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المؤلف الرئيسي:	Chick Alard, Ibaa
مؤلفين آخرين:	Gharayibah, Shadi(super)
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ABSTRACT:

THE MECHANICAL ENERGIES (WORK) ASSOCIATED WITH THE COMPACTION OF BOTH THE MONOCLINIC AND THE ORTHORHOMBIC FORMS OF PARACETAMOL POWDER

By

Iba`a N. Chick Al-Ard

Paracetamol is a widely used antipyretic and analgesic drug. Paracetamol in the solid state has three polymorphic forms. The monoclinic form (form I) which is the most stable form. However, the orthorhombic form (form II) and form III are metastable. Paracetamol is considered poorly compressible, and therefore paracetamol tablets are mainly manufactured by wet granulation. Orthorhombic form has better compressibility due to the presence of slip planes in its crystal structure. In this work the orthorhombic form of paracetamol was successfully produced in appreciable quantities by melting the monoclinic form in a test tube immersed in a heated paraffin oil bath. The melted paracetamol was then cooled in a water bat at 60-70°C.

The moisture content of both the monoclinic and the orthorhombic form of paracetamol stored for 3 weeks at 25°C at relative humidity condition of 23%, 43%, 57%, 75%, and 93% was investigated. It was found that neither forms acquire any significant amount of moisture in any of the stored condition. It was also found that the orthorhombic form is stable for 3 weeks of storage at 25°C at relative humidities of 23%, 43%, and 57%. However, orthorhombic form undergoes transformation to the monoclinic form at relative humidities of 75% and 93%.In addition, the mechanical energies associated with the compaction of both forms were investigated. It was found that when equal weights of monoclinic and orthorhombic forms of paracetamol are compacted, the orthorhombic form generates compacts with smaller volume and larger solid fraction. However, when comparing the work of compression, work of decompression, irrecoverable work, plasticity index, and EE/PE ratio of the compacted forms no appreciable difference can be seen when volume of the compacts is not considered. It can be concluded that for generating compacts of equal volumes of the two forms then the plasticity index would be larger for the orthorhombic form and the EE/PE ratio larger for the monoclinic form at any given compression force.

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By

Iba`a N. Chick Al-Ard

Advisor

Dr. Shadi Gharaibeh

Thesis submitted in partial fulfillment of the requirements for the degree of M.Sc. in Pharmaceutical Technology

At

The Faculty of Graduate Studies

Jordan University of Science and Technology

May, 2008

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Dr. Nizar Al-Zoubi (External Examiner, Applied Science University)	.....

May, 2008

DEDICATION

To my beloved grandfather, my inspiration, my guides in life for his love and support,
For teaching me the value of life and listening,
Who encouraged me daily, from a very young age, to reach for my dreams, no matter how far-fetched society may have deemed them,
Who hands I grew up between which became the light that shines my road,
Who made me a future that I have always dreamed of,
Who sacrificed much to provide me with the quality of life from which I could choose what I wanted to be and to do,
Words will not be enough to describe his kindness,

My grandfather"Dr. Adel Tarabein"

To someone very special in my life,
A very caring person,
Who gave her love unconditionally,
She is always there when I need to talk, have a problem, or just to say hi!!
Person that has always been there for me, my sister and my brother,
A person who scarified her own happiness for ours,
If I could buy you the world,
I would wrap it with gold and a ribbon of rainbows,
but all I can give you is my heart,
This person has taught me the meaning of being a "grandmother",

My grandmother "Hadya"

To my mother,
Who I can't thank enough for all she's done,
Who is always there when I am down, when I am sad, and when I am sick,
I love her so much and she's my best friend,
She will always be that special person in my life,
My mom always helps me out with anything I need Chores, homework, problems, you name it, she's there for me,
So thank you mommy for being the best you can be,
You're the smartest woman I know for so many reasons,
Thank you for being my Mom for all these years. If I had to choose a Mother it would be you,

My mom" Marah"

To the one I adore and tell my most inner thoughts,
I thank you. For always being there when I needed a shoulder to cry on,
You make gloomy days, bright!! You make a sad song seem not so sad,
Whenever we're together there's always a smile on our faces,
I have the best sister and I am glad it's you,
You're the best,

My sister "Marwa"

To my brother, who I have admired, loved and feel very proud of,

My brother "Adel"

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Many thanks to my colleagues Samer, Neeven, Tamara, Amani, Nouseba, Moath and Mohamad, whose friendly encouragement was greatly appreciated.

With love, I dedicate this thesis to my family. I thank them from the bottom of my heart, for all they have done for me throughout my life as well as their encouragement and support during my studies and the writing of this thesis.

Lot of thanks to Dima, who without her stories, this thesis would not have been existed.

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The moisture content of both the monoclinic and the orthorhombic form of paracetamol stored for 3 weeks at 25°C at relative humidity condition of 23%, 43%, 57%, 75%, and 93% was investigated. It was found that neither forms acquire any significant amount of moisture in any of the stored condition. It was also found that the orthorhombic form is stable for 3 weeks of storage at 25°C at relative humidities of 23%, 43%, and 57%. However, orthorhombic form undergoes transformation to the monoclinic form at relative humidities of 75% and 93%.In addition, the mechanical energies associated with the compaction of both forms were investigated. It was found that when equal weights of monoclinic and orthorhombic forms of paracetamol are compacted, the orthorhombic form generates compacts with smaller volume and larger solid fraction. However, when comparing the work of compression, work of decompression, irrecoverable work, plasticity index, and EE/PE ratio of the compacted forms no appreciable difference can be seen when volume of the compacts is not considered. It can be concluded that for generating compacts of equal volumes of the two forms then the plasticity index would be larger for the orthorhombic form and the EE/PE ratio larger for the monoclinic form at any given compression force.

Chapter One:
1. Introduction:

1. 1Paracetamol in Pharmaceutics:

Paracetamol (4-Hydroxyacetanilide, $C_8H_9NO_2$) figure (1) was first prepared by Morse in 1878[1]. Its pain and fever relieving properties were discovered in 1893[2]. Since the late 1950s and early 1960s it is widely used as an analgesic and antipyretic drug under the names paracetamol, or acetaminophen [3]. It is considered to be the most prominent among acetanilide derivatives [4].

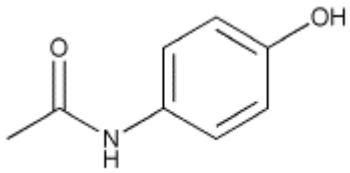

Figure 1: Chemical Structure of Paracetamol.

Paracetamol is a widely used analgesic and antipyretic [5, 6]. Paracetamol is readily absorbed by the gastrointestinal tract, and is metabolized by the microsomal enzyme system in the liver. While 80–85% of paracetamol biotransformation occurs via conjugation of glucuronide and sulfate by the transferase enzymes, 10–15% of paracetamol is oxidized to the reactive oxygen species (ROS) through P-450-dependent mixed-function oxidases [7, 8].

Paracetamol is generally considered to be a weak inhibitor of the synthesis of prostaglandins (PGs). However, the in vivo effects of paracetamol are similar to those of the selective cyclooxygenase-2 (COX-2) inhibitors. While paracetamol also decreases PG concentrations in vivo, it does not suppress the inflammation of rheumatoid arthritis. However, it has been reported that it decreases swelling after oral surgery and suppresses inflammation in rats and mice [4].

It has been reported that therapeutic concentrations of paracetamol inhibit PG synthesis in intact cells in vitro when the levels of the substrate arachidonic acid are low (less than about 5 mmol/L) [6]. When the levels of arachidonic acid are low, PGs are synthesized largely by COX-2. Thus, the apparent selectivity of paracetamol may be due to inhibition of COX-2-dependent pathways [8].

Swierkosz et al. (2005) has reported that paracetamol selectively blocks a variant of the COX enzyme that is different from the COX-1 and COX-2 [9]. This enzyme, which is only expressed in the brain and the spinal cord, is now referred to as COX-3. Its exact mechanism of action is still poorly understood.

1.2 Polymorphism in Pharmaceutical Industry:

A crystalline solid is characterized by a regular and indefinite repetition of unit cells in three dimensional space. The unit cell has a definite shape and specific properties of symmetry [10]. Because different crystalline forms differ in crystal packing, there are significant differences in their pharmaceutical properties such as compactibility, solubility, dissolution rate, and bioavailability. These differences are directly linked with the primary characteristics of the crystals, i.e. the crystalline structure, internal (polymorphism, and amorphous state) and external habits [11].

The knowledge of the crystalline structure of the granular systems used in pharmacy is essential, for both drugs and excipients.

Many pharmaceutical solids exhibit polymorphism, which is frequently defined as the ability of a substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice [12].

The polymorphic solids have different crystal structures and hence display different physical properties. These differences including those due to packing, thermodynamic, spectroscopic, kinetic, interfacial, and mechanical properties are summarized in table (1) [16,13, 14].

Polymorphism only exists in the solid state. Melting or dissolution destroys any distinctions. It is therefore important in examining polymorphs not to submit them to conditions under which they melt, dissolve, or interconvert. Heating and grinding are potentially hazardous operations in which interconversion are possible [15]. The presence of solvent, even one in which the substance appears insoluble will speed up the interconversion [16]. Trace moisture, acid or alkali on vessels can be similarly effective in interconverting polymorphs.

The compressibility of different polymorphs of the same compound can vary significantly. This variation is due to the differences in the three dimensional arrangement of molecules in the crystal structure. Certain arrangements of molecules could facilitate compressibility by providing groups of molecules that yield to pressure and could slide over each other i.e. slip plans.

Grant et al. (2001) studied the compressibility of bulk powders of sulfamerazine polymorph I and two batches; II (A) and II (B) of different particle size, of polymorph II. The powders were compressed to form tablets whose porosity and tensile strength were measured. Grant found that the slip planes present in form I provide crystals greater plasticity and therefore greater compressibility and tabletabillity over form II. He mentioned that it is possible to predict the tableteting performance of different polymorphs of a drug, provided that their crystal structures are available.

Table 1: Differences in Physical Properties of Different Polymorphs of the Same Compound.

Packing properties:	Molar volume and density.
	Refractive index.
	Conductivity, electrical and thermal.
	Hygroscopicity.
Thermodynamic properties:	Melting and sublimation temperature.
	Internal energy.
	Enthalpy.
	Heat capacity.
	Entropy.
	Free energy and chemical potential.
	Thermodynamic activity.
	Solubility.
Spectroscopic properties:	Electronic transitions (i.e., ultraviolet- visible absorption spectra.)
	Vibrational transitions (i.e., infrared absorption and Raman spectra.)
	Rotational transitions (i.e., far infrared or microwave absorption spectra.)
	Nuclear spin transitions (i.e., nuclear magnetic resonance spectra.)
Kinetic properties:	Dissolution rate
	Rates of solid state reactions.
	Stability.
Surface properties:	Surface free energy.
	Interfacial tensions.
	Habit (i.e., shape).
Mechanical properties:	Hardness
	Tensile strength.
	Compactibility, tableting.
	Handling, flow, and blending.

The polymorphs whose crystals have slip planes are expected to have superior tableting performance. In addition, it was reported that when the proportion of I increases in a powder mixture containing both polymorph, I and II, the tablet tensile strength increases and the tablet porosity decreases [(17)].

1.2.1 Methods of Preparation of Polymorphs:

In the last century many methods have been employed to obtain unique polymorphic form. These methods include [(12)]:

i. Sublimation:

On heating, most of organic compounds are converted partially from the solid to the gaseous state and back to solid, i.e., they sublime. The vapor could recrystallize back to the solid state in a different form. The term sublimation refers only to the phase change from solid to vapor without the intervention into the liquid phase. The distance of collecting surface from the material undergoing sublimation have a great influence on the form and size of crystals produced. In addition, the occurrence of polymorphic modifications depends on the temperature of sublimation. In general, it may be assumed that unstable crystals form preferentially at lower temperatures, while at higher temperatures stable forms are expected.

For a lab experiment it is possible to form good crystals by sublimation from one microscope slide to a second held above it, with the upper slide also being heated such that its temperature is only slightly below that of the lower slide.

Cooling of the cover slip by placing drops of various low-boiling point solvents on the top surface will cause condensation of the more unstable forms. The lower temperatures will lead to the crystallization of the most unstable forms.

Once crystals of various modifications have been obtained, they can be used as seeds for the solution phase crystallization of large quantities. It has been reported that form I of (9, 10-antraquinone-2-carboxylic acid) can be obtained as needle-like crystals upon sublimation at temperatures exceeding 250°C [(18)].

ii. Crystallization from a single solvent:

Slow solvent evaporation is a valuable method for producing crystals. Solution of the material being crystallized, preferably saturated, are filtered to remove most nuclei and then left undisturbed for a reasonable period of time. The rate of evaporation can be adjusted by covering the solution with parafilm containing few small holes. For a solvent to be useful for recrystallization purposes, the solubility of solute should be on the order of 5-200 mg/ml at room temperature.

Table 2: Example on Solvents Often Used In the Preparation of Polymorphs.

Solvent	Boiling point (°C)
Dimethylformamide	153
Acetic acid	118
Water	100
1-propanol	97
Acetonitrile	82
Ethanol	78
Methanol	65

The process of preparation of a polymorph from solution can be considered the result of two separate events, firstly dissolution of the initial phase, and secondly nucleation/growth of the final stable phase.

Behme et al. (1989) showed that when buspirone hydrochloride is crystallized from xylene above 95°C the higher melting point form is obtained. However, crystallization below 95°C yield the lower melting point form [(19)].

iii. Crystallization from a binary mixture of solvents

If single-solvent solutions do not yield the desired phase then mixtures of solvents can be tried. Multicomponent solvent evaporation methods depend on the differences in the solubility of the solute in various solvents. In this approach, a second solvent in which the solute is sparingly soluble is added to a saturated solution of the compound in another solvent.

The solvent system is usually selected such that the solute is more soluble in the component with the higher vapor pressure. As the solution evaporates, the volume of the solution is reduced and, because the solvents evaporate at different rates, the composition of the solvent mixture changes [11].

Occasionally, crystals are obtained by heating the solution of one solvent and then pouring the solution into another solvent or over cracked ice.

Otsuka et al. (1995) obtained Phenobarbital form B by adding drop wise a saturated solution of the compound in methanol to water at room temperature. Form E was obtained by the same technique, but using a saturated solution of Phenobarbital in dioxane [20].

iv. Vapor diffusion method:

In the vapor diffusion method, a solution of solute in a given solvent is placed in a small open container that is then stored in a larger vessel containing a small amount of miscible and volatile liquid that the solute is poorly soluble in (precipitant liquid). The larger vessel (often desiccators) is then tightly closed. As solvent equilibrium is approached, the non-solvent diffuses through the vapor phase into the solution, until saturation or supersaturation is achieved. The solubility of the compound in the precipitant liquid should be as low as possible (much less than 1 mg/ml), and the precipitant (the solvent in which the compound is poorly soluble) should be miscible with the solvent and the saturated solution.

v. Crystallization from the melt:

Quench cooling a melt can sometimes result in formation of an amorphous solid that on subsequent heating undergoes a glass transition followed by crystallization [21].

In accordance with Ostwalds rule [14], slow cooling of melts of polymorphic substances often first yield the least stable (metastable) modification, which subsequently rearranges into the stable modification. Since the metastable form will have the lower melting point, it follows that supercooling is necessary for its crystallization from the melt. Thus, after melting the system must be supercooled below the melting point of the metastable form, and at the same time the crystallization of the more stable form or forms must be prevented.

Yoshioka et al. (1994) observed that when the amorphous solidified melt of indomethacin was stored at 40°C, it partly crystallized into the thermodynamically stable γ- form. However, storage of amorphous solidified melt at 50°C, 60°C, and 70°C, resulted in the crystallization of mixtures of the α-and the γ- forms [22].

vi. pH manipulation to precipitate Acidic or Basic substances:

Many drug substances fall in the category of slightly soluble weak acids, or slightly soluble weak bases. Such drugs have salt forms that are much more soluble in water. Upon addition of acid to an aqueous solution of a soluble salt of a weak acid, or upon addition of alkali to an aqueous solution of a soluble salt of a weak base, crystals often results. Chikaraishi et al. (1996) found that when piretanide was dissolved in 0.1 N NaOH at room temperature and a strong acid was added in a 1:1 ratio (to pH 3.3), piretanide form C precipitated [23].

vii. Thermal desolvation of crystalline solvates:

The term “desolvated solvates” can be applied to compounds that are originally crystallized as solvates but from which the solvent has been removed (generally by vaporization induced by heat and vacuum).

Frequently, these "desolvated solvates" retain the crystal structure of the original solvate with relatively small changes in lattice parameters.

For this reason, these types have been referred to as pseudopolymorphic solvates.

However, in instances where presence of the solvent is important to stabilize the lattice, the process of desolvation may produce a change in lattice parameters resulting in the formation of either a new crystal form or an amorphous form.

Rocco et al. (1995) obtained form II of zantoerone by recrystallization from ethanol and vacuum drying at 45°C. Form III was isolated by desolvating the acetonitrile solvate form at 80°C under vacuum. This form was eventually chosen for use in clinical drug product due to the high reproducibility of its isolation during manufacture [24].

viii. Growth in the presence of additives:

The presence of impurities can have a profound effect on the growth of crystals. Some impurities can inhibit growth completely, while some may enhance growth. Nevertheless, some additives may exert a highly selective effect by acting only on certain crystallographic faces and thus modifying the crystal habit. Some impurities can exert an influence at very low concentrations (less than 1 part per million), whereas others need to be present in fairly large amounts to have any effect [25].

Davey et al. (1994) found that form I crystals of terephthalic acid could be obtained by crystallization only in the presence of ρ-toluic acid. On the other hand, form II the more stable polymorph at ambient temperatures, was recovered from a hydrothermal recrystallization experiment [26].

Ikede et al. (1994) determined that indomethacin can exist in three different crystal forms, denoted α, β, and γ. The α-form possesses higher solubility than the γ-form.

On recrystallization, crystals of the α-form were first to be deposited, but these converted gradually to the less solube γ-form. However, in the presence of hydroxypropylmethylcellose, conversion from the α-form to the γ-form was inhibited [27].

ix. Grinding:

Polymorphic transformations have been observed to occur on grinding of certain materials, such as sulfathiazole and chloramphenicol.

Otsuka et al. (1994) showed that metastable forms B and C of chloramphenicol palmitate were transformed into the stable form A upon grinding at room temperature [28]. In addition indomethacin transforms into a non-crystalline solid during grinding at 4°C and into metastable form A by grinding at 30°C.

1.2.2 Methods for Examination of Polymorphs:

Solid-state properties of different polymorphic modifications of a compound are expected to be marginally different. For this reason, it is important to examine potential polymorphic systems by a variety of techniques to avoid erroneous conclusions. Failure to recognize a polymorph is the more obvious situation but it is also possible to identify polymorphs where none exist particularly if reliance is placed on too few techniques [30]. Compounds with multiple polymorphic forms can require substantial effort for their complete elucidation [29, 31].

The techniques which can be used for the examination of polymorphs include those listed in Table (3).

The most common methods used in industrial practice include polarized light microscopy, infra red spectroscopy (IR), differential scanning calorimetry (DSC), X-ray powder diffraction, solubility and density measurements.

Table 3: Techniques which can be used for Examination of Polymorphs.

Methods	Sub-method
Hot –stage microscopy	
Thermal	Differential scanning calorimetry
	Differential thermal analysis
	Thermogravimetric analysis
Infrared spectroscopy	
Solubility measurement	
Density measurements	
	Flotation
	Pycnometry
	Dilatometry
X-ray powder diffraction	
X-ray single-crystal diffraction	
FT-IR	

1.3. Polymorphs of Paracetamol:

Paracetamol can exist in three polymorphic forms, the monoclinic form (I), the orthorhombic form (II), and a third form (III) [32, 33]. Figures (3, 4) show projection of the crystal structures of form I and form II [34].

Monoclinic paracetamol (form I), which is the commercially used form, is stable at ambient temperature and pressure. However, form (I) is characterized by poor pharmaceutical and industrial properties in terms of flowability, compactability, wettability and dissolution rate [35].

Form (I) is not suitable for direct compression into tablets. This is because it lacks slip planes in its crystal structure. The presence of such slip planes in the crystal structure of a powder is prerequisite for plastic deformation upon compaction.

Consequently, form (I) has to be mixed with binding agents before tableting. Thus, adding to the manufacturing cost in terms of processing time and materials [36]. Form (I) could be obtained by crystallization from aqueous solutions [33].

Moreover, tablets of form (I) paracetamol are usually manufactured by wet granulation which involves several steps including the following:

a. Milling of drug and excipients.
b. Mixing of the milled powder.
c. Preparation of the binder solution or slurry.
d. Mixing of the blinding solution with the powder mixture to form a wet mass.
e. Coarse screening of the wet mass.
f. Drying of the wet granules.
g. Screening of the screened granules.
h. Mixing of the screened granules with lubricants and disintegrates.
i. Tablet compression.

Sebastian et al. (2004) studied three types of paracetamol powder that were blended with microcrystalline cellulose (MCC). The three types were untreated paracetamol, micronized, and SAXS-processed (Solution Atomization and Xstallization by Sonication)[37]. The authors found that the blends containing the SAXS particles exhibited bulk densities, tap densities and Carr's indices which were similar to the blend containing untreated larger particle sized paracetamol.

However, blends containing the SAXS particles exhibit greater densities and smaller Carr's index when compared to those containing micronized paracetamol. Moreover, the Carr's index of all the blends suggested the formulations would exhibit relatively poor flow.

In addition, it was suggested that the moisture content of MCC is the major contributor in the compressibility of the blends. The tensile strengths of tablets of blend containing micronized or SAXS processed paracetamol were greater than that for a blend containing untreated paracetamol. An increase in relative humidity storage condition from 10% to 44% resulted in greater compactibility of the blends.

Mohammed et al. (2005) showed that blends containing paracetamol and MCC exhibited some ductility. Therefore, it was concluded that the coherence of the bi-component tablets is a function of the MCC volume fraction [38]. However, an examination of the tensile strength of the bi-component tablets, prepared at various ratios, against the volume fraction of paracetamol showed that paracetamol dominates and controls the behavior of the bi-component tablets up to a ratio of 46: 54% v/v of paracetamol to MCC. The tensile strength of tablets did not change until this ratio was exceeded. However, the behavior of the bi-component tablets is significantly dependent upon the MCC volume fraction once it exceeded 61%. The compaction data showed a very marked increase in the plastic work as the MCC mass fraction was increased. However, the elastic work remained unaltered. The tensile strength of a tablet is a function of the plastic work required for its formation. Nevertheless, compressed powders that exhibit a significant magnitude of elastic work during decompression are expected to produce weak tablets.

Crystallization of paracetamol by a combination of watering-out from an ethanolic solution and rapid cooling can cause marked modification to the crystal habit and produces thin plate-like crystals. This is indicative of strong inhibition of crystal growth at different crystal faces. Garkani et al. (1999) found that this modified form of paracetamol (thin plate-like) is a habit modification and not due to polymorphism. It was found that such crystal habit has a great influence on the compaction behavior of paracetamol.

Heckel plots and their constants, strain rate sensitivities, elastic recoveries and elastic energies were affected by different crystalline habits of paracetamol [39]. In addition, the results of the Heckel analysis and strain rate sensitivity indicated that polyhedral crystals underwent a greater plasticity during compression than thin plate-like crystals which were more brittle in nature during compression. The results of elastic recoveries and elastic energies indicated that thin plate-like crystals underwent more elastic deformation during compaction when compared with the polyhedral crystals [39].

العنوان:	The Mechanical Energies Work Associated with the Compaction of Both the Monoclinic and the Orthorhombic Forms of Paracetamol Powder
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THE MECHANICAL ENERGIES (WORK) ASSOCIATED WITH THE COMPACTION OF BOTH THE MONOCLINIC AND THE ORTHORHOMBIC FORMS OF PARACETAMOL POWDER

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