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THE DEVELOPMENT OF AN ORAL INHALATION DOSAGE FORM ANTINAUSEANT

A Dissertation

Presented to

the Faculty of the School of Pharmacy

the University of the Pacific

In Partial Fulfillment

of the Requirements for the Degree

Doctor of Philosophy

by

Kit Michael Mills

May 1971

This dissertation, written and submitted by

Kit Michael Mills ,

is approved for recommendation to the

Graduate Council, University of the Pacific.

Department Chairman or Dean:

Dennis J. Barker

Dissertation Committee:

Carl A Rudisill

Ivan W. Rowland

John K. Brown

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INTRODUCTION

Inhalation therapy may be described as a method of introducing medicinal compounds in the form of finely divided solid particles or fine liquid mists, into the respiratory system in order to produce intended local and/or systemic therapeutic effects (1).

Medicinals used in the treatment of nausea have traditionally been administered via oral, parenteral or rectal routes. Each of these methods has certain disadvantages:

1) oral medication requires at least one-half hour to produce an effect, and then it may not be tolerated by the patient,

2) parenterals are rapid, but they require sterile conditions for preparation and do not lend themselves to self-administration,

3) suppositories are both relatively slow acting and inconvenient to use.

For these reasons and the inherent advantages of aerosol therapy, an antinauseant effective via oral inhalation would be beneficial.

The following advantages of medicinals administered via oral inhalation have been summarized:

1) medicinals formerly given as an injection can be given by inhalation, thereby making it more convenient for self-medication by the patient rather than by medically

trained personnel,

2) response to drugs when administered by inhalation is prompt, faster in onset of activity as compared to drugs given orally, and with most drugs approaches intravenous therapy in rapidity of action,

3) since the drugs are absorbed directly into the blood stream via the lungs, there is no decomposition or loss of drug in the gastrointestinal tract, as when the drug is administered orally,

4) the dangers of giving medicinals by injection (trauma, embolism, sterile abscesses, etc.) are avoided since inhalation therapy will often replace an injectable product,

5) the use of medicinals by inhalation does away with the necessity for elaborate sterile preparations necessary for parenteral administration (2).

Accordingly, it would seem appropriate that studies be conducted on the development of an oral inhalation dosage form antinauseant. The present project will consist of developing and testing a series of aerosol formulations to determine their feasibility in antinauseant therapy. In vitro pressure, valve release, spray pattern, particle size, and aging studies will be performed. The present work will also include an in vivo evaluation of promising formulations.

SURVEY OF THE LITERATURE

The aerosol dosage form for the application of therapeutically active ingredients represents one of the major advances which has occurred in pharmaceutical technology during the past decade. Since the aerosol dosage form is convenient to use and allows for a greater degree of flexibility in administering medicinal agents than other dosage forms, its use has become widespread and has extended to almost all types of pharmaceutical and medicinal preparations (3).

The name "aerosol" in its scientific sense denotes a colloidal system consisting of finely divided liquid or solid particles dispersed in and surrounded by a gas; typical examples are smoke and fog. The particle sizes are usually less than ten microns. Now, however, the name "aerosol" is accepted for a container filled with a liquefied propellant plus functional product fitted with a press-button valve, and pressurized packs are commonly known as aerosols (4).

There are three broad groups of modern pressurized packages. These include:

1) space sprays, which are finely divided sprays, exhibiting particle size ranging up to 50 microns in diameter,

2) surface coatings, which are also sprays, but are coarser in size, "wetter," and designed for continuous film formation on a surface,

3) aerated foams, produced by the expansion of certain propellants "through" an emulsion, giving rise to numerous small bubbles. Examples include shaving creams and whipped toppings (5).

History

While the development of the pressurized package as it is known today is of rather recent origin, the atomization of particles for use in aerosol therapy is not new. Such devices as burning sulfur candles to disinfect air, spraying operating rooms with germicidal materials, and inhalation of the smoke of asthma powder are early examples of aerosol therapy (3). Steam, or medicated steam inhalation, and the inhalation of the smoke from burning stramonium leaves are also early and perhaps still useful examples of aerosol therapy of the lungs (6).

Shepherd (7) stated that as early as 1899, Helbing and Pertsch suggested means of propelling confined substances through use of liquids such as methyl and ethyl chloride. In 1901, 1902, and 1939 Gebauer was issued patents describing the use of pressurized packages for dispensing medicinal agents such as tannic acid and ethyl chloride. In fact the use of ethyl chloride as a local anesthetic is considered by many to be the forerunner of the present day aerosol (7). Several antiseptic solutions and perfume aerosols were developed using carbon dioxide as the propellant.

Other chemical agents were investigated during the 1930's as possible propellants, including fluorinated chloro-hydrocarbons which were originally developed as refrigerants.

One of these materials, dichlorodifluoromethane, was used by Goodhue and Sullivan as the propellant in their aerosol insecticide which they developed for the U. S. Department of Agriculture. These insecticides were used by the Armed Forces during World War II to combat the various insects which caused disease among overseas troops. The aerosol was packaged in a high-pressure cylinder of heavy steel construction and had a vapor pressure of 70 pounds per square inch guage (psig)[a] at 70° F. Interstate Commerce Commission regulations necessitated a heavy, bulky steel container for shipment of these products (3). The first low pressure formulation containing dichlorodifluoromethane was not developed until mid 1943 (8).

Following World War II newer propellants, valves, and containers were developed so that a spray possessing the proper particle size could be produced using a pressure of 35-40 psig. An amendment to the regulations of the Interstate Commerce Commission in 1947 made possible the use of a thin-walled container by permitting a pressure of 40 psig at 70° F in essentially a "beer-type" container. Other container developments included the use of stainless steel and aluminum as well as glass and plastic.

Another area of development essential to the success of the aerosol package concerned the valve. Various valves were developed in order to dispense the product in the form of a fine stream, a fine mist, a coarse spray, or solid stream.

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a - The term "psig" represents the uncorrected pressure and is to be distinguished from "psia" (pounds per square inch absolute) that is corrected to include atmospheric pressure (14.7 psig).

Still another development included the metered valves which are essential for medicinal aerosols. These valves make it possible to dispense quantities of medication ranging from 50 mg. to as much as 30 grams accurately.

The first aerosols for consumer use appeared in the United States in 1947. At that time, the aerosol insecticide was essentially the only aerosol product available. From 1947 to date the aerosol industry has grown from a total production of about 5½ million units per year and only one product, to a production of over 2½ billion units a year in 1968, representing a multitude of products (3).

The growth of pharmaceutical and medicinal aerosols has also been phenomenal. In 1964 there was a total volume of less than 50 million units (9). In 1968 well over 50 million units were produced in the United States. This rising total included a variety of over 60 different aerosol products. When it is noted that less than one million units of these products were produced in 1952, the newness of the development and the increased interest in this area are quickly realized (3).

The Aerosol Principle

The relatively simple principle upon which the aerosol mechanism is based considers that a compressed or liquefied gas exerts a force upon the internal surfaces of the container in which the gas is enclosed.

The pressure of an aerosol system refers to the pressure being exerted by the vapor within the container. A liquefied gas in a sealed container appears within the

container in two phases. One is the liquefied gas itself and the other is composed of the gas vapor which has volatilized from a part of the liquid and fills the space above the liquid. It is the pressure of the vapor in equilibrium with the liquid which exerts the force against the internal walls, the liquid, and all accessory packaging components within the container. As the aerosol valve is opened, and the container's contents have access to the atmosphere, these contents are propelled out of the container by the higher than atmospheric pressure condition within. The vapor pressure referred to may also be supplied by a noncondensable gas which has been compressed within the container (5).

Liquefied Gas Systems

Liquefied gases have been widely used as propellants for many aerosol products. These compounds are useful for this purpose since they are gases at room temperature and atmospheric pressure. However, they can easily be liquefied by lowering the temperature below the boiling point or by increasing the pressure.

Most of the liquefied propellants used in aerosol formulations exhibit solvent characteristics similar to non-polar organic solvents. They are very poor solvents for polar compounds and are immiscible with polar liquids. In instances where solutions of polar substances are desirable or required these propellants cannot be used alone. At times, however, the use of co-solvents can solve the solubility problems.

Aerosol terminology defines the two-phase system as having one vapor and one liquid phase. Any nonvolatile

material dissolved in the liquid phase is left suspended in air as a fine dispersion immediately after spraying as the liquefied propellants boil rapidly away. Because of the poor solvent power of the halocarbon propellants for polar compounds, only nonpolar materials are directly dissolved by them. Efforts to increase the solvent power of the liquefied halocarbon propellants have centered mainly on the use of co-solvents. The added solvent becomes an important factor in such systems. It not only diversifies and enhances the solvent action of the propellant, but also exercises a considerable role in determining the characteristics of the spray produced and the applicability of the solution (10).

One method of obtaining sprays containing water soluble compounds is the use of the three-phase system. This aerosol contains water or an aqueous solution plus the liquefied propellant which forms a separate layer, either below or above the aqueous layer, depending on relative liquid densities. The two immiscible liquid layers and the vapor in the headspace of the sealed container constitute the "three phases" of such systems. When the propellant layer is on the bottom of the container, a dip tube, or standpipe, must be attached to the valve and its length adjusted so that it does not extend into the liquid propellant phase. In such a system, the aqueous layer is maintained as a solution until sprayed. Actually the propellant phase serves to supply the pressure required to force the aqueous solution up the dip tube and out of the container. It does not materially affect the character of the spray; this becomes the function of the valve components and

solvent system (10).

Compressed Gas Aerosols

Compressed gases are used to dispense the aerosol product as a solid stream, wet spray, or foam. These products utilize an inert gas such as nitrogen, carbon dioxide, or nitrous oxide as the propellant. As the name indicates, the gas is compressed in the container, and it is the expansion of the compressed gas which provides the force necessary to expel the contents from the container (3). This type of system has certain inherent disadvantages:

1) a large gas space is required in the container to maintain sufficient pressure to empty the contents,

2) pressure decreases as the contents are discharged giving rise to changes in the nature of the spray,

3) the possibility of misuse causing an accidental discharge of gas content which produces an inoperable product (10).

Other Systems

1. Piston Type

Since it is difficult to completely empty the contents of a semisolid from an aerosol container, a piston type aerosol system has been developed. This utilizes a free moving plastic piston in a coated extruded aluminum container. The concentrate is placed into the upper portion of the container. The product itself provides the seal between the piston and the wall. The pressure from nitrogen (100 psig) or a liquefied gas pushes against the other side of the piston, and when the valve is

opened, the product is dispensed. The piston scrapes against the sides of the container and dispenses most of the product concentrate (11).

2. Plastic Bag Type

This system consists primarily of a metal container equipped with an inner plastic bag that holds the product. The pressure that forces the product out of the plastic bag and through the valve is supplied by the propellant which is loaded through the bottom of the can and remains outside the bag. The plastic bag, therefore, serves as a barrier that prevents the propellant from coming into contact with the product. These systems have a number of advantages and should open up the field for many new products (11).

3. Aspirator (Venturi) Systems

Several new systems are based on the aspirator principle. The propellant is kept apart from the product until discharge. The assembly consists of a power unit, which contains the propellant and a product container. The latter is at atmospheric pressure at all times; therefore, its construction is not limited by pressure regulations. This allows considerable flexibility in the design of the product container as well as in the materials of construction (12).

4. Co-Dispensing System

This system was developed to separate the reacting ingredients that are used in the production of hot foams. This unit is inserted into a regular aerosol container and crimped in place in the usual manner. The oxidizing agent is placed in the inner container. A reducing agent is mixed with the emulsion formulation and placed into the outer container.

When used, a measured amount of each component is dispensed and allowed to mix in the valve. An exothermic reaction results with the liberation of sufficient calories to heat the foam. This system has been used to dispense a hair conditioner and can be used for a variety of pharmaceutical products where heat may be desired or where incompatible ingredients may be present (3).

Propellants

One of the most intriguing aspects of aerosol formulation is the dual role played by most of the currently available propellants. These supply the necessary energy required by the self-propelling features of the aerosol, and, in addition, become an integral component of the contents. In many instances the propellant used may be quite satisfactory in supplying pressure, but at the same time introduces serious problems which affect therapeutic efficiency and product stability. It can be seen that the choice of propellant in an aerosol formulation is of critical importance.

1. Liquefied Gases

The liquefied gas compounds have found widespread use as propellants since they are extremely effective in dispersing the active ingredients into a mist or foam depending on the form desired. In addition they are relatively inert and nontoxic. They have the added advantage that the pressure within the container remains constant when these gases are used as propellants. Of the two types of liquefied gases used, the fluorinated hydrocarbons have found greater use due to their nonflammability than the flammable hydrocarbons.

However, the hydrocarbons are less expensive than the fluorocarbons and are finding increased use in shave foams and other water based aerosols.

Several of the fluorocarbons have been used as propellants. In fact a majority of commercial aerosol products make use of these materials as propellants (13). These propellants are primarily derived from methane, ethane, and cyclobutane by replacing one or more of the hydrogens of these compounds with chlorine and/or fluorine (3).

The most unique member of this family of propellants is octafluorocyclobutane (Propellant C-318). This non-chlorinated cyclic compound is considered the most stable of the halocarbon propellants and has been cleared for use with edible products (10).

In order to refer easily to the fluorinated hydrocarbons a relatively simple system of nomenclature was developed by the refrigeration industry. A numerical designation is used to identify each propellant (14). The rules for numerical designation are as follows:

1) all propellants are designated by three digits. When the first digit is zero, the propellant is designated by two digits,

2) the first digit is one less than the number of carbon atoms in the compound. Where there are only two digits, zero is understood to be this figure and indicates a methane derivative,

3) the second digit is one more than the number of hydrogen atoms in the compound,

4) the last digit represents the number of fluorine atoms,

5) the number of chlorine atoms in the compound is found by subtracting the sum of the fluorine and hydrogen atoms from the total number of atoms which can be added to saturate the carbon chain,

6) in the case of isomers each has the same number and the most symmetric one is indicated by the number alone. As the isomers become more and more asymmetric, the letter a, b, c, etc., follows the number,

7) for cyclic compounds a C is used before the number.

Several chlorinated hydrocarbons have been used as propellants or in combination with other propellants in various type aerosols. Vinyl chloride, methylene chloride, and trichloroethane have been used. They are especially useful in insecticidal sprays, certain hair sprays, and room deodorants (3).

Hydrocarbon propellant gases, such as propane, isobutane, and n-butane have seen limited use in nonpharmaceutical aerosols. Their chief disadvantage is their flammability when used alone, but it is claimed that this hazard is minimized when these compounds are mixed with halocarbon propellants. The possibility of leaks of these flammable propellants from stored containers, however, has become a matter of concern. The danger of containers failing or being crushed in shipment, when exposed to excessive temperatures, could present a serious explosion risk with gases such as butane (15).

2. Compressed Gases

The compressed gases such as nitrogen, nitrous oxide, and carbon dioxide have been used as aerosol propellants. Depending on the nature of the formulation and the valve design, the product can be dispensed as a fine mist, foam, or semisolid. Unlike the liquefied gases, however, the compressed gases possess little expansion power and will produce a fairly wet spray and foams which are not as stable as liquefied gas foams. This type of system has been used mainly to dispense food products and for nonfoods to dispense the product in its original form as a semisolid (16).

Containers

There are several requirements for containers which house products exerting a pressure greater than atmospheric. Perhaps the major concern is that they should be substantial enough to contain pressure safely throughout the anticipated shelf life of the product and during various expected conditions of storage and use. Such considerations prompted the early use of heavy, thick walled steel cartridges as the first fluorocarbon gases became available (5). The first disposable aerosol cans appeared in 1947. They were modeled after beer cans. Initially they were available only with plain tinplate interiors, but, later, containers with single, double, and even triple linings were developed to help control corrosion (17).

1. Tin-Plated Steel

The selection of containers is quite varied and each type of container presents different problems. Of all the

metal containers the most popular is three piece tin-plated steel because of its low cost, high strength, light weight, and relative ease of fabrication. It is also, however, susceptible to corrosion. Plastic linings increase the resistance of these containers to corrosion, but again increase the possibility of contamination of the formula with plasticizers and antioxidants. These linings must also be approved by the FDA[a] for use with drugs (18). Most aerosol cans have a soldered side seam where the body is joined together. The problems in completely covering this particular area are so serious that even today the side seam is considered the most critical part of the can, from a corrosion standpoint (17).

2. Aluminum

Aluminum containers may possibly serve where tin-plated steel containers are unsatisfactory. Aluminum containers are available as two-piece and one-piece units, and each is available with and without internal coatings. Corrosion is as much a consideration for aluminum cans as it is for steel containers. In fact, it is often more difficult to observe corrosion in aluminum. The one-piece aluminum can offers more resistance to electrolytic corrosion than the two-piece can. Even though the two-piece can is made completely of aluminum, there is a difference between the bottom and walls of the container. Because both pieces undergo a different type of fabrication, the metal alloys are a little different.

3. Stainless Steel

Stainless steel containers offer very good resistance to most products and can accommodate very high pressures.

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a - Food and Drug Administration.

However, these units are very costly, are available only in small sizes, and are designed to accept 20 mm. bottle valves which further increase the cost. These units usually serve very well when small dosages are to be dispensed at high pressures, and where cost is not a primary consideration (18).

4. Glass

Glass containers offer very good protection for pharmaceutical aerosol formulations since they do not corrode and do not affect the drug (except possibly by adsorptivity). There have been a few cases where the pH of the product had changed appreciably due to the alkalinity of the glass, but the problem can usually be solved by the addition of suitable buffering agents or if this is not practical, by requesting the manufacturer to use Type I glass which is borosilicate glass low in alkalinity. The maximum allowable pressure of 15 psig for uncoated glass limits its use; however, polyvinyl chloride coated glass bottles can hold pressures up to 25 psig and newer modifications will support pressures up to 40 psig (18).

5. Plastic

A great deal of interest has been focused on the development of a suitable plastic container. If and when this becomes readily available, it will be necessary to determine the degree of permeation of the propellant and co-solvent through the container walls, and the resultant effect on the concentration of the active ingredients over extended storage periods. Permeation of moisture from the atmosphere into the plastic container could affect water sensitive formulations.

Here, as in plastic coatings for metal containers, the extraction of plasticizers, antioxidants, and mold lubricants must be considered. Chemical compatibility between the plastic polymers and the formula must also be resolved (18).

Valves

One of the most critical components of the aerosol package is the valve. It serves to seal the container hermetically and to regulate the passage of product from the container. In this regard, it influences the characteristics of the product, complementing the design of the formulation. The valve, along with the actuating device, may be selected to produce a fine or coarse droplet distribution, a fully expanded foam, a slow or rapid rate of product release, a wide or narrow spray pattern, or a continuous or precisely measured amount of product.

1. Conventional Valves

The conventional aerosol valve is composed of several basic components assembled together. Regardless of the manufacturer, in most instances, these parts are present in every valve mechanism.

The actuator, which is often referred to as the button or spout, provides a rapid and convenient means for releasing the contents from a pressurized container. This component is fitted onto the stem of the valve or is inserted into the valve body and serves as the final exit for product leaving the container as well as a means of easily depressing the valve stem to start the process (5). The actuator provides the additional functional use in allowing the product to be dispensed in the

desired form; that is a fine mist, wet spray, foam or solid stream. Mechanical breakup actuators are used in three-phase or compressed gas aerosols. In addition, special actuators are available for use with pharmaceutical and medicinal aerosols which allow for the dispensing of products into the mouth, nose, throat, vagina, and eye (3).

The valve stem is the component actuated to bring product forth from the container. The stem holes are positioned so that when the stem is depressed or tilted, they are exposed below the stem seal into the product contained in the valve body and will permit its passage to the actuator.

The diaphragm or stem seal, which is made of rubber, most often Buna N or Neoprene, functions to seal the product from the stem orifice. The dimensional tolerances of this component are carefully controlled to assure that product will not pass around the stem when the aerosol is not in use.

The valve cup or ferrule is the external housing for the valve parts and is the component which is affixed to the container to hold the entire valve in place. The cup refers generally to the one inch metal valve exterior while the word ferrule is used to describe the same functional part for bottle valves.

The valve spring serves to return the valve stem to its rest position after actuation. Most valve stems contain a spring, constructed usually of thin guage stainless steel wire, which is located at or on the base of the stem and is contained by the internal valve housing (5). The material used to construct the spring is quite important. The iron

that can be extracted from certain springs has been known to cause problems in some formulations. An example of this is epinephrine, whose biological potency will decrease with as little as 50 ppm of iron (19).

The valve housing or body serves to contain the stem and spring and to hold the top of the dip tube at its base, if one is used. The top portion of the housing is held in place against the diaphragm, tightly sealed to prevent the flow of vapor or product other than through its bottom orifice.

The dip tube or eduction tube, when used, conducts the product from the bottom of the container to the housing tail orifice. When not used, the container is held in the inverted position to release product (5).

The dip tube comes into intimate contact with both product and propellant and therefore should be resistant to both physical and chemical attack. Nylon and specially developed polyethylene or polypropylene compounds are the materials most commonly used.

The tube should extend almost to the bottom of the container. If the tube is too short, all of the product will not be dispensed, while a tube touching the bottom of the container will tend to block the passage of liquid. In this connection, most materials used for dip tubes tend to elongate when immersed in certain solvents and propellants for long periods of time. This elongation should be anticipated when determining the length of the dip tube (3). Dip tubes are assembled onto the valve with usually a length tolerance of plus or minus a sixteenth of an inch. They are usually cut flat at the

bottom, however, the serrated bottom is much preferred to eliminate completely the possibility of sealing off on the base of the container (5).

2. Metering Valves

Since their introduction in 1956, aerosol metering valves have found widespread acceptance in the pharmaceutical area, particularly for inhalation aerosols. Aerosol metering valves are designed to deliver a fixed quantity of material upon each actuation of the valve. The basic principle involves a metering chamber and a dual valving mechanism. When the valve is in the closed position, a seal is created between the material in the metering chamber and the atmosphere. In this position the metering chamber is allowed to fill since it is in contact with the contents of the package. Depression of the actuator opens the metering chamber to the atmosphere through the channels in the stem and simultaneously creates a seal between the lower portion of the metering chamber and the contents of the package (20). The volume of the chamber in which the isolated portion is held determines the quantity of spray per actuation. However, trade practice has been to take no account of the specific gravity of the product-propellant mixture and to list valves with different capacities as being able to deliver a certain number of milligrams per actuation, e.g., 50 mg., 100 mg., etc.

Aside from delivering predetermined doses and thus minimizing overdosage of active compounds, metering valves offer another safety feature from the standpoint of aerosol packages for medical uses: they prevent the discharge of

large volumes of comparatively high pressure gas into body cavities. This is particularly true for nasal and oral applications (3).

Filling Methods

The filling of aerosol containers can be undertaken by two distinct methods. In cold filling, the product is placed in the container and cooled. The propellant, also at a low temperature, is then added and the container sealed. In pressure filling, the product is placed in the container at normal temperature and sealed. The propellant is then introduced under pressure through the valve. The danger of air being entrapped in the container can be avoided by evacuating or by purging the container by the addition of a small amount of propellant or nitrogen. Aqueous based systems must be pressure filled as the contents may solidify on cooling (4).

Applications

Aerosol technology has been applied to the formulation of products containing therapeutically active ingredients. Since there are various formulation factors to consider in different systems, some concise definitions would appear to be in order. The definitions of Sciarra (3) seem to be the most useful.

A pharmaceutical aerosol may be defined as an aerosol product containing therapeutically active ingredients dissolved, suspended, or emulsified in a propellant or a mixture of solvent and propellant and intended for topical administration or for administration into one of the body cavities such

as the ear, rectum, and vagina.

Medicinal aerosols, or inhalation aerosols as they may be called, may be defined as those aerosol products containing therapeutically active ingredients dissolved or suspended in a propellant or a mixture of a solvent and a propellant and intended for administration as fine, solid particles, or liquid mists via the respiratory system or the nasal passages. They are intended for local action in the nasal areas, throat, and lungs, as well as for prompt systemic effect when absorbed from the lungs into the bloodstream (inhalation therapy). The particle size must be considerably below 50 microns and in most instances should be below ten microns and preferably between 0.5 and 10 microns for maximum therapeutic response (21, 22).

Pharmaceutical Aerosols

Aerosol dermatological or topical preparations were probably the first aerosol pharmaceuticals to receive close attention by marketers and to receive widespread acceptance by consumers. Some of the advantages of dermatologicals, many of these also apply to all pharmaceutical aerosols, that have caused the rapid acceptance by marketers and consumers are:

1) convenient, fast, and efficient application,

2) no waste or messiness associated with applicator or cotton swab,

3) reduced danger of contamination of the product,

4) the elimination of air, oxygen or light in the product reducing unwanted reactions within the product or loss of active ingredients,

5) prevention of drying out of product,

6) reduction of irritation by mechanical application,

7) application in a thin layer, resulting in faster absorption (9).

Medicinal Aerosols and Oral Inhalation Therapy

Inhalation aerosols are probably one of the greatest areas of opportunity for future growth in the pharmaceutical industry. There are several advantages, previously mentioned in the introduction, to be considered in the use of oral inhalation aerosols for the administration of drugs. In addition to the aforementioned advantages, it has been stated that aerosols offer reproducibility of amounts delivered that is superior to oral liquid preparations dispensed by teaspoon or dropper and that compare favorably with weight variations permitted for hard gelatin capsules (23).

In light of these facts, it would be well to discuss the respiratory system before discussing aerosol therapy in detail.

The respiratory system or tract consists of the nasal passages and the mouth opening into the pharynx, the larynx, the trachea, the bronchi, and the lungs.

Air enters the nose or mouth, passes into the pharynx and thence into the larynx. The larynx and pharynx are separated from one another by the epiglottis, which permits the passage of air or materials suspended in air, but prevents the passage of liquids or solids into the larynx during the swallowing process. From the larynx, air enters the trachea, which divides to form the upper bronchi. Smaller air

passageways, called terminal bronchioles, arise from the bronchi. These terminal bronchioles subdivide into respiratory bronchioles which give rise to the alveolar ducts (five or six per bronchiole). After branching a variable number of times, each alveolar duct terminates in several alveolar sacs (three to six), the walls of which contain pouch-like structures termed pulmonary alveoli. From the area of the respiratory bronchioles to the pulmonary alevoli, true respiratory function occurs, that is, exchange of gases takes place.

From the oral and nasal cavities to the terminal bronchioles, these structures are for the most part lined with mucosal tissue well supplied with arteries and veins. Thus, the surface they present to materials to be absorbed is similar to the lining of the stomach or intestine. However, there are also cilia, or hair-like projections present which beat rhythmically and tend to propel the sheet of mucous which envelopes them in the direction of the mouth. This is the mechanism whereby the body entraps and expels foreign particles entering the respiratory passageways with atmospheric air. Not all suspended materials are eliminated in this way, the limiting factor being the size and mass of the particle, and the diameter of the air passageways. The latter is less important than the former when it is considered that the mechanism for removing particles from the air is so efficient that most particles larger than five microns in diameter are prevented from entering the lungs by this means. On the other hand, the smallest respiratory unit, the alveolar duct, has a diameter of about 200 microns. There is, of course, a

minimum to the size of a particle that will be retained within the alveolar sac. Thus, those particles that tend to remain suspended within the alveolar air would be expelled during expiration, those particles usually smaller than 0.5 microns. Particles between these limits (0.5 to 5.0 microns) would tend to fall against the alveolar walls and mix with the alveolar fluid.

A factor which contributes greatly to the respiratory function of the lung is the thickness of its walls. From the respiratory bronchiole to the alveolar sac, these walls consist of thin connective tissue in close contact with underlying blood vessels. In fact, the walls of the pulmonary alveoli consist of a single layer of epithelial cells with a single capillary between adjacent alveoli, so that, in most instances, material in the alveolar cavity is separated from circulating blood by only two membranes, the alveolar and the capillary walls. The area of the exchange surface of the lung must also be considered. This is estimated to be about 55 square meters or about 25 times the surface area of the skin. If it is kept in mind that this is also the area of the available adjacent blood supply, the rapidity of absorption in this area will be more readily understood (24).

One of the most important considerations in the usefulness of a drug substance is whether or not the material is soluble in body fluids and, therefore, capable of being absorbed. Thus, a drug to be given by inhalation therapy must be soluble in natural secretions. Very slowly soluble and absorbed substances would probably also be proscribed. These

materials are likely to act as foreign bodies and produce some degree of irritation or, as in the case of mineral oils, produce a type of lipid pneumonia. It should be pointed out, however, that the body does possess mechanisms for removing insoluble materials deposited in the alveolar sacs. The question then concerns the efficiency of these mechanisms. Small quantities of particles are usually handled without incidence by various types of tissue cells which engulf them and prevent harm, but in cases of large quantities of particles, the mechanism breaks down and fibrosis of the tissue frequently results.

If it is determined that a material may be administered by inhalation into the lungs, then the next step is to obtain an aerosol of the optimum particle size range of between 0.5 and 5.0 microns. It is necessary that a large majority of the particles fall within this size range. Larger particles would deposit on mucosal surfaces and be slowly absorbed, while smaller particles would be expelled. The former would defeat the purpose of inhalation therapy, whereas the latter would result in inadequate dosage.

In regard to particle size, two other physiological factors should be mentioned. First of all, the respiratory system functions as an efficient humidifying mechanism. It is obvious, then, that hygroscopic materials would tend to increase in size when introduced into the lungs. Secondly, if a material capable of causing broncho-constriction were inhaled, then the resulting narrowed lumen of the airways could conceivably reduce the amount of drug reaching the

alveolar spaces.

Finally, it should be pointed out that the rapid absorption of materials by the lung depends upon the efficiency of the absorption surface. If the lung is affected by some disease process, then absorptive efficiency is reduced. For example, in pneumonias, up to 75 per cent of the alveolar spaces could be rendered useless for either respiratory or absorptive function. It is necessary to consider the presence of pathological pulmonary conditions when aerosol inhalation therapy is being considered for anything other than its local effects (24).

There are several ways in which a medicinal can be formulated with a liquefied gas to produce an aerosol. If the medicinal is soluble directly in the propellant, a clear solution is produced. When this solution is dispensed from the container, the propellant will vaporize, leaving behind a fine dispersion of the medicinal either as liquid or solid particles, depending upon its physical characteristics. Proper choice of propellant, valve, and actuator will produce the proper sized particles. However, most medicinals are not soluble directly in the propellant and may be rendered soluble by use of a co-solvent. Considering the number of solvents that are miscible with the propellants and yet are safe to use internally, the problem becomes apparent. Very few solvents fall into this category. Ethyl alcohol has been used in a concentration of about 30 per cent as a co-solvent for some medicinal aerosols. The usual advantages and disadvantages of ethyl alcohol are present. Some other solvents that may

be useful but have not been fully tested to date are; polyethylene glycol 200 to 400, methoxypolyethylene glycols, dipropylene glycol, and hexylene glycol. The toxicity of these compounds must be considered not only when they are given orally but by inhalation as well.

Water is a good solvent for many medicinals but, unfortunately, water is not miscible with the propellants. However, it may be possible to formulate aqueous systems in a three-phase aerosol using suitable baffles to produce desired particle size. This type of system would overcome many of the problems dealing with the toxicity of the co-solvents and the propellant.

For those medicinals which are insoluble, or can be made insoluble in the propellant, a dispersed system may be possible.

To have the lungs retain a reasonable percentage of particles inspired, the particles must remain above a given critical radius, which has been shown to be approximately 0.5 micron. When the medicinals are liquids, the very fine mist of droplets which is formed disappears quite rapidly because of the small size of the droplets. This results in droplets of varying particle size, many of them falling below 0.5 micron. This rapid evaporation is due to the decreased pressure within the respiratory tract, making evaporation more rapid. The particle size can be stabilized by the addition of glycerin, urea, sugar, and some salts. These act by decreasing the vapor pressure of the medicinal solution, thus decreasing their rate of evaporation (24).

Many medicinal agents lend themselves to administration by inhalation. In fact, any drug given by intravenous injection can, in most cases, be reformulated into a suitable aerosol.

On the basis of the great number of possible advantages of oral inhalation therapy and the inherent disadvantages of many currently used dosage forms for the administration of antinauseants, it would seem appropriate that studies be conducted on the development of an oral inhalation dosage form antinauseant. Thus, the objectives of this research project will be to develop a series of aerosol formulations and to determine their feasibility in antinauseant therapy. Applicable *in vitro* and *in vivo* evaluation tests, including stability studies will be performed. Test results will be compared and correlated with the objective of devising useful formulations for further study and development.

EXPERIMENTAL

Formulation and Preparation

Initially, a review of the literature with special emphasis on formulation techniques, propellants, solvent systems, and medicinals useful in the treatment of nausea was required.

In the present work, it was proposed to use active ingredients of proven worth in controlling nausea. Scopolamine hydrobromide[a], Diphenhydramine hydrochloride[b], Dimenhydrinate[c], and Cyclizine lactate[d] were the agents chosen. All of these compounds have been used for several years and have demonstrated their safety and efficacy. These agents also possess the desired solubility for this project, i.e., water and/or alcohol solubility. These medicinals may also be administered by intravenous injection which indicated the possibility that they could be reformulated into suitable aerosols (24).

Since the ultimate preparation was intended for internal use, it was vital that the propellant chosen possess a

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a - Available from Inland Alkaloid Co., St. Louis, Mo.

b - Available as Benadryl[R] from Parke Davis and Co., Detroit, Mich.

c - Available as Dramamine[R] from G. D. Searle and Co., Chicago, Ill.

d - Available as Marezine[R] from Burroughs Wellcome and Co., Research Triangle Park, N. C.

very low toxicity. Therefore, the propellant chosen was octafluorocyclobutane, Freon C-318[a]. This compound has a reported vapor pressure of 25.4 psig, a density of 1.51 at 70° F., and is nonflammable. Freon C-318 propellant is the most chemically inert of the "Freon" propellants and has been approved by the Food and Drug Administration for use as a food propellant. Freon C-318 is considerably more expensive than the common "Freon" propellants, and is, therefore, limited in its use in nonfood aerosols. It is also an extremely poor solvent (25).

The choice of solvent system as well as propellant is of critical importance in any aerosol product. These agents profoundly influence the particle size of the aerosol product after delivery. The solvent system chosen must be non-toxic, non-irritating, and compatible with the other components of the system. Very few solvents fall into the above categories. Certain solvents have been mentioned in the literature (24). Therefore, on the basis of the above mentioned criteria, solvent characteristics, and literature review the solvent systems chosen consisted of varying proportions of water, alcohol 95%, and propylene glycol. The latter two ingredients may act as co-solvents. The solvents chosen have a low toxicity and, therefore, overcome many of the problems encountered in aerosol formulation. Propylene glycol also has been reported to stabilize particle size (24).

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a - Available from E. I. du Pont de Nemours and Co., Inc., Organic Chemicals Dept., "Freon" Products Division, Chambers Works - Deepwater, N. J.

Preliminary tests were carried out in Fischer-Porter tubes[a] to determine the type of system resulting from the mixture of solvents and propellant, to determine the amount of propellant necessary to dispense all of the product, and to determine the most efficient methods of handling the active ingredients, solvents, propellant, containers, and valve mechanisms.

Finally, four basic solvent-propellant systems were chosen for evaluation with each of the four active ingredients. On a volume-volume basis, the formulations were:

Formula A[b]

Water, purified	50%
Octafluorocyclobutane (Freon C-318)	50%

Formula B[b]

Water, purified	25%
Alcohol U. S. P.	25%
Octafluorocyclobutane (Freon C-318)	50%

Formula C[b]

Water, purified	33 1/3%
Alcohol U. S. P.	16 2/3%
Octafluorocyclobutane (Freon C-318)	50%

Formula D[b]

Water, purified	16 2/3%
Alcohol U. S. P.	16 2/3%
Propylene glycol U. S. P.	16 2/3%
Octafluorocyclobutane (Freon C-318)	50%

All formulating of active ingredients and solvent systems was performed in 50 ml. volumetric flasks. The Scopolamine HBr and Dimenhydrinate powders were weighed on a

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a - Available from the Fischer and Porter Co., Oakland, Calif.

b - The letters "A, B, C, D" hereinafter referred to in the tables of this work refer to the four formulations described on this page.

Sartorius balance[a]. The Diphenhydramine HCl and Cyclizine lactate were transferred from commercial ampuls to the volumetric flasks by use of a 50 ml. syringe and needle unit[b]. The final 50 ml. formulations contained, separately, 500 mg. of Scopolamine HBr per 50 ml., 500 mg. of Cyclizine lactate per 50 ml., 250 mg. of Dimenhydrinate per 50 ml., and 300 mg. of Diphenhydramine HCl per 50 ml.

Containers, Valves, and Accessory Equipment

The containers used in this work were aerosol cans with domed tops and standard one inch curled opening made of three piece tin plate[c].

The valves used in the study were pressure fill metered valves of 50, 100, or 200 mg.[d]. The valves consisted of a tin-plate mounting cap and a high density polyethylene body with a body orifice of 0.040 inch. The stem was stainless steel with a 0.020 inch stem orifice. The pressure fill orifice was 2 x 0.020 inch. The outlet valve seal was Buna N as was the inlet valve seal. The valves were equipped with a stainless steel spring, and the dip tube was a polypropylene capillary with a 0.045 inch internal diameter.

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a - Available from Aloe Scientific Division, A. S. Aloe Co., St. Louis, Mo.

b - Available from Becton, Dickinson and Co., Rutherford, N. J.

c - Available from Continental Can Co., New York, N. Y.

d - Manufacturer's designation of amount of product released per actuation. Available from Emson Research Inc., Bridgeport, Conn.

Both a regular and a mechanical break-up actuator were used in this experiment. These were used in conjunction with an inhalator/cap combination[a]. Both the regular and mechanical break-up actuators were one piece plastic with 0.018 inch orifices, however, the mechanical break-up actuator also contained a mechanical break-up insert.

Filling Methods

In the current work, all samples were filled by the pressure filling method using the General Kinetics model GK-1200-L Laboratory Unit[b]. In pressure filling, the product is placed in the container at normal temperature and sealed. The propellant is then introduced under pressure through the valve. The danger of air being entrapped in the container can be avoided by purging the container by the addition of a small amount of propellant.

In Vitro Testing Procedure

After formulating the aerosols according to the previously mentioned procedures, it was necessary to conduct a series of *in vitro* tests to evaluate the products.

1. Initial Pressure

This test was performed using a suitable pressure guage[c]. It is necessary to determine the pressure of formulations for several reasons:

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a - Available from Emson Research Inc., Bridgeport, Conn.

b - Available from General Kinetics, Inc., Atlanta, Ga.

c - Available as U. S. Guage from General Kinetics, Inc., Atlanta, Ga.

1) to aid in ascertaining the uniformity of formulation within a group of products,

2) to observe the effect of different solvent systems on the pressure,

3) to help find faulty seals and leaks,

4) to determine if pressures are within governmental regulations for the containers used.

A. Results

Results of the pressure determinations are shown in TABLE I.

2. Spray Pattern

Spray pattern studies were conducted to aid in determining possible formulation or valve defects. This was accomplished by spraying the formulation, with and without the oral adaptor attachment, on filter paper at varying distances from the actuator and measuring the diameter and shape of the spray pattern. An unusual spray pattern would be indicative of a possible defect.

A. Results

Results of the spray pattern studies can be seen in TABLE II.

3. Amount of Material Released Per Actuation

As was mentioned earlier, with metering valves the volume of the chamber in which the isolated portion of the product is held determines the quantity of the spray per actuation. However, trade practice has been to take no account of the specific gravity of the product-propellant mixture and to list valves with different capacities as being

TABLE I

INITIAL PRESSURE OF THE PACKAGED FORMULATIONS[a]

Valve Release[b]	Scopolamine HBr				Cyclizine Lactate				Dimenhydrinate				Diphenhydramine HCl			
	A	B	C	D	A	B	C	D	A	B	C	D	A	B	C	D
50 mg	37	31	33	30	33	33	37	33	40	35	33	33	33	32	36	32
100 mg	35	30	33	30	39	37	36	38	36	36	33	33	34	32	34	32
200 mg	37	33	30	31	39	38	38	38	38	34	34	37	32	32	34	32

a - Pressure is given in psig, which is pounds per square inch guage.

b - This refers to the manufacturer's classification of the valve.

TABLE II

SPRAY PATTERN STUDIES

Valve Release[a]	Scopolamine HBr				Cyclizine Lactate				Dimenhydrinate				Diphenhydramine HCl			
	A	B	C	D	A	B	C	D	A	B	C	D	A	B	C	D
50 mg Reg 6 in.	1.5[b]	1.75	1.5	1.75	1.0	2.5	2.0	2.0	3.0	2.0	2.0	2.0	2.5	2.0	3.0	2.0
	1.5[c]	1.25	1.5	1.5	1.0	2.5	1.5	2.0	3.0	2.0	2.0	2.0	2.5	2.0	2.0	2.0
100 mg Reg 6 in.	1.5	2.0	1.5	2.0	1.0	2.0	2.5	2.5	2.0	2.5	2.0	2.0	3.0	2.0	4.0	3.5
	1.5	2.0	1.5	1.25	1.0	1.25	2.0	2.0	2.0	2.5	2.0	2.0	3.0	2.0	3.0	3.5
200 mg Reg 6 in.	2.0	2.75	2.0	2.0	2.0	1.5	2.5	2.0	2.5	2.0	3.0	3.0	3.0	3.0	2.5	3.0
	2.0	2.25	1.5	2.0	2.0	1.5	2.5	2.0	2.5	2.0	2.0	2.5	3.0	3.0	2.0	3.0
50 mg Reg 9 in.	2.0	2.25	2.0	2.5	2.0	3.0	2.5	2.5	3.75	2.75	3.0	2.5	3.0	3.0	4.0	3.0
	2.0	1.75	2.0	2.25	1.5	2.75	2.0	2.5	3.5	2.5	2.5	2.5	3.0	2.5	2.5	2.5
100 mg Reg 9 in.	1.5	3.0	2.0	2.5	1.5	2.5	3.5	3.5	3.5	3.5	2.5	3.0	4.0	3.5	5.0	4.0
	1.5	3.0	2.0	2.25	1.5	2.5	3.0	3.0	3.5	3.0	2.5	3.0	4.0	3.0	4.5	4.0
200 mg Reg 9 in.	3.0	3.0	2.25	3.0	3.0	2.75	3.5	2.75	3.25	2.5	4.0	4.0	4.0	5.0	3.5	5.0
	2.5	2.75	1.5	2.5	2.5	2.5	3.0	2.5	3.0	2.5	3.0	3.0	4.0	4.0	3.0	4.0
50 mg Reg 12 in.	2.5	2.75	3.0	3.25	2.5	3.5	3.25	3.0	4.5	3.25	3.5	3.0	4.5	3.5	4.5	4.0
	2.0	2.5	2.75	3.0	2.0	3.5	3.0	2.75	4.0	3.0	3.0	3.0	4.0	3.0	3.5	3.0
100 mg Reg 12 in.	2.0	4.5	3.0	4.0	2.0	3.5	4.0	4.25	5.0	4.0	3.5	4.0	5.0	4.5	6.0	5.5
	2.0	4.0	3.0	3.5	1.75	3.5	4.0	4.0	4.5	3.5	3.0	3.5	5.0	4.0	5.5	5.0
200 mg Reg 12 in.	3.0	3.75	2.5	3.5	4.0	3.5	4.0	3.5	4.0	3.0	5.0	5.0	5.0	6.0	4.5	6.0
	2.5	3.5	2.0	3.0	3.5	3.25	3.5	3.0	3.5	3.0	4.0	4.0	5.0	5.0	4.0	5.0

TABLE II (continued)

Valve Release[a]	Scopolamine HBr				Cyclizine Lactate				Dimenhydrinate				Diphenhydramine HCl			
	A	B	C	D	A	B	C	D	A	B	C	D	A	B	C	D
50 mg MB 6 in.	1.5[b]	2.0	2.0	2.0	2.0	2.5	2.0	2.0	2.0	2.5	2.0	2.0	2.0	3.0	3.0	2.0
	1.5[c]	1.25	2.0	1.75	2.0	2.0	2.0	2.0	2.0	2.5	2.0	2.0	2.0	3.0	2.5	2.0
100 mg MB 6 in.	1.5	2.0	1.5	2.0	2.0	2.0	1.5	2.5	2.0	2.0	2.0	2.0	3.0	2.0	2.0	2.0
	1.5	2.0	1.5	2.0	2.0	2.0	1.5	2.5	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
200 mg MB 6 in.	1.75	2.0	1.75	2.5	1.5	2.0	2.0	2.0	3.0	2.0	2.0	3.0	3.0	3.0	2.0	3.0
	1.25	2.0	1.5	2.0	1.5	2.0	2.0	2.0	3.0	2.0	2.0	2.5	3.0	2.0	2.0	2.5
50 mg MB 9 in.	2.0	2.5	2.5	2.5	3.0	3.0	2.75	2.5	2.75	3.0	3.0	3.0	3.0	4.0	4.0	3.0
	2.0	2.0	2.5	2.0	2.5	2.5	2.5	2.25	2.5	3.0	2.5	2.5	3.0	4.0	4.0	2.5
100 mg MB 9 in.	2.0	3.0	2.75	2.5	3.0	3.0	2.5	3.5	2.75	3.0	2.5	3.0	4.0	3.5	3.0	3.0
	2.0	2.5	2.0	2.25	2.5	2.5	2.0	3.0	2.5	2.5	2.5	2.5	3.0	3.0	3.0	2.5
200 mg MB 9 in.	2.5	2.75	2.0	3.0	2.5	3.0	3.0	3.0	4.0	3.0	3.5	4.0	5.0	4.0	3.5	4.0
	2.0	2.5	1.75	2.5	2.0	2.5	2.5	2.5	3.5	3.0	3.0	4.0	5.0	3.0	3.0	3.5
50 mg MB 12 in.	3.0	3.25	2.0	3.0	4.0	3.25	3.25	3.0	3.25	3.0	3.5	3.5	4.0	5.0	5.5	3.5
	2.5	2.75	2.0	2.5	3.0	2.75	3.0	2.5	3.0	3.5	3.0	3.0	3.5	5.0	5.0	3.0
100 mg MB 12 in.	3.0	3.25	2.75	3.75	4.0	4.0	2.75	4.5	3.25	3.5	3.0	3.5	5.0	4.5	4.5	4.0
	2.5	2.75	2.25	3.0	3.0	3.0	2.5	4.0	3.0	3.0	3.0	3.0	4.0	3.5	4.0	3.0
200 mg MB 12 in.	3.0	3.5	3.0	3.5	4.0	4.0	3.25	3.75	5.0	4.5	4.5	5.0	7.0	5.0	5.0	5.0
	2.0	3.0	2.0	2.75	2.5	3.5	3.0	3.5	4.0	4.0	4.0	5.0	6.0	4.0	4.0	4.5

a - These figures denote valve release capacity as stated by the manufacturer, actuator type (Reg=regular, MB=mechanical break-up), and the distance from the oral adaptor at which the measurements were made.

b - This is the spray pattern diameter, in inches, resulting from actuation without the use of the oral adaptor.

c - This is the spray pattern diameter, in inches, resulting from actuation using the oral adaptor.

able to deliver a certain number of milligrams per actuation (3). Therefore, for each particular formula, it is necessary to determine the amount of product released per actuation. The uniformity in delivery from metering valves is indispensable in the development of dependable medicinal preparations. Limits of ± 15 per cent of the calculated dose have been suggested (26). The amount of product released was compared with the amount stated for each valve by taring the container, actuating five times and re-weighing. The weighing was done on a torsion balance[a].

After this and other in vitro tests, satisfactory formulations were subjected to a stability study. The aerosol formulations were stored in a Thelco Model 12 oven[b] at a temperature of 37-38° C. for one month. This is approximately the equivalent of one year storage at room temperature. After this storage, the formulations were again tested for valve release to aid in determining if there had been any formulation deterioration or valve malfunction.

A. Results

Results of the valve release study are tabulated in TABLE III.

B. Results

Results of the valve release study after storage are summarized in TABLE IIIa.

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a - Available from The Torsion Balance Co., Clifton, N. J.

b - Available from Central Scientific Co., Chicago, Ill.

TABLE III

AMOUNT OF FORMULATION RELEASED PER ACTUATION[a]

Valve Release[b]	Scopolamine HBr				Cyclizine Lactate				Dimenhydrinate				Diphenhydramine HCl			
	A	B	C	D	A	B	C	D	A	B	C	D	A	B	C	D
50 mg reg.[c]	54	50	50	50	46	50	50	48	52	54	56	56	50	54	48	54
50 mg MB[d]	50	50	50	50	50	54	52	50	54	50	56	50	54	50	54	46
100 mg reg.	90	90	90	96	104	80	80	88	104	104	90	90	88	104	96	94
100 mg MB	90	94	90	92	90	80	92	92	106	102	90	100	88	96	88	92
200 mg reg.	164	160	160	178	180	155	162	140	178	164	190	158	170	200	168	184
200 mg MB	160	160	160	158	184	160	160	140	160	160	166	160	160	170	160	180

a - The results are the averages of five actuations determined by taring the container, actuating and re-weighing. Amounts are given in mg.

b - This refers to the manufacturer's classification of the valve.

c - "reg" refers to a regular actuator.

d - "MB" refers to a mechanical break-up actuator.

TABLE IIIa

AMOUNT OF FORMULATION RELEASED PER ACTUATION AFTER STORAGE[a]

Valve Release[b]	Scopolamine HBr		Cyclizine Lactate		Dimenhydrinate		Diphenhydramine HCl	
	B	D	B	D	B	C	B	D
50 mg reg.[c]	50	50	50	50	50	52	48	50
50 mg MB[d]	50	50	50	50	48	52	50	54
100 mg reg.	88	90	80	88	92	90	96	88
100 mg MB	88	92	80	80	92	98	106	90
200 mg reg.	160	158	150	140	160	180	160	180
200 mg MB	160	154	160	160	158	162	160	190

a - The results are the averages of five actuations determined by taring the container, actuating and re-weighing. Amounts are given in mg.

b - This refers to the manufacturer's classification of the valve.

c - "reg" refers to a regular actuator.

d - "MB" refers to a mechanical break-up actuator.

4. Particle Size Determination

Particle size studies were conducted using an American Optical microscope[a] with an ocular micrometer calibrated against a stage micrometer for direct measurement. The calibration was done according to the method of Trease (27). The particles were deposited on slides coated with white petrolatum to prevent merging of adjacent particles and to delay evaporation. This general method has been mentioned by Tollin (28). Microscopic techniques have been classified as being among the most accurate of the direct methods. Microscopic measurement of the actual dimensions of particles is more accurate than indirect methods which measure some other property of particles which is related to their size (29). Particle size determination is important because the aerosol particles must fall into an optimum size range to give the desired effects and advantages of oral inhalation therapy. This size range is now generally accepted as being between 0.5 and 5.0 microns. Larger particles are deposited in the respiratory tract above the alveoli, while most particles below 0.5 micron are lost by exhalation. The former would slow absorption and, therefore, defeat the purpose of inhalation therapy, whereas the latter would result in inadequate dosage.

Ten particles per slide were counted, using five slides at each interval of 6 inches, 9 inches, and 12 inches from the actuator. In the present work, both mechanical break-up

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a - Available from American Optical Co., Instrument Division, Buffalo, N. Y.

and regular actuators with the oral adaptors were tested. The three distances from the actuator were chosen to give a more complete picture of the particle size distribution. The criteria for formulation selection was the production of particles with an average diameter of between 0.5 and 5.0 microns and with no particle greater than 10 microns.

This test was also repeated, on the aerosols that were subjected to the stability study mentioned earlier, to determine if there was an increase in particle size on aging.

A. Results

The results of the particle size determinations are indicated in TABLE IV.

B. Results

The results of the particle size determinations after storage are indicated in TABLE IVa.

In Vivo Testing Procedure

Formulations complying with established standards were then subjected to an in vivo test using guinea pigs.

Since all of the active ingredients employed were of established effectiveness, a formulation could be considered successful if it could be established that the active ingredient passed the pulmonary membrane barriers and entered the blood stream.

The test was based on the hypothesis that all of the ingredients demonstrate significant anticholinergic properties (30, 31, 32, 33). Upon administration, with subsequent absorption into the blood stream, bronchodilation should occur, and a respiratory rate increase should be

TABLE IV

INITIAL PARTICLE SIZE

Valve Release[a]	Scopolamine HBr				Cyclizine Lactate			
	A	B	C	D	A	B	C	D
50 mg Reg 6 in.	5.54[b]	2.88	4.94	4.88	10.86	4.88	3.62	6.19
	14.20[c]	7.81	14.20	11.36	28.40	14.20	10.65	10.65
100 mg Reg 6 in.	7.68	3.74	4.63	4.44	9.73	3.75	9.83	4.77
	16.33	8.52	14.20	12.07	24.85	14.20	21.30	10.65
200 mg Reg 6 in.	6.62	2.61	7.23	6.01	10.01	3.59	9.98	4.81
	14.20	7.81	17.75	21.30	28.40	8.52	24.18	8.52
50 mg Reg 9 in.	4.88	2.85	4.83	4.87	10.45	4.84	3.34	6.17
	14.20	7.81	14.20	11.36	21.30	14.20	14.20	10.65
100 mg Reg 9 in.	7.55	2.56	4.08	4.43	9.68	2.84	9.71	4.66
	17.75	10.65	14.20	10.65	28.40	7.81	21.30	9.23
200 mg Reg 9 in.	6.56	2.58	5.91	5.24	9.30	3.54	9.90	4.71
	14.20	8.52	12.78	14.20	21.30	7.81	21.30	7.81
50 mg Reg 12 in.	4.39	2.84	4.36	4.39	10.41	4.74	2.83	4.17
	14.20	7.10	10.65	9.94	21.30	14.20	10.65	10.65
100 mg Reg 12 in.	5.41	2.50	4.06	4.42	9.07	2.71	9.40	3.96
	14.20	9.94	14.20	7.81	17.75	14.20	21.30	8.52
200 mg Reg 12 in.	6.55	2.51	5.89	5.21	9.26	3.52	9.85	4.63
	14.20	7.10	12.78	9.94	21.30	10.65	17.75	9.94

TABLE IV (continued)

Valve Release[a]	Dimenhydrinate				Diphenhydramine HCl			
	A	B	C	D	A	B	C	D
50 mg Reg 6 in.	5.06	3.48	4.05	4.94	5.35	2.61	3.68	3.95
	14.20	9.94	12.78	9.26	14.20	7.81	9.23	8.52
100 mg Reg 6 in.	6.08	3.93	4.53	4.83	4.33	3.28	4.56	4.17
	14.20	8.52	14.20	9.23	9.94	8.52	11.36	8.52
200 mg Reg 6 in.	5.94	3.07	5.42	4.22	7.70	2.69	3.82	4.25
	14.20	5.68	10.65	9.94	14.20	4.97	13.49	7.10
50 mg Reg 9 in.	4.98	3.20	3.91	4.76	5.24	2.56	3.58	3.51
	14.20	7.81	8.52	14.20	14.20	4.97	12.07	7.81
100 mg Reg 9 in.	4.79	3.86	4.12	4.79	4.22	3.20	4.52	4.16
	13.49	9.23	14.91	13.49	12.07	9.23	9.23	7.10
200 mg Reg 9 in.	5.82	3.02	4.76	4.10	7.63	2.60	3.76	3.85
	10.65	7.81	10.65	12.78	12.78	4.97	9.23	5.68
50 mg Reg 12 in.	4.60	3.14	3.76	4.12	4.96	2.06	3.34	3.49
	14.20	5.68	14.20	9.26	8.52	7.10	9.23	5.68
100 mg Reg 12 in.	4.64	3.17	3.86	4.26	3.71	3.18	4.46	3.65
	10.65	7.10	14.20	12.07	14.20	7.81	10.65	6.39
200 mg Reg 12 in.	5.77	2.94	4.10	4.06	5.89	2.47	3.45	3.69
	10.65	5.68	9.94	8.52	17.75	5.68	10.65	5.68

TABLE IV (continued)

Valve Release[a]	Scopolamine HBr				Cyclizine Lactate			
	A	B	C	D	A	B	C	D
50 mg MB 6 in.	2.61[b]	1.74	4.74	4.40	10.31	2.95	3.27	4.19
	7.10[c]	7.10	9.23	9.23	28.40	7.81	8.52	8.52
100 mg MB 6 in.	6.06	2.63	4.03	4.43	8.17	1.56	9.77	4.76
	12.07	8.52	9.94	8.52	28.40	4.97	21.30	8.52
200 mg MB 6 in.	6.60	2.10	6.92	5.07	8.90	3.52	9.80	4.13
	14.20	7.81	14.20	10.65	24.85	8.52	28.40	8.52
50 mg MB 9 in.	2.58	1.68	4.69	4.39	10.27	2.91	3.24	3.79
	7.81	4.97	10.65	9.94	28.40	7.81	7.10	8.52
100 mg MB 9 in.	5.96	2.51	3.97	4.42	8.14	1.55	9.71	4.64
	14.20	5.68	14.20	10.65	14.20	3.55	28.40	9.94
200 mg MB 9 in.	6.55	2.04	5.89	4.96	8.51	2.93	9.77	4.03
	17.75	7.81	21.30	10.65	21.30	10.65	28.40	8.52
50 mg MB 12 in.	2.57	1.66	4.23	3.68	8.09	2.27	2.71	3.02
	5.68	3.55	14.20	7.81	17.75	5.68	7.81	6.39
100 mg MB 12 in.	5.34	2.34	3.92	4.35	8.12	1.41	9.39	3.89
	14.20	7.10	14.20	10.65	17.75	3.55	21.30	7.10
200 mg MB 12 in.	6.49	2.03	4.73	3.98	8.22	2.22	9.73	3.93
	14.20	4.97	14.20	7.81	28.40	4.97	21.30	8.52

TABLE IV (continued)

Valve Release[a]	Dimenhydrinate				Diphenhydramine HCl			
	A	B	C	D	A	B	C	D
50 mg MB 6 in.	4.36	3.29	3.89	4.87	5.27	2.53	3.34	3.54
	14.20	8.52	7.81	14.20	9.23	7.81	12.07	8.52
100 mg MB 6 in.	3.66	3.28	4.44	4.81	3.59	3.24	3.71	3.27
	9.52	7.10	9.94	14.20	11.36	8.52	9.23	8.52
200 mg MB 6 in.	4.42	3.02	4.54	4.10	7.58	2.59	3.79	3.21
	9.23	8.52	8.52	12.78	14.20	7.81	12.07	4.97
50 mg MB 9 in.	4.19	3.18	3.88	4.76	5.21	2.27	3.32	3.44
	10.65	7.81	14.20	12.78	17.75	6.39	11.36	7.81
100 mg MB 9 in.	3.65	3.01	3.28	4.77	3.56	3.15	3.68	3.21
	8.52	7.81	13.49	14.20	12.78	8.52	9.94	7.10
200 mg MB 9 in.	4.29	3.01	4.43	4.09	7.54	2.50	3.71	2.85
	10.65	5.68	12.78	14.20	14.91	4.97	9.23	5.68
50 mg MB 12 in.	2.61	3.17	3.58	4.03	4.83	2.04	3.31	3.18
	6.39	5.68	10.65	14.20	12.78	4.97	11.36	4.97
100 mg MB 12 in.	3.54	2.90	3.15	4.25	3.24	3.10	3.66	3.17
	9.94	4.97	6.39	13.49	9.94	7.10	10.65	5.68
200 mg MB 12 in.	3.86	2.93	3.98	4.05	5.10	2.46	3.31	2.74
	7.10	4.97	9.94	9.23	12.78	4.97	6.39	4.97

a - These figures denote valve release capacity as stated by the manufacturer, actuator type (Reg=regular, MB=mechanical break-up), and the distance from the actuator at which the particles were collected.

b - The figure in this position is the average diameter of 10 particles counted per slide using 5 slides for a total of 50 particles. Data is in microns.

c - This is the largest single particle of the 50 particles observed. Data is in microns.

TABLE IVa

PARTICLE SIZE AFTER STORAGE

Valve Release[a]	Scopolamine HBr		Cyclizine Lactate		Dimenhydrinate		Diphenhydramine HCl	
	B	D	B	D	B	C	B	D
50 mg 6 in.	3.17[b]	4.26	4.37	4.06	3.68	4.05	3.32	4.02
	7.10[c]	7.10	8.52	9.94	8.52	7.10	8.52	7.81
100 mg 6 in.	3.64	4.00	3.35	4.03	4.30	4.27	3.83	4.50
	4.97	7.10	8.52	7.81	7.81	8.52	9.94	9.94
200 mg 6 in.	3.83	4.35	4.52	3.46	4.10	4.17	4.06	4.36
	7.10	7.10	8.52	9.23	9.94	6.39	9.94	9.23
50 mg 9 in.	2.83	3.55	3.72	3.15	3.33	3.46	3.28	3.82
	7.81	6.39	8.52	9.23	7.81	7.10	9.23	7.10
100 mg 9 in.	3.38	3.65	3.24	3.59	4.23	3.61	3.32	4.44
	7.10	6.39	5.68	7.10	7.10	5.68	4.97	7.10
200 mg 9 in.	2.98	3.86	3.56	3.10	3.56	3.88	3.81	4.27
	7.10	4.97	5.68	4.97	7.81	7.10	7.81	8.52
50 mg 12 in.	2.81	3.08	3.15	3.10	2.91	2.87	2.46	2.67
	5.68	5.68	5.68	6.39	4.97	7.10	6.39	8.52
100 mg 12 in.	2.49	2.60	2.32	2.71	2.75	2.64	3.08	3.31
	7.10	4.26	5.68	4.97	7.10	7.10	9.23	7.10
200 mg 12 in.	2.93	3.27	3.08	2.77	2.83	3.18	3.29	3.07
	7.10	4.97	7.10	7.10	4.97	6.39	9.94	4.97

a - These figures denote valve release capacity as stated by the manufacturer and the distance from the actuator at which the particles were collected. Mechanical break-up actuators were used in this test.

b - The figure in this position is the average diameter of 10 particles counted per slide using 5 slides for a total of 50 particles. Data is expressed in microns.

c - This is the largest single particle of the 50 particles observed. Data is expressed in microns.

observed (34, 35). Through the use of placebo formulations, which consisted of all substances with the exception of the active ingredients, in conjunction with the formulations containing the active ingredients, the normal "excitatory" increase in respiration could be observed and compensated for in the results. It should be noted that it was not necessary to tranquilize or sedate the experimental animals prior to testing, therefore, there should have been no interference from other drugs. The medication was administered to the test animals by inserting the oral adaptor directly into the mouth and actuating the aerosol. Animals given placebos were not re-tested for at least one hour after administration, and animals given a formulation containing an active ingredient were not re-tested for at least six hours, and usually 18 to 24 hours. These time intervals should be sufficient to eliminate the danger of an overlap of results from one test to another. A period of three minutes was chosen as the time limit for an aerosol formulation to exert an effect. The normal respiratory rate was observed, as well as that three minutes after placebo administration. Then, the rate three minutes after active ingredient administration was determined. Since the purpose of the in vivo test was to demonstrate that the medication entered the blood stream of the test animal, the change in respiratory rate should provide ample evidence of this fact.

A. Results

The results of the in vivo study can be seen in TABLE V.

TABLE V

IN VIVO RESPIRATORY RATE STUDIES

Respiratory Information	Scopolamine HBr[a]		Cyclizine Lactate		Dimenhydrinate		Diphenhydramine HCl	
	B	D	B	D	B	C	B	D
Normal Rate[b]	78/80/78	80/80/82	84/78/80	98/96/96	90/90/90	80/78/82	100/106/110	98/98/10
Increase Over Normal With Placebo[c]	12/6/2	10/-2/-6	8/12/6	18/10/10	0/-2/-4	14/6/12	18/12/14	22/22/2
Increase Over Normal With Active Ingredient[d]	18/12/4	18/14/16	12/14/10	20/16/14	34/30/20	26/22/32	42/40/34	32/34/26
Increase Attributed To Active Ingredient[e]	6/6/2	8/16/22	4/2/4	2/6/4	34/32/24	12/16/20	24/28/20	10/12/24

a - In addition to respiratory changes, the sedative effect of Scopolamine HBr was visually observed.

b - This indicates three observations of the normal respiratory rate per minute, determined at one minute intervals.

c - This indicates three observations, conducted at one minute intervals, of the increase in respiratory rate over normal, three minutes after placebo administration. The increase is attributed to "excitement."

d - This indicates three observations, conducted at one minute intervals, of the increase in respiratory rate over normal, three minutes after active ingredient administration.

e - This is the increase in respiratory rate per minute that is attributed to the active ingredient.

DISCUSSION

All of the formulations used were three phase aerosol systems. This was to be anticipated due to the extremely poor solubility characteristics of the propellant, octafluorocyclobutane, and the use of polar solvent systems. The solvent systems were seen to be quite satisfactory for solubilizing the active ingredients. In addition to their solubilizing properties, the various co-solvents used were chosen for the possible influence they would exert on particle size.

Consistent aerosol pressure was observed within formulation groups. As indicated in the literature (24), preparations containing propylene glycol generally demonstrated a somewhat lower pressure. Only one faulty seal was noted in any of the pressurized packages, and this appeared to be due to faulty crimping. No formulation had a pressure in excess of 40 psig, therefore, any of these aerosols could be packaged not only in tin-plate steel, but also stainless steel and suitable coated glass containers (18).

The stability study yielded no evidence of container or formula degradation, but, as was mentioned previously, tin-plate containers are at times susceptible to attack. Glass and stainless steel containers are, of course, practically corrosion free.

Spray pattern studies were conducted to aid in determining possible formulation or valve defects. All patterns

observed were circular and increased in diameter as the distance from the actuator was increased. Also, the patterns formed while using an oral adaptor were smaller than those formed without the use of an oral adaptor. All formulas appeared to be uniform and consistent in this test.

The amount of formulation released per actuation was consistent within a product group, falling within the generally acceptable ± 15 per cent (26). This reproducibility is extremely important in medicinal aerosols. Also, no significant changes were noticed in amounts released after aging. This would seem to indicate that there was no formulation alteration or valve malfunction on storage. Generally, it can be said that the 50 mg. valves dispensed 50 mg. of material quite accurately, the 100 mg. valves usually dispensed slightly less than 100 mg., and the 200 mg. valves usually dispensed between 80 and 90 per cent of the stated amount.

As mentioned previously, particle size is of critical importance in any aerosol. This is undoubtedly one of the most important *in vitro* tests that was conducted. The criteria for formulation selection was the production of particles with an average diameter of between 0.5 and 5.0 microns and with no particle greater than 10 microns. Particle sizes were reduced considerably through the use of the mechanical break-up actuator. This type of actuator is generally recommended for any water based aerosol (24). Formulations "A", containing equal parts of water and octafluorocyclobutane, and "C", containing water, alcohol, and octafluorocyclobutane in a ratio of 2:1:3, did not pass the established requirements, with the exception of formula

"C" containing Dimenhydrinate as the active ingredient. This variation may be due to the influence of the active ingredient since all other components within the group are constant. Formulas "B", containing water, alcohol, and octafluorocyclobutane in a 1:1:2 ratio, and "D", containing water, alcohol, propylene glycol and octafluorocyclobutane in a 1:1:1:3 ratio, were shown to pass the requirements, again with the exception of "D" containing Dimenhydrinate as the active ingredient. The "promising" formulations that were tested following the stability study also yielded satisfactory results. Therefore, it was concluded that there was no increase in particle size on aging.

Formulations complying with established *in vitro* standards were subjected to an *in vivo* test using guinea pigs. As can be seen from the increase in respiratory rate following active ingredient administration, it appears that the medicinals did, in fact, enter the blood stream and provoke a response. Therefore, the formulas considered valuable, on the basis of this study, are:

I

Water, purified	33 1/3%
Alcohol U. S. P.	16 2/3%
Octafluorocyclobutane (Freon C-318)	50%

containing Dimenhydrinate as the active ingredient.

II

Water, purified	25%
Alcohol U. S. P.	25%
Octafluorocyclobutane (Freon C-318)	50%

containing Scopolamine HBr, Cyclizine lactate, Dimenhydrinate, or Diphenhydramine HCl as the active ingredient.

III

Water, purified	16 2/3%
Alcohol U. S. P.	16 2/3%
Propylene Glycol U. S. P.	16 2/3%
Octafluorocyclobutane (Freon C-318)	50%

containing Scopolamine HBr, Cyclizine lactate, or Diphenhydramine HCl as the active ingredient.

SUMMARY

1. The literature surveying the history of aerosols, the aerosol principle, various aerosol systems, propellants, containers, valves, packaging methods, applications, and oral inhalation therapy has been presented.

2. The factors influencing the choice of ingredients and procedures used to develop preliminary formulations have been discussed.

3. Applicable *in vitro* evaluation studies were presented. The studies tested for initial pressure of the packaged formulations, spray pattern, amount of material released per actuation, and particle size.

4. A stability study was performed on promising formulations. Aerosols were re-checked for amount of formula released per actuation and particle size.

5. Formulations complying with *in vitro* standards were then subjected to an *in vivo* evaluation to determine whether the active ingredients entered the blood streams of the experimental animals.

CONCLUSIONS

A study has been conducted to determine the possibility of developing an oral inhalation dosage form antinauseant.

The results of this study indicated that the development of an aerosol useful in the treatment of nausea is possible. Consistent, reproducible valve release, spray pattern, and particle size results were demonstrated before and after aging studies. Since all of the active ingredients employed were of proven effectiveness, a formulation would appear successful if it could be established that the active ingredient passed the pulmonary membrane barriers and entered the blood stream. Results obtained from the animal studies indicated that the active ingredients did enter the blood stream to presumably exert their characteristic action.

As discussed previously, an antinauseant effective via oral inhalation would offer many advantages over conventional antinauseant dosage forms. Those screened formulations complying with established criteria appear to have specific therapeutic possibilities.

Aerosol formulations of the type studied in this experiment may find application with a wide range of active ingredients. Other drugs that may prove more effective when applied as aerosols than when administered by other means may include antihistamines, anti-infective agents, analgesics, sterols, steroids, antitussive agents, hormones, cardiotonics,

diuretics, and many others. Most of these drugs would require further study before they could be used as liquified gas aerosols. However, once their behavior in the liquified gases is determined (solubility, stability, toxicity, etc.) they would be readily acceptable as aerosols (24). We must keep in mind, however, that the problems of aerosol formulation must be studied in view of each other, and that in resolving one problem we may create another. Aerosols designed for inhalation therapy must be carefully balanced systems capable of delivering the amount of drug to that portion of the respiratory system in which it will be most effective.

The results of this study provide encouragement for future work in this area. Based on the findings of this study, it appears that this relatively unexplored dosage form offers potential advantages for a wide range of ingredients and products in the pharmaceutical industry. The use of previously unreported combinations of active ingredients, solvent systems, and propellants present, as they did in this project, interesting and stimulating possibilities for new original research and development.

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