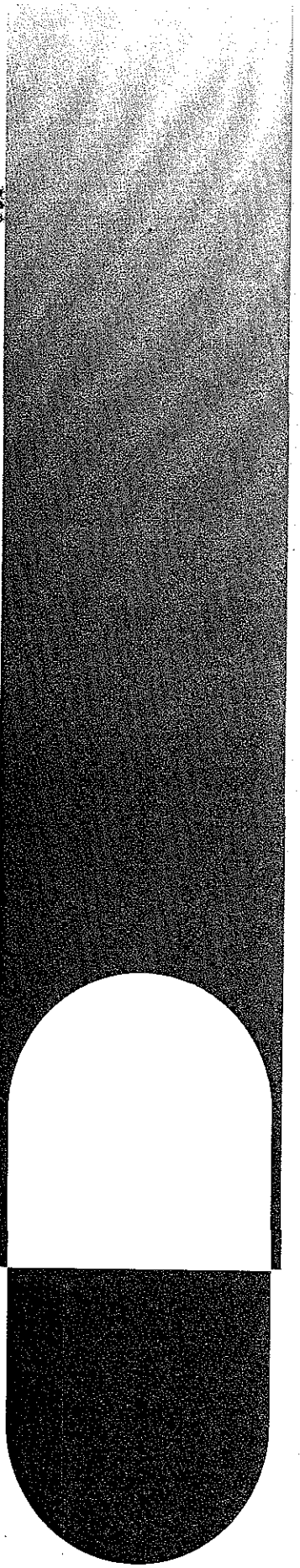

Pharmaceutical Dosage Forms and Drug Delivery Systems

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Accurate indications, adverse reactions, and dosage schedules for drugs are provided in this book, but it is possible they may change. The reader is urged to review the package information data of the manufacturers of the medications mentioned.

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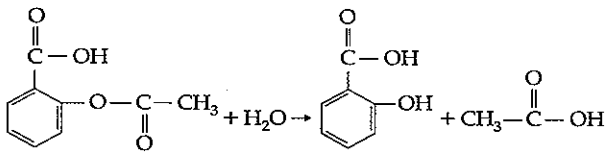
Drug Stability

One of the most important activities of preformulation work is the evaluation of the physical and chemical stability of the pure drug substance. It is essential that these initial studies be conducted using drug samples of known purity. The presence of impurities can lead to erroneous conclusions in such evaluations. Stability studies conducted in the preformulation phase include solid state stability of the drug alone, solution phase stability, and stability in the presence of expected excipients.

Initial investigation begins through knowledge of the drug's chemical structure which allows the preformulation scientist to anticipate the possible degradation reactions.

Chemical instability of medicinal agents may take many forms, because the drugs in use today are of such diverse chemical constitution. Chemically, drug substances are alcohols, phenols, aldehydes, ketones, esters, ethers, acids, salts, alkaloids, glycosides, and others, each with reactive chemical groups having different susceptibilities toward chemical instability. Chemically, the most frequently encountered destructive processes are hydrolysis and oxidation.

Hydrolysis is a solvolysis process in which (drug) molecules interact with water molecules to yield breakdown products of different chemical constitution. For example, aspirin or acetylsalicylic acid combines with a water molecule and hydrolyzes into one molecule of salicylic acid and one molecule of acetic acid:



The process of hydrolysis is probably the most important single cause of drug decomposition mainly because a great number of medicinal agents are esters or contain such other groupings as substituted amides, lactones, and lactams, which are susceptible to the hydrolytic process.

Another destructive process is oxidation. The oxidative process is destructive to many drug types, including aldehydes, alcohols, phenols, sugars, alkaloids, and unsaturated fats and oils.

Chemically, oxidation involves the loss of electrons from an atom or a molecule. Each electron lost is accepted by some other atom or molecule, thereby accomplishing the reduction of the recipient. In inorganic chemistry, oxidation is accompanied by an increase in the positive valence of an element—for example, ferrous (+2) oxidizing to ferric (+3). In organic chemistry, oxidation is frequently considered synonymous with the loss of hydrogen (dehydrogenation) from a molecule. The oxidative process frequently involves free chemical radicals, which are molecules or atoms containing one or more unpaired electrons, as molecular (atmospheric) oxygen (•O—O•) and free hydroxyl (•OH). These radicals tend to take electrons from other chemicals, thereby oxidizing the donor. Many of the oxidative changes in pharmaceutical preparations have the character of autoxidations. Autoxidations occur spontaneously under the initial influence of atmospheric oxygen and proceed slowly at first and then more rapidly as the process continues. The process has been described as a type of chain reaction commencing by the union of oxygen with the drug molecule and continuing with a free radical of this oxidized molecule participating in the destruction of other drug molecules and so forth.

In drug product formulation work, steps are taken to reduce or prevent the occurrence of drug substance deterioration due to hydrolysis, oxidation, and other processes. These techniques are discussed in a later section.

Pharmaceutic Ingredients

In order to prepare a drug substance into a final dosage form, pharmaceutic ingredients are required. For example, in the preparation of pharmaceutic 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 4–2 presents the principal categories of pharmaceutic ingredients, with examples of some of the official and commercial agents currently used. Additional discussion of many of the pharmaceutic ingredients may be found in the chapters where they are most relevant; for example, pharmaceutic materials used in tablet and capsule formulation are discussed in Chapter 5, *Peroral Solids, Capsules, Tablets, and Controlled-Release Dosage Forms.*

The reader should also be aware of the *Hand-*

Table 4–2. Examples of Pharmaceutic Ingredients

Ingredient Type	*Definition*	*Examples*
Acidifying Agent	Used in liquid preparations to provide acidic medium for product stability.	acetic acid citric acid fumaric acid hydrochloric acid nitric acid
Alkalinizing Agent	Used in liquid preparations to provide alkaline medium for product stability.	ammonia solution ammonium carbonate diethanolamine monoethanolamine potassium hydroxide sodium borate sodium carbonate sodium hydroxide triethanolamine 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.	carbon dioxide 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. The effectiveness of the parabens is usually enhanced when they are used in combination.	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

Table 4–2. Continued

Ingredient Type	*Definition*	*Examples*
Antioxidant	An agent which inhibits oxidation and thus is used to prevent the deterioration of preparations by the oxidative process.	ascorbic acid ascorbyl palmitate butylated hydroxyanisole butylated hydroxytoluene hypophophorous acid monothioglycerol propyl gallate sodium ascorbate 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 sodium citrate anhydrous and dihydrate
Chelating Agent	A substance that forms stable, water soluble complexes (chelates) 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 liquid and solid (e.g., tablets and capsules) pharmaceutical preparations.	FD&C Red No. 3 FD&C Red No. 20 FD&C Yellow No. 6 FD&C Blue No. 2 D&C Green No. 5 D&C Orange No. 5 D&C Red No. 8 caramel ferric oxide, red
Clarifying Agent	Used as a filtering aid because of adsorbent qualities.	bentonite
Emulsifying Agent	Used to promote and maintain the dispersion of finely subdivided particles of a liquid in a vehicle in which it is immiscible. The end product may be a liquid emulsion or semisolid emulsion (e.g., a cream).	acacia cetomacrogol cetyl alcohol glyceryl monostearate 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. In addition to the natural flavorants listed, many synthetic flavorants are also used.	anise oil cinnamon oil cocoa menthol orange oil peppermint oil vanillin

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