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Secundum Artem

Current & Practical Compounding Information for the Pharmacist.

INHALATION PRODUCTS

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INTRODUCTION AND DEFINITIONS

Drugs can be introduced into the lungs easily by the patient inhaling a "dose" of a drug in a properly designed dosage form that is caught up in the flow of air and carried into the deep recesses of the pulmonary environment. Drugs generally can be transported by the air stream into the respiratory bronchiole and the alveolar region when in the form of a vapor, very fine powder or as a solution in the form of an "aerosol". An aerosol is generally a dispersed system consisting of a solid or liquid internal phase in an outer gaseous phase. An example of a natural aerosol is a mist (water/air) and dust (solid/air). Products administered by inhalation can produce either a local or a systemic effect. Drugs commonly administered for respiratory purposes include bronchodilators corticosteroids, antitussives, expectorants, surfactants, respiratory stimulants and therapeutic gases.

Aromatherapy is a contemporary term used to describe one of the age-old methods of drug administration. Today, however, the term aromatherapy is used primarily to refer to the use of volatile/aromatic oils that are used as room sprays, massage products, room fresheners and even as inhalants when placed in hot water.

There are numerous advantages of oral inhalation products, including a rapid onset of action, bypassing the first-pass effect, avoiding drug degradation in the gastrointestinal tract, low dosages to minimize adverse reactions, dose titration capability, good for prn dosing, alternate route when other drugs may chemically or physically interact with concurrent drugs, and an alternate route for drugs with erratic oral or parenteral administration pharmacokinetics. The ultimate deposition of inhalation aerosols is dependent upon (1) the products formulation, (2) the design of components/packaging/container, (3) administration skills and techniques of the product user, and (4) the anatomical and physiological status of the respiratory system.

Numerous terms are used to describe the various dosage forms and methods of drug administration by inhalation, including aerosols, atomizers, inhalations, insufflations, metered dose inhalers, nebulizers and vaporizers.

By definition, an aerosol is a colloidal dispersion of a liquid or a solid in a gas. Oral inhalation and nasopharyngeal medications can both be administered in aerosol form. These products are commonly produced by manual sprays or from pressurized packages. Aerosols have become so widespread in use that the term has come to mean a self-contained product that is sprayed and the propelling force is supplied by a liquefied or compressed gas. In pharmacy, these pressure-packaged products consist of the active drug dissolved in, suspended in, or emulsified in a propellant or a mixture of a solvent and a propellant. These aerosols are generally designed for either topical administration or for inhalation into the nasopharyngeal region or bronchopulmonary system. For pulmonary delivery, particles greater than 60µ diameter usually are deposited in the trachea, and those 60 - 20 µ between the trachea and the bronchioles, but not into the bronchioles. Particles about 1µ often remain airborne and are exhaled. Consequently, particles between about 5 to 20 µ would be desired to reach the bronchioles. Inhalation aerosols is the largest group of oral aerosol products formulated either as solutions or suspensions. Factors influencing the deposition of inhalation aerosols include the formulation, device, administrative technique of the user and the anatomical and physiological status of the respiratory system.

An atomizer is an instrument used to disperse a liquid in a fine spray. Many of the older pressure-type atomizers used the Bernoulli principle. When a stream of air moves at a high velocity over the tip of a dip tube, the pressure is lowered, and the liquid is drawn into the air flow. The liquid is broken

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up into a spray as it is taken up into the air stream. To produce smaller droplets, a baffle, bead or other device may be put in the flow to break the droplets into smaller droplets as they collide with the stationary device. These smaller droplets are then carried by the air flow into the inhaled stream of air. Many different configurations are available using the Bernoulli principle. A finer spray can be obtained using a pressure type atomizer. Today's plastic spray bottles are similar to the pressure atomizers. When the plastic bottle is squeezed, the air inside is compressed, forcing the liquid up a dip tube into the tip. The liquid stream is mixed with air as it is emitted from the nozzle, producing a spray.

Inhalations are preparations designed to deliver the drug into the respiratory tree of the patient for local or systemic effect. Rapid relief is obtained when the vapors or the mist/droplets reach the affected area. The USP 23/NF 18 definitions of inhalations states "inhalations are drugs or solutions or suspensions of one or more drug substances administered by the nasal or oral respiratory route for local or systemic effect". The drugs may be nebulized to produce droplets sufficiently fine and uniform in size to reach the bronchioles. The mist may be breathed directly from the nebulizer or a face mask; tent or intermittent positive pressure breathing (IPPB) machines may be used to produce a contained environment to maximize the quantity of drug available in the breathing environment to be delivered into the lungs.

According to the British Pharmacopeia, "inhalations" are solutions or suspensions of one or more active ingredients that may contain an inert, suspended diffusing agent. These liquids are designed to release volatile constituents for inhalation, either when placed on a pad or when added to hot water. An example of the latter is the use of one teaspoonful of Benzoin Inhalation BP in 1 quart of hot water where the vapors are inhaled.

Inhalants are drugs that are characterized by a high vapor pressure and can be carried by an air current into the nasal passage where they generally exert their effect. The devices or the container from which the inhalant is generally administered is called an "inhaler". An inhalant consists of cylindrical rolls of a fibrous material that has been impregnated with the drug, usually containing an aromatic substances in addition to an active substance. These devices are often cylindrical in nature with a cap in place to retard the loss of the medication. To use, the cap is removed and the inhaler inserted into a nostril. Upon inhaling, the air passes through the inhaler and carries the vapor of the medication into the nasal passage. An actual "drug vapor" is being delivered to the patient. For example, menthol, camphor, propylhexedrine and tuaminoheptane inhalants are of this type. Another type, amyl nitrite inhalant, is packaged with the drug contained in a thin glass ampule encased in a gauze netting. When the product is squeezed and the glass ampule broken, the amyl nitrite is released and is absorbed on the gauze netting for inhalation by the patient. There are currently 25 inhalation products and 2 inhalants listed in the USP 23/NF 18.

Insufflations are powders administered using a powder blower (puffer) or insufflator. These may consist of a rubber bulb connected to a container and a delivery pipe. As the bulb is squeezed, air is blown into the container causing turbulence which causes the powder to fly around. As the air leaves the container, some of the fine particles are carried out with the air through the delivery tube and are ready for inhalation.

Another device (puffer) consists of a plastic accordion-shaped container with a spout on one end. The powder is placed in the "puffer" and, as the puffer is sharply squeezed, a portion of the powder is ejected from the spout into the air available for inhalation or application. Contemporary delivery systems include powders that may be delivered by various mechanical devices designed for the patient to breathe deeply to inhale the powder particles. The inspiration step provides energy to spin a propeller that

serves to break up and distribute the particles as they are inhaled.

Metered Dose Inhalants (MDIs) are propellant driven drug products, either as solutions or suspensions, containing the drug, a liquified gas propellant with or without a cosolvent and are designed to deliver a metered dose of the drug. These devices commonly deliver from 25 to 100 µL volumes of liquid drug for inhalation.

Nebulae, or spray solutions, were intended for spraying into the throat and nose. The Latin term for "mist" is nebula. Generally, these were simple solutions. Sprays in plastic spray bottles work similarly to the pressure atomizers. When the flexible plastic container is squeezed, the air is compressed, forcing the liquid in the container up through a dip tube into the tip where it mixes with a stream of air. Droplets are formed depending upon the geometry of the device and the pressure of the individual squeezing the bottle.

A nebulizer was formerly described as a small, vacuum type of atomizer inside a chamber. Large droplets would strike the walls of the chamber, fall back and be reprocessed. The smaller particles are carried in the air stream out of the unit. For use, the nebulizer is placed in the mouth and the patient inhales while simultaneously squeezing the bulb. Nebulizers must produce droplets sufficiently fine and uniform in size (optimally 0.5 to 7 micron) such that the mist reaches the bronchioles, in order for nebulizers to be suitable for the administration of inhalation solutions. An advantage of the newer pressurized aerosols is the fine mist they produce and more uniform doses as compared with the older, manual nebulizers.

A vaporizer is an electrical device producing moist steam, either with or without medication, for inhalation. It is often used to soothe upper respiratory irritations but is relatively ineffective in providing medications to the deeper areas of the respiratory tract.

BACKGROUND

One of the earliest methods for inhaling drug products was the burning of materials and inhalation of the smoke. A natural vegetable product was dried and broken up and burned, or an oil was burned, or combustible material was combined with the medication, burned and the resulting vapors inhaled. Until recent years, an asthma "cigarette" (Asthmador) containing the drug was available. It was "smoked" and inhaled, delivering the bronchodilator to the lungs. This principle is still used by recreational drug users for substances such as marijuana and opium. Some recreational drugs are simply inhaled as the powder form, resulting in a very rapid onset of action. There is no question about the effectiveness of this route of administration for drugs.

An earlier problem of inhaled drug delivery related to the accuracy of dose delivery. With the newer metered dose inhalers, this problem has been partly overcome, since the same volume of drug will be administered. Not addressed, however, is the variability in the rate of inspiration, breath holding, and expiration, where varying quantities of drug may be absorbed.

Inhalations formerly were simple solutions of volatile medications, usually volatile oils, in alcohol or an alcoholic preparation. Often Compound Benzoin Tincture was used. An example formula is:

Pine Oil	5 mL
Eucalyptus Oil	5 mL
Compound Benzoin Tincture	30 mL

Sig: Inhale the vapor of one teaspoonful when added to one pint of hot water.

Other inhalations designed for addition to hot water were aqueous preparations containing a volatile oil, water and light magnesium carbonate. The light magnesium carbonate was used as a distributive or dispersing agent. The volatile material was distributed on the light magnesium carbonate. which in turn was mixed with the water. This ensured uniform dispersion of the oil upon shaking, since the oil was distributed throughout the mixture, rather than remaining as a globule or being dispersed as large globules. The presence of the light magnesium carbonate did not interfere with the free volatilization of the oil when the product was added to hot water. Emulsification of the oil would retard volatilization. An approximate ratio of 100 mg of light magnesium carbonate to 0.2 mL of oil was used. An example formula is as follows:

Menthol		325 mg
Eucalyptus Oil		3.7 mL
Light Magnesium Carbonate		2 g
Purified Water	qs	30 mL

Sig: Add one teaspoonful to a pint of hot water (not boiling). Inhale the vapor. Shake the bottle before using.

In the early 1950s, the first contemporary pressurized aerosol dosage form was introduced by Riker Laboratories. The Medihaler Epi™ consisted of epinephrine hydrochloride in a hydroalcoholic solvent system containing sorbitan trioleate as a dispersing agent and a fluorinated hydrocarbon propellant system. These small, self-contained aerosol propellant systems generally contain up to about 30 mL of product in a small stainless steel container fitted with a metered dose valve. The four components include a product concentrate, propellant, container and suitable dispensing/metering valve. Products available in this dosage form have included epinephrine bitartrate, isoproterenol hydrochloride, albuterol, triamcinolone acetonide, dexamethasone sodium phosphate, beclomethasone dipropionate, isoetharine mesylate and metaproterenol sulfate.

FORMULATION

Solution aerosols can be formulated easily if the active drug is soluble in the propellant system. If it ixnot soluble, a suspension or emulsion aerosol can be prepared. For oral inhalation, either solution or suspension aerosols are used. Example ingredients of an oral inhalation or nasal aerosol solution are shown in Table 1.

Suspension aerosols have been used to formulate antiasthmatic aerosols, steroids, antibiotics and others. Precautions to be considered include caking, agglomeration, particle size growth and clogging of the valve systems. Example ingredients in a nasal aerosol solution or suspension are shown in Table 2.

Table 1: General formula components of Oral, Inhalation and Nasal Aerosol Solutions

Component	Example
Active Ingredient	Soluble in vehicle
Solvents	Ethyl Alcohol, Propylene Glycol, Purified Water, Surfactants
Antioxidants	Ascorbic Acid
Flavor	Aromatic Oils
Propellants	As needed

Table 2: General formula components for nasal aerosol solutions or suspensions

Component	Example
Active Ingredient	Solubilized or suspended
Antioxidants	Ascorbic Acid, Bisulfites
Preservatives	Benzalkonium Chloride
Buffers	Phosphate Buffer
Tonicity Adjustment	Sodium Chloride
Surfactants	Sorbitan esters
Vehicle	Purified Water

VARIABLES

When compounding, or formulating, products for oral inhalation, the variables to consider include particle size, solubility, vehicles, tonicity, pH, sterility, preservatives, viscosity,buffers, surfactants and moisture content.

Particle Size: Generally, the particle size should lie in a range of about 0.5 to 10 µ, more preferably between about 3 to 6 µ, for a drug which, when inhaled, is intended to penetrate to the small bronchioles and the lung alveoli and to provide a rapid effect. This size range of particles will deposit in the lung by gravitational sedimentation, inertial impaction and by diffusion into terminal alveoli via Brownian motion. For inhalation aerosols, particles 5 to 10 µ are common, whereas for topical sprays 50 to 100 µ are common.

Solubility: Active drugs soluble in the matrix and in the pulmonary fluids will have a rapid onset of action and ordinarily a shorter duration of action, compared to drugs that are somewhat less soluble in the matrix and in the pulmonary fluids. Drugs that are poorly soluble in the pulmonary fluids may irritate the lung tissue. For suspensions, it is best to select a vehicle in which the drug is not very soluble to minimize the phenomenon of particle size growth, resulting from the drug in solution crystallizing out onto crystals that are present. Polymorphic forms of crystalline drugs should not be used for suspension aerosols. To enhance the stability of a suspension aerosol, selection of a liquid phase with density similar to that of the suspensoid, will minimize the tendency to settle .

Vehicle: Sterile Water for Inhalation or 0.9% Sodium Chloride Inhalation Solution are used commonly vehicles to carry the drugs in inhalations. Some inhalations are simple solutions of nonvolatile or volatile medications in water or cosolvent mixtures. Small quantities of alcohol or glycerin may be used to solubilize ingredients.

Tonicity: It generally is best to make inhalation solutions isotonic with physiological fluids, i.e., equivalent to 0.9% sodium chloride, or an osmolality of about 290 mOsm. To enhance movement of the fluid and drug through the alveoli, it may be best to have the solution slightly hypotonic. If it were hypertonic, the tendency would be to move fluids from the alveoli into the pulmonary space to reach an isotonic equilibrium. If hypotonic, the administered drug solution will have a greater tendency to move into the tissue for more rapid absorption and therapeutic effect.

pH: A pH in the neutral range, similar to body fluids, would be desired to minimize any cough-reflex that might occur if the pH were too low. However, consideration must be made for the solubility and stability characteristics of the drug.

Sterility: A new requirement for inhalation solutions is sterility, and has been suggested because of contamination problems with inhalation solution products and adverse experience reports for commercially available products. To ensure patients get the best products available, extemporaneously compounded oral inhalation solutions should be sterilized. This easily can be accomplished using 0.2µ filtration systems designed for extemporaneous compounding.

Preservative: Any preparation not dispensed in sealed unit dose containers should include a preservative, especially with the latest requirement of sterility for this class of dosage forms. The minimum amount of preservative that is still effective should be used. If too high a concentration is used, it may initiate a cough reflex in the patient. Also, too high a concentration of preservatives that are also surfactants may result in foaming that may interfere with the delivery of the complete dose.

Viscosity: External phase viscosity for most aerosol products is very low, consequently, they are very sensitive systems. Evaporation, sedimentation and increase in particle size are processes which may occur and change rapidly.

Buffer: A buffer, when used, should be at low buffer strength to maintain the desired pH and not induce pH changes in a microenvironment in the pulmonary cavity.

Surfactants: Surfactants can be used as dispersing agents for suspensions, solubilizing agents to enhance solubility of the drug, and as spreading agents when the drug is deposited in the lungs. The sorbitan esters, especially sorbitan trioleate, are used as well as lecithin derivatives, oleyl alcohol and others. One should keep the surfactant concentration as low as possible to minimize foaming that might interfere with proper administration.

Moisture Content: For inhalation dispersion aerosols generally, the moisture content should be kept extremely low for all active and inactive ingredients. The ingredients should be anhydrous to minimize caking.

FORMULAS

The example formulas illustrated here are for preservative-free formulations. Reports are now appearing in the literature concerning the potential adverse affects of benzalkonium chloride with some patients. In 1994, a case was described of occupational asthma caused by prolonged exposure to a cleaning solution containing benzalkonium chloride in th workplace (Bernstein JA, Stauder T. Bernstein DI, Bernstein IL. A combined respiratory and cutaneous hypersensitivity syndrome induced by work exposure to quaternary amines. J

Allergy Clin Immunol 1994 Aug; 94*2 Pt 1):25709). Benzalkonium chloride is reported to be a potent bronchoconstictor when inhaled in similar concentrations to those used in bronchodilator nebulizer solutions. This can result in an overall reduction in bronchodilator efficacy. This may not affect the short term bronchodilator response to a single dose, but its repeated use in sever asthma may possibly result in a paradoxical bronchoconstriction. (Fishwick D, Miles JF, Hendeles L, Beasley R. Preservatives in nebulizer solutions: Risks without benefits. Pharmacotherapy - In Press, 41 references).

The formulations presented here should be packaged as single-use or unit-dose products. Formulations are provided for 100 mL quantities for ease of calculations. The formulas should be reduced or expanded based upon the total quantity to be compounded. If they are to be preserved, add 4 mg of benzalkonium chloride per 100 mL of solution (3 mL of a Benzalkonium Chloride 1:750 Solution).

General Method of Preparation:

1. Calculate the quantity of the individual ingredients required for the total amount to be prepared.
2. Accurately weigh / measure each of the ingredients.
3. Dissolve the solids in about 2 / 3 of the volume of vehicle for the preparation.
4. Add the liquid ingredients and mix well.
5. Add sufficient vehicle to volume and mix well.
6. Filter through a 0.2 µ filter system into sterile containers.
7. Package and label.

Formulas:

Albuterol Sulfate 0.5% Inhalant Solution (Preservative Free)

Albuterol Sulfate		500 mg
Citric Acid, Anhydrous		100 mg
Sodium Chloride		800 mg
Sterile Water for Inhalation	qs	100 mL

Albuterol Sulfate 2.7% Inhalant for Hand Held Nebulizer (Preservative Free)

Albuterol Sulfate		2.7 g
Citric Acid, Anhydrous		100 mg
Sterile Water for Inhalation	qs	100 mL

Beclomethasone Dipropionate 0.042% Nasal Solution (Preservative Free)

Beclomethasone Dipropionate, Monohydrate		43 mg
Dextrose		5.4 g
Polysorbate 80		1 mL
Hydrochloric Acid (3%-5%)		Adjust to pH 7
Ethanol, 95%		13 mL
0.9% Sodium Chloride Solution	qs	100 mL

Cromolyn Sodium 1% Inhalation Solution (Preservative Free)

Cromolyn Sodium		1 g
Sterile Water for Inhalation	qs	100 mL

Cromolyn Sodium 4% Inhalation Solution (Preservative Free)

Cromolyn Sodium		4 g
Sterile Water for Inhalation	qs	100 mL

Flunisolide 0.025% Inhalation Solution (Preservative Free)

Flunisolide		25 mg
Ethanol, 95%		2 mL
0.9% Sodium Chloride Solution	qs	100 mL

Ipratropium Bromide 0.02% Solution (Preservative Free)

Ipratropium Bromide		20 mg
Citric Acid, Anhydrous		50 mg
0.9% Sodium Chloride Solution	qs	100 mL

Metaproterenol Sulfate 0.3% Solution (Preservative Free)

Metaproterenol Sulfate		300 mg
Citric Acid, Anhydrous		250 mg
0.9% Sodium Chloride Solution	qs	100 mL

Metaproterenol Sulfate 0.6% Solution (Preservative Free)

Metaproterenol Sulfate		600 mg
Citric Acid, Anhydrous		500 mg
0.9% Sodium Chloride Solution	qs	100 mL

Metaproterenol Sulfate 5% Concentrate (Preservative Free)

Metaproterenol Sulfate		5 g
Citric Acid, Anhydrous		500 mg
0.9% Sodium Chloride Solution		50 mL
Sterile Water for Inhalation	qs	100 mL

Terbutaline 0.1% Inhalant Solution (Preservative Free)

Terbutaline Sulfate		100 mg
Citric Acid, Anhydrous		100 mg
0.9% Sodium Chloride Solution	qs	100 mL

Albuterol-Cromolyn-Betamethasone for Inhalation (Preservative Free)

Albuterol Sulfate		500 mg
Cromolyn Sodium		1 g
Betamethasone Sodium Phosphate		250 mg
Citric Acid, Anhydrous		100 mg
Sodium Chloride		800mg
Sterile Water for Inhalation	qs	100 mL
Adjust pH to 6.8-7.0.		

Albuterol-Ipratropium for Inhalation (Preservative Free)

Albuterol Sulfate		100 mg
Ipratropium Bromide		20 mg
Citric Acid, Anhydrous		50 mg
Sterile Water for Inhalation	qs	100 mL

Ipratropium-Metaproterenol-Betamethasone for Inhalation Concentrate (Preservative Free)

Ipratropium Bromide		125 mg
Metaproterenol Sulfate		5 g
Betamethasone Sodium Phosphate		250 mg
Citric Acid, Anhydrous		100 mg
Sterile Water for Inhalation	qs	100 mL

Physicochemical characteristics of the ingredients and their purpose in the formulations.

Active Drugs

Albuterol sulfate is a beta-2-adrenergic agonist used as a bronchodilator that is a white or practically white powder, freely soluble in water and slightly soluble in alcohol.

Beclomethasone dipropionate is an anti-inflammatory agent used by oral inhalation that occurs as a white to creamy white, odorless powder. It is very slightly soluble in water and freely solublein alcohol.

Betamethasone dipropionate is an anti-inflammatory agent used by oral inhalation that occurs as a white to creamy white, odorless powder that is insoluble in water and sparingly soluble in alcohol.

Cromolyn sodium is an antiallergic inhalation agent that is a white, odorless, crystalline powder that is initially tasteless but then develops a slightly bitter aftetaste. It is hygroscopic, soluble in water and insoluble in alcohol.

Flunisolide is an anti-inflammatory agent used by oral inhalation that is a white to creamy-white, crystalline powder that is practically insoluble in water.

Ipratropium bromide is a bronchodilator, anticholinergic agent that occurs as a white, bitter-tasting crystalline powder that is soluble to the extent of 90 mg/mL in water and 28 mg/mL in ethanol.

Metaproterenol sulfate is a beta-2-adrenergic agonist agent used as a bronchodilator that is a white to off-white, crystalline powder that is freely soluble in water.

Terbutaline sulfate is a beta-2-adrenergic agonist agent used as a bronchodilator that occurs as an odorless, white to gray-white, crystalline powder that is soluble in water.

Excipients

Citric acid occurs as colorless, translucent crystals, or white, granular to fine, crystalline powder. It is odorless or practically odorless and has a stong, acidic taste; is very soluble in water and freely soluble in alcohol. It is used as an acidifying agent.

Polysorbate 80 is a lemon to amber colored, oily liquid with a faint, characteristic odor and a warm, somewhat bitter taste. It is very soluble in water and soluble in alcohol. It is used as anemulsifying and solubilizing agent.

Sodium chloride occurs as colorless, cubic crystals or a white crystalline powder with a saline taste. It is freely soluble inw ater and slightly soluble in alcohol. It is classified as a tonicity adjusting agent.

Dextrose occurs as colorless crystals or a white, crystalline or granular pwoder. It is odorless and has a sweet taste. It is freely soluble in water and slightly soluble in alcohol. It is used as a tonicity adjusting agent.

FUTURE

Oral and nasal inhalation administration holds promise for many local and systemic-acting drugs in the future. This may provide many opportunities for extemporaneous compounding in the future for drug products that can be administered nasally or by oral inhalation. With the rapid onset of action, generally good stability profiles, easy titration and easy formulation development, this area of meeting patients needs and solving problems is likely to continue to grow.

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