http://www.esrl.noaa.gov/gmd/hats/publictn/elkins/cfcs.html
9. GlaxoSmithKline. “Ventolin Inhaler CFC-Free Inhaler.” 2012. http://www.gsk.com.au/resources.ashx/prescriptionmedicinesproductschilddataproinfo/1757/FileName/4C800F2C0864CC24030FD7142DA3074D/Ventolin_Inhaler_CFC_Free_PI_-_Clean.pdf

B.4 Degradation of Dissolvable Strips Lab

Degradation of Dissolvable Strips – Instructor's Version
Developed by: Alex Jannini, David Krause, Heather Malino and Kevin Sweeney, Rowan University, Department of Chemical Engineering
Edited by: C. Stewart Slater and Mariano Savelski, Rowan University, Department of Chemical Engineering
Date of Experiment:

OBJECTIVES

- Students will learn about mass transfer and degradation rates of drug delivery films
- Students will learn how to properly operate a spectrophotometer
- Students will determine the effect of temperature on this process

INTRODUCTION

In 2000, the pharmaceutical company Pfizer introduced a new over-the-counter product for the treatment of bad breath. This product came in a novel form that was not seen before; a small, orally dissolvable strip. This product revolutionized the industry, generating roughly 250 million dollars in sales. By 2002, many other brands of dissolvable strips were also on the shelves.[1] In 2011, the energy supplement industry also saw the potential profits of sheets. One company, known as Sheets, introduced a caffeine based strip which they claim has zero calories, zero sugar, and has the same caffeine as one cup of coffee, shown in Figure 1. The brand also states that negative side effects, such as a "crash," are not common when taking the product. Although the company has faced controversy, especially with the endorsement of LeBron James, Sheets continues to make energy supplement strips.[2]

Figure 1. The energy strips you will be using in class.

While the use of dissolvable strips is a relatively new delivery method, it has become a popular method of drug delivery. In fact, many other fields of over-the-counter pharmaceutical products have introduced dissolvable strip products. Dissolvable strips that contain medicines for flu and sinus infection symptoms can now be found in most pharmacies.[3]

With dissolvable strips, the delivery vehicle is a thin, flexible sheet of polymer. The active pharmaceutical ingredient (API) is incorporated into this polymer to form the final product. Depending on the nature of the medicine, the API can be incorporated in one of two ways; either through liquid dissolution or solid suspension in the polymer. The size and thickness of these strips is dependent on the dosage of API that needs to be delivered.[3]

In this experiment, you will investigate the dissolution and degradation rate of a dissolvable strip that contains menthol. You will be using a spectrophotometer to take absorbance readings. These absorbance readings will then be used to find the amount of menthol that was released from the strips. You will also be comparing these rates for two different temperatures; ambient, otherwise known as room (roughly 20°C), and body (37°C).

MATERIALS NEEDED

- 2 Sheets™ brand Mint Boost dissolvable strips
- 2 petri dishes
- 2 timers
- Incubator or oven capable of reaching and maintaining 37°C
- Pair of tweezers
- Deionized water
- 500 µL to 5000 µL pipette
- Spectrophotometer capable of measuring absorbance at 630 nm
- Cuvettes
- Thermometer/thermocouple

INSTRUCTOR'S NOTE

This laboratory requires deionized (DI) water at a temperature of 37 °C (98.6 °F). It may be necessary that you have a batch of DI water kept in an incubator/oven at this temperature overnight or a few hours before the start of experimentation.

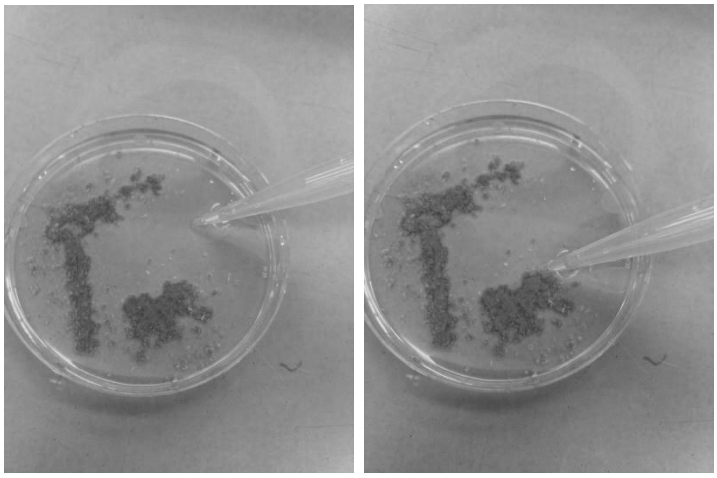
In addition, this lab models the release of blue food dye, not caffeine. To model the release of caffeine, an advanced spectrophotometer that can take absorbance readings at 273 nm must be used. While it may be possible to take readings at the 273 nm wavelength, it is encouraged to use the 630 nm for this experiment. A separate time versus absorbance chart is shown in the appendix, along with separate answers based on using this other absorbance.

SAFETY CONDITIONS

Laboratory gloves and eyewear must be worn at all times inside the lab. Be sure to keep water away from the spectrophotometer.

PROCEDURE

1. Start by turning on the spectrophotometer and setting it to take absorbance readings at 630 nm.
2. While the spectrophotometer warms up, place 2.5 mL of deionized water into each of the petri dishes.
3. Place one of the petri dishes into the oven/incubator that is set at 37°C.
4. Allow 20 minutes to pass so that the water may reach 37°C and the spectrophotometer may warm up.
5. After the 20 minutes have passed, fill a cuvette with deionized water and zero the spectrophotometer.
6. Now that the spectrophotometer has been zeroed, use the tweezers to place a strip into one of the petri dishes. Once the strip has been placed in the petri dish, cover and start the timer.



Figures 2 and 3. From left to right, the proper (l) and improper (r) way to take a sample.

7. Place the other strip in the other petri dish using the tweezers. Once placed, close the petri dish and start a secondary timer. NOTE: It is a good idea to stagger the starting times so that you do not find yourself rushing to take two measurements. It may also be a good idea if you are working in teams to split the team so that one section of the group is in charge of one specific temperature study.
8. After five minutes have elapsed, take a sample of your water into a cuvette. Make sure that this sample is relatively far from the dissolvable strip so that you do not accidentally pick up any large portions of the dissolvable strip, as in Figures 2 and 3.
9. Take an absorbance reading then return the sample to the corresponding petri dish.
10. Take absorbance readings every five minutes for the first thirty minutes. After that, take absorbance readings every ten minutes until you have reached 90 minutes. You may use Table 1, but you should also record your results in your laboratory notebook.

Table 1. Empty data table to record absorbance at 630 nm data for the dissolvable strips laboratory.

Time (min)	Absorbance readings at 630 nm	
	Room Temperature (20°C)	Body Temperature (37°C)
0	0	0
5		
10		
15		
20		
25		
30		
40		
50		
60		
70		
80		
90		

11. Once you have taken all the necessary measurements, make sure to turn off the spectrophotometer and the incubator/oven.
12. Dispose of all equipment used in this lab, and make sure that any water spills were cleaned up before exiting the laboratory.

RESULTS

Be sure to record all the data you collected in this experiment into your laboratory notebook. If you split into two groups to complete this experiment, be sure that you share the data sets.

DATA ANALYSIS

To analyze the data, the best method is to create a graph of the time versus absorbance reading. In this case, the x-axis will be the time axis and the y-axis will be the absorbance axis. Create one of these graphs using Excel or another program and turn it in along with the rest of your laboratory report.

QUESTIONS

7. Now, you will take your absorbance readings and figure out the concentration of menthol in your solutions. You will do this using the following graph, which correlates absorbance at 630 nm to concentration in mg/mL. Once you have the concentrations, create another graph of concentration versus time for both temperature sets. In addition, fill in Table 2. Make a copy of this table and turn in along with the rest of the deliverables for this experiment.

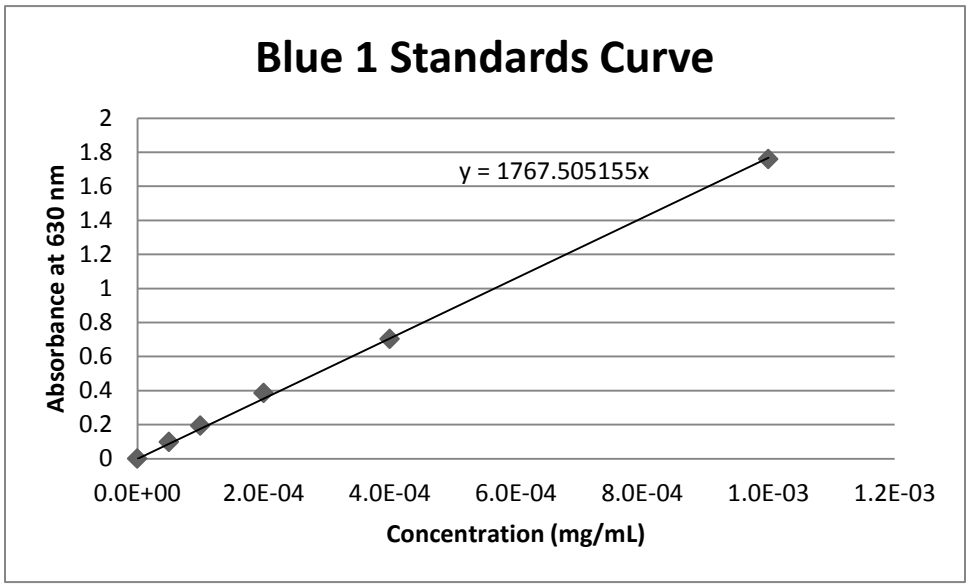


Table 2. Empty data table for recording concentrations in the dissolvable strips laboratory.

Time (min)	Concentration (mg/mL)	
	Room Temperature (20°C)	Body Temperature (37°C)
0	0	0
5		
10		
15		
20		
25		
30		
40		
50		
60		
70		
80		
90		

8. Now that you have found the concentration of the solution over time, you will need to use concentration and absorbance readings to determine the molar absorptivity of the blue food dye. The molar absorptivity, or the molar absorption coefficient, is defined as how strongly a substance absorbs light at a particular wavelength[4]. This coefficient is seen in the Beer-Lambert Law, an important law that governs the absorbance of light. This law is shown below:

$$A = \varepsilon \ell c \tag{3}$$

With:

$$A = absorbance\ (dimensionless)$$
$$\varepsilon = molar\ absorption\ coefficient$$
$$\ell = length\ the\ light\ has\ to\ travel\ through\ the\ solution\ (cm)$$
$$c = concentration\ of\ solution\ in\ moles\ per\ liter\ (M)$$

c) Use one of the higher time points (70 to 90 minutes) of both the room temperature and body temperature experimental runs to determine the molar absorption coefficients of both runs. Use the following constants to help you in this calculation.

$$\ell = 1\ cm$$
$$molar\ mass\ of\ Blue\ 1 = 793\ \frac{g}{mol}$$

d) Based on the values, do you think that the temperature affects the molar absorption coefficient?

9. Determine how well the molar absorption coefficients can determine the concentration of the solution based on absorbance readings. Use the molar coefficients you previously found and determine the concentration that the solution should be at based on the Beer-Lambert Law. Use a time point between 30 and 50 minutes in both cases. Determine how different these two numbers are by using percent difference. The equation for percent difference is shown below. In this case, the "E" terms are the molar concentrations. It should be noted that percent difference is a dimensionless number. Make sure you do all the necessary unit conversions before calculating the percent difference.

$$Percent\ Difference = \frac{|E_1 - E_2|}{\left(\frac{E_1 + E_2}{2}\right)} * 100\% \tag{4}$$

10. It is known that the molar absorptivity coefficient of the blue food dye used in these sheets is 1.3×10^6 $M^{-1}cm^{-1}$.[5]

    c) How different is the molar absorptivity coefficient that you found using your experimental data from this known value? Use experimental error to determine this difference. The equation for percent error is shown below.

$$Percent\ Error = \frac{|E - A|}{A} * 100\% \quad (3)$$

    Here, the "E" term is the molar absorptivity coefficient obtained through the experimental data, while the "A" term is the molar absorptivity coefficient given to you above. It should be noted that when using this equation, the two terms need to be in the same units. It should be noted that percent error is also a dimensionless number.

    d) Now, use the same time point that you used in Question 6 and determine the concentration based on the given molar absorptivity coefficient. Again, compare using percent error. Do this for both experimental runs. Here, the "E" term will be the concentration that you obtained during experimentation, while the "A" term will be the concentration that you obtained using the given molar absorptivity coefficient.

11. The Beer-Lambert Law is one of the most important laws used in spectroscopy (the interactions between light and matter). How could you use this law in an engineering aspect?

12. Now, we will discuss a rate law. A rate law, or rate equation, is an equation that governs the rate of a process as a function of a variable, such as time. These laws are used by engineers to determine the design of a chemical process. Rate laws applied to this experiment relate absorbance with time. For example, an important variable of a rate law, the rate coefficient/constant (k), can be determined using absorbance data. This can be done using the following equation:

$$\ln \frac{(A - A_\infty)}{(A_0 - A_\infty)} = -k * t \quad (4)$$

Where:

t	Time
A	Absorbance at time t
A_0	Absorbance at t=0
A_∞	Absorbance at t=∞
k	Rate coefficient

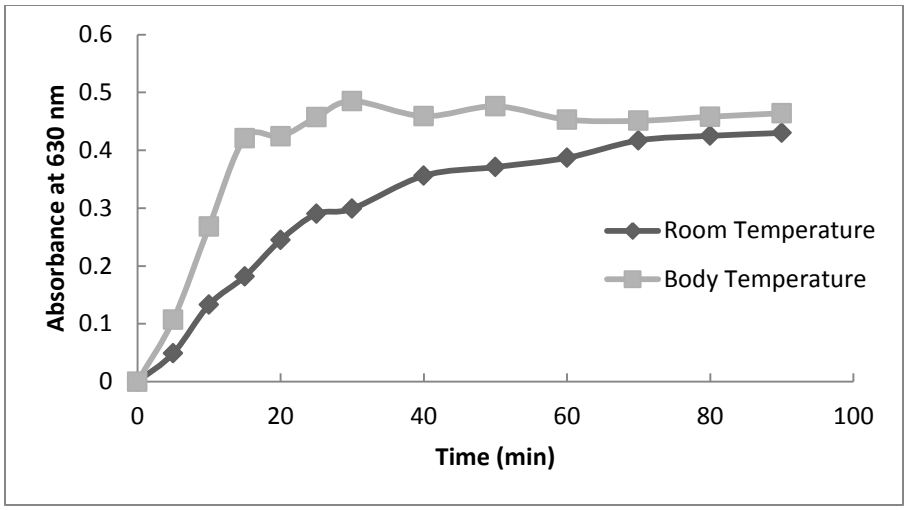
c) Determine the rate coefficient from your absorbance data. To do this, you will need to determine A_∞ based on your data. Use a point earlier in your experiment, and determine a rate coefficient for both sets of data.
d) Based on these results, does temperature affect the dissolution rate? Use the rate constant values you obtained to verify your answer.

ANSWER KEY

The following data shown in Table 3 will be used when answering the questions section of this report:

Table 3. Sample absorbance readings at 630 nm for the dissolvable strips laboratory

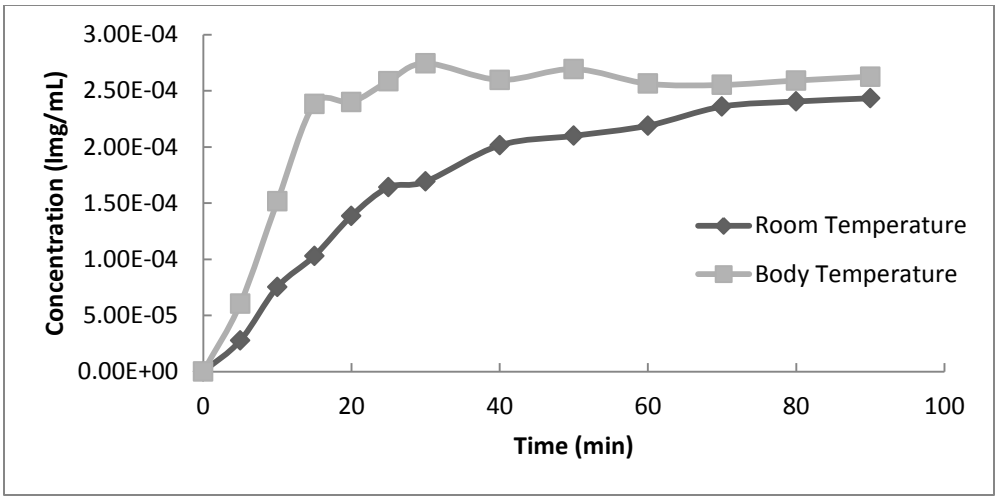
Time (min)	Absorbance readings at 630 nm	
	Room Temperature (20°C)	Body Temperature (37°C)
0	0	0
5	0.049	0.107
10	0.133	0.268
15	0.182	0.421
20	0.245	0.424
25	0.29	0.457
30	0.299	0.485
40	0.356	0.459
50	0.371	0.476
60	0.387	0.453
70	0.417	0.451
80	0.425	0.458
90	0.43	0.464



1. Once you have the concentrations, create another graph of concentration versus time for both temperature sets. Fill in the table and turn in along with the graphs generated and the rest of the report.
   Ans: The unit conversions were made and the table was filled in with the following data points, yielding the graph shown below.

Table 4. Sample data for the concentrations in the dissolvable strips laboratory

	Concentration (mg/mL)	
Time	Room Temp (20°C)	Body Temp (37 °C)
0	0.00E+00	0.00E+00
5	2.77E-05	6.05E-05
10	7.52E-05	1.52E-04
15	1.03E-04	2.38E-04
20	1.39E-04	2.40E-04
25	1.64E-04	2.59E-04
30	1.69E-04	2.74E-04
40	2.01E-04	2.60E-04
50	2.10E-04	2.69E-04
60	2.19E-04	2.56E-04
70	2.36E-04	2.55E-04
80	2.40E-04	2.59E-04
90	2.43E-04	2.63E-04



2. a) Use one of the higher time points (70 to 90 minutes) of both the room temperature and body temperature experimental runs to determine the molar absorption coefficients of both runs. **Ans.** For this answer, the time point of 80 minutes was used. The molar absorption constants were found to be:

ε at room temperature = $1.401 * 10^6\ M^{-1}\ cm^{-1}$
ε at body temperature = $1.401 * 10^6\ M^{-1}\ cm^{-1}$

This was found by first calculating the molar concentration:

$$Concentration\ at\ 80\,min = 2.40 * 10^{-4}\ \frac{mg}{mL} = 2.4 * 10^{-4}\ \frac{g}{L}$$

$$Molar\ Concentration\ at\ 80\,min = c = \frac{2.4 * 10^{-4}\ \frac{g}{L}}{793\ \frac{g}{mol}} = 3.03 * 10^{-7}\ \frac{mol}{L}$$

$$= 3.03 * 10^{-7} M$$

Now, using the Beer-Lambert Law:

$$\varepsilon = \frac{A}{\ell\, c}$$

$$\varepsilon = \frac{0.425}{1\ cm * 3.03 * 10^{-7} M} = 1.40 * 10^{-6}\ M^{-1} cm^{-1}$$

b) Based on the values, do you think that the temperature affects the molar absorption coefficient? **Ans.** Since the molar absorptivity coefficient is identical between the two sets of data, the temperature of the system does not affect the molar absorption coefficient. This is interesting, considering that it is mentioned in several articles that the

molar absorptivity coefficient does depend on the temperature of the system.[6,7] Then again, it might be different since we are working in the visible spectrum range, and not the ultra violet region or the infrared region. It should also be noted that we are only working in a temperature range of 17 °C. This might not be enough of a difference to thoroughly conclude that temperature has no effect on the molar absorption coefficient.

3. Determine how well the molar absorption coefficients can determine the concentration of the solution based on absorbance readings. Use the molar coefficients you found previously and determine the concentration that the solution should be at based on the Beer-Lambert Law. Use a time point between 30 and 50 minutes in both cases. Determine how different these two numbers are by using percent difference. **Ans.** Using the time of 40 min, the Beer-Lambert Law was completed:

$$A = \varepsilon lc = 1.40 * 10^{-6} M^{-1} cm^{-1} * 1 cm * \frac{2.01 * 10^{-4} \, {}^{g}/_{L}}{793 \, {}^{g}/_{mol}} = 0.355$$

Then, find the percent difference:

$$Percent\ Difference = \frac{|0.355 - 0.356|}{\left(\frac{0.355 + 0.356}{2}\right)} * 100\% = 0.28\%$$

The percent difference should be very small, as the molar absorption coefficient was found using these readings.

4. a) How different is the molar absorptivity coefficient that you found using your experimental data from this known value? Use experimental error to determine this difference. **Ans.** Using the percent error equation, the percent error was found to be:

$$Percent\ Error = \frac{|1.4 * 10^{6}\ M^{-1} cm^{-1} - 1.3 * 10^{6} M^{-1} cm^{-1}|}{1.3 * 10^{6} M^{-1} cm^{-1}} * 100\% = 7.69\%$$

b) Now, use the same time point that you used in Question 6 and determine the concentration based on the given molar absorptivity coefficient. Again, compare using percent error. Do this for both experimental runs. **Ans.** The sample calculations were done with the room temperature experimental run. Using the Beer-Lambert Equation:

$$A = 1.3 * 10^{6} M^{-1} cm^{-1} * 1\ cm * c$$

$$c = 2.74 * 10^{-7} M * 793\ \frac{g}{mol} = 2.17 * 10^{-4}\ \frac{g}{L} = 2.17 * 10^{-4}\ \frac{mg}{mL}$$

Now, find the percent difference:

$$Percent\ difference = \frac{\left|2.01 * 10^{-4}\ {}^{mg}/_{mL} - 2.17 * 10^{-4}\ {}^{mg}/_{mL}\right|}{2.17 * 10^{-4}\ {}^{mg}/_{mL}} * 100\%$$

$$= 7.25\%$$

The same was done for the body temperature experimental run. The concentration was found to be 2.27 *10^{-4} and a percent error of 14.5%.

5. How could you use this law in an engineering aspect? **Ans.** This law is one of the governing laws of spectrophotometry. This is used in several areas for determining concentrations based on absorbance data. Some of these areas are analytical chemistry, algal studies, and organic chemistry. In the case of engineering aspects, this can be useful to chemical and civil/environmental engineers. For example, civil/environmental engineers would use this to determine the growth of algae or the concentration of a contaminant in water. Chemical engineers can use this to determine contaminants in a system, determine the dissolution rate of a drug, and determine the concentration of product in a chemical reaction.

6. a) Determine the rate coefficient from your absorbance data. To do this, you will need to determine A_∞ based on your data. Use a point earlier in your experiment, and determine a rate coefficient for both sets of data. **Ans.** Using the time of 15 minutes, the calculations were followed, and k was determined for both of the data sets. These values are shown below:

k @ room temperature	0.0374 min^{-1}
k @ body temperature	0.1683 min^{-1}

This is obtained through the following calculation:

$$\ln\frac{(A - A_\infty)}{(A_0 - A_\infty)} = -k * t$$

$$\ln\frac{(0.182 - 0.424)}{(0 - 0.424)} = -k * (15\ min)$$

$$k = 0.0374\ min^{-1}$$

A_∞ was determined taking the average of the last three points of the absorbance data.

b) Based on these results, does temperature affect the dissolution rate? Use the rate constant values you obtained to back up your answer. **Ans.** Based on the rate constants, the temperature of the system does affect the dissolution rate. From the values obtained, we can see that the rate constant increases as the temperature increases. This means that the dissolution rate also increases with temperature. This makes sense, especially when you look at the graph made of the absorbance data.

REFERENCES

1. InnovateUs, Inc. “What are Breath Strips?” http://www.innovateus.net/health/what-are-breath-strips.
2. Donaldson James, Susan. “Sheets Give Caffeine Jolt, Potential for Abuse.” ABC News. 10 June, 2011. http://abcnews.go.com/Health/lebron-james-shills-sheets-caffeine-strips-bad-idea/story?id=13805037#.UeWj2m1nA6e.
3. Particle Sciences Drug Development Services. “Dissolving Films.” 2010. Volume 3.
4. Biology Online. Molar Extinction Coefficient. Biology Online.org. 22 June 2008. Accessed 11 September 2013. http://www.biology-online.org/dictionary/Molar_extinction_coefficient.
5. Reeves, J. Beer’s Law. Laboratory for science majors at The University of North Carolina Wilmington. Accessed 12 September 2013. http://uncw.edu/chem/Courses/Reeves/OnLineLabs/scienceMajors/BeersLaw_PH.pdf.
6. Seton Hall University. UV Absorbance. HPLC Book for the Chemistry Department. http://hplc.chem.shu.edu/NEW/HPLC_Book/Detectors/det_uvab.html.
7. McComb, R.B., Bond, L.W., Burnett, R.W., Keech, R.C., Bowers, G.N. Jr. Determination of the Molar Absorptivity of NADH. Clinical Chemistry. Vol. 2. pp. 141-150. 1976.

B.5 Effervescence Reaction Lab

Effervescence Reaction – Instructor's Version

Developed by: Alex Jannini, David Krause, Heather Malino and Kevin Sweeney, Rowan University, Department of Chemical Engineering

Edited by: C. Stewart Slater and Mariano Savelski, Rowan University, Department of Chemical Engineering

Date of Experiment:

OBJECTIVES

- Students will perform a basic mass balance on an effervescence reaction in pharmacology
- Students will conduct theoretical stoichiometric calculations and compare to experimental results
- Students will learn about the equilibrium constants and other fundamental aspects of reactions

INTRODUCTION

Alka-Seltzer® is an effervescent antacid ($NaCO_3$, KCO_3 plus anhydrous citric acid) containing acetylsalicylic acid (aspirin), which is an analgesic, antipyretic, and anti-inflammatory drug. Simply put, Alka-Seltzer® relieves upset stomach, provides pain relief, breaks fevers, and reduces inflammation.

Figure 1. Standard original strength packet

The effervescence allows for a faster rate of drug dissolution into a liquid medium (water in this case) by increasing the surface area of the drug exposed to solution and by "bubbling" the mixture, causing a stirring effect. The effervescence reaction is:

$$C_6H_8O_7(aq) + NaHCO_3(aq) \rightarrow H_2O(l) + CO_2(g) + Na_3C_6H_5O_7(aq) \quad (1)$$

Figure 2. Weighing the tablets

In this lab you will determine how much CO_2 is generated and released to the atmosphere by taking the initial and final weights of an Alka-Seltzer® solution. This is an introduction to mass balances, an important concept for engineers. This experimental value will then be compared to the theoretical amount of CO_2 mass generated, found through stoichiometry.

MATERIALS NEEDED

- 2 Alka-Seltzer® tablets (1 packet)
- Analytical scale (+/- 0.0001 g)
- Weigh boat
- Graduated cylinder
- 200 mL plastic beaker
- Timer

Figure 3. Creating the solution

PROCEDURE

1. Make sure safety glasses and examination gloves are on before entering the lab.
2. Remove both Alka-Seltzer® tablets from the packet. If the tablets are broken, be careful to not lose any pieces. How do you think a broken tablet will affect the rate of the tablets dissolving?
3. Place a weigh boat on the scale. Tare the instrument so it calibrates to zero with the added weight of the boat.
4. Weigh the Alka-Seltzer® tablets and record in your notebook.
5. Alka-Seltzer® is supposed to be dissolved in 4 oz. (118.3 mL) of water according to the manufacturer's directions. Using deionized water, measure out this volume of water with a graduated cylinder and add it to the beaker.
6. Weigh the beaker plus the added water and record it in your notebook. This weight plus the weight of the Alka-Seltzer® tablets is your initial weight.
7. Drop both tablets into the beaker.
8. For the first five minutes, take a weight every 60 seconds. After five minutes have passed, measure the weight every five minutes until an hour has elapsed. Tap the bubbles off of the sides of the beaker as they form.
9. Dispose of the solution down the sink.

PART II

10. Fill the beaker back up with the same amount of deionized water and weigh the water and the beaker.
11. On a weigh boat, measure out 2.0 g citric acid and 3.832 g sodium bicarbonate.
12. Drop the powder into the beaker and record weights at the same time intervals as Part I.
13. Dispose of the solution down the sink and clean up the lab area.

QUESTIONS

1. Fill in the tables:

Tablet	**Weight**	**Time**
Initial:		0 m
		1 m
		2 m
		3 m
		4 m
		5 m
		10 m
		15 m
		20 m
		25 m
		30 m
		35 m
		40 m
		45 m
		50 m
		55 m
Final:		60 m

Raw	**Weight**	**Time**
Initial:		0 m
		1 m
		2 m
		3 m
		4 m
		5 m
		10 m
		15 m
		20 m
		25 m
		30 m
		35 m
		40 m
		45 m
		50 m
		55 m
Final:		60 m

2. You should notice that the initial weights of the two solutions are different.
    a. What may cause this?
    b. To fix this, take the difference between the two sets, find the difference between the two initial points. This difference will need

to be subtracted from the solution with the higher weights. Find the new weights and record them in the table below.

Adjusted	**Weight**	**Time**
Initial:		0 m
		1 m
		2 m
		3 m
		4 m
		5 m
		10 m
		15 m
		20 m
		25 m
		30 m
		35 m
		40 m
		45 m
		50 m
		55 m
Final:		60 m

c. Please graph the revised data set along with the other set that was not changed.

3. Determine the experimental amount of CO_2 generated and released to the atmosphere by subtracting the initial weight from the final weight.

4. Balance the reaction given in the beginning of the laboratory.

5. According to the manufacturer's website, each tablet contains 1000 mg of citric acid and 1916 mg of sodium bicarbonate. Determine the moles of each reactant.

6. Determine which reactant is the limiting reactant. What is the percent excess? Why do you think there is extra added?

7. Using the effervescence reaction given in the beginning of the lab, determine the moles produced of CO_2 gas.

8. How many milligrams of CO_2 were made in both reactions?

9. What is the theoretical final weight of each solution? Use the weight of the beaker and water measured in the lab.

10. Determine your percent error at each point with the given equation:

$$\%_{Error} = \left(\frac{\left(M_{theoretically\ lost} - \left(M^{inital}_{experimental} - M^{point\ in\ time}_{experimental} \right) \right)}{M_{theoretically\ lost}} \right) x\ 100 \qquad (3)$$

11. What were some sources of error in this lab?

12. Was there if a difference in the way the pure components dissolved versus the tablets? Why do you think they behaved the same/differently? Do you think that the use of milling the powders when forming the tablets adds into the difference in behavior?

13. What is a different way that this experiment can be designed so that the gas released could be directly measured?

14. In reaction engineering, it is important to understand the mathematics behind chemical reactions. One of the important concepts is the reaction rate of a chemical reaction. This reaction rate determines how many moles of a reactant are being converted to a product over a period of time. The rate of reaction is commonly symbolized by r_A. The basic equation of the r_A is:

$$r_A = k\,[C_A]^x \qquad (4)$$

Where k is the rate constant and C_A is the concentration of the limiting reactant in a chemical reaction. This is also known as a rate law. A rate law can be linear or nonlinear in regards to the concentration. In most

cases, rate laws are zero-order (x=0), first-order (x=1), or second-order (x=2). Now, you will determine the rate constant and order of the rate law for a sub-reaction that takes place in the effervescent reaction.

This sub-reaction is the formation of bicarbonate to carbon dioxide:

$$HCO_3^- + H_3O^+ \rightarrow CO_2 + 2H_2O \qquad (5)$$

In this reaction, the limiting reactant is the bicarbonate ion. To determine the concentration of the bicarbonate ion (C_{HCO_3}), we can use the following equation.

$$C_{HCO_3} = \frac{initial\ mol\ HCO_3^- - mol\ CO_2}{Volume_{Water}} \qquad (6)$$

We can assume that there is 0.029 moles of bicarbonate ions in solutions.

a. Using the data you collected, determine the moles of CO_2 generated at each time point, and use that to determine the concentration of bicarbonate ions at each time point. Once this is done, make graphs of the following: C_{HCO_3} vs. time, ln(C_{HCO_3}) vs. time, and 1/C_{HCO_3} vs. time. Print out all three graphs. Do this for just the tablet set of data.
b. Now, determine the order of both sets of data. As a reminder; a zero-order reaction will be linear for concentration vs. time; a first-order reaction will be linear for ln(concentration vs. time; a second-order reaction will be linear for 1/concentration vs. time.
c. The rate constant can be found by determining the slope of the linear relationship. Find the k for the tablet.

ANSWER KEY

1. Fill in the table:
   Ans: Data will vary depending on the team. However, the table should have data similar to the set shown below:

Tablet	Weight	Time
Initial:	123.1220	0 m
	122.4068	1 m
	122.2695	2 m
	122.2130	3 m
	122.1810	4 m
	122.1624	5 m
	122.1017	10 m
	122.0683	15 m
	122.0376	20 m
	122.0133	25 m
	121.9917	30 m
	121.9694	35 m
	121.9462	40 m
	121.9228	45 m
	121.8983	50 m
	121.8742	55 m
Final:	121.8485	60 m

Raw	Weight	Time
Initial:	119.9593	0 m
	119.7013	1 m
	119.4425	2 m
	119.3279	3 m
	119.2654	4 m
	119.2233	5 m
	119.1223	10 m
	119.0740	15 m
	119.0437	20 m
	119.0232	25 m
	119.0066	30 m
	118.9913	35 m
	118.9780	40 m
	118.9654	45 m
	118.9531	50 m
	118.9412	55 m
Final:	118.9294	60 m

2. You should notice that the initial weights of the two solutions are different.
    a. What may cause this?
    Ans: This may be due to the aspirin in the Alka-Seltzer® tablets. However, this would only account for roughly 0.6 g of difference. The other difference in mass could be due differences in the volume of water. Human error could have led to the difference in water volume between the two trials.
    b. To fix this, take the difference between the two sets, find the difference between the two initial points. This difference will need to be subtracted from the solution with the higher weights. Find the new weights and record them in the table below.
    Ans: The difference found between the two starting points was 3.163 g. The first trial (Alka-Seltzer® tablets) had to have this difference subtracted from all points taken during experimentation. Below is the corrected data set.

Adjusted	**Weight**	**Time**
Initial:	119.9593	0 m
	119.2441	1 m
	119.1068	2 m
	119.0503	3 m
	119.0183	4 m
	118.9997	5 m
	118.9390	10 m
	118.9056	15 m
	118.8749	20 m
	118.8506	25 m
	118.8290	30 m
	118.8067	35 m
	118.7835	40 m
	118.7601	45 m
	118.7356	50 m
	118.7115	55 m
Final:	118.6858	60 m

c. Please graph the revised data set along with the other set that was not changed.
Ans: The following graph was made using the fixed Alka-Seltzer® data and the pure components.

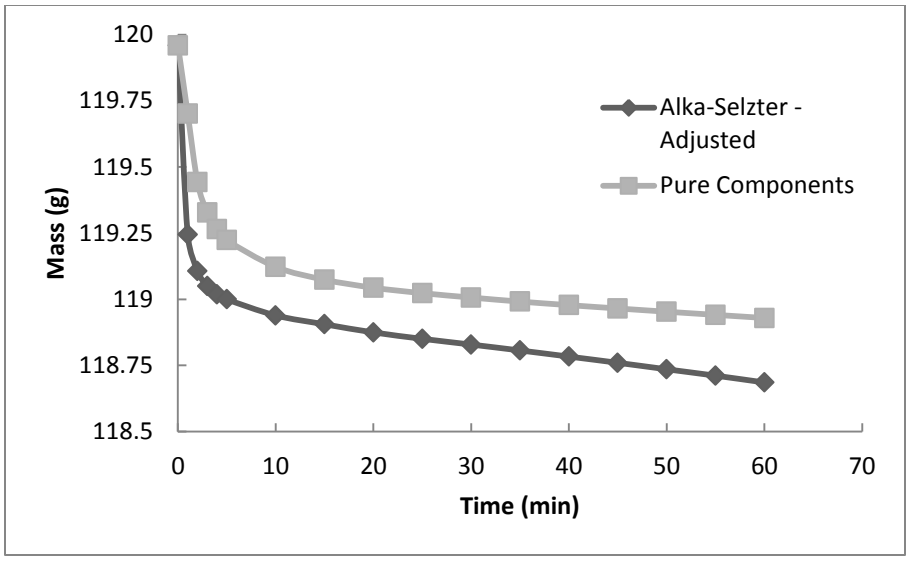


Figure 4. Mass lost over time during the effervescence reactions.

3. Determine the experimental amount of CO_2 generated and released to the atmosphere by subtracting the initial weight from the final weight.
   Ans: With the data obtained above for part I, it was determined that the mass lost was 1.36 grams.

$$148.501 - 147.14 = 1.36\ g$$

   The amount of mass lost in Part II was 0.338 grams.

$$145.504\ g - 145.166\ g = 0.338\ g$$

4. Balance the reaction given in the beginning of the laboratory.
   Ans:

$$C_6H_8O_{7(aq)} + 3NaHCO_{3(aq)} \rightarrow 3H_2O_{(l)} + 3CO_{2(g)} + Na_3C_6H_5O_{7(aq)}$$

5. According to the manufacturer's website, each tablet contains 1000 mg of citric acid and 1916 mg of sodium bicarbonate. Determine the moles of each reactant by converting each mass.
   Ans:

$$(1\ g)\left(\frac{1\ mol}{192.124\ g}\right) = 5.21x10^{-3}\ moles\ citric\ acid$$

$$(1.916\ g)\left(\frac{1\ mol}{84.007\ g}\right) = 2.28x10^{-2}\ moles\ NaHCO_3$$

6. Determine which reactant is the limiting reactant. How much of the other reactant is left over? Why do you think there is extra added?

Ans:

$$(5.21x10^{-3} mols\ of\ citric\ acid)\left(\frac{3\ mols\ NaHCO_3}{1\ mol\ citric\ acid}\right)$$
$$= 1.563x10^{-2}\ moles\ of\ NaHCO_3\ required$$

Therefore, citric acid is the limiting reactant

$$0.0228\ mol\ total - 0.01563\ mol\ required = 0.00717\ mol\ remaning$$

There is extra sodium bicarbonate added. In addition to driving the reaction, it also acts as an antacid when it enters the stomach.

7. Using the effervescence reaction given in the beginning of the lab, determine the moles produced of CO_2 gas.
   Ans:

$$(5.21x10^{-3} mols\ of\ citric\ acid)\left(\frac{3\ mols\ CO_2}{1\ mol\ citric\ acid}\right)$$
$$= 1.563x10^{-2}\ moles\ of\ CO_2\ produced$$

8. How many milligrams of CO_2 are made in this reaction?
   Ans:

$$(1.563x10^{-2} mols\ CO_2)\left(\frac{44010\ mg}{1\ mol\ CO_2}\right) = 687.8763\ mg\ theoretically\ lost$$

9. What is the theoretical final weight of the solution? Use the weight of the beaker, water, and tablets measured in the lab.
   Ans:
   Part I

$$(116.6280\ g) + [6.4940\ g - ((0.68788\ g)(2\ tablets))] = 121.75\ g$$

   Part II

$$(114.1293\ g) + [\ 5.8300g - ((0.68788\ g)(2\ tablets))] = 118.58\ g$$

10. Determine your percent error at each point with the given equation:
    Ans: A sample calculation for this is shown. Using this, the table was filled out:

$$\%_{Error} = \left(\frac{\left(M_{theoretically\ lost} - \left(M^{inital}_{experimental} - M^{point\ in\ time}_{experimental}\right)\right)}{M_{theoretically\ lost}}\right) x\ 100$$

$$\%_{Error} = \left(\frac{\left(1.376\ g - (123.1220\ g - 121.8485\ g)\right)}{1.376\ g}\right) x\ 100 = 7.433$$

Time (min)	Alka-Seltzer difference from theoretical	Pure difference from theoretical
0	100	100
1	48.014	81.247
2	38.034	62.435
3	33.927	54.105
4	31.601	49.562
5	30.249	46.502
10	25.837	39.161
15	23.410	35.650
20	21.178	33.448
25	19.412	31.958
30	17.842	30.751
35	16.221	29.639
40	14.535	28.672
45	12.834	27.756
50	11.053	26.862
55	9.3010	25.997
60	7.4330	25.140

A graph of this was made:

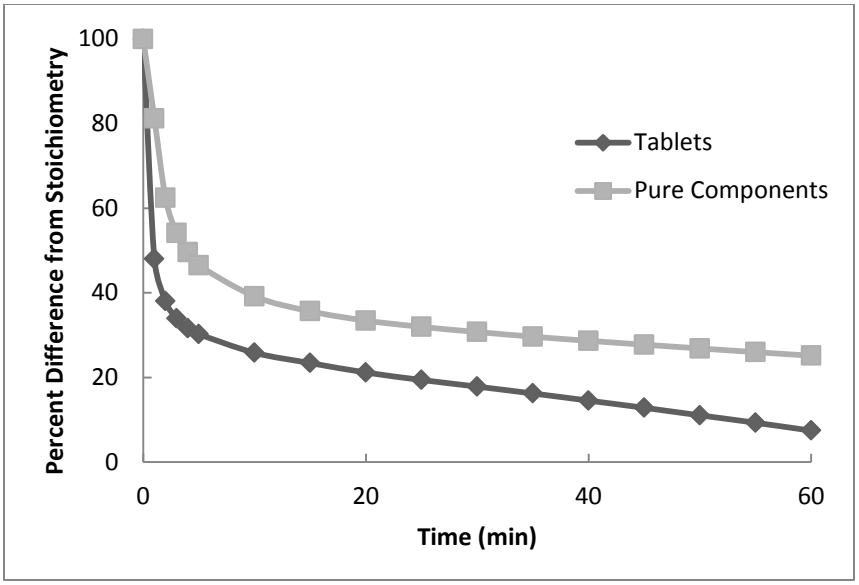


Figure 5. The percent difference from stoichiometry seen in the effervescence reaction.

11. What were some sources of error in this lab?
    Ans. Some sources of error in this lab include (most obviously) not all of the CO_2 leaving solution. In addition, a portion of CO_2 could have been absorbed by the water, as described by Henry's Law. The addition of aspirin (an acid) could have had some effect on the pH of the system, which could affect the rate and extent of the reaction. The pure powder may have not been well-mixed, which may have caused the reaction to not occur in optimal conditions.
12. Was there if a difference in the way the pure components dissolved versus the tablets? Why do you think they behaved the same/differently? It is known that Alka-Seltzer tablets use a milling process to reduce the size of their powder.[1] Do you think that the use of milling the powders when forming the tablets adds into the difference in behavior?
    Ans: The pure components will dissolve at a much slower rate if not properly mixed. It is not specified in the procedure to thoroughly mix the components together, so it is expected of students to realize why this case dissolves slower. The milling of the powder, the first step listed in the Handbook of Pharmaceutical Manufacturing Formulations[2] for the creation of effervescent tablets, will of course affect the behavior of the reaction. Milling the powder creates particles of smaller size, and the smaller the particle, the greater the surface area for the reaction to take place. Since the powder is finer in the tablets, the powder will dissolve quicker, which is shown above in Question 10.
13. What is a different way that this experiment can be designed so that the gas released could be directly measured?

Ans: If the reaction is carried out in a container that has a flow meter attached to it than the amount of CO_2 released can be directly measured. A similar, but more crude method, would be to attach a balloon to the top of a flask then estimate the volume occupied by the gas and density of CO_2 at experimental conditions to find a mass released.

14. Now, you will determine the rate constant and order of the rate law for a sub-reaction that takes place in the effervescent reaction.
    a. Using the data you collected, determine the moles of CO_2 generated at each time point, and use that to determine the concentration of bicarbonate ions at each time point. Once this is done, make graphs of the following: C_{HCO_3} vs. time, ln(C_{HCO_3}) vs. time, and 1/C_{HCO_3} vs. time. Print out all three graphs. Do this for just the tablet set of data.

    Ans: First, we need to find the mass of CO_2 that is being generated in the reaction. This can be found by taking the total weight and subtracting the weight at the different time points.

    $$g_{CO_2} = Total\ weight - weight\ at\ time\ point$$

    Then we can find the moles by dividing the grams of CO_2 by the molar mass (44 g/mol).

    $$mol_{CO_2} = \frac{g_{CO_2}}{44\ \frac{g}{mol}}$$

    Then, we use Equation 6 to find the concentration HCO_3 in mol/L. A sample of this calculation is shown for the time of 10 minutes:

    $$g_{CO_2} = 119.9593\ g - 119.1223\ g = 0.837\ g$$

    $$mol_{CO_2} = \frac{0.837\ g}{44\ \frac{g}{mol}} = 0.019\ mol$$

    $$C_{HCO_3} = \frac{0.029\ g - 0.019\ mol}{0.1183\ L} = 0.084\ \frac{mol}{L}$$

    This was done for each point, and the following table of data was made:

Time (min)	CO2 (g)	CO2(mol)	HCO3 (mol/L)	ln(HCO3)	1/HCO3
0	0.0000	0.0000	0.2451	-1.4059	4.0793
1	0.2580	0.0059	0.1956	-1.6318	5.1129
2	0.5168	0.0117	0.1459	-1.9250	6.8551
3	0.6314	0.0143	0.1239	-2.0886	8.0733
4	0.6939	0.0158	0.1119	-2.1905	8.9397
5	0.7360	0.0167	0.1038	-2.2655	9.6363
10	0.8370	0.0190	0.0844	-2.4725	11.8518
15	0.8853	0.0201	0.0751	-2.5890	13.3159
20	0.9156	0.0208	0.0693	-2.6696	14.4345
25	0.9361	0.0213	0.0653	-2.7281	15.3043
30	0.9527	0.0216	0.0622	-2.7782	16.0894
35	0.9680	0.0220	0.0592	-2.8266	16.8879
40	0.9813	0.0223	0.0567	-2.8707	17.6494
45	0.9939	0.0226	0.0542	-2.9144	18.4369
50	1.0062	0.0229	0.0519	-2.9589	19.2765
55	1.0181	0.0231	0.0496	-3.0039	20.1649
60	1.0299	0.0234	0.0473	-3.0507	21.1307

Now, we make the three graphs:

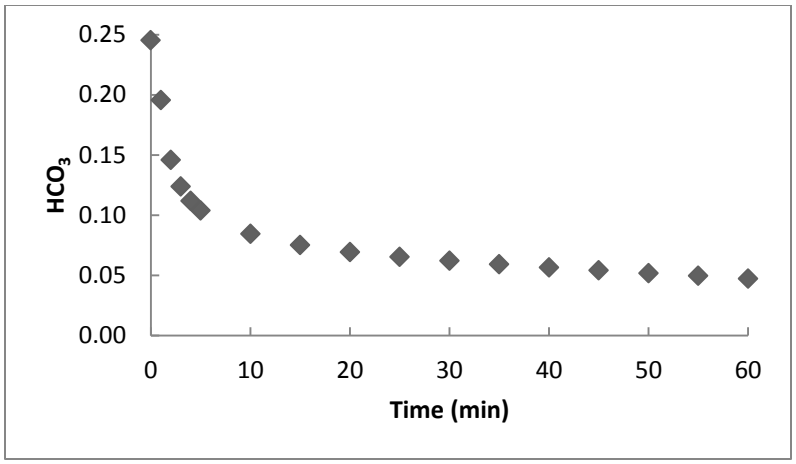


Figure 6. The bicarbonate concentration versus time.

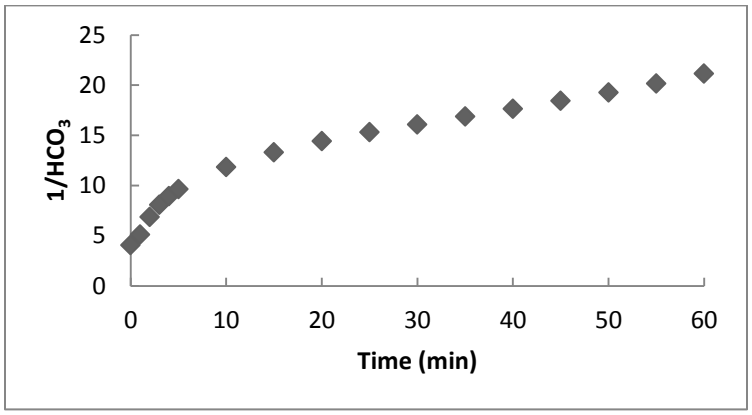


Figure 7. The natural log of the bicarbonate concentration versus time.

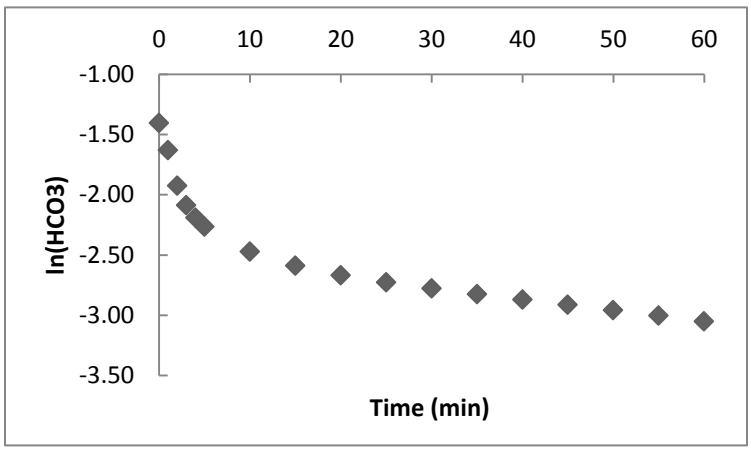


Figure 8. The inverse of the bicarbonate concentration versus time.

b. Now, determine the order of both sets of data. As a reminder; a zero-order reaction will be linear for concentration vs. time; a first-order reaction will be linear for ln(concentration vs. time; a second-order reaction will be linear for 1/concentration vs. time.
Ans: Of the three graphs, the inverse of the bicarbonate concentration versus time is the closest to being linear. With this in mind, it is determined that the tablet effervescence reaction is a second-order reaction. A trendline was put through the figure, which had an R^2 value of 0.91. This is shown below.

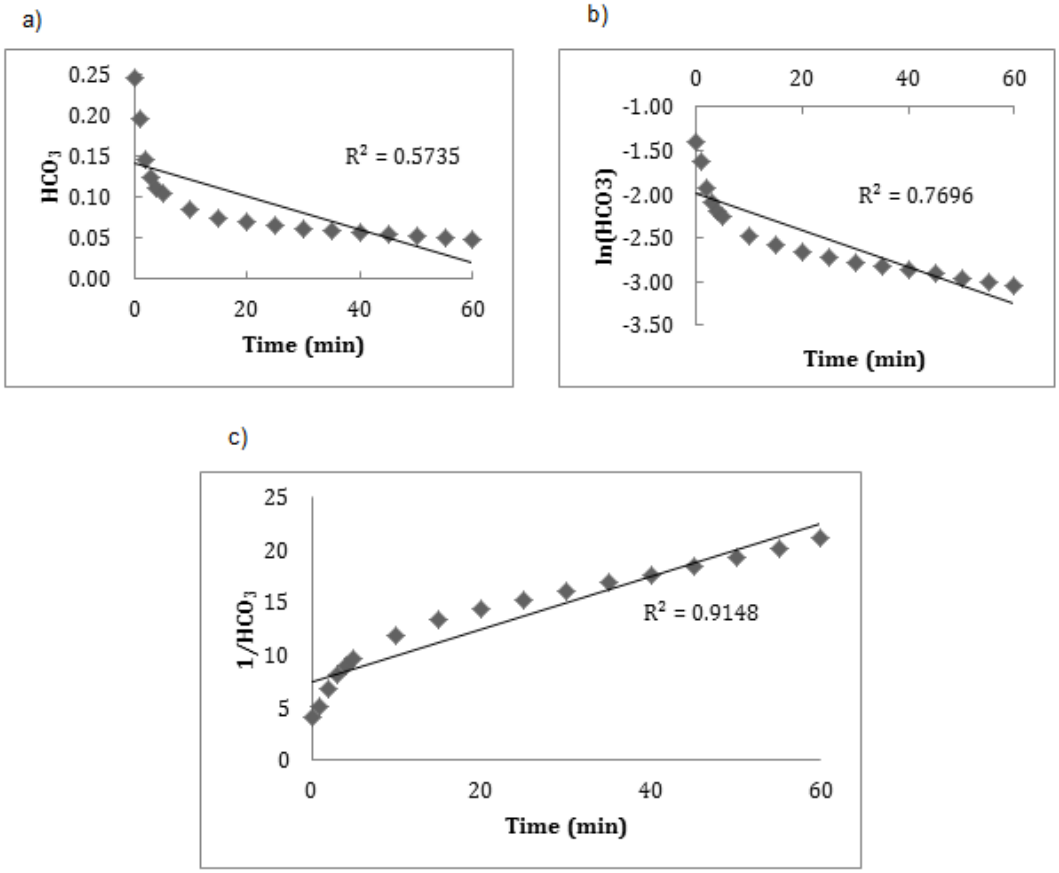


Figure 9. Trendlines added to a) the bicarbonate concentration, b) the natural log of the bicarbonate concentration, and c) the inverse of the bicarbonate concentration versus time graphs. From the R^2 values, it would appear that the reaction is second order in nature.

c. The rate constant can be found by determining the slope of the linear relationship. Find the k for the tablet.
Ans: The equation that fits through the trendline was found to be:

$$y = 0.2504x + 7.475$$

The k would then be 0.2504.

REFERENCES

1. H. Phykitt, "Analgesic Composition and Method of Making the Same". United States of America Patent 8,580,853, 13 June 2011.
2. Niazi, S.K. Handbook of Pharmaceutical Manufacturing Formulations: Compressed Solid Products. Volume One. 2009. New York. INFORMA Healthcare USA, Inc.

B.6 Dextromethorphan Crystallization Lab

Dextromethorphan Crystallization Laboratory – Instructor's Version

Developed by: Alex Jannini, David Krause, Heather Malino and Matthew Van der Wielen

Edited by: C. Stewart Slater and Mariano J. Savelski, Rowan University, Department of Chemical Engineering

Date of Experiment:

OBJECTIVES

- Students will develop a solubility curve for dextromethorphan.
- Students will gain an understanding of the techniques of crystallization and how it is used in the pharmaceutical industry.
- Students will learn the fundamentals of energy balances and heat transfer.

INTRODUCTION

A crystal is defined as a solid material whose atoms, molecules, or ions are arranged in an ordered pattern in three dimensions. Crystallization is the process by which solid crystals precipitate out of a solution. After the precipitation occurs, there will be a solid phase and a liquid phase in the solution. Then, the solution will be filtered to separate the two phases. Sometimes the solid phase is the desirable phase while other times the liquid phase is desired. Crystallization is a commonly used method of separating solid-liquid solutions in industry. Crystallization has been utilized in many different processes for decades. For example, many commodity chemicals like xylene and inorganic salts such as sodium chloride are formed using crystallization[1].

In more recent years, crystallization is used in the pharmaceutical industry. The most common reason for using crystallization in the pharmaceutical industry is to obtain a high purity active pharmaceutical ingredient (API). In the case of vitamin C purification, crystals are formed in either an aqueous or alcohol based media and then filtered out of solution[2].

One of the tools used in designing crystallization processes is the solubility curve. A solubility curve can be used to determine the saturated concentration of a solution of solids in a liquid. An example solubility curve is shown on the next page. The solubility curve is usually based on the concentration of solid in the solution and the temperature of the solution. In most cases, solubility curves are made with a solute in a solvent. In this lab, you will be making a solubility curve for the salt form of dextromethorphan in water.

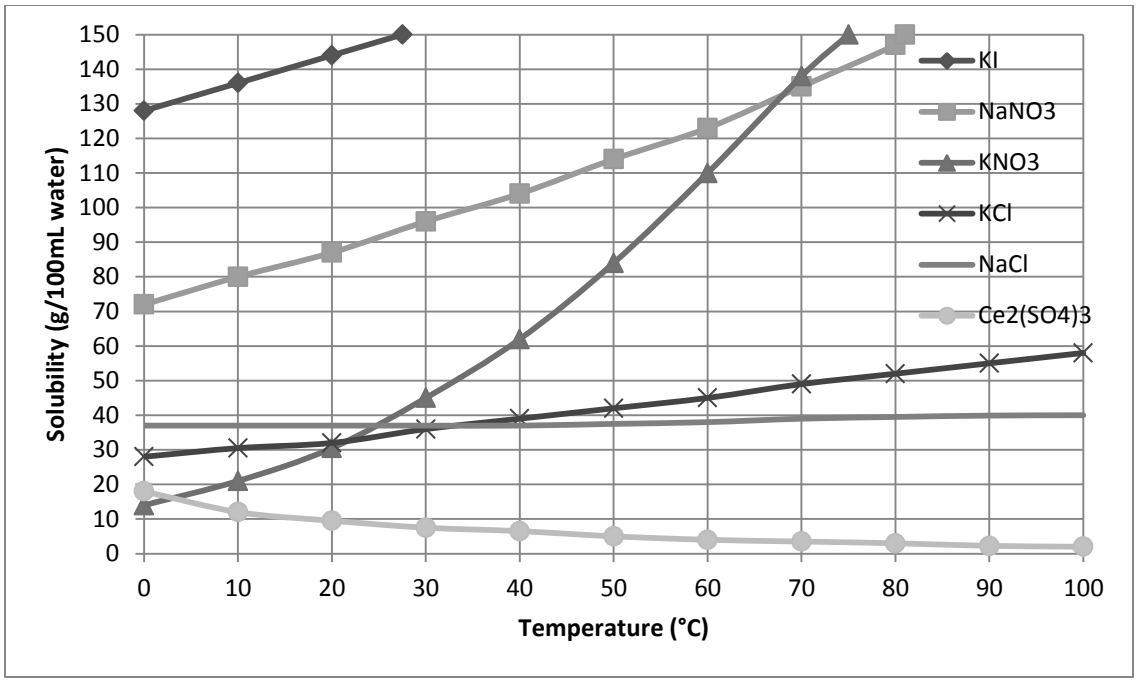


Figure 1. A sample solubility curve for several different salts. Adapted from the Halifax Regional School Board.[3]

Dextromethorphan (DXM) is the active pharmaceutical ingredient (API) in several cough syrups. Dextromethorphan is a strong antitussive agent.[4] It is often found as a monohydrated hydrobromated salt. This means that one molecule of HBr is attached to the dextromethorphan crystal. It belongs to the morphine group of alkaloids. A typical amount of dextromethorphan in one dose of cough medicine is approximately 15 mg.

INSTRUCTOR'S NOTE

Each group will need roughly 5 grams of DXM. Dextromethorphan HBr is a controlled substance. In order to obtain the API, you may need to send in a formal request letter stating the purpose of the experiment to your preferred vendor (Dextromethorphan HBr was obtained through Spectrum Chemical®). It should be noted that dextromethorphan can be illicitly used as a recreational drug. For this reason, we suggest that you provide a lecture on the dangers of working with pure API's and the discussion of specific MSDS information (LC50/LD50, toxicological effects, etc.). It is also suggested that you have the students look up a dextromethorphan MSDS and bring it in for the experiment.

SAFETY AND CONSIDERATIONS

Safety googles must be worn at all times in the lab. Gloves should also be worn during this experiment. When working with the powder, a dust mask should be worn. The chemical is of USP grade.

MATERIALS NEEDED

- Dextromethorphan HBr (one lab that contains 6 groups of students will need approximately 30 grams)
- Citric Acid, Anhydrous (one lab that contain 6 groups of students will need approximately 180 grams)
- Analytical scale (capable of reading 10^{-3} grams)
- Weigh boats
- 14 test tubes
- Test tube rack
- 1 large (approximately 800 mL or higher) beaker
- Heat/stir plate
- Stir bar
- 2 thermocouples with rod attachments
- Large graduated cylinder (1000 mL)
- 5mL micropipette
- Sharpie® or marking pencil
- Ring stand with test tube clamp

PROCEDURE

PART 1: DXM

For time limitations, divide the lab up so that half the team completes steps 1-2 while the other half of the group completes step 3-6.

1. Using the marking pencil or Sharpie®, number 7 test tubes and place them into a test tube rack.
2. Using the analytical scale, measure the dextromethorphan and prepare the test tubes as indicated below:

Test tube #	Milligrams (mg) of DXM
1	200
2	400
3	600
4	800
5	1000
6	1200
7	450-750

Tube #7 is a choice. You may choose any value (other than 600 mg) to place in this vial. Make sure to record this number.

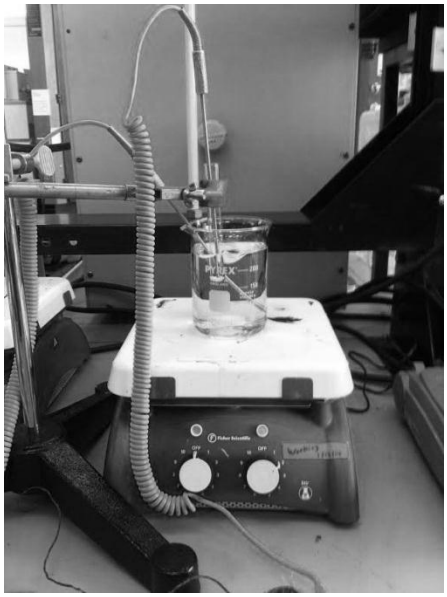


Figure 2. Proper setup of a test tube in the hot water bath.

3. Note the maximum volume of the large beaker. You will need to fill the beaker ¾ of the way full. Use the large graduated cylinder in order to precisely measure the amount of water you add to the beaker. Record the volume of water that you added to the beaker.
4. The beaker that you filled with water will be used as a hot water bath. Place the water bath on the hot/stir plate, and place a stir bar in the beaker. Place the heat control setting somewhere in the middle, and set the stir setting to the lowest possible setting.
5. Place one of the thermocouple rods in the water. The water bath needs to stay within 80 to 90 °C, which is the temperature suitable for dissolving all the DXM. This will require supervision and maintenance.
6. Now, setup the test tube clamp on the ring stand so that the clamp is just above the beaker.
7. Once you have measured out the masses of DXM necessary, use the micropipette and place 5 mL of water in each of the test tubes.
8. Now, secure test tube #1 in the tube clamp, and place the second thermocouple rod in the tube. Lower the clamp so that the test tube is as submerged as possible in the water bath.
9. Stir the test tube with the rod of the thermocouple. Keep stirring the solution until you see the DXM completely dissolve in the water. Loosen the clamp and remove the tube. Use a test tube holder if the tube is too hot.
10. Now hold the thermocouple in the solution. You may also need to wipe off the tube if there is excess condensation on the tube. Hold the test tube up

to the light and examine the solution for the first signs of crystallization. Record the temperature immediately as crystallization begins in the data table.

11. Repeat steps 8 through 10 for the other test tubes. Record all data. You may use the table below, but you should also record all results in your lab notebook.

Figure 3. The DXM and water solution once completely dissolved.

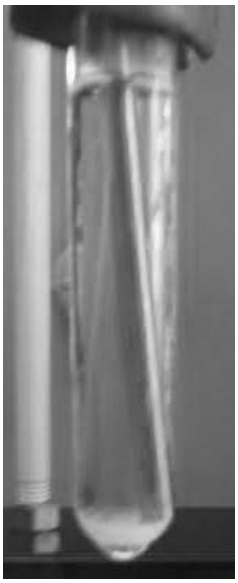


Figure 4. The DXM and water solution once crystallization has begun. Notice the white substance at the bottom of the tube.

RESULTS

You may use the table below to record your data. However, it is encouraged to also write your results down in your lab notebook.

Test Tube Number	Temperature of Recrystallization (°C)
1	
2	
3	
4	
5	
6	
7	

DATA ANALYSIS

For this section, you will be using Microsoft Excel. Once you have completed the lab and collected all the data, open up a new Excel file and place the data in a spreadsheet. Now, the concentration that we have right now is in mg/5mL. Change this to g/L. Remember that there are 1000 mg per g and 1000 mL per L.

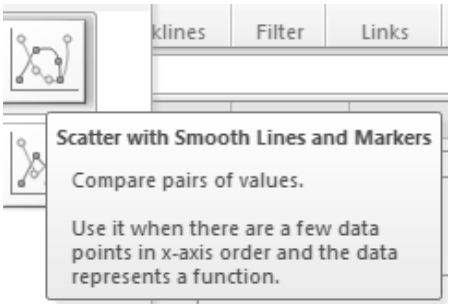


Figure 5. A screenshot of the graph you will need in Excel.

Once this is done, we need to create a solubility curve. To do this, we will be using the chart wizard. In excel, go to the insert tab and chose to insert a scatter graph. Look specifically for the "scatter with smooth lines and markers" option. Create a scatterplot that has temperature on the X-axis and concentration on the Y-axis for the first six points of the data collected. In addition, please use the following data points when creating your graph of the DXM data:

Table 1. Additional points for the solubility curve for DXM. Obtained from DrugBank and INCHEM.[5,6]

Concentration (g/L)	Temperature (°C)
0.00851	0
0.0747	20
15.0	25

Once this is done, change the chart layout so that you have titles for the x- and y-axis. This should be the first option in the chart layout section. Once you have titles for the axes, label them accordingly. Label the chart with your group number or the last names of your group members, and then delete the "Series 1" label.

Once you have a chart, you will need to edit the x-axis. To do this, click on the values on the x-axis. You should see these values boxed. Once done, right click, and click on the "Format Axis" option. You should now see the Axis Option menu. In this menu, look for "Major tick mark type." In the dropdown menu, select the inside option. Once this is done, print out your graph. Do the same thing for the citric acid data. Make sure to print out that graph as well. You will need these later.

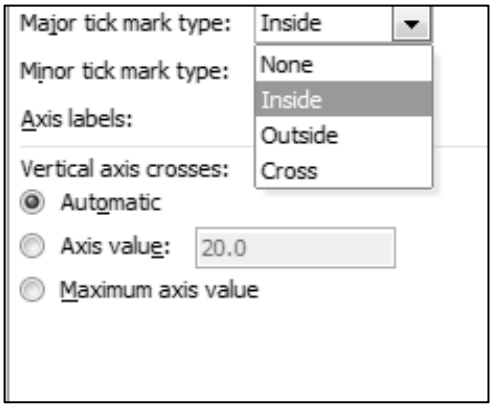


Figure 6. A screenshot of the "Major tick mark" option.

QUESTIONS

1. Now that we have a graph, we can check the accuracy of it. We will do this by using the random point that you collected during the procedure.
    a. We will check the accuracy of the graph through a process known as interpolation. In interpolation, you determine a new data point that lies within data that has already been collected. To do this, you will need a ruler. First, determine the concentration of your unknown in grams/L. Once you know that value, locate it on your chart. If your concentration lies within two tick marks, you will need to use the ruler. First, determine the length between the two tick marks. Next, solve the following equation:

$$\frac{(higher\ tick\ mark - lower\ tick\ mark)}{length\ between\ tick\ marks} = \frac{(random\ point\ - lower\ tick\ mark)}{length\ between} \quad (1)$$

Once you have found the length between the concentration and the lower tick, mark that on your graph. Once that is done, draw a straight line from this point to the line generated. Then, draw a straight line down to the x-axis. Now, you will have to determine the temperature this corresponds to. Here, you will have to do the same thing that you did previously. Determine the length between the tick marks on the x-axis, and then determine the length

between the lower tick mark and the line you drew down. Using the equation below, determine the temperature:

$$\frac{(higher\ tick - lower\ tick)}{length\ between\ ticks} = \frac{(temperture - lower\ tick)}{length\ between\ line\ and\ tick} \qquad (2)$$

b. Now that we have the temperature obtained from interpolation, we will determine the percent error between the temperature obtained through part a. and the temperature obtained experimentally. Use the following equation:

$$\%\ Error = \frac{|value\ obtained - value\ observed|}{value\ observed} * 100\% \qquad (3)$$

What does this tell you about the possible shape of the solubility curve?

2. Energy is required to heat the water bath to 90°C. The most basic equation that models the energy required to heat the water from room temperature to 90°C is:

$$Q = mC_p\Delta T \qquad (4)$$

Where "Q" is the energy required in J/g, "m" is the mass of water and "Cp" is the specific heat capacity of water.

a. Using the specific heat as 4.18 J/(g * °C) and the density of water as 1.00 g/mL, determine the amount of energy required to heat the water to 90°C. You may assume that the water was at room temperature (20 °C) before heating.
b. If a tank in an industrial process needs to heat 200 gallons of water to 90°C, how much energy would be needed?

3. Whenever there is a flow of heat from one source to another, there is an exchange of energy. This flow of energy is studied in the field of heat transfer. We will now discuss one of the basic conventions of heat transfer; conduction. Conduction can be defined as the transfer of energy from more energetic particles to less energetic particles due to their interactions.[7] One important term in conduction is the thermal diffusivity of a substance. The thermal diffusivity (represented from now on by the

variable, α) measures the ability of a material to conduct thermal energy in relation to its ability to store thermal energy.[7] To find α, we can use the following equation:

$$\alpha = \frac{k}{\rho C_p} \qquad (5)$$

With:

$$k = thermal\ conductivity\ \left[\frac{W}{m * K}\right]$$

$$\rho = density\ \left[\frac{kg}{m^3}\right]$$

$$C_p = specific\ heat\ at\ constant\ pressure\ \left[\frac{J}{kg * K}\right]$$

a. The term α is considered a dimensionless constant. With the units provided, prove that this is so.
b. Determine the thermal diffusivity of water at 25 °C and aluminum at 25 °C. Which is higher? What does this tell you about the two substances in regards to the conduction and storage of thermal energy? To do this, you will need to use the following table:

Table 2. Thermophysical properties for water and aluminum at varying temperatures. Adapted from Incropera et al and Thermal Fluids Central.[7,8]

Temperature (K)	Water			Aluminum		
	$k\ \left[\frac{W}{m * K}\right]$	$\rho\ \left[\frac{kg}{m^3}\right]$	$C_p\ \left[\frac{kJ}{kg * K}\right]$	$k\ \left[\frac{W}{m * K}\right]$	$\rho\ \left[\frac{kg}{m^3}\right]$	$C_p\ \left[\frac{kJ}{kg * K}\right]$
290	0.598	0.999	4.184	235	2708	0.868
300	0.613	0.997	4.179	237	2702	0.903

Obviously, you will need to use interpolation in order to obtain the correct data points. Use a similar method as used in Question 1.

c. Now, determine the thermal diffusivity for aluminum at 200 and 400 K. Use the following data below. What does this tell you about the thermal diffusivity of aluminum in regards to temperature? Do you think this is true for all temperature ranges? Try with 400 and 800. Does this provide more insight into the thermal diffusivity of aluminum with respect to temperature?

Table 3. Thermophysical data for aluminum at varying temperatures. Adapted from Incropera et al and Thermal Fluids Central.[7,8]

Temperature (K)	$\rho \left[\frac{kg}{m^3}\right]$	$\frac{k}{C_p}\left[\frac{W/_{m*K}}{J/_{kg*K}}\right]$
200	2719	237
400	2681	240
800	2591	218

4. In simple heat transfer, we can model the flow of heat using one-dimensional, steady-state conduction. What this means is that we model the flow of energy as though it were in one direction at an unvarying rate. This allows us to model the flow of heat over a certain distance. We will do this for the case of the test tubes we used in this experiment.

   First, we must show how to properly model this flow of heat. Picture the test tubes used in this. We will say that in the direct middle of the water will be the starting point. Then, we will say that top of the water level (where water meets air) is the ending point. So with these start and end points, we will be modeling the flow of heat from the middle of the test tube water level to the top of the test tube water level.

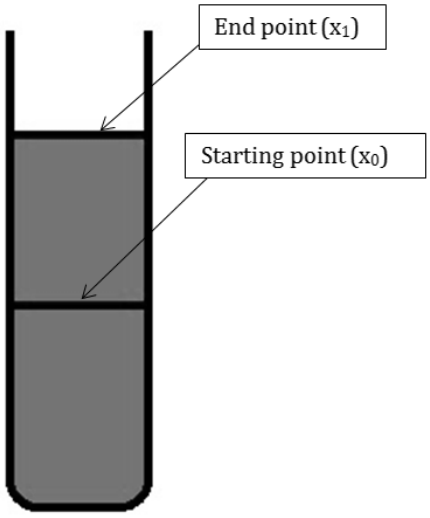


Figure 7. A representation of the one-dimensional, steady-state conduction model for the test tube.

In order to model this, we need to make two assumptions: 1) that the heat flows at a steady-state (does not fluctuate over time) and 2) that all the sides except for the end point are perfectly insulated. (NOTE: The other assumption that is made in order to use this model is that the surface temperature of the water is the same as the air temperature. If this assumption is not made, the flow of heat from the surface via natural convection, or the natural flow of air on the surface of the water, needs to be taken into account. This makes the model much more difficult; and as such, is eliminated from the model.)
With these assumptions made, we can use the following equation to model the flow of heat from the starting point to the end point. To do this, we can use the following equation to solve for the heat flow[7]:

$$\frac{q_x \Delta x}{A} = -k\,\Delta T \qquad (6)$$

With:

$$q_x = heat\ transfer\ rate\ in\ the\ x-direction\ [W]$$
$$\Delta x = length\ from\ x_0\ to\ x_1 = x_1 - x_0\ [m]$$
$$A = surface\ area\ of\ the\ heat\ transfer\ [m^2]$$
$$k = thermal\ conductivity\ \left[\frac{W}{m*K}\right]$$
$$\Delta T = difference\ in\ temperatures\ from\ end\ point\ to\ start\ point = T_1 - T_0\ [K]$$

Now, we will also say that half the volume of the water added to the test tube is in this specific space used for the model (2.5 mL). Assuming that the water is a perfect cylinder, and that the test tube has an inner diameter of 0.55 in, you find all the information necessary to model this flow of heat.

a. First, we will model this as though it were pure water. Take the temperature of recrystallization you found for test tube #1 in your DXM experiments, and state that this is T_o. T_1 will be the temperature of the air (20 °C). Determine the heat transfer rate if the thermal conductivity of water is at a weighted average of 0.58 W/m*K.
b. Now, we are going to find the thermal conductivity (k) for a mixture of the salts used in this experiment. To do this, we will use a thermal conductivity approximation for salt solutions. This is shown below[9]:

$$k = 0.29411 - 0.174 * C + 0.0008791 * T - 2 * 10^{-6} * T^2$$

Where:

$$C = concentration\ of\ salt\ (wt.fraction)$$
$$T = temperature\ of\ the\ system\ (°F)$$

$$k = \frac{BTU}{hrft°F} = {}^{W}/_{mK} \Big/ 1.5 \; {}^{BTU}/_{hrft°F}$$

Make sure to use these units when using the calculation. Again, use data obtained from test tube #1 for this. For the temperature, determine the average between the air and the temperature of crystallization. Determine the k value for DXM using this equation, then find q_x using the equation from part a.

c. Determine the percent difference between parts a and b. Is there a considerable difference? Which do you think is more accurate? Keep in mind that the thermal conductivity approximation you were given was developed using sea salt.

d. In order to calculate this, we made two assumptions about the heat flow. Can these assumptions be made for our experiment? Why or why not?

5. Citric acid is often used as a flavoring agent in pharmaceuticals. The saturation point for citric acid in water is provided. This is another way of showing the solubility of a substance, but with different units. Instead of concentration in mass solute per volume solution, we give the concentration in mass solute per mass solution.

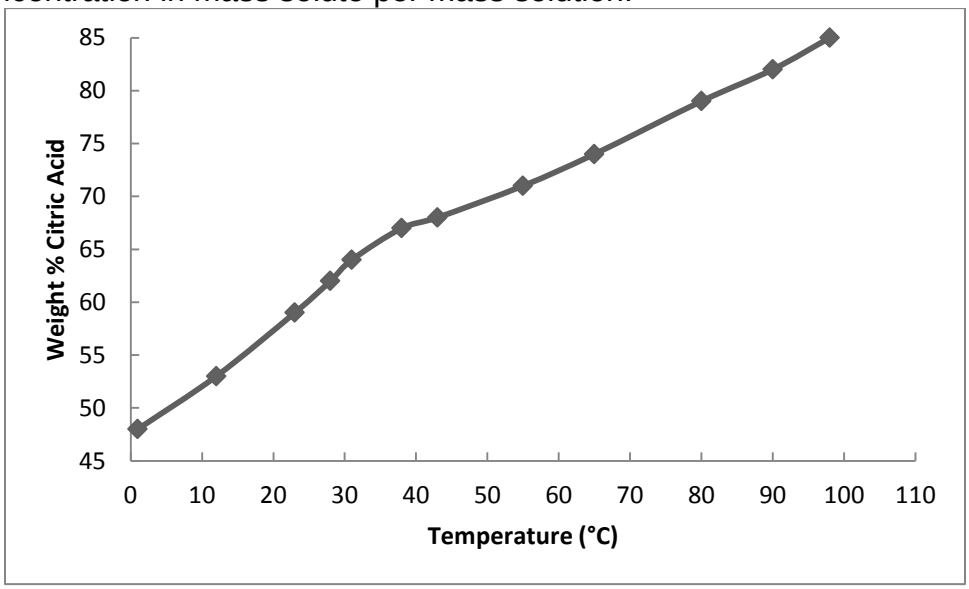


Figure 8. The saturated weight percent of citric acid in water with respect to temperature. Adapted from Dalman.[10]

a. Now, we have discussed solubility curves in great detail. In the introduction of this experiment, we discussed how a solubility curve tells you the point where a solution of solid crystals will completely dissolve into a solvent. Using the graph above, describe what would happen if you picked a point above the solubility curve

(example, 60 wt% and 10 °C) and what would happen if you picked below the solubility curve (example, 50 wt% and 60°C).

b. During the production of the new pharmaceutical tablet, 75 kg of citric acid is placed in a mixer with 100 kg water at 40 °C. The operators on duty notice that not all of the powder is dissolving into the water. Using the solubility curve, explain why this occurs. If we needed to fully dissolve the citric acid in the water, what would you recommend doing?

c. In another operation that uses citric acid, 78 pounds of citric acid is dissolved in 60 pounds of water and is heated to 80 °C. The solution needs to be cooled so that 18 pounds of crystals can be collected. To what temperature should this solution be cooled to?

6. In the previous question, you were given a scenario in which a solution of crystals and solvent were cooled past the solubility point. Indeed, this is what is commonly done in industry in order to separate crystals from liquids. Usually, the solution is sent to a cooler, a type of machine that drops the temperature of the solution. This allows crystals and saturated solution to form. This mixture is sent to a filter, which physically separates the liquid from the solid. Then, the solid (known as "cake") is sent to a dryer, so that more liquid can be removed from the crystals. An example of this can be seen below:

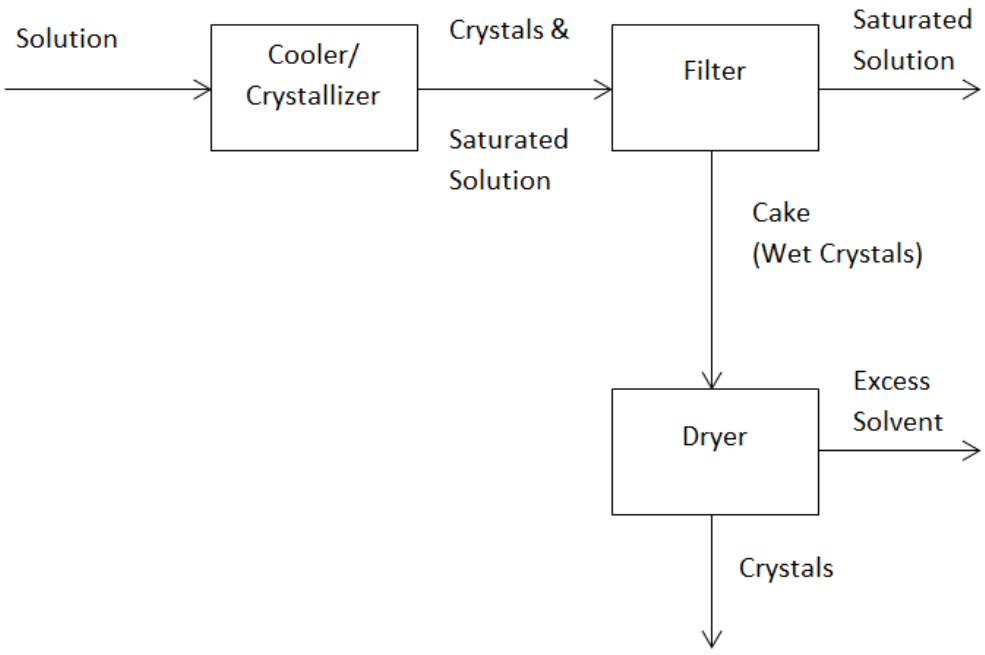


Figure 9. A simplified version of the setup used to separate crystals from solution. Adapted from Felder and Rousseau.[11]

a. 100 kg of a solution with a concentration of 150 grams of DXM per liter of water is sent through this process. The temperature of the solution is initially 75 °C, and is cooled down to 45 °C. Using your DXM data, determine the mass of crystals that would precipitate out. Assume that the solution has the same density as water.
b. Now, say this cooled solution is sent to a filter. The filter is considered 100% effective at removing the crystals. If the composition of the cake is 80% crystal by mass, calculate the mass of saturated solution that has been separated with the crystals.
c. If the dryer only allows the water to evaporate, what is the overall mass of crystals that was collected? If compared to the original amount of crystals in solution, what is the overall yield of this process?

ANSWER KEY

DATA ANALYSIS

The following data was collected and used for the data analysis section:

Test tube #	Milligrams (mg) of DXM /5 mL water	Temperature of Recrystallization (°C)
1	200	32.2
2	400	43.4
3	600	52.4
4	800	53.0
5	1000	56.1
6	1200	58.2
7	750	52.5

Since the concentrations are in mg/5mL water, the concentration was changed to g/L. An example of the conversion is shown below using the 200 mg/5mL concentration:

$$\frac{200\ mg}{5\ mL} = \frac{40\ mg}{mL} * \frac{g}{1000\ mg} * \frac{1000\ mL}{L} = 40\ \frac{g}{L}$$

Using this conversion, the data is now:

Test tube #	Concentration (g/L)	Temperature of Recrystallization (°C)
1	40	32.2
2	80	43.4
3	120	52.4
4	160	53.0
5	200	56.1
6	240	58.2
7	150	52.5

Using this data, and the extra data provided, the following chart was made:

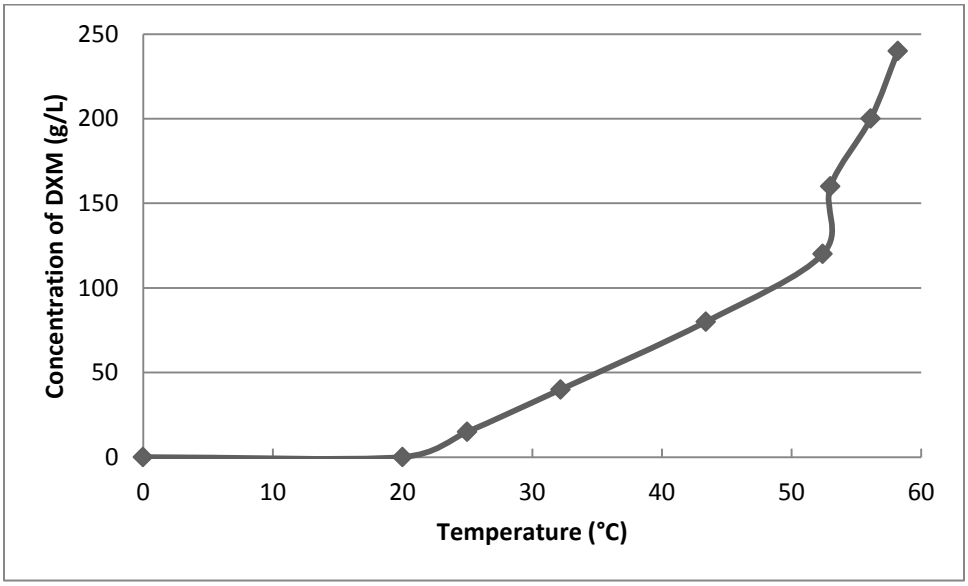


Figure 10. Example data for the Dextromethorphan Crystallization Lab.

The solubility curve generated has similar features to other solubility curves shown previously. In fact, this appears to be similar to the solubility curve of KNO_3, where it grows in a large, nonlinear way with increasing temperature.[2] Some of the limitations to this data is that it can only be used for concentrations and temperatures that were used in this experiment. This isn't a severe limitation, though, as the boiling point of water is 100 °C. Going beyond the boiling point of a solvent is never done when making a solubility curve.

QUESTIONS

1. Now that we have a graph, we will be checking the accuracy of it. We will do this by using the random point that you collected during the procedure.
   a. First, we will check the accuracy of the graph through a process known as interpolation…

   ANS. Using point 7, we found that the concentration in g/L was 150. This was already marked on the y-axis, so interpolation was not needed. If needed, however, Equation (1) would be:

$$\frac{100\ g/L}{4.3\ cm} = \frac{50\ g/L}{length\ between} \rightarrow length\ between = 2.2\ cm$$

   From there, a horizontal line would be drawn until it intersected the trendline at that concentration. Again, since this was already marked, the developers simple marked where the intersection occurred. From there, a vertical line was drawn until it intersected the x-axis. Equation (2) was used to determine the temperature:

$$\frac{(60-50)°C}{4\ cm} = \frac{(x-50)°C}{1.1\ cm} \rightarrow x = 53\ °C$$

   b. Now that we have the temperature obtained from interpolation, we will determine the percent error between the temperature obtained through part a. and the temperature obtained experimentally. What does this tell you about the possible shape of the solubility curve?

   ANS. Using Equation 3, the percent error was found to be 0.95% for part a. An example calculation for part a) is shown below:

$$\%\ Error = \frac{|53-52.5|}{52.5} * 100\% = 0.95\%$$

   This shows us that the solubility curve seems to be an accurate model of the effects of temperature on concentration.

2. Energy is required to heat the water bath to 90°C…
   a. Using the specific heat as 4.18 J/g and the density of water as 1.00 g/mL, determine the amount of energy required to heat the water to 90°C. You may assume that the water was at room temperature (20 °C) before heating.

   ANS. First, the mass of water was found using the volume of water for the bath (650 mL) and the density of water:

$$m = 650\ mL * 1\ \frac{g}{mL} = 650\ g$$

Then, using Equation (4), and assuming water was at room temperature prior to heating:

$$Q = 650\ g * 4.18\ \frac{J}{g * °C} * (90 - 20)°C = 1.90 * 10^5\ J = 190\ kJ$$

b. If a tank in an industrial process needs to heat 200 gallons of water to 90°C, how much energy would be needed?

ANS. First, to obtain the mass, we use the same density:

$$m = 200\ gal * 3785.41\ \frac{mL}{gal} * 1\ \frac{g}{mL} = 7.57 * 10^5\ g$$

Then, we use Equation (4) and again assume room temperature at the starting point:

$$Q = 7.57 * 10^5 g * 4.18\ \frac{J}{g * °C} * (90 - 20)°C = 2.22 * 10^8 J$$
$$= 2.22 * 10^5\ kJ$$

3. The thermal diffusivity (represented from now on by the variable, α) measures the ability of a material to conduct thermal energy in relation to its ability to store thermal energy.[7]

a. The term α has specific units. With the terms provided, find the units of α.

ANS. If we plug in the units of the equation:

$$\alpha = \frac{k}{\rho C_p} = \frac{{}^{W}/_{mK}}{{}^{kg}/_{m^3}\ {}^{J}/_{kgK}} = \frac{{}^{J}/_{smK}}{{}^{kg\,J}/_{m^3 kgK}}$$

After cancelling out all like terms, α can be found to have the following units:

$$\alpha = \frac{m^2}{s}$$

b. Determine the thermal diffusivity of water at 25 °C and aluminum at 25 °C. Which is higher? What does this tell you about the two substances in regards to the conduction and storage of thermal energy?

ANS. To do this, interpolation is needed. Using the table of data available, interpolation can be carried out to find the k, Cp, and ρ values. An example of this is shown for the k value of water:

$$\frac{(0.613 - 0.518)\frac{W}{mK}}{(300 - 290)K} = \frac{(0.613 - k)\frac{W}{mK}}{(300 - 298)K}$$

$$k = 0.610\ \frac{W}{mK}$$

Using this technique, the following values were calculated:

Substance	$k\left[\frac{W}{m*K}\right]$	$\rho\left[\frac{kg}{m^3}\right]$	$C_p\left[\frac{kJ}{kg*K}\right]$
Water	0.6100	0.9974	4.18
Aluminum	236.6	2703	0.896

Using these values, α was determined. The following is a sample calculation for water:

$$\alpha = \frac{k}{\rho C_p} = \frac{0.6100\ {}^{J}/_{smK}}{0.9974\ {}^{kg}/_{m^3} * 4180\ {}^{J}/_{kgK}} = 1.46 * 10^{-4}\frac{m^2}{s}$$

The α value for aluminum was found to be 9.77 * 10^{-5} m^2/s. It appears that water has a higher thermal diffusivity than aluminum at 25 °C. It appears that a higher thermal diffusivity means that it has more of an ability to conduct thermal energy than to store it.

c. Now, determine the thermal diffusivity for aluminum at 200 and 400 K. What does this tell you about the thermal diffusivity of aluminum in regards to temperature? Do you think this is true for all temperature ranges? Try with 400 and 800. Does this provide more insight into the thermal diffusivity of aluminum with respect to temperature?

ANS. Again, we will go through the thermal diffusivity calculation. A sample calculation is shown for the 200 K:

$$\alpha = \frac{k}{\rho C_p} = \frac{237\ {}^{W}/_{mK}}{798\ {}^{J}/_{kgK}} * \frac{1}{2719\ {}^{kg}/_{m^3}} = 1.09 * 10^{-4}\frac{m^2}{s}$$

Using this calculation, the thermal diffusivity was found to be:

Temperature (K)	α (m^2/s)
200	$1.09*10^{-4}$
400	$9.43*10^{-5}$
800	$7.34*10^{-5}$

From the first range in temperatures, it would appear that the thermal diffusivity will decrease with temperature. By looking at the list of terms that are used to determine the thermal diffusivity, it might be thought that the thermal diffusivity will increase at the 800 K temperature point. However, when the thermal diffusivity is calculated at 800 K, it was found to decrease from the value at 400 K. This reinforces the idea that the thermal diffusivity will decrease with temperature.

4. Now, we will also say that half the volume of the water added to the test tube is in this specific space used for the model (2.5 mL). Assuming that the water is a perfect cylinder, and that the test tube has an inner diameter of 0.045 in, you can find all the information necessary to model this flow of heat.
    a. First, we will model this as though it were pure water. Take the temperature of recrystallization you found for test tube #1 in your DXM experiments, and state that this is T_o. T_1 will be the temperature of the air (20 °C). Determine the heat transfer rate if the thermal conductivity of water is at a weighted average of 0.58 W/m*K.

    ANS. First, using the information, we determine the surface area using the inner diameter.

$$A = \frac{1}{4} * \pi * D^2 = \frac{1}{4} * \pi * \left(0.55\ in * \frac{2.54\ cm}{in}\right)^2 = 1.55\ cm^2$$

Now, we determine the height of the cylinder with the area and the volume:

$$L = x_1 = \frac{V}{A} = \frac{2.5mL}{1.55\ cm^2} = \frac{2.5\ cm^3}{1.55\ cm^2} = 1.61\ cm$$

Now, we can find q_x:

$$\frac{q_x \Delta x}{A} = -k\,\Delta T = \frac{q_x(x_1 - x_0)}{A} = -k(T_1 - T_0)$$

$$\frac{q_x(1.61 - 0)cm}{1.55\ cm^2} = -0.58\frac{W}{mK} * \frac{m}{100cm} * (305.2 - 293)K$$

$$q_x = 0.04\,W$$

b. Now, we are going to find the thermal conductivity (k) for a mixture of the salts used in this experiment. To do this, we will use a thermal conductivity approximation for salt solutions. Make sure to use these units when using the calculation. Determine the k value for DXM using this equation, then find q_x using the equation from part a.

ANS. First, we determine the temperature:

$$T = \frac{T_1 + T_0}{2} = \frac{(32.2 + 20)°C}{2} = 26.1\,°C = 78.98\,°F$$

And, we use the approximation equation:

$$k = 0.29411 - 0.174 * C + 0.000879 * T - 2 * 10^{-6} * T^2$$

$$= 0.29411 - 0.174 * \left(\frac{0.2g}{(0.2 + 5)g}\right) + 0.000879 * 78.98°F$$

$$- 2 * 10^{-6} * (78.98\,°F)^2 = 0.969\ \frac{BTU}{fthr°F} * \frac{W/_{mK}}{1.5\ BTU/_{fthr°F}}$$

$$= 0.56\ \frac{W}{mK}$$

And then, we use this k for the q_x equation.

$$\frac{q_x(1.61 - 0)cm}{1.55\ cm^2} = -0.56\frac{W}{mK} * \frac{m}{100cm} * (305.2 - 293)K$$

$$q_x = 0.038\,W$$

c. Determine the percent difference between parts a and b. Is there a considerable difference? Which do you think is more accurate? Keep in mind that the thermal conductivity approximation you were given was developed using sea salt.

ANS. The percent difference was found to be:

$$\%\, Difference = \frac{|0.04W - 0.038W|}{\left(\frac{0.04W + 0.038W}{2}\right)} * 100\% = 3.51\,\%$$

It is hard to determine which is more accurate. Since the concentration is quite dilute, the thermal diffusivities probably wouldn't vary too much. The fact that the thermal conductivity approximation was gathered with sea salt solutions is probably not the most accurate approximation method for DXM, but again, the fact that the sample was a small concentration accounted for minimal difference between the two.

d. In order to calculate this, we made two assumptions about the heat flow. Can these assumptions be made for our experiment? Why or why not?

ANS. Technically, we cannot assume that all but one side is perfectly insulated. These sides are not perfectly insulated, and therefore, heat is being lost from all sides.

5. Citric acid is often used as a flavoring agent in pharmaceuticals
   a. Using the graph above, describe what would happen if you picked a point above the solubility curve (example, 60 wt% and 10 °C) and what would happen if you picked below the solubility curve (example, 50 wt% and 60°C).

   ANS. If you were to pick a point above the solubility curve, such as the one provided, the concentration is passed the saturation point. Therefore, crystals will not be dissolved in the solvent. Any point below the solubility curve is below the saturation point, so the crystals will fully dissolve in the solvent.

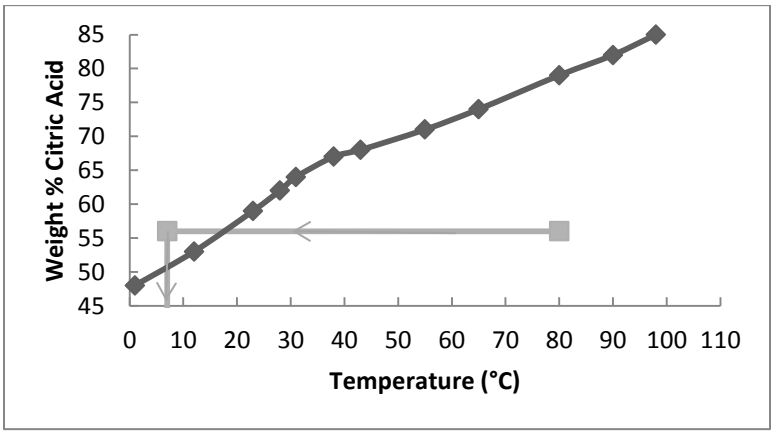
   b. During the production of the new pharmaceutical tablet, 75 kg of citric acid is placed in a mixer with 100 kg water at 40 °C. The operators on duty notice that not all of the powder is dissolving into the water. Using the solubility curve, explain why this occurs. If we needed to fully dissolve the citric acid in the water, what would you recommend doing?

   ANS. Upon reviewing the graph, it is clear that the concentration of this mixture is beyond the saturation point for that specific temperature. This would explain the powder will not dissolve fully in the water. For a temperature of 40 °C, the saturation concentration is roughly 65 kg of

citric acid per 100 kg of water. In order to get the citric acid to fully dissolve into the citric acid into the solution, it would be suggested to be somewhere between 65 and 70 °C. It would be safe to be on the higher end of this temperature range, just to make sure that the concentration is below the saturation point, and that crystals will not start forming in the solution.

c. In another operation that uses citric acid, 78 pounds of citric acid is dissolved in 60 pounds of water and is heated to 80 °C. The solution needs to be cooled so that 18 pounds of crystals can be collected. To what temperature should this solution be cooled to?

ANS. First, we find that the weight percent of citric acid in the initial solution is roughly 56%. If we needed to crystallize out 18 pounds, the weight percent of citric acid would change to 50%. Therefore, we need to cool the solution down to the temperature where the saturation point of the solution would be 50% citric acid. Using the graph, we can determine that to be around 7°C. A graph of this is shown below.

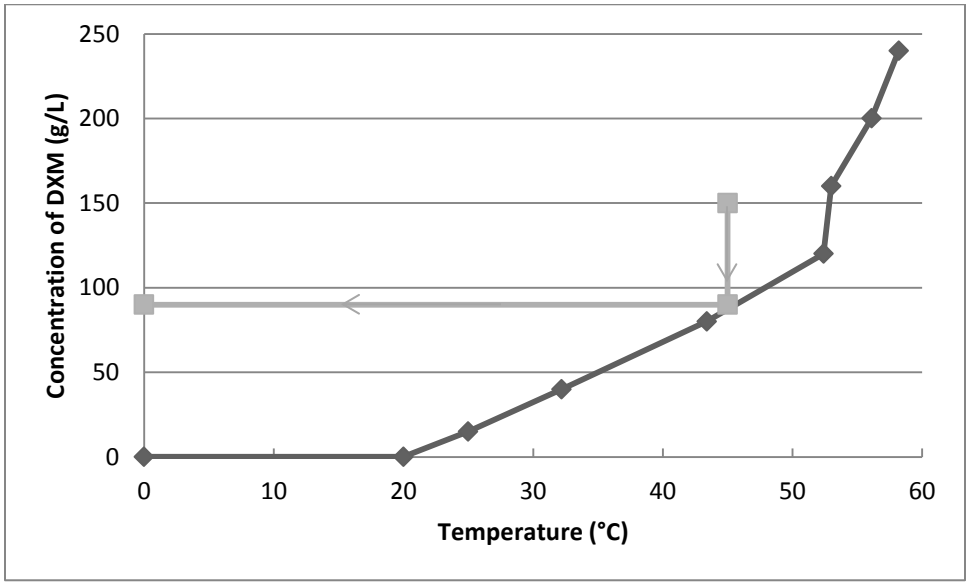


Here, the gray line is how to answer the problem. Interpolation is used to determine the initial weight percent and the final temperature.

6. In the previous question, you were given a scenario in which a solution of crystals and solvent were cooled past the solubility point. Indeed, this is what is commonly done in industry in order to separate crystals from liquids.
   a. 100 kg of a solution with a concentration of 150 grams of DXM per liter of water is sent through this process. The temperature of the solution is initially 75 °C, and is cooled down to 45 °C. Using your

DXM data, determine the mass of crystals that would precipitate out. Assume that the solution has the same density as water.

ANS. We know that 75°C is beyond the point of saturation for a 150 g/L solution of DXM and water. So, we first go to the point of 150 g/L and 45°C. This is above the saturation point, so we should first determine the saturation concentration at 45°C. First, a vertical line is made to intersect the point of this example and the solubility curve. Then, a horizontal line is drawn to connect the y-axis to the point of the solubility curve. This is shown below:



Once again, the gray squares represent the solution to this problem. Then, using interpolation:

$$\frac{(100-50)\,{}^{g}/_{L}}{2.15\ cm} = \frac{(x-50)\,{}^{g}/_{L}}{1.72\ cm} \rightarrow x = 90\frac{g}{L}$$

Now, assuming that the density of this solution is the same as water, the volume of solution is:

$$V_{solution} = 100\ kg * 1\ \frac{L}{kg} = 100\ L$$

So on a 1 liter basis, 40 grams of crystals are precipitated out. Using the volume of 100 L, we get 4000 grams, or 4 kg, precipitated out.

b. Now, say this cooled solution is sent to a filter. The filter is considered 100% effective at removing the crystals. If the composition of the cake is 80% crystal by mass, calculate the mass of saturated solution that has been separated from the crystals.

ANS. If the filter is 100% effective at removing the crystals, then we know 40 grams of crystals makes up the cake, then, using the definition of mass percent:

$$mass\ \% = 80\% = \frac{m_{crystals}}{m_{crystals} + m_{liquid}} * 100\% = \frac{4\ kg}{4\ kg + m_{liquid}} * 100\%$$

$$m_{liquid} = 1\ kg$$

c. If the dryer only allows the water to evaporate, what is the overall mass of crystals that was collected? If compared to the original amount of crystals in solution, what is the overall yield of this process?

ANS. If 1 kg of solution is with the crystals, there is 1 L of saturated solution. If the dryer only evaporates water, and the solution had a concentration of 90 grams of DXM per liter, then 90 grams, or 0.09 kg, of crystals is left after drying. This gives:

$$m_{crystals-total} = m_{crystals-cake} + m_{crystals-solution} = 4.0\ kg + 0.09\ kg = 4.09\ kg$$

The original amount of crystals is:

$$m_{crystals-start} = \frac{150\ g}{L} * 100\ L = 15{,}000\ g * \frac{kg}{1000g} = 15\ kg$$

The yield is:

$$Yield = \frac{m_{crystals-total}}{m_{crystals-start}} = \frac{4.09\ kg}{15\ kg} = 0.273$$

REFERENCES

1. C. Wibowo, "Solid-Liquid Equilibruim: The Foundation of Crystallization Process Design," Chemical Engineering Progress, pp. 38-45, March 2014.
2. I. Le Fur, J.-P. Richard and G. Wolff, "Process for preparing ascorbic acid". United States of America Patent 5391770, 21 February 1995.
3. Halifax Regional School Board. "Solubility Curves (ANSWERS)." Halifax Regional School Board Staff. Accessed 19 May 2014. Available: http://hrsbstaff.ednet.ns.ca/benoitn/chem12/solutions/exercises/ans_solubility_curves.htm
4. G. Y. S. K. Swamy, K. Ravikumar and A. Bhujanga Rao, "Dextromethorphan, an antitussive agent." Acta Crystallographica Online, Sanathnagar, India, 2003.
5. J. Magarey. International Program on Chemical Safety. "Dextromethorphan." INCHEM. Available: http://www.inchem.org/documents/pims/pharm/pim179.htm. August 1997. Accessed: 21 May 2014.
6. The Metabolomics Innovation Center. "Dextromethorphan." Available: http://www.drugbank.ca/drugs/DB00514. 22 November 2014. Accessed: 21 May 2014.
7. F.P. Incoprera, D.P. Dewitt, T.L. Bergman, and A.S. Lavine. "Introduction to Heat Transfer." 5th ed. John Wiley and Sons. Hoboken. 2007.
8. Thermal-Fluids Central. "Thermophysical Properties: Aluminum and Aluminum Alloy." Available: https://www.thermalfluidscentral.org/encyclopedia/index.php/Thermophysical_Properties:_Aluminum_and_Aluminum_Alloy. 14 July 2010. Accessed: 22 May 2014.
9. J.V. Wilson. Approximations for Physical Properties of Sea Salt Solutions. Office of Saline Water. March 1973.
10. L.H. Dalman, "The Solubility of Citric and Tartaric Acids in Water." Journal of the American Chemical Society, vol. 59, no. 12, pp. 2547-2549. December 1937.
11. R.M. Felder and R.W. Rousseau. *Elementary Principles of Chemical Processes*. 2nd Edition. New York. John Wiley and Sons. 1986.

B.7 Creation of Dissolvable Strips Lab

Creation of Dissolvable Strips – Instructor's Version
Developed by: Alex Jannini, David Krause, Heather Malino, and Matthew van der Wielen, Rowan University, Department of Chemical Engineering
Edited by: C. Stewart Slater and Mariano J. Savelski, Rowan University, Department of Chemical Engineering
Date of Experiment:

OBJECTIVES

- Students will learn about the commonly used processes for industrial thin film production
- Students will learn and use basic quality control testing methods
- Students will gain insight into energy requirements for drying thin films

INTRODUCTION

Dissolvable strips have become an important mechanism for drug delivery. Orginially created as candy, dissolvable strips fill a niche role, providing rapid-release drug delivery. Due to the drug being dissolved directly into the blood stream through the tounge, it bypasses the metabolism of the body, which can cause drugs to lose some of their bioavaliability (the amount of drug that will circulate through the body). Other advantages of using thin films include not having to take the drug with water, no risk of choking, and reduced dose size because the drug is more bioavailable sublingually (tissues under the tounge).[1]

The ingredients of a dissolvable strip will vary, depending on the desired drug release rate, the sensitivity of the drug, and several other factors. However, all strips will contain the following ingredients; an active pharmaceutical ingredient (API), polymers, placticzers, and sweetners/flavoring.[2] A polymer is often determined based on its reactions with water. The more hydrophilic (attraction to water) the polymer is, the faster the film will dissolve and release the API. The plasticzer helps improve flexibilty and prevent brittleness in the strip, while the sweetners and flavorings help to improve palatability and increases patient compliance.

On an industrial level, dissolvable strips are primarily made with either a solvent-casting film system or a film extrustion system. Solvent-casting systems are the most common process, as they do not require heat, which could damage an API, and are relatively inexpensive to construct. A typical setup for a solvent-casting system can be seen on the next page.[3] The drawbacks to solvent-casting techniques can include variances in film thickness and non-uniform drying.

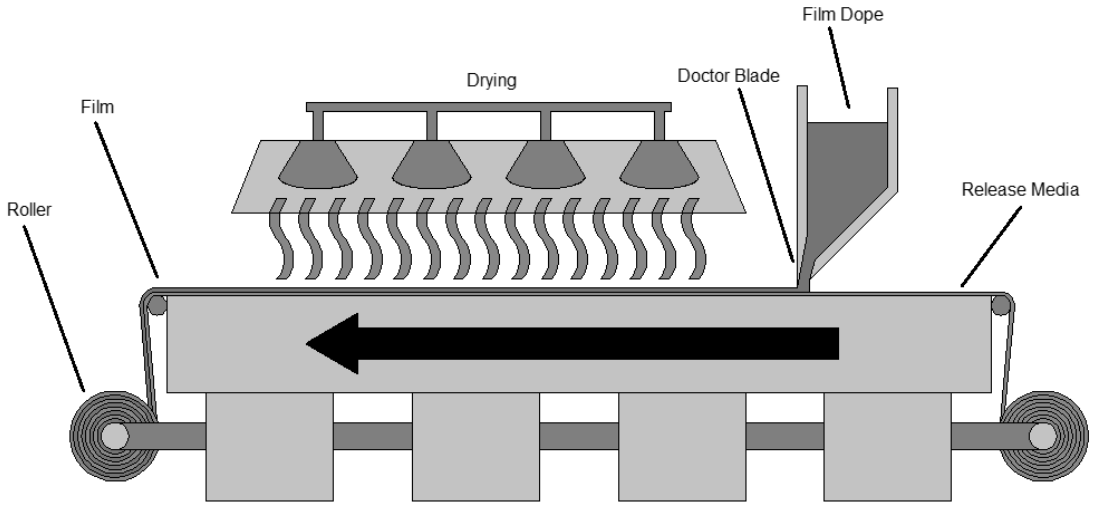


Figure 1. A diagram of a solvent-casting system as adapted from Particle Sciences.[3]

Alternatively, hot melt extrusion is also used to create strips. The advantages to extrusion are a simpler design and the lack of water needed to run the process, but the materials used in the dissolvable strip must be heat resistant and be able to flow as a dry powder. A sample of both of these systems can be seen in Figures 1 and 2.

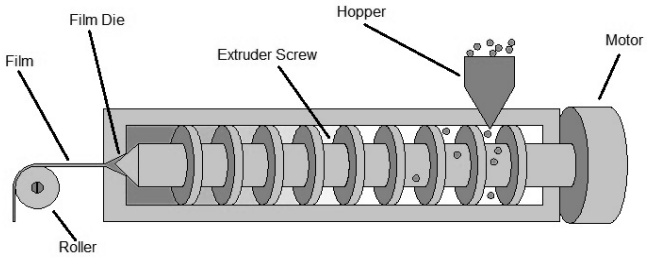


Figure 2. Screw-forced extrusion of dry feedstock as adapted from Particle Sciences.[3]

In this lab, you will be creating your own dissolvable strips. This procedure is based on the solvent casting method described above. Through this lab, you will have a better understanding of the way that dissolvable strips are created, and some of the engineering principles behind the process.

INSTRUCTOR'S NOTE

In this experiment, no API is added to the dissolvable strips, as no drug modeling is being analyzed. If you wish to use an API, that is acceptable, and caffeine is recommended as an inexpensive API. In addition, it is possible to obtain food-grade versions of each of these chemicals. If possible, you may wish to do this in a food-safe area, and allow the students to try their strips once they are done the experiment. Lastly, the apparatus used in this experiment is a Teflon sheet

that has metal thickness guides adhered to the surface. A model is shown below:

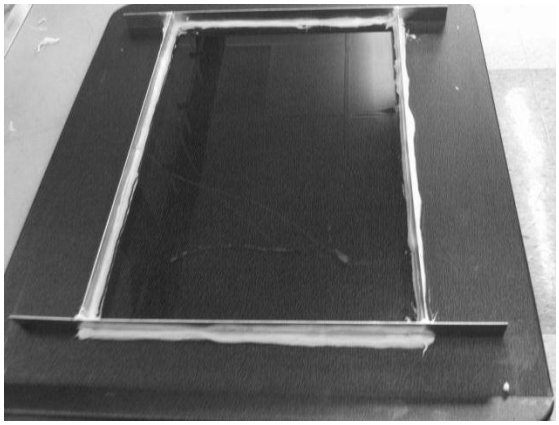


Figure 3. The sheet used to make dissolvable strips.

These thickness guides have dimensions as follows: Length of 31 cm, a height of 2.7 cm, and a thickness of 0.06 cm. The thickness guides were made from aluminum metal sheets. Note that the thickness guides are adhered to the surface. This was done through silicone adhesive caulk. The adhesive caulk takes time to dry (48-72 hours), so it is suggested to have these sheets prepared ahead of time for the experiment.

SAFETY CONSIDERATIONS

Make sure to wear safety goggles at all time. Laboratory safety gloves should also be worn.

MATERIALS NEEDED

- 1000 mL beaker
- Hot plate and mixer
- Magnetic stir bar
- CMC (carboxymethylcellulose)
- Sodium lauryl sulfate
- Citric acid (anhydrous)
- Glycerol
- Sucrose
- Peppermint oil
- Dropper
- Deionized water
- 3 mL syringe
- 2 Büchner (vacuum) flasks
- Funnel
- Fine mesh screen
- Vacuum tubing
- Vacuum source
- Spatula
- Petri Dish
- Teflon-lined sheet/plate apparatus with thickness guides
- Analytical scale
- Tubing and stoppers
- Blue food dye (Blue #40)

PROCEDURE

Table 6: Recipe for CMC preparation

Species*	Weight (g)	Weight %
CMC	7.7	1.6
Glycerol	2.6	0.6
Peppermint oil	0.5	0.1
Citric acid	1.0	0.2
Sodium lauryl sulfate	1.0	0.2
Sucrose	1.5	0.3
Water	500	97
TOTAL	514.3	100

* Instructor's Note: All chemicals can be obtained from Fisher Scientific. Peppermint oil can be found in specialty food stores or online.

1. Weigh out the appropriate amounts of all powdered ingredients.
2. Add the required amount of deionized water to the large beaker. Reminder: density of water = 1 g/mL.
3. Place the beaker on the hot plate and add the stir bar. Set the heat to the lowest setting and set the stir to a low-medium rate (4 out of 10).

4. Add the CMC to the water at a very slow rate, dusting the powder over the surface of the water and waiting for it to be absorbed. Once most of it is mixed in, the solution will become very viscous and trap air bubbles. Once the viscosity increases, you will need to increase the stirring intensity. Do this slowly.
5. Add the glycerol to the solution with the 3 mL syringe. You will need approximately 2 mL of glycerol to correspond to the weight shown in Table 1.
6. Add the remaining components to the solution similarly to how the CMC was added. At this point, the solution should be extremely viscous and appear opaque white.
7. Add three drops of peppermint oil to the solution.
8. Add one drop of blue food dye. The mixture should now be a light blue color.
9. Transfer the solution into the vacuum flask with the mesh and funnel, pouring through the mesh, to catch any large clumps of solidified product and the stir bar. Discard the solidified product.
10. We will now make a vacuum filtration system. The purpose of this is to de-aerate the mixture. This minimizes the bubbles in the solution. Hook the vacuum flask up to a tube and place a rubber stopper in the top of the flask. Then, connect the tube to the other vacuum flask. Next, place a stopper with an attachment into the top of the other flask and connect this to the vacuum source. See Figure 5 for the appropriate setup. This second beaker will stop any foam from entering the vacuum.
11. Turn on the vacuum and wait approximately 30 minutes for the gas to leave the solution. The solution should slowly turn clear and may get frothy. The froth will subside.

Figure 4. Funnel and screen setup for pouring into flask.

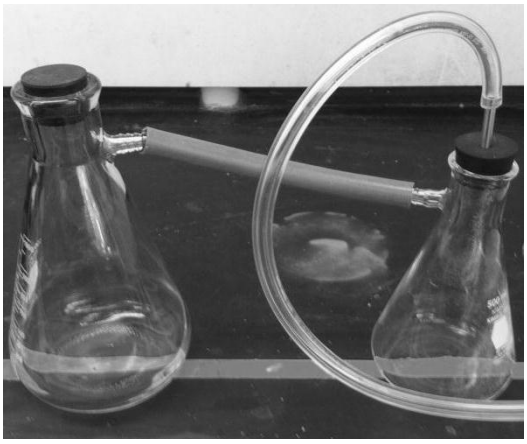


Figure 5. The setup that should be used when using the vacuum.

12. Turn off the vacuum and disconnect the tubing from the vacuum source. Then, remove the beaker with solution from the setup.
13. Carefully pour some of the solution into a 500 mL graduated cylinder. This will make it easier to transfer the solution to the Teflon sheet or petri dish.
14. Take a petri dish and weigh it. Record this weight.

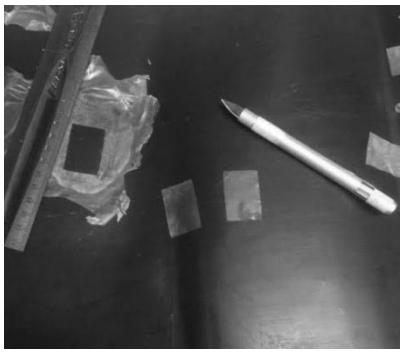


Figure 6. Strips being cut

15. Prepare a sample of the film in the petri dish by adding 10 mL to the dish. Do this by using a small graduated cylinder (10 to 25 mL). If any bubbles remain on top of the solution, be sure to draw solution from under the surface.
16. Weigh the wet petri dish and record this weight.
17. Pour out 400 mL of the remaining solution onto the sheet using the 500 mL graduated cylinder.
18. Allow 1-2 days for the samples to dry. The batch should appear much thinner and have a glossy finish on its surface. Take a final weight of the petri dish sample and record its weight.

QUALITY ANALYSIS

How uniform is your batch? In industry, this is done by sampling a batch and testing it in several ways to ensure that specifications are met. Several samples are taken and their results are averaged. Quality analysis is critical to the success of a company, so that deviations can be caught and fixed before they become a costly problem.

Figure 7. How to use the calipers to determine thickness

Sample Creation

1. Carefully peel the strip out of the mold with a spatula.
2. Take a ruler and measure 4 samples with dimensions of 1” x 1.5”. Try to find room for samples from each of the four corners so that the samples are representative of the entire batch.
3. Using a scalpel carefully cut out the four samples.

Thickness Measurements

1. Using a caliper, take each sample and place it in the jaws of the caliper.

2. Adjust the jaws so that the sample fits snugly between them. Do not over tighten the caliper so that the sample tears. The sample should be pinched, but also be able to slide out from between the jaws when a small force is applied to it.
3. Record your results and repeat for all samples.

Folding endurance

1. Take a sample and fold it in half along the 1.5" face (At the 0.75" mark). Pinch the folding point with your fingers so that a distinct crease is formed.
2. Unfold the strip and flip it over. Carefully fold the strip in the opposite direction, along the same crease and pinch. This has now been 2 folds.
3. Repeat steps 1 and 2, counting the number of folds that you perform.
4. Record the final number of folds, and repeat for the rest of the samples.

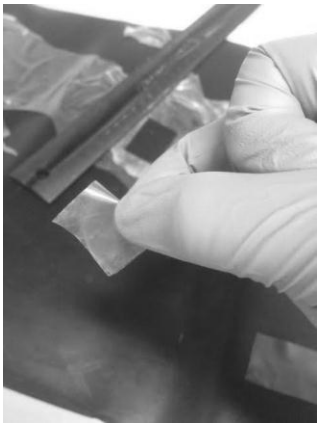


Figure 8. Ensure a good fold by pinching the strip

Surface pH

1. Using one of the halves from each sample, use a pipette to drop a small quantity of DI water on the strip.
2. Place a broad-range litmus paper strip in the drop.
3. Compare the color of the strip to the package to determine the pH of the sample.
4. Record your results and repeat for the rest of the samples. Again, you only need to measure the pH from one half of each sample.

Analysis

1. Average the results from each test.
2. Find the range of results for all tests. Was there significant variance in the data you collected?
3. Do you think that the average pH of the samples would be dangerous to ingest? What about the highest/lowest pH sample?
4. The average number of folds it takes to break a Sheets® brand strip was found to be in the range of 15-20 folds. Does your average fall in this range? If not, why do you think it didn't?
5. What could be a dangerous consequence from a lot of variance in the thickness of each sample? Would you sell the strips you made to pharmacies?

Moisture Content Analysis

In this section, you will use the initial and final weights of the petri dish sample, as well as an introductory energy balance, to find the energy required to dry the sample and the amount of water remaining in the sample.

1. Find the change in mass of the sample. Assume that the mass that evaporated was 100% water.
2. Find the moisture content with the following equation:

$$\%_{moisture} = \left[1 - \left(\frac{m_1 - m_0}{m_0}\right)\right] * 100$$

Where,
m_1 = final weight of the sample
m_0 = initial weight of the sample

3. You will now calculate the amount of energy required to evaporate all of the water that was lost. This energy was transferred into the sample from its surroundings, so the balance of energy transferred appears as such:

$$Q = m_{vap} * L_{vap}^{H_2O}$$

Where,
Q = energy required to dry the sample
m_{vap} = mass of water vaporized, $(m_1 - m_0)$
$L_{vap}^{H_2O}$ = Latent heat of vaporization for water, 2260 kJ/kg
Make sure to watch your units!

4. Where do you think this energy came from?

INSTRUCTOR'S NOTE: For an in-class exercise, the averages from each group can be compiled on the board, and then used to create a control chart. Was the "process" of the student's lab activity in control or out of control? This can be used as an introduction to control charts, Western Electric rules, and Six-Sigma manufacturing.[4]

QUESTIONS

1. For the following APIs, research the drug's therapeutic use and determine if a hydrophilic or hydrophobic polymer matrix would be best suited for drug delivery:
    a) Salbutamol
    b) Zolpidem tartrate
    c) Ondansetron
    d) Fentanyl citrate

2. Your boss approaches you with a new design project. The pharmaceutical company you work for has recently signed a contract with a client, requiring that you produce 800,000 dissolvable strips/year of a new API designed to treat the common cold. The API, referred to as DK-12, is potent in very small doses, but degrades rapidly when it hits stomach acid. Therefore, a dissolvable strip is the perfect method for introducing the drug into the body. The film must be fast-dissolving.
    a) Before any equipment can be decided upon, you must create the formulation. The required ingredients are:
        - DK-12 (10% w/w)
        - Water soluble polymer (40-50% w/w)
        - Plasticizers (0-20% w/w)
        - Sweetening agent (3-6% w/w)
        - Saliva stimulating agent (2-6% w/w)
        - Colors and flavors (1-10% w/w)

        Find a suitable chemical for each of these components and compile a list for your boss.

    b) Now that you've selected the ingredients for the strip film, you have to select whether you are going to use a hot-melt extruder or a solvent casting system. The material dissolves easily in water and polar solvents, and is not friable (does not degrade from heat). It must be noted that since DK-12 is new, it is very expensive, and therefore it is important to minimize wasted API. Explain your reasoning.

ANSWER KEY

The following data was used for the answer key:

Sample	Thickness (mm)	Folds endured	Surface pH
1	0.08	32	5.0
2	0.10	28	5.5
3	0.12	39	5.5
4	0.07	23	6.0
Average	0.09	30.5	5.5

The following data was for the petri dish portion of the experiment:

Initial weight of sample (g)	Final weight of sample (g)
20.65	0.335

Analysis

1. Average the results from each test.
   ANS: See the above table.

2. Find the range of results for all tests. Was there significant variance in the data you collected?
   ANS: "Significant" is used loosely here. This does not mean statistical significance, but the student should be able to relatively compare the ranges of the three tests against each other. For example, the ranges above are 0.05 mm, 16 folds, and 1 pH. A student should realize that the folding test generated inconsistent results.

3. Do you think that the average pH of the samples would be dangerous to ingest? What about the highest/lowest pH sample?
   ANS: For this set of data, the strips would be safe to ingest. Humans can ingest foods such as lemon juice, which has a pH of 2. However, stomach discomfort or heartburn may result from ingesting something this acidic. A student thinking critically will realize the potential side effects.

4. The average number of folds it takes to break a Sheets® brand strip was found to be in the range of 15-20 folds. Does your average fall in this range? If not, why do you think it didn't?
   ANS: The strips in this mock scenario do not. The folding endurance study was found to be highly dependent on the humidity of the room. In very dry air, the strips will become brittle and shatter after 1 or 2 folds. In humid air, the strips can be folded a near-indefinite amount of times with little fatigue. Commercial strips are packaged in controlled climates so they always have ideal properties. Opening a commercial strip package and leaving the strip out to reach equilibrium with the surroundings should yield similar fold endurance to the experimental strips.

5. What could be a dangerous consequence from a lot of variance in the thickness of each sample? Would you sell the strips you made to pharmacies?

ANS: Large variance means concentrated areas of API, and areas with little API. The highly-dosed strips could lead to an overdose, and the under-dosed strips could lead to diminished therapeutic value. Obviously, these strips would not be sold commercially. This question segues nicely into the importance of process control.

Moisture Content Analysis

1. Find the change in mass of the sample. Assume that the mass that evaporated was 100% water.
   ANS: The Δm = 20.315 g.

2. Find the moisture content with the following equation:

$$\%_{moisture} = \left[1 - \left(\frac{m_1 - m_0}{m_0}\right)\right] * 100$$

   Where,
   m_1 = final weight of the sample
   m_0 = initial weight of the sample

   ANS:

$$\%_{moisture} = \left[1 - \left(\frac{20.315\ g}{20.65\ g}\right)\right] * 100 = 1.63\%$$

3. You will now calculate the amount of energy required to evaporate all of the water that was lost. This energy was transferred into the sample from its surroundings, so the balance of energy transferred appears as such:

$$Q = m_{vap} * L_{vap}^{H_2O}$$

   Where,
   Q = energy required to dry the sample
   m_{vap} = mass of water vaporized, $(m_1 - m_0)$

   $L_{vap}^{H_2O}$ = Latent heat of vaporization for water, 2260 kJ/kg
   Make sure to watch your units!

   ANS:

$$Q = \frac{(20.95\ g - 0.635\ g)}{1000\ g/kg} * 2260 \frac{kJ}{kg} = 45.91\ kJ$$

4. Where do you think this energy came from?
   ANS: This energy was transferred into the liquid from the natural convection of the air.

Questions

1. For the following APIs, research the drug's therapeutic value and determine if a hydrophilic or hydrophobic polymer matrix would be best suited for drug delivery:
    a) Salbutamol

        ANS: Because salbutamol is used for immediate relief of an asthma attack[5], a fast dissolving hydrophilic polymer would be best suited for this application.

    b) Zolpidem tartrate

        ANS: Zolpidem tartrate has only been shown to induce sleep, but not maintain it, unless it is in a controlled release form.[6] Therefore, a hydrophobic polymer would be best suited for this application. The strip would most likely be applied sublingually or to the cheek.

    c) Ondansetron

        ANS: Again, ondansetron is used primarily for immediate relief of nausea in chemotherapy patients.[7] Therefore, a hydrophilic polymer would be best in this application.

    d) Fentanyl citrate

        ANS: Being a highly potent opioid analgesic that is used for moderate to severe pain relief,[8] it can be found in both hydrophilic and hydrophobic polymer matrices. It may even be found in a layered strip that uses both types of polymer.

2. Your boss approaches you with a new design project. The pharmaceutical company you work for has recently signed a contract with a client, requiring that you produce 800,000 dissolvable strips/year of a new API designed to treat the common cold. The API, referred to as DK-12, is potent in very small doses, but degrades rapidly when it hits stomach acid. Therefore, a dissolvable strip is the perfect method for introducing the drug into the body. The film must be fast-dissolving.
    a) Before any equipment can be decided upon, you must create the formulation. The required ingredients are:
        - DK-12 (10% w/w)
        - Water soluble polymer (40-50% w/w)
        - Plasticizers (0-20% w/w)
        - Sweetening agent (3-6% w/w)
        - Saliva stimulating agent (2-6% w/w)

- Colors and flavors (1-10% w/w)

Find a suitable chemical for each of these components and compile a list for your boss.

ANS: *Make sure the ingredient is safe for consumption!*

- DK-12 (10%)
- Pectin, HPMC, hypromellose, etc. (40-50%)
- Glycerol, etc. (0-20%)
- Sucrose, dextrose, aspartame, etc. (3-6%)
- Ascorbic acid, malic acid, citric acid (2-6%)
- Peppermint oil, various esters, Red No.40, etc. (1-10%)

b) Now that you've selected the ingredients for the strip film, you have to select whether you are going to use a hot-melt extruder or a solvent casting system. The material dissolves easily in water and polar solvents, and is not friable (does not degrade from heat). It must be noted that since DK-12 is new, it is very expensive, and therefore it is important to minimize wasted API. Explain your reasoning.

ANS: Hot melt extrusion would be the best operation for creating the strips. They do not degrade from heat, and extrusion minimizes product lost. While a more expensive process, it is worth it if a contract has been made with a client.

REFERENCES

1. K. Mandeep, A. C. Rana and S. Nimrata, "Fast Dissolving Films: An Innovative Drug Delivery System," *International Journal of Pharmaceutical Research & Allied Sciences,* vol. 2, no. 1, pp. 14-24, 2013.
2. T. Kalra, M. Madhra, K. Gandhi, A. Dahiya and Khushboo, "Fast dissolving film: A review," *International Journal of Research in Pharmaceutical Sciences,* vol. 3, no. 4, pp. 542-551, 2012.
3. Particle Sciences, "Dissolving Films," *Particle Sciences,* vol. 3, 2010.
4. D.C. Montgomery, G.C. Runger, and N.F. Hubele. Engineering Statistics. 5th Edition. Wiley, John and Sons, Incorporated. New York. 2010.
5. "Ventolin." Health Express. 2014. Available: http://www.healthexpress.co.uk/ventolin.html. Accessed 20 May 2014.

6. R. P. Rosenberg, "Sleep maintenance insomnia: strengths and weaknesses of current pharmacologic therapies," *Annals of Clinical Psychiatry,* vol. 18, no. 1, pp. 49-56, 2006.
7. Glaxo-Smith-Kline. “Zofran: Perscribing Information.” U.S. Food and Drug Administration.
8. Janssen Pharmaceuticals. “What is DURAGESIC?” 31 March 2014. Available: http://www.duragesic.com/. Accessed: 20 May 20, 2014.

Appendix C

Test and Survey for the Advil Statistical Analysis Lab

Rowan University – Freshman Clinic

Fall/Spring Semester

Please answer the following questions as best you can:

1. What does API stand for?
   - Active Pharmaceutical Ingredient
   - Appropriate Pharmaceutical Ingredient
   - Abridged Pharmaceutical Inspection
   - Altered Pharmaceutical Ingredient

2. What is the purpose of an API?
   - To test the production process
   - To make sure that you are meeting safety regulations
   - To perform the treatment of the patient
   - To keep the pill intact until swallowed

3. What are the non-active ingredients in a pharmaceutical product called?
   - Glue
   - Binders
   - By-products
   - Excipients

4. A binder is:
   - A substance to ensure the drug is fully dissolved in the body
   - A substance that makes components in the drug stick together
   - A piece of equipment that makes tablets stick to each other
   - A device that keeps two pieces of equipment attached to each other

5. The substance used in a tablet to take up space in a pharmaceutical product is:
   - A filler
   - A settler
   - A spacer
   - A glidant

6. The purpose of an F-test is to:
   - To compare a sample to a known value
   - To compare a sample to an unknown value
   - To compare a set of data to a known value
   - To compare two sets of data with one another

7. The purpose of a t-test is to:
   - To compare two sets of data to one another
   - To compare a sample to a known value
   - To compare averages of two sets of data
   - To compare a known value to an unknown value

8. What is the purpose of a flow diagram?
   - To model the flow of material for a process
   - To determine the curvature in a model
   - To compare a material balance to an energy balance
   - To determine the costs of utilities

9. What is the definition of variance?
   - The dispersion of data from the mean
   - The probability of a number being the mean
   - The average of the squared difference of the mean
   - The mean of the data

10. What is the purpose of a box-and-whisker plot?
   - To determine the cost of utilities
   - To determine if any outliers exist in a set of data
   - To determine the variance of a set of data
   - To find critical values for an F-test and t-test

This survey is in regards to the laboratory experiment: Tablet Statistical Analysis Lab. Please fill in the column that most closely resembles your opinion with the statement to the left. This survey in no way affects your grade for this class. Please be honest with your answers. If you fell a specific statement does not pertain to the lab, please fill in the N/A column for that question. If you were absent from lab, please fill in the N/A column for all questions relating to the experiment.

		Strongly Disagree	**Disagree**	**Neither Agree nor Disagree**	**Agree**	**Strongly Agree**	**N/A**
	Statement	**1**	**2**	**3**	**4**	**5**	**6**
1	The experiment introduced a concept of pharmaceutical engineering						
2	I have been, or am now, interested in pharmaceutical engineering						
3	I wish to pursue more studies in the field of pharmaceutical engineering						
4	The experiment helped me understand the application of statistics to pharmaceutical product quality control						
5	I can apply the statistical principles I learned in this lab to other engineering problems						
6	I had to appropriately use laboratory equipment (scales, etc.) for measurements						
7	I felt I could complete the experiment in the time given						
8	I knew exactly what was expected of me from the write-up given						
9	I felt challenged by the experiment						
10	I felt safe in the laboratory while under the supervision of faculty						

Major: _____

Appendix D

Tablet Statistical Analysis Test and Survey Data

For this raw data, the questions were the same as those presented in Appendix C. Students remain anonymous for this, but their major is stated. For the "Test" portion of this data, a "C" represents a correct response, while an "I" represents an incorrect one.

Pre-Lab Test Results											
Student NO.	Major	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
1	Mechanical Engineering	I	I	I	C	C	I	I	C	I	C
2	Chemical Engineering	C	I	C	C	C	I	I	C	I	I
3	Chemical Engineering	I	C	C	C	C	I	I	C	C	C
4	Chemical Engineering	C	C	I	I	C	C	C	C	I	C
5	Chemical Engineering	C	I	I	C	I	I	I	I	C	C
6	Chemical Engineering	I	C	I	C	C	I	I	C	C	I
7	Chemical Engineering	C	C	I	C	C	C	C	C	I	C
	Number of Incorrect	3	3	5	1	1	5	5	1	4	2
	Percent Correct	57	57	29	86	86	29	29	86	43	71

Post-Lab Test Results											
Student NO.	Major	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
1	Mechanical Engineering	C	C	C	C	C	C	C	C	I	C
2	Chemical Engineering	C	C	C	C	C	C	C	C	C	C
3	Chemical Engineering	C	C	C	C	C	C	C	C	C	C
4	Chemical Engineering	C	C	C	C	C	C	C	C	C	C
5	Chemical Engineering	C	C	C	C	C	C	C	C	C	C
6	Chemical Engineering	C	C	C	C	C	C	C	C	C	C
7	Chemical Engineering	C	C	C	C	C	C	C	C	I	C
	Number of Incorrect	0	0	0	0	0	0	0	0	2	0
	Percent Correct	100	100	100	100	100	100	100	100	71	100

The results of the survey are shown below. Again, student names are kept confidential, and only the student's majors will be shown. Responses are numbered 1 to 6, 1 being "I strongly disagree with the statement" and 6 being "I strongly agree to the statement." The statement numbers coincide with those shown in Appendix C.

Post-Lab Survey Responses											
Student NO.	Major	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10
1	Mechanical Engineering	5	1	1	4	5	5	5	4	3	4
2	Chemical Engineering	4	5	4	5	5	5	4	5	3	4
3	Chemical Engineering	4	5	4	4	4	5	5	3	3	5
4	Chemical Engineering	5	5	5	3	4	5	5	5	2	5
5	Chemical Engineering	4	4	3	4	4	4	4	3	3	4
6	Chemical Engineering	4	4	5	5	5	1	1	4	2	1
7	Chemical Engineering	3	4	4	5	5	4	4	4	1	1
	Average Response	4	4	4	4	5	5	5	4	2	4