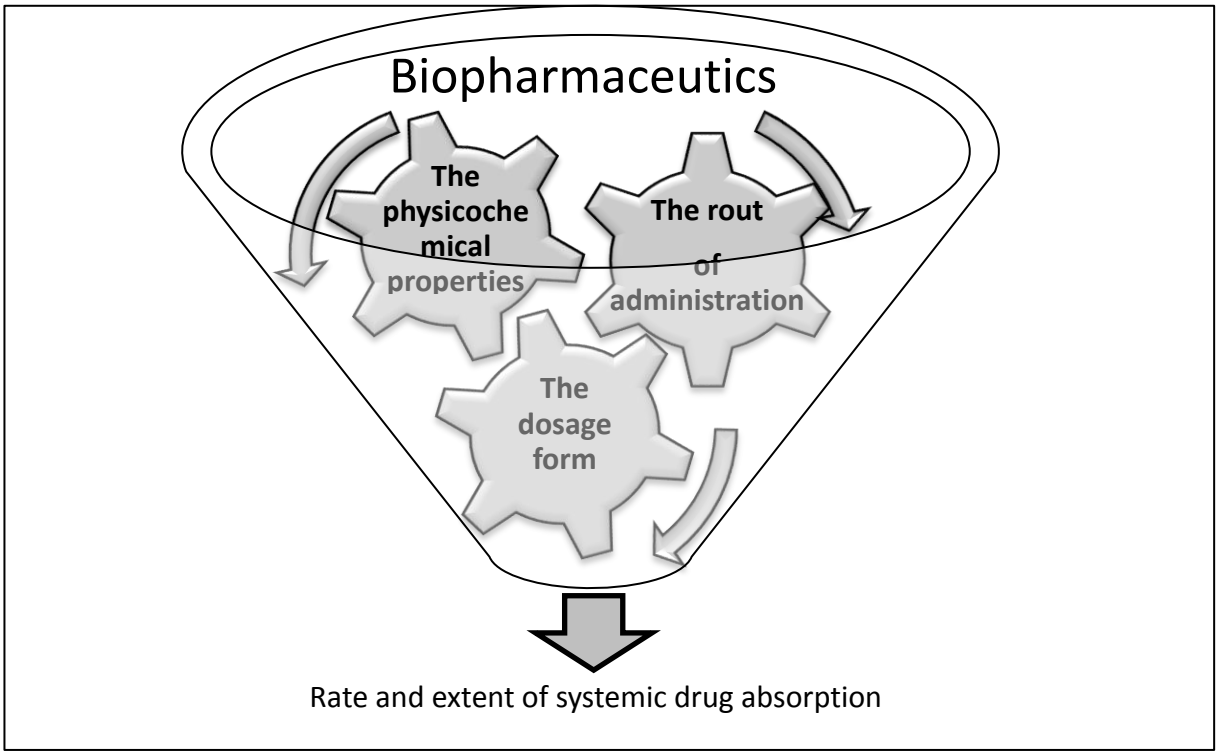
General concepts in biopharmaceutics and pharmacokinetics

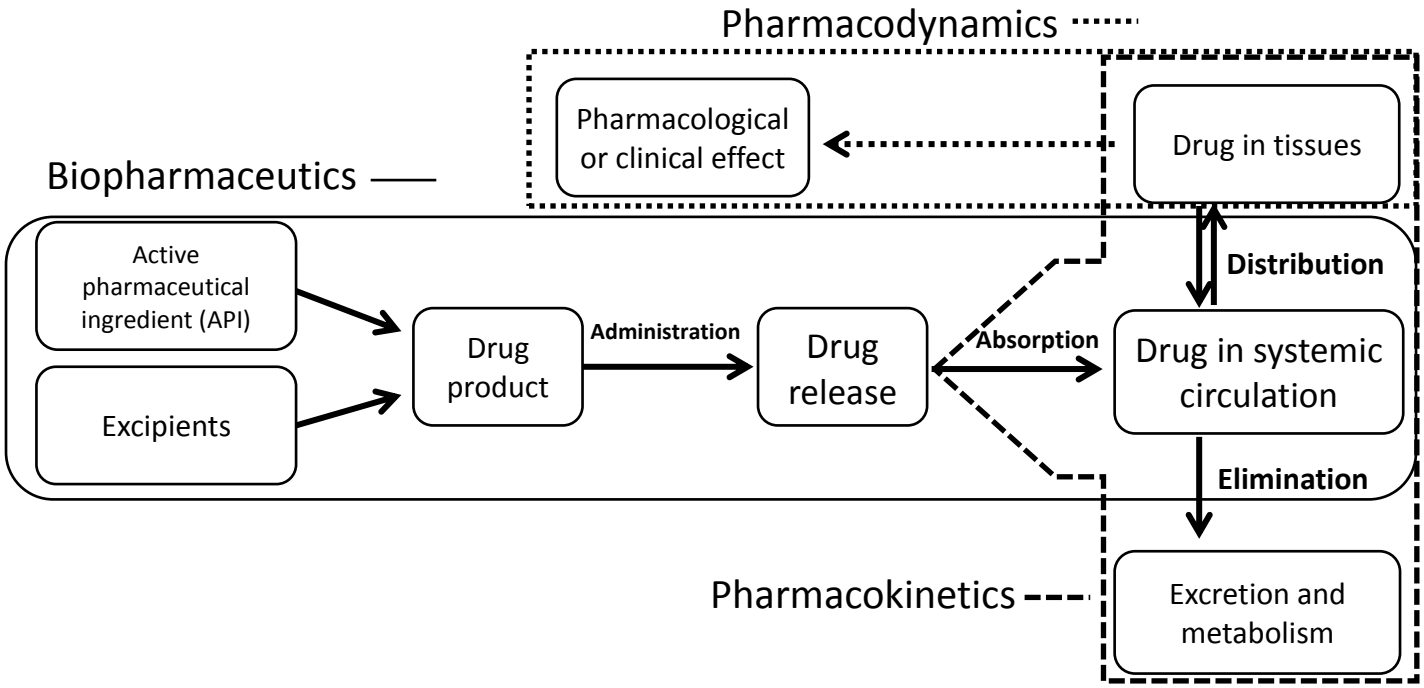
Biopharmaceutics

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 (both





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, injectables, suppositories, transdermal systems, 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 of drug administration

Table 1. Common routes of drug administration

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.

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 **(Figure 1).**

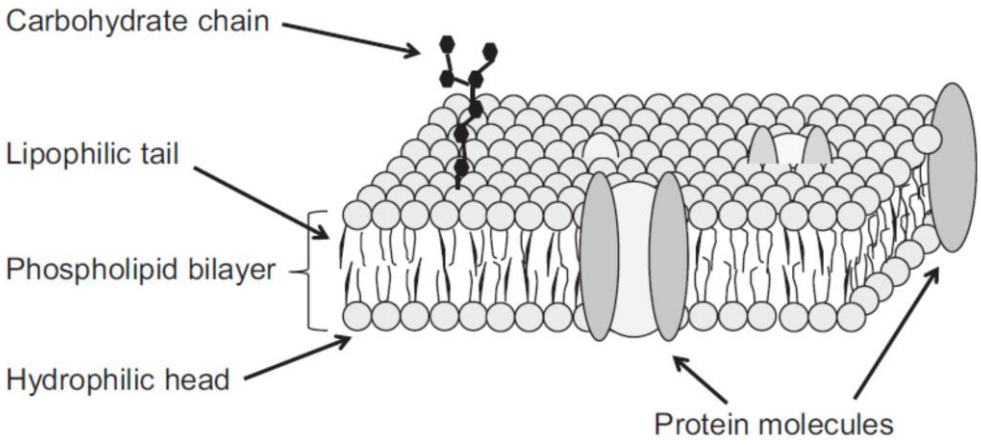


Figure 1. Schematic representation of a cell membrane.

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.

Some drugs are probably absorbed by a mixed mechanism involving one or more processes.

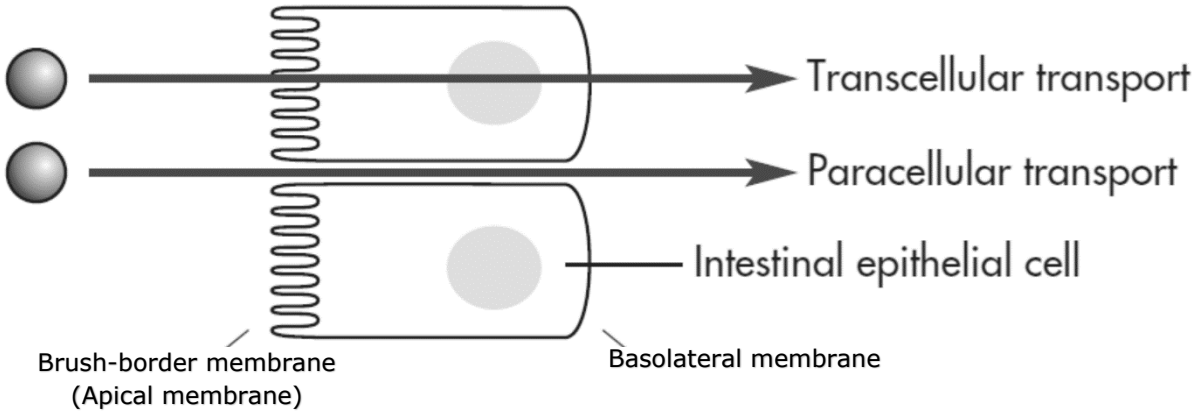


Figure 2. Transport mechanisms across cell membranes, epithelial cells (enterocytes) of the GIT as example.

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.

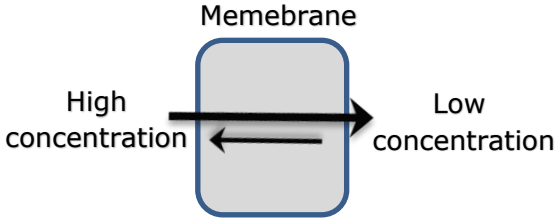


Figure 3. Schematic representation for net movements of molecules across cell membrane based on passive diffusion law.

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.

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

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 µg/mL or ng/mL range. If the drug is given orally, then $C_{GI} >> C_p$ 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.

The extent of ionisation depends on the pKa of the drug and the pH of the medium according to ***Henderson and Hasselbalch*** **equation.**

For weak acids,

$$AH \overset{Ka}{\rightleftharpoons} A^- + H^+$$

$$\text{Ratio} = \frac{[\text{Salt}]}{[\text{Acid}]} = \frac{[A-]}{[HA]} = 10^{(\text{pH-p}Ka)}$$

For weak bases,

$$BH^+ \overset{Ka}{\rightleftharpoons} B + H^+$$

$$\text{Ratio} = \frac{[\text{Base}]}{[\text{Salt}]} = \frac{[B]}{[BH+]} = 10^{(\text{pH-p}Ka)}$$

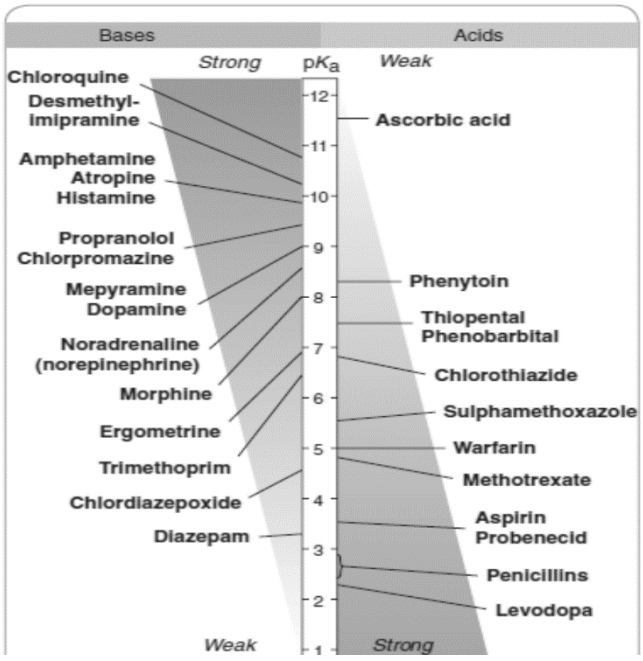


Figure 4 . pKa values for some acidic and basic drugs

Examples;

- Calculate the extent of ionisation for salicylic acid (pKa = 3.0) in plasma.

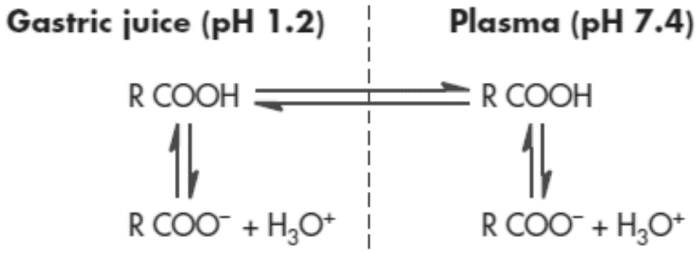
  The pH of plasma is 7.4

  - Ratio = $\frac{[\text{Salt}]}{[\text{Acid}]} = 10^{(7.4 - 3)}$
  - Log $\frac{[\text{Salt}]}{[\text{Acid}]} = 7.4 - 3 = 4.4$
  - $\frac{[\text{Salt}]}{[\text{Acid}]} = 2.51 \times 10^4$

  At plasma pH, salicylic acid exists mostly in its ionized or water-soluble form.

Note: For nonelectrolyte drugs or drugs that do not ionize, the drug concentrations on either side of the membrane are the same at equilibrium. However, for electrolyte drugs or drugs that ionize, the total drug concentrations on either side of the membrane are not equal at equilibrium if the pH of the medium differs on respective sides of the membrane.

For example, the concentration of salicylic acid (pKa = 3.0) in the stomach (pH 1.2) as is different from its concentration in the plasma (pH 7.4) as shown in the following figure.



In the plasma, at pH 7.4

Ratio = $\frac{[\text{RCOO}-]}{[\text{RCOOH}]} = 2.51 \times 10^4$

In gastric juice, at pH 1.2

Ratio = $\frac{[\text{RCOO}-]}{[\text{RCOOH}]} = 1.58 \times 10^{-2}$

If the pH on one side of a cell membrane differs from the pH on the other side of the membrane, then
(1) the drug (weak acid or base) will ionize to different degrees on respective sides of the membrane;
(2) the total drug concentrations (ionised plus nonionised drug) on either side of the membrane will be unequal; and
(3) the compartment in which the drug is more highly ionized will contain the greater total drug concentration.

- **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.

Such drugs may have a higher **total drug** concentration on the side where binding occurs, yet the **free drug** concentration that diffuses across cell membranes will be the same on both sides of the membrane.

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 ie, 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 biding sites may become saturated if high concentration of the 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).

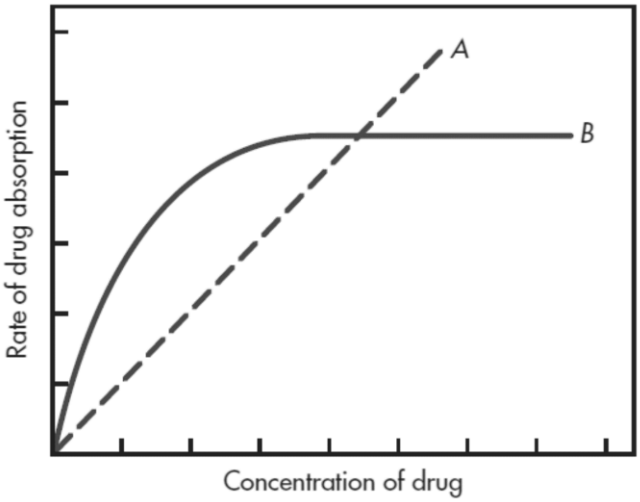


Figure 5. Comparison of the rate of absorption for a drug absorbed by passive diffusion (Line A) and drug absorbed by carrier mediated absorption (Line B).

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 (ie, 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.

Transporters and Carrier-Mediated Intestinal Absorption

Both influx and efflux transporters are present in the brush border and basolateral membrane that will increase drug absorption (influx transporter) or decrease drug absorption (efflux transporter). Please refer to **Figure 6** for examples.

Many drugs are absorbed by carrier systems because of the structural similarity to natural substrates. The small intestine expresses a variety of **uptake transporters** for amino acids, peptides, hexoses, organic anions, organic cations, nucleosides, and other nutrients.

P-glycoprotein (P-gp or called MDR1)) is an example of **efflux transporters**. MDR1 is one of the many proteins known as *multidrug-resistance associated protein*. It is important in pumping drugs out of cells and causing treatment resistance. P-gp is also present in various human tissues like the kidney, brain, adrenal medulla, and the prostate.

The expression of P-gp is often triggered in many cancer cells making them drug resistant due to drug efflux.

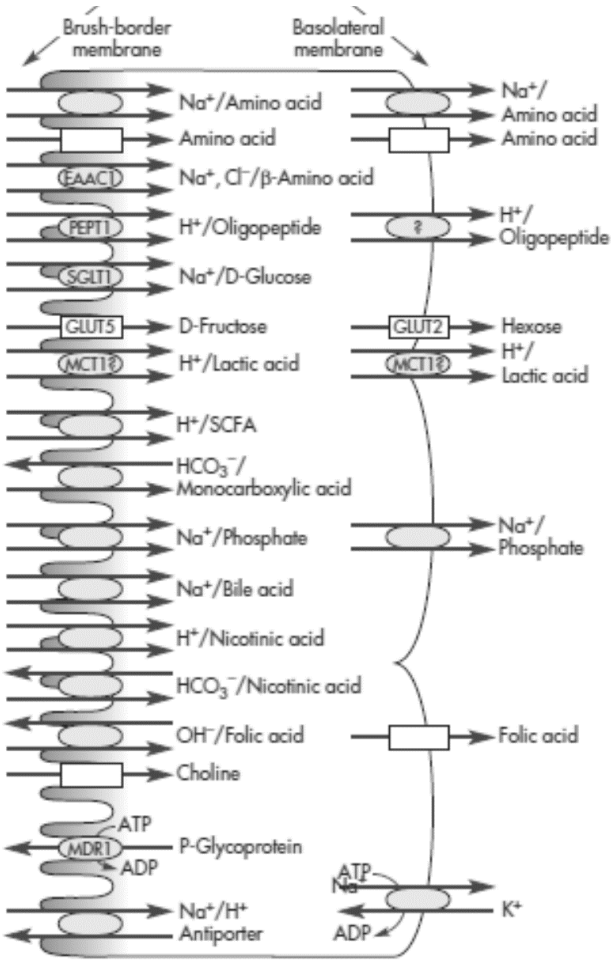


Figure 6 . Summary of intestinal epithelial transporters. Transporters shown by a square represent ***active transporters***. Oval transporters represent ***facilitated transporters***.

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 (see **Figure 1** in this lecture notes). Small molecules including drugs move through the channel by diffusion more rapidly than at other parts of the membrane.

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 (**Figure 7**).
2. The presence or absence of food.
3. Degradative enzymes.
4. Varying drug permeability in the different regions of the intestine.

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.**

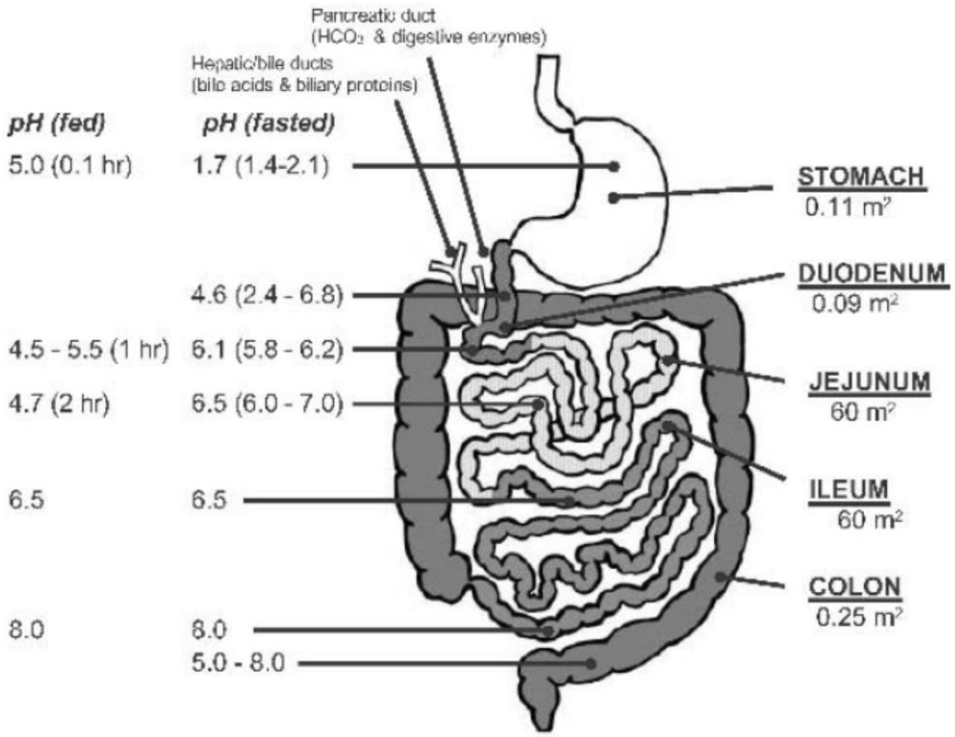


Figure 7. Schematic representation of the main parts of the gastrointestinal tract (GIT) showing the differences in pH and surface areas at each part.

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 it the case 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. Disease, any disease 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. Examples include achlorhydric patients (decrease gastric pH), HIV–AIDS patients (decreased gastric transit time, diarrhea, and achlorhydria), Crohn's disease (thickening of the bowel wall), and congestive heart failure (CHF) patients (reduced splanchnic blood flow).

6. Drugs such as anticholinergic (reduce stomach acid secretion), metoclopramide (increases intestinal peristalsis), antacids containing aluminum, calcium, or magnesium (complex with drugs such as tetracycline and ciprofloxacin), proton pump inhibitors (decrease gastric acid production), and cholestyramine (binds warfarin, thyroxine, and loperamide).

Effect of Food on Gastrointestinal Drug Absorption

1. Delay in gastric emptying
2. Stimulation of bile flow
3. A change in the pH of the GI tract
4. An increase in splanchnic blood flow
5. A change in luminal metabolism of the drug substance
6. Physical or chemical interaction of the meal with the drug product or drug substance

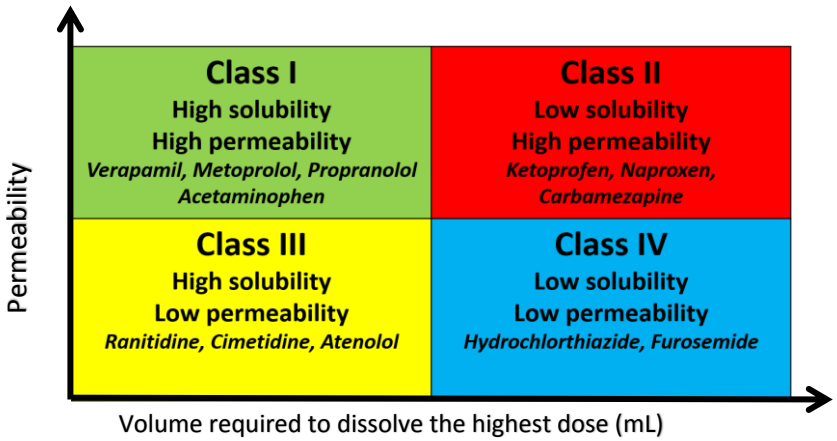
Rate-limiting Steps in Oral Drug Absorption

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.

The slowest step in a series of kinetic processes is called the ***rate-limiting step***

THE BIOPHARMACEUTICS CLASSIFICATION SYSTEM (BCS)



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 (**Figure 8**).

Solid drug products exempted from disintegration tests include troches (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.

Complete disintegration is defined by the USP-NF (National Formulary) as "that state in which any residues of the tablet remaining on the screen of the test apparatus in the soft mass have no palpably firm core.

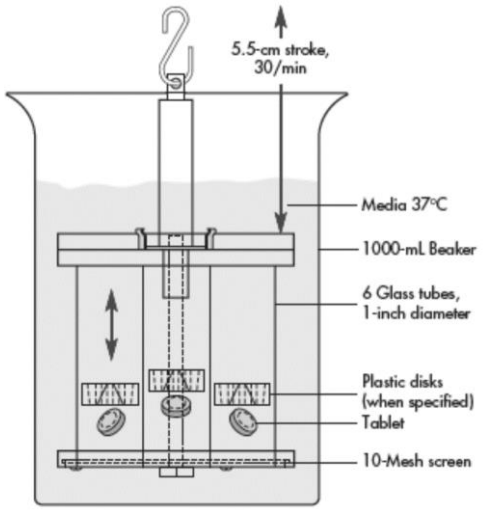


Figure 8. USP disintegration testing apparatus.

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 ± 2º 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

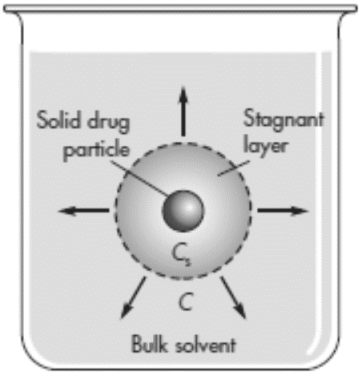


Figure 9 . Representation of dissolution process.

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 include

(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 (**Figure 9**).

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.

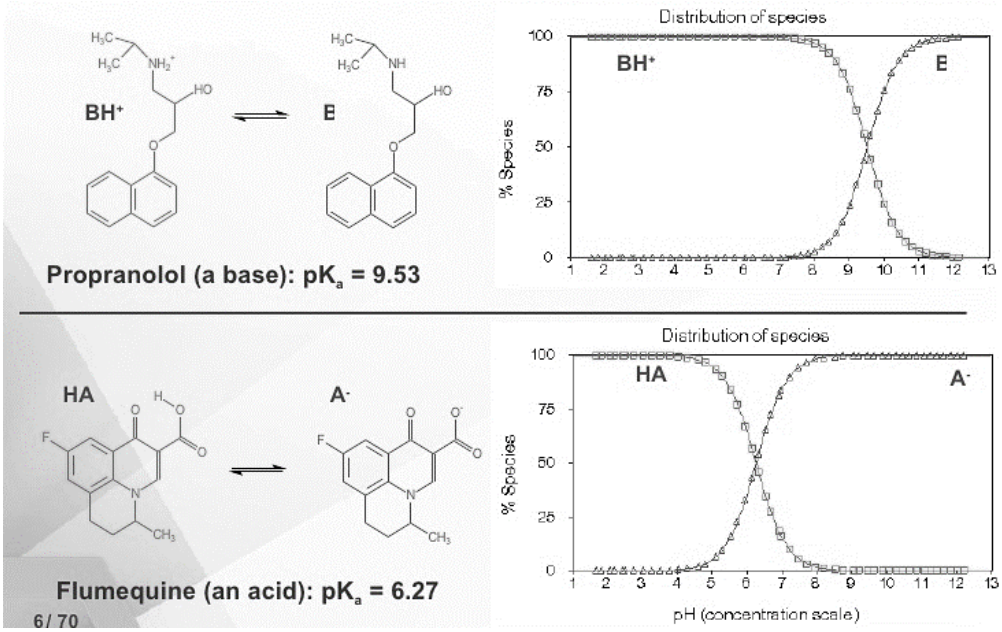


Figure 10. Ionisation of weak base (propranolol) and weak acid (flumequine) at different pH.

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 (**Figure 11**).

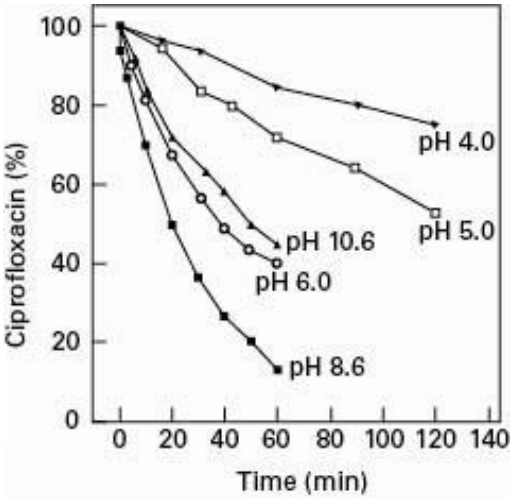


Figure 11 . Stability of ciprofloxacin at different pH

Pharmaceutical approaches for the enhancement of drug stability

For example, erythromycin has a pH-dependent stability profile.

The knowledge of erythromycin stability subsequently led to the preparation of a less water-soluble erythromycin salt that is more stable in the stomach. The dissolution rate of erythromycin drug substance powder, without excipients, varied from 100% dissolved in 1 hour for the water-soluble version to less than 40% dissolved in 1 hour for the less water-soluble version. The slow-dissolving erythromycin drug substance also resulted in slow-dissolving drug products formulated with the modified drug.

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 (BCS II); 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.

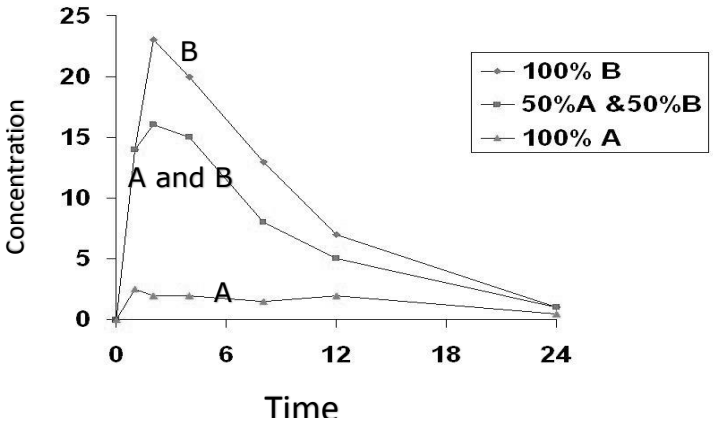


Figure12 . Plasma concentration-time profiles following oral administration of **A, B**, and a mixture of **A** and **B** polymorph forms of chloramphenicol.

- **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 (**Figure 13**).
2. Ampicillin trihydrate was reported to be less absorbed than the anhydrous form of ampicillin because of faster dissolution of the latter

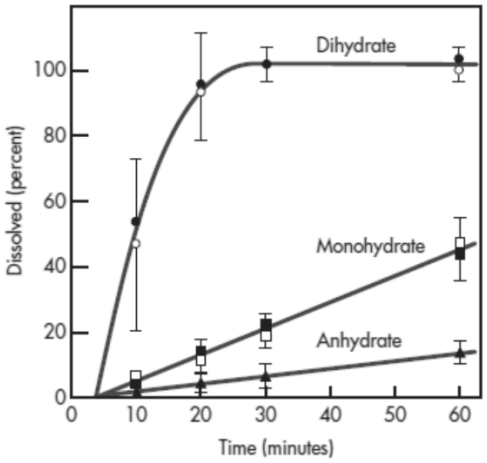


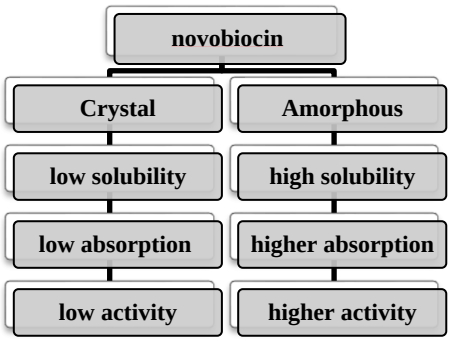
Figure 13 . Dissolution profile of mon-, di-, and anhydrate erythromycin

- **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.



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 (**log *P***)	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.

Examples of excipients and their role in the dosage form

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
Titinium dioxide	Combined with dye as colored coating
Methylcellulose	Coating or granulating agent
Cellulose acetate phthalate	Enteric-coating agent

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

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 (**Figure 14**).

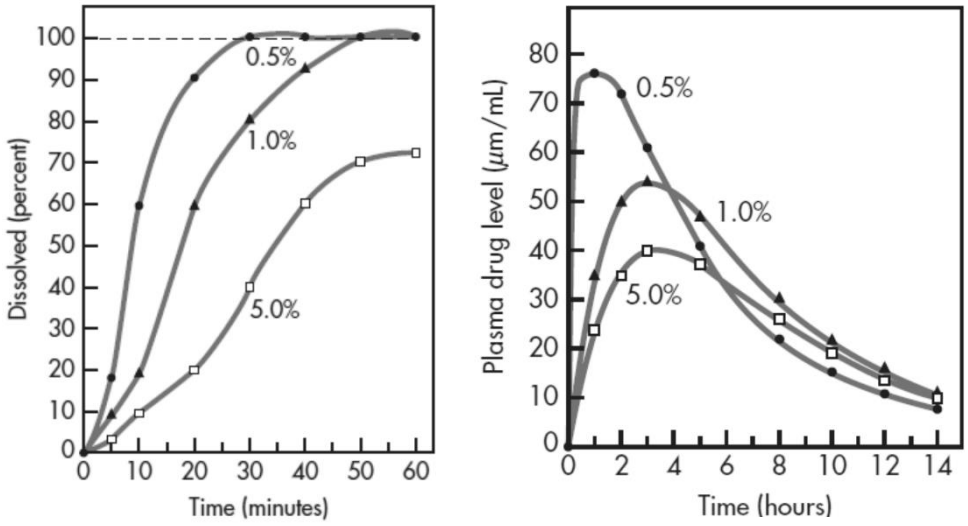


Figure 14. The effect of adding different concentrations of magnesium stearate to a tablet formulation on the dissolution profile (left panel) and plasma conc.-time profile (right panel).

- Coatings, particularly shellac, will crosslink upon aging and 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. The term for this process is ***dissolution in a reactive medium***.

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.

Effect of excipients on the pharmacokinetic parameters of oral drug products

Excipients	**Example**	k_a	t_{max}	**AUC**
Disintegrants	Avicel, Explotab	↑	↓	↑/−
Lubricants	Talc, hydrogenated vegetable oil	↓	↑	↓/−
Coating agent	Hydroxypropylmethyl cellulose	−	−	−
Enteric coat	Cellulose acetate phthalate	↓	↑	↓/−
Sustained-release agents	• Methylcellulose, ethylcellulose • Castorwax, Carbowax (waxy agents) • Veegum, Keltrol (gum/viscous)	↓	↑	↓/−

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 shelflife).

4. Establish *in vivo–in vitro* correlations (IVIVC)
5. Evaluate the biopharmaceutic implications of a product change, rather than to require a bioequivalence study (SUPAC—scale-up and postapproval changes).

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

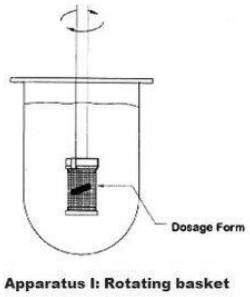
1. The size and shape of the dissolution vessel.
2. The amount of agitation and the nature of the stirrer affect hydrodynamics of the system.
3. The temperature of the dissolution medium (most dissolution tests are performed at 37°C. However, for transdermal drug products, the recommended temperature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

***Sink conditions**:* the quantity of medium used should not be less than 3 times that needed to form a saturated solution of the drug substance

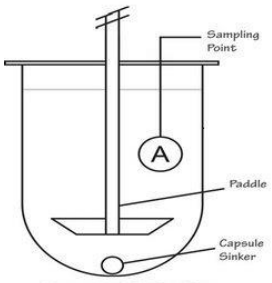
USP-NF Dissolution Apparatus

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

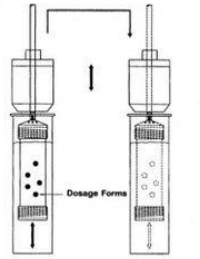
Apparatus 5	Paddle over disk	Rotating stirrer	Transdermal drug products	Modification of USP II apparatus stainless steel disk to hold the transdermal system at the bottom of the vessel
Apparatus 6	Cylinder	Rotating stirrer	Transdermal drug products	Modification of USP I apparatus Samples are hold in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



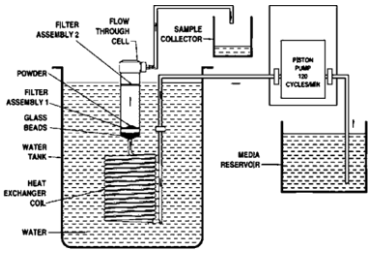
Apparatus I: Rotating basket

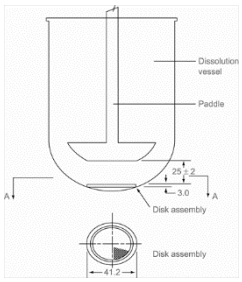


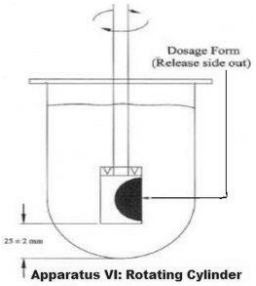
Apparatus II: Paddle



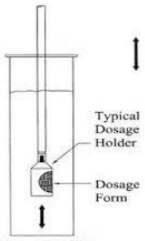
Apparatus III
Reciprocating cylinder





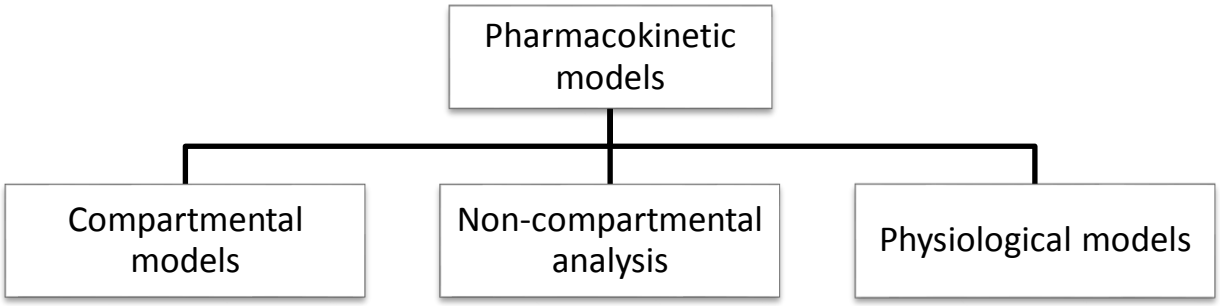


Apparatus VI: Rotating Cylinder



Apparatus VII:
Reciprocating Holder

Pharmacokinetic Models

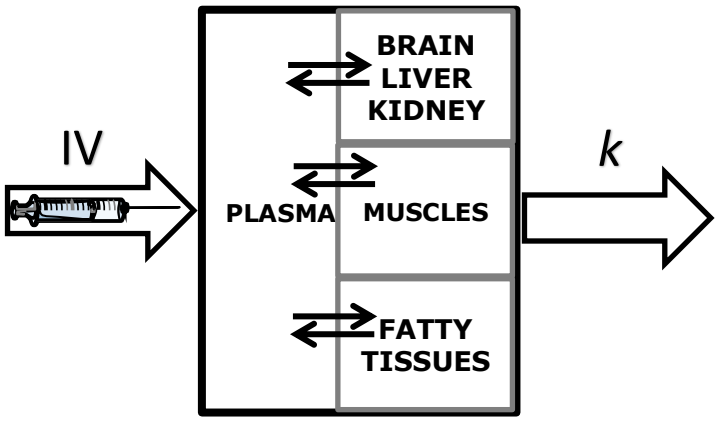


Compartmental models

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:
- $K = k_e + k_m + k_b + ...$

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

$$\frac{dDB}{dt} = - K.\ D_B$$

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.

$$D_B = D_B^0 \,.\, e^{-kt}$$

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*)

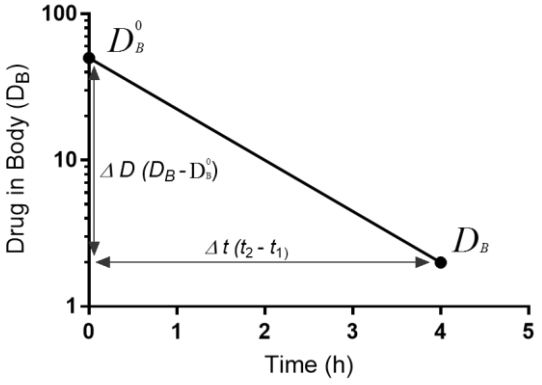
$\log D_B = \log D_B^0 - \frac{kt}{2.3}$

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

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

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

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



The volume of distribution (V_D)

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 (V_D) 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

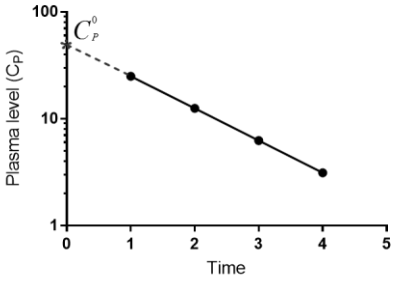
$\log C_P = \log C_P^0 - \frac{kt}{2.3} \quad \Longleftrightarrow \quad C_P = C_P^0 \cdot e^{-kt}$

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 V_D.

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 V_D. Drugs with a large apparent V_D 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 V_D 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 V_D is 3500 mL for a subject weighing 70 kg, the V_D expressed as percent of body weight is

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

If V_D 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 V_D is a useful parameter in considering the relative amounts of drug in the vascular and in the extravascular tissues.

For each drug, the apparent V_D is a **constant**. In certain pathologic cases, the apparent V_D 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 V_D 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 V_D.

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.

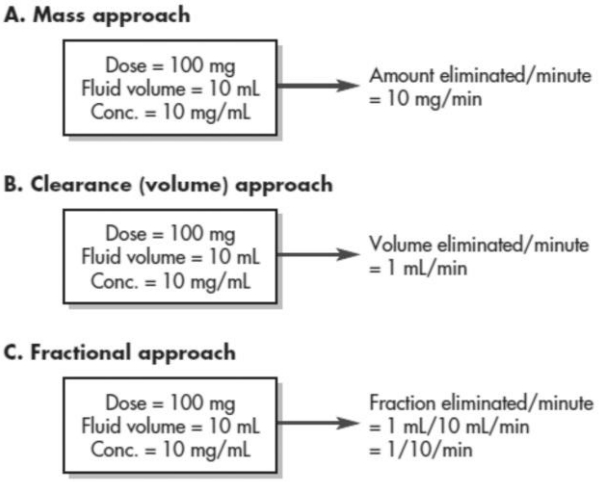


Diagram illustrating three different ways of describing drug elimination after a dose of 100 mg injected IV into a volume of 10 mL.

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*/*V*D.

- 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 ∝ Amount of the drug in the body

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

$$\frac{dDu}{dt} = K_e \,.\, D_B$$

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*.

- $D_B = D_B^0 \,.\, e^{-kt}$

Then,

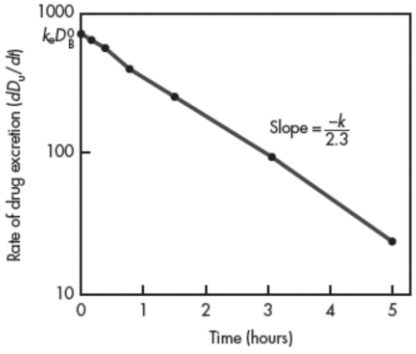
$$\frac{dDu}{dt} = K_e \,.\, D_B^0 \,.\, e^{-kt}$$

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

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

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

- 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 $K_e \,.\, D_B^0$.
- 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 (μg/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

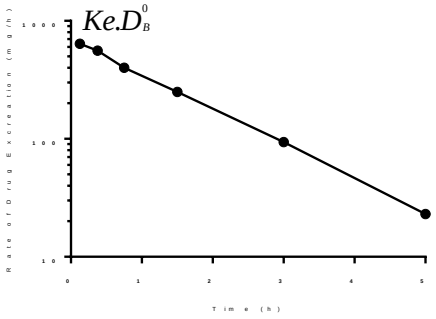
What is the elimination rate constant, k, for this antibiotic?

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.

Plot the data on a semilog paper



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

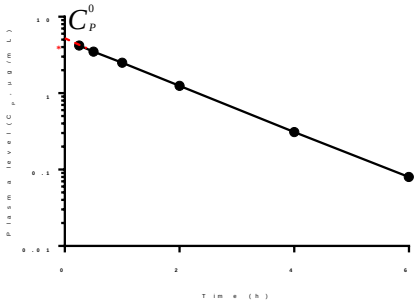
$$\textbf{Slope} = \frac{(y_2 - y_1)}{(x_2 - x_1)} = \frac{-k}{2.3}$$

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

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

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

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

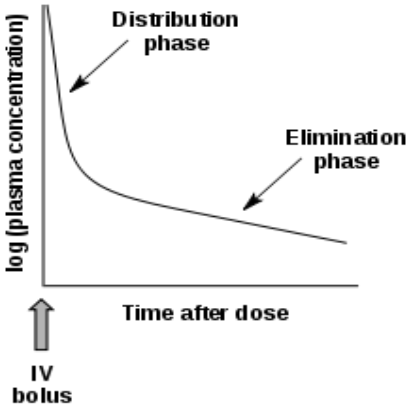


Time (hours)	C_p (μg/mL)
0.25	4.2
0.50	3.5
1.0	2.5
2.0	1.25
4.0	0.31
6.0	0.08

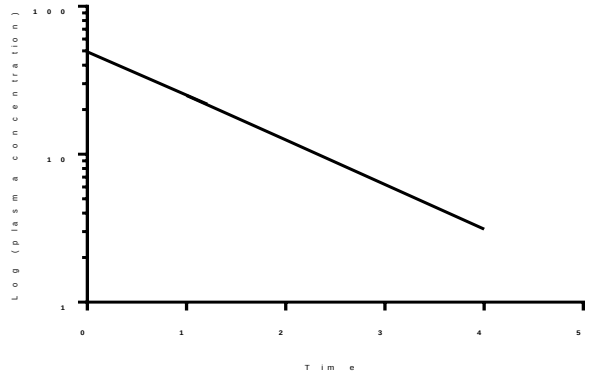
$$\frac{(\log 1.25 - \log 3.5)}{(2-0.5)} = \frac{-k}{2.3} \qquad k = 0.685\ h^{-1}$$

Multicompartments 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
Biexponentional



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.

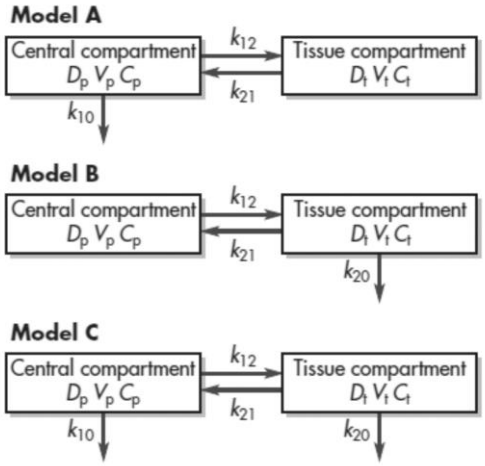
The nonlinear profile of plasma drug concentration–time is the result of many factors interacting together, including

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

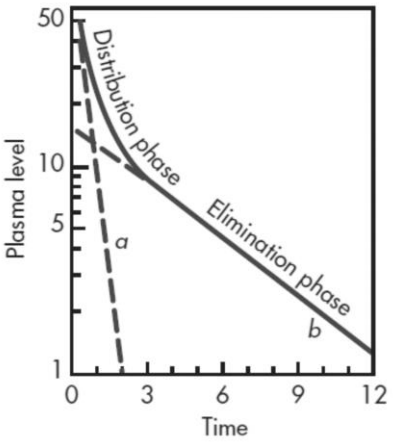
The drug that shows biexponential plasma-concentration time curve is said to follow the two-compartment model. Drug movement to and out of these compartments can be described as first-order processes.

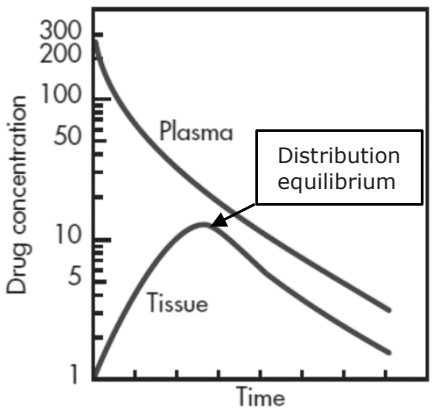
There are several possible two-compartment models based on the compartment from which elimination process occurs. These possibilities are described in the figure below:



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.*

Method of Residuals for PK analysis of Two-compartments Plasma Curves

This method allows the separation of biexponential plot of plasma concentration against time into its monoexponential constituents.

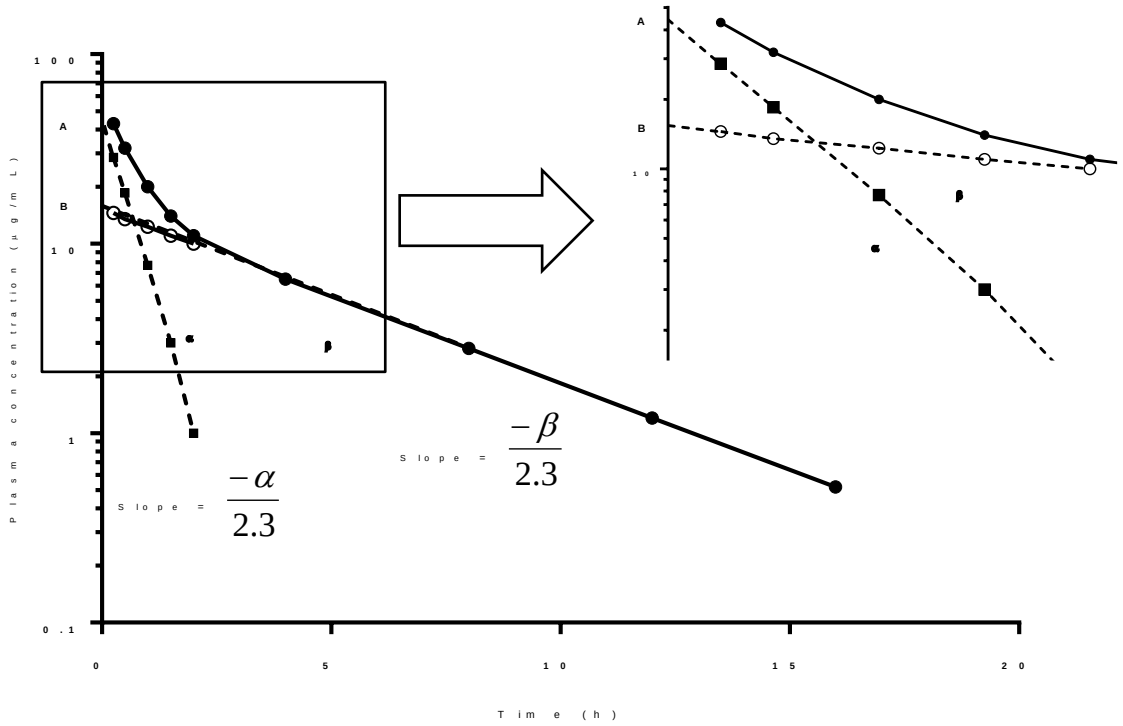
Example:
For example, 100 mg of a drug was administered by rapid IV injection to a healthy 70-kg adult male. Blood samples were taken periodically and assayed for drug. The following data were obtained:

Time (h)	Plasma concentration (µg/mL)
0.25	43
0.5	32
1	20
1.5	14
2	11
4	6.5
8	2.8
12	1.2
16	0.52

When these data are plotted on semilogarithmic graph paper, a curved line is observed which indicates that the drug is distributed in more than one compartment. From these data a biexponential equation can be derived by the method of residuals.

$$C_P = Ae^{-\alpha t} + Be^{-\beta t}$$

The constants ***α*** and **ß** are rate constants for the distribution phase and elimination phase, respectively. The constants ***A*** and ***B*** are intercepts on the *y* axis for each exponential segment. ***A*** and ***B*** can be obtained from the semilogarithmic graph as shown below.



- From the graph, the elimination phase (**ß** phase) is extrapolated and the y intercept is found to be **15 µg/mL = B.**
- Values from the extrapolated **ß** phase (Shown as empty circles in the graph) are subtracted from the original experimental data points to get a straight line that represents the **α** phase (distribution phase). These values are shown in the table below:

Application of the Method of Residuals			
Time (h)	**C_P Observed plasma level**	**C'_p Extrapolated plasma conc. (Empty circles in the graph)**	**$C_P - C'_p$ Residual plasma concentration**
0.25	43	14.5	28.5
0.5	32	13.5	18.5
1	20	12.3	7.7
1.5	14	11	3
2	11	10	1
4	6.5		

At time = 0,

$$C_P^0 = Ae^{-\alpha t} + Be^{-\beta t}$$

Since e^0 = 1, therefore

$$C_P^0 = A + B$$

- The rapid distribution phase is confirmed with the constant **α** being larger than the rate constant **ß.** At a time following the **distribution equilibrium,** the term $\boldsymbol{Ae^{-\alpha t}}$

will approach **0**. Therefore, plasma concentration after this time will be obtained by the following equation:

$$C_P = Be^{-\beta t}$$

$$K = \frac{\alpha ß(A+B)}{Aß+B\alpha}$$

Apparent Volumes of Distribution (V_D)

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 $(V_D)_{area}$ or $(V_D)_ß$**

$$(V_D)_ß = \frac{K V_p}{ß}$$

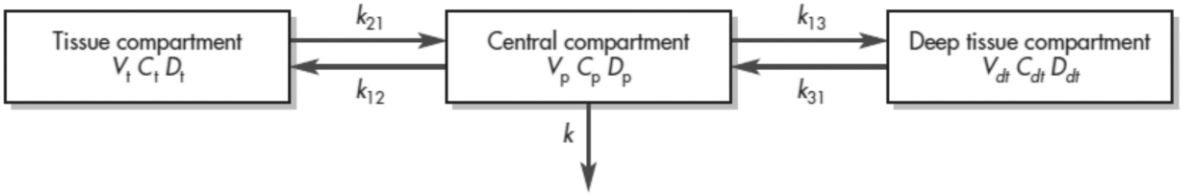
The value of $(V_D)_ß$ might decrease as a result of the reduction in the clearance of the drug as in the case of renal problems.

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

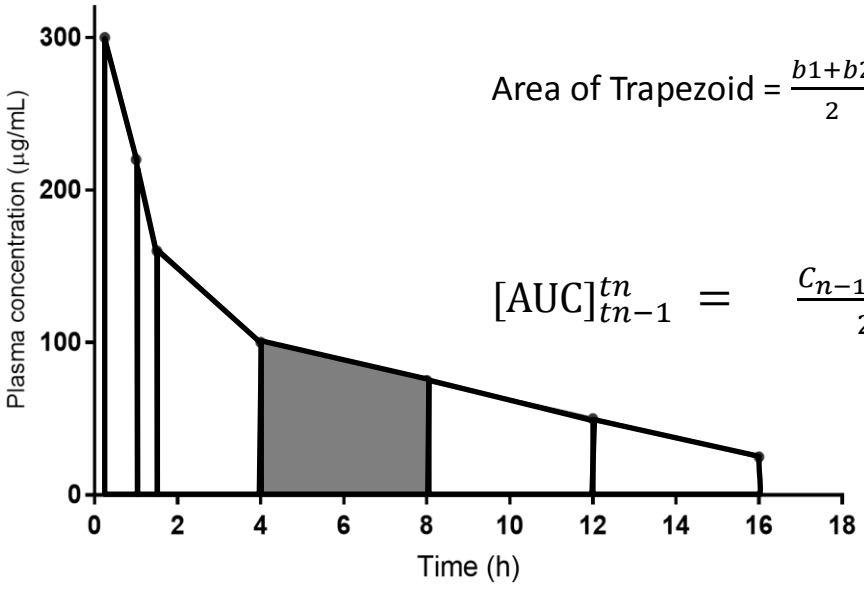
Non-compartmental analysis (NCA) is the most commonly used technique of pharmacokinetic data analysis directly from plasma-concentration data without the need to assume that drug disposition follows compartmental model.

Application of NCA include:

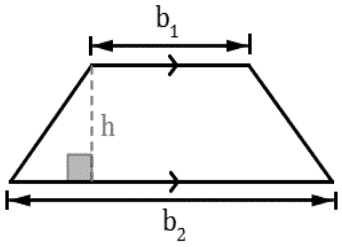
1. The area under the concentration time curve (e.g., in plasma or serum) describes the extent of systemic drug exposure; the peak concentration and its timing indicate the rate of drug input (absorption).
2. Provides estimates for clearance, volume of distribution, terminal half-life, and mean residence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



Area of Trapezoid = $\frac{b1+b2}{2}\ h$



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

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

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.

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

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

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

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

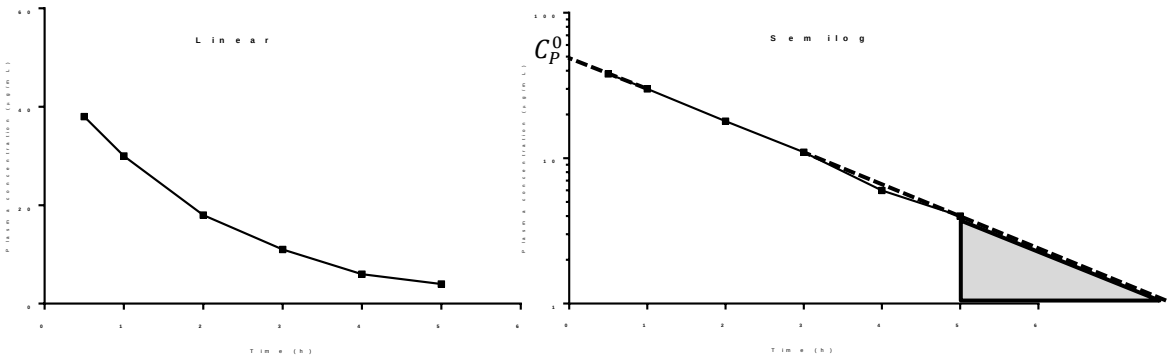
- The trapezoidal rule written in its full form to calculate the AUC from t = 0 to t = ∞ is as follows:

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

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

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

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

$$[\text{AUC}]_0^{t\ terminal} = \sum [\text{AUC}]_{tn-1}^{tn}$$

$$[\text{AUC}]_0^{t\ terminal} = [(\frac{50+38}{2})\ x\ (0.5-0) + (\frac{38+30}{2})\ x\ (1-0.5) + (\frac{30+18}{2})\ x\ (2-1) + (\frac{18+11}{2})\ x\ (3-2) + (\frac{11+6}{2})\ x\ (4-3) + (\frac{6+4}{2})\ x\ (5-4)] = 91 \text{ ng/mL*h}$$

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

Slope = $\frac{\log 4 - \log 6}{5-3} = -0.219$, ***k* = - slope x 2.3**

K = 0.5

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

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

Calculation of Volume of Distribution

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

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

Note that the V_D calculated from this equation is equivalent to V_P (volume of the central compartment) if the drug follows multicompartment model.

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

Using $[AUC]_0^{\infty}$ we ca also calculate $(V_D)_{ß}$. In this case the elimination constant to be used is ***ß*** as follows:

$$(V_D)_{ß} = \frac{D_0}{ß[AUC]_0^{\infty}}$$

Calculation of Clearance

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

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

Clearance can be calculation 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 t½ 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 ($t_{½}$) can be determined directly by plotting actual concentrations on semilog graph paper. Other method for the calculation of t1/2 is through the estimation of the slope in the plasma-concentration time curve using the following equations:

K = - slope x 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.

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 elimination is described in terms of clearance from a hypothetical well-stirred compartment containing uniform drug distribution.

DRUG CLEARANCE

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 the drug) removed from the drug 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 V_D of 12 L, then from the clearance definition, 15 mL of the 12 L will be removed from the drug per minute.

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

$$\text{Cl} = \frac{Elemination\ rte}{Plasma\ concentration\ (Cp)}$$

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

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 μg/mL.
Solution
Elimination rate = $C_p \times Cl$
dD_E/dt = 2 μg/mL x 15 mL/min = 30 μg/min.

Using the previous penicillin example, assume that the plasma penicillin concentration is 10 μg/mL.
dD_E/dt = 10 μg/mL x 15 mL/min = 150 μg/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:

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

- Elimination rate constant:

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

Similarly, *Cl* is the total sum of all of the different clearance processes in the body
$Cl = Cl_R + Cl_H + Cl_{other}$

Renal clearance: $Cl_R = k_R \times V$

Hepatic clearance: $Cl_H = k_H \times V$

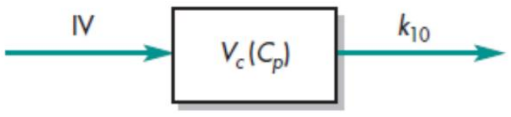
Total clearance:
$Cl = k \times V = (k_R + k_H + k_{other}) \times V$

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).

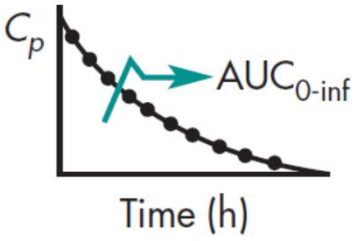
- **Compartmental**

One-compartment model
$Cl = k \times V_D$

Multicompartment model
$Cl = k_{10} \times V_p = (k_R + k_H + k_{other}) \times V_p$
The volume of distribution used is the volume of the central compartment.

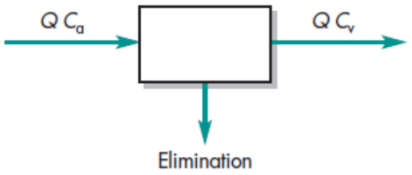


- **Non-compartmental**



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

- **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 m^2, or normalized for a "typical" adult of 72 kg or 1.72 m2. This approach is similar to the method for expressing V, because both pharmacokinetic parameters vary with body weight or body size.

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 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.

RPF = RBF - (RBF × 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

RPF = RBF (1 - Hct)

The average ***glomerular filtration rate*** **(GFR)** is about 120 mL/min in an average adult,[3] 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 acids or weak bases is influenced by the pH of the fluid in the renal tubule (ie, urine pH) and the pK_a 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**

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

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

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.

From the Henderson-Hasselbalch relationship, a concentration ratio for the distribution of a weak acid or basic drug between urine and plasma may be derived. The urine-plasma (*U/P*) ratios for these drugs are as follows.

For weak acids,

$$\frac{U}{P} = \frac{1 + 10^{pH_{urine} - pKa}}{1 + 10^{pH_{plasma} - pKa}}$$

For weak bases,

$$\frac{U}{P} = \frac{1 + 10^{pKa - pH_{urine}}}{1 + 10^{pKa - pH_{plasma}}}$$

Practice problem

Let pKa = 5 for an acidic drug. Compare the *U*/*P* at urinary pH **(a)** 3, **(b)** 5, and **(c)** 7.

Solution

a. At pH = 3,

$$\frac{U}{P} = \frac{1 + 10^{3-5}}{1 + 10^{7.4-5}} = \frac{1}{252}$$

b. At pH = 5,

$$\frac{U}{P} = \frac{1 + 10^{5-5}}{1 + 10^{7.4-5}} = \frac{2}{252}$$

c. At pH = 7,

$$\frac{U}{P} = \frac{1 + 10^{7-5}}{1 + 10^{7.4-5}} = \frac{101}{252}$$

Renal clearance

Renal clearance, Cl_R, is defined as the volume that is removed from 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 sing IV administration is

$$Cl_R = \frac{f_e \text{ x Dose}}{AUC_{0-inf}}$$

$$Cl_R = \frac{Ae_{0-inf}}{AUC_{0-inf}}$$

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%.

$$Cl_R = \frac{Ae_{0-x}}{AUC_{0-x}}$$

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

Practice problem

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, fe, is calculated by the following equation:

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

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

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

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

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

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

Hepatic elimination

The excretion rate constant (k_e) is easily evaluated for drugs that are primarily renally excreted. Nonrenal drug elimination is usually assumed to be due for the most part to hepatic metabolism. Therefore, the rate constant for metabolism (k_m) is difficult to measure directly and is usually obtained from the difference between k and k_e.

$k_m = k - k_e$

A drug may be biotransformed to several metabolites (metabolite A, metabolite B, metabolite C, etc); thus, the metabolism rate constant (k_m) is the sum of the rate constants for the formation of each metabolite when the drug does not saturate the metabolic enzymes (first-order processes).

$K_m = K_{mA} + K_{mB} + K_{mC}$ .....

$\%\ drug\ metabolised = \frac{k_m}{k} \times 100$

Hepatic clearance

Hepatic clearance may be defined as the volume of blood that perfuses the liver which is cleared of drug per unit of time.

$Cl_T = Cl_{nr} + Cl_r$

$Cl_h = Cl_T - Cl_R$

- **Examples:**
  1. The total body clearance for a drug is 15 mL/ min/kg. Renal clearance accounts for 10 mL/ min/kg. What is the hepatic clearance for the drug?

Solution

Hepatic clearance = 15 – 10 = 5 mL/min/kg

The total body clearance of a drug is 10 mL/ min/kg. The renal clearance is not known. From a urinary drug excretion study, 60% of the drug is recovered intact and 40% is recovered as metabolites. What is the hepatic clearance for the drug, assuming that metabolism occurs in the liver?
Solution
Hepatic clearance = total body clearance × (1 – f_e)
where f_e = fraction of intact drug recovered in the urine.
Hepatic clearance = 10 × (1 – 0.6) = 4 mL/min/kg

Extrahepatic Metabolism

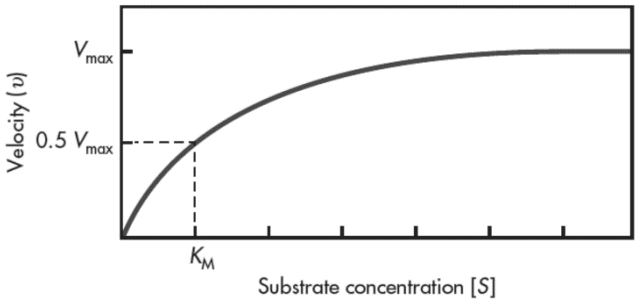
- Few drugs (eg, nitroglycerin) are metabolized extensively outside the liver.
- Extrahepatic metabolism is assessed by calculating hepatic (metabolic) and renal clearance of the drug and compare these clearances to total body clearance.

Example: Morphine clearance, Cl_T, for a 75-kg male patient is 1800 mL/min. After an oral dose, 4% of the drug is excreted unchanged in the urine (f_e = 0.04). The fraction of drug absorbed after an oral dose of morphine sulfate is 24% (F = 0.24). Hepatic blood flow is about 1500 mL/min. Does morphine have any extrahepatic metabolism?

Solution
Since f_e = 0.04,
Renal clearance Cl_r = 0.04 Cl_T
nonrenal clearance Cl_{nr} = (1 – 0.04) Cl_T = 0.96 Cl_T.
Cl_{nr} = 0.96 × 1800 mL/min = 1728 mL/ min.
Since hepatic blood flow is about 1500 mL/ min, the drug appears to be metabolized faster than the rate of hepatic blood flow. Thus, at least some of the drug must be metabolized outside the liver. The low fraction of drug absorbed after an oral dose indicates that much of the drug is metabolized before reaching the systemic circulation.

ENZYME KINETICS—MICHAELIS– MENTEN EQUATION

- *biotransformation* or *metabolism* is the enzymatic conversion of a drug to a metabolite.
- the metabolic enzyme concentration is constant at a given site, and the drug (substrate) concentration may vary.
- When the drug concentration is low relative to the enzyme concentration, the rate of metabolism is a first-order process.
- At high plasma drug concentration the rate process then becomes a zero-order process



- The *maximum reaction rate* is known as V_{max}
- The drug concentration at which the reaction occurs at half the maximum rate corresponds to a composite parameter K_M (*Michaelis constant)*.
- The relationship between V_{max} and K_M is given by *Michaelis–Menten equation*

$$v = \frac{V_{max}\,[D]}{[D]K_M}$$

Competitive and sequential metabolism

- The most common metabolic reactions are oxidation, reduction, hydrolysis and conjugation
- Frequently, a drug simultaneously undergoes metabolism by several competing (**primary**) pathways. The fraction going to each metabolite depends on the relative rates of each of the parallel pathways
- Metabolites may undergo further (**secondary**) metabolism. For example oxidation, reduction and hydrolysis are frequently followed by a conjugation reaction. These reactions occur in series and are said to be **sequential**

Phase I and Phase II reactions

- Because they often occur first, oxidation, reduction, and hydrolysis are commonly referred to as a phase I reactions
- Because they often occur second, conjugations are commonly referred as phase II reactions
- Phase I reactions are commonly considered to be a "preparation" of the drug molecule for phase II reactions
- This is NOT an absolute rule since some drugs undergo primary elimination via phase II reactions. In addition, some drugs undergo only phase I reactions without subsequent phase II step

Phase I metabolism

- Oxidation involving CYP450
- Oxidation – others
- Reduction
- Hydrolysis
- Hydration
- Isomerisation

In most cases, the final product contains a chemically reactive functional groups (-OH, -NH_2, -SH, -COOH): ready for phase II!
Many drugs can undergo a number of phase I reactions, therefore it is difficult to predict exact pathway from the chemical structure.

Phase II metabolism

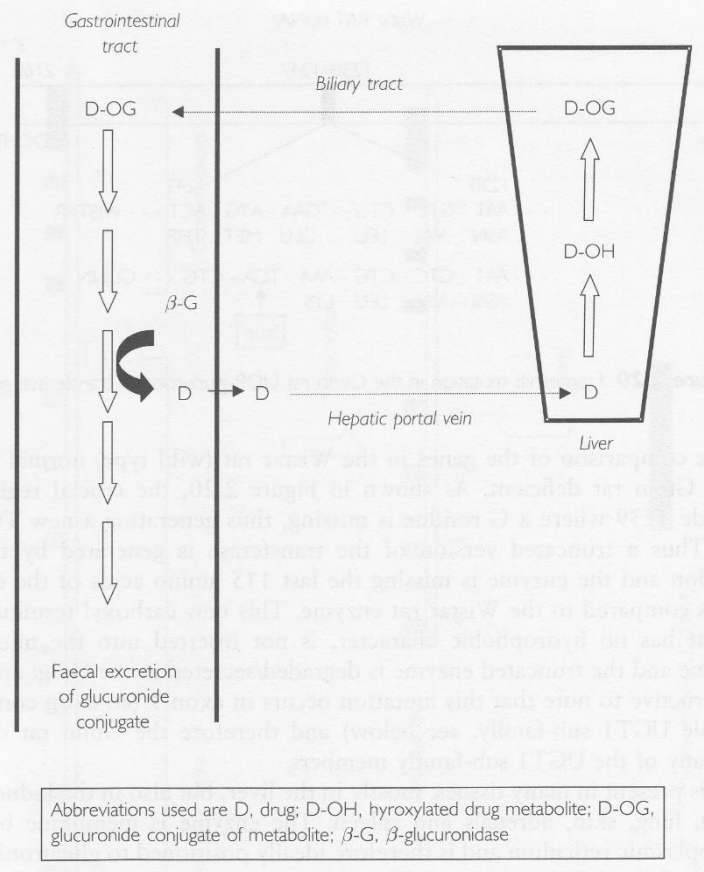
Phase II metabolism generally leads to a water soluble product which can be excreted in bile or urine

Reaction	Enzyme	Functional group
Glucuronidation	UDP–Glucuronosyltransferase	–OH –COOH –NH_2 –SH
Glycosidation	UDP–Glycosyltransferase	–OH –COOH –SH
Sulfation	Sulfotransferase	–NH_2 –SO_2NH_2 –OH
Methylation	Methyltransferase	–OH –NH_2
Acetylation	Acetyltransferase	–NH_2 –SO_2NH_2 –OH
Amino acid conjugation		–COOH
Glutathione conjugation	Glutathione-*S*-transferase	Epoxide Organic halide
Fatty acid conjugation		–OH
Condensation		Various

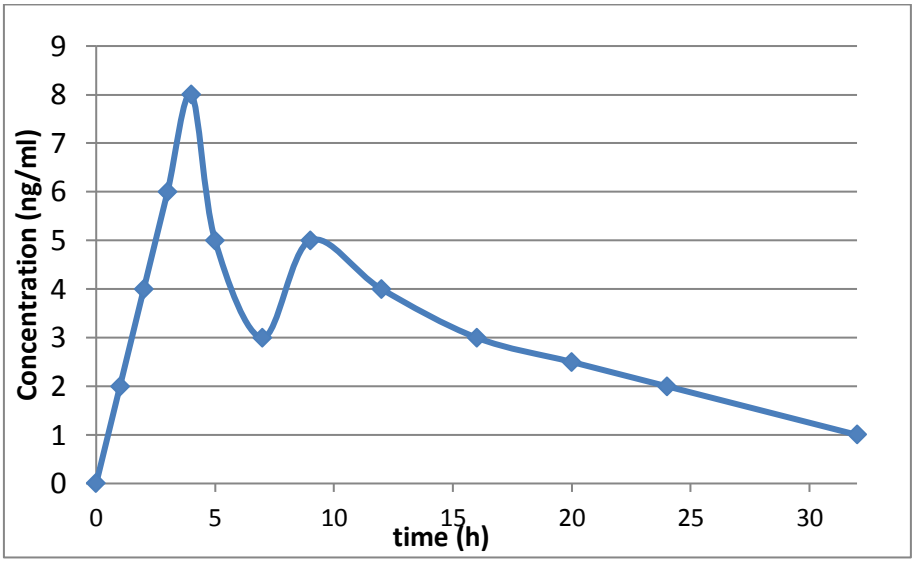
Enterohepatic circulation

Consequences of enterohepatic circulation:

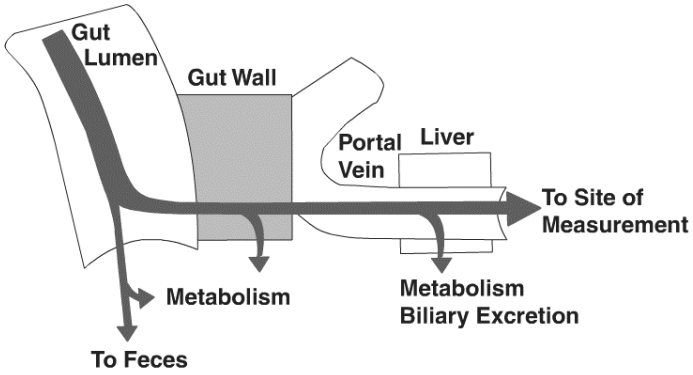
- Prolonged half-life
- Prolonged pharmacological action



- Enterohepatic circulation can be seen sometimes as a "second peak" phenomenon on plasma-concentration time profile after oral administration



FIRST-PASS METABOLISM

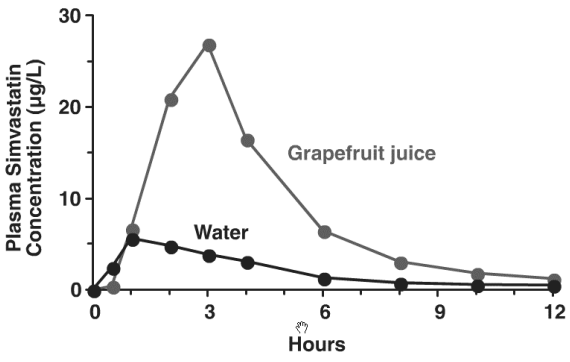


Metabolism during the first passage across the intestinal wall and through the liver reduces the amount reaching the general circulation. The drug is then said to undergo first-pass metabolic loss (or first-pass metabolism).

Example: the oral bioavailability (F) of simvastatin is about 5% when taken with water. The low metabolism is mostly due to first-pass metabolism in the gut and liver.

The oral bioavailability is increased 3.6-fold when simvastatin is given with grapefruit juice

Grapefruit juice components are known inhibitors of CYP3A



Avoiding hepatic first-pass metabolism:

1. Oral cavity

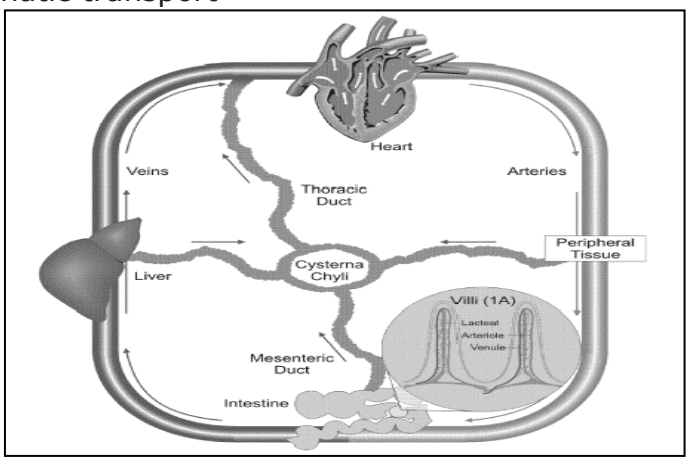
Drugs that are absorbed through the oral mucosa enter the blood stream directly via jugular vein (without passing through liver first) and therefore they avoid metabolism in the liver before they reach the systemic circulation (avoid hepatic first-pass metabolism)

2. Lower rectum and anal canal

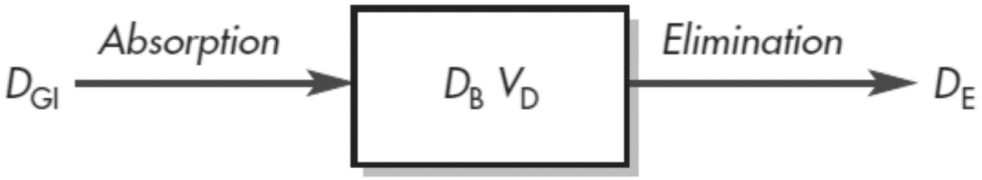
Drugs absorbed from the colon and upper rectum are absorbed into portal vein and therefore are subjected for hepatic first-pass metabolism.

Drugs absorbed from the lower rectum and anal canal are not getting into portal vein and therefore avoid hepatic first-pass metabolism.

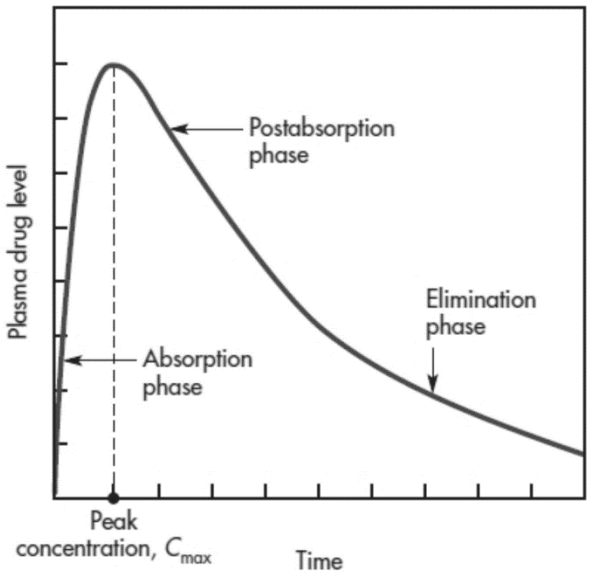
3. Intestinal lymphatic transport



PK of Oral Drug Absorption



The rate of change in the amount of drug in the body, dD_B/dt, is dependent on the relative rates of drug absorption (dD_{GI}/dt) and elimination (dD_E/dt).



At the *absorption phase*
The rate of drug absorption > the rate of drug elimination
$\frac{dD_{GI}}{dt} > \frac{dD_E}{dt}$
At the *peak drug concentration*
$\frac{dD_{GI}}{dt} = \frac{dD_E}{dt}$
At the *postabsorption phase*
$\frac{dD_{GI}}{dt} < \frac{dD_E}{dt}$
At the elimination phase
The rate of drug absorption approaches zero $\frac{dD_{GI}}{dt} = 0$
$\frac{dD_B}{dt} = - kD_B$
Where K is the first-order elimination rate constant

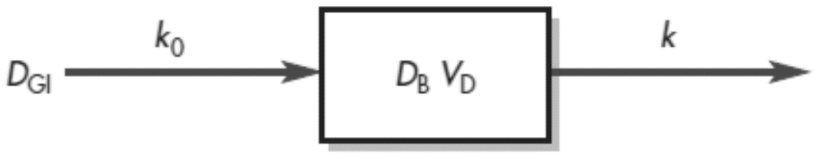
The Absorption Rate Constant

- The overall rate of systemic drug absorption from an orally administered solid dosage (*Ka*) = the net result of rate of dissolution of the drug, rate of GI motility, rate of blood flow, and the rate of transport of the drug across the capillary membranes and into the systemic circulation.
- The actual drug absorption process may be **zero-order, first-order, or a combination of both.**

ZERO-ORDER ABSORPTION MODEL
Zero-order drug absorption from the dosing site into the plasma occurs when either:

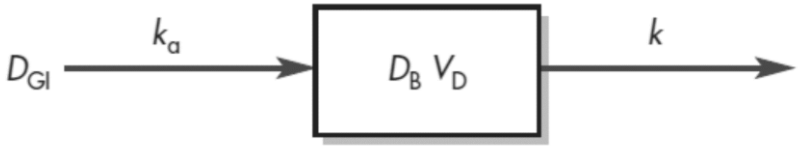
1. The drug is absorbed by a saturable process.
2. Zero-order controlled-release delivery system is used.

- Drug in the gastrointestinal tract, D_{GI}, is absorbed systemically at a constant rate k_0.
- Drug eliminated from the body by a first-order rate process defined by a first-order rate constant (k).
- Rate of drug change in the body $\frac{dD_B}{dt} = K_0 - kD_B$



FIRST-ORDER ABSORPTION MODEL

Systemic drug absorption after oral administration of a drug product (eg, tablet, capsule) is usually assumed to be a first-order process. This model assumes a first-order input across the gut wall and first-order elimination from the body



The rate of disappearance of drug from the gastrointestinal tract is described by
$\frac{dD_{GI}}{dt} = - k_a D_{GI} F$
Where k_a is the first-order absorption rate constant from the GI tract, F is the fraction absorbed, and D_{GI} is the amount of drug in solution in the GI tract at any time *t.*
$\frac{dD_B}{dt}$ = rate in – rate out
$\frac{dD_B}{dt} = F k_a D_{GI} - k D_B$

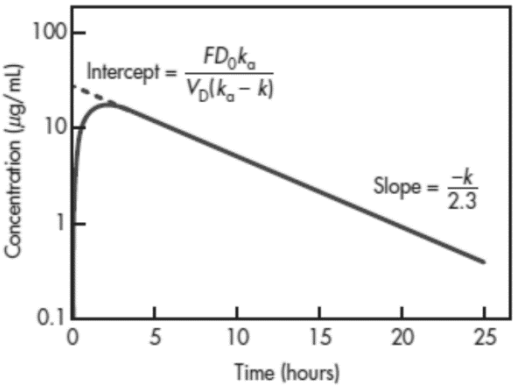
$$C_P = \frac{F k_a D_0}{V_D(k_a - k)} \left(e^{-kt} - e^{-k_a t}\right)$$

The maximum plasma concentration after oral dosing is C_{max} (*peak concentration)* and the time needed to reach maximum concentration is t_{max}
At C_{max} $\quad k e^{-kt} = k_a e^{-k_a t}$
$t_{max} = \frac{2.3 \log (k_a/k)}{(k_a - k)}$
The t_{max} is independent of dose and is dependent on the rate constants for absorption (k_a) and elimination (k)
For the calculation of C_{max}, t_{max} is calculated first and then substituted in the equation above

Determination of *K* and k_a from plasma concentration-time curve

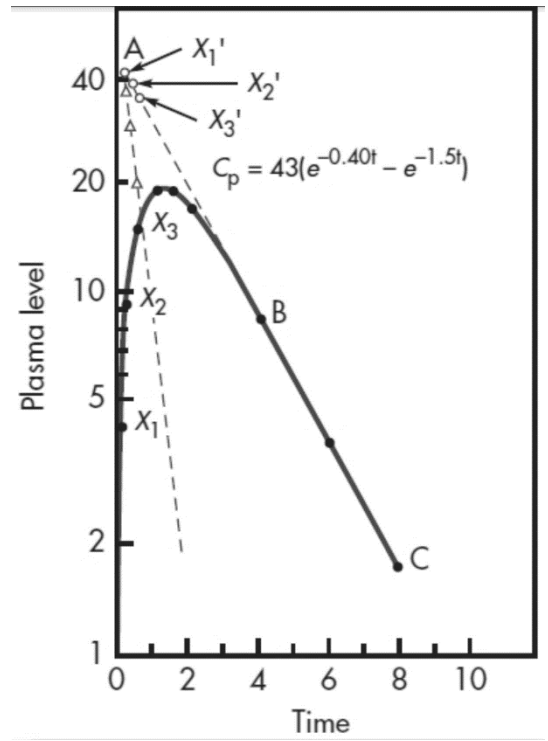
- **Determination of k**
  - A graph constructed by plotting C_p versus time on a semilog paper will yield a straight line with a slope of -k/2.3

- The points used for the calculation of k should be from the elimination phase in the graph.



- **Determination of k_a from Oral Absorption Data by Method of Residuals**

1. Plot the drug concentration versus time on semilog paper with the concentration values on the logarithmic axis.
2. Obtain the slope of the terminal phase by extrapolation.
3. Take any points on the upper part of the extrapolated line (eg, *x*′1, *x*′2, *x*′3, …) and drop vertically to obtain corresponding points on the curve (eg, *x*1, *x*2, *x*3, …).
4. Read the concentration values at *x*1 and *x*′1, *x*2 and *x*′2, *x*3 and *x*′3, and so on. Plot the values of the differences at the corresponding time points Δ1, Δ2, Δ3, … . A straight line will be obtained with a slope of **-*ka*/2.3**.
5. When using the method of residuals, a minimum of three points should be used to define the straight line.

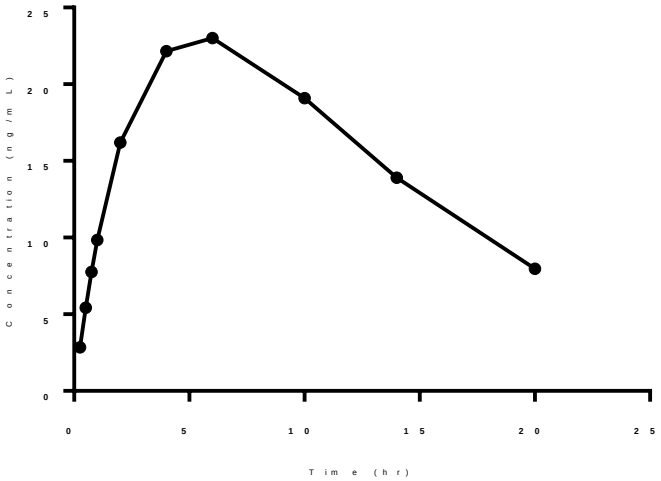


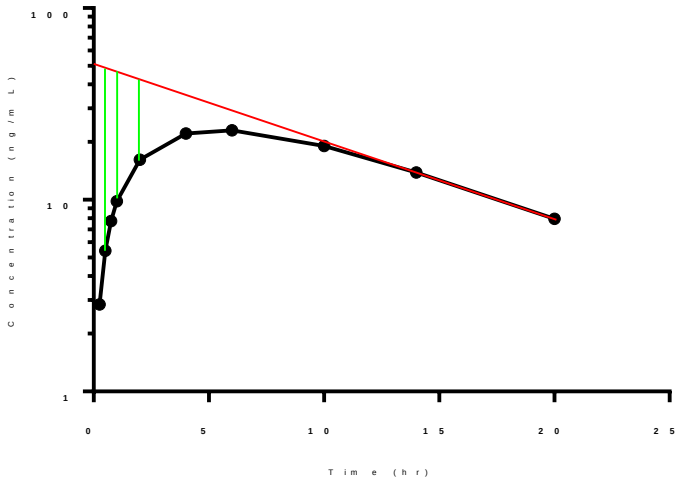
Example:
Plasma samples from a patient were collected after an oral bolus dose of 10 mg of a new benzodiazepine solution as follows:

Time (hours)	Concentration (ng/mL)
0.25	2.85
0.50	5.43
0.75	7.75
1.00	9.84
2.00	16.20
4.00	22.15
6.00	23.01
10.00	19.09
14.00	13.90
20.00	7.97

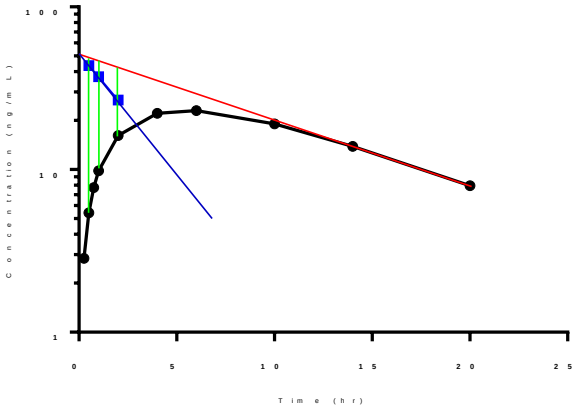
Calculate k, k_a, t_{max} and C_{max}

Note: Assume that the drug in is 80% absorbed





Time (hr)	Observed plasma concentration $(C_p)_{obs}$	Extrapolated plasma concentration $(C_p)_{extrap}$	$(C_p)_{diff} = (C_p)_{extrap}-(C_p)_{obs}$
0.5	5.43	49	43.57
1	9.84	47	37.16
2	16.2	43	26.8



Slope = $\frac{log7.9-log13.9}{20-14}$ = **- 0.04**

K = 0.094 hr^{-1} $t_{1/2} = \frac{0.693}{k}$ = **7.37**

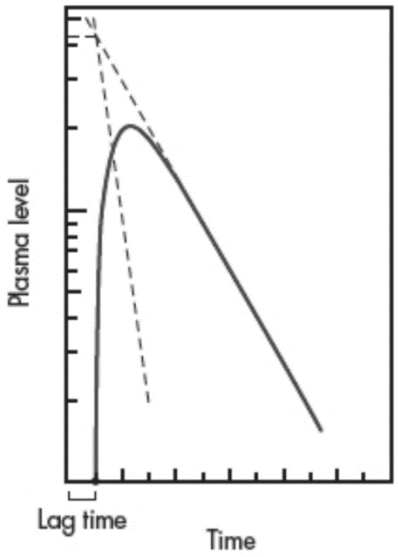
Slope = $\frac{log26.8-log37.16}{2-1}$ = **- 0.142**

K_a = 0.32 hr^{-1}

- $t_{max} = \frac{2.3\ log\ (k_a/k)}{(k_a-k)} = \frac{2.3\ log\ (0.32/0.094)}{(0.32-0.094)} = \frac{1.22}{0.226}$ = 5.4 hr
- **$C_P = \frac{F\ k_a D_0}{V_D(k_a-k)}\ (e^{-kt} - e^{-k_a t})$**
- **$9.84 = \frac{0.8\ x\ 0.32\ x\ 10000000}{V_D(0.32-0.094)}\ (e^{-0.094} - e^{-0.32})$**
- $9.84 = \frac{471}{VD\ 0.226}$
- V_D = 211.8 L
- **$C_{max} = \frac{F\ k_a D_0}{V_D(k_a-k)}\ (e^{-ktmax} - e^{-k_a tmax})$**
- **C_{max} =23 ng/mL**

Lag Time

The time delay prior to the appearance of the drug in the plasma.



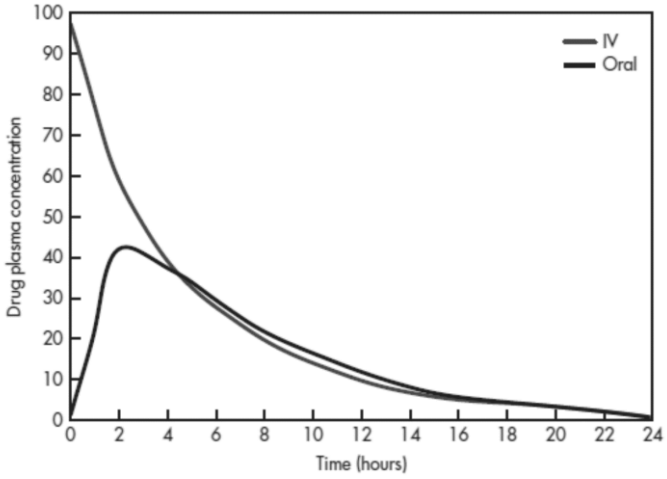
Bioavailability and Bioequivalence

Bioavailability and bioequivalence studies are important in the process of approving pharmaceutical products for marketing.

- *Bioavailability is* the rate and extent to which the active ingredient is absorbed from a drug product and becomes available at the site of action
- *Bioequivalence* is the absence of a significant difference in the rate and extent to which the active ingredient becomes available at the site of drug action when administered at the same dose under similar conditions.

Absolute Bioavailability (F_{abs})

Absolute bioavailability compares the bioavailability of the active drug in the systemic circulation following extravascular administration with the bioavailability of the same drug following intravenous administration.



$$F_{abs} = \frac{AUC_{po}\, D_{iv}}{AUC_{iv}\, D_{po}}$$

where

- F_{abs} is the fraction of the dose absorbed;
- AUC_{po} is the AUC following oral administration;

- D_{iv} is the dose administered intravenously;
- AUC_{iv} is the AUC following intravenous administration; and
- D_{po} is the dose administered orally.
- F_{abs}, may be expressed as a fraction or as a percent by multiplying F_{abs} × 100. A drug given by the intravenous route will have an absolute bioavailability of 100% (f = 1). A drug given by an extravascular route may have an F_{abs} = 0 (no systemic absorption) and F_{abs} = 1.0 (100% systemic absorption).

Relative Bioavailability (F_{rel})

The systemic exposure of a drug in a formulation (formulation A) is compared with that of the same drug administered in a reference formulation (formulation B). For example assessing F_{rel} of new oral formulation using oral solution of the drug as a reference.

$$F_{rel} = 100 \times \frac{AUC_A \, D_B}{AUC_B \, D_A}$$

The value of F_{rel} can be more than 100%

PRACTICE PROBLEM

A new investigational drug was studied. Each volunteer received either a single oral tablet containing 200 mg of the drug, 5 mL of a pure aqueous solution containing 200 mg of the drug, or a single IV bolus injection containing 50 mg of the drug. $AUC_{0\text{-}48}$ values were calculated as follows:

Calculate (a) the relative bioavailability of the drug from the tablet compared to the oral solution and (b) the absolute bioavailability of the drug from the tablet.

Drug Product	Dose (mg)	AUC (μg·h/mL)
Oral tablet	200	89.5
Oral solution	200	86.1
IV bolus injection	50	37.8

- Relative bioavailability = $\frac{89.5}{86.1}$= 1.04 or 104%
- F_{abs}= $\frac{89.5 \, x \, 50}{37.5 \, x \, 200}$ = 0.592 or 59.2%

Bioequivalence

- Bioequivalence is a type of relative bioavailability study. However, in a bioequivalence study, AUC , peak plasma concentration and peak time are determined for two or more chemically or pharmaceutically equivalent products (**identical dosage forms**) where at least one of them is an innovator product (also known as the Brand Name or Reference Standard).
- $F_{rel} = \frac{AUC_{generic} \, D_{standard}}{AUC_{standard} \, D_{generic}}$
- Example: Comparing Propranolol - Inderal® Tablet (innovator product by Wyeth Laboratories) and propranolol HCl tablet (generic brand).

Factors affecting bioavailability

Factors affecting bioavailability may be classified into two general categories:

1. **Formulation factors will include:**

A. Excipients (type and concentration) used in the formulation of a dosage form
B. Particle size of an active ingredient
C. Crystalline or amorphous nature of the drug
D. Hydrous or anhydrous form of the drug
E. Polymorphic nature of a drug.

2. **Physiological factors will include:**

A. Gastric emptying
B. Intestinal motility
C. Changes in gastrointestinal pH
D. Changes in nature of intestinal wall.

Practice Problem

Plasma theophylline concentrations after intravenous and oral administration were described by a one-compartment open model. The doses administered were as follows:

1. Intravenous bolus: 50mg aminophylline (85% theophylline)
2. Oral administration (A): Elixophylline (theophylline, 100mg capsules); administered one capsule
3. Oral administration (C): Aminophylline (aminophylline, 200 mg tablets, 170 mg theophylline); administered one tablet.

Time (h)	Plasma theophylline concentrations ($\mu g\,mL^{-1}$)		
	Intravenous bolus	Oral administration A	Oral administration C
0.25	4.70	0.40	1.65
0.50	4.40	2.40	12.65
0.75	4.10	6.95	14.30
1.00	3.95	11.15	15.70
1.50	3.75	11.15	13.90
2.00	3.60	9.50	14.60
3.00	2.95	8.45	13.75
4.00	2.75	8.15	11.15
6.00	2.05	6.65	10.00
8.00	1.45	4.60	7.30
12.00	0.80	2.90	3.60
24.00	0.25	1.00	0.85

Plot the data and, using the plot, determine the following:

a. The elimination half life ($t_{1/2}$) of theophylline following the administration of intravenous solution, oral capsule and oral tablet doses.

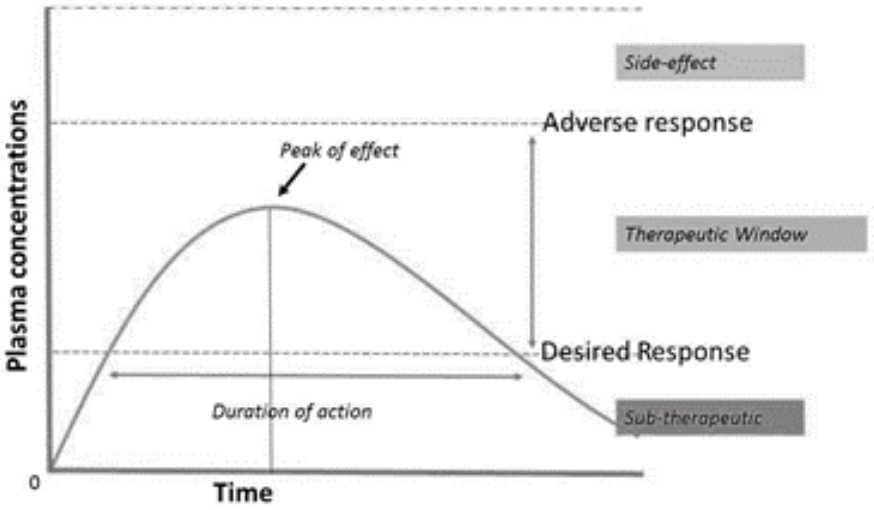
b. The elimination rate constant (K) of theophylline following the administration of intravenous solution, oral capsule and oral tablet doses.

c. The apparent volume of distribution (V) of theophylline from the intravenous bolus data.

d. The absorption rate constant (K_a) for each orally administered theophylline dose.
e. The area under the plasma concentration–time curve, $(AUC)_0^{24}$, by trapezoidal rule for each dose.
f. Using the trapezoidal data for $(AUC)_0^{24}$ determined in (e), calculate the total area under the plasma concentration–time curve $(AUC)_0^{\infty}$for each dose.
g. Determine the absolute bioavailability (i.e. fraction F) of the administered dose reaching the general circulation for the two orally administered (i.e. capsule and tablet) theophylline doses.

Multiple-Dosage Regimens

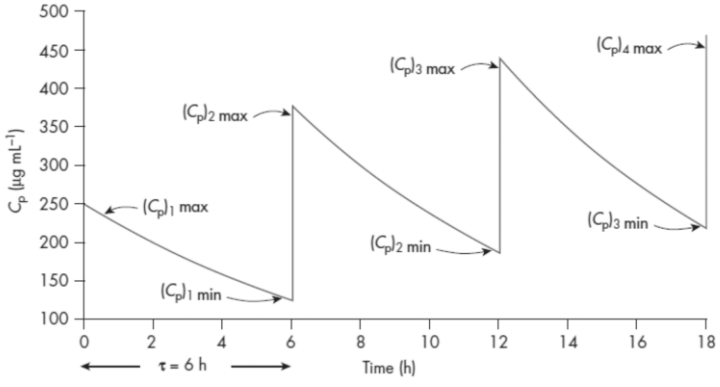
Some drugs, such as analgesics, hypnotics and antiemetics, may be used effectively when administered as a single dose. However, single dose is not convenient for the treatment of chronic diseases. After single-dose drug administration, the plasma drug level rises above and then falls below the ***minimum effective concentration*** **(MEC)**, resulting in a decline in therapeutic effect.



To treat chronic disease, multiple-dosage or IV infusion regimens are used to maintain the plasma drug levels within the narrow limits of the therapeutic window (eg, plasma drug concentrations above the MEC but below the *minimum toxic concentration* or MTC) to achieve optimal clinical effectiveness.

Important definitions in multiple dosing

- **Dosage regimen.** The systematized dosage schedule for a drug therapy, or the optimized dose (D_0) and dosing interval (τ, tau) for a specific drug.
- **Drug accumulation (R)**. The buildup of drug in the blood/body through sequential dosing.
  - **Drug *superposition*:** early doses of drug do not affect the pharmacokinetics of subsequent doses. Blood levels after the second, third, or *n*th dose will overlay or superimpose the blood level attained after the previous dose.



- **Steady-state condition.** Steady state is achieved at a time when, under a given dosage regimen, the mass (amount) of drug administered (for intravenous) or absorbed (for extravascular route), is equal to the mass (amount) of drug eliminated over a dosing interval.
- **Loading dose (D_L).** A single dose administered in order to reach steady-state condition instantly.
- **Maintenance dose (D_m).** The dose administered every dosing interval to maintain the steady-state condition.

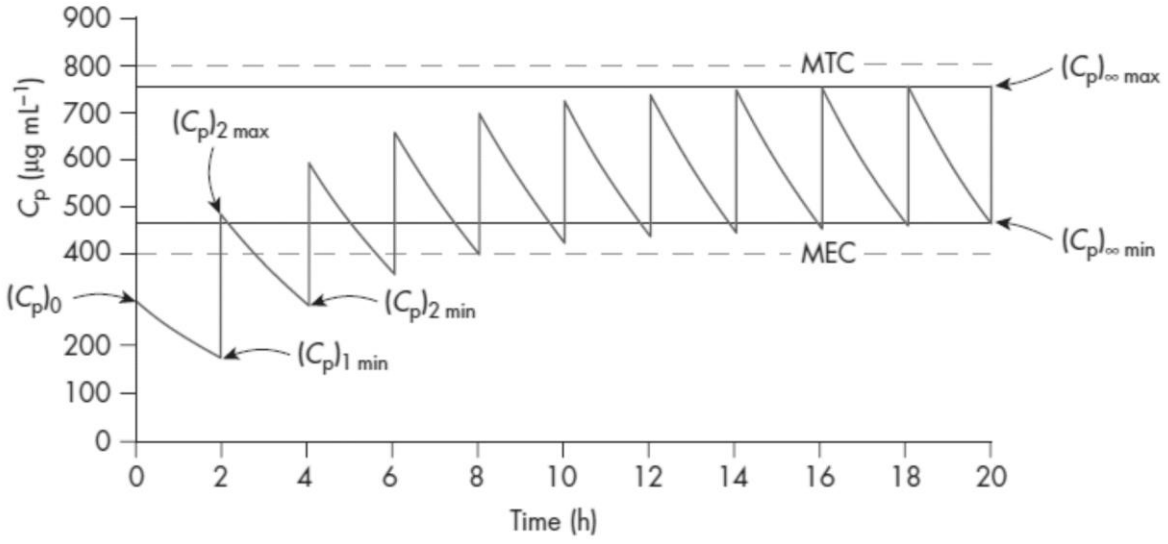
There are two main parameters that can be adjusted in developing a dosage regimen:
(1) the size of the drug dose.
(2) τ, the frequency of drug administration (ie, the time interval between doses).

DRUG ACCUMULATION (R)
Accumulation is affected by the elimination half-life of the drug and the dosing interval. The index for measuring drug accumulation *R* is

$$\boldsymbol{R = \frac{1}{1 - e^{-k\tau}}}$$

The value of *R* simply indicates how high the plasma concentration will be at steady state compared with the first dose of the drug at a comparable time within the dosage regimen.

Steady-state plasma concentration – Multiple IV Bolus Inj



$$\boldsymbol{C_t^{\infty} = \frac{C_p^0 \cdot e^{-kt}}{1 - e^{-k\tau}}}$$

Where (C_t^{∞}) is plasma concentration at any time after the drug reaches steady-state concentration; C_p^0 is initial plasma concentration which is equal to is equal to D_0/V_D.

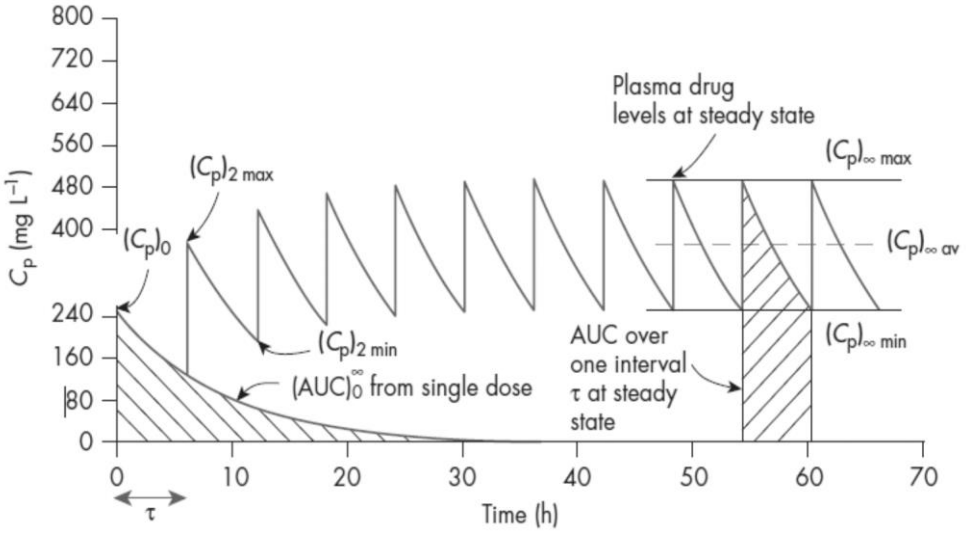
$$\boldsymbol{C_{min}^{\infty}\ (\text{trough}) = \frac{C_p^0 \cdot e^{-k\tau}}{1 - e^{-k\tau}}} \qquad \boldsymbol{C_{min}^{\infty} = C_{max}^{\infty} \cdot e^{-k\tau}}$$

$$\boldsymbol{C_{max}^{\infty}\ (\text{peak}) = \frac{C_p^0}{1 - e^{-k\tau}}}$$

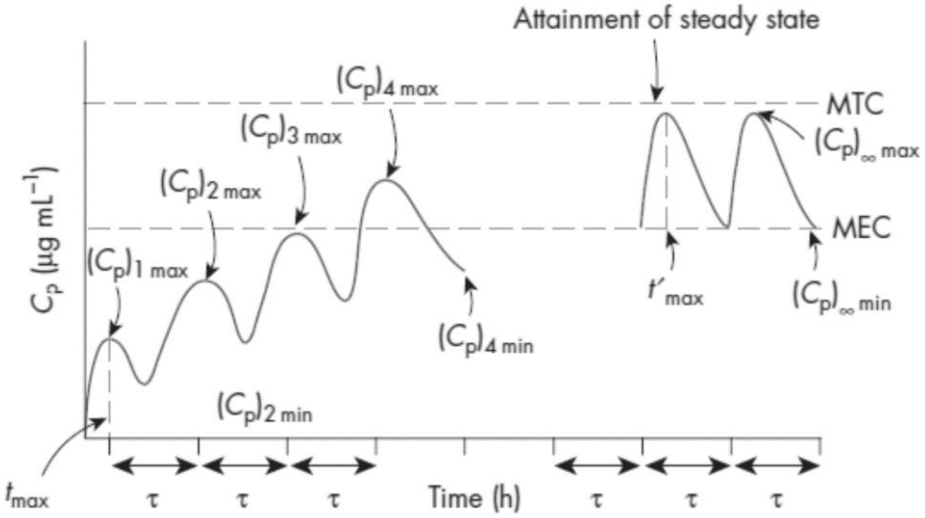
$$C_{av}^{\infty} = \frac{C_p^0}{k\tau} = \frac{D_0}{V_D k\tau}$$

Average plasma concentration at steady state (C_{av}^{∞}) can also be calculated from AUC by the following equation:

$C_{av}^{\infty} = \frac{[AUC]_{t1}^{t2}}{\tau}$ or by $C_{av}^{\infty} = \frac{[AUC]_0^{\infty}}{\tau}$



Steady-state plasma concentration – Multiple Oral Administrations



- **$C_P = \frac{F\,k_a D_0}{V_D(k_a - k)}\ (e^{-kt} - e^{-k_a t})$ ……. Plasma concentration at any time after single dose administration.**
- **$C_p^{\infty} = \frac{F\,k_a D_0}{V_D(k_a - k)}\ [(\frac{1}{1 - e^{-k\tau}})e^{-kt} - (\frac{1}{1 - e^{-k_a\tau}})e^{-k_a t}]$**
- Where (C_p^{∞}) is plasma concentration at any time after the drug reaches steady-state concentration.

$$C_{min}^{\infty}\,(\text{trough}) = \frac{F\,k_a D_0}{V_D(k_a - k)}\;\left(\frac{1}{1-e^{-k\tau}}\right)e^{-k\tau}$$

$$C_{max}^{\infty}\,(\text{peak}) = \frac{F\,D_0}{V_D}\;\left(\frac{1}{1-e^{-k\tau}}\right)e^{-kt_p}$$

t_p is the time of peak plasma concentration following multiple doses.

$t_{max} = \frac{2.3\,log\,(k_a/k)}{(k_a - k)}$ …. t_{max} following single dose administration

$t_p = \frac{1}{k_a - k}\;\ln\left[\frac{k_a(1-e^{-k\tau})}{k(1-e^{-k\tau})}\right]$

$C_{av}^{\infty} = \frac{F\,D_0}{V_D k\tau}$

The ''average'' steady-state plasma concentration is influenced by the following parameters:

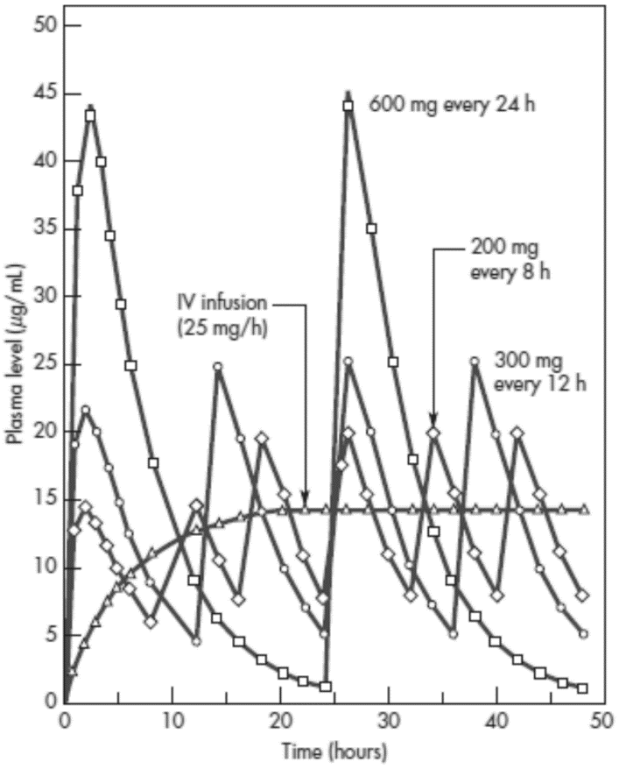
1. The dose administered.
2. The chosen dosing interval.
3. The absolute bioavailability (F), when applicable.
4. The systemic clearance of the drug.

Since systemic clearance for a drug is constant, at normal conditions, the three first parameters are the most important.

The larger the dosing interval, the lower will be the ''average'' steady-state plasma concentration. However, if the ratio of dose over dosing interval is maintained constant, the ''average''steady-state concentration will remain unchanged.

For example, administration of a 400 mg dose of a drug at every 8 h or the administration of 200 mg dose at every 4 h will provide identical ''average'' steady-state plasma concentrations.

In renally impaired subjects, there will be a decrease in the systemic clearance of a drug eliminated by the kidneys; and, therefore, the normal dosage regimen of that drug will provide higher ''average'' steady-state concentration



- The dosage adjustment in case of decreased clearance can be accomplished by three approaches.

1. Administration of a smaller dose at a normal dosing interval.
2. Administration of a normal dose at a longer dosing interval (i.e. decreasing the frequency of drug administration).
3. A combination of both (i.e. administration of a smaller dose less frequently).

Designing or establishing the dosage regimen for a drug

1. Know the therapeutic range and/or the effective concentration range for the drug.
2. Select the desired or targeted "average" steady state plasma concentration. For example, if the therapeutic range is 10– 30mg/L, choose 20mg/L as the targeted "average" steady-state concentration.
3. Use $C_{av}^{\infty} = \frac{D_0}{V_D k \tau}$ (for an intravenous bolus administration):
4. Select the dosing interval (it is a safe and good practice to start with a dosing interval equal to the drug's elimination half-life).
5. Using this dosing interval, and rearranging the equation in Step 3, calculate the dose (D_0) needed to attain the desired "average" steady-state concentration.
$D_0 = C_{av}^{\infty}$ V_D K τ
6. Using the calculated dose and dosing interval (numbers may be rounded off to the nearest whole no. like 109.15 mg to 100 or 125 mg), calculate the "average" steady-state concentration, peak steady-state concentration and trough steady-state concentration.
8. Make sure that the calculated peak steady-state concentration is below the minimum toxic concentration and calculated trough steady-state concentration is above the minimum effective concentration.
9. If necessary, make small adjustments (fine tuning) in the dose and dosing interval.

Calculation of loading and maintenance doses

The steady state plasma concentration is usually attained after 6.6 $t_{1/2}$ (if the drug is administered at time interval $\tau = t_{1/2}$). This is a long time before the desired "average" steady-state drug concentration is attained. Therefore, an intravenous bolus loading dose (D_L) may be administered to obtain an instant steady-state condition.
Maintenance dose (D_M): is the dose required to maintain plasma concentration level at steady state.

$$\textbf{Dose ratio} = \frac{D_L}{D_M} = \frac{1}{1 - e^{-k\tau}}$$

If the calculated dose ration equals to 2, the loading dose will be equal to double the initial drug dose.