Dosage form design: pharmaceutical and formulation consideration

Chapter 4

Dosage forms are needed to get safe and effective dose and for additional reasons:

1- To protect drug from **destructive influences of atmospheric oxygen or humidity** (coated tablets, sealed ampules).

2- To protect the drug substance from **destructive influence of gastric acid** after oral administration (enteric-coated tablets).

3- **To mask bitter, salty, or odor** of a drug substance (capsules, coated tablets, flavored syrups).

4- To **provide liquid** preparations of drug substances, either as dispersions (suspensions) or as clear preparations (solutions).

5-To provide **rate controlled drug** action (controlled-release tablets, capsules, and suspensions).

6- To provide **topical** administration sites (ointments,

creams, transdermal patches, and ophthalmic, ear, and nasal preparations).

7- To provide for **insertion of a drug into body's orifices** (rectal or vaginal suppositories).

8-To provide for **placement of drugs directly in blood** stream or body tissues (injections).

9-To provide for **optimal drug action** through **inhalation** therapy (inhalants and inhalation aerosols)

General concideration for dosage form design

- If drug is intended for **systemic use** and **oral** administration is desired, **tablets** and/or **capsules** are usually prepared.
- If drug used in emergency in patient with **coma**, **injectable** form of medication may be prepared.
- motion sickness, nausea, and vomiting, for which **tablets and skin patches** are used for prevention and suppositories and injections for treatment.
- **The age of patient plays a role in dosage form design:**
- For **infants and children** younger than 5 years of age, pharmaceutical **liquid**s are preferred for oral administration.
- These liquids, which are flavored aqueous solutions, syrups, or suspensions, are usually administered directly into the infant's or child's mouth by drop, spoon, or oral dispenser or incorporated into the child's food. The palatability of some commercial products may not be acceptable to some patients so different flavoring additives may be indicated to enhance compliance; an example would be the FLAVORx flavoring
- system.

- A single liquid paediatric preparation may be used for infants and children of all ages, with the dose of the drug varied by the volume administered.
- Medications intended for the elderly are commonly formulated into oral liquids or may be extemporaneously prepared into an oral liquid by the pharmacist. In many patient-care facilities, as nursing homes, tablet-crushing devices are utilized by the nursing staff preparatory to mixing with food (as applesauce) for administration. However, certain tablets and capsules that are designed for controlled release should not be crushed or chewed, because that would interfere with their integrity and intended performance.
- person with difficulty in swallowing tablet can use chewable tablets or orodispersible tablets that dissolve in mouth in about 10 to 15 seconds; this allows patient to take a tablet but actually swallow a liquid.

- Many patients, particularly the elderly, take multiple medications daily. The more distinctive the size, shape, and color of solid dosage forms, the easier is proper identification of the medications. Errors in taking medications among the elderly occur frequently because of their multiple drug therapy and impaired eyesight. Dosage forms that allow reduced frequency of administration without sacrifice of efficiency are particularly advantageous.

- Capsules have been found by many to be more **easily swallowed than whole tablets**. If a capsule is moistened in the mouth before it is swallowed, it becomes slippery and readily slides down the throat with water.
- Also, a teaspoonful of gelatin dessert, liquid candy, or syrup placed in the mouth and partially swallowed before placing the solid dosage form in the mouth aids in swallowing them.
- Medications intended for **elderly** are commonly formulated into **oral liquids.**

- Formulating a drug substance into a proper dosage form, research pharmacists employ knowledge gained through experience with other chemically similar drugs and through the proper use of the physical, chemical, biologic, and pharmaceutical sciences. The early stages of any new formulation include studies to collect basic information on the physical and chemical characteristics of the drug substance. These basic studies are the preformulation work needed before actual product formulation begins.

Excipients

- **flavors** and **sweeteners.**
- **Colorants**
- **Preservatives**
- **Antioxidant**s
- **chelating agents**
- lubricants

There is some psychologic basis to drug therapy, and the odor, taste, and color of a pharmaceutical preparation can play a part.

- An appropriate drug has its most beneficial effect when it is accepted and taken properly by the patient. The proper combination of flavor, fragrance, and color in a pharmaceutical product contributes to its acceptance.

- An “electronic tongue” is used to aid in providing a global “taste fingerprint” during formulation development. It provides information on bitterness levels and the stability of flavours in terms of taste

FIGURE 4.4 Electronic tongue to assist in formulation development. (Courtesy of Alpha MOS.)

- **Acidifying agent** Used in liquid preparations to provide acidic medium for product stability:Citric acid, Acetic 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 bicarbonate, Sodium borate, Sodium carbonate, Sodium hydroxide.
- **Adsorbent** An agent capable of holding other molecules onto its surface by physical or chemical (chemisorption)means: Powdered cellulose, Activated charcoal.
- **Aerosol** propellantAgent 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** Agent employed to displace air in a hermetically sealed container to enhance product stability: Nitrogen,Carbon dioxide

- **Antifungal preservative** Used in liquid and semisolid preparations to prevent growth of fungi. Effectiveness of parabens is usually enhanced by use in combination Butylparaben, Ethylparaben, Methylparaben, Benzoic acid, Propylparaben, Sodium benzoate, Sodium propionate.
- **Antimicrobial preservative** Used in liquid and semisolid preparations to prevent growth of microorganisms: Benzalkonium chloride.
- **Antioxidant** Used to prevent deterioration of preparations by oxidation: Ascorbic acid, Ascorbyl palmitate, Butylated hydroxyanisole.
- **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** Substance that forms stable water-soluble complexes (chelates) with metals; used in some liquid pharmaceuticals as stabilizers to complex heavy metals that might promote instability. In such use, they are also called sequestering agents: Edetic acid Edetate disodium.

- **Colorant** Used to impart color to liquid and solid (e.g., tablets and capsules) preparations: FD&C Red No. 3, FD&C Red No. 20, Caramel, Ferric oxide, red.
- **Flavorant** Used to impart a pleasant flavor and often odor to a preparation. In addition to the natural flavorants listed, many synthetic ones are used: Anise oil, Cinnamon oil, Cocoa, Menthol, Orange oil,Peppermint oil.
- **Humectant** Used to prevent drying of preparations, particularly ointments and creams: Glycerin, Propylene glycol, Sorbitol.
- **Sweetening** agent Used to impart sweetness to a preparation: Aspartame, Dextrose, Glycerin2, Mannitol, Saccharin sodium, Sorbitol, Sucrose.
- **Tablet antiadherents** Prevent tablet ingredients from sticking to punches and dies during production: Magnesium stearate.
- **Tablet binders** Substances used to cause adhesion of powder particles in tablet granulations: Acacia, Alginic acid, Carboxymethylcellulose sodium, gelatin.
- **Tablet and capsule diluent** Inert filler to create desired bulk, flow properties, and compression characteristics of tablets and capsules: Dibasic calcium phosphate, Kaolin, Lactose, Mannitol, Microcrystalline cellulose, Powdered cellulose, Precipitated calcium carbonate, Sorbitol, Starch.

- **Tablet-coating agent** Used to coat a tablet to protect against decomposition by atmospheric oxygen or humidity, to provide a desired release pattern, to mask taste or odor, or for aesthetic purposes. Coating may be sugar, film, or thick covering around a tablet. Sugarcoated tablets generally start to break up in the stomach. Film forms a thin cover around a formed tablet or bead. Unless it is enteric, film dissolves in the stomach. Enteric coating passes through the stomach to break up in the intestines. Some water insoluble coatings (e.g., ethylcellulose) are used to slow the release of drug in the gastrointestinal tract:
- **Sugar coating**: Liquid glucose, Sucrose.
- **Film coating:** Hydroxyethyl cellulose, Hydroxypropyl cellulose, Hydroxypropyl methylcellulose, Methylcellulose (e.g., Methocel) ,Ethylcellulose (e.g., Ethocel).
- **Enteric coating**:Cellulose acetate phthalate, Shellac (35% in alcohol.
- **Tablet or capsule opaquant:** Used to render a coating opaque. May be used alone or with a colorant:Titanium dioxide.
- **Tablet polishing agent** Used to impart an attractive sheen to coated tablets:Carnauba wax, White wax.

- **Not all salts are salty but their taste is function of both cation and anion.**

- Salty tastes :NaCl, KCl, NH_4Cl and by NaBr, KBr.
- ammonium give bitter and salty sensations.
- **potassium iodide** and **magnesium sulfate** (epsom salt) are predominantly bitter.

- In general, low-molecular-weight salts are salty, and high-molecular-weight salts are bitter.

- With organic compounds, increase number of hydroxyl groups (—OH) increase the sweetness of the compound.

Flavoring Pharmaceuticals

- The flavour sensation of a food or pharmaceutical is actually a complex blend of taste and smell, with lesser influences of texture, temperature, and even sight. In flavour formulating a pharmaceutical product, the pharmacist must give consideration to the color, odor, texture, and taste of the preparation. It would be incongruous, for example, to color a liquid pharmaceutical red and give it a banana taste and a mint odor. The color of a pharmaceutical must have a psychogenic balance with the taste, and the odor must also enhance that taste. Odor greatly affects the flavor of a preparation or foodstuff. If one's sense of smell is impaired, as during a head cold, the usual flavor sensation of food is similarly diminished.

Flavoring Pharmaceuticals

- **Added to liquid** mask **taste**.
- **Chewable tablets**, such as antacid and vitamin products, usually are **sweetened and flavored** to improve acceptance.
- Organic compounds: Increase number of **hydroxyl** groups (-OH) **increase sweetness** of compound.
- **Sucrose**(**8 -**OH), sweeter than **glycerin**(3-OH)
- In general: organic esters, alcohols, and aldehydes are pleasant to the taste
- volatile, affect odor and flavor of preparations

- **Many nitrogen-containing** (e.g., quinine) **bitter**, but other nitrogen-containing (e.g., **aspartame**) are **sweet**.
- Even **simple structural change alter taste**.
- D-Glucose is **sweet**, but L-glucose has slightly **salty.**

- **saccharin** is very **sweet** but **N-methyl-saccharin** is **tasteless**.

- **Selection of appropriate flavor depends on several factors:**

A: Taste of drug: Certain flavoring materials are more effective than others in masking bitter, salty, sour, or otherwise undesirable taste of medicinal agents. Although individuals' tastes and flavor preferences differ, **cocoa-flavored** vehicles are considered effective for masking the taste of **bitter drugs**. **Fruit or citrus** flavors are frequently used to combat **sour or acid**-tasting drugs, and **cinnamon, orange, raspberry**, and other flavors have been successfully used to make preparations of **salty** drugs more palatable.

- B: The age of patient:
- The age of the intended patient should also be considered in the selection of the flavoring agent, because certain age groups seem to prefer certain flavors.

1. **Children prefer sweet candy-like with fruity flavors.**
2. **Adults prefer less sweet with tart rather than a fruit flavor.**

Flavors can consist of oil- or water-soluble liquids and dry powders; most are diluted in carriers. Oil-soluble carriers include soybean and other edible oils; water-soluble carriers include water, ethanol, propylene glycol, glycerin, and emulsifiers. Dry carriers include maltodextrins, corn syrup solids, modified starches, gum arabic, salt, sugars, and whey protein. Dry carriers include maltodextrins, corn syrup, modified starches, gum, salt, sugars, and whey protein.

Flavors can degrade as a result of exposure to light, temperature, headspace oxygen, water, enzymes, contaminants, and other product components, so they must be carefully selected and checked for stability.

Flavoring agents may be derived from natural sources (e.g., fruit components) or prepared artificially. They may be either water soluble or oil soluble.

Artificial flavor: Any substance used to give flavor that is not derived from spice, fruit or fruit juice, vegetable or vegetable juice, herb, bark, bud, root, leaf eggs, dairy

- Their selected use in pharmaceutical products is based on desired **flavor**, their **solubility** characteristics, and their **chemical and physical compatibility** with the active therapeutic agent and other components of the formulation.
- Flavoring agents in liquid pharmaceutical products are added to the **solvent or vehicle** component of the formulation in which it is most soluble or miscible. That is, water soluble flavorings are added to the aqueous component of a formulation and oil-soluble flavorings are added to the nonaqueous components. In general, artificial flavors are used in liquid pharmaceutical at levels of 0.1% to 0.2%, whereas natural flavors are used within the 1% to 2% range.

Sweetening Pharmaceuticals

In addition to sucrose, a number of artificial sweetening agents have been used in foods and pharmaceuticals over the years. Some of these, including aspartame, saccharin, and cyclamate, have faced challenges over their safety by the FDA and restrictions to their use and sale.

At the present time, the following artificial sweeteners are approved by the FDA with, in parenthesis, the number of times (×) each one

is sweeter than table sugar:

- Acesulfame potassium (~200 ×)
- Aspartame (~180 to 200 ×)
- Sucralose (~600 ×)
- Saccharin (~300 ×)
- **saccharin** excreted **unchanged** by kidneys but it has bitter after taste sensation.
- **Cyclamate**, is **metabolized**, in GIT, and excreted by kidneys.
- **Aspartame** breaks down to three basic components: amino acids **phenylalanine** and **aspartic acid**, and **methanol**. **So aspartame** are metabolized through regular pathways in the body.

- metabolism to phenylalanine.
- So the use of aspartame by persons with **phenylketonuria** (PKU) is discouraged.Why?

Any diet foods and drinks that contain aspartame must have a label **warning** not be consumed by phenyl ketone urea individuals because they cannot metabolize phenylalanine adequately, so they undergo an increase in the serum levels of the amino acid (hyperphenylalaninemia will happen). result in **mental retardation** and can affect the fetus of a pregnant woman who has PKU.

Other arteficial sweetners

- Acesulfame potassium, a non nutritive sweetener Structurally similar to saccharin, it is 130 times as sweet as sucrose and is excreted unchanged in urine.
- **Acesulfame is more stable than aspartame at elevated temperatures** use in candy, chewing gum, and instant coffee and tea.
- Stevia powder30 times as sweet as sucrose.used in both hot and cold preparations.

Coloring Pharmaceuticals

Coloring agents are used in pharmaceutical preparations for esthetics. A distinction should be made between agents that have inherent color and those that are employed as colorants. An example of a natural substance with inherent color that is employed as a colorant is red ferric oxide. It is mixed in small proportions with zinc oxide powder to give calamine its characteristic pink color, which is intended to match the skin tone upon application.

- sulfur (yellow), riboflavin (yellow), cupric sulfate (blue), ferrous sulfate (bluish green), cyanocobalamin (red), and red mercuric iodide (vivid red).
- **most pharmaceutical colorants in use synthetic, a few are natural mineral and plant sources**.
- ferric oxide mixed with zinc oxide to give calamine pink color.
- 0.0005% to 0.001% FD&C, D&C, dyes or lake.
- **30 to 60 coats:tablet dyes**. With **lakes, fewer** color coats are used

- ointments, suppositories, and ophthalmic and parenteral products **assume the color of their ingredients and do not contain color additives.**

PRESERVATIVES

- **Ophthalmic and injectable preparations, sterilized by physical methods (autoclaving for 20 minutes at 15 lb pressure and 121°C, or dry heat in oven at 180°C for 1 hour, or bacterial filtration for drugs which is sensative to high teperatures) during manufacture.**
- **syrups, emulsions, suspensions, and some semisolid creams** protected by addition of antimicrobial preservative.
- **hydroalcoholic and most alcoholic preparations not require addition of preservative** when the alcoholic content is sufficient to prevent microbial growth.

- **15% V/V alcohol will prevent microbial growth in acidic media and 18% V/V in alkaline media.**
- elixirs, spirits, and tinctures, are self-sterilizing and do not require additional preservation.

Preservative selection should do the followings:

1. **prevents growth** of microorganisms.
2. **Soluble in water** to achieve adequate concentrations in aqueous phase.
3. Concentration of preservative does not affect the safety of patient.
4. has **adequate stability** and not reduced in concentration by **decomposition** during desired shelf life of preparation.
5. **compatible** with all formulative ingredients.
6. The preservative **does not adverse**ly affect container or closure.

General Preservative Considerations

- intravenous preparations given in large volumes as blood replenishers or nutrients **not contain bacteriostatic additives**.
- Microorganisms **molds, yeasts it prefere acidic** medium while **bacteria** favoring slightly **alkaline** medium.
- few microorganisms grow **below pH 3 or above pH 9**
- Aqueous preparations are within favorable pH range must be protected against microbial

- Preservative must **dissolve in sufficient concentration** in **aqueous phase** of preparation. (The preservative is soluble enough in water to achieve adequate concentrations in the aqueous phase of a system with two or more phases).
- , only **undissociated fraction** of preservative possesses preservative capability, because the ionized portion is incapable of penetrating the microorganism.
- preservative selected must be largely undissociated at pH of the formulation prepared.

- Acidic preservatives **benzoic** acid, **boric acid, and sorbic acids** more **undissociated** more effective as the medium is made more **acid.** Conversely,
- **alkaline preservatives** are less effective in acid or neutral media and more effective in **alkaline media**.
- if formula interfere with solubility or availability of preservative t, its chemical concentration may **misleading**, because it may not be a true measure of the effective concentration.

- tragacanth, **attract and hold preservative**, such as the **parabens and phenolic** rendering them unavailable for preservative function.
- preservative **must not interact with container**, such as a metal ointment tube or a plastic medication bottle, or closure, such as a rubber or plastic cap or liner.

Mode of Action of preservatives

1. **Modification of cell membrane permeability**.
2. **Lysis and cytoplasmic leakage** Irreversible coagulation of cytoplasmic constituents (e.g., protein precipitation)
3. **Inhibition of cellular metabolism**, such as by interfering with enzyme systems or inhibition of cell wall synthesis
4. **Oxidation** of cellular constituents
5. **Hydrolysis**

Preservatives concentrations

- benzoic acid (**0.1% to 0.2%).**
- sodium benzoate (**0.1% to 0.2%)**
- alcohol (15% to 20%),
- phenol (0.1% to 0.5%),
- cresol (0.1% to 0.5%),
- benzalkonium chloride (**0.002% to 0.01%)**
- combinations of methylparaben and propylparaben (0.1% to 0.2)against fungus.

- **Preservative in ophthalmic preparation**

must have **low degree of irritant** qualities, like **chlorobutanol**, **benzalkonium** chloride.

- Single dose eye drop not contain preservative.

Preformulation studies

Preformulation Studies

- Before the formulation of a drug substance into a dosage form, it is essential that it be chemically and physically characterized. The following preformulation studies and others provide the type of information needed to define the nature of the drug substance. This information provides the framework for the drug's combination with pharmaceutical ingredients in the fabrication of a dosage form.

Physical Description

Most drug substances in use today are solid materials so

Solid drugs :are pure chemical compounds of either crystalline or amorphous constitution.

The **purity of chemical substance** is essential for its identification and for evaluation of its chemical, physical, and biologic properties.

Chemical properties include **structure**, **form**, and **reactivity**.

Physical properties include: **physical description**, **particle size**, **crystalline structure**, **melting point**, and **solubility**.

Biologic properties relate to its **ability to get to a site of action** to give **biologic response**.

- Drugs can be used therapeutically as solids, liquids, and gases. Liquid drugs are used to a much lesser extent than solid drugs, gases even less frequently.
- Liquid drugs pose an interesting problem in the design of dosage forms and delivery systems. Many liquids are volatile and must be physically sealed from the atmosphere to prevent evaporation loss.

Liquid drugs

- Many liquids are **volatile** and must be **physically sealed from atmosphere** to prevent evaporation loss.

- **Amyl nitrite**, for example, is a clear yellowish liquid that is volatile even at low temperatures and highly flammable. It is kept in small sealed glass cylinders wrapped with gauze.
- 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 patient requiring vasodilation.

Other example

Propyl hexedrine is volatile liquid that must be contained in a closed system. This drug is used as a nasal inhalant for vasoconstrictor action.

A cylindrical roll of fibrous material is impregnated with

Propyl hexedrine, and the saturated cylinder is placed in a suitable, **plastic, sealed nasal inhaler**. The inhaler's cap must be securely tightened each time it is used.

Even then, the inhaler maintains its effectiveness for only a **limited time** because of the volatility of the drug.

Another problem associated with **liquid drugs** is that those intended for oral administration **cannot generally be formulated into tablet** without chemical modification.

An exception to this is liquid drug **nitroglycerin**, which is formulated into **sublingual tablets** that **disintegrate within seconds** after placement under the tongue.

However, because the drug is volatile, it has a tendency to escape from the tablets during storage,

the tablets sould be **stored in a tightly sealed glass container**.

when a liquid drug is to be administered orally and a solid dosage form is desired, one of two approaches is used.

First, liquid sealed in soft gelatin capsule. Vitamins A, D, and E are liquids available in capsule form.

Second, liquid drug developed into solid ester or salt so will be suitable for tablets or capsules.

Example: **scopolamine hydrobromide** is a solid salt of liquid drug scopolamine and is easily pressed into tablets.

Another approach to formulate liquids into solids is by **mixing drug with a solid or melted semisolid material**, such as a high molecular weight PEG. The melted mixture is poured into hard gelatin capsules to harden, and the capsules are sealed.

liquid drugs, that **taken orally in large doses** or **applied topically**, their liquid nature may have some advantage in therapy.

For example, 15-mL doses of mineral oil may be administered conveniently as such.

However, for pharmacists **prefer solid** materials in formulation work because they can easily form them into tablets and capsules.

- **Formulation and stability difficulties** arise less frequently with **solid dosage forms** than with **liquid preparations**, and for this reason, many new drugs first reach the market as tablets or dry-filled capsules.
- Later, when the pharmaceutical problems are resolved, liquid form of the same drug may be marketed. This procedure is doubly advantageous, because for the most part, physicians and patients alike prefer small, generally tasteless, accurately dosed tablets or capsules to the analogous liquid forms.
- Therefore, marketing a drug in solid form first is more practical for the manufacturer and suits most patients. It is estimated that tablets and capsules constitute the dosage form dispensed 70% of the time by community pharmacists, with tablets dispensed twice as frequently as capsules.

Microscopic Examination

Microscopic examination of raw drug substance is important step in preformulation work. It gives an indication of particle size and size range of the raw material along with the crystal structure.

. Photomicrographs of the initial and subsequent batch lots of the drug substance can provide important information in case of problems in formulation processing attributable to changes in **particle or crystal** characteristics of the drug.

During some processing procedures, the solid drug powders must **flow freely**. Spherical and oval powders flow more easily than needle-shaped powders and make processing easier.

Heat of Vaporization

- The use of **vapor pressure** is important in the operation of **implantable pumps** delivering medications as well as in aerosol dosage forms.
- Another application is the use of **nasal inhalants** (propylhexedrine with menthol and lavender oil—Benzedrex) for treating nasal congestion. In this latter dosage form, the quantity of drug required for effectiveness and a reasonable estimate of time of usefulness can be determined. Also, in the case of spills in inaccessible places, the time to evaporation of a substance can also be calculated.

Some **volatile** drugs can **migrate within a tablet** dosage form so the distribution may not be uniform any longer. So drug in one portion may be higher or lower than in the other portion.

- heat of vaporization of liquid: is the **amount of heat absorbed when 1 g of liquid vaporizes** and measured in calories.
- The heat of vaporization of water at 100°C is 540 cal/g or about 9.720 cal/mole. T

Melting Point Depression

A characteristic of a pure substance is a defined melting point or melting range.

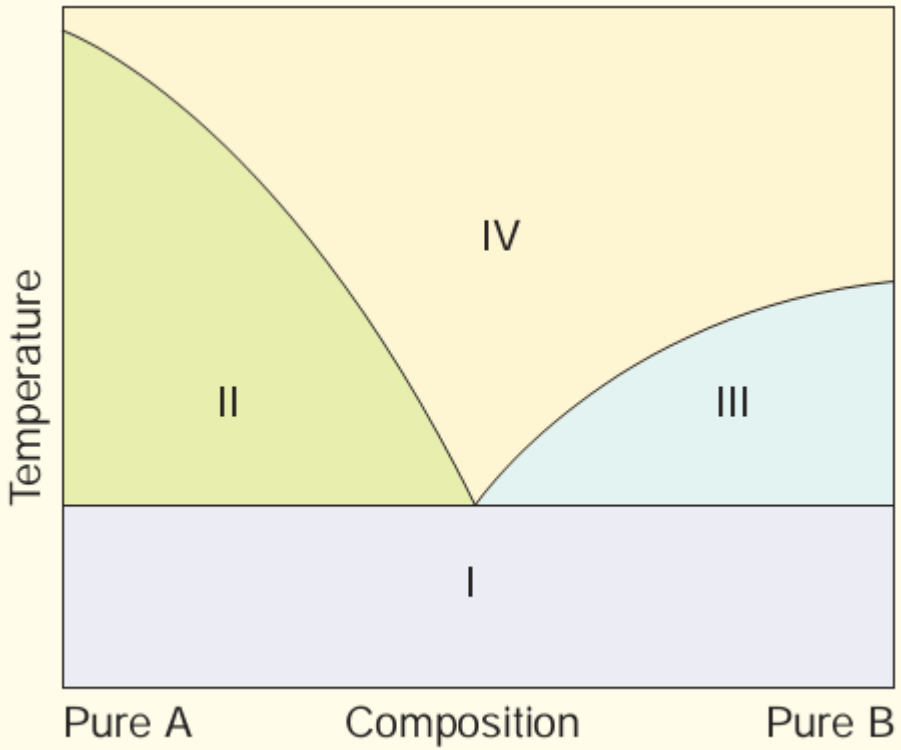
If **not pure**, the substance will exhibit a **change in melting point**.

This phenomenon is commonly used to determine the purity of a drug and compatibility of various substances before inclusion in the same dosage form.

The Phase Rule

Phase diagrams are used to **provide visual picture of the existence and extent of the presence of solid and liquid phases in binary, ternary**, and other **mixtures.**

I. Solid A + solid B
II. Solid A + melt
III. Solid B + melt
IV. Melt



The Phase Rule

A phase diagram, or temperature composition diagram, represents the melting point as a function of composition of two or three component systems.

The figure is an example of such a representation for a two-component mixture. This phase diagram depicts a two component mixture in which the components are completely miscible in the molten state and no solid solution or addition compound is formed in the solid state. As is evident, starting from the extremes of either pure component A or pure component B, as the second component is added, the melting point of the pure component decreases.

Particle Size

physical and chemical properties of drug are affected by particle size which are :**dissolution rate**, **bioavailability**, **content uniformity**, **taste**, **texture, color, stability**.

In addition**, flow ch**aracteristics and **sedimentation rates**, are important factors related to particle size.

particle size affect absorption profiles of certain drugs, including **griseofulvin, nitrofurantoin, spironolactone, and procaine penicillin.**

Also, satisfactory **content uniformity** in solid dosage forms depends on **particle size** and the equal distribution of the active ingredient through-out the formulation.

Polymorphism

An important factor on formulation is crystal or amorphous form of drug.

Polymorphic forms usually exhibit different physicochemical properties, including **melting point** and **solubility**.

Polymorphic forms in drugs are relatively common. It has been estimated that at least **one third** of all organic compounds **exhibit polymorphism**

In addition to polymorphic forms, compounds may occur in non crystalline or amorphous forms. The energy required for a molecule of drug to escape from a crystal is much greater than is required to escape from an amorphous powder. Therefore, amorphous form is **always more soluble than crystal form**.

- The changes in crystal characteristics can influence **bioavailability** and **chemical and physical stability**. For example, it can be a significant factor relating to tablet formation because of flow and compaction behaviors.

Various techniques are used to determine crystal properties:

1. **hot stage microscopy**,
2. **thermal analysis**,
3. **infrared spectroscopy**, and
4. **x-ray diffraction**

Solubility

- important especially **aqueous solubility**. A drug must possess some aqueous solubility for therapeutic efficacy.

For a drug to **enter the systemic circulation** and exert a **therapeutic** effect, it must first be in solution.

- Relatively **insoluble compounds exhibit incomplete absorption**.

If the solubility of the drug substance is less than desirable, should improve solubility. The methods used depend on chemical nature of drug and type of drug product under consideration.

- Chemical modification of the drug into **salt or ester** forms is frequently used to increase solubility.

Equilibrium solubility method

A drug's solubility is usually determined by the equilibrium solubility method, by which an excess of the drug is placed in a solvent and shaken at a constant temperature over a long period until equilibrium is obtained. Then chemical analysis of the drug content in solution is performed to determine degree of solubility.

Solubility and Particle size

The **particle size** and **surface area** of a drug exposed to a medium can affect actual solubility within reason, for example, in the following relationship:

$$\log \frac{S}{S_0} = \frac{2\gamma V}{2.303\ RTr}$$

where

S is the solubility of the small particles,
S_0 is the solubility of the large particles,
γ is the surface tension,
V is the molar volume,
R is the gas constant,
T is the absolute temperature, and
r is the radius of the small particles.

The equation can be used to estimate the decrease in particle size required to increase solubility. For example, a desired increase in solubility of 5% would require an increase in the S/S_0 ratio to 1.05; that is, the left term in the equation would become log 1.05. If a powder has a surface tension of 125 dynes/cm, molar volume of 45 cm^3, and temperature of 27°C, what is the particle size required to obtain the 5% increase in solubility?

$$\log 1.05 = \frac{(2)(125)(45)}{(2.303)(8.314 \times 10^7)(300)r}$$

$$r = 9.238 \times 10^{-6} \text{ cm or } 0.0238\ \mu$$

A number of factors are involved in actual solubility enhancement, and this is only an introduction to the general effects of particle size reduction.

Solubility and pH

- To formulate liquid product, should adjust the pH of solvent to enhance solubility.

for many drug substances, pH adjustment is not an effective means of improving solubility.

- Weak acidic or basic drugs may require extremes in pH that are outside accepted physiologic limits or that may cause stability problems with formulation ingredients.

Adjustment of pH usually has little effect on the solubility of substances other than electrolytes. In many cases, it is desirable to improve aqueous solubility by:

1-use cosolvents

2-complexation,

3-micronization,

4-solid dispersion.

Dissolution

dissolution rate, or the time it takes for the drug to dissolve in the fluids at the absorption site, is the rate-limiting step in absorption.

This is true for drugs administered orally in **solid forms**, such as **tablets**, **capsules**, or **suspensions**,

and for those administered **intramuscularly**.

When the dissolution rate is the rate-limiting step, anything that affects it will also **affect absorption**. Consequently, **dissolution rate** can affect the **onset**, **intensity**, and **duration of response** and **control the overall bioavailability** of the drug from the dosage form

- The dissolution rate of drugs increased by:

1. decreasing drug's particle size.
2. Increase solubility in diffusion layer.
3. Use **highly water-soluble salt** of parent substance.

Dissolution rates of chemical compounds determined by two methods:

1. **The constant surface method**, which provides intrinsic dissolution rate of the agent.
2. **Particulate dissolution**, in which a suspension of the agent is added to a fixed amount of solvent without exact control of surface area.

fick's laws of diffusion and Noyes-Whitney equation

- All drugs must diffuse through various barriers when administered to the body.

- Ficks low govern **absorption** through membrane
- Noyes-Whitney equation govern **dissolution** rate.

Membrane Permeability

- **passage of drug molecules across biologic membranes to produce a biologic response.**

- The biologic membrane acts as a **lipid barrier** to most drugs and permits the absorption of **lipid-soluble substances** by **passive diffusion**.
- while **lipid-insoluble** substances cannot diffuse across the barrier.

technique using **everted intestinal sac used to evaluate absorption of drug:**

In this method, a **piece of e intestine** is removed from intact animal, is **everted, and is filled with a solution** of drug, and the degree and rate of passage of the drug through the membrane sac are determined.

- In the latter stages of preformulation testing or early formulation studies, **animals and humans** must be studied to **assess absorption efficiency** and **pharmaco kinetic** parameters and to establish possible **in vitro and in vivo correlation** for dissolution and bioavailability.

Partition coefficient

$$P = \frac{(\text{Concentration of drug in octanol})}{(\text{Concentration of drug in water})}$$

P depends on drug concentration only if drug molecules have a tendency to associate in solution.

The oil–water partition coefficient is a measure of a molecule's **lipophilic character**; that is, its preference for the hydrophilic or lipophilic phase.

- If a solute is added to a mixture of two immiscible liquids, it will distribute between the two phases and reach an equilibrium at a constant temperature.

pKa /Dissociation constant

The extent of dissociation or ionization is highly dependent on **pH of medium** containing drug.

- In formulation, the vehicle is adjusted to a certain pH to obtain a certain level of ionization of drug for solubility and stability.
- In pharmacokinetic area, the extent of ionization of a drug has a strong effect on its extent of absorption, distribution, and elimination.
- dissociation constant, or pKa , is usually determined by potentiometric titration.

Hydrates and Solvates

Many active pharmaceutical agents exist as hydrates or solvates; some are hygroscopic, deliquescent, and/or efflorescent.

Hygroscopic powders are those that will tend to **absorb moisture** from the air.

Deliquescent powders are those that will absorb moisture from the air and even liquefy.

Efflorescent powders are those that may give up their water of crystallization and may even become damp and pasty.

When working with these powders, extra care must be taken.

if a hygroscopic or deliquescent powder is being weighed on a balance, the powder may absorb moisture from air and weigh heavier than it should. Therefore, weighings should be made quickly after opening the bulk chemical containers and then resealing them.

Solvates and hydrates must be packaged in "tight" containers to prevent the loss or gain of moisture.

In fact, it is best to have **all chemicals stored** in "tight" containers and to keep them closed at all times except for the short time when a weighing step is involved. Storage at the indicated temperatures is also important and to minimize any exposure to very high humidity levels.

organic Salt considerations

Because many drugs are either weak acids or weak bases and have limited water solubility, they are often used as their "salts" to increase their aqueous solubility.

For example: sodium salicylate is salt of weak acid, salicylic acid, and sodium hydroxide).

Also, ephedrine hydrochloride can be prepared between a weak base, ephedrine, and hydrochloric acid.

Generally, the "**unionized" portion of drug in solution that will be absorbed for systemic effect**.

This is described by the "dissociation constant" or "pKa " of the drug.

Active pharmaceutical ingredient (API) in a salt form is not 100% active drug, it is important to know whether or not the dose of drug is based upon drug salt or drug base form.

The purpose of “salt” form is usually **to enhance solubility** of drug; but it may also **enhance stability** and change other attributes of the drug that **make it easier to handle** and manipulate for producing dosage forms.

the “unionized” portion of drug will exert effect in body

Potency–Designated active Pharmaceutical ingredients

API, is not 100% active drug in all cases. It is important to know the assayed potency designation of the ingredient so that appropriate allowances can be made to obtain the correct amount. This may be on the label or on the Certificate of Analysis.

Some APIs, including some antibiotics, endocrine products, biotechnology-derived products, biologics, etc., have potencies that are based on "activity" and are expressed in terms of "**units** of activity," "**micrograms per milligram**," or other standard terms of measurements. These are described for each API in USP.

drug and drug Product stability

Stability studies conducted in preformulation phase include:

1- **solid-state stability of drug alone**

2- **solution-phase stability**

3-stability in presence of excipients.

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

Drug Stability: Mechanisms of Degradation

Chemical : Chemically, drug substances are **alcohols**, **phenols**, **aldehydes**, **ketones**, esters, ethers, acids, salts, alkaloids, glycosides, and others, each with **reactive chemical groups** having different susceptibilities to chemical instability.

Chemically, the most frequently encountered destructive processes are **hydrolysis** and **oxidation**.

Hydrolysis is a **solvolysis** process in which (**drug) interact with water** to yield **breakdown products**.

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.

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**,

which destroys many drug, including: **aldehydes, alcohols, phenols, sugars, alkaloids, and unsaturated fats and oils.**

Chemically, oxidation is loss of electrons from atom or molecule. Each electron lost is accepted by some other atom or molecule, reducing the recipient.

In inorganic chemistry, oxidation is accompanied by

increase in positive valence of an element: for example, ferrous (+ 2) oxidizing to ferric (+ 3).

In organic chemistry, oxidation is frequently considered synonymous with **loss of hydrogen dehydrogenation**) from molecule.

Drug and Drug Product Stability: Kinetics and Shelf Life

Stability is the extent to which a product retains within specified limits and through out its period of storage and use (i.e., its **shelf life**) the same properties and characteristics that it possessed at the time of its manufacture.

Five types of stability concern pharmacists:

1. **Chemical:** Each active ingredient retains its chemical integrity and labeled potency within the specified limits.
2. **Physical:** The original physical properties, including appearance, palatability, uniformity, dissolution, and suspendability, are retained.
3. **Microbiologic:** Sterility or resistance to microbial growth is retained according to the specified requirements. Antimicrobial agents retain effectiveness within specified limits.
4. **Therapeutic:** The therapeutic effect remains unchanged.
5. **Toxicologic:** No significant increase in toxicity occurs.

Chemical stability is important for **selecting storage conditions** (temperature, light, humidity), selecting the proper container for dispensing (glass versus plastic, clear versus amber or opaque, cap liners), and anticipating interactions when mixing drugs and dosage forms.

Stability and expiration dating are based on reaction kinetics, that is, the study of the rate of chemical change and the way this rate is influenced by concentration of reactants, products, and other chemical species and by factors such as solvent, pressure, and temperature.

In considering chemical stability of a pharmaceutical, one must know the **reaction order and reaction rate**. The reaction order may be the overall order (the sum of the exponents of the concentration terms of the rate expression) or the order with respect to each reactant (the exponent of the individual concentration term in the rate expression).

Reaction rate: The reaction rate is a description of drug concentration with respect to time. Most commonly, zero-order and first-order reactions are encountered in pharmacy.

Zero-order rate reactions

- If the loss of drug is independent on concentration of reactants and constant with respect to time (i.e., 1 mg/mL/h), the rate is called zero order. The mathematical expression is

$$\frac{-dC}{dt} = k_0$$

where k_0 is the zero-order rate constant [concentration (C)/time (t)].

The integrated and more useful form of the equation:

$$C = -k_0 t + C_0$$

where C_0 is the initial concentration of the drug.

- **units for zero rate constant** K_0 are concentration per unit time such as:
- **Mole/liter/ second** or **mg/ml/min**

- It is meaningless to attempt to describe the time required for all material in a reaction to decompose that is infinity therefore reaction rate are commonly described by K or by their half life $t_{1/2}$
- The half life equation for a zero order reaction
- $\mathbf{t_{1/2} = ½ (C_0/K_0)}$
- If the C_0 changes the $t_{1/2}$ changes . There is inverse relationship between $t_{1/2}$ and K

Example1

- A drug suspension (125 mg/mL) decays by zero-order kinetics with a reaction rate constant of 0.5 mg/mL/h. What is the concentration of intact drug remaining after 3 days (72 hours), and what is its $t_{1/2}$?

$$C = -(0.5\,mg/mL/h)(72\,h) + 125\,mg/mL$$
$$C = 89\,mg/mL \text{ after } 3\,d$$
$$t_{1/2} = 1/2(125\,mg/mL)/(0.5\,mg/mL/h)$$
$$t_{1/2} = 125\,h$$

EXAMPLE 2

How long will it take for the suspension to reach 90% of its original concentration?

$$90\% \times 125\ \text{mg/mL} = 112.5\ \text{mg/mL}$$

$$t = \frac{C - C_0}{-k_0} = \frac{112.5\ \text{mg/mL} - 125\ \text{mg/mL}}{-0.5\ \text{mg/mL/h}} = 25\ \text{h}$$

Drug suspensions are examples of pharmaceuticals that ordinarily follow zero-order kinetics for degradation.

First order reactions

- If loss of drug is **directly proportional to concentration** remaining with respect to time, it is called a first-order reaction and has the units of **reciprocal time**, that is, time^{-1}. The mathematical expression is:

$$\frac{-dC}{dt} = kC$$

where

C is the concentration of intact drug remaining,
t is time,
(dC/dt) is the rate at which the intact drug degrades, and
k is the specific reaction rate constant.

The integrated and more useful form of the equation:

$$\log C = \frac{-kt}{2.303} + \log C_0$$

where C_0 is the initial concentration of the drug.
In natural log form, the equation is

$$\ln C = -kt + \ln C_0$$

The units of k for a first-order reaction are per unit of time, such as per second.
The half-life equation for a first-order reaction is

$$t_{1/2} = 0.693 / k$$

and can be easily derived from first-order equation by substituting values of C = 50% and C0 = 100%, representing a decrease in concentration by 50%.

Example 3

An ophthalmic solution of a mydriatic drug at 5 mg/mL exhibits first-order degradation with a rate of 0.0005/day. How much drug will remain after 120 days, and what is its half-life?

$$\ln C = -(0.0005/\text{d})(120) + \ln(5\ \text{mg/mL})$$
$$\ln C = -0.06 + 1.609$$
$$\ln C = 1.549$$
$$C = 4.71\ \text{mg/mL}$$
$$t_{1/2} = 0.693 / 0.0005/\text{d}$$
$$t_{1/2} = 1,386\ \text{d}$$

- Example 4

In Example 3, how long will it take for drug to degrade to 90% of its original concentration?

$$90\%\ \text{of}\ 5\ \text{mg/mL} = 4.5\ \text{mg/mL}$$
$$\ln 4.5\ \text{mg/mL} = -(0.0005/\text{d})t + \ln(5\ \text{mg/mL})$$
$$t = \frac{\ln 4.5\ \text{mg/mL} - \ln 5\ \text{mg/mL}}{-0.0005/\text{d}}$$
$$t = 210\ \text{d}$$

Enhancing Stability of Drug Products

- Many pharmaceutical ingredients used to prepare the desired dosage form of a drug substance. Some of these agents used to achieve the desired physical and chemical characteristics of the product or enhance its appearance, odor, and taste. Other substances used to increase the stability of drug substance, against hydrolysis and oxidation.

There are several **approaches** to **stabilize pharmaceutical** preparations containing drugs subject to **hydrolysis**:

1-reduction or elimination of water from pharmaceutical system.

2- solid dosage forms containing water-labile drugs must be protected from humidity in the atmosphere. This may be accomplished by applying a waterproof protective coating over tablets or by keeping the drug in a tightly closed container. It is fairly common to detect hydrolyzed aspirin by noticing odor of acetic acid upon opening a bottle of aspirin tablets.

3-In liquid preparations, **water can frequently be or reduced in the formulation through the use of substitute liquids such as glycerin, propylene glycol**, and **alcohol**.

- In certain injectable products, anhydrous vegetable oils may be used as the drug's solvent to reduce the chance of hydrolytic decomposition.
- 4- hydrolysis prevented in liquid drugs by suspending them in nonaqueous vehicle rather than dissolving them in aqueous solvent. Particularly for unstable antibiotic drugs, when aqueous preparation is desired, the drug supplied in a dry form for reconstitution by adding a specified volume of purified water just before dispensing. The dry powder is mixture of antibiotic, suspending agents, flavorants, and colorants; when reconstituted by the pharmacist, it remains stable for the period of use.

5-Refrigeration is advisable for most preparations considered subject to hydrolysis. Together with temperature, pH is a major determinant of the stability of drug prone to hydrolytic decomposition. Hydrolysis of most drugs depends on relative concentrations of the hydroxyl and hydronium ions, and a pH at which each drug is optimally stable can be easily determined. For most hydrolysable drugs, optimum stability is on the acid side, somewhere between pH 5 and 6. Therefore, through use of buffering agents, the stability can be increased.

Buffers are used to maintain a certain pH

Buffer Capacity

$$pH = pK_a + \log(base / acid)$$

pH, buffers, and buffer capacity are especially important in drug product formulation, since they affect the drug's solubility, activity, absorption, and stability and the patient's comfort.

A buffer is a system, usually an **aqueous solution, that can resist changes in pH upon addition of acid or a base**. Buffers are composed of a **weak acid and its conjugate base or a weak base and its conjugate acid**. Buffers are prepared by one of these processes:

1. **Mixing a weak acid and its conjugate base or a weak base and its conjugate acid**
2. Mixing a **weak acid and a strong base** to form the conjugate base or a **weak base and a strong acid to form the conjugate acid**

Using the Henderson-Hasselbalch equation:

Remember that **acid is the proton donor** and the **base is the proton acceptor.**

Example1

A buffer is prepared by mixing 100 mL of 0.2 M phosphoric acid with 200 mL of 0.08 M sodium phosphate monobasic. What is the pH of this buffer? (K_a of phosphoric acid = 7.5×10^{-3})

Moles acid = (0.2 mol/1,000 mL) (100 mL) = 0.02 mol; (0.02 mol)/(0.3 L) = 0.067 M

Moles base = (0.08 mol/1,000 mL) (200 mL) = 0.016 mol; (0.016 mol)/(0.3 L) = 0.053 M

$pKa = -\log 7.5 \times 10^{-3} = 2.125$

pH = 2.125 + log (0.016 mol/0.02 mol) = 2.028

Pharmaceutically, **oxidation** of a susceptible drug substance is most likely to occur when it is **not kept dry in the presence of oxygen** or when it is **exposed to light** or **combined with other chemical agents** without proper regard to their influence on oxidation.

Oxidation of a chemical in a pharmaceutical preparation is usually accompanied by an **alteration in the color** of that preparation. It may also result in **precipitation** or a change in **odor**.

The oxidative process is inhibited by agents called antioxidants, which react with one or more compounds in drug to prevent progress of reaction.

- antioxidants act by providing electrons and easily available hydrogen atoms that are accepted more readily by the free radicals than are those of the drug being protected. Various antioxidants are employed in pharmacy.
- Among those, most frequently used in aqueous preparations are sodium sulfite (Na2 SO3 , at high pH values), sodium bisulfite (NaHSO3 , at intermediate pH values), sodium metabisulfite (Na2 S2 O5 , at low pHvalues), hypophosphorous acid (H3PO2), and ascorbic acid. In oleaginous (oily or unctuous) preparations, alpha-tocopherol, butyl hydroxy anisole, and ascorbyl palmitate find application.

- In its labeling regulations for pharmaceutical products containing sulfites, the FDA requires a warning about possible allergictype reactions, including possible life-threatening anaphylaxis symptoms and/or asthma episodes, in susceptible persons.
- Sulfites are used as preservatives in many injectable drugs, such as antibiotics and local anesthetics. Some inhalants and ophthalmic preparations also contain sulfites, but relatively few oral drugs contain these chemicals. The purpose of the regulation is to protect the estimated 0.2% of the population who are subject to allergic reactions to the chemicals. Many sulfite-sensitive persons have asthma or other allergic conditionsPrevious to the regulations dealing with prescription medication, the FDA issued regulations for the use of sulfites in food. Asthmatics and other patients who may be sulfite sensitive should be reminded to read the labels of packaged foods and medications to check for the presence of these agents.

- Sulfite agents covered by the regulations are potassium bisulfite, potassium metabisulfite, sodium bisulfite, sodium metabisulfite, sodium sulfite, and sulfur dioxide. The FDA permits the use of sulfites in prescription products, with the proper labeling, because there are no generally suitable substitutes for sulfites to maintain potency in certain medications. Some but not all epinephrine injections contain sulfites.

- The proper use of antioxidants permits their specific application only after appropriate biomedical and pharmaceutical studies.
- In certain instances, other pharmaceutical additives can inactivate a given antioxidant.
- In other cases, certain antioxidants can react chemically with the drugs they were intended to stabilize without a noticeable change in the appearance of the preparation.

- Because oxygen may adversely affect their **stability**, certain pharmaceuticals require an **oxygen-free atmosphere** during preparation and storage.
- Oxygen may be present in pharmaceutical liquids in the airspace within the container or may be dissolved in the liquid vehicle.
- To avoid these exposures, oxygen-sensitive drugs may be prepared in the **dry state** and packaged in **sealed containers** with the **air replaced by an inert gas** such as nitrogen, as may liquid preparations. This is a common practice in commercial production of vials and ampules of easily oxidizable preparations intended for parenteral use.

- Trace metals originating in the drug, solvent, container, or stopper are a constant source of difficulty in preparing stable solutions of oxidizable drugs. The rate of formation of color in epinephrine solutions, for instance, is greatly increased by the presence of ferric, ferrous, cupric, and chromic ions. Great care must be taken to eliminate these trace metals from labile preparations by thorough purification of the source of the contaminant or by chemically complexing or binding the metal through the use of specialized agents that make it chemically unavailable for participation in the oxidative process. These chelating agents are exemplified by calcium disodium edetate and EDTA.

Light can also **act as a catalyst to oxidation** reactions, , transferring its energy (photons) to drug molecules, making the latter more reactive through increased energy capability.

As a precaution against acceleration of oxidation, sensitive preparations are packaged in light-resistant or opaque containers.

Because most drug degradations proceed more rapidly as **temperature increases**, it is advisable to maintain oxidizable drugs in a cool place. Another factor that can affect stability of oxidizable drug in solution is the pH of the preparation. Each drug must be maintained in solution at pH most favorable to its stability. This varies from preparation to preparation and must be determined on an individual basis for the drug in question.

- Potassium iodide in solution is prone to photocatalyzed oxidation and the release of free iodine, with a resultant yellow to-brown discoloration of the solution.
- The use of light-resistant containers is essential to its stability.
- As a further precaution against decomposition if the solution is not to be used within a short time, the USP recommends the addition of 0.5 mg of sodium thiosulfate for each gram of potassium iodide. In the event, free iodine is released during storage, and the sodium thiosulfate converts it to colorless and soluble sodium iodide.
- Product containers, closures, and other packaging features must be considered in stability testing. For instance, tablets or capsules packaged in glass or plastic bottles require different stability test protocols from those for blister packs or strip packaging.

- Drug instability in pharmaceutical formulations detected by change in physical appearance, color, odor, taste of formula, whereas in other instances chemical changes may not be self-evident and may be ascertained only through chemical analysis.

In summary, for easily oxidizable drugs, the formulation pharmacist may stabilize the preparation by the selective **exclusion from the system:** of **oxygen**, **oxidizing agents**, **trace metals**, **light**, **heat**, and other **chemical catalysts** to oxidation process.

Antioxidants, **chelating agents**, and **buffering agents** may be added to create and **maintain a favorable pH**.

In addition to oxidation and hydrolysis, destructive processes include:

- **polymerization**,
- **chemical decarboxylation**, and
- **deamination**. However, these processes occur less frequently and are peculiar to only small groups of chemical substances.

Stability Testing

Drug and drug product stability testing during every stage of development is critical to the quality of the product.

Drug stability is important during preclinical testing and in clinical (human) trials to obtain a true and accurate assessment of the product being evaluated.

For a **marketed drug product**, assurance of stability is vital to its safety and effectiveness during the course of its shelf life and use.

FDA-required demonstration of drug stability is necessarily different for each stage of drug development, such as for a **2-week preclinical study**, an early **phase I study**, a **limited phase II trial**, **a pivotal phase III clinical study**, or for a new drug application.

As a drug development program progresses, so do the requisite data to demonstrate and document the product's **stability profile**.

- Drug product: The dosage form in the final immediate packaging intended for marketing.
- Drug substance: The unformulated drug substance that may subsequently be formulated withexcipients to produce the dosage form.
- Excipient: Anything other than the drug substance in the dosage form.
- Expiration date: The date placed on the container label of a drug product designating the time prior to which a batch of the product is expected to remain within the approved shelf life specification, if stored under defined conditions, and after which it must not be used.

- Shelf life (also referred to as expiration dating period): The time period during which a drug product is expected to remain within the approved shelf life specification, provided that it is stored under the conditions defined on the container label.
- Stress testing (drug substance): Studies undertaken to elucidate the intrinsic stability of a drug substance. Such testing is part of the drug development process and is normally carried out under more severe conditions than those used for accelerated testing.
- Stress testing (drug product): Studies undertaken to assess the effect of severe conditions on the drug product. Such studies include photostability testing as well as the specific testing of certain product types (e.g., metered dose inhalers, creams, emulsions).

- For the drug substance, the testing should evaluate its susceptibility to hydrolysis across a wide range of pH values when in solution or suspension.
- Photostability testing should be an integral part of stress testing.
- Data should be obtained from at least three pilot-scale batches of the drug substance, manufactured by the method and procedures that mirror the process to be used for final full-scale production batches.
- Stability studies also should be conducted on the drug substance packaged in the container closure system that is the same or simulates the packaging proposed for the final product.

Accelerated testing

- Accelerated testing: Studies designed to increase the rate of chemical degradation or physical change of a drug substance or drug product by using exaggerated storage conditions as part of long-term, intermediate, and accelerated studies. Data from these studies are used to assess degradation that might occur under normal (nonexaggerated) or slight deviations in storage conditions as during shipping and storage. Results allow the development of product labeling with regard to expiration dating and recommended conditions for storage

Before approval for marketing a product's stability must be assessed with regard to its formulation;

1. influence of its pharmaceutical ingredients;
2. influence of container and closure;
3. manufacturing and processing conditions (e.g., heat);
4. packaging components;
5. conditions of storage;
6. conditions of shipping,
7. temperature,
8. light, and
9. humidity; and
10. duration and conditions of pharmacy shelf life and patient use.
11. Holding intermediate product components (such as drug granulations for tablets) for long periods before processing into finished pharmaceutical products can affect the stability of

Both intermediate component and finished product.

Therefore, **in-process stability testing**, including **retesting of intermediate components**, is important.

Product containers, closures, and other packaging features must be considered in stability testing.

For instance, **tablets or capsules packaged in glass or plastic bottles** require **different stability test protocols from those for blister packs or strip packaging**.

Drugs particularly subject to **hydrolysis** or **oxidative** decomposition must be evaluated accordingly.

And sterile products must meet **sterility test** standards to ensure **protection against microbial contamination**. All **preservatives** must be tested for effectiveness in the finished product.

- **Study stability of drug products** by:

1. **long-term storage at room temperature and relative humidity**.
2. **accelerated stability studies** as indication of shelf life stability.

Drug instability in pharmaceutical formulations may be detected by change in physical appearance, color, odor, taste, or texture of formulation, whereas in other instances, chemical changes may not be self-evident and may be ascertained only through chemical analysis.

Scientific data pertaining to stability of formulation can lead to prediction of **expected shelf life** of proposed product, and when necessary to redesign of drug (e.g., into more stable salt or ester form) and to reformulation of the dosage form. Obviously, the rate at which a drug product degrades is important.

- **study of rate of chemical change** and the way it is influenced by such factors as:

1. **concentration of drug or reactant**,
2. the **solvent,**
3. **temperature and**
4. **pressure**, and
5. **other chemical agents** in the formulation .

In general, a kinetic study begins by measuring:
the concentration of drug at given intervals under a specific set of conditions, including **temperature, pH, ionic strength, light intensity, and drug concentration.**

The measurement of the drug's concentration at the various times reveals the stability or instability of the drug under the specified conditions with the passage of time.

From this starting point, each of the original conditions may be varied to determine the influence of such changes on drug's stability.

For example, the **pH of the solution may be changed** while the **temperature, light intensity, and original drug concentration** are held **constant**.

accelerated Stability Studies

stability testing is to provide evidence on how the quality of a drug product varies with time under the influence of environmental factors, such as **temperature**, **humidity, oxidation, light and microbial exposure**. Stability testing is also used to establish the shelf life for a drug product and recommended storage conditions

Accelerated testing:

Studies designed to increase the rate of chemical degradation or physical change of a drug substance or drug product by using exaggerated storage conditions as part of long-term, intermediate, and accelerated studies.

Drug product: The dosage form in the final immediate packaging intended for marketing.

Drug substance: The unformulated drug substance that may subsequently be formulated with excipients to produce dosage form.

Excipient: Anything other than the drug substance in dosage form.

Expiration date: **The date placed on container label** of drug product designating the time prior to which a batch of the product is expected to remain within approved shelf life specification, if stored under defined conditions, and after which it must not be used.

Shelf life (also referred to as **expiration dating** period):The time period during which a drug product is expected to remain within the approved shelf life specification, provided that it is stored under the conditions defined on container label.

Stress testing (drug substance):

Studies undertaken to elucidate the **intrinsic stability of a drug** substance. Such testing is part of the drug development process and is normally carried out under more severe conditions than those used for accelerated testing.

Stress testing (drug product):**Studies undertaken to assess the effect of severe conditions on drug product**. Such studies include photostability testing as well as the specific testing of certain product types (e.g., metered dose inhalers, creams, emulsions).

For the drug substance, the testing should evaluate its **susceptibility to hydrolysis across a wide range of pH values** when **in solution or suspension**.

Photo stability testing should be an integral part of stress testing.

Data should be obtained from at least **three pilot-scale batches** of the drug substance, manufactured by the method and procedures that mirror the process to be used for final full-scale production batches.

Stability studies also should be **conducted on drug substance packaged in the container closure system** that is the same or simulates the packaging proposed for final product.

Table 4.2 EXAMPLE PROTOCOL FOR DRUG AND/OR DRUG PRODUCT STABILITY STUDIES[a]

STUDY TYPE	STORAGE CONDITION	MINIMUM TIME PERIOD
Long term	25°C ± 2°C @ 60% RH[b] ± 5% RH	12 mo
Intermediate	30°C ± 2°C @ 65% RH[a] ± 5% RH	6 mo
Accelerated	40°C ± 2°C @ 75% RH[a] ± 5% RH	6 mo

[a]For chemical entities. Adapted from Stability and Testing of New Drug Substances and Products. Available at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm128204.pdf. (Accessed September 28, 2012).
[b]RH, relative humidity.

on at least **three batches of manufactured dosage** form, packaged in the container and closure system, including all secondary packaging (e.g., outer carton) proposed for marketing.

The studies should include testing product that susceptible to change during storage, thereby affecting quality and efficacy.

The testing should cover, as appropriate, the **physical, chemical, biological, and microbiological** attributes;

preservative content (e.g., **antioxidant, anti-microbial preservative**); and functionality tests (e.g., metered-dose delivery system).

Table 4.2 presents an example protocol for long-term, intermediate, and accelerated stability studies for a chemical drug entity and dosage form product.

Protocols vary for products intended to be maintained under conditions of refrigeration, for those to be

frozen, for products known to be destined for geographic areas of temperature extremes, and for biotechnological /biological products, which have separate protocols for stability studies.

Following FDA product approval and initial marketing, pharmaceutical manufacturers retain production samples of drug/drug product for **5 years or longer** and continue studies for signs of degradation under various conditions of storage.

Pharmacy practitioners should also observe **signs of product instability** (e.g., color change, distorted capsules, softened tablets, etc.) and report such findings.

Prescriptions requiring compounding by pharmacist do not require extended shelf life that commercially manufactured and distributed products do because they are intended to be **used immediately** by patient and used only during immediate course of prescribed treatment.

These compounded prescriptions must remain stable and efficacious during the course of use, and compounding pharmacist must employ formulative components and techniques that will result in a stable product.

Today, there are a number of literature sources for the pharmacist to utilize in compounding of high quality and stable prescriptions.

- Following FDA product approval and initial marketing, pharmaceutical manufacturers retain production samples of drug/drug product for 5 years or longer and continue studies for signs of degradation under various conditions of storage. Pharmacy practitioners should also observe signs of product instability (e.g., color change, distorted capsules, softened tablets, etc.) and report such findings.

- Prescriptions requiring extemporaneous compounding by the pharmacist do not require the extended shelf life that commercially manufactured and distributed products do because they are intended to be used immediately on receipt by the patient and used only during the immediate course of the prescribed treatment. However, these compounded prescriptions must remain stable and efficacious during the course of use, and the compounding pharmacist must employ formulative components and techniques that will result in a stable product. Today, there are a number of literature sources for the pharmacist to utilize in the compounding of high quality and stable prescriptions.

USP guidelines on stability

USP guidelines on stability of extemporaneous compounded formulations state that in the absence of stability information applicable to a specific drug and preparation, the following guidelines can be used:

non aqueous liquids and solid formulations when manufactured drug is the source of the active ingredient, not later than 25% of the time remaining until the product's expiration date or 6 months until the product's expiration date or 6 months, whichever is earlier.

nonaqueous liquids and solid formulations in which a USP or National Formulary (NF) substance is the source of active ingredient, a beyond-use date of 6 months.

for water-containing formulations prepared from ingredients in solid form, a beyond-use date **not later than 14 days** in storage at cold temperatures.

for all other formulations, a beyond-use date of the intended duration of therapy or 30 days, whichever is earlier .

Thus, if oral aqueous liquid preparation is made from a tablet or capsule formulation, the pharmacist should make up only at most 14 days' supply, and it must be stored in a refrigerator.

- Furthermore, the pharmacist must dispense the medication in a container conducive to stability and use and must advise the patient of proper method of use and conditions of storage of the medication.
- Finally, when compounding on the basis of extrapolated or less than concrete information, the pharmacist is well advised to keep the formulation simple and not to shortcut but use the necessary pharmaceutical adjuvants to prepare the prescription.
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