Dosage Form Design

Pharmaceutical and Formulation Considerations

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Introduction

- Drug substances are seldom administered alone; rather they are given as part of a formulation in combination with one or more nonmedicinal agents that serve varied and specialized pharmaceutical functions.
- Selective use of these nonmedicinal agents, referred to as pharmaceutical ingredients or excipients, produces dosage forms of various types.
- The proper design and formulation of a dosage form requires

1. consideration of the physical, chemical, and biologic characteristics of all of the drug substances and pharmaceutical ingredients to be used in fabricating the product.
2. The drug and pharmaceutical materials must be compatible with one another to produce a drug product that is stable, efficacious, attractive, easy to administer, and safe.
3. The product should be manufactured with appropriate measures of quality control and packaged in containers that keep the product stable.
4. The product should be labelled to promote correct use and be stored under conditions that contribute to maximum shelf life.

The need for dosage forms

- The potent nature and low dosage of most drugs in use today precludes (not permits) any expectation that general public could safely obtain the appropriate dose of a drug from the bulk material.
- Most drug substances are administered in milligram quantities, much too small to be weighed on anything but a sensitive prescription or electronic analytical balance.
- For example, the dose of ethinyl estradiol, 0.05 mg, is 1/6,500 the amount of aspirin in an aspirin tablet. To put in another way, 6,500 ethinyl estradiol tablets, each containing 0.05 mg of drug, could be made from an amount of ethinyl estradiol equal to the amount of aspirin in just one standard tablet.

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

1. To protect the drug substance from the destructive influences of atmospheric oxygen or humidity (coated tablets, sealed ampoules)
2. To protect the drug substance from the destructive influence of gastric acid after oral administration (enteric coated tablets)
3. To control the bitter, salty, or offensive taste or odor of a drug substance (capsule, coated tablets, flavored syrups)
4. To provide liquid preparations of substances that are either insoluble or unstable in the desired vehicle (suspensions)
5. To provide clear liquid dosage forms of substances (syrups, solutions)

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

1. To provide rate-controlled drug action (various controlled-release tablets, capsules, and suspensions)
2. To provide optimal drug action from topical administration sites (ointments, creams, trans-dermal patches, and ophthalmic, ear, and nasal preparations)
3. To provide for insertion of a drug into one of the body's orifices (rectal or vaginal suppositories)
4. To provide for placement of drugs directly in the bloodstream or body tissues (injections)
5. To provide for optimal drug action through inhalation therapy (inhalation aerosols)

General considerations in dosage form design

- The formulation that best meet the goals for the product is selected to be its **master formula**. Each batch of product subsequently prepared must meet the specifications established in the master formula.
- Most commonly, a manufacturer prepares a drug substance in **several dosage forms and strengths** for the efficacious and convenient treatment of disease.
- Before medicinal agent is formulated into one or more dosage forms, among the **factors considered** are such therapeutic matters as

1. **the nature of the illness**,
2. **the manner in which it is treated (locally or through systemic action)**
3. **the age and anticipated condition of the patient**.

Examples

- If the medication is intended for systemic use and oral administration is desired**, tablets and/or capsules** are usually prepared because they are easily handled by the patient and are most convenient in the self-administration of medication.
- If a drug substance has application in an emergency in which the patient may be comatose or unable to take oral medication, an injectable form of the medication may also be prepared.
- Many other example of therapeutic of therapeutic situations affecting dosage form design could be cited, including motion sickness, nausea, and vomiting, for which tablets and skin patches are used for prevention and suppositories and injections for treatment.
- **The age of the intended patient also plays a role in the dosage form design.**
- For infant and children younger than 5 years of age, pharmaceutical liquids rather than solid forms preferred for oral administration.
- These liquids which are flavored aqueous solutions, syrups, or suspensions, are usually administered directly into infant's or child's mouth by drop, spoon, or oral dispenser or incorporated into child's food.

- When a young patient has a productive cough or is vomiting, gagging, or simple rebellious, there may be some question as to how much of the medicine administered is actually swallowed and how much is expectorated.
- In such instance, injections may be required. Infant-size suppositories may also be employed, although drug absorption from the rectum is often erratic.

How to solve the difficulty of swallowing

- During childhood and even adulthood, a 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.

- **Capsules** have been found by many to be more easily swallowed than whole tablets. If a capsule is moistened in mouth before it is swallowed, it becomes slippery and readily slides down the throat with water.

Also, a teaspoonful of gelatine desert, liquid candy, or syrup placed in the mouth and partially swallowed before placing the solid dosage form in the mouth aids in swallowed them.

1. Also, if a person has difficulty swallowed a capsule; the contents may be emptied into a spoon, mixed with jam, honey, or other similar food to mask the taste of the medication and swallowed.

- **Medications intended for the elderly** are commonly formulated into oral liquids or may be extemporaneously prepared into an oral liquid by the pharmacist.
- 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.

Excipients

- **flavors** and **sweeteners.**
- **Colorants**
- **Preservatives**
- **Antioxidants**
- **chelating agents**
- lubricants

Flavoring Pharmaceuticals

- The flavoring of pharmaceuticals applies primarily to liquids intended for oral administration, mostly liquids and chewable tablets.

Selection of flavours and colours

In flavor-formulating a pharmaceutical product, the pharmacist must give consideration to the color, odor, texture, and taste of the preparation.

- There are no rules for accurately predicting the taste sensation of a drug based on its chemical constitution however there are some rules…..

EX Not all salts are salty but The salt taste is a function of both cation and anion.

1. Chlorides of sodium, potassium, and ammonium and by sodium bromide, NaCl, KCl, NH_4Cl, NaBr and KBr have salty tastes
2. Ammonium give bitter and salty sensations
3. potassium iodide KI, magnesium sulfate $MgSO_4$ **(Epsom salt)** are predominantly bitter.

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

- **Flavoures are added to liquid** mask **taste**.
- **Chewable tablets**, such as antacid and vitamin products, usually are **sweetened and flavored** to improve acceptance.
- With organic compounds, an increase in the number of hydroxyl groups (—OH) seems to increase the sweetness of the compound.
- **Sucrose**(**8 -**OH), sweeter than **glycerin**(3-OH)
- organic esters, alcohols, and aldehydes are pleasant to the taste
- Many nitrogen-containing compounds, especially the plant alkaloids (e.g., **quinine)** are extremely bitter, but certain other nitrogen-containin compounds (e.g., **aspartame)** are extremely sweet.

Even simple structural change alter taste for example

1. D-Glucose is **sweet**, but L-glucose has slightly **salty.**
2. **saccharin** is very **sweet** but **N-methyl-saccharin** is **tasteless**.

The selection of an appropriate flavoring agent depends on several factors, primarily

1. The taste of the drug substance itself.

- cocoa flavored used to mask bitter taste
- Fruit or citrus flavors used to mask sour or acid tasting
- cinnamon, orange, raspberry make preparations of salty drugs

2. The age of the intended patient

- Children prefer sweet candy-like with fruity flavors.
- Adults prefer less sweet with tart flavor.

Flavors can consist of oil- or water-soluble liquids and dry powders; most are diluted in carriers.

- Oil-soluble carriers (soybean and oils)
- water-soluble carriers (include water, ethanol, propylene glycol, glycerin, and emulsifiers.
- Dry carriers (include maltodextrins, corn syrup, modified starches, gum, salt, sugars, and whey protein).

- Flavors degrade by light, temp, oxygen, water, enzymes
- **The different types of flavors include natural, artificial, and spice:**
- 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

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
- saccharin is excreted by the kidneys virtually unchanged.
- Cyclamate is metabolized in GIT and excreted by kidneys
- Aspartame breaks down in the body into three basic components: **the amino acids phenylalanine and aspartic acid, and methanol**. are metabolized through regular pathways in the body
- use of aspartame by persons with **phenylketonuria** (PKU) is discouraged. They cannot metabolize phenylalanine adequately, so they undergo an increase in the serum levels of the amino acid (hyperphenylalaninemia). result in **mental retardation** and can affect the fetus of a pregnant woman who has PKU.

- diet foods and drinks must bear label **warning** not be consumed by such individuals.
- **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 powder 30 times as sweet as sucrose or cane sugar. Used in both hot and cold preparations. It is natural, nontoxic, safe

Coloring Pharmaceuticals

- Coloring agents are used in pharmaceutical preparations for esthetics.
- Although most pharmaceutical colorants in use today are synthetic, a few are obtained from natural mineral and plant sources.
- sulfur (yellow), riboflavin (yellow), cupric sulfate (blue), ferrous sulfate (bluish green), cyanocobalamin (red), and red mercuric iodide (vivid red).
- **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.

Certified color additives are classified according to their approved use:

(a) FD&C color additives

(b) D&C color additives

(c) external D&C color additives

For color additives, the study protocols usually call for a 2-year study

- The amount of colorant generally added to liquid preparations ranges from 0.0005% to 0.001% depending upon the colorant and the depth of color desired.
- **dyes generally are added to pharmaceutical preparations in the form of diluted solutions rather than as concentrated dry powders.**

PRESERVATIVES

Certain liquid and semisolid preparations must be preserved against microbial contamination.

Although some types of pharmaceutical products, for example, ophthalmic and injectable preparations, are sterilized by physical methods (autoclaving for 20 minutes at 15 lb pressure and 121°C or dry heat at 180°C for 1 hour, or bacterial filtration) during manufacture

many of them also require an antimicrobial preservative to maintain their aseptic condition throughout storage and use

* **syrups, emulsions, suspensions, and some semisolid creams** protected by addition of antimicrobial preservative

Other types of preparations that are not sterilized during their preparation but are particularly susceptible to microbial growth because of the nature of their ingredients are protected by the addition of an antimicrobial preservative.

Certain hydroalcoholic and most alcoholic preparations not require the addition of a chemical preservative when the alcoholic content is sufficient to prevent microbial growth.

- 15% V/V alcohol will prevent microbial growth in acid media
- 18% V/V in alkaline media.

Most alcohol-containing pharmaceuticals, are self-sterilizing and do not require additional preservation

elixirs, spirits, and tinctures, are self-sterilizing and do not require additional preservation.

Preservative Selection

* When experience or shelf storage experiments indicate that a preservative is required in a pharmaceutical preparation, **Preservative selection should do the followings:**

- **prevents growth** of microorganisms.
- **Soluble in water** to achieve adequate concentrations in aqueous phase.
- Concentration of preservative does not affect safety of patient.
- has **adequate stability** and not reduced in concentration by decomposition during desired shelf life of preparation.
- **compatible** with all formulative ingredients.
- The preservative **does not advers**ely 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 (acid** medium). **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 growth.
- Preservative must **dissolve in sufficient concentration** in **aqueous phase** of preparation.
- 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.

General Preservative Considerations

- Acidic preservatives **benzoic**, **boric, 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 conc 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

Preservatives interfere with microbial growth, multiplication, and metabolism through one or more of the following mechanisms:

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

Preservative 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.

Performulation Studies

- Before the formulation of a drug substance into a dosage form, it is essential that it be chemically and physically characterized.
  - Chemical properties include structure, form, and reactivity.
  - Physical properties include such characteristics as its physical description, particle size, crystalline structure, melting point, and solubility.
  - Biologic properties relate to its ability to get to a site of action and elicit a biologic response.

Physical Description

- It is important to understand the physical description of a drug substance prior to dosage form development.
- solid drugs are pure chemical compounds of either **crystalline or amorphous** constitution.
- The purity of the chemical substance is essential for its identification and for evaluation of its chemical, physical, and biologic properties.

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 design of dosage forms and delivery systems. Many liquids are volatile and must be physically sealed from atmosphere to prevent evaporation loss.
- **Amyl nitrate**, for example, is clear yellowish liquid that is volatile even at low temperatures and is also highly flammable. It is kept 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** is another volatile liquid that must be contained in a closed system. This drug is used as a nasal inhalant for its vasoconstrictor action. A cylinder roll of fibrous material is impregnated with propylhexedrine, and the saturated cylinder is placed in a suitable, usually 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 form, the most popular form of oral medication.
  - An exception to this is the liquid drug nitroglycerin, which is formulated into sublingual tablets that disintegrate within seconds after replacement under the tongue. However, because the drug is volatile, it has a tendency to escape from the tablets during storage, and it is critical that the tablets be stored in a tightly sealed glass container.

Approaches

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

First, the liquid substance may be sealed in a soft gelatine capsule.

- Vitamins A, D, and E, cyclosporine and ergoloid mesylates are liquids commercially available in capsule form.

Second, the liquid drug may be developed into a solid ester or salt form that will be suitable for tablets or drug capsules.

- For instance, scopolamine Hydrobromide is a solid salt of the liquid drug scopolamine and is easily pressed into tablets.

Third approach to formulate liquids into solids is by mixing the drug with a solid or melted semisolid material, such as a high-molecular-weight polyethylene glycol. The melted mixture is poured into hard gelatine capsules to harden and the capsules sealed.

Advantages of liquid drugs

- For certain liquid drugs, especially those taken orally in large doses or applied topically, their liquid nature may have some advantage in the therapy. For example,

1. 15-mL doses of mineral oil may be administered conveniently as such.
2. Also, the liquid nature of undecylenic acid certainly does not hinder but rather enhances its use topically in the treatment of fungus infections of the skin,

- however, pharmacists prefer solid materials in formulation work because they can easily form them into tablets and capsules.

Why solid dosage forms are preferred ?

- Formulation and stability difficulties arise less frequently with solid dosage form than with liquid preparations, and for this reason many new drugs first reach the market as tablet or dry-filled capsules.
- Later, when the pharmaceutical problems are resolved, a liquid form of the same drug may be marked. 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 is important step in preformulation
- 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 following situations:

1. The operation of implantable pumps delivering medication
2. Aerosol dosage forms

An example is The use of nasal inhalants (propylhexedrine with menthol and lavender oil-benzedrex) or treating nasal congestion.

Some volatile drugs can even migrate within a tablet dosage form so the distribution may not be uniform any longer. This may have an impact in tablet that are scored for dosing where the 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

Some drugs, such as carmustine, experience greater vapor pressures with increased temperature as compared to cyclophosphamide, etoposide, cisplatin, and 5-fluorouracil).

Note: particle size affects vapor pressure; the smaller the particle size, the greater the vapor pressure.

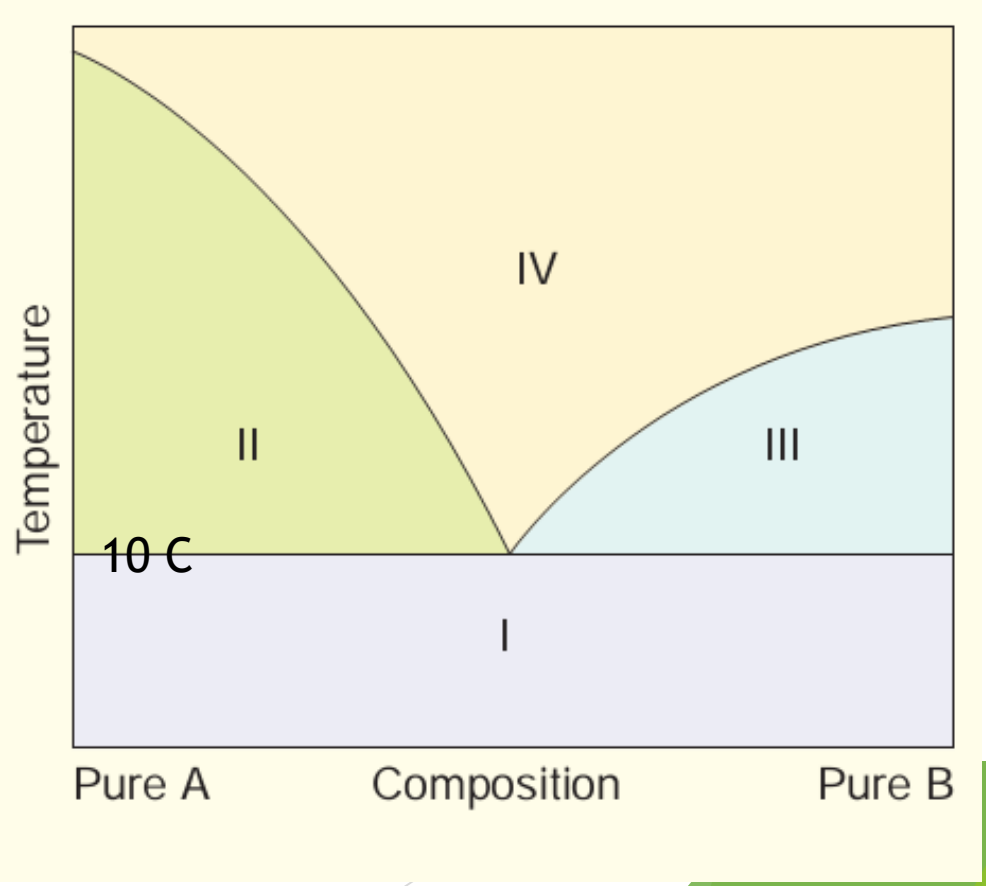
Melting point Depression

- The melting point, or freezing point, of a pure crystalline solid is defined as the temperature at which the pure liquid and solid exist in equilibrium. Drugs with a low melting point may soften during a processing step in which heat is generated, such as particle size reduction, compression, sintering, and so on
- 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. (A pure chemical is ordinarily characterised by a very sharp melting peak).
- This phenomenon is commonly used to determine the purity of a drug substance and in some cases the compatibility of various substances before inclusion in the same dosage form.
- The addition of a second component to a pure compound (A), resulting in a mixture, will result in a melting point that is lower than that of the pure compound

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.

There is a point on this phase diagram at which a minimum melting point occurs (i.e., the eutectic point).

Particle Size

physical and chemical properties of drug substances, including dissolution rate, bioavailability, content uniformity, taste, texture, color, and stability, are affected by the particle size distribution.

In addition, flow characteristics and sedimentation rates, among other properties, are important factors related to particle size.

It is essential to establish as early as possible how the particle size of the drug substance may affect formulation and efficacy of special interest is the effect of particle size on absorption.

Particle size significantly influences the oral absorption profiles of certain drugs, including griseofulvin, nitofurantoin, spironolactone, and procaine penicillin.

Also, satisfactory content uniformity in solid dosage forms depends to a large degree on particle size and the equal distribution of the active ingredient throughout the formulation.

Polymorphism

- An important factor on formulation is the crystal or amorphous form of the drug substance.
- 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 noncrystalline 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, the amorphous form of a compound is always more soluble than a corresponding crystal form.

Polymorphism

- Evaluation of crystal structure, polymorphism, and solvate form is an important performulation activity.
- The changes in crystal characteristics can **influence bioavailability and chemical and physical stability** and can have important implications in dosage form process functions.
- For example, it can be a significant factor relating to tablet formation because **of flow and compaction behaviours**
- Various techniques are used to determine crystal properties.
- The most widely used methods are hot stage microscopy, thermal analysis, infrared spectroscopy, and X-ray diffraction.

Solubility

- An important physicochemical property of a drug substance is solubility, especially aqueous system 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 often exhibit incomplete or erratic absorption.
- If the solubility of the drug substance is less than desirable, consideration must be given to improve its solubility.
- The methods to accomplish this depend **on the chemical nature of the drug and the type of drug product under consideration.**
- Chemical modification of the drug into salt or ester forms is frequently used to increase solubility.
- A drug's solubility is usually determined by the equilibrium solubility method, by which excess of the drug is placed in a solvent and shaken at a constant temperature over a long period until equilibrium is obtained. 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:

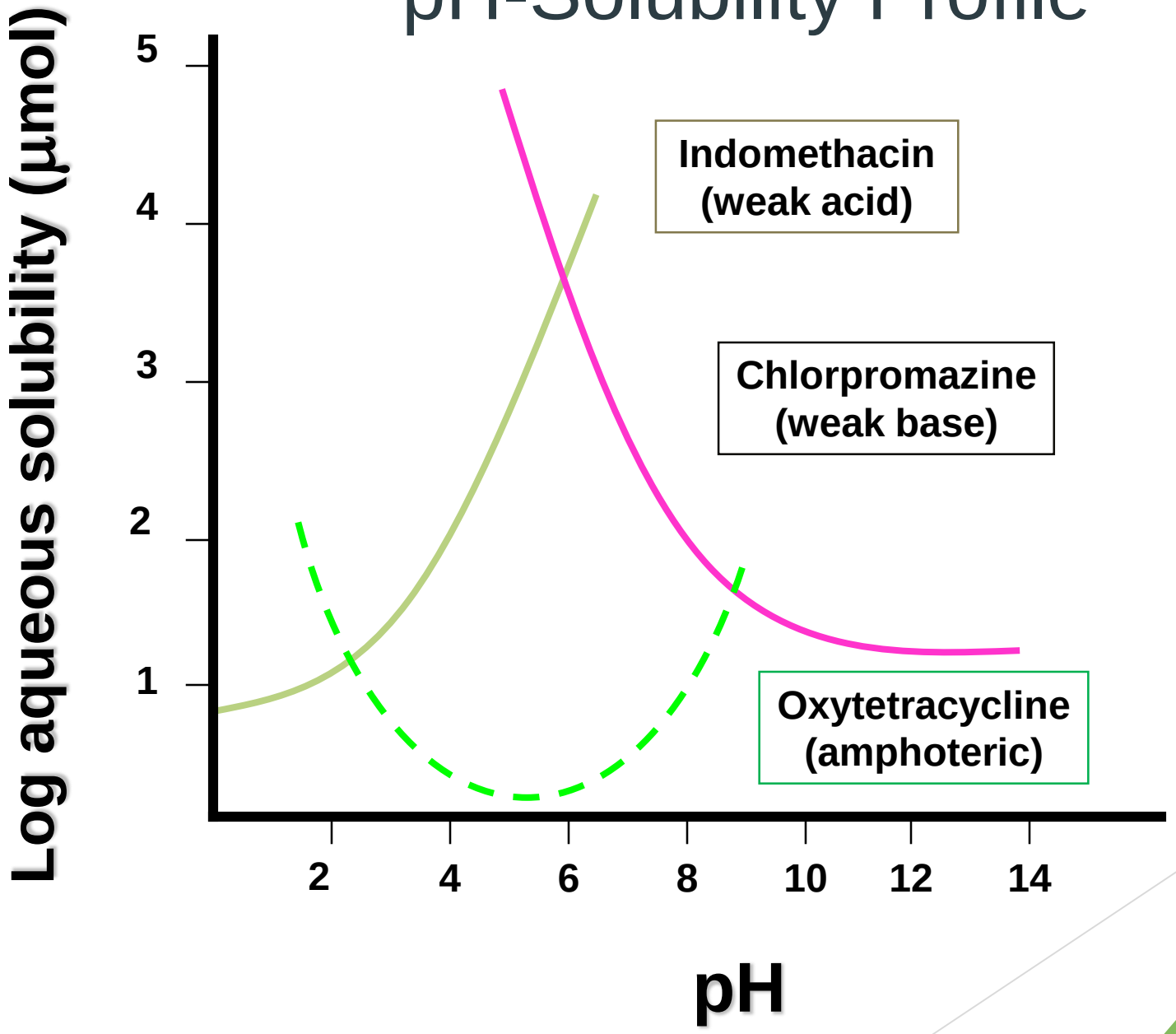
1-use cosolvents

2-complexation,

3-micronization,

4-solid dispersion.

pH-Solubility Profile



Buffer Capacity

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

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

- **Poorly-soluble weakly-acidic drugs:**

$$pH = pK_a + \log [(S_t - S_o)/S_o] \qquad (2)$$

- **Poorly-soluble weakly-basic drugs:**

$$pH = pK_a + \log [S_o/(S_t - S_o)] \qquad (3)$$

where

S_o = solubility of unionized free acid or base

S_t = total solubility (unionized + ionized)

Example

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

Dissolution

- dissolution rate, or 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

Means of enhancing the slow dissolution:

1. Particle size reduction (most commonly used).
2. Increase solubility in diffusion layer.
3. Enhanced surface area by adsorbing the drug on an inert excipient with a high surface area, i.e., fumed silicon dioxide.
4. Co-melting, co-precipitating, or triturating the drug with some excipients.
5. Incorporation of suitable surfactant.
6. the most effective means of obtaining higher dissolution rates is to use a highly-water soluble salt of the parent substance

Dissolution rates of chemical compounds are determined by 2 methods:

1. Constant-surface method – which provides the 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.

Early formulation studies should include the effects of pharmaceutical ingredients on the dissolution characteristics of the drug substance.

Particulate dissolution

- a weighed amount of powdered sample is added to the dissolution medium in a constant agitation system.
- This method is used to study the influence of particle size, surface area, and excipients upon the active agent.

Constant-surface method

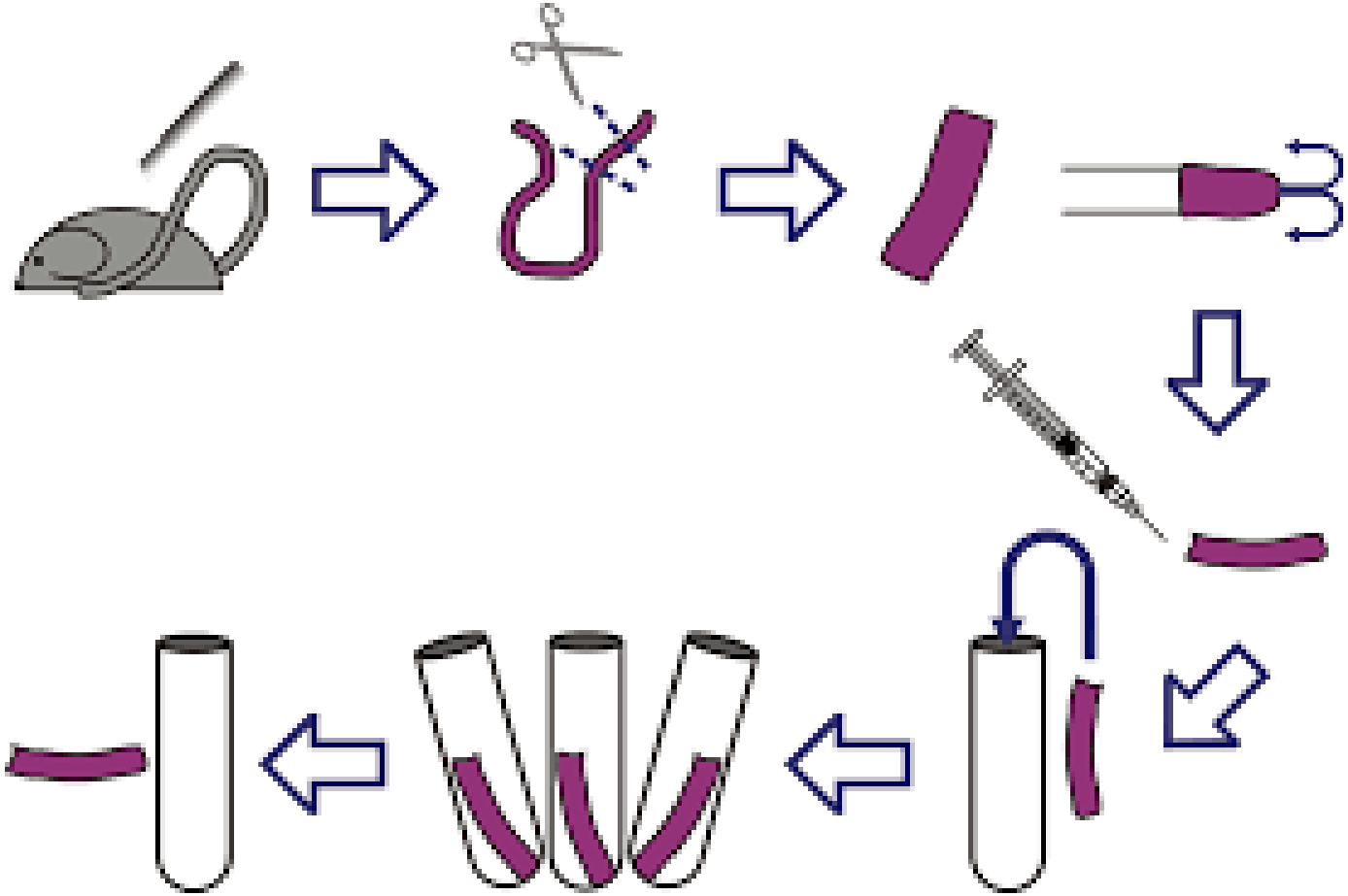
* uses a compressed disc of known area.
* This method eliminates surface area and surface electrical charges as dissolution variables.
* The dissolution rate obtained by this method, the **intrinsic dissolution rate,** is characteristics of each solid compound and a given solvent in the fixed experimental conditions.
* The value is expressed in **milligrams dissolved per minute per centimeters squared.**
* It has been suggested that this value is useful in predicting probable absorption problems due to dissolution rate.

Fick’s laws of diffusion and Noyes-Whitney equation

- All drugs must diffuse through various barriers when administered to the body.
- Fick’s Laws describe the relationship of diffusion and dissolution of the active drug in the dosage form and when administered in the body.
- Ficks low govern **absorption** through membrane
- Noyes-Whitney equation govern **dissolution** rate.

Membrane Permeability

- To produce a biologic response, the drug molecule must first cross a biologic membrane.
- 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 or diffuse only with considerable difficulty.
- **Everted intestinal sac** may be used to evaluate absorption characteristics of drug substances. A piece of intestine is removed from an intact animal, everted, filled with a solution of the drugs substance, and the degree and rate of passage of the drug through membrane sac is determined.
- This method allows evaluation of **both passive and active transport.**
- In the latter stages of preformulation testing or early formulation studies, **animals and humans** must be studied to **assess absorption efficiency** and **pharmacokinetic** parameters and to establish possible **in vitro and in vivo correlation** for dissolution and bioavailability.



Partition Coefficient

- the octanol water partition coefficient is commonly used in formulation development

P = (Conc. Of drug in octanol) / (Conc. Of drug in water)

- P depends on the drug concentration only if the drug molecules have 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.
- For an ionizable drug, the following equation is applicable:

  P = (Conc. Of drug in octanol) / [1-α] (Conc. Of drug in water)

Where α equals the degree of ionization

pka / Dissociation constants

- The extent of ionization has an effect on formulation and pharmacokinetics parameters of the drug.
- In many cases it is dependent on the pH of the medium containing the 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.
- For the practicing pharmacist, it is important in predicting precipitation in admixtures and in calculating the solubility of drugs at certain pH values.
- 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.

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, weighing 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**. the "unionized" portion of drug will exert effect in body
- 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.

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

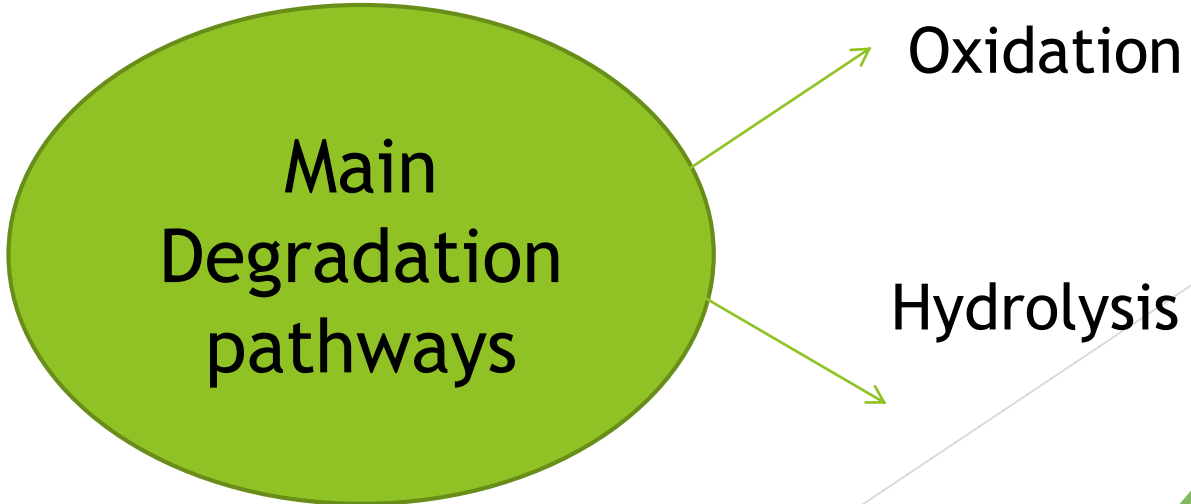
- One of the most important activities of preformulation work is evaluation of the physical and chemical stability of the pure drug substance.
- It is essential that these initial studies be conducted using drug samples of known purity. The presence of impurities can lead to erroneous conclusions in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

1. **Solid-state stability of the drug alone**
2. **Solution phase stability**
3. **Stability in presence of expected excipients.**

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

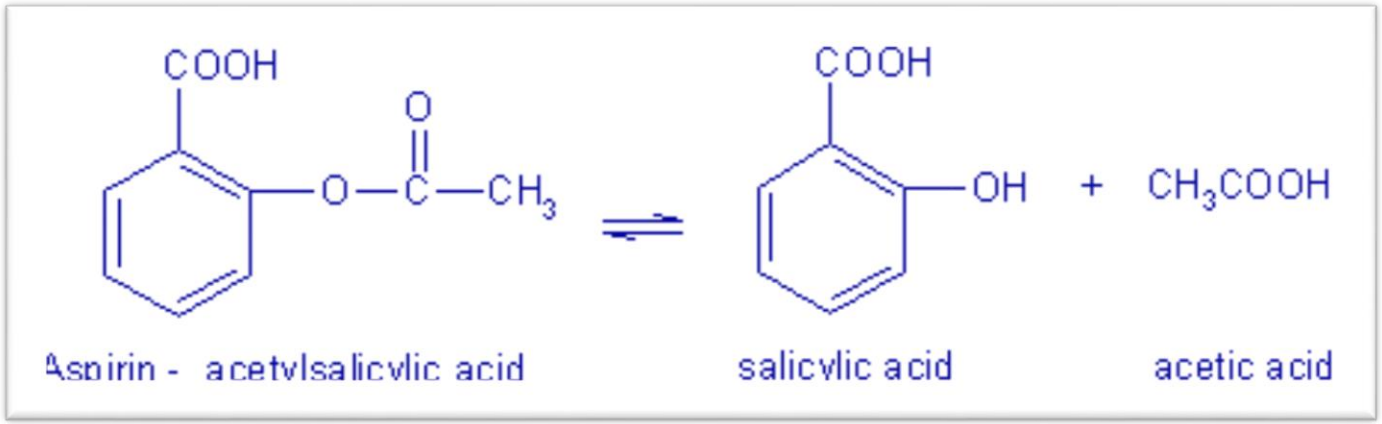
Drug stability: Mechanism of Degradation

- 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 to chemical instability.



Hydrolysis

- Hydrolysis is a solvolysis process in which (drug) molecules interact with water molecules to yield breakdown products.
- For example, aspirin, or acetylsalicylic acid, combines with a water molecule



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

Oxidation

- Destroys many drug types, including aldehydes, alcohols, phenols, sugars, alkaloids, and unsaturated fats and oils.
- Oxidation frequently involves free chemical radicals
- Many of the oxidative change in pharmaceutical preparation have a character of **autoxidations.**
- **Autoxidations** occur spontaneously under initial influence of atmospheric oxygen and proceed slowly at first and then more rapidly.
- The process has been described as a type of chain reaction commencing with 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.

- 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.
- In drug product formulation work, steps are taken to reduce or prevent deterioration due to hydrolysis, oxidation, and other processes.

Drug and product stability: kinetics and shelf life

Stability is the extent to which a product retains within specified limits and throughout 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:.**
2. **Physical:.**
3. **Microbiologic:.**
4. **Therapeutic:.**
5. **Toxicologic:.**

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 tothe 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

1. selecting storage conditions (Temperature, light , humidity)
2. selecting the proper container for dispensing(glass versus plastic, clear versus amber or opaque, cap liners)
3. anticipating interactions when mixing drugs and dosage forms.

- Stability and expiration dating are based on **reaction kinetics**
- It 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).
- The reaction rate is a description of the 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 $t_{1/2} = \frac{1}{2} (C_0/K_0)$
- If the C_0 changes the $t_{1/2}$ changes . There is inverse relationship between $t_{1/2}$ and K

EX: 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

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

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?

$$\ln C = -(0.0005/\text{d})(120) + \ln(5\ \text{mg/mL})$$
$$\ln C = -0.06 + 1.609$$
$$\ln C = 1.549$$
$$C = 4.71\ \text{mg/mL}$$
$$t_{1/2} = 0.693 / 0.0005/\text{d}$$
$$t_{1/2} = 1.386\ \text{d}$$

In the above example, 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 may be used to prepare the desired dosage form of a drug substance.
- substances may be used to increase the stability of the drug substance, particularly against hydrolysis and oxidation.
- In each instance, the added pharmaceutical ingredient must be **compatible** with and must not detract from the stability of the drug substance.

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 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 be replaced by 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.

5-unstable antibiotic drugs, when an aqueous preparation is desired, the drug may be supplied to the pharmacist in a dry form for reconstitution by adding a specified volume of purified water just before dispensing.

6-Refrigeration is advisable for most preparations considered subject to hydrolysis.

7-Together with temperature, pH is a major determinant of the stability of a drug prone to hydrolytic decomposition. Hydrolysis of most drugs depends on relative concentrations of hydroxyl and hydronium ions, and a pH at which each drug is optimally stable can be easily determined.

For most hydrolyzable drugs, optimum stability is on the acid side, somewhere between pH 5 and 6. Therefore, use of buffering agents, the stability of otherwise unstable compounds can be increased.

Buffers are used to maintain a certain pH

oxidation

- Pharmaceutically, oxidation of a susceptible drug substance is most likely to occur when

1. it is not kept dry in the presence of oxygen
2. it is exposed to light
3. combined with other chemical agents without proper regard to their influence on oxidation.

- Oxidation of a chemical in pharmaceutical preparation is usually accompanied by

1. an alteration in the color of that preparation.
2. It may also result in precipitation
3. a change in odor.

- The oxidative process is diverted and the stability of the drug is preserved by agents called **antioxidants** which react with one or more compounds in the drug to prevent progress of the chain reaction.
- In general, 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.

1- Among those most frequently used in aqueous preparations are

sodium sulfite (Na_2SO_3 at high pH values),

sodium bisulfite ($NaHSO_3$ at intermediate pH values),

sodium metabisulfite ($Na_2S_2O_5$ at low pH values),

hypophosphorous acid (H_3PO_2), and ascorbic acid.

2- In oleaginous (oily or unctuous) preparations, alpha-tocopherol, butyl hydroxy anisole, and ascorbyl palmitate find application.

- In June 1987, U.S. FDA labeling regulations went into effect requiring a warning about possible allergic-type reactions, including anaphylaxis, in the package insert for prescription drugs to whose final dosage form sulfites have been added.
- 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

- 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

1. thorough purification of the source of the contaminant
2. by chemically complexing or binding the metal through the use of specialized agents that make it chemically unavailable for participation in the oxidative process (EDTA and calcium di sodium edetate).

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 also advisable to maintain oxidizable drugs in a cool place.
- Another factor that can affect the stability of an oxidizable drug in solution is the pH of the preparation. Each drug must be maintained in solution at the pH most favorable to its stability.
- This varies from preparation to preparation and must be determined on an individual basis for each drug.
- In some instances, the specific agent to employ as a stabilizer is mentioned in the monograph, and in others the term “suitable stabilizer” is used.

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, is a reaction between two or more identical molecules that forms a new and generally larger molecule.

- Formaldehyde In solution it may polymerize to paraformaldehyde (CH2O)n. The official formaldehyde solution contains approximately 37% formaldehyde and according to the USP, should be stored at temperatures not below 15°C (59°F).

chemical decarboxylation, and **deamination** processes in which one or more of their active chemical groups are removed

- most preparations of insulin are neutralized to reduce the rate of decomposition.
- 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.

1. Drug stability is important during preclinical testing and in clinical (human) trials to obtain a true and accurate assessment of the product being evaluated.
2. For a marketed drug product, assurance of stability is vital to its safety and effectiveness during the course of its shelf life and use

The FDA-required demonstration of drug stability is necessarily different for each stage of drug development,

1. for a 2-week preclinical study,
2. an early Phase I study,
3. a limited Phase II trial,
4. a pivotal Phase III clinical study,
5. 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.

- Before approval for marketing, a product's stability must be assessed with regard to

1. its formulation;
2. the influence of its pharmaceutical ingredients;
3. the influence of the container and closure;
4. the manufacturing and processing conditions (e.g., heat);
5. packaging components;
6. conditions of storage;
7. anticipated conditions of shipping, temperature, light, and humidity; and
8. anticipated duration and conditions of pharmacy shelf life and patient use.
9. 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 the intermediate component and the 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.
- Sterile products must meet sterility test standards to ensure protection against microbial contamination.
- All preservatives must be tested for effectiveness in the finished product.

How to detect product instability

- **Physical appearance** color, odor, taste, or texture of the formulation,
- **Chemical changes (**chemical changes may not be self-evident and may be ascertained only through chemical analysis)

- Obviously, the rate at which a drug product degrades is of prime importance.
- The study of the rate of chemical change and the way it is influenced by such factors as **the concentration of the drug or reactant, the solvent, temperature and pressure, and other chemical agents in the formulation** is **reaction kinetics**.
- In general, a kinetic study begins by measuring the concentration of the 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 the 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

- **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.

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.

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

- From the experimental data, the reaction rate may be determined and a rate constant and half-life calculated.

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.

Data from these studies are used to assess degradation that might occur under normal (non-exaggerated) 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.

The use of **exaggerated conditions** of temperature, humidity, light, and others to test the stability of drug formulations is termed **accelerated stability testing.**

- conducted for 6 months at 40°C ± 2°C with 75% ± 5% relative humidity. To detect if a significant change in the product occurs

Short-term accelerated studies are used to determine the most stable of the proposed formulations for a drug product.

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.

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

- 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.

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. 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).

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.

In addition to the accelerated stability studies, drug products are subjected to **long-term stability studies** under the usual conditions of transport and storage expected during product distribution.

- Geographic regions are defined by zones: zone I, temperate; zone II, subtropical; zone III, hot and dry; and zone IV, hot and humid.
- Samples maintained under these conditions may be retained for 5 years or longer
- These studies, considered with the accelerated stability studies previously performed, lead to a more precise determination of drug product stability, actual shelf life, and the possible extension of expiration dating.

- Under usual circumstances, most manufactured products must have a shelf life of 2 or more years to ensure stability at the time of consumption.
- Commercial products must bear an appropriate expiration date that sets out the time during which the product may be expected to maintain its potency and remain stable under the designated storage conditions.

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

However, Tthese 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.

USP guidelines on stability

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

1. **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; non aqueous 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;
2. for water-containing formulations prepared from ingredients in solid form, a beyond-use date not later than 14 days in storage at cold temperatures;
3. for all other formulations, a beyond-use date of intended duration of therapy or 30 days. 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

Reference

Ansel's pharmaceutical dosage forms and drug delivery systems , tenth edition