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Dosage Form Design: Pharmaceutic Ingredients, Product Formulation, and Current Good Manufacturing Practice

THE PROPER design of a dosage form requires consideration of the physical, chemical and biological characteristics of all of the drug substances and pharmaceutic ingredients to be used in fabricating the product. The drug and pharmaceutic materials utilized must be compatible with one another to produce a drug product that is stable, efficacious, attractive, easy to administer and safe. The product should be manufactured under appropriate measures of quality control and packaged in containers that contribute to product stability. The product should be labeled to promote correct use and be stored under conditions that contribute to maximum shelf life.

Methods for the preparation of specific types of dosage forms are described in subsequent chapters. This chapter presents some general considerations regarding pharmaceutic ingredients, drug product formulation, stability, preservation, flavoring, coloring, packaging, storage, and standards for good manufacturing practice.

Pharmaceutic Ingredients

In order to prepare a drug substance into a final dosage form, pharmaceutic ingredients are required. For example, in the preparation of pharmaceutical solutions, one or more *solvents* are utilized to dissolve the drug substance, *preservatives* may be added to prevent microbial growth, *stabilizers* may be used to prevent drug decomposition, and *colorants* and *flavorants* added to enhance product appeal. In the preparation of tablets, *diluents* or *fillers* are commonly added to increase the bulk of the formulation, *binders* to cause the adhesion of the powdered drug and pharmaceutic substances, *antiadherents* or *lubricants* to assist the smooth tableting process, *disintegrating agents* to promote tablet break-up after administration, and coatings to improve stability, control disintegration, or to enhance appearance. Ointments, creams, and suppositories achieve their characteristic features due to the pharmaceutic *bases* which are utilized. Thus, for each dosage form, the pharmaceutic ingredients establish the primary features of the product, and contribute to the physical form, texture, stability, taste and overall appearance.

Table 5–1 presents the principal categories of pharmaceutic ingredients, with examples of some of the official agents currently used.

General Considerations in Drug Product Formulation

In dealing with the problem of formulating a drug substance into a proper dosage form, research pharmacists employ knowledge that has been gained through experience with other similar drugs and through the proper utilization of the disciplines of the physical, chemical, and biological sciences. The early stages of any new

Table 5–1. Examples of Official Pharmaceutic Ingredients

Ingredient Type	*Definition*	*Examples*
Acidifying Agent	Used in liquid preparations to provide acidic medium for product stability.	acetic acid hydrochloric acid nitric acid
Alkalinizing Agent	Used in liquid preparations to provide alkaline medium for product stabiltiy.	ammonia solution ammonium carbonate potassium hydroxide sodium borate sodium carbonate sodium hydroxide trolamine
Adsorbent	An agent capable of holding other molecules onto its surface by physical or chemical (chemisorption) means.	powdered cellulose activated charcoal
Aerosol Propellant	An agent responsible for developing the pressure within an aerosol container and expelling the product when the valve is opened.	dichlorodifluoromethane dichlorotetrafluoroethane trichloromonofluoromethane
Air Displacement	An agent which is employed to displace air in a hermetically sealed container to enhance product stability.	nitrogen
Antifungal Preservative	Used in liquid and semi-solid preparations to prevent the growth of fungi.	benzoic acid butylparaben ethylparaben methylparaben propylparaben sodium benzoate sodium propionate
Antimicrobial Preservative	Used in liquid and semi-solid preparations to prevent the growth of microorganisms.	benzalkonium chloride benzethonium chloride benzyl alcohol cetylpyridinium chloride chlorobutanol phenol phenylethyl alcohol phenylmercuric nitrate thimerosal
Antioxidant	An agent which inhibits oxidation and thus is used to prevent the deterioration of preparations by the oxidative process.	ascorbyl palmitate butylated hydroxyanisole butylated hydroxytoluene hypophophorous acid monothioglycerol propyl gallate sodium bisulfite sodium formaldehyde sulfoxylate sodium metabisulfite
Buffering Agent	Used to resist change in pH upon dilution or addition of acid or alkali.	potassium metaphosphate potassium phosphate, monobasic sodium acetate

Table 5–1. Continued

Ingredient Type	*Definition*	*Examples*
Chelating Agent	A substance that forms stable complexes with metals. Chelating agents are used in some liquid pharmaceuticals as stabilizers to complex heavy metals which might promote instability. In such use they are also called *sequestering* agents.	edetate disodium edetic acid
Colorant	Used to impart color to pharmaceutical preparations.	erythrosine (FD&C Red No. 3) caramel ferric oxide, red
Emulsifying Agent	Used to promote and maintain the dispersion of finely subdivided particles of a liquid in a vehicle in which it is immiscible.	acacia sorbitan monooleate polyoxyethylene 50 stearate
Encapsulating Agent	Used to form thin shells for the purpose of enclosing a drug substance or drug formulation for ease of administration.	gelatin cellulose acetate phthalate
Flavorant	Used to impart a pleasant flavor and often odor to a pharmaceutical preparation.	anise oil cinnamon oil cocoa menthol orange oil peppermint oil vanillin
Humectant	Used to prevent the drying out of preparations—particulalry ointments and creams—due to the agent's ability to retain moisture.	glycerin propylene glycol sorbitol
Levigating Agent	A liquid used as an intervening agent to reduce the particle size of a drug powder by grinding together, usually in a mortar.	mineral oil
Ointment Base	The semisolid vehicle into which drug substances may be incorpoated in preparing medicated ointments.	lanolin hydrophilic ointment polyethylene glycol ointment petrolatum hydrophilic petrolatum white ointment yellow ointment rose water ointment
Solvent	An agent used to dissolve another pharmaceutic substance or a drug in the preparation of a solution.	alcohol isopropyl alcohol mineral oil oleic acid peanut oil purified water water for injection sterile water for injection sterile water for irrigation
Stiffening Agent	Used to increase the thickness or hardness of a pharmaceutical preparation, usually an ointment.	cetyl alcohol paraffin white wax yellow wax

Table 5–1. Continued

Ingredient Type	*Definition*	*Examples*
Suppository Base	Used as a vehicle into which drug substances are incorporated in the preparation of suppositories.	cocoa butter polyethylene glycols (mixtures)
Surfactant (surface active agent)	Substances which adsorb to surfaces or interfaces to reduce surface or interfacial tension. May be used as wetting agents, detergents or emulsifying agents.	benzalkonium chloride nonoxynol 10 octoxynol 9 polysorbate 80 sodium lauryl sulfate sorbitan monopalmitate
Suspending Agent	A viscosity increasing agent used to reduce the rate of sedimentation of dispersed particles.	agar bentonite carboxymethylcellulose sodium hydroxypropyl methylcellulose methylcellulose tragacanth xanthan gum
Sweetening Agent	Used to impart sweetness to a preparation.	dextrose saccharin sodium sucrose
Tablet Antiadherents	Agents which prevent the sticking of tablet formulation ingredients to punches and dies in a tableting machine during production.	magnesium stearate talc
Tablet Binders	Substances used to cause adhesion of powder particles in tablet granulations.	acacia ethylcellulose gelatin methylcellulose
Tablet and Capsule Diluent	Inert substances used as fillers to create the desired bulk, flow properties, and compression characteristics in the preparation of tablets and capsules.	microcrystalline cellulose lactose
Tablet Coating Agent	Used to coat a formed tablet for the purpose of protecting against drug decomposition by atmospheric oxygen or humidity, to provide a desired release pattern for the drug substance after administration, to mask the taste or odor of the drug substance, or for aesthetic purposes.	cellulose acetate phthalate sucrose pharmaceutical glaze (shellac in alcohol)
Tablet Disintegrant	Used in solid dosage forms to promote the disruption of the solid mass into smaller particles which are more readily dispersed or dissolved.	cornstarch sodium alginate
Tablet Glidant	Agents used in tablet and capsule formulations to improve the flow properties of the powder mixture.	colloidal silica cornstarch talc
Tablet Lubricant	Substances used in tablet formulations to reduce friction during tablet compression.	calcium stearate magnesium stearate stearic acid

Table 5–1. Continued

Ingredient Type	*Definition*	*Examples*
Tablet Polishing Agent	Used to impart an attractive sheen to coated tablets.	carnauba wax white wax
Tonicity Agent	Used to render a solution similar in osmotic characteristics to physiologic fluids.	dextrose sodium chloride
Vehicle	A carrying agent for a drug substance.	*Flavored/Sweetened* Acacia Syrup Aromatic Elixir Cherry Syrup Cocoa Syrup Orange Syrup Syrup *Oleaginous* Corn Oil Mineral Oil Peanut Oil Sesame Oil *Sterile* Bacteriostatic Sodium Chloride Injection Bacteriostatic Water for Injection

formulation involves studies to collect basic information on the physical and chemical characteristics of the drug substance to be prepared into pharmaceutical dosage forms. These basic studies comprise the *preformulation* work needed before actual product formulation begins.

Preformulation Studies[1]

Physical Description

It is important to have an understanding of the physical description of a drug substance prior to dosage form development. The majority of drug substances in use today occur as solid materials. Most of them are pure chemical compounds of either crystalline or amorphous constitution. Liquid drugs are used to a much lesser extent; gases, even less frequently. Of the official medicinal gases, nitrous oxide and cyclopropane are used as general anesthetics by inhalation and oxygen and carbon dioxide are respiratory aids.

Among the few liquid medicinal agents are the following:

Amyl nitrite, vasodilator by inhalation
Castor oil, cathartic
Clofibrate, antihyperlipidemic
Dimercaprol, antidote for arsenic, gold, and mercury poisoning
Ethchlorvynol, hypnotic
Glycerin, cathartic in suppository form
Mineral oil, cathartic
Nitroglycerin (as tablets), anti-anginal
Paraldehyde, sedative-hypnotic
Paramethadione, anticonvulsant
Prochlorperazine, tranquilizer and antiemetic
Propylhexedrine, vasoconstrictor by nasal inhalation
Tetrachloroethylene, anthelmintic
Undecylenic acid, fungistatic agent

Liquid drugs pose an interesting problem in dosage form design. Many of them are volatile substances and as such must be physically sealed from the atmosphere to insure their continued presence. Amyl nitrite, for example, is a clear yellowish liquid that is volatile even at low temperatures and is also highly flammable. It is maintained for medicinal purposes in small sealed glass cylinders wrapped with gauze or another suitable material. When amyl nitrite is administered, the glass is broken between the fingertips and the liquid wets the gauze covering, producing vapors that are inhaled by the patient requiring vasodilation. Propylhexedrine

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