Current Good Manufacturing Practices and Current Good Compounding Practices

cGMP and cGCP

GMP

GMP regulations established by FDA to

- **Ensure that minimum standards present for drug product quality.**

- The cGMP regulations for:

bulk and **finished pharmaceutical products**).

c GMP REGULATIONS include

1. **Organization and Personnel**
2. **Personnel qualifications and Personnel responsibilities.**
3. **Buildings:** Design and Lighting, Ventilation, air filtration, air heating and cooling, Sanitation , Maintenance
4. **Equipment:** design, size, and location, Equipment construction, cleaning and maintenance.

1. **Filters**
2. **Containers and Closures**
3. Test drug: **approval or rejection of components**, **drug product containers, and closures**
4. Use of approved components, drug product containers, and closures
5. **Retesting of approved components**, drug product containers, and closures
6. **Rejected** components, drug product containers, and closures

F. **Production and Process Controls**: **Written procedures should present**.

1. Calculation of yield
2. Equipment identification
3. **Sampling and testing of in-process materials and drug products**

- **Active pharmaceutical ingredient (API):** Any component have pharmacologic activity in diagnosis, cure, mitigation, treatment or prevention of disease.
- **Batch:** **A specific quantity of a drug** of uniform specified quality produced according to single manufacturing order during the same cycle of manufacture.
- **Certification:** Documented testimony by qualified authorities that a system qualification, calibration, validation, or revalidation has been performed.
- **Compliance:** manufacturer acting with prescribed regulations, standards, and practices.

- **Component:** Any ingredient used in manufacture of drug product.
- **Drug product:** Finished form contains active drug and inactive ingredients.
- **Inactive ingredient:** Any component other than the active ingredients in drug product.
- **Lot:** A batch or any portion of a batch having uniform specified quality and a distinctive identifying lot number.
- **Lot number, control number, or batch number:** combination of letters, numbers, or symbols from which the complete history of manufacture, processing, packaging, holding, and distribution of a batch or lot of a drug product may be determined.

- **Master record:** **Record containing the formulation**, specifications, manufacturing procedures, quality assurance requirements, and labeling of finished product.
- **Quality assurance:** all evidence needed that activities relating to quality are being performed adequately.
- **Quality control:** process through which industry measures actual quality performance, compares it with standards.

- **Quality control unit:** organizational element designated by a firm to be responsible for work related to quality control.

- **Quarantine:** An area that is marked, designated, or set aside for the holding **of incoming components** **prior to acceptance testing** and qualification for use.

- **Representative sample:** A sample that represent the whole product.
- **Reprocessing:** **recycling:**The activity that finished product or any of its components is recycled through all or part of the manufacturing process.
- **Strength:** concentration of drug per unit dose or volume.
- **Verified:** Signed by a second individual or recorded by automated equipment.
- **Validation:** Documented evidence that a system (e.g., equipment, software, controls) does what it purpots to do.
- Process validation: Documented evidence that a process (e.g., sterilization) does what it purports to do.
- Validation protocol: experimental plan to produce documented evidence that the system has been validated.

Organization and personnel

- deals with responsibilities of quality control unit, employees, and consultants.
- quality control unit have responsibility for all functions that affect product quality. This includes **accepting** or **rejecting** product components, product specifications, finished products, packaging, and labeling. Adequate laboratory facilities shall be provided, written procedures followed, and all records maintained.
- All personnel required to have **education, training, and experience**
- Appropriate programs of education and training, and performance evaluations are essential for maintaining quality assurance.

EQUIPMENT

- Each piece of equipment must be :**appropriate design** and **size** to facilitate **use, cleaning, and maintenance**.
- equipment's surfaces and parts **must not interact** with processes or product s so not affect **purity, strength**, or **quality.**
- Standard operating **procedures must be written** and followed for proper use, maintenance, and cleaning of each piece of equipment.
- equipment and computers used in the processes must be **routinely calibrated**, maintained, and validated for accuracy.
- Filters used in the manufacture or processing of injectable drug products **must not** release fibers into such products.

Control of componants, containers and closure

- Written procedures, identification, storage, handling, sampling, testing, and **approval or rejection** of all product components, containers, and closures must be maintained and followed.
- Bulk pharmaceutical chemicals, containers, and closures must meet the required property.
- Raw materials should verified through sampling and qualitative and quantitative analysis.
- **Rejected components**, containers, and closures are identified and controlled under a **quarantine system** to prevent their use in manufacturing and processing operations.

- Mainly bulk chemicals (APIs) are synthesized in **China and India**
- it is important to confirm their identity and purity with **USP** and **NF** prior to use in finished pharmaceuticals.

PRODUCTION AND PROCESS CONTROLS

- **Written procedures** are required to ensure that drug products have correct **identity**, **strength**, **quality**, and **purity**.

- In-process samples taken from production batches periodically for product control.

Packaging and labeling control

- Written procedures are required for the receipt, identification, storage, handling, sampling, and testing of drug product and issurance of labeling and packaging materials.
- **Expiration Dating**

Expiration Dating

- To ensure that a drug product meets standards of identity, strength, quality, and purity at time of use.

- Except from this requirement are **homeopathic drug products**, **allergenic extracts**, and investigational drugs that meet the standards established during preclinical and clinical studies.

HOLDING AND DISTRIBUTION

- Written procedures must be established and followed for the holding and distribution of product.
- Finished pharmaceuticals must be quarantined in storage until released by the quality control unit.
- Products must be stored and **shipped** under conditions that **do not affect product quality.**
- the oldest approved stock is distributed first.
- The distribution control system must allow the distribution point of each lot of drug product to be readily determined to facilitate its recall if necessary.

LABORATORY CONTROLS

- Laboratory controls are requirements for the establishment of and conformance to :
- **written specifications**,
- **standards**,
- **sampling plans**,
- **test procedures**.
- The specifications, which apply to each batch of drug product, include **sample size**
- **test intervals**
- **sample storage**
- **stability testing**

special testing requirements for parenterals, ophthalmics , controlled-release products, and radioactive pharmaceuticals.

Complete master production and control records for each batch must be kept and include the following:

- Name and strength of the product
- Dosage form
- Quantitative amounts of components.
- Complete manufacturing and control procedures
- Equipment used
- In-process controls
- Sampling and laboratory methods and assay results
- Calibration of instruments
- Distribution records
- Dated and employee-identified records

ADDITIONAL cGMP REQUIREMENTS

Active Pharmaceutical Ingredients and Exciepients

The quality of any finished product depends on the quality of the components, and active ingredients.

GMP focuses on all elements of chemical purity and quality, including following:

- **Specifications and analytical methods for all reactive and nonreactive components** used.
- chemical reaction steps
- Handling of chemical intermediates
- Quality of water used.
- Solvent handling and recovery systems
- Analytical methods to detect impurities or chemical residues and limits set
- Stability studies of bulk pharmaceutical chemical

MEDICAL DEVICES

1. devices are approved for marketing when shown to be safe and effective through premarket approval.
2. Medical devices are subject to the reporting of adverse events, to recall, and to termination of approval.
3. The regulations for "good manufacturing practice for medical devices" are similar to those for finished pharmaceuticals. They include **personnel**; **buildings**; **equipment**; **control of components**; production and process controls; packaging and labeling; holding, distribution, and installation; device evaluation; and records.

- Devices covered by cGMP regulations include:

1. **intraocular lenses,**
2. **hearing aids,**
3. **intrauterine devices,**
4. **cardiac pacemakers,**
5. **clinical chemistry analyzers,**
6. **catheters,**
7. **cardiopulmonary bypass heart-lung machine console,**
8. **dental X-ray equipment,**
9. **surgical gloves,**
10. **prosthetic hip joints,**
11. **traction equipment,**
12. **computed tomography equipment, and**
13. **powered wheelchairs.**

USP-NF FORMULARY

- In the **absence of stability information**, the following maximum time use after opening are recommended for **non sterile** compounded drug preparations that are packaged in tight, light-resistant containers and stored at controlled room temperature:

1. For **non aqueous liquids and solid** formulations:

(a) Where manufactured drug product is the source of active ingredient, the beyond-use date is **not later than 25%** of the time remaining until the product's expiration date or 6 months.

(b) where a USP or NF substance is the source of active ingredient, the beyond-use date is not later than 6 months.

- For water-containing formulations prepared from ingredients in solid form, the beyond-use date is not later than **14 days** when stored at cold temperatures.

- For all other formulations, use date is not later than intended duration of therapy or **30 days**.
- **If no sterility testing program is in place, the following apply:**

1. For low-risk preparations at room temperature use dates not more than **48 hours** and for refrigerated temperatures, not more than **14 days**.
2. For medium-risk preparations at room temperature, use **not more than 30 hours** and for **refrigerated temperatures, not more than 9 days.**
3. For high-risk preparations at room temperature, **not more than 24 hours** and for **refrigerated temperatures, not more than 3 days.**

In all three instances, if stored at -25°C to -10°C, the beyond use dates are 45 days in the solid state.

CONTAINERS

- must **provide adequate drug stability**.

qualities tested for containers

1. Physicochemical properties.
2. Light-transmission for glass or plastic.
3. Drug compatibility.
4. Leaching and/or migration.
5. Vapor transmission for plastics.
6. Moisture barrier.
7. Toxicity for plastics.
8. Valve, actuator, metered dose, particle size, spray characteristics, and leaks for aerosols.
9. Sterility and permeation for parenteral containers.
10. Drug stability for all packaging.

- According to USP, a **container is** “that which **holds the article** and is **or in direct contact with article**.” The immediate container is “that which is in direct contact with the article at all times.”
- The closure is part of the container.

- The container, should be **clean and dry** before it is filled with drug.
- must not interact physically or chemically with the drug.

- Ex:sorption of diazepam, to low density plastics resulting in a loss of drug avoided with the use of glass containers.

The USP classifies containers according to their ability to protect their contents from external conditions.

1. **well-closed container**. "protects contents from solids and from loss under ordinary conditions of handling, shipment, storage, and distribution."
2. **A tight container** "protects contents from contamination by liquids, solids, or vapors, or evaporation under the ordinary conditions of handling, shipment, storage, and distribution and is capable of tight re-closure."

3. **A hermetic container** "is impervious to air or any other gas under the ordinary conditions of handling, shipment, storage, and distribution."

4. **Sterile hermetic containers** hold preparations intended for injection or parenteral administration.

- **A single-dose container :**when opened, cannot be resealed with assurance that sterility has been maintained.
- These containers include **fusion sealed ampoules** and **prefilled syringes and cartridges**.

- **A multiple-dose container** is a **hermetic container** that permits withdrawal of successive portions of the contents without changing the strength or affect the quality or purity of the remaining portion. These containers are commonly called **vials**.

- **unit dose package:** positive identification of each dosage unit and **reduction of errors**, **reduced contamination** of the drug.
- packaging materials may be combinations of paper, foil, plastic, or cellophane.

Oral liquids

- dispensed in single units in paper, plastic, or foil cups or prepackaged and dispensed in glass containers having threaded caps or crimped aluminum caps.
- disposable plastic oral syringes with rubber or plastic tips on the orifice for closure.

- suppositories, powders, ointments, creams, and ophthalmic solutions, are also commonly found in single-unit packages.

unit-of-use packaging

- the quantity of drug product prescribed is packaged in a container.

- Ex: if certain antibiotic capsules are prescribed to be taken 4 times a day for 10 days, unit-of-use packaging would contain 40 capsules. Other products may be packaged to contain a month's supply.

light-resistant containers

- **Amber glass** or a light-resistant **opaque plastic** will reduce light transmission sufficiently to protect a **light-sensitive** pharmaceutical.
- **ultraviolet absorbers** may be added to plastic to decrease the transmission of short ultraviolet rays.
- USP standards that define the acceptable limits of light transmission at any wavelength between 290 and 450 nm.

- recent innovation in plastic packaging is the **coextruded two-layer high-density polyethylene bottle**, which has an **inner layer** of **black polyethylene coextruded** with an **outer** layer of **white polyethylene**. The container provides:

1. **light resistance.**
2. **moisture protection**.

Increasingly being used in packaging of tablets and capsules.

Glass used in packaging pharmaceuticals

- 4 categories :
- **Types I, II, and III** intended for **parenteral products**, and type**IV: NP** is intended for other products.
- Each type tested according to resistance to water attack.
- Degree of attack is determined by **amount of alkali released** from glass in specified test conditions.
- leaching of alkali from glass to preparation could alter

1. pH
2. Stability of product.

- Type I is most resistant glass of 4 categories.

- **Today**, most products are packaged in **plastic**.
- intravenous fluids, plastic ointment tubes, plastic film-protected suppositories, and plastic tablet and capsule vial.

- **Advantage over glass:**

1. **Light** and resistance to impact, which reduces costs and losses due to container damage
2. Versatility in container design, consumer acceptance
3. Consumer preference for plastic squeeze bottles in administration of ophthalmics, nasal sprays, and lotions
4. The popularity of blister packaging and unit-dose dispensing.

- **Example**, Addition of **methyl groups** to every other carbon atom in the polymer chains of **polyethylene** will give **polypropylene**, material that can be **autoclaved**.
- If a **chlorine** atom is added to every other carbon in the **polyethylene** polymer, **polyvinyl chloride** (PVC) is produced. This material is **rigid and has good clarity**, making it particularly useful in the **blister packaging** of tablets and capsules. However, it has a significant drawback for packaging medical devices (e.g., syringes): it is **unsuitable for gamma sterilization**, a method that is being used increasingly.

- The placement of other functional groups on the main chain of **polyethylene** or added to polymers can give a variety of alterations to final plastic material. Among the newer plastics are **polyethylene terephthalate** (PET), **amorphous polyethylene terephthalate** glycol (APET), and polyethylene terephthalate glycol (PETG). Both APET and PETG have excellent **transparency** and can be **sterilized with gamma radiation**.

- Among **problems** encountered in the use of **plastics** in packaging are:
- (a) **Permeability of containers to atmospheric oxygen and moisture vapor.**
- (b) **Leaching of constituents of to the internal contents.**
- (c) **Absorption of drugs from contents to container.**
- (d) **transmission of light through container**.
- (e) **Alteration of container upon storage**.
- **plasticizers, stabilizers, antioxidants, antistatic agents, antifungal agents, colorants, and others.**

- The permeability of a plastic is a function of:

1. Nature of polymer;
2. the amounts and types of plasticizers,
3. fillers, lubricants, pigments and other additives;
4. pressure; and temperature.

- Increases in temperature, pressure, and the use of additives tend to increase permeability of plastic. Glass containers are less permeable than plastic containers.

- Many products liable to deteriorate in humidity unless protected by high-barrier packaging.
- Desiccant silica gel in small packets, commonly included as protection against effects of moisture vapor.
- Drug substances that are subject to **oxidative degradation** may undergo a greater degree of degradation when packaged in plastic than in glass.
- Liquid in plastic may **lose drug molecules** or solvent to the container, altering the concentration of drug in product and affecting its potency.

- **Leaching** is term used to describe **movement of components of container to contents**.
- Compounds leached: polymer additives, such as the plasticizers, stabilizers, or antioxidants. **The leaching occurs when liquids or semisolids are packaged in plastic.** Little leaching occurs when tablets or capsules are packaged in plastic.
- influenced by temperature, agitation

- **Sorption** indicate **binding of molecules to polymer** includes both **adsorption and absorption**.
- Sorption occurs through chemical or physical means.
- **un-ionized species of solute has greater tendency to bound than ionized species.**
- degree of ionization of a solute affected by pH of solution, the pH may influence sorption of particular solute.
- **Plastic materials with polar groups are prone to sorption.** Because **sorption depends on penetration or diffusion of a solute into plastic.**

- **Sorption** may occur with **active pharmacologic agents** or **with excipients**.
- Sorption may be initiated by the **adsorption of a solute to the inner surface of a plastic container.**
- After saturation of the surface, the solute may diffuse into the container and bound within plastic.
- The sorption of excipients :colorants, preservatives, or stabilizers would likewise alter the quality of product.
- Methylparaben may be sorbed to some types of plastics, resulting in a decrease in the available concentration of preservative.

- Deformations, softening, hardening, and other physical changes in plastic containers can be caused by the action of container's contents or external factors, including changes in temperature and physical stress placed upon the container in handling and shipping.

Child-Resistant & Adult-Senior use Packaging

- Defined as one that is significantly difficult for children under 5 years of age to open or to obtain a harmful amount of its contents within a reasonable time and that is not difficult for “normal adults” to use properly.

Compliance packaging

- blister packaging in a calendar pack.
- These medication compliance useful for :**patients taking multiple medications.**

LABELING

- company literature
- advertising and promotional material
- booklets, mailing pieces, file cards, price lists, catalogs, sound recordings, film strips, motion picture films, slides, exhibits, displays, literature reprints, and computer-accessed information; and other materials related to the product.
- Important information for a prescription-only drug.

MANUFACTURER'S LABEL

- The nonproprietary name of drug or The name of the manufacturer, packer, or distributor of the product.
- A quantitative statement of the amount of each drug per unit of weight, volume, or dosage unit.
- The pharmaceutical type of dosage form constituting the product
- The net amount of drug product contained in the package, in units of weight, volume, or number of dosage units, as appropriate
- The logo "Rx only" or the federal legend "Caution—Federal law prohibits dispensing without prescription" or a similar statement.
- A label reference to refer to the accompanying package insert or other product literature for dosage and other information.
- Special storage instructions when applicable.
- The National Drug Code identification number for the product (and often a bar code)
- An identifying lot or control number.
- An expiration date.
- "Warning—May be habit forming" may also appear.

PRESCRIPTION LABEL

- **Name and address of the pharmacy**
- Serial number of prescription
- Date of the prescription or the date of its filling or refilling (state law often determines which date is to be used).
- Name of prescriber
- Name of patient
- Directions for use, include any precautions, as indicated on prescription.

1. The address of the patient
2. The initials or name of the dispensing pharmacist
3. The telephone number of the pharmacy
4. The drug name, strength, and manufacturer's lot or control number
5. The expiration date of the drug
6. The name of the manufacturer or distributor
7. In an effort to decrease medication errors, there is thought to include the “indication” on the prescription label to help the pharmacist assure the prescribed drug is appropriate.

OVER-THE-COUNTER LABELING

- Product name.
- Name and address of manufacturer, packer or distributor.
- Quantity of contents.
- Names and quantities of all active ingredients /dosage unit. Inactive ingredients also listed.
- Name of any habit-forming substance or substances in the preparation.
- Statement of pharmacologic category (e.g., antacid) and adequate directions for safe and effective use, for example, dose, frequency of dose, dose and age considerations, route of administration, and preparation for use, such as shaking or dilution.

- Cautions and warnings.
- Sodium content for certain oral products intended for ingestion, when the product contains 5 mg of sodium or more/single dose or 140 mg or more in maximum daily dose.
- Storage conditions.
- Lot number and expiration date.

- geriatric patients, might be unable to read a label physically, easy-to-read font size is required along with other graphical features that promote the ability to read the label information.

Dietary Supplement Labeling

- Should write: "**improve mood**" rather than treat depression
- Should write :**This product is not intended to diagnose, treat, cure, or prevent any disease**."
- For herbal products, the label must also state **the part of the plant used to make the product**, for example, root, stem, leaf.
- minimum information about the product prior to its use.

STORAGE

- product must be stored in proper conditions.
- The labeling of product includes **the desired conditions of storage.**
- **Cold:** Any temperature not exceeding **8°C.**
- A **refrigerator** is a cold place in which the temperature is maintained thermostatically between **2° and 8°C**.
- **A freezer** is a cold place in which the temperature is maintained thermostatically **between -25° and -10°C.**
- **Cool:** Any temperature between **8° and 15°C**.

- **Room temperature:** The temperature in a working area. 20° to 25°C.
- **Warm:** Any temperature between **30° and 40°**C.
- **Excessive heat**: **Above 40°**C.
- Protection from freezing: in addition to the **risk of breakage** of container, freezing subjects a product to **loss of strength** or **potency** or to **destructionof dosage form**.
- TRANSPORTATION
- The stability protection of a pharmaceutical product during transportation is important.

Chapter 4 part 2

Preformulation studies

Physical Description

Solid drugs :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**.

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 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** for this reason, many new drugs first reach the market as tablets or capsules.

Later, liquid form of same drug marketed. This procedure is doubly advantageous, because physicians and patients prefer small, tasteless, accurately dosed tablets or capsules.

It is estimated that tablets and capsules constitute 70% of dosage forms.

pharmacists, dispense tablets twice as capsules.

Microscopic Examination

Microscopic examination of raw is important step in preformulation. It gives an indication of **particle size** and **crystal structure**.

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

- **use of vapor pressure is important in implantable pumps delivering medications and in aerosol dosage forms.**

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

Melting Point Depression

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

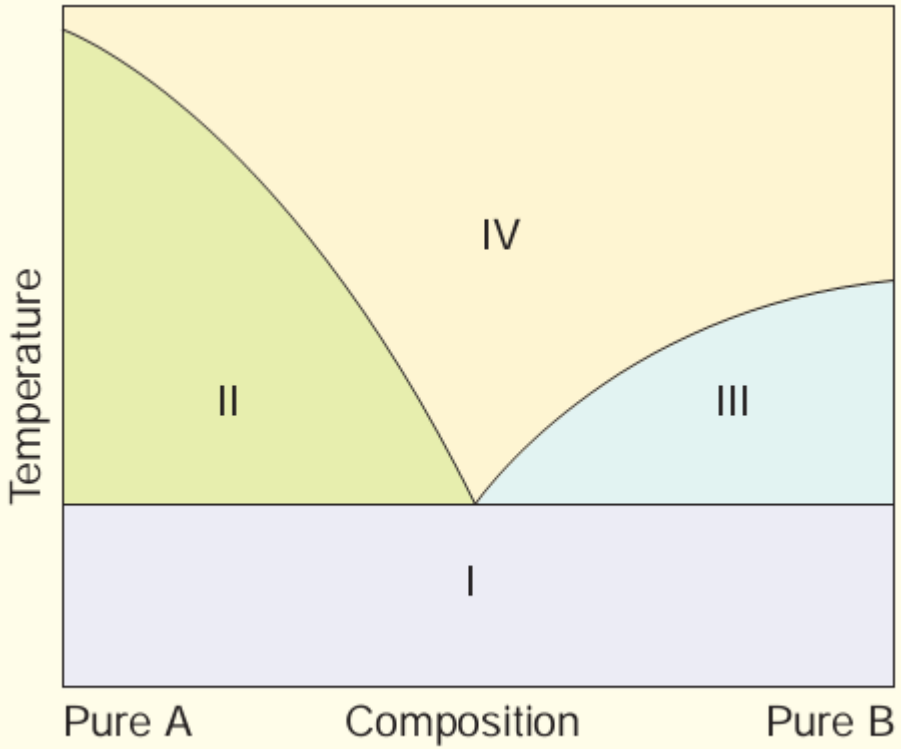
If **not pure**, the substance will exhibit a **change in melting point**.

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.

- **<u>units for zero rate constant</u>** 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
- **$t_{1/2} = ½ (C_0/K_0)$**
- 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?

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

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

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**. stability of the drug is preserved by agents called **antioxidants**

- 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.

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 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.

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**.

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.

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:

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;

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 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

Dosage Form Design: Biopharmaceutical and Pharmacokinetic Considerations

Chapter 5

Biopharmaceutics

- Is the science that study relation of **physicochemical properties of drug**, **dosage form**, & **route of administration** on **rate and extent** of drug absorption.

pharmacokinetics

- It is the study of the kinetics of absorption, distribution, metabolism, and excretion (ADME) of drugs and their pharmacologic, therapeutic, or toxic effects in animals and man.

- drugs given IV go directly into blood.
- **elimination refers to both metabolism and. excretion.**

- **drug in blood exists in equilibrium with drug in tissues.**
- In equilibrium **concentration of the drug in blood different** (greater or lesser) than the **concentration** of the drug in tissues. This is due to the **physicochemical** properties of the drug.
-
- the rate of transfer of a drug from one compartment to another is **proportional to concentration of the drug in the compartment from which it exits**; the greater the concentration, the greater is the amount of drug transfer.

- During metabolism a drug substance may be biotransformed into:

1. pharmacologically active,
2. inactive metabolites,
3. or both.

For example, anticonvulsant drug carbamazepine is metabolized in the liver to active epoxide metabolite.

- **metabolism of drug to inactive products is irreversible process.**
- In some instances, a pharmacologically inactive drug (termed a prodrug) administered for known effects of its active metabolites.
- (k_{el}) : elimination rate constant for drug describe its rate of elimination from body.

PRINCIPLES OF DRUG ABSORPTION

Passive Diffusion:

1. From high to low concentration
2. depends on the molecule's **lipid solubility**, particle **size**, **degree of ionization**, and **area** of absorptive surface.
3. Primary mechanism for most drugs
4. No need for energy or carrier.

- ***Fick's law of Absorbtion***, drug molecules diffuse from a region of high drug concentration to a region of low drug concentration.

$$\frac{dQ}{dt} = \frac{DAK}{h}(C_{GI} - C_p)$$

- Where dQ/dt = rate of diffusion, D = diffusion coefficient,
- K = lipid water partition coefficient
- A = surface area of membrane;
- h = membrane thickness, and
- $C_{GI} - C_p$ = difference between the concentrations of drug in the gastrointestinal tract and in the plasma.

- Because D, A, K, and h are constants under usual conditions for absorption, a combined constant P or permeability coefficient may be defined.

$$P = \frac{DAK}{h} \qquad (13.2)$$

- drug concentration in plasma, C_p, is extremely small compared to the drug concentration in the gastrointestinal tract, C_{GI}. If C_p is negligible and P is substituted

$$\frac{dQ}{dt} = P(C_{GI}) \qquad (13.3)$$

2-Facilitated Passive Diffusion:

1. From high to low concentration
2. Need **Carrier** in the membrane combines reversibly with the substrate molecule outside the cell membrane
3. No need for energy.
4. specific molecular configuration
5. Limited number of carrier

3-Active Transport:

1. Against concentration gradient.
2. selective,
3. requires energy
4. limited to drugs structurally similar to endogenous substances (eg, ions, vitamins, sugars, amino acids).
5. These drugs are usually **absorbed from specific sites in the small intestine**.

Many body nutrients, such as **sugars** and **amino acids**, are transported across the membranes of the gastrointestinal tract by **carrier** processes.

Certain **vitamins**, such as **thiamine, niacin, riboflavin, and pyridoxine**, and drug substances, such as **methyldopa** and **5-fluorouracil**, require **active transport** mechanisms for their absorption.

DISSOLUTION

- The process by which a drug particle dissolves.

For a drug to be absorbed, it must first dissolved in the fluid at absorption site.

- As a drug particle undergoes dissolution, the drug molecules on the surface are the first to enter into solution, creating a saturated layer of drug solution that envelops the surface of the solid drug particle. This layer of solution is the **diffusion layer**.
- From diffusion layer the drug molecules pass throughout the dissolving fluid and make contact with biologic membranes, and absorption ensues.

- **If dissolution is rapid** or if the drug is administered as a solution the rate at which the drug becomes absorbed depends mainly on its ability **to traverse the membrane barrier**.
- **If dissolution slow** because of the physicochemical characteristics of the drug substance or dosage form, **dissolution is a rate-limiting step in absorption**.

- Drug remain in stomach :2 to 4 hours.
- In small intestine: 4 to 10 hours.

Various techniques used to determine gastric emptying time like:

- **Gamma scintigraphy**: tracking dosage forms labeled with gamma-emitting radionuclides.
- **The gastric emptying time for a drug is rapid with fasting stomach**.

1. slower as food content is increased.

Changes in gastric **emptying time** or **intestinal motility** can affect drug transit time and thus opportunity for drug dissolution and absorption.

a. **anticholinergic drug, slows gastric emptying**. Which increases drugs absorption from stomach and reduce drugs absorption from small intestine.

b. drugs that **enhance gastric motility**, for example, laxatives, **reduce** amount of drug absorbed.

c. **Aging** decrease absorption (geriatrics)

- **decrease in gastric emptying time** is advantageous for **drugs absorbed** from stomach but disadvantage for **drugs prone to acid degradation**, like penicillins and erythromycin, or **inactivated by stomach enzymes**, like L-dopa.

The rate of dissolution

- Rate of dissolution described by **Noyes-Whitney equation** :

$$\frac{dW}{dt} = \frac{DA(C_s - C)}{L}$$

- where
- **dw/dt is the rate of dissolution,**
- **D** is the **dissolution rate constant**,
- **A** is the **surface area** of dissolving solid,
- c_s is **saturation concentration of drug** in diffusion layer (which may be approximated by the maximum solubility of the drug in the solvent, because the diffusion layer is considered saturated), and
- **c_t is the concentration of the drug in dissolution medium** at time t ($c_s - c_t$ is concentration gradient).
- **L: length of diffusion layer.**

- **rate of dissolution governed by rate of diffusion of solute through diffusion layer.**

dissolution rate increased by:

1. **increasing surface area** (reducing the particle size),
2. **by increasing the solubility of drug in diffusion layer**, by factors embodied in dissolution rate constant, D, including the **intensity of agitation of the solvent** and **diffusion coefficient of dissolving drug**. For a given drug, the diffusion coefficient and usually concentration of the drug in diffusion layer will increase with **increasing temperature.**
3. **Increasing rate of agitation of the dissolving medium** will increase the rate of dissolution.
4. **reduction in the viscosity** of solvent enhance dissolution rate of a drug.
5. **Changes in pH** or nature of solvent that influence the solubility of the drug may be used to increase dissolution rate.

Henderson–Hasselbalch equation:

$$pH = pK_a + \log \frac{[A^-]}{[HA]}$$ **for** acidic drugs

$$pH = pKa + \log \frac{unionized}{ionized}$$ for basic drugs

$$pK_a = -\log(K_a) = -\log\left(\frac{[H_3O^+][A^-]}{[HA]}\right)$$

- Drug movement **not always affected by pH.**
- Very weak acids and bases completely **non ionized** at physiological p H ,their transfer rapid and independent of p H. .
- strong acids and bases are completely ionized and so their transfer is usually slow and pH-independent.

- drugs include acids within the pK range 3 to 7.5 and bases in the pK range 7 to 11
- **Stomach pH: 1-2**
- **Duodenum pH: 2-4**
- **Small intestine pH: 4-6**
- **Large intestine 6-7.8**

Bases	pK_a
Amphetamine	9.8
Apomorphine	7.0
Atropine	9.7
Caffeine	0.8
Chlordiazepoxide	4.6
Cocaine	8.5
Codeine	7.9
Guanethidine	11.8
Morphine	7.9
Procaine	9.0
Quinine	8.4
Reserpine	6.6

Acids	pK_a
Acetylsalicylic acid	3.5
Barbital	7.9
Benzylpenicillin	2.8
Boric acid	9.2
Dicoumarol	5.7
Phenobarbital	7.4
Phenytoin	8.3
Sulfanilamide	10.4
Theophylline	9.0
Thiopental	7.6
Tolbutamide	5.5
Warfarin sodium	4.8

Surface area

- When a drug particle is broken up, surface area increased. For drug substances that are poorly or slowly soluble, this generally results in increase in the rate of dissolution.

- **To increase surface are**a, use **micronized** powders in their solid products. micronized powders consist of drug particles reduced in size to about **5 µm** and smaller.

Crystal or Amorphous Drug form

- Solid drug materials may occur as crystalline or amorphous.
- Amorphous usually more soluble than crystalline form, different extents of drug absorption :
- **antibiotic chloramphenicol** palmitate, are inactive when administered in crystalline, but when administered **amorphous**, absorption from GIT rapidly, with good therapeutic response.

- **In other instances:** crystalline forms of drugs may be used because of greater stability than amorphous forms.

For example, **the crystalline forms of penicillin G** as potassium salt or sodium salt are **more stable than amorphous forms**. Thus, in formulation work on penicillin G, the **crystalline forms are preferred** and result in excellent therapeutic response.

- The **amorphous**, or **Prompt Insulin Zinc Suspension**, USP, is **rapidly absorbed** upon intramuscular. The larger **crystalline** material, called **ultralente insulin** or Extended Insulin Zinc Suspension, USP, is more **slowly absorbed** and has a resultant longer duration of action.
- By combining the two types in various proportions, a physician can provide patients with intermediate-acting insulin of varying degrees of onset and duration of action. A physical mixture of **70% of the crystalline form and 30% of the amorphous** form, **called lente insulin** or Insulin Zinc Suspension, USP, is **intermediate acting** and meets the requirements of many diabetics.

- **Polymorphism:**
- Only one form of a pure drug is **stable**, the other is **metastable forms**, converting in time to the stable crystalline form. It is therefore fairly common for a metastable form of a medicinal agent to change form even in a completed pharmaceutical preparation.
- **time required for a complete change may exceed the normal shelf life of the product.**
- **any change in crystal structure of agent affect the stability and therapeutic efficacy of the product** .

- **Salt forms**
- The dissolution rate of a salt of a drug is different from that of the parent compound.
- Sodium and potassium salts of weak organic acids and hydrochloride salts of weak organic bases dissolve more than free acids or bases.
- The **addition of the ethylenediamine** moiety to **theophylline increases the water solubility** of theophylline **fivefold.**

- The use of the ethylenediamine salt of theophylline has allowed the development of oral aqueous solutions of theophylline.

Other factor

The state of hydration of a drug molecule can affect its solubility and pattern of absorption.

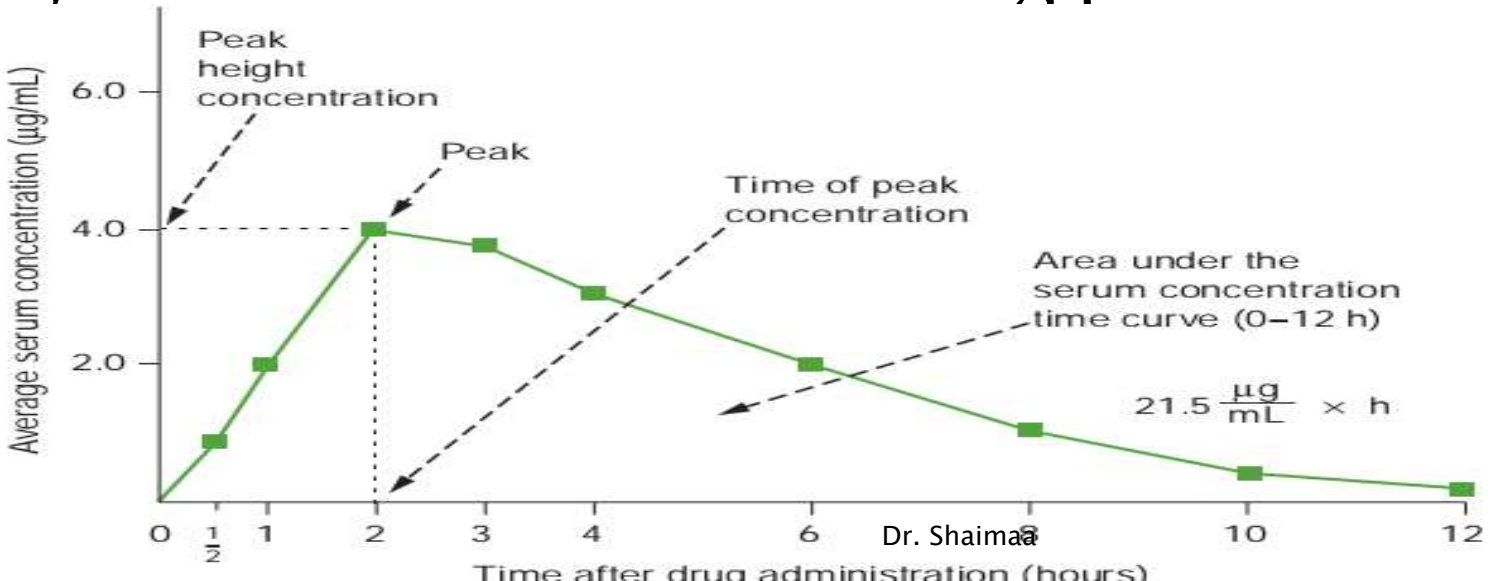
Usually, the anhydrous form of an organic molecule is more readily soluble than the hydrated form. This characteristic was demonstrated with the drug ampicillin, when the anhydrous form was found to have a greater rate of solubility than the trihydrate. The rate of absorption for the anhydrous form was greater than that for the trihydrate form of the drug.

Other factors

- A drug's solubility in GIT can be affected by **pH** also by **food**. A drug may interact with agents present to form a **chemical complex** that result in reduced drug solubility and decreased absorption.
- The classic example of this **complexation: between tetracycline and calcium, magnesium, and aluminum**, resulting in non absorbable complex so decreased absorption of the tetracycline.

Bioavailability and Bioequivalence

- **bioavailability** is the **rate and extent** of drug absorption from site of administration to the general circulation.
- The term **bioequivalence** refers to a comparison of bioavailabilities of different formulations, drug products, or batches of the same drug product.



- **Bioavailability used to determine**

1. **amount of drug absorbed** from a formulation or dosage form,
2. **rate at which the drug was absorbed**,
3. **duration of the drug's** presence in biologic fluid or tissue correlated with the patient's response, and
4. **relationship between drug blood levels and clinical efficacy and toxicity**.

During product development stage:

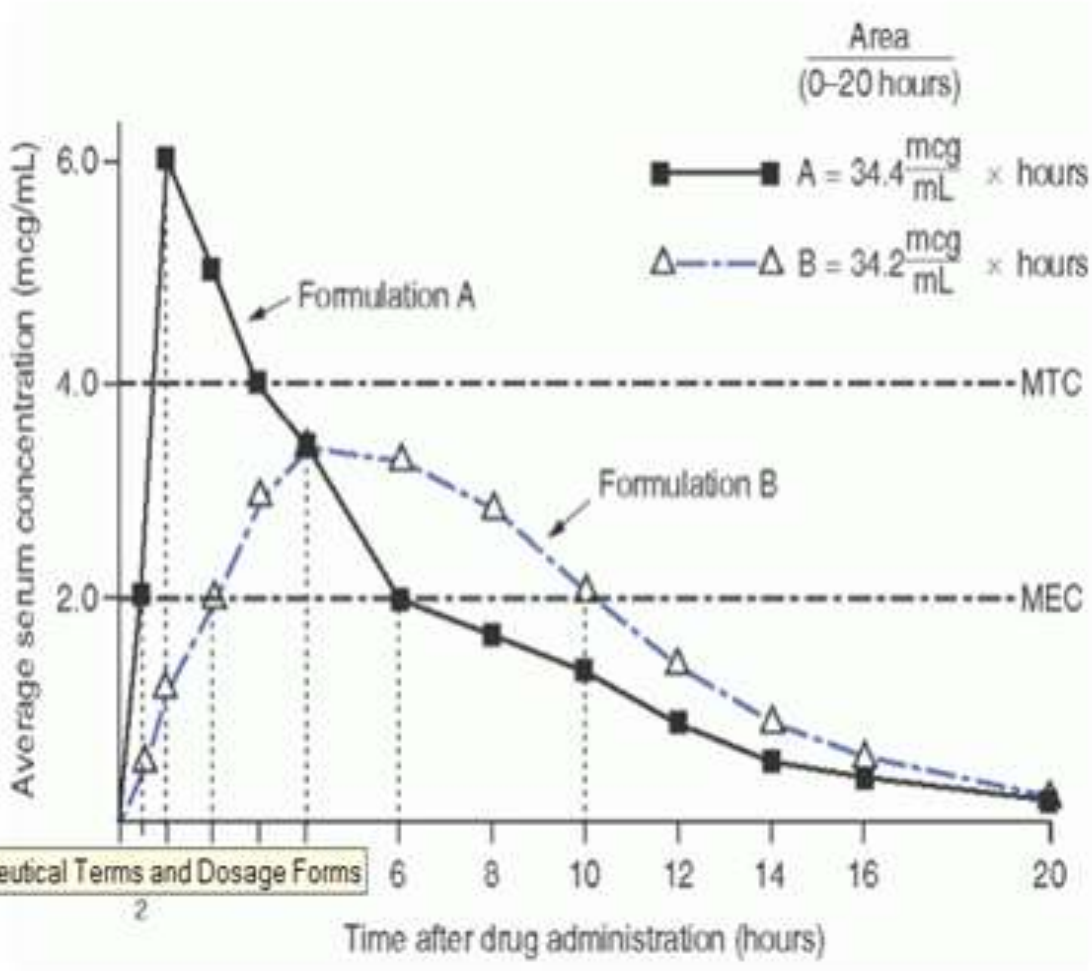
1. **studies bioavailability** to **compare different formulations** of the drug substance to ascertain which one allows the most desirable absorption pattern.
2. Later **bioavailability studies** used to compare the **availability of the drug** substance **in different production batches**.
3. They may also be used to compare **the availability of the drug substance in different dosage forms** (e.g., tablets, capsules, elixirs),
4. or in the **same dosage form produced by different (companies) manufacturers.**

Blood, Serum, or Plasma Concentration time curve

- Following oral administration of drug, blood samples are withdrawn at specific time intervals and analyzed for drug content.
- The vertical presents the concentration of drug in blood, and horizontal axis presents time the samples were obtained following drug administration.
- **time zero the blood concentration of drug should be zero**.
- As the drug passes into the stomach and/or intestine, dissolves, and absorbed. As the sampling and analysis continue, the blood samples reveal increasing concentrations of drug until maximum (peak) concentration (C_{max}) is reached. Then the blood level of the drug decreases.
- Absorption does not terminate after the peak blood level is reached; it may continue for some time.
- process of drug elimination is continuous. It begins as soon as the drug first appears in the blood stream and continues until all the drug has been eliminated.
- The positive or negative slope of the curve indicates which process is faster.

Parameters for assessment and comparison of bioavailability

- Following oral administration of single doses of two formulations of the same drug :
- **The peak height concentration (C_{max})**
- The time to peak concentration (T_{max})
- The area under the blood (or serum or plasma) concentration time curve (AUC)
- **C_{max} observed in blood following a dose of the drug, indicating a slope of zero**, meaning the **rates of absorption and elimination are equal**.



maceutical Terms and Dosage Forms

2

FIGURE 5.7 Serum concentration-time curve showing peak height concentrations, peak height times, times to reach MEC and areas under the curves for equal amounts of drug from two different formulations following oral administration. MEC, minimum effective concentration; MTC, minimum toxic concentration. (Courtesy of D. I. Chodos and A. R. Disanto, Upjohn.)

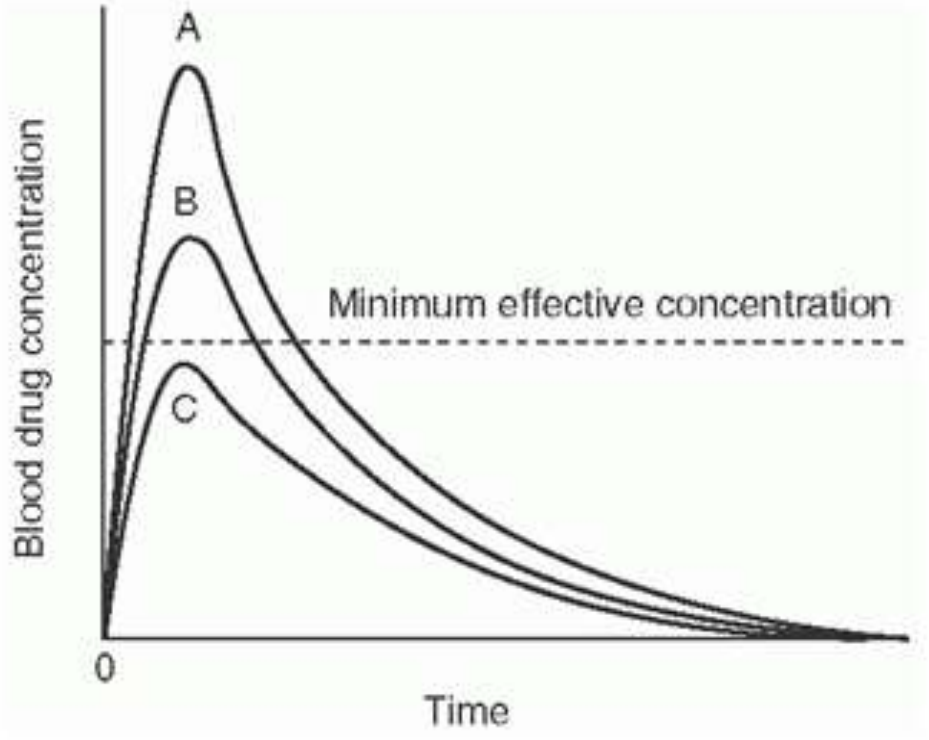


FIGURE 5.8 The influence of dose size on the blood drug concentration-time curves when three different doses of the same drug are administered and the rates of drug absorption and elimination are equal after the three doses. A, 100 mg; B, 80 mg; C, 50 mg. (Adapted with permission from Ueda CT. Concepts in Clinical Pharmacology: Essentials of Bioavailability and Bioequivalence. Upjohn, 1979.)

When the rate of absorption is decreased, the C_{max} is lowered and T_{max} occurs at a later time.

Area under the Serum Concentration Time Curve

- The AUC of concentration-time curve) represent **total amount of drug absorbed** following administration of a single dose of that drug.
- If similar doses of drug in **different formulas produce different AUC values**, differences exist in **extent of absorption** between formulations.
- In general, the smaller AUC, the lesser drug absorbed.

- F: bioavailability of orally administered drug calculated by comparison of AUC after oral administration with that obtained after intravenous administration:
- **$F = (AUC)_{oral}/(AUC)_{IV} \times DOSE\ IV/DOSE\ oral$**

- The absolute bioavailability following oral dosing is generally compared to intravenous dosing.

Bioequivalence of drug products

- Bioavailability: rate and extent to which a drug in a dosage form becomes available for biologic absorption.
- the **same drug** when formulated in **different dosage forms** have **different bioavailability** and exhibit **different clinical effectiveness**.
- Furthermore, two identical or equivalent products of **same drug** in the **same dosage strength** and in the **same dosage form** but **differing in formulative** materials or **method of manufacture** may vary widely in bioavailability and thus, in clinical effectiveness.

- **FDA uses the following terms to define type or level of equivalency between drug products.**

- **Pharmaceutical equivalents:** are drug products that **contain identical amounts of identical active ingredient**, that is, the **same salt** or ester of the **same therapeutic moiety**, in **identical dosage forms** but **not necessarily containing the same inactive ingredients**.
- **Pharmaceutical alternatives** are **drug products** that contain the **identical therapeutic moiety** or its precursor but **not necessarily in the same amount or dosage form** or as **the same salt or ester.**

- bioequivalent drug products **are pharmaceutical equivalents or pharmaceutical alternatives** whose **rate and extent of absorption are similar**.
- Some **pharmaceutical equivalents** or **pharmaceutical alternatives** equivalent in **extent absorption but not in rate of absorption** and yet may be considered **bioequivalen**t. because such differences in rate of absorption are intentional and are reflected in the labeling, are not essential to the attainment of effective body drug concentrations on chronic use, or are considered **medically insignificant** for the drug product studied.

- **therapeutic equivalents:** used to indicate pharmaceutical equivalents that provide **same therapeutic effect** when administered to **same individuals in same dosage regimens.**

- **The most common experimental plan to compare the bioavailability of two drug products :is simple crossover design study.**
- 12 to 24 individuals carefully matched subjects (usually healthy men aged 18 to 40 years and having similar height and weight) is administered both products under fasting conditions.
- each test subject is randomly assigned one of the two products for the first phase of the study.
- Once the first assigned product is administered, samples of blood or plasma are drawn from the subjects at predetermined times and analyzed for the active drug moiety and its metabolites as a function of time.
- The same procedure is then repeated (crossover) with the second product after an appropriate interval, that is, a washout period to ensure that there is no residual drug from the first administered product that would artificially inflate the test results of the second product. Afterward, the patient population data are tabulated and the parameters used to assess and compare bioavailability; that is, C_{max}, T_{max}, and AUC are analyzed with statistical procedures. Statistical differences in bioavailability parameters may not always be clinically significant in therapeutic outcomes.
- The value in the crossover experiment is that each individual serves as his own control by taking each of the products. Thus, inherent differences between individuals are minimized.

- **Absolute bioequivalency** between drug products **rarely occurs**. Such absolute equivalency would yield serum concentration-time curves for the products that would be exactly superimposable.
- This simply is not expected of products that are made at different times, in different batches, or indeed by different manufacturers.
- In most studies of bioavailability, the originally marketed product (**brand name drug product**) is recognized as the established product of the drug and is used as the **standard for the bioavailability** comparative studies.

- According to the FDA: generic drug is considered **bioequivalent if the rate and extent of absorption do not show a significant difference from that of standard drug when administered at the same molar dose of the therapeutic ingredient under the same experimental conditions**.
- Because in the case of a systemically absorbed drug blood levels even if from identical product may **vary in different subjects**, in bioequivalence studies each subject receives both the standard and the test drug and thus serves as his own control.

Under the **1984** act, to gain FDA **approval a generic drug product** must have these characteristics:

1. **The same active ingredients** as the standard drug .
2. **Identical strength**, **dosage form**, and **route of administration**
3. The **same indications** and **precautions** for use .

- **<u>Bioequivalency</u>**
- The same batch-to-batch requirements for **identity**, **strength**, **purity**, and **quality**
- If a standard manufacturer reformulates an FDA-approved product, the subsequent formulation must meet the same bioequivalency standards that are required of generic manufacturers of that product .

- The sampling time for blood and/or urine is usually at least three times the half-life of the active drug ingredient or therapeutic moiety, its metabolite(s), or at least three times the half-life of the acute pharmacological effect.
- Measured are the peak concentration in the blood and the total area under the curve

Multiple-dose bioavailability studies

Multiple dose bioavailability studies compare **test product** and **reference** after **repeated** administration to determine steady-state levels (Css) of drug in the body. Studies are conducted in human subjects in fasting or nonfasting state, depending upon the conditions reflected in the proposed labeling of the test product.

A multiple-dose study may be required for a test product if :

(a) there is a difference in **rate of absorption** but not in extent of absorption

(b) (b) there is excessive **variability in bioavailability** from subject to subject

(c) (c) the concentration of drug or its metabolites, in blood resulting from a single dose is too low

(d) (d) the drug product is an extended-release dosage form.

A multiple-dose study is generally **crossover in design** unless scientific reasons dictate otherwise (e.g., if the study is designed to establish pharmacokinetic profile of a **new drug product**, a **new drug delivery** system, or an **extended-release** dosage form). At least **five times the half-life** of active drug ingredient, its therapeutic moiety or its active metabolite(s) is measured in the blood or urine.

Conditions under which the FDA may waive in vivo bioavailability requirement are as follows:

1. If drug product is **parenteral, ophthalmic, or otic solution** and contains **same active agent** in **same concentration** and **solvent** as a product previously approved through a full NDA.
2. If drug product is administered by **inhalation** as a **gas or vapor and contains the same active agent** in the **same dosage form** as a product previously approved through a full NDA.
3. The drug product is an **oral solution, elixir, syrup, tincture**, or similar other solubilized form and contains the **same active** agent in the **same concentration** as a previously approved drug product through a full NDA and **contains no inactive ingredient** known to significantly affect absorption of the active drug ingredient.
4. The drug product is a **topically applied** preparation (e.g., ointment) intended for local therapeutic effect.
5. The drug product is an **oral** form that is **not intended to be absorbed** (e.g., antacid or radiopaque medium).
6. The drug product is a **solid oral** that is identical or similar to drug product that has met the in vivo bioavailability requirement

ROUTES OF DRUG ADMINISTRATION

- The difference in absorption between dosage forms is a function of the **formulation** and the **route of administration.**
- the **bioavailable fraction** is determined by the **fraction of drug that is absorbed** from the gastrointestinal tract and the fraction that escapes metabolism during its first pass through the liver.

ORAL ROUTE

- most drug absorbed from various surfaces along GIT.
- oral route is considered natural, uncomplicated, convenient, and safe means of administering drugs.
- **Disadvantages of the oral route** include:

1. **slow** response.
2. chance of **irregular absorption** of drugs, depending on factors : **amount or type of food** in GIT and **destruction of certain drugs by the acid** of stomach or by enzymes.

Dosage Forms Applicable

- tablets, capsules, suspensions, and various pharmaceutical solutions. Briefly, tablets contains medicinal substances with or without suitable diluents, disintegrants, coatings, colorants, and other pharmaceutical adjuncts.
- **Diluents** are fillers used to prepare tablets of the proper size and consistency.
- **Disintegrants** are used for the breakup or separation of the tablet's compressed ingredients. This ensures prompt exposure of drug particles to the dissolution process, enhancing drug absorption, .
- **Tablet coatings** are of several types and for several purposes. Some, called enteric coatings, are employed to permit safe passage of a tablet through the acid environment of the stomach, where certain drugs may be destroyed, to the more suitable juices of the intestines, where tablet dissolution safely takes place.
- Other coatings protect the drug substance from the destructive influences of moisture, light, and air during storage or to conceal a bad or bitter taste from the taste buds of a patient.

- **Capsules** are solid dosage forms contain, fillers, are enclosed in either a hard or a soft shell, .
- Drug materials are released from capsules **faster** than from tablets.
- Capsules of gelatin rapidly disfigured within GIT permitting the gastric juices to permeate and reach the contents.
- Also, **capsule-shaped and coated tablets**, called **caplets**, are increasingly used. These are easily swallowed, but their contents are sealed and protected from tampering like tablets.

- **Suspensions** aqueous vehicle, whereas those employed for other purposes may use a different vehicle. Suspensions of certain drugs to be used for intramuscular injection, for instance, may be maintained in a suitable oil.
- To be suspended, the drug particles must be insoluble in the vehicle. Nearly all suspensions must be **shaken before use** because they tend to settle.
- Suspensions are a **useful to administer large amounts of solid drugs** that would be inconvenient to take in tablet or capsule form. In addition, suspensions have the advantage over solid dosage forms in that they are presented to body in fine particle size, ready for dissolution immediately upon administration.

- Drugs administered in **aqueous solution are absorbed much more rapidly than those administered in solid form**.
- Pharmaceutical solutions may differ in type of solvent employed and fluidity characteristics.
- Among the solutions frequently administered orally are **elixirs,** which are solutions in a sweetened hydroalcoholic vehicle and are more mobile than water; **syrups**, which generally use a sucrose solution as the sweet vehicle, resulting in a viscous preparation; and solutions themselves, which officially are preparations in which the drug substance is dissolved predominantly in an aqueous vehicle and do not for reasons of their method of preparation (e.g., injections, which must be sterilized.

Absorption

- Absorption of drugs after oral administration may occur at various body sites between mouth and rectum.
- In general, the higher up a drug is absorbed along the **alimentary tract**, the more rapid will be its action, a desirable feature in most instances. Because of the differences in chemical and physical nature among drug substances, a given drug may be better absorbed from one site than from another in the alimentary tract.

- Sometimes the oral cavity is the absorption site. Physically, oral absorption of drugs is managed by allowing the drug substance to dissolve within the oral cavity with little or no swallowing until the taste of the drug has dissipated. This process is accommodated by providing the drug as extremely soluble and rapidly dissolving uncoated tablets.
- Drugs capable of being **absorbed in the mouth present** themselves to the absorbing surface in a much more concentrated form than when swallowed, because drugs become progressively more diluted with gastrointestinal secretions and contents as they pass along the alimentary tract.

The oral or sublingual

- **Nitroglycerin**, a coronary vasodilator used in the prophylaxis and treatment of **angina pectoris**, is available in the form of tiny **tablets that are allowed to dissolve under the tongue**, producing therapeutic effects a few minutes after administration. The dose of nitroglycerin is so small (usually 400 µg) that if it were swallowed,
- **nitroglycerin is rapidly destroyed by the liver through the first-pass effect.**
- Retaining drug substances in the mouth is unattractive because of the bitter taste of most drugs.

- Drugs **altered within the gastrointestinal** tract to render them less available for absorption. This may result from the **drug's interaction** with or **binding to** some **normal constituent of the gastrointestinal** tract or a **food** stuff or even **another drug**.
- For instance, the absorption of the **tetracycline** group of antibiotics is greatly interfered with by the simultaneous presence of **calcium**. Because of this, tetracycline drugs must not be taken with **milk** or other **calcium-containing foods** or **drugs**.

- **Gastric emptying time decreased** by presence of **fatty foods** or **lying on the back** when bedridden (lying on the right side facilitates passage in many instances), **or decreased, as by the presence of drugs** (e.g., morphine) .

- If a drug is administered in the form of a **solution**, it may be expected to pass into the intestines more rapidly than drugs administered in solid form.
- As a rule, **large volumes of water** facilitate gastric emptying and passage into the intestines.

- pH 1 in stomach, pH 8 at the far end of the intestines.
- **pH affect degree of ionization** of most drugs, and this in turn affects **lipid solubility**, **membrane permeability**, and **absorption**.
- **lipid-water partition coefficient and the pK_a** of the drugs are of prime importance to both the **degree and the site of absorption**.
- As a general rule, **weak acids** are **largely un-ionized in the stomach** and are absorbed fairly well from this site.
- weak bases are highly ionized in the stomach and are not significantly absorbed from the gastric surface.
- **Alkalinization of the gastric environment** by artificial means (simultaneous administration of alkaline or **antacid drugs**) would be expected to **decrease the gastric absorption of weak acids** and to **increase that of weak bases**. Strong acids and bases are generally poorly absorbed because of their high degree of ionization.

- The **small intestine** is the **major absorption pathway** for drugs because:

1. **suitable pH .**
2. **great surface area available** for drug absorption along its approximately 20-foot length.
3. Presence of drug for large time

The pH of intestine lumen is 6.5 and **both weakly acidic and weakly basic drugs are well absorbed** from intestinal surface, which behaves in the ionization and distribution of drugs between it and the plasma on the other side of the membrane as though its pH were 5.3

RECTAL ROUTE

- drugs are administered rectally for their **local** effects or **systemic** effects.
- The composition of the **suppository base**, can influence the degree and **rate of drug release** and should be selected on an individual basis for each drug.
- The use of **rectal ointments** is generally limited to treat of **local conditions**.
- Rectal solutions are usually employed as **enemas or cleansing** solutions.

- **The rectum and colon can absorb many soluble drugs.**
- **Rectal** administration for **systemic action** preferred for **drugs destroyed or inactivated by** the environments of the **stomach and intestine**s.
- rectal route also indicated when oral route is precluded because of **vomiting** or when the patient is **unconscious** or **incapable of swallowing**.
- Colon Protect from first pass effect

PARENTERAL ROUTE

1. **disadvantage of parenteral is that once the drug is injected, there is no retreat.**
2. Drugs in **solution** act more **rapidly** than drugs in **suspension**,
3. with an **aqueous vehicle** providing **faster** action in each instance than an **oleaginous vehicle**.
4. **suspension of a drug in a vegetable oil slowly absorbed than an aqueous solution** of the same drug.

- **Slow absorption means prolonged drug action** is referred to as a **depot** or repository injection, because it provides a storage **reservoir** of the drug substance within the body from which it is **slowly removed** into the systemic circulation.
- the use of **subcutaneous implantation** of **compressed tablets**, termed pellets, slowly dissolved, releasing their medication at a fairly constant rate **over several weeks to many months.**

Subcutaneous Injections

1. prepared **as aqueous solutions or suspensions** administered **small volumes, 2 mL** or less.
2. **blood supply to the site of injection is an important** .
3. the more the capillaries, the more surface area for absorption and the faster the rate of absorption.
4. The **addition of a vasoconstrictor** to the injection formulation (or its prior injection) **will diminish drug absorption** by causing constriction of the blood and reducing blood flow and the capacity for absorption.

This principle is used in the administration of local anesthetics by use of the vasoconstrictor epinephrine.

- Conversely, **vasodilators** may be used to enhance subcutaneous absorption by increasing blood flow to the area.

Physical exercise can also influence the absorption of drug from an injection site

Intramuscular Injections

1. Intramuscular injections are performed deep into the **skeletal muscles.** Drugs that are irritating to **subcutaneous** tissue are often administered **intramuscularly.**
2. **Aqueous or oleaginous solutions or suspensions** may be used intramuscularly.
3. volumes (**2 to 5 mL**). When a volume greater than 5 mL is to be injected, it is frequently administered in divided doses to two injection sites. Injection sites are best rotated when a patient is receiving repeated injections over time.
4. Certain drugs, because of their inherent **low solubility**, provide **sustained drug** action after an **intramuscular injection.**

For instance:one deep intramuscular injection of a suspension of **penicillin G benzathine** results in effective blood levels of the drug for **7 to 10 days**. Addition of decanoate ester decreases the solubility of haloperidol and, extends haloperidol's t½ from 18 hours orally to 3 weeks, an advantage in antipsychotic drug

Intravenous Injections

aqueous solution is injected directly into the **vein** at a rate commensurate with efficiency, safety, comfort to patient, and the desired duration of drug response.

Drugs may be administered intravenously as a **single, small-volume** or as a **large-volume** **slow intravenous drip** infusion. Intravenous injection allows the desired blood level of drug to be achieved in an optimal and quantitative manner.

Intravenous injections are usually made into the veins of the forearm and are especially useful in **emergencies** when immediate drug response is desired. It is essential that the drug be maintained in **solution** after injection and not be precipitated within circulatory system, an event that might produce **emboli.** Because of a fear of the development of **pulmonary embolism**, oleaginous vehicles are not usually intravenously administered. However, an **intravenous fat emulsion** is used for patients receiving parenteral **nutrition**.

ocular, oral, otic, and nasal routes

- Drugs are frequently applied topically to **eye, ear, and mucous membranes of nose**, usually as **ointments**, **suspensions**, and **solutions**.
- Ophthalmic solutions and suspensions are sterile aqueous preparations with other ingredients essential to the safety and comfort of the patient. Ophthalmic ointments must be sterile and free of grit.
- **Ocusert**, is an elliptical unit designed for **continuous release** of **pilocarpine** following placement in the **cul-de-sac of the eye**.
- Most **nasal** preparations are **solutions or suspensions** administered by **drops or as a fine mist**.
- **Ear preparations** are usually **viscid** so that they have **prolonged contact** with the affected area.
- **Eye, ear, and nose** preparations usually are **not used for systemic** effects

other routes

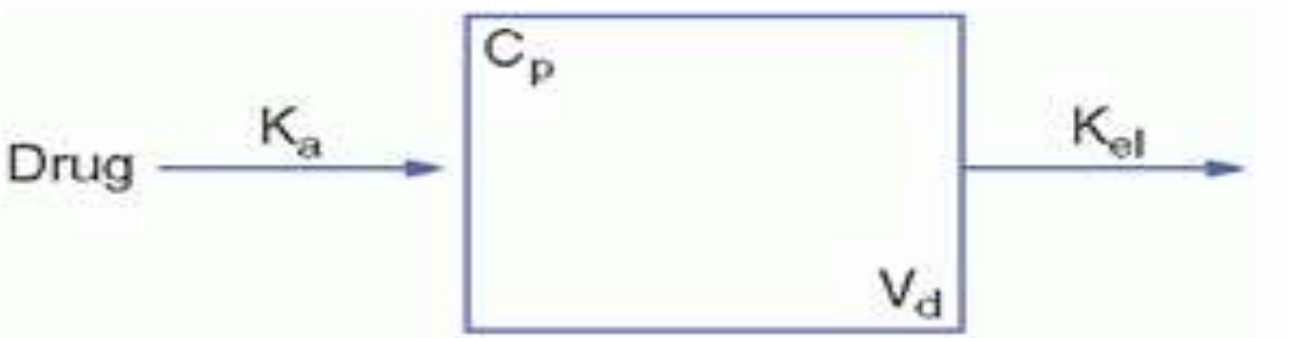
- **lungs** provide an excellent absorbing surface for administration of **gases** and for **aerosol** mists of **very minute particles of liquids or solids**.
- **rich capillary area** of **alveoli** of the lungs, covers nearly 1000 square feet, **provides rapid absorption** and drug effects comparable in speed with those following **intravenous** injection.
- In the case of drug particles, their size largely determines the depth to which they penetrate the alveolar regions and their solubility, the extent to which they are absorbed.
- **Soluble drug particles** that are approximately **0.5 to 1.0 mm** in size reach the **minute alveolar sacs** and are most prompt and efficient in providing **systemic effects**.
- Particles smaller than **0.5 mm** are **expired** to some extent, and thus, their absorption is not total but variable. Particles **1 to 10 mm** effectively reach the **terminal bronchioles** and to some extent the alveolar ducts and are favored for **local therapy**. Therefore, in the pharmaceutical manufacture of aerosol sprays for inhalation therapy, the manufacturers not only must attain the proper drug particle size but also must ensure their uniformity for consistent penetration of the pulmonary tree and uniform effects.

- **Bound drug** is **neither exposed to metabolism** nor filtered through the **renal glomeruli**.
- Bound drug is inactive portion in the blood.
- unbound drug, with its ability to penetrate cells, is active blood portion.
- The bound portion of drug serves as a reservoir or depot from which the drug is released as the free form when the level of free drug in the blood no longer is adequate to ensure protein saturation.

PHARMACOKINETIC PRINCIPLES

- Simplest pharmacokinetic model is **one compartment** open-model system.
- This model depicts the body as one compartment characterized by **volume of distribution (V_d)** that remains constant. Each drug has its own distinct volume of distribution, and this influenced by **age** and **disease**.
- the drug is absorbed at a certain rate and is characterized by **absorption rate constant K_a**. Finally, the drug is eliminated from the compartment at a certain rate that is characterized by an **elimination rate constant, K_{el}.**

volume of distribution, V_d, a proportionality constant that refers to the volume into which the total amount of drug in the body must be uniformly distributed to provide the concentration of drug actually measured in plasma or blood.



Where:
C_p is the drug concentration in plasma
V_d is the volume of the compartment or volume of distribution

FIGURE 5.12 A one-compartment system.

- It is influenced by the **plasma protein binding** and **tissue binding of a drug.**
- the total amount of drug in the body (Q_b) can be calculated from the following equation:

$$Q_b = [C_p^0][V_d]$$

$$\text{Log } C_p = \text{Log } C_p^0 - K_d / 2.303(t)$$

two-compartment model

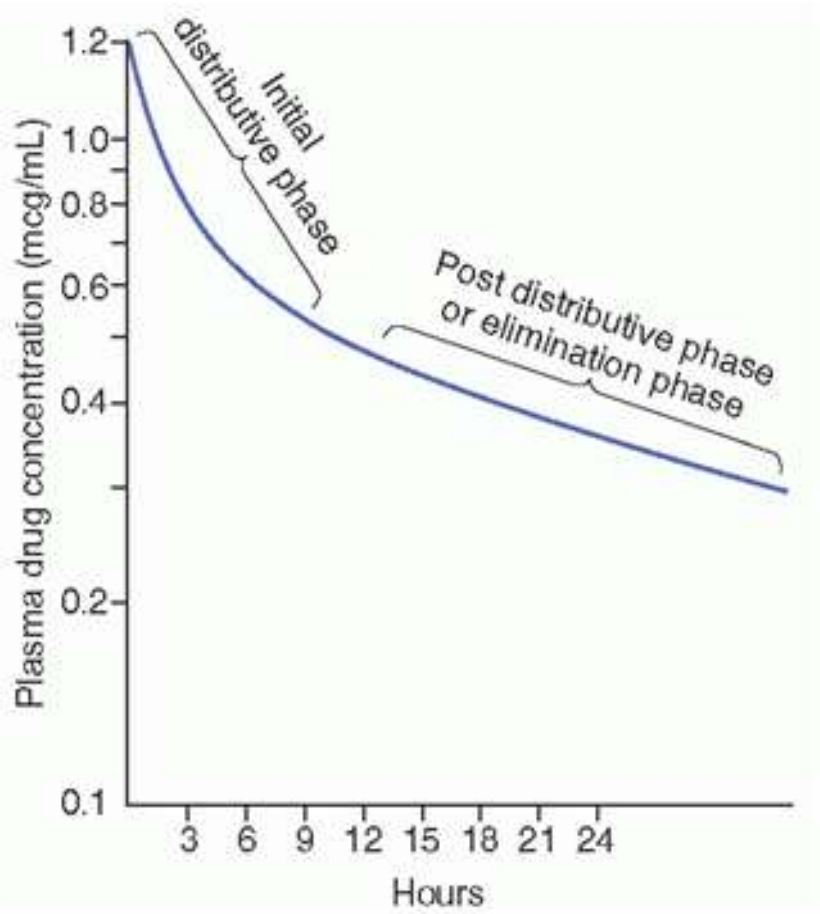
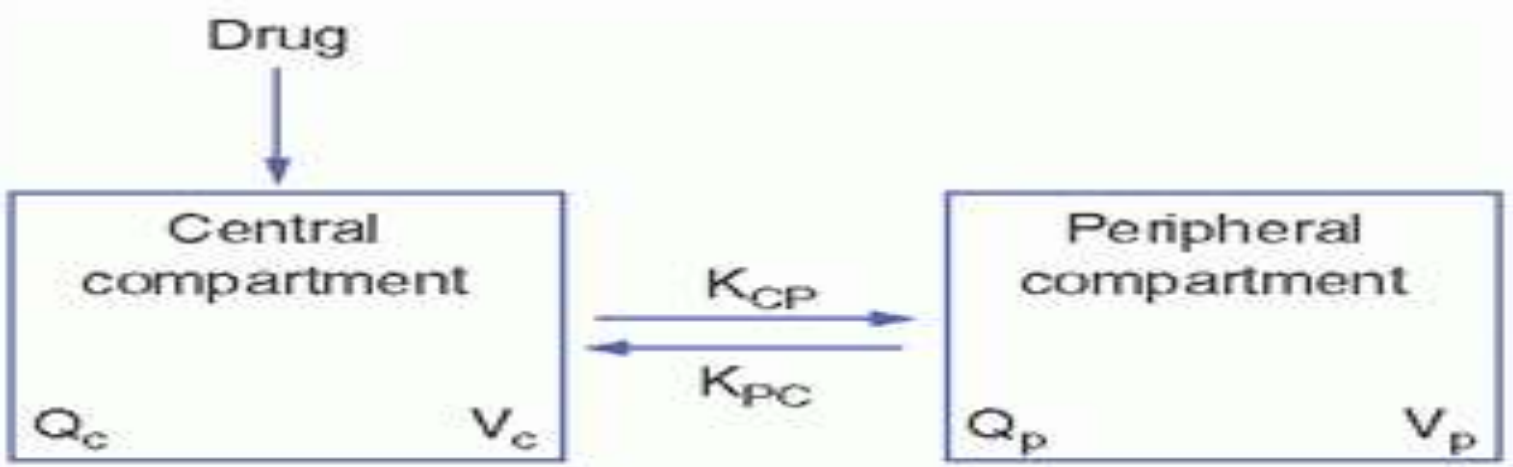


FIGURE 5.14 A semilogarithmic plot of plasma concentration versus time of an intravenous drug that follows first-order two-compartment



Where:
Q_c = Quantity of drug in central compartment
V_c = Volume of the central compartment
Q_p = Quantity of drug in peripheral compartment
V_p = Volume of the peripheral compartment

FIGURE 5.15 A two-compartment system.

- **In two-compartment system**: a drug enters and distributed throughout the central compartment. Its subsequent distribution into second or peripheral compartment is slower.
- The central compartment is usually blood, the extracellular space, and organs **with good blood perfusion**, such as lungs, liver, kidneys, and heart.
- The peripheral compartment usually comprises tissues and organs that are **poorly perfused by blood**, such as skin, bone, and fat.

HALF-LIFE

- The half-life ($T_{1/2}$) of a drug is the time required for a drug's blood or plasma concentration to decrease by half.
- T1/2= 0.693/k
- Clearance: Cl=Vd× k

CHAPTER 4

Besides providing the mechanism for safe and convenient delivery of accurate dosage, dosage forms are needed 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 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.
- 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 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.**

EXCIPIENTS

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

- **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

- **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.

1. **cocoa-flavored** masking bitter.
2. Fruit or citrus flavors sour or acid-tasting.
3. cinnamon, orange, raspberry, make preparations of salty drugs
4.

- B: The age

1. **Children prefer sweet candy-like with fruity flavors.**
2. **Adults prefer less sweet with tart flavor**.
3. soybean and oils; 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**

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

- **saccharin** excreted **unchanged** by kidneys.
- **Cyclamate**, is **metabolized**, in GIT, and excreted by kidneys.
- **Aspartame** breaks down to three basic components: amino acids **phenylalanine** and **aspartic acid**, and **methanol**. are metabolized through regular pathways in the body.

- metabolism to phenylalanine.
- use of aspartame by persons with **phenylketonuria** (PKU) is discouraged.
- diet foods and drinks must bear label **warning** not be consumed by such individuals.
- 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.

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

- 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, dry heat at 180°C for 1 hour, or bacterial filtration) 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 acid media and 18% V/V in alkaline media.**
- elixirs, spirits, and tinctures, are self-sterilizing and do not require additional preservation.

PRESERVATIVE SELECTION SHOULD

- **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 conc 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.

- 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 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.