

BIOPHARMACEUTICS

(Introduction)

Dr. Ahmed Faisal

Drug Product Performance

Drugs are **substances** intended for **use** in the diagnosis, cure, mitigation, treatment, or prevention of disease.

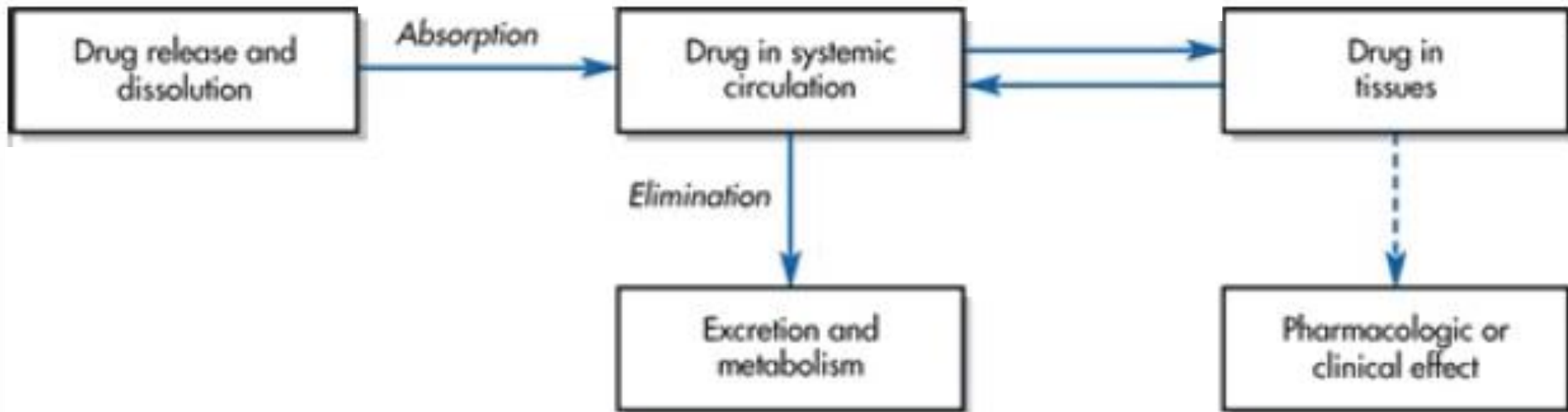
Given in a **variety** of **dosage forms**: solids (tablets, capsules), semisolids (ointments, creams), liquids, suspensions, emulsions, etc, for **systemic** or **local** therapeutic activity.

Drug product performance is the **release** of **drug** substance **from** the **drug product** either for **local** drug action **or** for drug **absorption** into the **plasma** for **systemic** therapeutic activity.

It **should** be **focused** on **developing** quality drug **products** that are **safer**, more **effective**, and more **convenient** for the patient.

Biopharmaceutics

Examines the interrelationship of the physical/chemical properties of the drug, the dosage form, and the route of administration on the rate and extent of systemic drug absorption.



Scheme demonstrating the dynamic relationship between the drug, the drug product, and the pharmacologic effect

First, the **drug** in its dosage form is **taken** by the patient either **by** an oral, intravenous, subcutaneous, transdermal, etc, **route** of **administration**.

Next, the **drug** is **released** from the **dosage form** in a predictable and characterizable manner.

Then, some fraction of the drug is **absorbed** from the **site** of **administration** into either the surrounding tissue, into the body (as with oral dosage forms), or both.

Finally, the drug **reaches** the **site** of **action** (A pharmacologic **response** results when the **drug concentration** at the site of action **reaches** or **exceeds** the minimum effective concentration (**MEC**)).

This sequence of **events** is **affected** by the design of the **dosage form** and the **physicochemical properties** of the drug.

Biopharmaceutical Considerations in Drug Product Design

Items	Considerations
Therapeutic objective	Drug is intended for rapid relief of symptoms, slow extended action given once per day (week or longer), or chronic use; is drug for local action or systemic action
Drug (active pharmaceutical ingredient, API)	Physical chemical properties of API, including solubility, polymorphic form, particle size
Route of administration	Oral, topical, parenteral, transdermal, inhalation, etc
Drug dosage and dosage regimen	Large or small drug dose, frequency of doses, patient acceptance of drug product, patient compliance
Type of drug product	Orally disintegrating tablets, immediate release tablets, extended release tablets, transdermal, topical, parenteral, implant, etc
Excipients	Although very little pharmacodynamic activity, excipients affect drug product performance including release of drug from drug product
Method of manufacture	Variables in manufacturing process, including weighing, blending, release testing, sterility

Thus, **biopharmaceutics** involves **factors** that **influence**:

- (1) the **design** of the drug product,
- (2) **stability** of the drug within the drug product,
- (3) The **manufacture** of the drug product,
- (4) the **release** of the drug from the drug product,
- (5) the **rate of dissolution/release** of the drug at the **absorption site**, and
- (6) **delivery** of drug to the **site of action**, which may involve **targeting** a localized area (eg, colon for Crohn's disease) for action or systemic absorption of the drug.

The **study** of **biopharmaceutics** is **based** on fundamental **scientific principles** and **experimental** methodology.

Studies in biopharmaceutics **use** both **in vitro** and **in vivo** methods.

In vitro methods are procedures employing test apparatus and equipment **without** involving laboratory **animals** or **humans**.

In vivo methods are more complex studies **involving** **human** subjects or laboratory **animals**.

These **methods** must be able to **assess** the impact of the **physical** and **chemical properties** of the drug, drug **stability**, and **large-scale production** of the drug and drug product on the **biologic performance** of the drug.

Pharmacokinetics

After a drug is **released** from its **dosage form**, the drug is **absorbed** into the **surrounding tissue**, the **body**, or both.

The **distribution** through and **elimination** of the drug in the body **varies** for **each patient** but can be **characterized** using **mathematical** models and **statistics**.

Pharmacokinetics is the **science** of the **kinetics** of drug **absorption**, **distribution**, and **elimination** (ie, metabolism and excretion).

Characterization of drug **disposition** (distribution and elimination) is an **important** for **determination** or **modification** of **dosing regimens** for individuals and groups of patients.

Clinical Pharmacokinetics

During the drug development process, large numbers of **patients** are **tested** by the manufacturer to **determine** optimum **dosing regimens**, which are then recommended in the package insert to **produce** the **desired pharmacologic response** in the majority of the anticipated patient population.

However, **intra** and **inter** individual **variations** will frequently **result** in **either** a **subtherapeutic** (drug concentration below the MEC) or **toxic response** (drug concentrations above the minimum toxic concentration, MTC), which may **then require adjustment** to the **dosing regimen**.

Clinical pharmacokinetics is also **applied** to therapeutic drug monitoring (**TDM**) for very **potent drugs**, such as those with a **narrow therapeutic range**, in order to **optimize efficacy** and to **prevent** any adverse **toxicity**.

For these drugs, it is **necessary** to **monitor** the patient, **either** by monitoring plasma **drug concentrations** (eg, theophylline) **or** by monitoring a specific **pharmacodynamic endpoint** such as prothrombin **clotting time** (eg, warfarin).

Some **drugs frequently monitored** are the **aminoglycosides** and **anticonvulsants**. Other drugs closely monitored are those used in **cancer chemotherapy**, in order to minimize adverse side effects.

Relationship of Drug Concentrations to Drug Response

The **initiation of drug therapy** starts with the **manufacturer's recommended dosage regimen** that **includes the drug dose and frequency of doses** (eg, 100 mg every 8 hours).

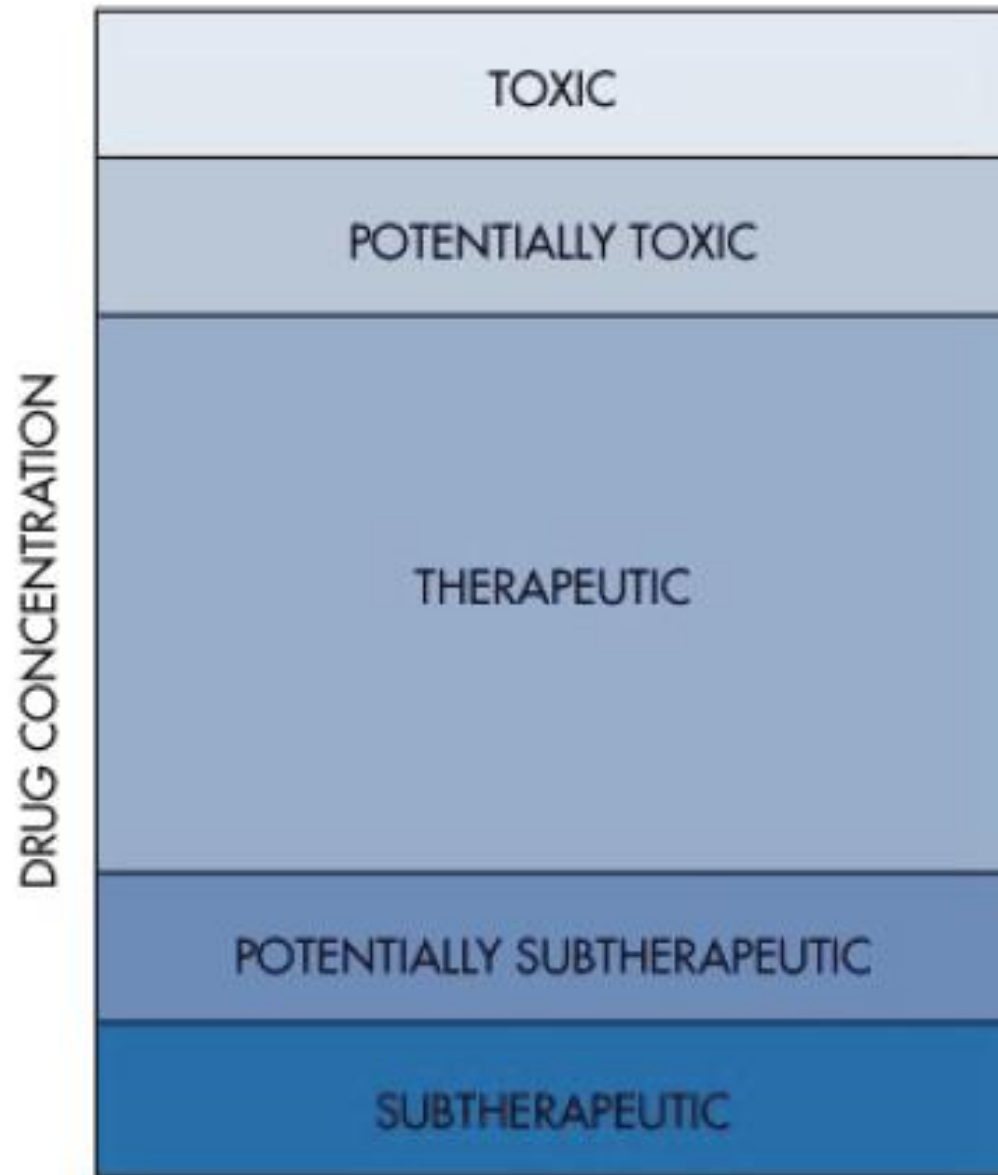
Due to individual differences in the patient's genetic makeup or pharmacokinetics, the **recommended dosage regimen** drug **may not** provide the **desired therapeutic outcome**.

The **measurement of plasma drug concentrations** can **confirm** whether the **drug dose** was **subtherapeutic** due to the patient's individual pharmacokinetic profile (observed by **low plasma drug concentrations**) or was **not responsive** to **drug therapy** due to genetic difference in receptor response. In this case, the **drug concentrations** are in the **therapeutic range** but the **patient** does **not respond** to drug treatment.

In contrast, **some** patients **respond** to drug treatment at **lower** drug **doses** that results in lower drug concentrations.

Other patients may need **higher** drug **concentrations** to **obtain** a **therapeutic effect** which requires higher drug doses.

It is **desirable** that **adverse** drug **responses** occur at drug **concentrations higher** relative to the **therapeutic** drug **concentrations**, **but** for many **potent drugs**, **adverse effects** can also **occur close** to the same drug **concentrations** as **needed** for the **therapeutic effect**.



Relationship of drug concentrations to drug response

Pharmacodynamics

Pharmacodynamics refers to the **relationship** between the **drug concentration** at the **site of action** (receptor) and **pharmacologic response**, including biochemical and physiologic effects that influence the interaction of drug with the receptor.

The **interaction** of a **drug** molecule **with** a **receptor** causes the **initiation** of a sequence of molecular **events** resulting in a **pharmacologic** or **toxic response**.

Drug Exposure and Drug Response

Drug exposure refers to the **dose** (drug input to the body) and various measures of acute or integrated **drug concentrations** in **plasma** and other biological fluid (eg, C_{max} , C_{min} , C_{ss} , AUC).

Drug response refers to a direct measure of the **pharmacologic effect** of the drug.

Toxicologic and efficacy studies provide information **on** the **safety** and **effectiveness** of the **drug** during development and in **special patient** populations such as subjects with **renal** and **hepatic insufficiencies**.

For many drugs, clinical use is based on weighing the risks of favorable and unfavorable outcomes at a particular dose.

For some potent drugs, the **doses** and **dosing rate** may **need** to be **titrated** in order to **obtain** the **desired effect** and be **tolerated**.

Question

BIOPHARMACEUTICS & PHARMACOKINETICS

Dr. Ahmed Faisal

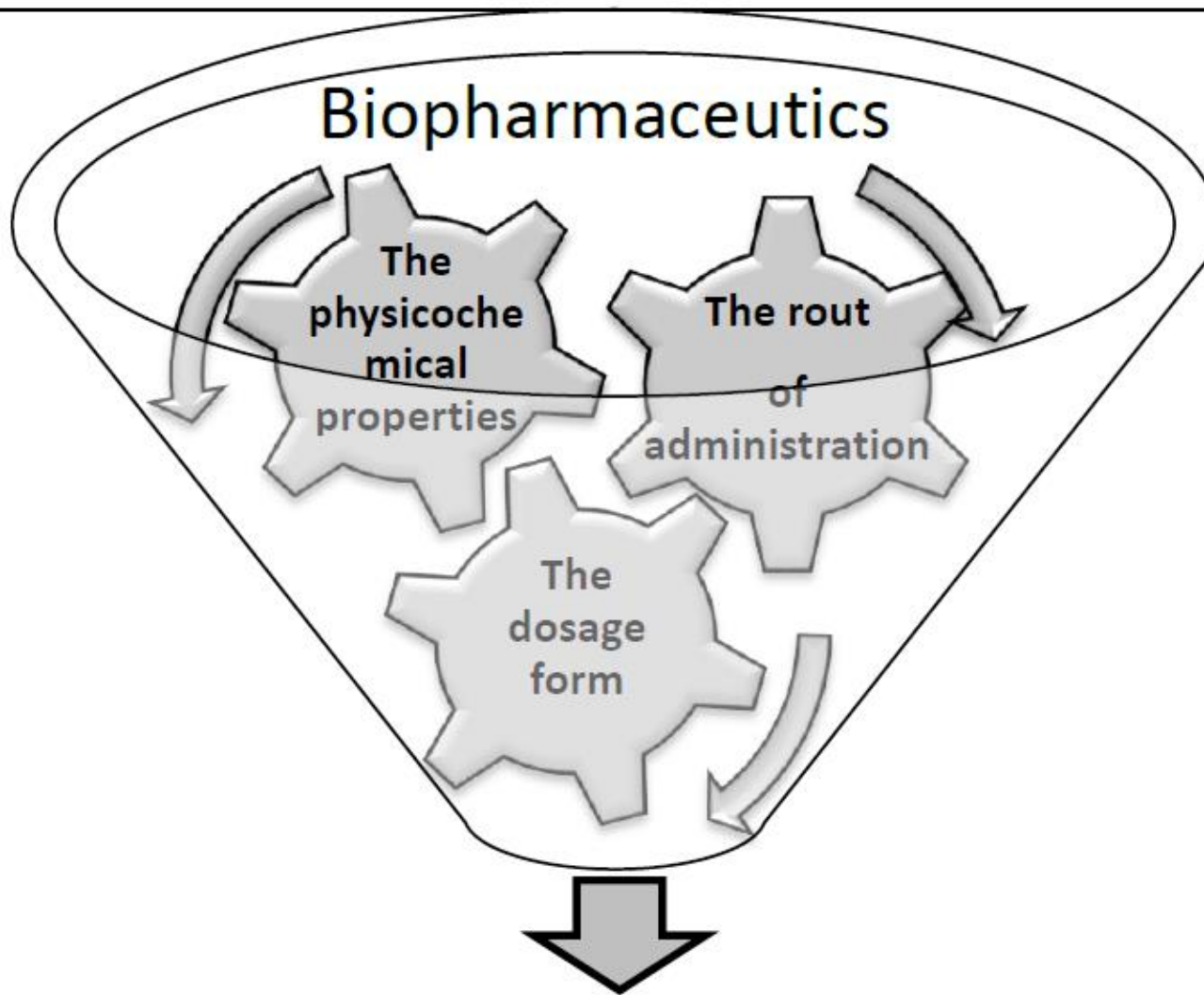
General Concepts in Biopharmaceutics and Pharmacokinetics

Biopharmaceutics

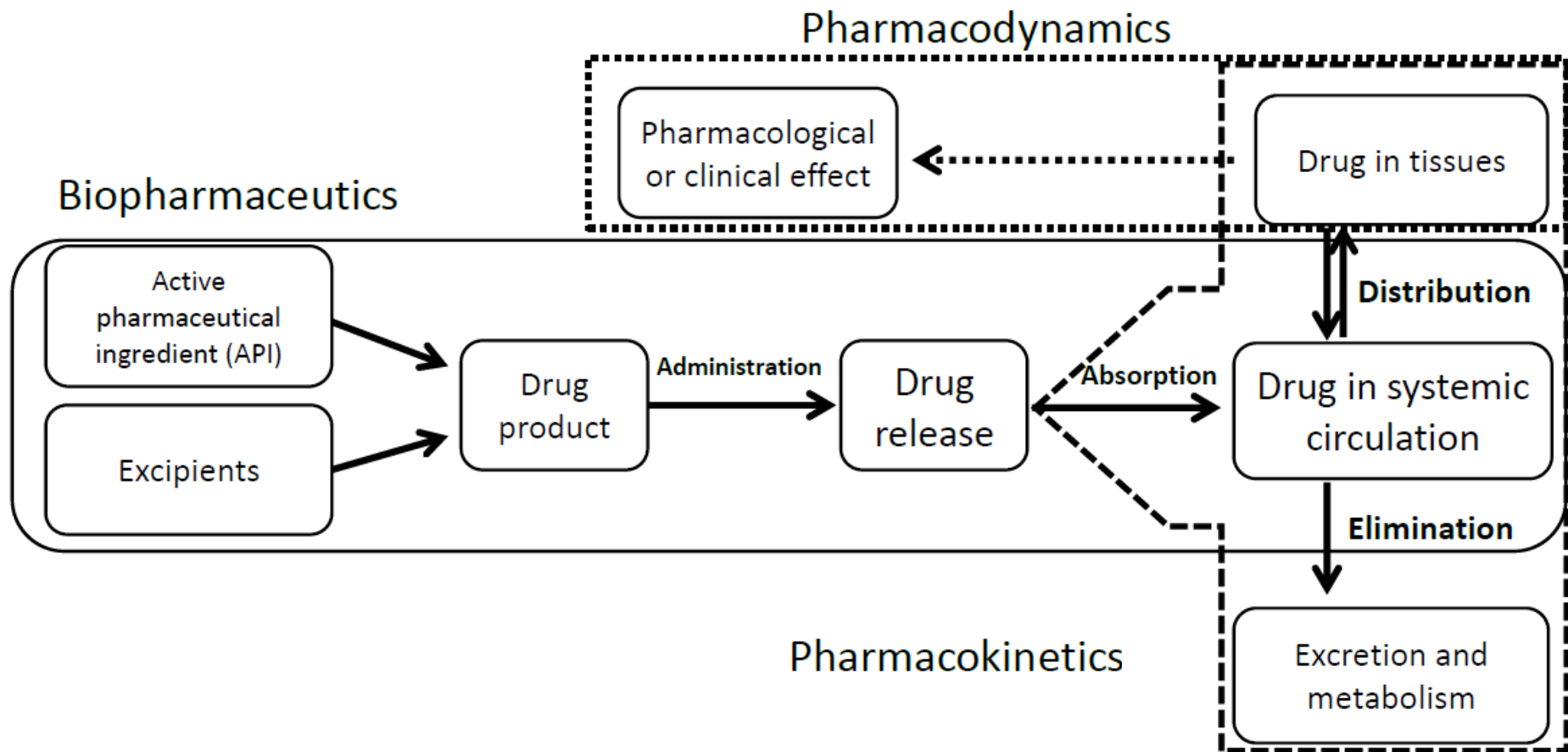
In biopharmaceutics we will study the factors that affect the entry of the drug to the body

Pharmacokinetics

In pharmacokinetics we will study the kinetics (rate and extent) of drug movement in the body



Rate and extent of systemic drug absorption



Biopharmaceutical Aspects of Products

Drugs are **not** generally given as **pure chemical** drug substances but are formulated into finished dosage forms (drug products) before being administered to patients for therapy.

Formulated drug products usually include the **active** drug **substance** and **selected ingredients** (*excipients*) that make up the dosage form.

Drug products are designed to deliver drug for **local** or **systemic** effects.

Common **drug products include** liquids, tablets, capsules, injections, suppositories, transdermal, and topical products such as creams and ointments.

Biopharmaceutics directly correlates with the **bioavailability** of the drug.

Bioavailability represents the **fraction** of the administered dose that reaches the systemic blood circulation.

Because the systemic blood circulation delivers therapeutically active drug to the tissues and to the site of action of the drug, **changes in bioavailability** affect changes in the pharmacodynamics and toxicity of a drug.

The **aim of biopharmaceutics** is to adjust the delivery of drug from the drug product in such a manner as to provide **optimal therapeutic activity** and **safety** for the patient.

Drug Absorption

Major considerations in the design of a drug product include the therapeutic objective, the application site, and systemic drug absorption from the application site.

Absorption can be defined as the transfer of a drug from its site of administration to the blood stream.

If the drug is intended for **systemic activity**, the drug should ideally be completely and consistently absorbed from the application site.

In contrast, if the drug is intended for **local activity**, then systemic absorption from the application should be minimal to prevent systemic drug exposure and possible systemic side effects.

For **extended-release** drug products, the drug product should remain at or near the application site and then slowly release the drug for the desired period of time.

The systemic absorption of a drug is **dependent** on **(1)** the physicochemical properties of the drug, **(2)** the nature of the drug product, and **(3)** the anatomy and physiology of the drug absorption site.

Route	Bioavailability
Parenteral Routes	
Intravenous bolus (IV)	Complete (100%) systemic drug absorption. Rate of bioavailability considered instantaneous.
Intravenous infusion (IV inf)	Complete (100%) systemic drug absorption. Rate of drug absorption controlled by infusion rate.
Subcutaneous injection (SC)	Prompt from aqueous solution. Slow absorption from repository formulations.
Intradermal injection	Drug injected into surface area (dermal) of skin.
Intramuscular injection (IM)	Rapid from aqueous solution. Slow absorption from nonaqueous (oil) solutions.
Intra-arterial injection	100% of solution is absorbed.
Intrathecal Injection	100% of solution is absorbed
Intraperitoneal injection	In laboratory animals, (eg, rat) drug absorption resembles oral absorption.
Enteral Routes	
Buccal or sublingual (SL)	Rapid absorption from lipid soluble drugs.
Oral (PO)	Absorption may vary. Generally, slower absorption rate compared to IV bolus or IM injection.
Rectal (PR)	Absorption may vary from suppository. More reliable absorption from enema (solution).
Other Routes	
Transdermal	Slow absorption, rate may vary. Increased absorption with occlusive dressing.
Inhalation and intranasal	Rapid absorption. Total dose absorbed is variable.

Common Routes of Drug Administration

Nature of cell membrane

Drugs that are administered by **extravascular** routes (eg, oral, topical, intranasal, inhalation, rectal) are either designed for local effect or designed to be absorbed from the site of administration into the systemic circulation.

For systemic drug absorption, the drug has to **cross cellular membranes** to reach the site of action.

The general principles and kinetics of absorption from these extravascular sites follow the same **principles** as **oral dosing**, although the physiology of the site of administration differs.

The permeability of a drug at the absorption site into the systemic circulation is mainly related to (1) the molecular structure and properties of the drug and to (2) the physical and biochemical properties of the cell membranes.

Once in the plasma, the drug may act directly or have to cross biological membranes (biomembranes) to reach the site of action.

Therefore, biological membranes represent a significant **barrier** to drug delivery.

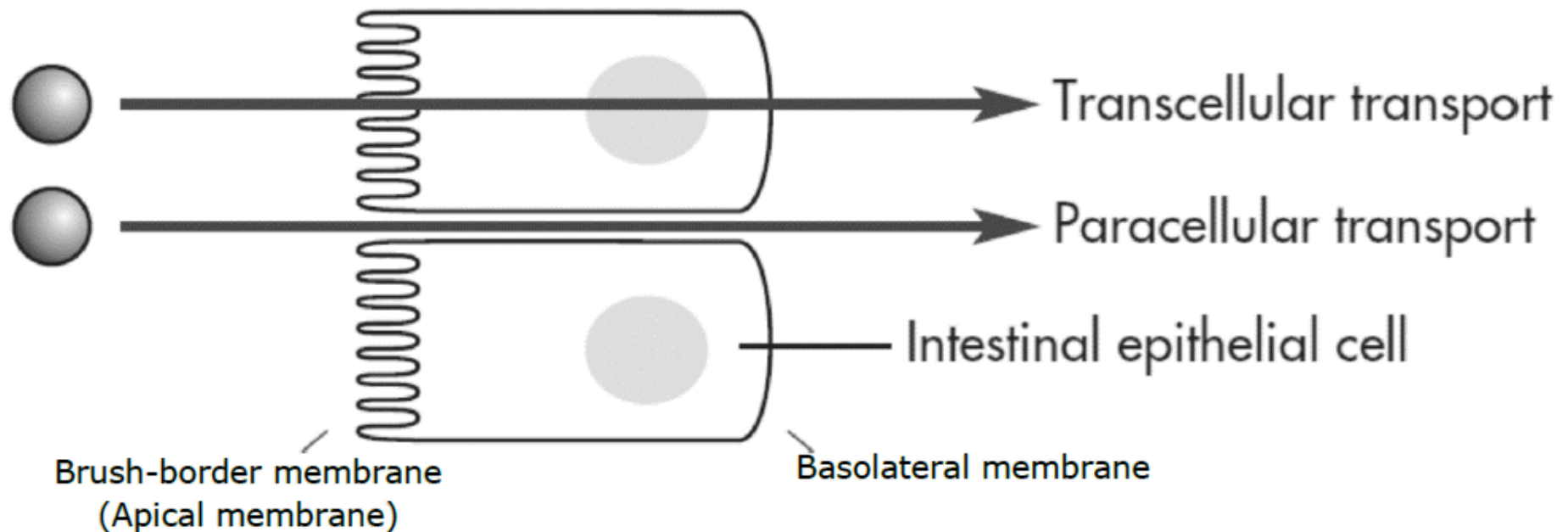
Epithelial and endothelial membrane barriers separate the body from its environment and individual body compartments from each other.

- The **epithelium** is a membrane tissue that **covers** almost all **body surfaces** such as the skin, lungs, nasal cavity, buccal cavity, intestine, and other body cavities.
- The **endothelium** consists of thin layer of cells that lines the **interior surface of blood vessels**.

The basic structure of cellular membranes is the lipid bilayer, composed of double layer of phospholipids, with occasional proteins, some of these **proteins function** as channel formers, drug transporters, or drug-metabolizing enzymes.

Transport mechanisms of drugs through biomembranes

- **Transcellular transport** is the process of drug movement across a cell.
- **Paracellular transport** is the process of drug movement through gaps or tight junctions between cells. Usually limited to drug molecules smaller than 500 MW.



Transport mechanisms across cell membranes, epithelial cells (enterocytes) of the GIT as example

Passage of Drugs across Cell Membrane

1. PASSIVE DIFFUSION

Passive diffusion is the process by which molecules spontaneously diffuse from a region of higher concentration to a region of lower concentration.

This process is *passive* because **no external energy** is expended.

Drug molecules can move forward and back across a membrane; the net movement of molecules depends on the concentration differences on both sides of the membrane.

Passive diffusion is the **major absorption process** for most drugs. The driving force for passive diffusion is higher drug concentrations, typically on the mucosal side compared to the blood as in the case of oral drug absorption. According to ***Fick's law of diffusion***, drug molecules diffuse from a region of high drug concentration to a region of low drug concentration.

$$\frac{dQ}{dt} = \frac{DAK}{h} (C_{GI} - C_p) \dots\dots\dots \text{Fick's law of diffusion}$$

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

Notes:

- Once the drug is absorbed to the blood it distributes rapidly into a large volume. The concentration in the blood will be quite low with respect to the concentration at the site of drug administration. For example, a drug is usually given in milligram doses, whereas plasma concentrations are often in the $\mu\text{g/mL}$ or ng/mL range. If the drug is given orally, then $C_{\text{GI}} \gg C_p$ and a large concentration gradient is maintained until most of the drug is absorbed, thus driving drug molecules into the plasma from the gastrointestinal tract.

- Drugs that are more lipid soluble have a larger value of K .
- The surface area, A , of the membrane also influences the rate of absorption. The duodenal area of the small intestine shows the most rapid drug absorption, due to such anatomic features as villi and microvilli, which provide a large surface area. These villi are less abundant in other areas of the gastrointestinal tract.
- The thickness of the membrane, h , affects the diffusion. Drugs usually diffuse very rapidly through capillary plasma membranes in the vascular compartments, in contrast to diffusion through plasma membranes of capillaries in the brain (the brain has a thicker lipid membrane).

- The diffusion constant, D , is constant for each drug.
- Because D , A , K , and h are constants under usual conditions for absorption, a combined constant P or permeability coefficient can be used instead.

$$P = \frac{DAK}{h}$$

- The drug concentration in the 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 into the equation, the following relationship for Fick's law is obtained:

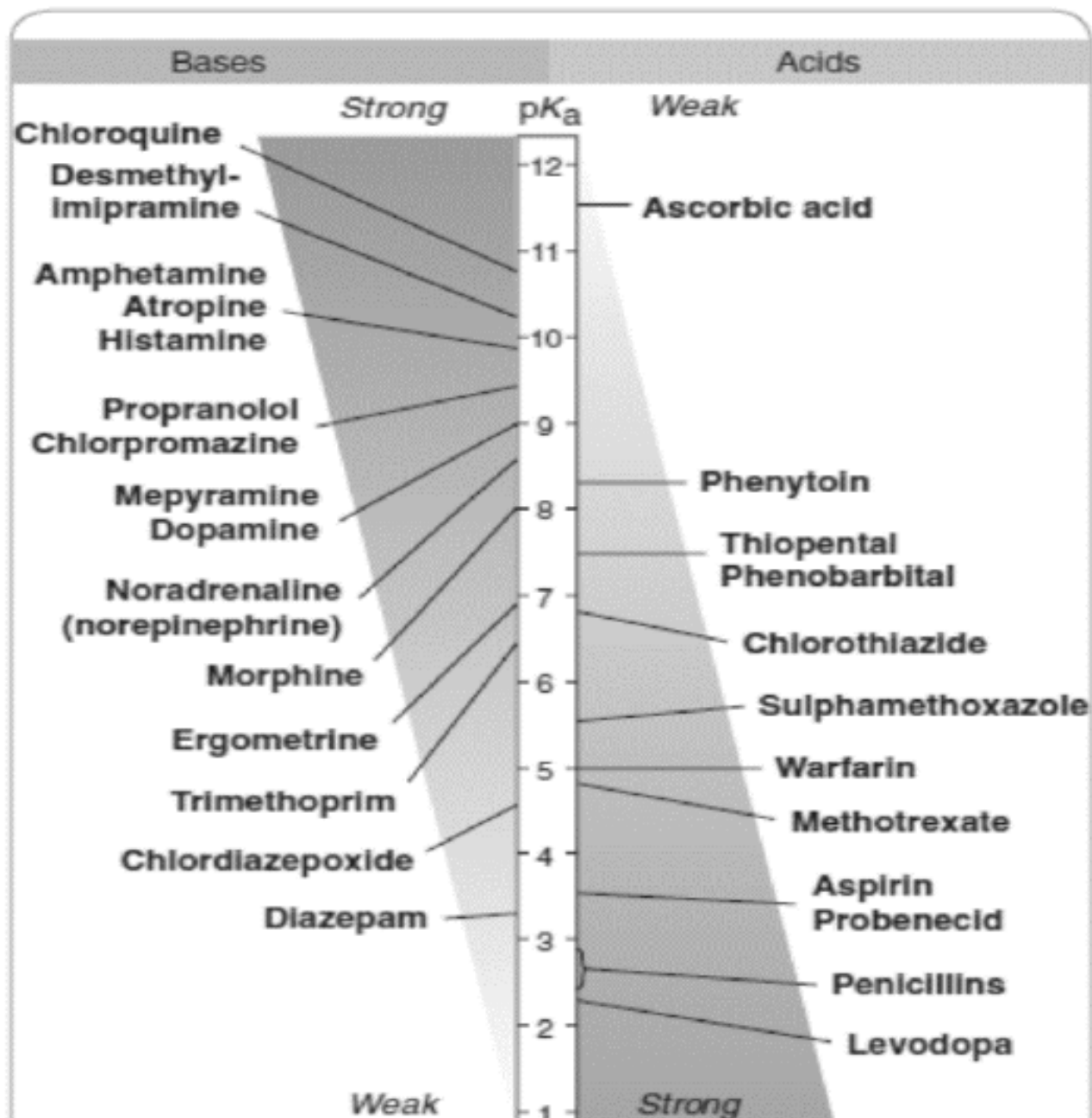
$$\frac{dQ}{dt} = P (C_{GI})$$

Factors affecting the drug diffusion across biomembranes

Effect of pH and the extent of ionisation on diffusion

Many drugs act as weak electrolytes, such as weak acids and bases, the extent of ionization influences the drug's diffusional permeability. Weak electrolytes exist in both unionised and ionised form, the ratio of the two forms varying with pH.

- The ionized form of the drug contains a charge and is water soluble and has very low lipid solubility.
- The non-ionised form of the drug is more lipid soluble and in most cases this lipid solubility is sufficient for membrane permeation.



pKa values for some acidic and basic drugs

The affinity of the drug for a tissue component

Binding or uptake of the drug by a tissue component prevents the drug from moving freely across the membrane. Examples of binding include:

1. Binding to plasma or tissue proteins;

- Dicumarol binds to plasma proteins.
- Digoxin binds to tissue proteins.

2. Partitioning to the adipose tissues;

- Chlordane is a very lipid soluble drug and will partition to adipose (fat) tissues.

3. Complexation with a tissue component;

- Tetracycline forms a complex with calcium in the bones and teeth.

4. Active transport uptake by the tissue;

- Uptake of iodide by the thyroid tissue.
- Some catecholamines into adrenergic storage sites.

2. CARRIER-MEDIATED TRANSPORT

This mechanism of drug transport across the cell membrane involve the use of drug transporter (carrier).

- Uptake (influx) transporters move drug to the blood and increase plasma concentration.
- Efflux transporters move drug back to the lumen (GIT for example) and decrease plasma concentration.

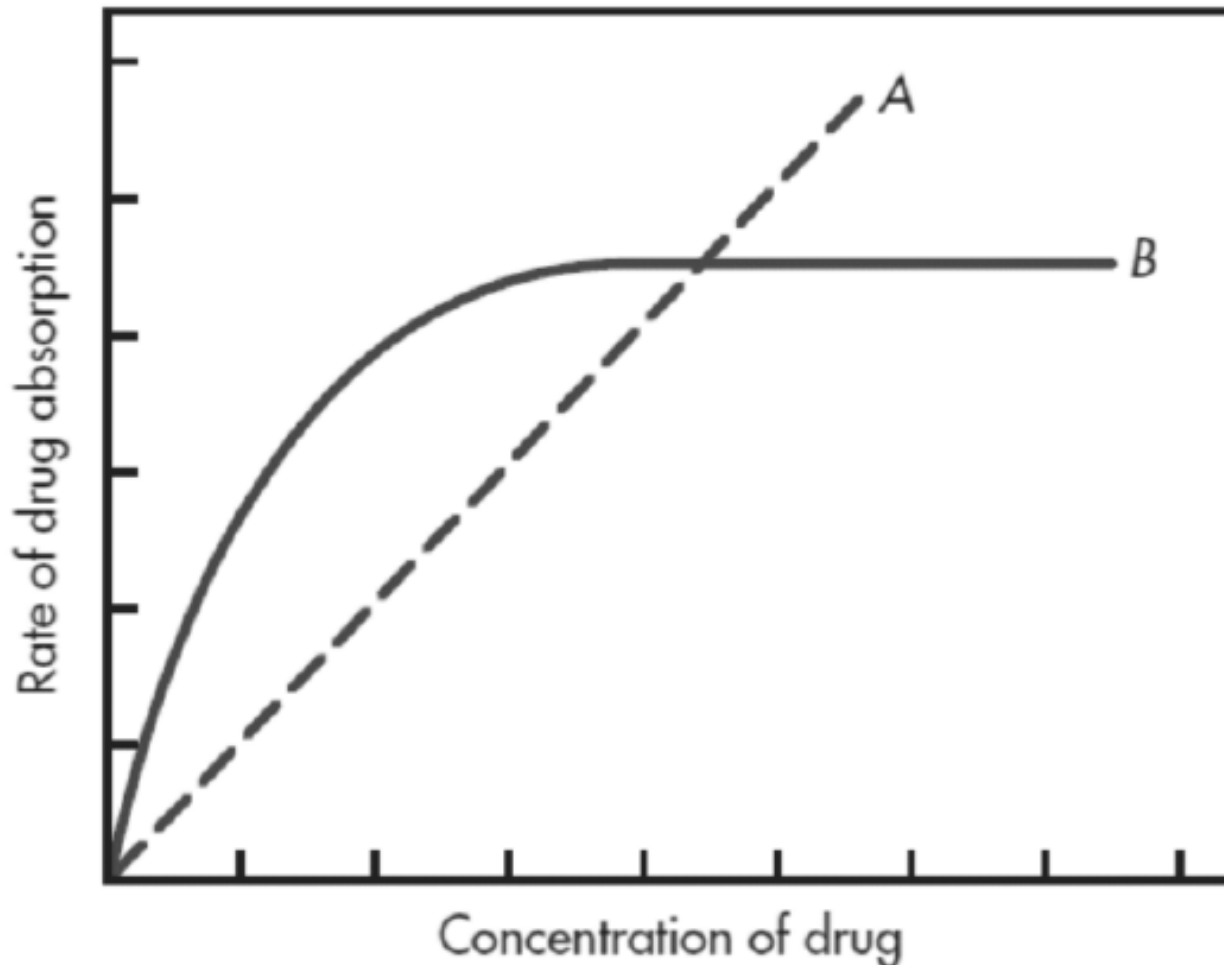
Numerous specialized carrier-mediated transport systems are present in the body, especially in the intestine for the absorption of ions and nutrients required by the body.

A. Active Transport

Active transport is a type of carrier mediated transport and it is characterized by the ability to transport drug against a concentration gradient, from regions of low drug concentrations to regions of high drug concentrations.

- The carrier molecule may be highly selective for the drug molecule.
- It is an energy consuming process.
- If a drug is structurally similar to the natural substance that is actively transported by the carrier, then it is likely to be transported by the same carrier.

- Only a fixed number of carriers are available, the binding sites may become saturated if high concentration of the drug is applied.
- The rate of drug absorption increases with the increase in the concentration of the drug until all the carrier molecules are saturated. At higher concentrations, the rate of absorption remains constant (zero order).
- For the passive diffuse the rate of absorption is directly related to the concentration of the drug at the site of administration (first order rate).



Comparison of the rate of absorption for a drug absorbed by passive diffusion (Line A) and drug absorbed by carrier mediated absorption (Line B).

B. Facilitated Diffusion

Facilitated diffusion is also a carrier-mediated transport system, differing from active transport in that the drug moves along a concentration gradient (moves from a region of high drug concentration to a region of low drug concentration).

- This system does not require energy input.
- It is saturable and structurally selective for the drug and shows competition kinetics for drugs of similar structure.
- In terms of drug absorption, facilitated diffusion seems to play a very minor role.

3. VESICULAR TRANSPORT

Vesicular transport is the process of engulfing particles or dissolved materials by the cell.

- a. Pinocytosis refers to the engulfment of small solutes or fluid.
- b. Phagocytosis refers to the engulfment of larger particles or macromolecules, generally by macrophages.

- c. Endocytosis and exocytosis are the processes of moving specific macromolecules into and out of a cell, respectively. During pinocytosis and phagocytosis the cell membrane invaginates to surround the material and then engulfs the material, incorporating it inside the cell. Subsequently, the cell membrane containing the material forms a vesicle within the cell.
- d. Transcytosis is the process by which various macromolecules are transported across the interior of a cell. In transcytosis, vesicles are employed to intake the macromolecules on one side of the cell, draw them across the cell, and eject them on the other side. Transcytosis (sometimes referred to as vesicular transport) is the proposed process for the absorption of orally administered various large proteins.

4. PORE (CONVECTIVE) TRANSPORT

Very small molecules (such as urea, water, and sugars) are able to cross cell membranes rapidly, as if the membrane contained channels or pores.

A certain type of protein called a transport protein may form an open channel across the lipid membrane of the cell.

Small molecules including drugs move through the channel by diffusion more rapidly than at other parts of the membrane.



BIOPHARMACEUTIC

Lecture 3

Oral Drug Absorption

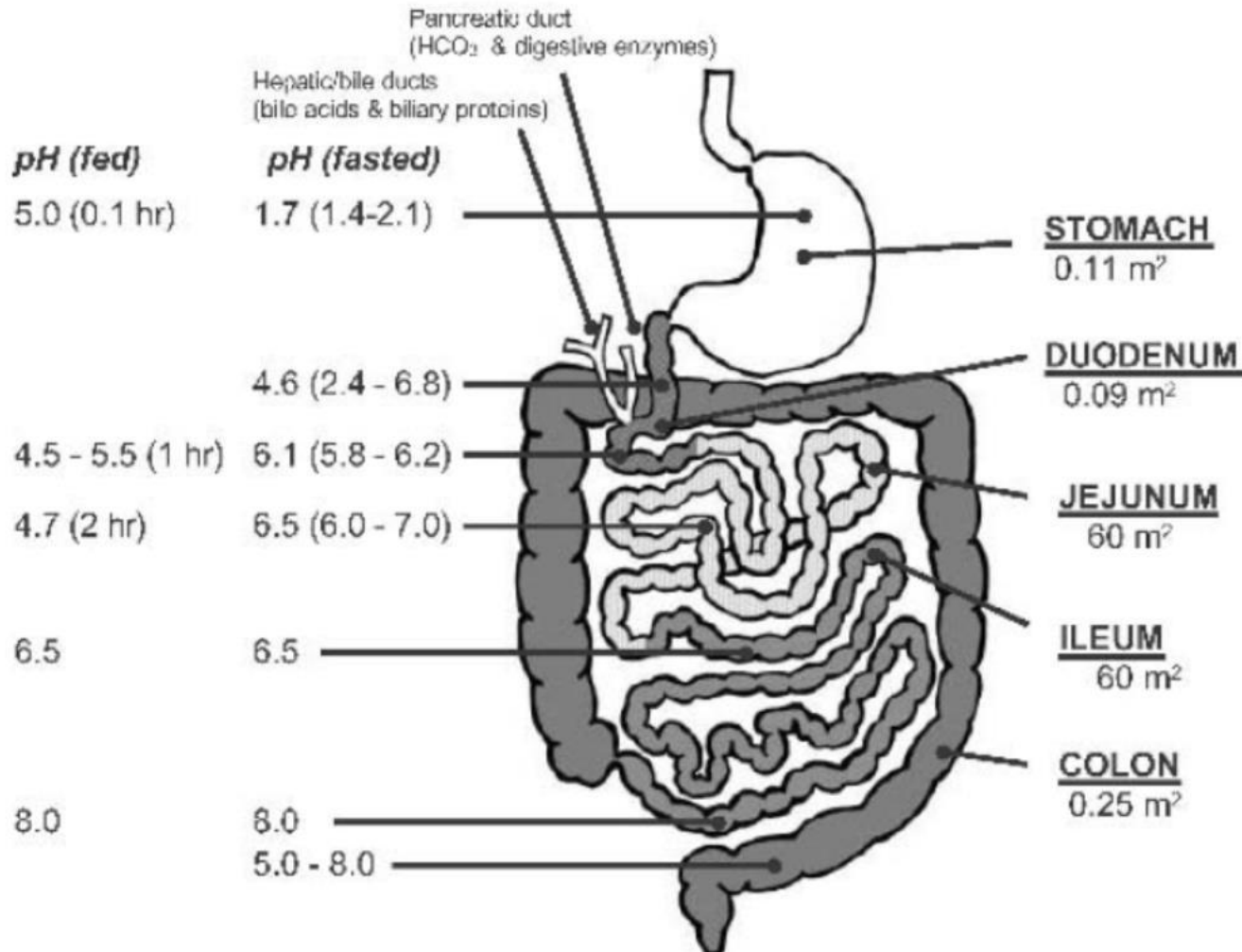
The oral route of administration is the most common and popular route of drug dosing.

Considerations for the design of oral dosage forms

1. Extreme pH ranges.
2. The presence or absence of food.
3. Degradative enzymes.
4. Varying drug permeability in the different regions of the intestine.
5. Motility of the gastrointestinal tract.

Anatomic and physiologic considerations in the GIT

The major physiologic processes that occur in the GI system are secretion, digestion, and absorption.



Factors affecting the normal physiology of the gastrointestinal tract (GIT)

1. Diet (high-fat meal increases the intestinal transit time such as decreasing gastric emptying, the absorption of hydrophilic drugs decreases with food as with penicillin and tetracycline while the absorption of lipid-soluble drugs increases with high-fat food such as griseofulvin and metaxalone).
2. Contents of GIT, such as bile salts.
3. Hormones, such as gastrin and CCK.
4. The visceral nervous system (controls contractile, secretory, and endocrine functions of GIT).

5. Diseases that affect **(1)** intestinal blood flow, **(2)** gastrointestinal motility, **(3)** changes in stomach emptying time, **(4)** gastric pH that affects drug solubility, **(5)** intestinal pH that affects the extent of ionization, **(6)** the permeability of the gut wall, **(7)** bile secretion, **(8)** digestive enzyme secretion, or **(9)** alteration of normal GI flora.
6. Drugs such as anticholinergic (reduce stomach acid secretion), metoclopramide (increases intestinal peristalsis).

Effect of Food on Gastrointestinal Drug Absorption

1. Delay in gastric emptying
2. A change in the pH of the GI tract
3. An increase in splanchnic blood flow
4. Chemical interaction of the meal with the drug product or drug substance

Rate-limiting Steps in Oral Drug Absorption

For solid oral, immediate-release drug products (eg, tablets, capsules), the rate processes include:

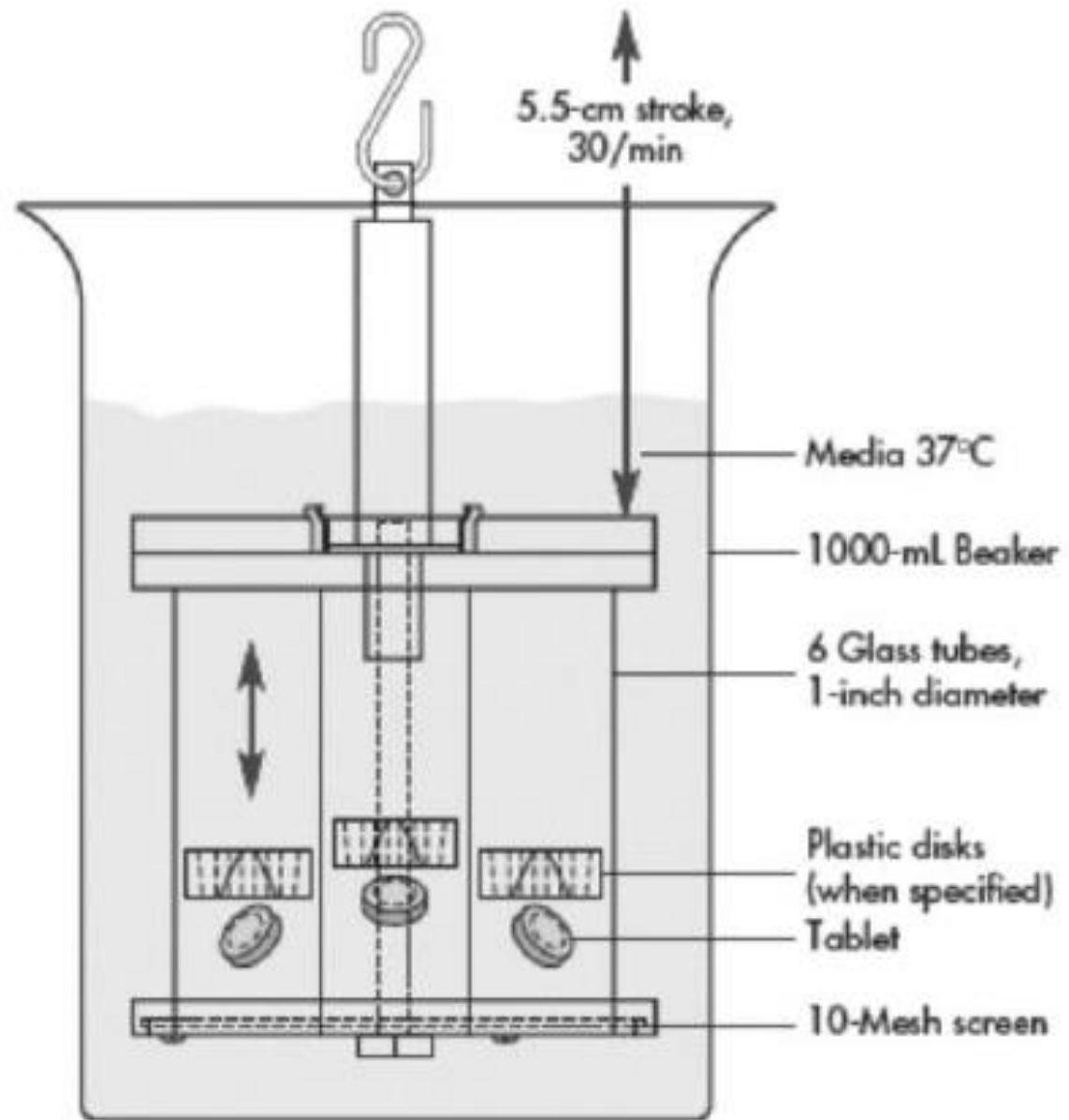
1. **Disintegration** of the drug product and subsequent release of the drug,
2. **Dissolution** of the drug in an aqueous environment, and
3. **Absorption** across cell membranes into the systemic circulation.

1. Disintegration

For immediate-release, solid oral dosage forms, the drug product must disintegrate into small particles and release the drug.

To monitor uniform tablet disintegration, the *United States Pharmacopeia* (USP) has established an official disintegration test.

Solid drug products exempted from disintegration tests include lozenges, tablets that are intended to be chewed, and drug products intended for sustained release or prolonged or repeat action as well as liquid-filled soft gelatin capsules.



USP disintegration testing apparatus.

Recommended timing of the disintegration test

1. For immediate-release preparation, place 1 dosage unit in each of the six tubes of the basket, operate the system using water as the immersion fluid, maintained at 37 ± 2 °C, carry out the test for 20 minutes for capsules, 30 minutes for plain tablets, and 60 minutes for coated tablets and pills.
2. For enteric coated preparations perform the following two tests, (a) the test with 1st fluid (pH 1.2) for disintegration, carry out the test for 120 minutes according to the procedure described in immediate release preparations test, (b) perform the test with the 2nd fluid for disintegration test (pH 6.8) according to the procedure described in immediate-release preparations, carry out the test with new dosage units for 60 minutes. Tablets should not disintegrate in the 1st fluid but only in the 2nd fluid.

2. Dissolution and Solubility

The rate at which drugs with poor aqueous solubility dissolve from an intact or disintegrated solid dosage form in the gastrointestinal tract often controls the rate of systemic absorption of the drug.

Thus, dissolution tests may be used to predict bioavailability and may be used to discriminate formulation factors that affect drug bioavailability.

Dissolution is the process by which a solid drug substance becomes dissolved in a solvent over time.

Solubility is the mass of solute that dissolves in a specific mass or volume of solvent at a given temperature (eg, 1 g of NaCl dissolves in 2.786 mL of water at 25°C).

Noyes–Whitney equation

$$\frac{dC}{dt} = \frac{DA}{h} (C_s - C)$$

dC/dt = rate of drug dissolution at time t ,

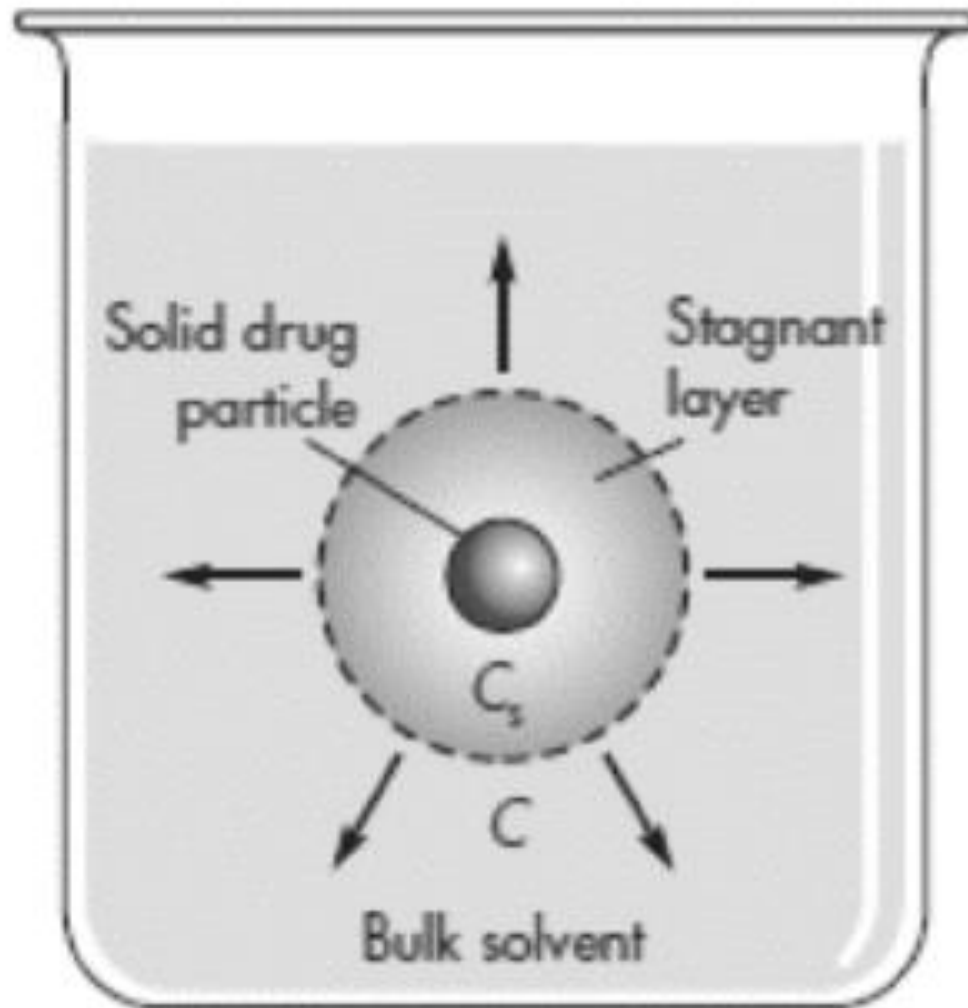
D = diffusion rate constant,

A = surface area of the particle,

C_s = concentration of drug (equal to solubility of drug) in the stagnant layer,

C = concentration of drug in the bulk solvent, and

h = thickness of the stagnant layer



Representation of dissolution process.

In addition to these factors, the temperature of the medium and the agitation rate also affect the rate of drug dissolution.

An increase in temperature will increase the kinetic energy of the molecules and increase the diffusion constant, ***D***.

Moreover, an increase in agitation of the solvent medium will reduce the thickness, ***h***, of the stagnant layer, allowing for more rapid drug dissolution.

In addition, the viscosity of the dissolution medium affects ***D***, food increases the viscosity of the medium and therefore increases ***D***.

Factors affecting drug dissolution of a solid oral dosage form

- (1) The physical and chemical nature of the active drug substance.
- (2) The nature of the excipients, such as the use of surfactant.
- (3) The method of manufacture, such as milling (decrease in particle size).
- (4) The dissolution test conditions, temp and agitation.

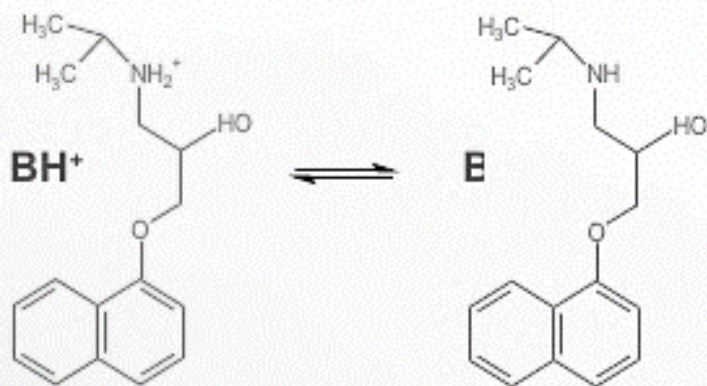
Physicochemical Properties of the Drug

A. Solubility, pH, and Drug Absorption

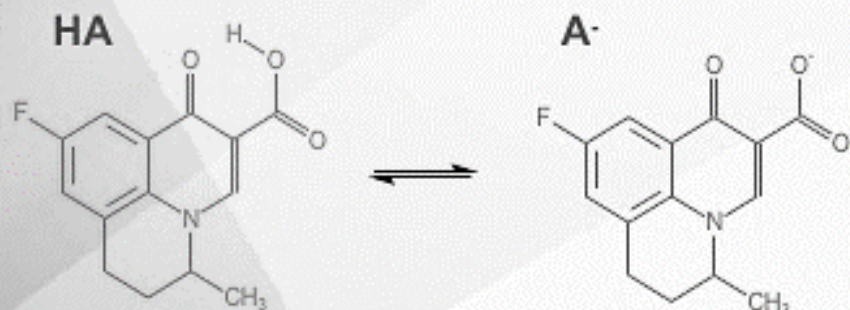
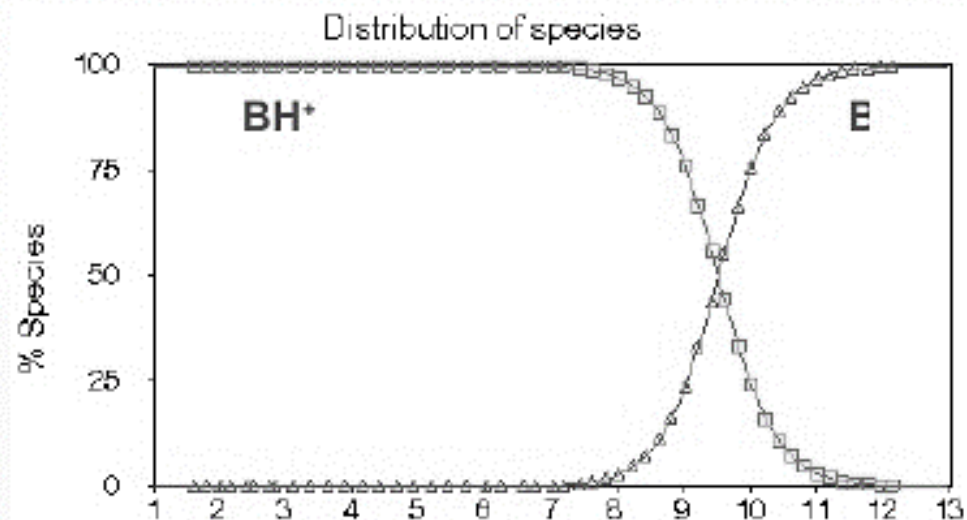
The solubility–pH profile is a plot of the solubility of the drug at various physiologic pH values.

A basic drug is more soluble in an acidic medium, forming a soluble salt. Conversely, an acid drug is more soluble in the intestine, forming a soluble salt in the more alkaline pH environment found there.

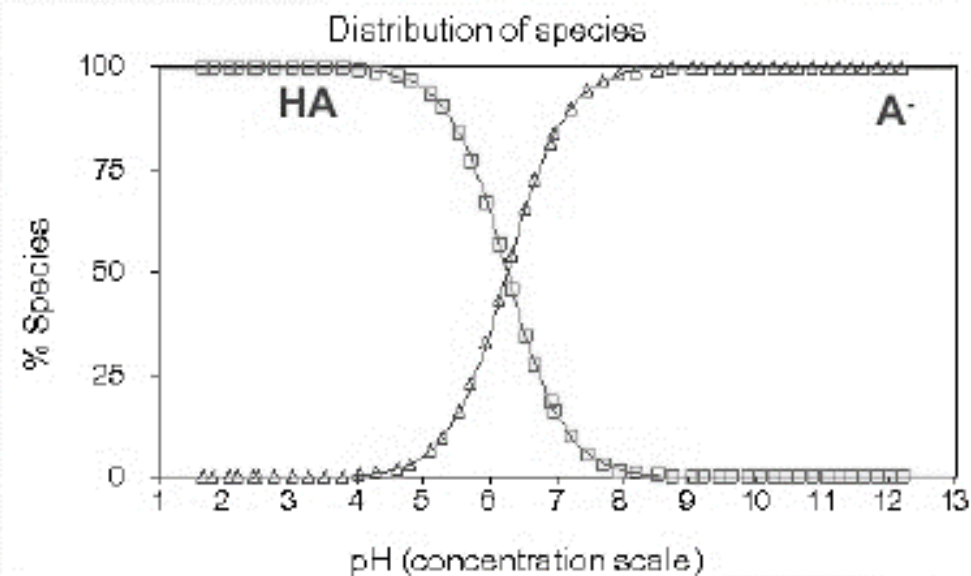
Solubility may be improved with the addition of an acidic or basic excipient.



Propranolol (a base): $pK_a = 9.53$



Flumequine (an acid): $pK_a = 6.27$

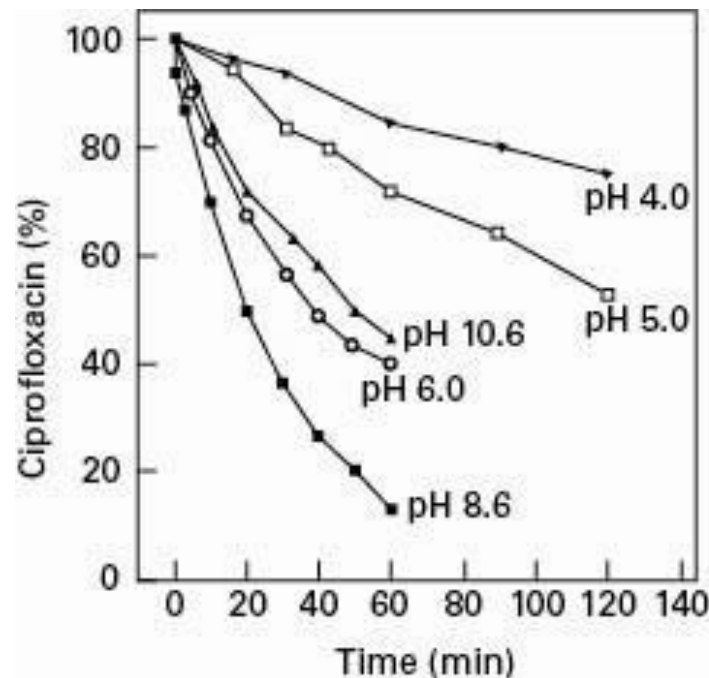


Ionisation of weak base (propranolol) and weak acid (flumequine) at different pH.

B. Stability, pH, and Drug Absorption

The *stability–pH profile* is a plot of the reaction rate constant for drug degradation versus pH.

For example, the stability of ciprofloxacin decreases with the increase in the pH of the medium.



C. Particle Size and Drug Absorption

Dissolution takes place at the surface of the solute (drug), and thus, the greater the surface area, the better the water saturation, and the more rapid the rate of drug dissolution.

Griseofulvin, nitrofurantoin, and many steroids are drugs with low aqueous solubility; reduction of the particle size by milling to a micronized form has improved the oral absorption of these drugs.

In these cases, so-called nanosizing, or producing even smaller drug substance particles, may be beneficial.

D. Polymorphs, solvates, and amorphous solids

- **Polymorphism**

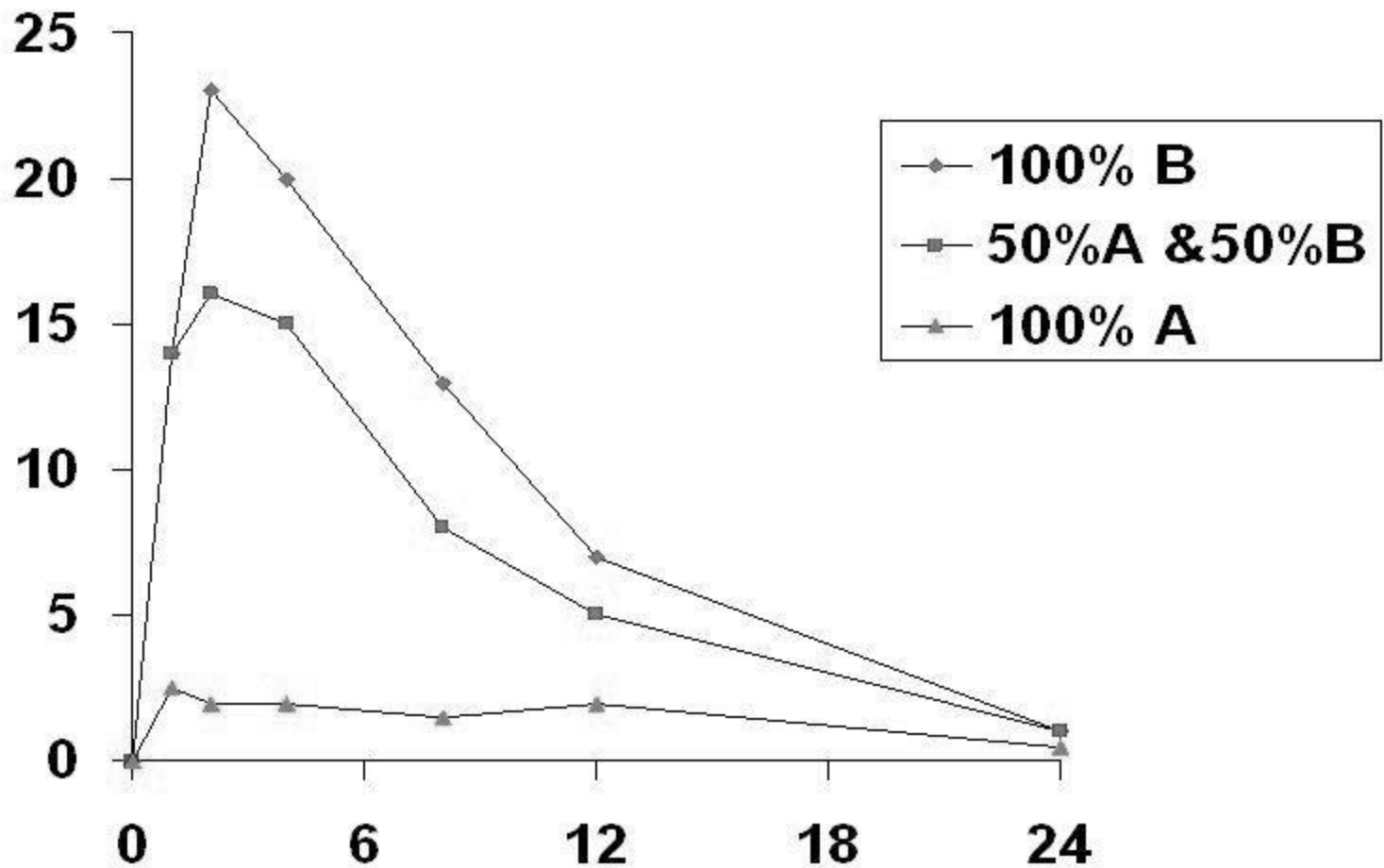
The ability of solid material to exist in more than one crystalline form is called polymorphism

Properties of Polymorphs

1. They are chemically identical but they are different in the crystalline structure in the solid state.
2. Polymorphs have different melting points, solubility, hygroscopicity, density, hardness, and compression characteristics.
3. Polymorphs have different stabilities and may spontaneously convert from the metastable (less stable) form to the stable form.

Example:

Chloramphenicol has several crystal forms, and when given orally as a suspension, the drug concentration in the body was found to be dependent on the percent of B -polymorph in the suspension. The B form is more soluble and better absorbed.



Plasma concentration-time profiles following oral administration of A, B, and a mixture of A and B polymorph forms of chloramphenicol.

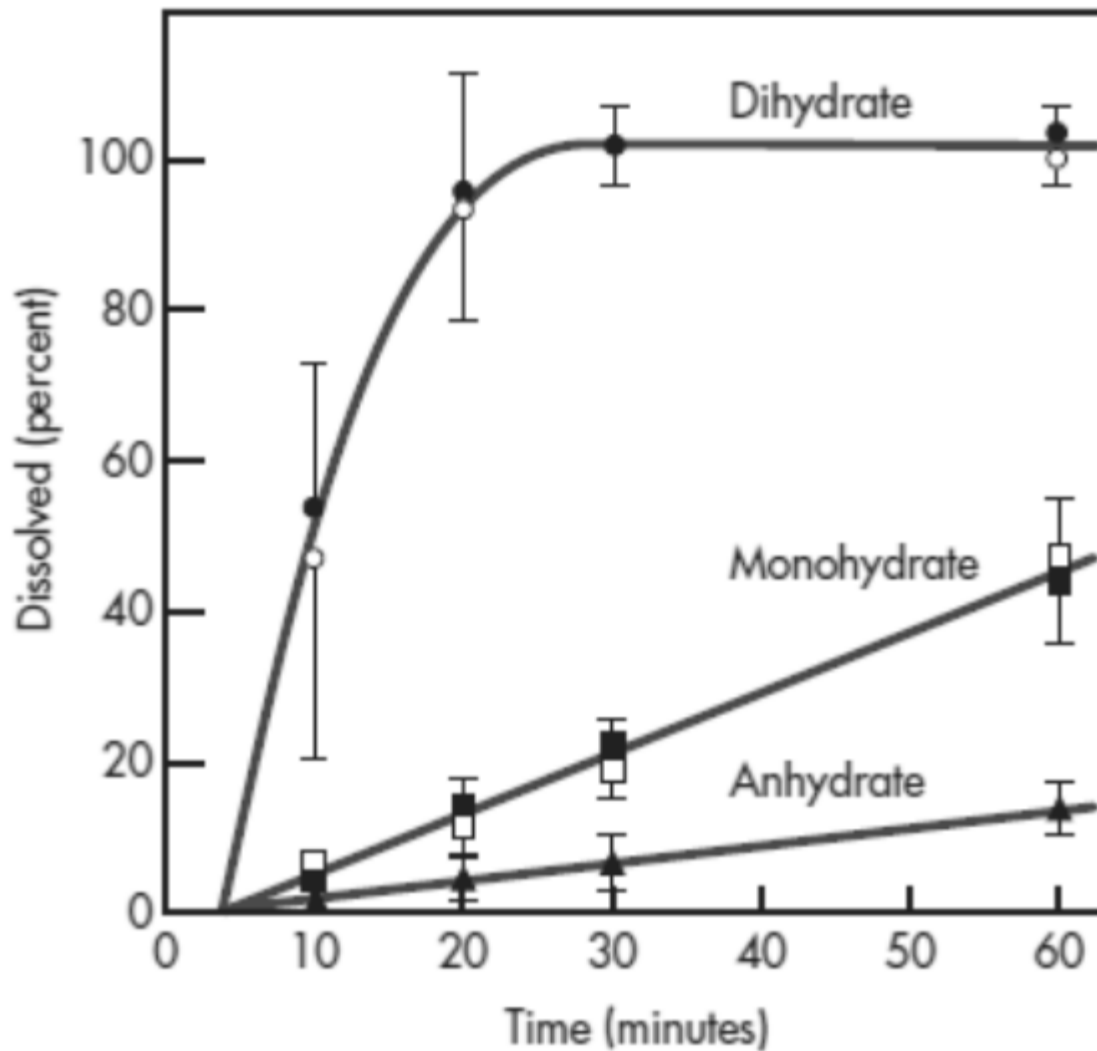
- **Solvates (Pseudopolymorphs)**

Pharmaceutical synthesis includes purification and crystallization; residual solvent can be trapped in the crystalline structure. This results to solvate formation. The residual solvent could be water, and therefore called hydrate.

Drugs that are formed by removing the solvent from the solvate or hydrate are called ***desolvated*** or ***anhydrous***, respectively.

Examples:

1. Erythromycin hydrates have quite different solubility compared to the anhydrous form of the drug.
2. Ampicillin trihydrate was reported to be less absorbed than the anhydrous form of ampicillin because of faster dissolution of the latter.



Dissolution profile of mono-, di-, and anhydrate erythromycin

- **Amorphous solids**

Amorphous solids can be considered as supercooled liquids in which the molecules are arranged in a random manner as in the liquid state.

A drug that exists as an amorphous form (noncrystalline form) generally dissolves more rapidly than the same drug in a more structurally rigid crystalline form.

The presence of pharmaceutical substances as amorphous or crystalline form will affect the therapeutic activity. Example: the antibiotic novobiocin acid.

novobiocin

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graph TD; A[novobiocin] --> B[Crystal]; A --> C[Amorphous]; B --> D[low solubility]; B --> E[low absorption]; B --> F[low activity]; C --> G[high solubility]; C --> H[higher absorption]; C --> I[higher activity];
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Crystal

low solubility

low absorption

low activity

Amorphous

high solubility

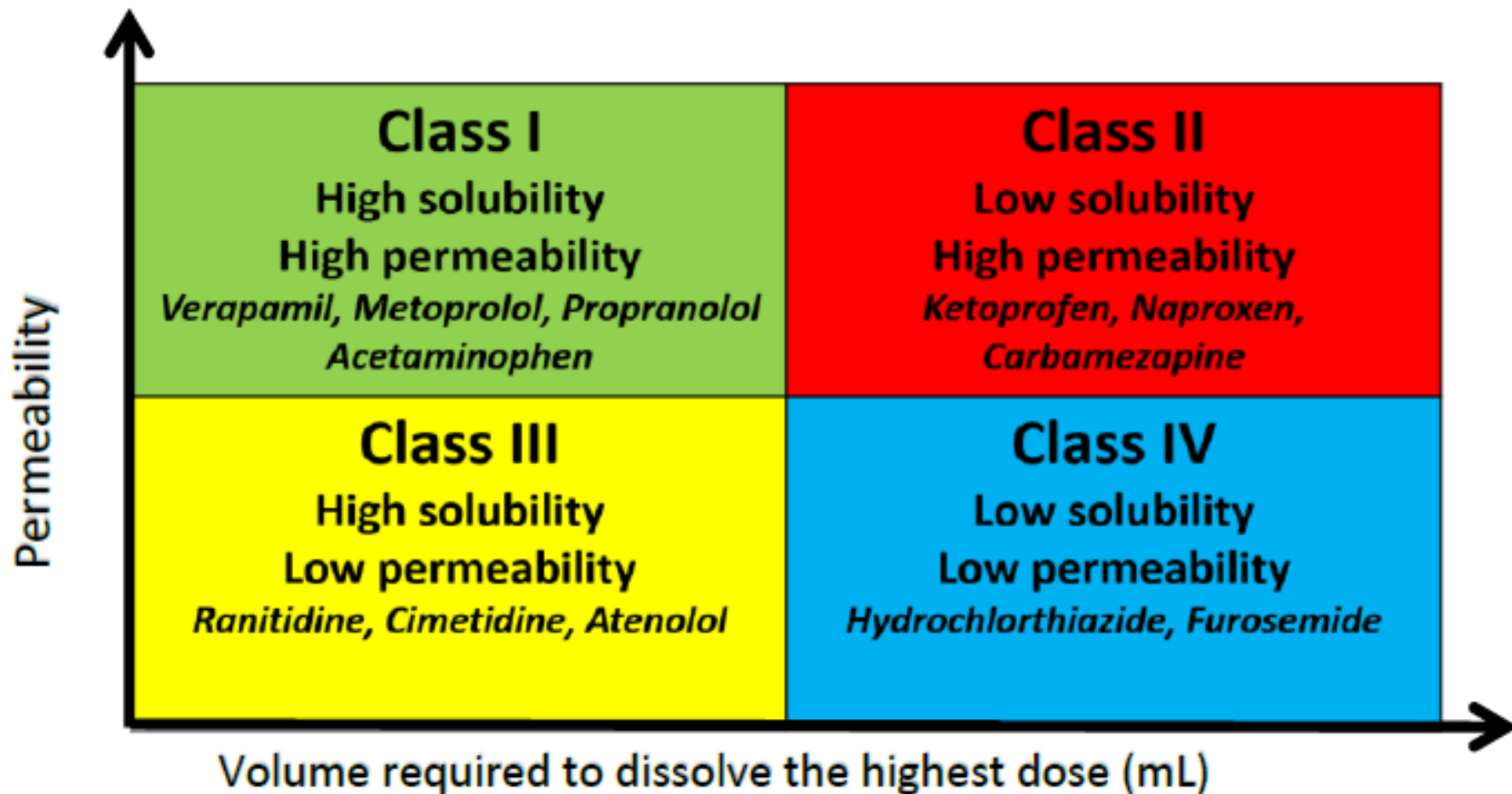
higher absorption

higher activity



BIOPHARMACEUTICS

Lecture 4



The Biopharmaceutics Classification System (bcs)

Formulation approach to enhance the absorption of each BCS

BCS	Absorption rate control	Formulation approaches for oral administration
Class 1	Gastric emptying	Can easily be formulated as tablets or capsules
Class 2	Dissolution	Particle size reduction (e.g., formation of microparticles or nanoparticles), solid dispersions, salt formation, addition of surfactants, self-emulsifying systems, liquid capsules, complexation
Class 3	Permeability	Addition of permeation enhancers, efflux inhibitors
Class 4	Dissolution and Permeability	Combination of Class II and III approaches

Other Physicochemical Properties for Consideration in Drug Product Design

Hygroscopicity	Moisture absorption may affect the physical structure as well as stability of the product
Partition coefficient	May give some indication of the relative affinity of the drug for oil and water. A drug that has high affinity for oil may have poor release and dissolution from the drug product.
Impurity profile	The presence of impurities may depend upon the synthetic route for the active drug and subsequent purification. Impurities need to be “qualified” or tested for safety. Changes in the synthetic method may change the impurity profile
Chirality	The presence of chirality may show that the isomers have differences in pharmacodynamic activity.

Excipient	Property in Dosage Form
Lactose	Diluent
Dibasic calcium phosphate	Diluent
Starch	Disintegrant, diluent
Microcrystalline cellulose	Disintegrant, diluent
Magnesium stearate	Lubricant
Stearic acid	Lubricant
Hydrogenated vegetable oil	Lubricant
Talc	Lubricant
Sucrose (solution)	Granulating agent
Polyvinyl pyrrolidone (solution)	Granulating agent
Hydroxypropylmethyl-cellulose	Tablet-coating agent
Titanium dioxide	Combined with dye as colored coating
Methylcellulose	Coating or granulating agent
Cellulose acetate phthalate	Enteric-coating agent

Examples of excipients and their role in the dosage form

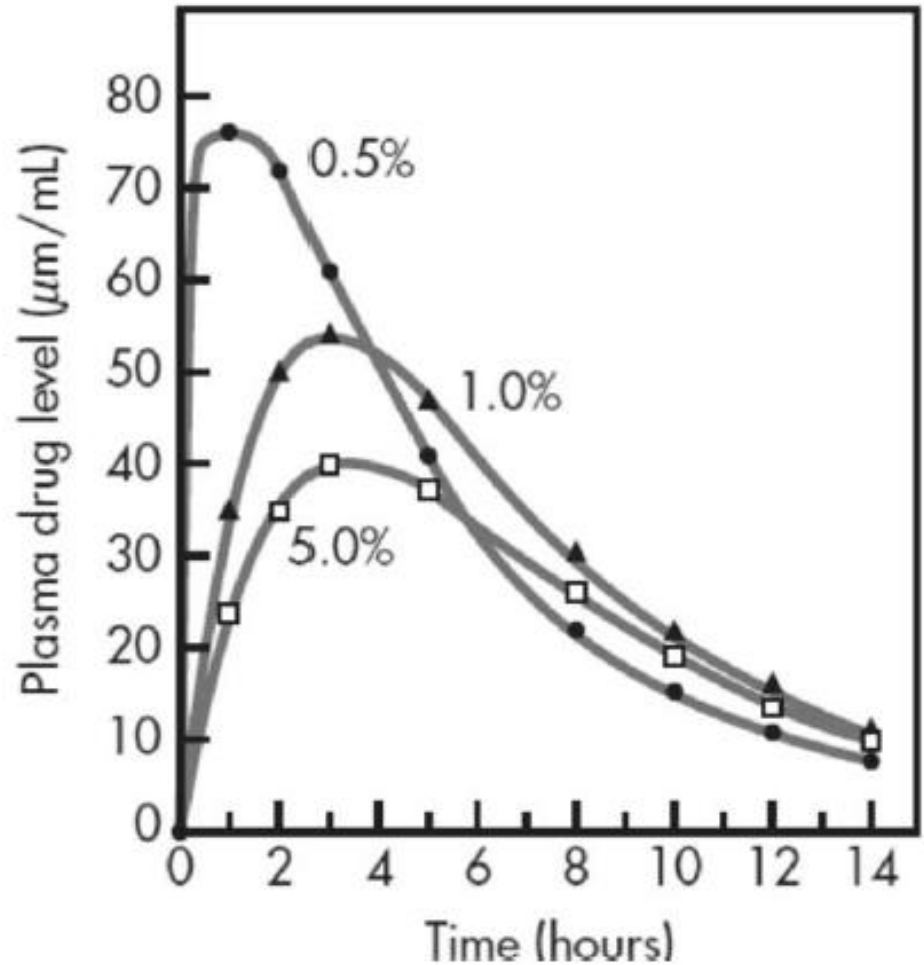
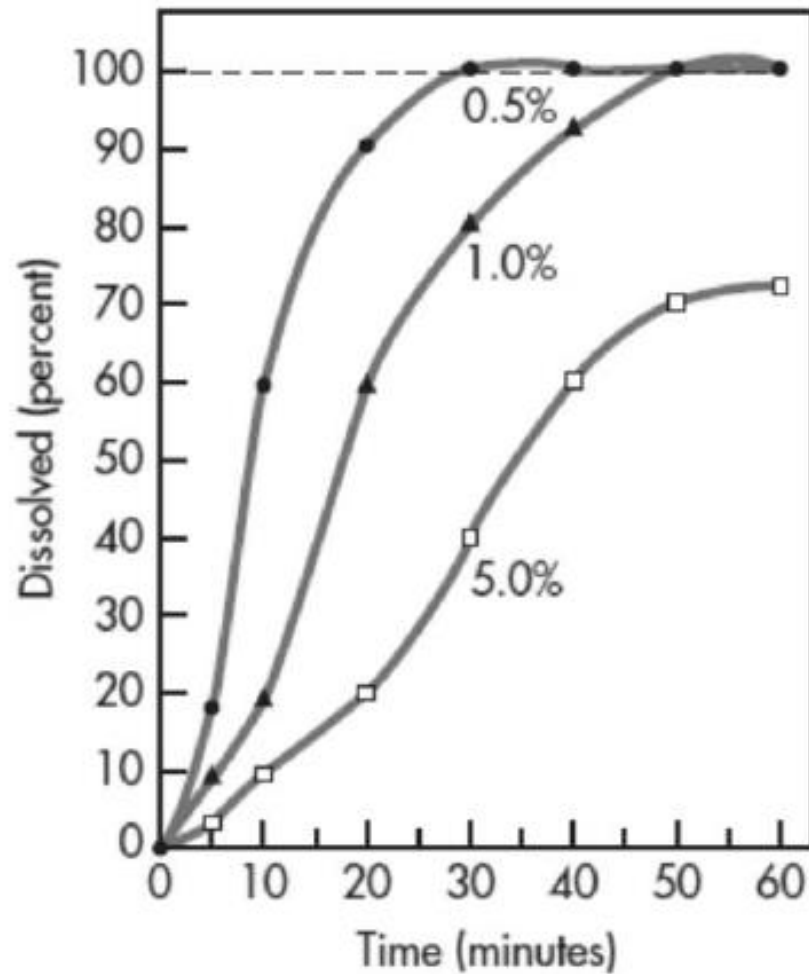
The advantages of using excipients on drug product performance

1. Improve the manufacturability of the dosage form.
2. Stabilize the drug against degradation.
3. Decrease gastric irritation.
4. Control the rate of drug absorption from the absorption site.
5. Increase drug bioavailability.

The mechanisms by which excipients affect the dissolution kinetics of the drug

1. Altering the medium in which the drug is dissolving

- Suspending agents can increase the viscosity of the drug vehicle and thereby diminish the rate of drug dissolution from suspensions.
- Tablet lubricants, such as magnesium stearate, may repel water and reduce dissolution when used in large quantities.



The effect of adding different concentrations of magnesium stearate to a tablet formulation on the dissolution profile (left panel) and plasma conc.-time profile (right panel).

- Coatings, particularly shellac, will decrease the dissolution rate.
- Surfactants: low concentrations of surfactants decrease the surface tension and increase the rate of drug dissolution, whereas higher surfactant concentrations tend to form micelles with the drug and thus decrease the dissolution rate.
- Some excipients, such as sodium bicarbonate, may change the pH of the medium surrounding the active drug substance.
Example: Aspirin, a weak acid when formulated with sodium bicarbonate, will form a water-soluble salt in an alkaline medium, in which the drug rapidly dissolves.

2. Directly in interaction with the drug to form a water-soluble or water-insoluble complex.

For example, if tetracycline is formulated with calcium carbonate, an insoluble complex of calcium tetracycline is formed that has a slow rate of dissolution and poor absorption.

DISSOLUTION AND DRUG RELEASE TESTING

Dissolution and drug release tests are *in vitro* tests that measure the rate and extent of dissolution or release of the drug substance from a drug product, usually in an aqueous medium under specified conditions.

Purpose of Dissolution and Drug Release Tests:

1. Formulation development and selection.
2. Confirmation of batch-to-batch reproducibility.
3. Establish drug product stability (demonstrate that the product performs consistently throughout its use period or shelf life).
4. Establish *in vivo*–*in vitro* correlations (IVIVC) .

The choice of apparatus and dissolution medium is based on:

1. The physicochemical characteristics of the drug (including solubility, stability).
2. The type of formulation (such as immediate release, enteric coated, extended release, rapidly dissolving, etc).

Apparatus factors that affect the rate and extent of dissolution:

1. The size and shape of the dissolution vessel.
2. The amount of agitation and the nature of the stirrer affect hydrodynamics of the system.
3. The temperature of the dissolution medium (most dissolution tests are performed at 37°C. However, for transdermal drug products, the recommended temperature is 32°C).
4. The nature of the dissolution medium.

USP-NF Dissolution Apparatus

Apparatus	Name	Agitation Method	Drug Product	Notes
Apparatus 1	Rotating basket	Rotating stirrer	Tablets, capsules	rotating speed 100-150 rpm formulation may clog to mesh
Apparatus 2	Paddle	Rotating stirrer	Tablets, capsules, modified drug products, suspensions	50 - 75 rpm for solid dosage form 25 rpm for oral suspensions. May require the use of sinker to prevent floating of tab or capsules
Apparatus 3	Reciprocating cylinder	Reciprocation	Extended-release drug products	Flat bottom The agitation rate is generally 5-30 dpm (dips per minute) The media can be changed easily.
Apparatus 4	Flow cell	Fluid movement	Drug products containing low water-soluble drugs	Flow rate ranges from 4 to 32 mL/min Maintains sink condition for dissolution

Apparatus 5	Paddle over disk	Rotating stirrer	Transdermal drug products	Modification of USP II apparatus stainless steel disk to hold the transdermal system at the bottom of the vessel
Apparatus 6	Cylinder	Rotating stirrer	Transdermal drug products	Modification of USP I apparatus Samples are hold in cuprophan
Apparatus 7	Reciproca ting disk	Reciprocation	Extended- release drug products	Samples are hold in disk- shaped holders using cuprophan supports

Ch!



BIOPHARMACEUTICS

Lecture 5

Pharmacokinetic Models

Pharmacokinetic
models

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graph TD; A[Pharmacokinetic models] --> B[Compartmental models]; A --> C[Non-compartmental analysis]; A --> D[Physiological models];
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Compartmental
models

Non-compartmental
analysis

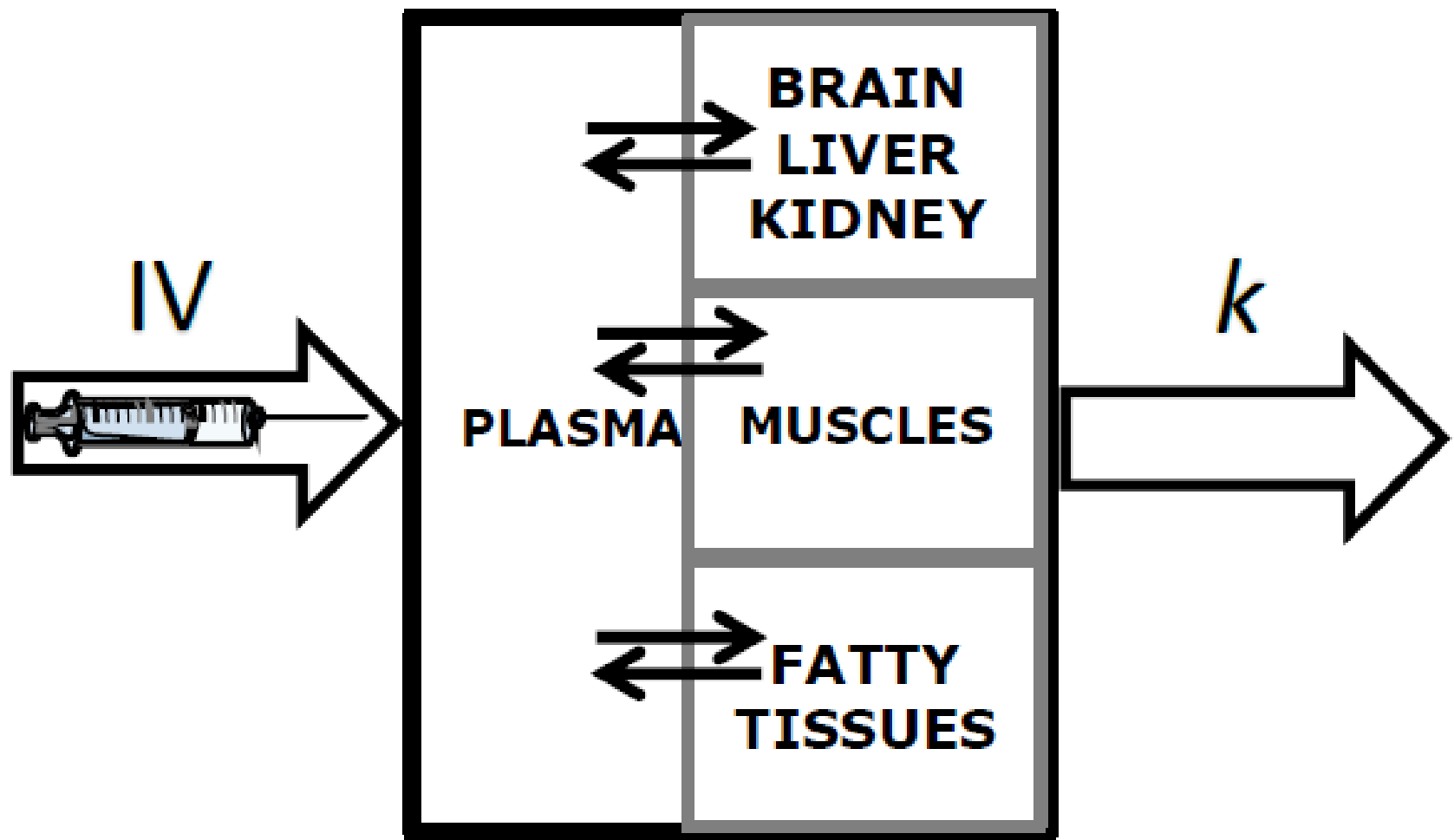
Physiological models

Compartmental models

The most commonly employed approach to the pharmacokinetic characterization of a drug is to represent the body as a system of compartments, even though these compartments usually have no physiologic or anatomic reality, and to assume that the rate of transfer between compartments and the rate of drug elimination from compartments follow first-order or linear kinetics.

One-compartment open model

- The one-compartment open model assumes that the body can be described as a single, uniform compartment (ie, one compartment), and that drugs can enter and leave the body (ie, open model).
- This model is useful for the pharmacokinetic analysis of drugs that distribute rapidly throughout the body.
- Following IV bolus administration, it assumes that the drug is administered instantly into the body, and it is instantaneously and rapidly distributed throughout the body.
- Drug elimination occurs immediately upon entering the body.



Elimination rate constant

- Drug elimination from the body can occur by several pathways, including urinary and biliary excretion, excretion in expired air, and biotransformation in the liver or other fluids or tissues.
- The elimination of most drugs in humans and animals at therapeutic doses can be characterized as a first-order process (ie., the rate of elimination of drug from the body at any time is proportional to the amount of drug in the body at that time).
- The first-order elimination rate constant, K , characterizing the overall elimination of a drug from a one compartment model represents the sum of two or more rate constants characterizing individual elimination processes:

$$K = k_e + k_m + k_b + \dots$$

The rate of loss of drug from the body is given by

$$\frac{dD_B}{dt} = -K \cdot D_B$$

Where D_B is the amount of drug in the body at time t after injection. K is the first-order elimination rate constant for the drug. The negative sign indicates that drug is being lost from the body.

$$D_B = D_B^0 \cdot e^{-kt}$$

Where **e** represents the base of the natural logarithm (ln). Taking the natural logarithm of both sides gives:

$$\ln D_B = \ln D_B^0 - kt$$

The equation can be converted to common logarithms

$$\log D_B = \log D_B^0 - \frac{kt}{2.3}$$

$\ln x = 2.303 \log x$

The slope and the elimination rate constant (k)

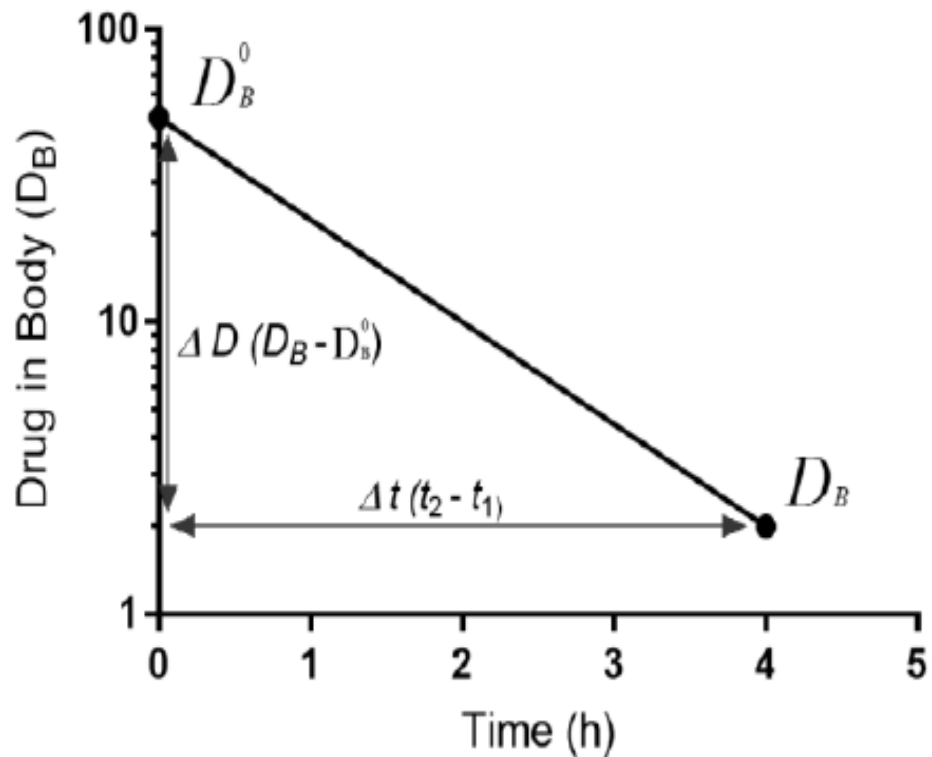
$$\log D_B = \log D_B^0 - \frac{kt}{2.3}$$

$$\log D_B - \log D_B^0 = \frac{-kt}{2.3}$$

$$\frac{(\log D_B - \log D_B^0)}{t} = \frac{-k}{2.3}$$

$$\frac{(y_2 - y_1)}{(x_2 - x_1)} = \frac{-k}{2.3}$$

$$\text{Slope} = \frac{-k}{2.3}$$



The volume of distribution (VD)

The rate and extent of distribution to the tissue organs depends on several processes and properties.

1. Tissues in the body are presented the drug at various rates, depending on the blood flow to that organ.
2. The drug may have different abilities to cross from the vasculature to the organ depending on the molecular weight of the drug.
3. Tissues also have different affinity for the drug, depending on lipophilicity and drug binding.
4. Large organs may have a large capacity for drugs to distribute to.

In one-compartment model, we assume that the rate of change of drug concentration in plasma reflects quantitatively the change in drug concentrations throughout the body.

In other words, if we see a 20% decrease in drug concentration in plasma over a certain period of time, we assume that the drug concentrations in kidney, liver, cerebrospinal fluid, and all other fluids and tissues also decrease by 20% during this time.

The ratio of drug concentrations in the various tissues and fluids is constant. Consequently, there will exist a constant relationship between drug concentration in the plasma C and the amount of drug in the body:

$$D_B = V_D C_P$$

The volume of distribution is the apparent volume (**VD**) in which the drug is dissolved. The term **apparent** volume of distribution is used because the value of the volume of distribution does not have a true physiologic meaning in terms of an anatomic space.

$$\log D_B = \log D_B^0 - \frac{kt}{2.3}$$

If $D_B = V_D C_P$ then

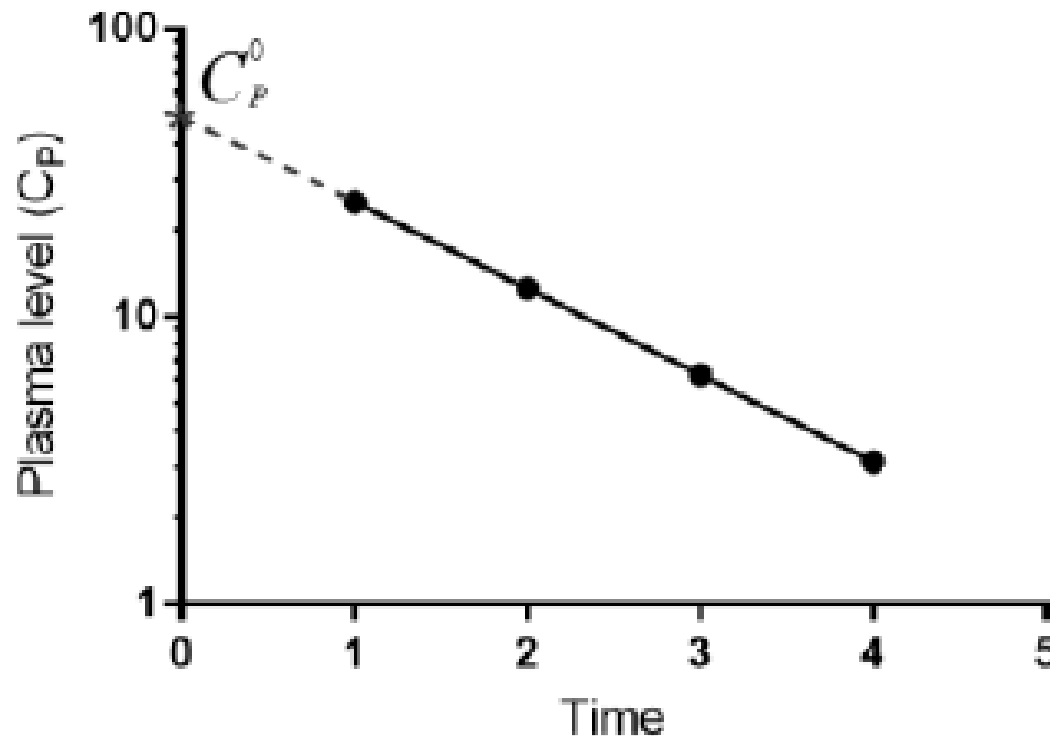
$$\log C_P = \log C_P^0 - \frac{kt}{2.3} \quad \longleftrightarrow \quad C_P = C_P^0 \cdot e^{-kt}$$

Calculation of the volume of distribution in one-compartment model

- The one-compartment open model considers the body a constant-volume system or compartment. Therefore, the apparent volume of distribution for any given drug is a constant.
- If the volume of solution in which the drug is dissolved and the drug concentration of the solution are known, then the total amount of drug present in the solution may be calculated. This relationship between drug concentration, volume in which the drug is dissolved, and total amount of drug present is given in the following equation:

$$V_D = \frac{Dose}{C_P^0} = \frac{D_B^0}{C_P^0}$$

- The dose of drug given by IV bolus (rapid IV injection) represents the amount of drug in the body, D_B^0 , at $t = 0$.
- C_P^0 can be determined by extrapolating the linear line of plasma concentration (semilog presentation) to t_0 as shown in the figure:



Most drugs have an apparent volume of distribution smaller than, or equal to, the body mass. If a drug is highly bound to plasma proteins or the molecule is too large to leave the vascular compartment, then C_p^0 will be higher, resulting in a smaller apparent VD.

For example, the apparent volume of distribution of warfarin is small, approximately 0.14 L/kg, much less than the total body mass. This is because warfarin is highly bound to plasma proteins, making it hard to leave the vascular compartment.

For some drugs, the volume of distribution may be several times the body mass. In this case, a very small C_p^0 may occur in the body due to concentration of the drug in peripheral tissues and organs, resulting in a large VD.

Drugs with a large apparent VD are more concentrated in extravascular tissues and less concentrated intravascularly. For example, the apparent volume of distribution of digoxin is very high, 7.0 L/kg, much greater than the body mass.

This is because digoxin binds extensively to tissues, especially muscle tissues.

The apparent VD is a volume term that can be expressed as a simple volume or in terms of percent of body weight. A 1-L volume is assumed to be equal to the weight of 1 kg. For example, if the VD is 3500 mL for a subject weighing 70 kg, the VD expressed as percent of body weight is

$$\frac{3.5 \text{ kg}}{70 \text{ kg}} \times 100 = 5\%$$

If VD is a very large number, that is, $>100\%$ of body weight, then it may be assumed that the drug is concentrated in certain tissue compartments. In the digoxin example above, 7.0 L/kg is estimated to be 700% of body weight. Thus, the apparent VD is a useful parameter in considering the relative amounts of drug in the vascular and in the extravascular tissues.

For each drug, the apparent VD is a constant. In certain pathologic cases, the apparent VD for the drug may be altered if the distribution of the drug is changed.

For example, in edematous conditions, the total body water and total extracellular water increases; this is reflected in a larger apparent VD value for a drug that is highly water soluble.

Similarly, changes in total body weight and lean body mass (which normally occur with age, less lean mass, and more fat) may also affect the apparent VD .

Clearance (Cl)

Clearance is a measure of drug elimination from the body without identifying the mechanism or process.

Drug Clearance in the One-Compartment Model

Clearance considers the entire compartment as a drug-eliminating system from which many elimination processes may occur

Expression of Clearance

1. Drug elimination expressed as amount per unit time

Expression of drug elimination as mass per unit time (eg, mg/min, or mg/h). It is more convenient for zero-order elimination processes because it is constant.

2. Drug elimination expressed as volume per unit time

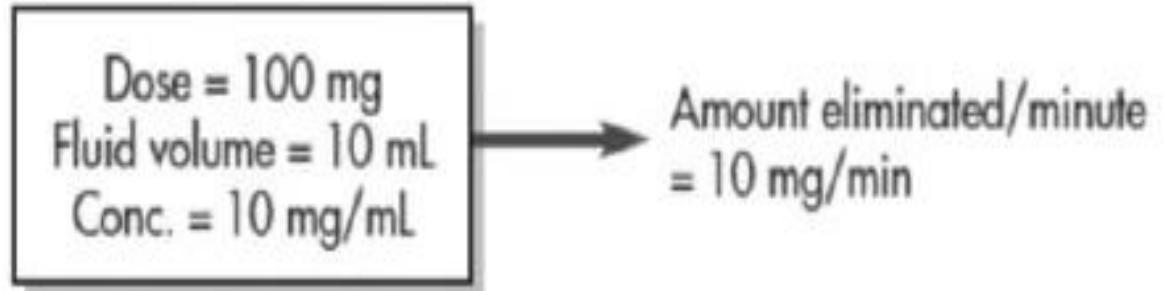
Clearance expressed as volume per unit time (eg, L/h or mL/min). It is convenient for first-order processes. Clearance (volume of fluid removed of drug) for a first-order process is constant regardless of the drug concentration because clearance is expressed in volume per unit time rather than drug amount per unit time.

3. Drug elimination expressed as fraction eliminated per unit time

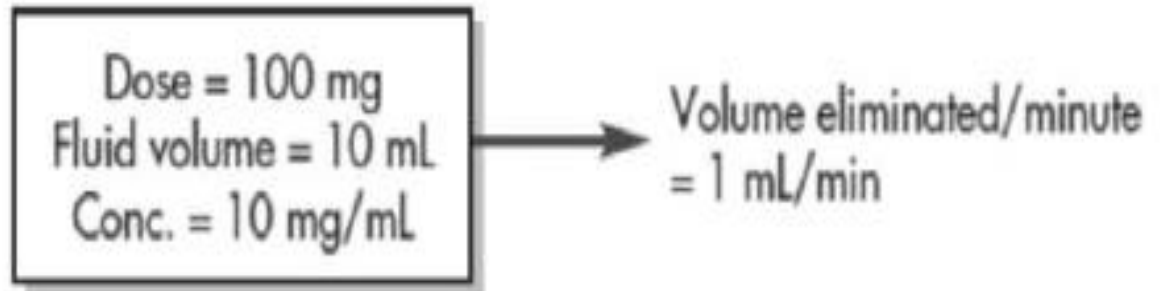
Expressing drug elimination as the fraction of total drug eliminated. This expression is applicable if we are dealing with an amount or a volume.

Diagram
illustrating three
different ways of
describing drug
elimination after
a dose of 100 mg
injected IV into a
volume of 10 mL.

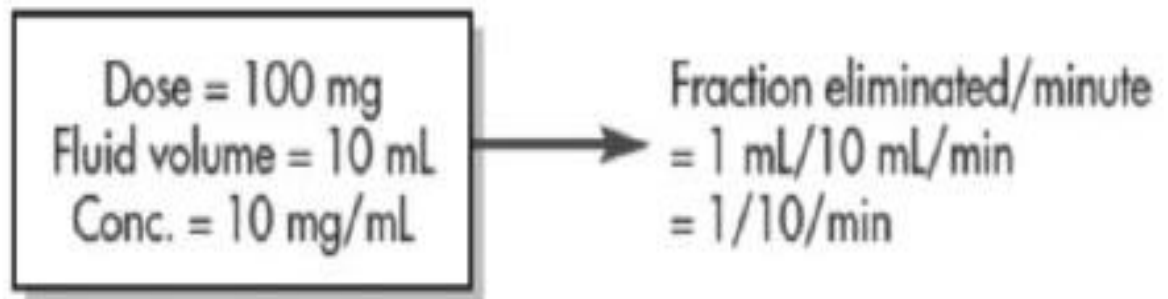
A. Mass approach



B. Clearance (volume) approach



C. Fractional approach



In case that clearance is expressed in liters per minute (L/min), then the fraction of drug cleared per minute in the body is equal to Cl/VD .

- Drug clearance and the volume of distribution as independent parameters (both values are independent of plasma concentration).

$$K = \frac{Cl}{VD}$$

Calculation of k from urinary excretion data

For first-order kinetics,

Excretion rate \propto Amount of the drug in the body

Excretion rate = K_e . Amount of the drug in the body

$$\frac{dD_u}{dt} = K_e \cdot D_B$$

Where k_e is the renal excretion rate constant, D_u is the amount of drug excreted in the urine, and D_B is the amount of the drug in the body at time t .

$$\triangleright D_B = D_B^0 \cdot e^{-kt}$$

Then,

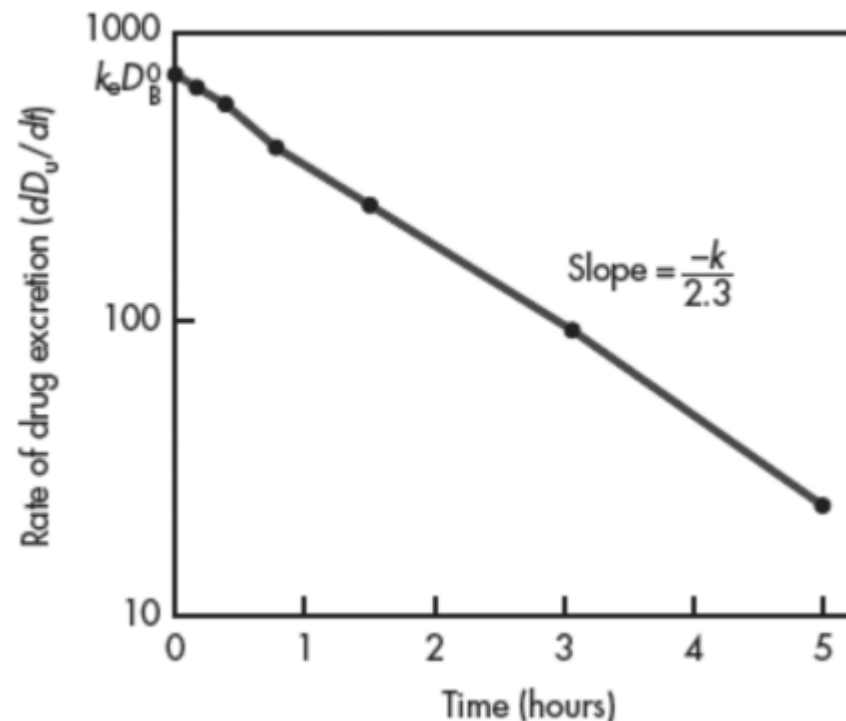
$$\frac{dDu}{dt} = K_e \cdot D_B^0 \cdot e^{-kt}$$

$$\ln \frac{dDu}{dt} = \ln K_e \cdot D_B^0 - kt \text{ (natural log for both sides)}$$

$$\log \frac{dDu}{dt} = \log K_e \cdot D_B^0 - \frac{kt}{2.3} \text{ (change to common log)}$$

$$\frac{(\log \frac{dDu}{dt} - \log K_e \cdot D_B^0)}{t} = \frac{-k}{2.3}$$

- A straight line is obtained from this equation by plotting $\log dD_u/dt$ versus time on a semilog paper dD_u/dt against time.
- The slope of this curve is equal to $-k/2.3$ and the y intercept is equal to $K_e \cdot D_B^0$.
- For rapid intravenous administration, D_B^0 is equal to the dose D_0
- Both k_e and k can be determined by this method



Notes,

- Urine is produced at an approximate rate of 1 mL/min and collected in the bladder until voided for collection. Thus, the drug urinary excretion rate (dD_u/dt) cannot be determined experimentally for any given instant.
- Therefore, the average rate of urinary drug excretion, D_u/t , is plotted against the time corresponding to the midpoint of the collection interval, t^* .

Example:

- A single IV dose of an antibiotic was given to a 50-kg woman at a dose level of 20 mg/kg. Urine and blood samples were removed periodically and assayed for parent drug. The following data were obtained:

Time (hours)	C_p ($\mu\text{g/mL}$)	D_u (mg)
0.25	4.2	160
0.50	3.5	140
1.0	2.5	200
2.0	1.25	250
4.0	0.31	188
6.0	0.08	46

What is the elimination rate constant, k , for this antibiotic?

Solution

Time (hours)	D_u (mg)	D_u/t	mg/h	t^* (hours)
0.25	160	160/0.25	640	0.125
0.50	140	140/0.25	560	0.375
1.0	200	200/0.5	400	0.750
2.0	250	250/1	250	1.50
4.0	188	188/2	94	3.0
6.0	46	46/2	23	5.0

Here t^* = midpoint of collection period and t = time interval for collection of urine sample.

Time (hours)	D_u (mg)	D_u/t	mg/h	t^* (hours)
0.25	160	160/0.25	640	0.125
0.50	140	140/0.25	560	0.375
1.0	200	200/0.5	400	0.750
2.0	250	250/1	250	1.50
4.0	188	188/2	94	3.0
6.0	46	46/2	23	5.0

$$\textit{Slope} = \frac{(y_2 - y_1)}{(x_2 - x_1)} = \frac{-k}{2.3}$$

$$\frac{(\log 250 - \log 400)}{(1.5 - 0.75)} = \frac{-k}{2.3}$$

$$\frac{(2.398 - 2.602)}{0.75} = \frac{-k}{2.3}$$

$$k = 0.626 \text{ h}^{-1}$$

- The elimination rate constant, K , can also be calculated from the slope of the plasma-concentration time curve.

Time (hours)	C_p ($\mu\text{g/mL}$)
0.25	4.2
0.50	3.5
1.0	2.5
2.0	1.25
4.0	0.31
6.0	0.08

$$\frac{(\log 1.25 - \log 3.5)}{(2 - 0.5)} = \frac{-k}{2.3}$$

$$k = 0.685 \text{ h}^{-1}$$



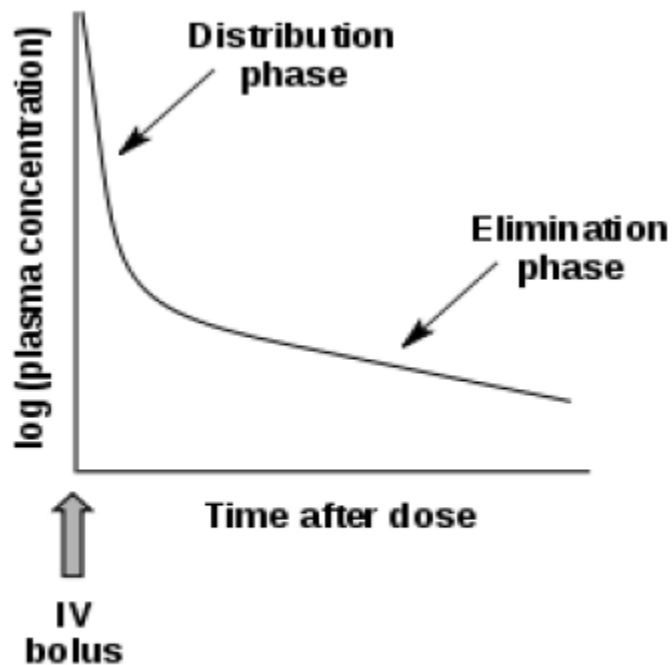
BIOPHARMACEUTICS

Lecture 6

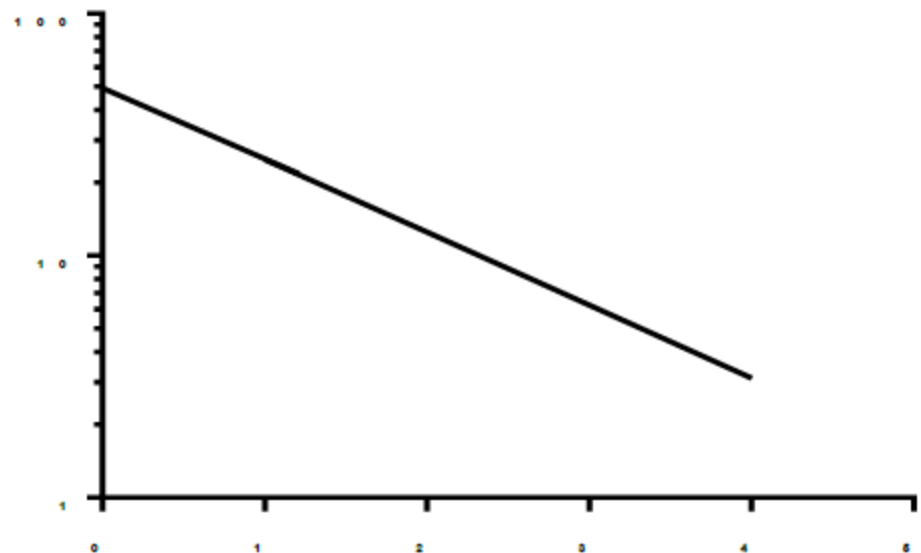
Multicompartment Models

Most drugs entering the systemic circulation require a time to distribute fully throughout the available body space (need time for homogenous distribution).

When given by IV bolus dose, drug concentration declines in a ***biphasic fashion or triphasic fashion***, that is, plasma drug concentrations rapidly decline soon after IV bolus injection, and then decline moderately as some of the drug that initially distributes (equilibrates) into the tissue moves back into the plasma.



**Biphasic
Biexponential**



**Monophasic
Monoexponential**

The early decline phase is commonly called the distribution phase (changes in the concentration of drug in plasma primarily reflect the movement of drug within the body rather than elimination) and the latter phase is called the terminal or elimination phase (the decline of the plasma concentration is associated primarily with elimination of drug from the body).

Unlike the one-compartment model, the multicompartment model assumes that the body composed of more than one-compartment, usually a central compartment and peripheral compartment(s).

- The central compartment usually composed of the blood and highly perfused tissues like the kidney and the liver.
- The tissue or peripheral compartments are composed of groups of tissues with lower blood perfusion and different affinity for the drug like fat, muscle, and cerebrospinal fluid.

The transfer rate processes for the passage of drug into or out of individual compartments are first-order processes.

The nonlinear profile of plasma drug concentration–time is the result of many factors interacting together, including:

1. Blood flow to the tissues.
2. The permeability of the drug into the tissues (fat solubility).
3. Partitioning.
4. The capacity of the tissues to accumulate drug.
5. The effect of disease factors on these processes.

Two-compartment Open Model

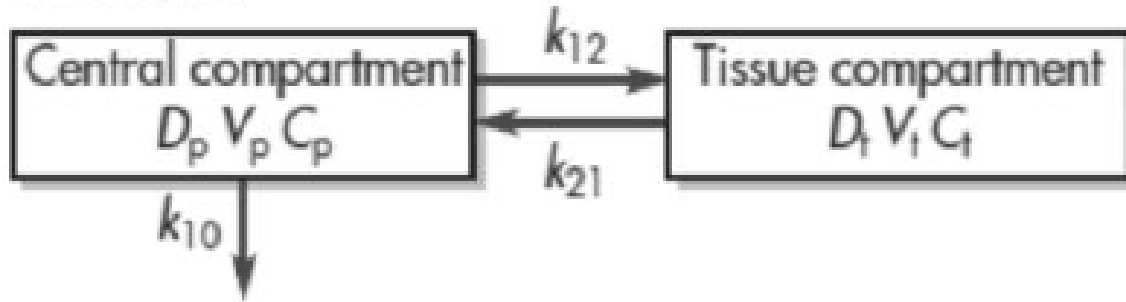
The drug that shows biexponential plasma-concentration time curve is said to follow the two-compartment model.

Drug movement to and out of these compartments can be described as first-order processes.

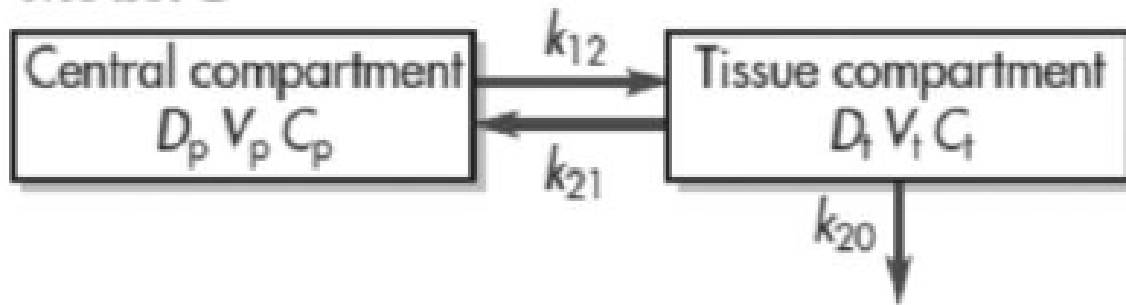
There are several possible two-compartment models based on the compartment from which elimination process occurs.

These possibilities are:

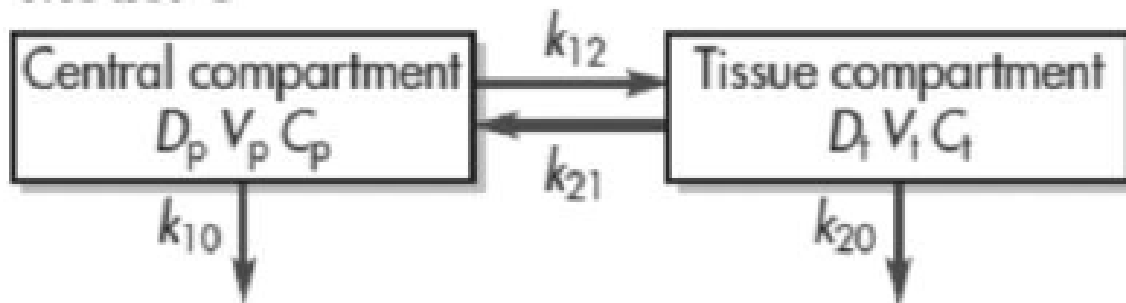
Model A



Model B



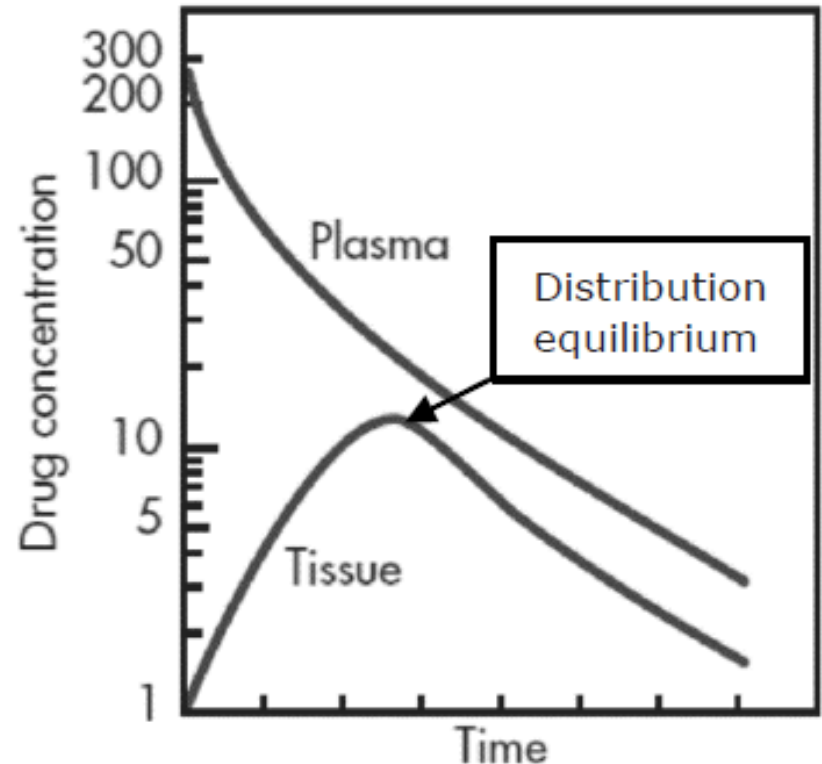
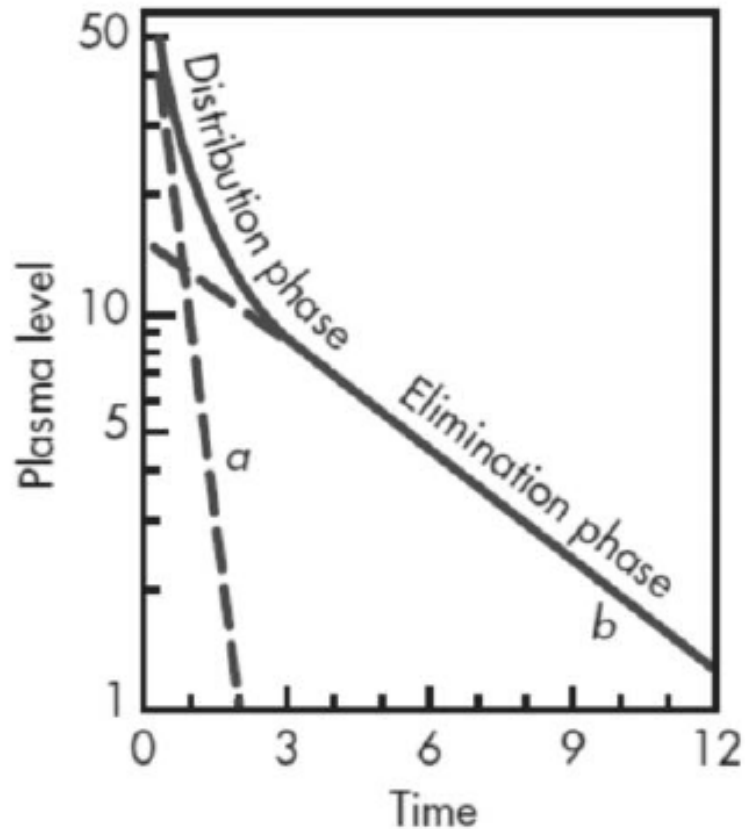
Model C



The rate constants k_{12} and k_{21} represent the first-order rate transfer constants for the movement of drug from compartment 1 to compartment 2 (k_{12}) and from compartment 2 to compartment 1 (k_{21}).

Most two-compartment models assume that elimination occurs from the central compartment model, as shown in the figure, model A. This is because the major sites of drug elimination (renal excretion and hepatic drug metabolism) occur in organs such as the kidney and liver, which are highly perfused with blood.

The plasma level–time curve for a drug that follows a two-compartment model may be divided into two parts, (a) a distribution phase and (b) an elimination phase.



At the distribution phase, plasma concentration decreases rapidly as a result of drug distribution to the peripheral (tissue) compartment and drug concentration in the tissues increases until it reaches maximum.

At maximum tissue concentrations, the fraction of drug in the tissue compartment is now in equilibrium (distribution equilibrium) with the fraction of drug in the central compartment, and the drug concentrations in both the central and tissue compartments decline in parallel and more slowly compared to the distribution phase.

This decline is a first-order process and is called the elimination phase or the beta (b) phase.

Apparent Volumes of Distribution (VD)

In the two-compartment model the term apparent volume of distribution does not consider individual volumes of different compartments. Other terms are more representative to the situation in the two-compartment model like:

Volume of the Central Compartment (V_p)

The volume of the central compartment is useful for determining the drug concentration directly after an IV injection into the body.

$$V_p = \frac{D_0}{C_P^0} \quad , \quad C_P^0 = \frac{D_0}{V_p}$$

Apparent Volume of Distribution at Steady State $(V_D)_{ss}$

This constant relates the plasma concentration and the amount of drug remaining in the body at the time following practical steady state.

At steady-state conditions, the rate of drug entry into the tissue compartment from the central compartment is equal to the rate of drug exit from the tissue compartment into the central compartment.

$$(V_D)_{ss} = \frac{D_p + D_t}{C_p}$$

Where D_p is the amount of the drug in the plasma and D_t is the amount of the drug in the tissue compartment.

Volume of Distribution by Area $(VD)_{\text{area}}$ or $(VD)_\beta$

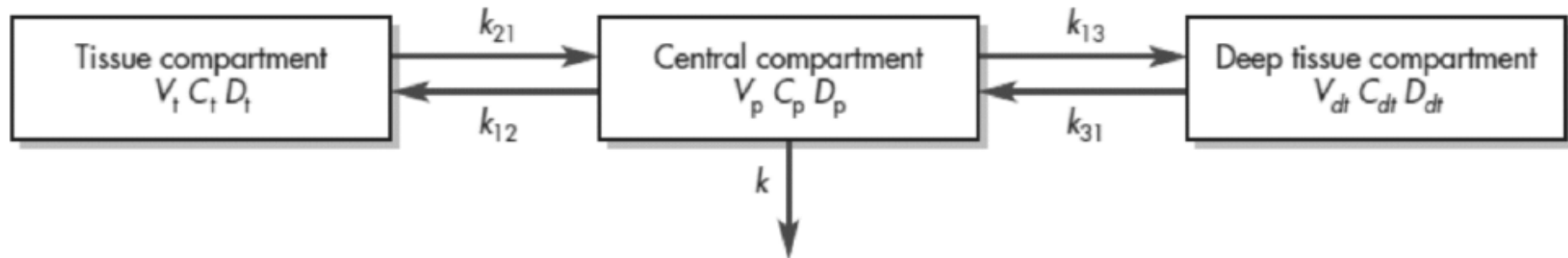
The value of $(VD)_\beta$ might decrease as a result of the reduction in the clearance of the drug as in the case of renal problems.

Clearance

The definition of clearance of a drug that follows a two-compartment model is similar to that of the one-compartment model.

Three-compartment Open Model

The three-compartment model is an extension of the two-compartment model, with an additional deep tissue compartment.



Non-compartmental Analysis

Non-compartmental analysis (NCA) is the most commonly used technique of pharmacokinetic data analysis directly from plasma-concentration data without the need to assume that drug disposition follows compartmental model.

Application of NCA include:

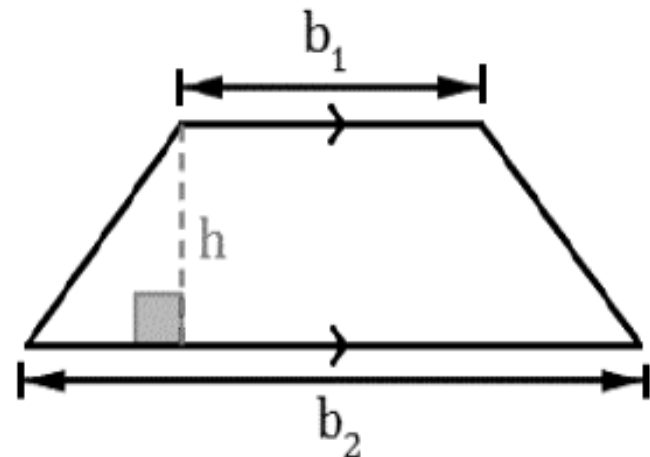
1. The area under the concentration time curve (e.g., in plasma or serum) describes the extent of systemic drug exposure; the peak concentration and its timing indicate the rate of drug input (absorption).
2. Provides estimates for clearance, volume of distribution, terminal half-life, and mean residence time.

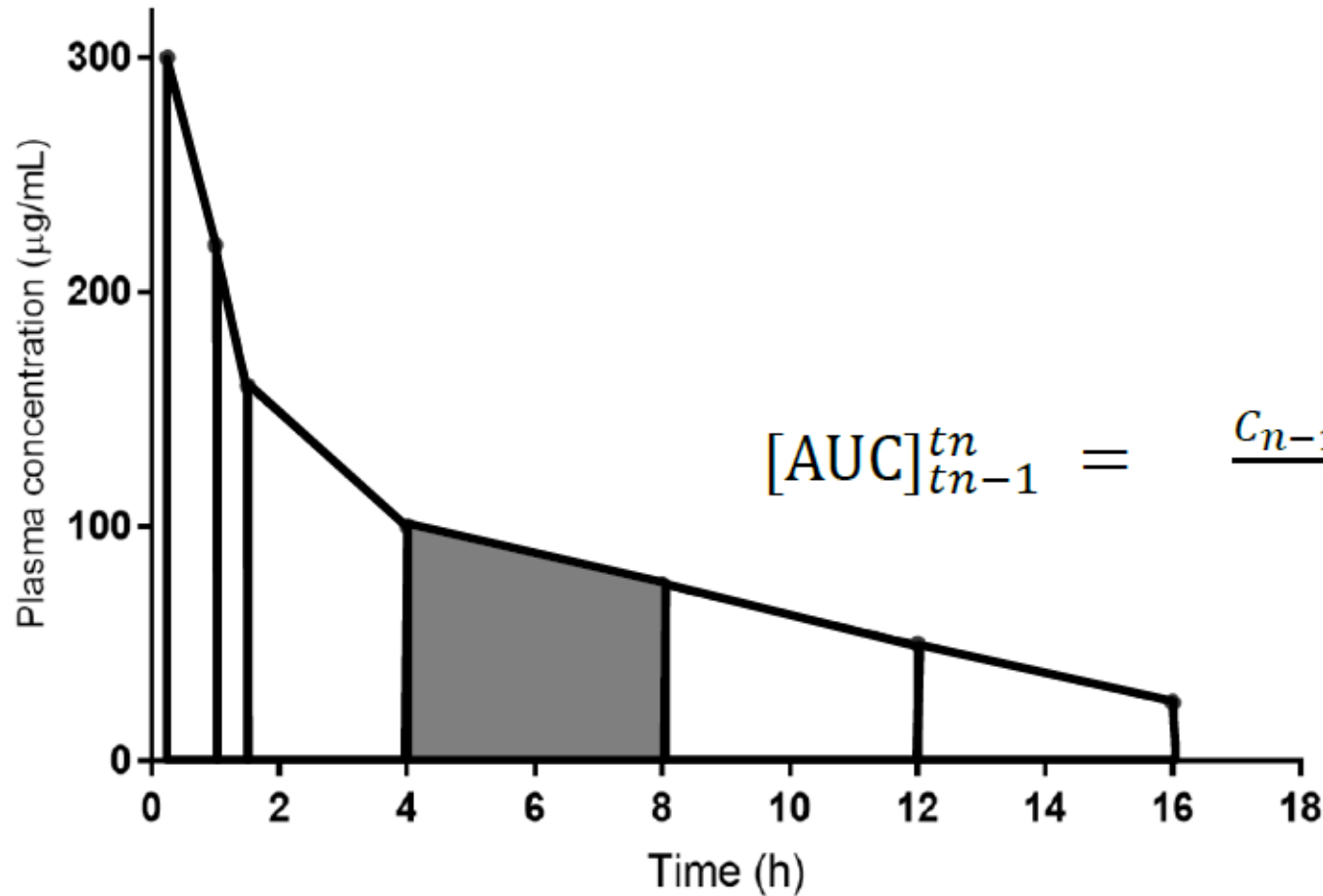
The area under the concentration time curve (AUC)

Area under the concentration time curve (AUC) is the pharmacokinetic parameter reflecting the exposure of the drug.

It can be calculated by trapezoidal rule by assuming the area under the curve is the sum of several small trapezoids as illustrated in the figure below:

$$\text{Area of Trapezoid} = \frac{b_1 + b_2}{2} h$$





$$[AUC]_{t_{n-1}}^{t_n} = \frac{C_{n-1} + C_n}{2} (t_n - t_{n-1})$$

Where [AUC] = area under the curve, t_n = time of observation of drug concentration C_n , and t_{n-1} = time of prior observation of drug concentration corresponding to C_{n-1} .

- To calculate AUC from $t = 0$ to the last observed point $t = n$, we sum all the calculated trapezoid areas.

$$[AUC]_{t0}^{tn} = \sum [AUC]_{tn-1}^{tn}$$

- The calculation of AUC from $t = 0$ to $t = \infty$, we have to calculate the residual area from last time point to $t = \infty$. This can be done by calculating the slope of the last plasma-time curve (the curve has to be plotted on a semilogarithm paper for proper calculations).

$$[AUC]_{tn}^{t\infty} = \frac{C_{pn}}{k}$$

where C_{pn} = last observed plasma concentration at t_n and $k = -\text{slope} \times 2.3$ obtained from the terminal portion of the curve.

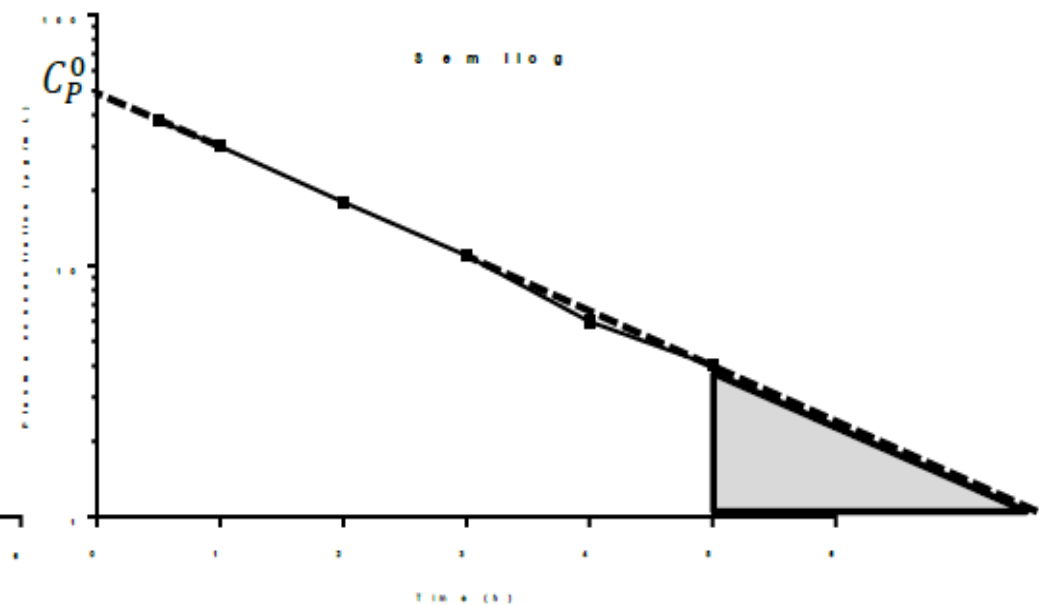
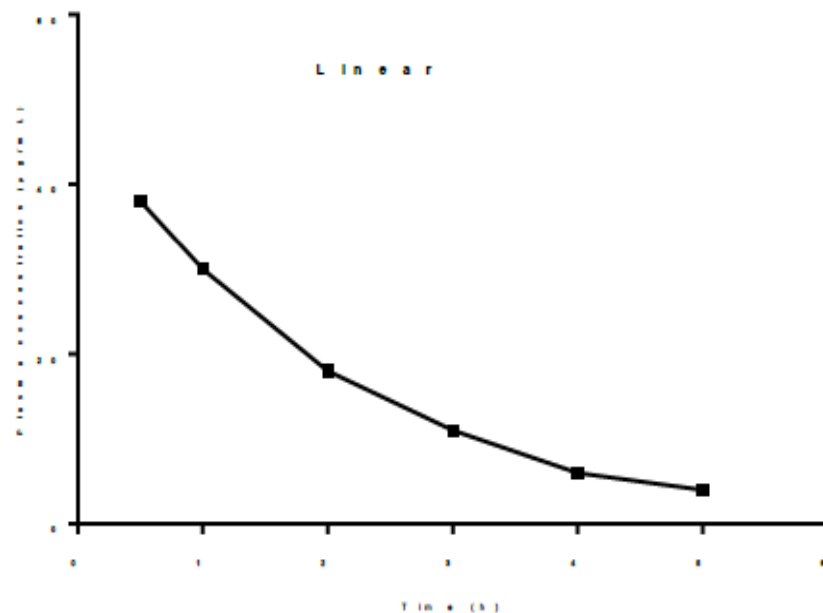
The trapezoidal rule written in its full form to calculate the AUC from $t = 0$ to $t = \infty$ is as follows:

$$[AUC]_0^\infty = \sum [AUC]_{t_{n-1}}^{t_n} + \frac{C_{pn}}{k}$$

The unit of AUC is concentration x time (such as ng/mL . h)

Example: Drug A has the following concentration time profile. Calculate $[AUC]_0^{t_{terminal}}$ and $[AUC]_0^{\infty}$.

Time (h)	Concentration (ng/mL)
0.5	38
1	30
2	18
3	11
4	6
5	4



Solution:

By extrapolating the plasma-concentration time curve to time = 0, the y intercept
= $C_p^0 = 50$ ng/mL

$$[AUC]_0^{t_{terminal}} = \sum [AUC]_{t_{n-1}}^{t_n}$$

$$[AUC]_0^{t_{terminal}} = \left[\left(\frac{50+38}{2} \right) \times (0.5 - 0) + \left(\frac{38+30}{2} \right) \times (1 - 0.5) + \right. \\ \left. \left(\frac{30+18}{2} \right) \times (2 - 1) + \left(\frac{18+11}{2} \right) \times (3 - 2) + \left(\frac{11+6}{2} \right) \times (4 - 3) + \left(\frac{6+4}{2} \right) \times (5 - 4) \right] = 91 \text{ ng/mL} \cdot \text{h}$$

For the calculation of $[AUC]_0^\infty$, we have to calculate the residual area $t=5$ to $t = \infty$ by calculating the slope.

$$\text{Slope} = \frac{\log 4 - \log 6}{5-3} = -0.219 \quad , \quad k = -\text{slope} \times 2.3$$

$$K = 0.5$$

$$[AUC]_0^\infty = [AUC]_0^{t \text{ terminal}} + \frac{C_{p \text{ last observed}}}{k}$$

$$[AUC]_0^\infty = 91 + \frac{4}{0.5} = 99 \text{ ng/mL} \cdot \text{h}$$

Calculation of Volume of Distribution

The apparent VD can be calculated from knowledge of the dose, elimination rate constant, and the area under the curve (AUC) from $t = 0$ to $t = \infty$.

$$V_D = \frac{D_0}{k[AUC]_0^{\infty}}$$

Calculation of Clearance

Clearance can be determined directly from the plasma drug concentration–time curve by:

$$C_l/T = \frac{D_0}{[AUC]_0^\infty}$$

Clearance can be calculated based on AUC without the need for the assumption of compartmental models.

Half-life ($t_{1/2}$)

The time required to reduce the plasma concentration to one half its initial value.

The $t_{1/2}$ provides an index of:

1. The time-course of drug elimination.
2. The time-course of drug accumulation.
3. Choice of dose interval.

The half-life of elimination ($t_{1/2}$) can be determined directly by plotting actual concentrations on semilog graph paper. Other method for the calculation of $t_{1/2}$ is through the estimation of the slope in the plasma-concentration time curve using the following equations:

$$K = - \text{slope} \times 2.3$$

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

The selection of the time points from the plasma-concentration time curve for the calculation of the slope is crucial in the determination of elimination $t_{1/2}$. The last few points of the curve represent the elimination phase. Therefore, the slope should be determined from the elimination phase by using at least the last three points of the curve.



BIPHARMACEUTICS

Lecture 7

DRUG ELIMINATION

Drug elimination refers to the irreversible removal of drug from the body by all routes of elimination.

Drug elimination is usually divided into two major components: excretion and biotransformation.

Drug excretion is the removal of the intact drug.

Nonvolatile and polar drugs are excreted mainly by renal excretion. Other pathways for drug excretion may include the excretion of drug into bile, sweat, saliva, milk (via lactation), or other body fluids. Volatile drugs, such as gaseous anesthetics, alcohol, or drugs with high volatility, are excreted via the lungs into expired air.

Biotransformation or drug metabolism is the process by which the drug is chemically converted in the body to a metabolite.

DRUG CLEARANCE is a pharmacokinetic term for describing drug elimination from the body without identifying the mechanism of the process.

There are several definitions for clearance, the simplest one is the fixed volume of fluid (containing amount of a drug) removed per unit of time.

The units for clearance are volume/ time (eg, mL/min, L/h).

For example, if the Cl of penicillin is 15 mL/min in a patient and penicillin has a VD of 12 L, then from the clearance definition, 15 mL (containing amount of penicillin) of the 12 L will be removed per minute.

Clearance may also be defined as the rate of drug elimination divided by the plasma drug concentration.

$$Cl = \frac{\text{Elimination rte}}{\text{Plasma concentration } (C_p)}$$

$$Cl = \frac{dD_E/dt}{C_P} = \frac{\mu g/min}{\mu g/mL} = mL/min$$

Where D_E is the amount of drug eliminated and dD_E/dt is the rate of elimination.

Rearrangement of the above equation gives:

$$\text{Rate of elimination} = \frac{dD_E}{dt} = C_P Cl$$

The two definitions for clearance are similar because dividing the elimination rate by the C_p yields the volume of plasma cleared of drug per minute.

For first-order elimination rate, dD_E/dt , equals kD_B or kC_pV_D therefore:

$$Cl = \frac{kC_P V_D}{C_P} = k V_D$$

As both volume of distribution, V_D , and a rate constant, k , are constants when the PK is linear, clearance remains constant but the rate of drug elimination, dD_E/dt , might be different.

Example:

Penicillin has a Cl of 15 mL/min. Calculate the elimination rate for penicillin when the plasma drug concentration C_p is 2 $\mu\text{g/mL}$.

Solution:

Elimination rate = $C_p \times \text{Cl}$

$$dD_E/dt = 2 \mu\text{g/mL} \times 15 \text{ mL/min} = 30 \mu\text{g/min}.$$

Using the previous penicillin example, assume that the plasma penicillin concentration is 10 $\mu\text{g/mL}$.

$$dD_E/dt = 10 \mu\text{g/mL} \times 15 \text{ mL/min} = 150 \mu\text{g/min}$$

Thus, 150 µg/min of penicillin is eliminated from the body when the plasma penicillin concentration is 10 µg/mL.

Clearance may be used to estimate the rate of drug elimination at any given concentration.

Using the same example, if the elimination rate of penicillin was measured as 150 µg/min when the plasma penicillin concentration was 10 µg/mL, then the clearance of penicillin is calculated:

$$Cl = \frac{dD_E/dt}{C_P} = \frac{150 \mu g/min}{10 \mu g/mL} = 15 \text{ mL/min}$$

- Elimination rate constant:

$$k = k_R + k_H + k_{\text{other}}$$

Similarly, Cl is the total sum of all of the different clearance processes in the body

$$Cl = Cl_R + Cl_H + Cl_{\text{other}}$$

Renal clearance: $Cl_R = k_R \times V$

Hepatic clearance: $Cl_H = k_H \times V$

Total clearance:

$$Cl = k \times V = (k_R + k_H + k_{\text{other}}) \times V$$

Clearance calculations

Clearance can be calculated using compartmental, noncompartmental, or physiologic methods (all methods will lead to the same results if they are applied correctly).

Compartmental:

- **One-compartment model**

$$Cl = k \times V_D$$

- **Multicompartment model:**

$$Cl = k_{10} \times V_p = (k_R + k_H + k_{\text{other}}) \times V_p$$

The volume of distribution used is the volume of the central compartment.

Non-compartmental:

$$Cl = \text{DOSE} / \text{AUC}_{0-\text{inf}}$$

Physiological model:

Clearance is the product of the flow through an organ (Q) and the extraction ratio of that organ (E). For example, the hepatic clearance is:

$$Cl_H = Q_H \times E_H$$

Clearance values are often adjusted on a per-kilogram-of-actual-body-weight (ABW) or on a per-meter-square-of-surface-area basis, such as L/h per kilogram or per m², or normalized for a “typical” adult of 72 kg or 1.72 m².

The Kidney

The kidney is the main excretory organ for the removal of metabolic waste products and plays a major role in maintaining the normal fluid volume and electrolyte composition in the body.

The renal blood flow (RBF) is the volume of blood flowing through the renal vasculature per unit of time. RBF exceeds 1.2 L/min or about 1700 L/d. Renal plasma flow (RPF) is the RBF minus the volume of red blood cells present. RPF is an important factor in the rate of drug filtration at the glomerulus.

$$\text{RPF} = \text{RBF} - (\text{RBF} \times \text{Hct})$$

where Hct is the hematocrit.

Hct is the fraction of blood cells in the blood, about 0.45 or 45% of the total blood volume.

Rearrangement of the above equation gives:

$$\text{RPF} = \text{RBF} (1 - \text{Hct})$$

The average glomerular filtration rate (GFR) is about 120 mL/min in an average adult, or about 20% of the RPF. The ratio GFR/RPF is the filtration fraction.

Renal Drug Excretion

Renal excretion is a major route of elimination for many drugs. Drugs that are nonvolatile, are water soluble, have a low molecular weight (MW), or are slowly biotransformed by the liver are eliminated by renal excretion. The processes by which a drug is excreted via the kidneys may include any combination of the following:

1. Glomerular filtration
2. Active tubular secretion
3. Tubular reabsorption

Glomerular filtration

Glomerular filtration is a unidirectional process that occurs for most small molecules ($MW < 500$), including undissociated (nonionized) and dissociated (ionized) drugs. Protein-bound drugs behave as large molecules and do not get filtered at the glomerulus.

Glomerular filtration rate (GFR) is measured by using a drug that is eliminated primarily by filtration only (ie, the drug is neither reabsorbed nor secreted). Clinically inulin and creatinine are used for this purpose, although creatinine is also secreted. The clearance of inulin is approximately equal to the GFR, which can equal 120 mL/min.

Active tubular secretion

Active tubular secretion is an active transport process.

As such, active renal secretion is a carrier-mediated system that requires energy input, because the drug is transported against a concentration gradient.

The carrier system is capacity limited and may be saturated.

Drugs with similar structures may compete for the same carrier system.

Tubular reabsorption

Tubular reabsorption occurs after the drug is filtered through the glomerulus and can be an active or a passive process involving transporting back into the plasma. If a drug is completely reabsorbed (eg, glucose), then the value for the clearance of the drug is approximately zero. For drugs that are partially reabsorbed without being secreted, clearance values are less than the GFR of 120 mL/min.

The reabsorption of drugs that are weak acids or bases is influenced by the pH of the fluid in the renal tubule (ie, urine pH) and the pKa of the drug.

The pKa of the drug is a constant, but the normal urinary pH may vary from 4.5 to 8.0, depending on diet, pathophysiology, and drug intake.

Vegetable and fruit diets (alkaline residue diet) result in higher urinary pH, whereas diets rich in protein result in lower urinary pH.

Drugs such as ascorbic acid and antacids such as sodium carbonate may decrease (acidify) or increase (alkalinize) the urinary pH, respectively.

Intravenous fluids, such as solutions of bicarbonate or ammonium chloride, are used in acid-base therapy to alkalinize or acidify the urine, respectively.

The ratio of ionisation is calculated according to ***Henderson and Hasselbalch equation***

$$\text{For weak acids, Ratio} = \frac{[\text{Salt}]}{[\text{Acid}]} = \frac{[\text{A}^-]}{[\text{HA}]} = 10^{(\text{pH}-\text{pKa})}$$

$$\text{For weak bases, Ratio} = \frac{[\text{Base}]}{[\text{Salt}]} = \frac{[\text{B}]}{[\text{BH}^+]} = 10^{(\text{pH}-\text{pKa})}$$

For example, amphetamine, a weak base, will be reabsorbed if the urine pH is made alkaline and more lipid-soluble nonionized species are formed. In contrast, acidification of the urine will cause the amphetamine to become more ionized (form a salt). The salt form is more water soluble, less likely to be reabsorbed, and tends to be excreted into the urine more quickly. In the case of weak acids (such as salicylic acid), acidification of the urine causes greater reabsorption of the drug and alkalinization of the urine causes more rapid excretion of the drug.

Renal clearance

Renal clearance, Cl_R , is defined as the volume that removed of the drug per unit of time through the kidney. Also it can be defined as the urinary drug excretion rate (dD_u/dt) divided by the plasma drug concentration (C_p).

$$Cl = \frac{dD_u/dt}{C_P}$$

The total body clearance can be defined as the sum of the renal clearance (Cl_R) and the nonrenal clearance (Cl_{NR})

$$Cl = Cl_R + Cl_{NR}$$

Therefore,

$$Cl_R = f_e \times Cl$$

where f_e is the proportion of the bioavailable dose that is eliminated unchanged in the urine.

Since,

$$Cl = \text{DOSE}/AUC_{0-\text{inf}}$$

Then renal clearance after single IV administration is:

$$C_{/R} = \frac{f_e \times \text{Dose}}{AUC_{0-\text{inf}}}$$

$$C_{/R} = \frac{Ae_{0-\text{inf}}}{AUC_{0-\text{inf}}}$$

where $Ae_{0-\text{inf}}$ is the amount of drug eliminated unchanged in the urine from time 0 to infinity after a single dose.

In practice it is not possible to measure the amount of drug excreted unchanged in the urine until infinity. Therefore, it is recommended to collect the urine and observe the AUC for the longest time period possible, ideally more than 3-4 terminal half-lives, so that the error made using this formula is less than 10%.

$$C/R = \frac{Ae_{0-x}}{AUC_{0-x}}$$

where x is the maximum length of time during which both urinary excreted amounts and the AUC can be observed.

Example

An antibiotic is given by IV bolus injection at a dose of 500 mg. The drug follows a one-compartment model. The total volume of distribution was 21 L and the elimination half-life was 6 hours. Urine was collected for 48 hours, and 400 mg of unchanged drug was recovered. What is the fraction of the dose excreted unchanged in the urine? Calculate k , k_R , Cl , Cl_R , and Cl_{NR} .

Solution

Since the elimination half-life, $t_{1/2}$, for this drug is 6 hours, a urine collection for 48 hours represents $8 \times t_{1/2}$, which allows for greater than 99% of the drug to be eliminated from the body. The fraction of drug excreted unchanged in the urine, f_e , is calculated by the following equation:

$$f_e = \frac{\text{The amount excreted unchanged}}{\text{Dose}} = \frac{400}{500} = 0.8$$

$$k = \frac{0.693}{6} = 0.1155 \text{ h}^{-1}$$

$$k_R = f_e \times k = 0.8 \times 0.1155 = 0.0924 \text{ h}^{-1}$$

$$Cl = k \times V_D = 0.1155 \times 21 = 2.43 \text{ L/h}$$

$$Cl_R = k_R \times V_D = 0.0924 \times 21 = 1.94 \text{ L/h}$$

$$Cl_{NR} = Cl - Cl_R = 2.43 - 1.94 = 0.49 \text{ L/h}$$

