Pharmacology I

Pharmacokinetics

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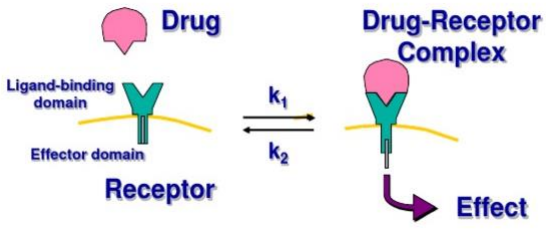
Lecture No. : 1

Introduction

- **Pharmacology** can be defined as the study of **substances, drugs or chemicals** that interact with living systems through chemical processes, usually **by binding to regulatory molecules** and **activating or inhibiting normal body processes**.



Introduction

- The interactions between a drug and the body are divided into two classes which is **Pharmacodynamics and Pharmacokinetics**
- The actions of the drug on the body are termed **pharmacodynamic processes**.

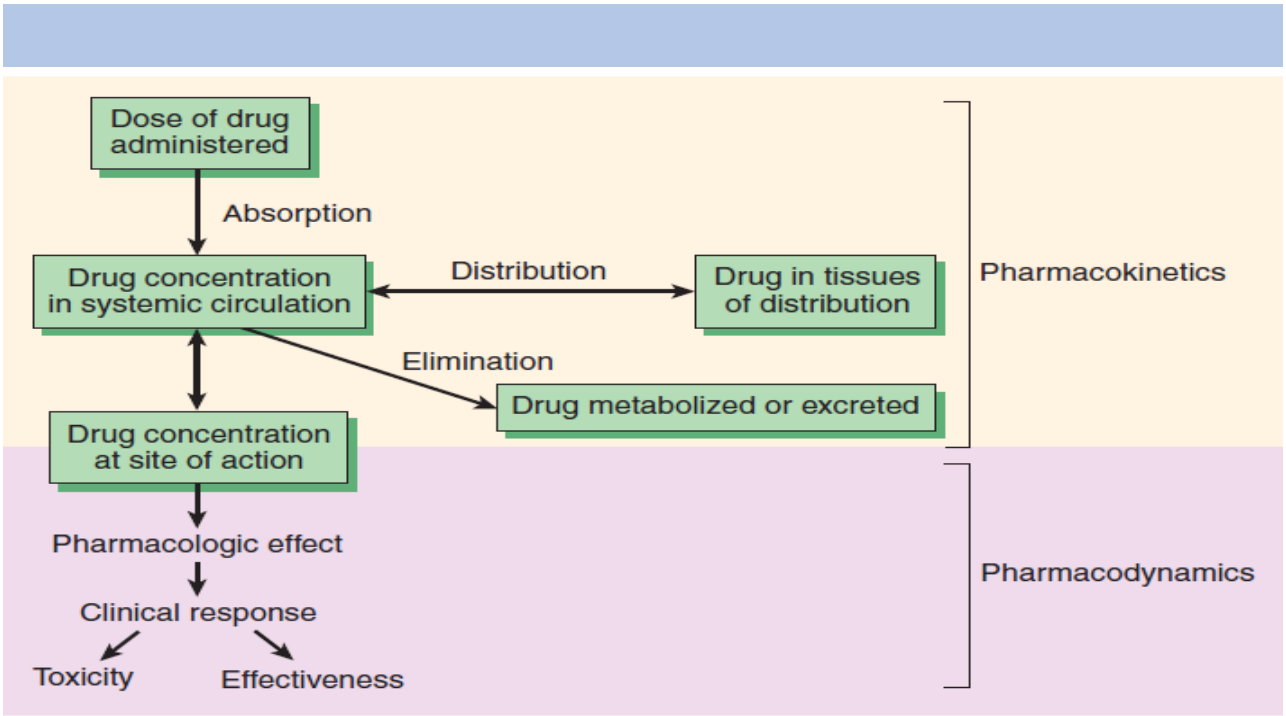
The pharmacodynamic properties determine:

1. The **group** in which the drug is classified
2. They play the major role in deciding whether that group is **appropriate therapy for a particular symptom or disease**.

Introduction

- The actions of the body on the drug are called **Pharmacokinetic processes**.
- **Pharmacokinetic processes** govern the **absorption, distribution, and elimination of drugs (metabolism and excretion)** and are of great practical importance in **the choice** and **administration of a particular drug** for a **particular patient**, eg, a patient with impaired renal function.

- **Drug A 4hour DOA qid oral hepatic**
- **Drug B 8 hour DOA tid oral and IV Renal**
- **Drug C 12 hour DOA bid oral, IV Renal and hepatic**



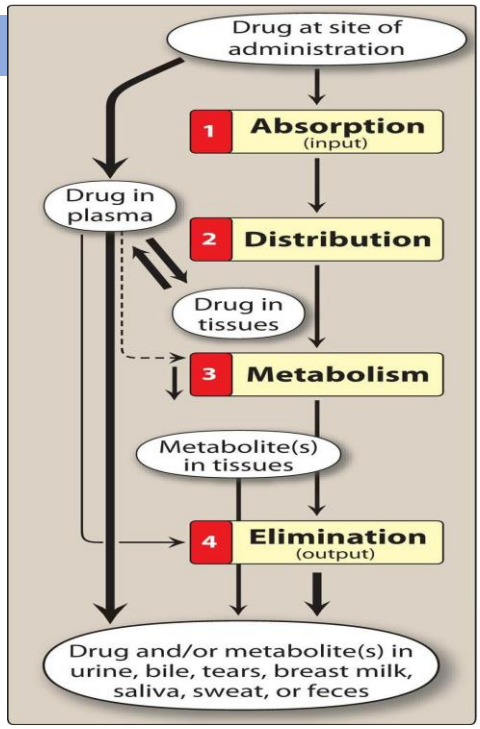
Pharmacokinetics

- **Absorption, distribution, metabolism** and **elimination** are four pharmacokinetic properties determine :

1. **The onset of drug action**,
2. **Intensity of drug**, and
3. **Duration of drug action**.

Definition of pharmacokinetics properties

- **Absorption:** First, **absorption** from the site of administration permits entry of the drug (either directly or indirectly) into plasma.
- **Distribution:** Second, the drug may **reversibly** leave the bloodstream and **distribute** into the interstitial and intracellular fluids.
- **Metabolism:** Third, the drug may be **biotransformed** through metabolism by the liver or other tissues.
- **Elimination:** Finally, the drug and its metabolites are **eliminated** from the body in urine, bile, or feces.



Optimal drug regimens

❑ Using knowledge of pharmacokinetic parameters, clinicians can design optimal drug regimens, including

1. **The route of administration**
2. **Dose**
3. **Frequency**
4. **Duration of treatment.**

- Route of administration oral , paracentral topical;
- Dose **Amoxillin** 125mg/5ml , 250mg/5ml, 500mg capsules
- Frequency, **Amoxiclav** 625 mg tid
  1gm bid
- 7-10 day,

Routes of administrations

- The route of administration is determined by :

1. **Properties of the drug** (for example, water or lipid solubility, ionization)
2. **Therapeutic objectives** (for example, the need for a rapid onset, the need for long-term treatment, or restriction of delivery to a local site).

Routes of drug administrations

❑**Major routes of administration** include

✓Enteral,

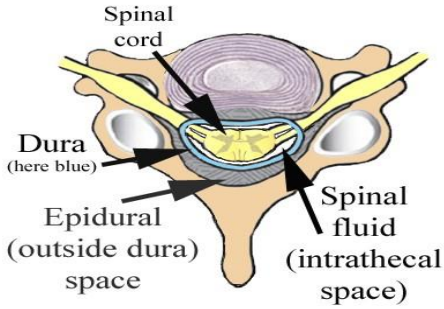
✓Parenteral,

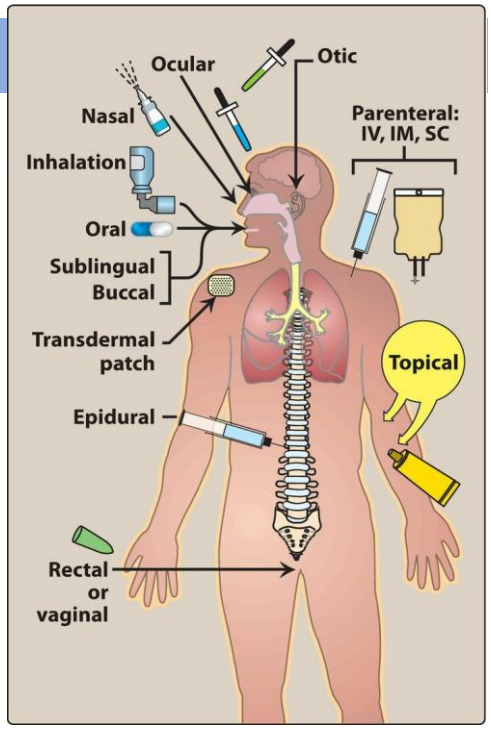
✓Oral inhalation and nasal preparations

✓Intrathecal/intraventricular

✓Transdermal

✓Topical,

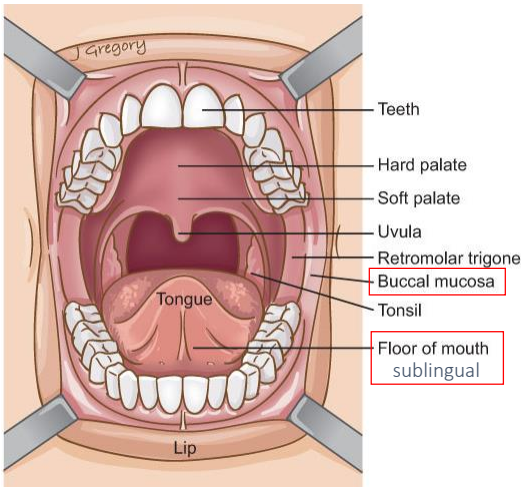




A. Enteral Administration

❑Administering a drug by mouth**, is the most common, convenient, and economical method of drug administration.**

❑The drug may be **swallowed**, allowing oral delivery, or it may be placed **under the tongue (sublingual)** or **between the gums and cheek (buccal),** facilitating direct absorption into the bloodstream.



Oral Administration

❑ **Oral administration provides many advantages:**

1. Oral drugs are **easily self-administered**, and
2. Toxicities and/or overdose of oral drug **treated with antidotes**, such as activated charcoal.

❑ **However, disadvantages of oral routes:**

1. Complexity of absorption pathways of orally administered drugs
2. The low gastric pH inactivates some drugs.

ROUTE OF ADMINISTRATION	ABSORPTION PATTERN	ADVANTAGES	DISADVANTAGES	EXAMPLES
Oral	• Variable; affected by many factors	• Safest and most common, convenient, and economical route of administration	• Limited absorption of some drugs • Food may affect absorption • Patient compliance is necessary • Drugs may be metabolized before systemic absorption	• *Acetaminophen* tablets • *Amoxicillin* suspension

A. Enteral Administration

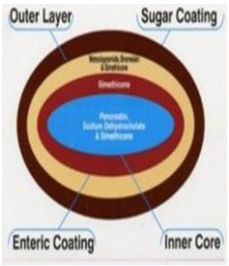
- A wide range of oral preparations is available including tablet, capsules, syrups, and also:

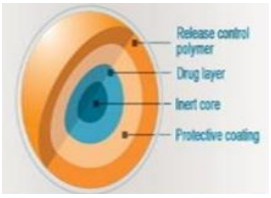
1. **Oral**

   A. Enteric coated formulations

   B. Extended release formulations

2. **Sublingual/ buccal**



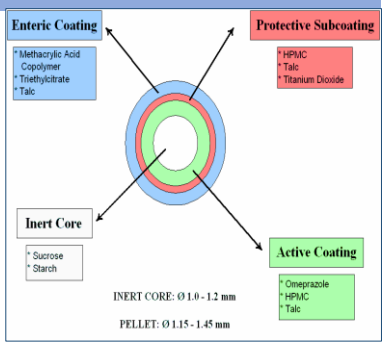


Types of oral preparations

A. Enteric-coated preparations

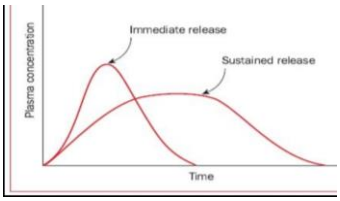
➢**An enteric coating** is a chemical envelope that protects the drug from stomach acid, delivering it to the intestine, where the coating dissolves and releases the drug.

➢Enteric coating is useful for drugs (***omeprazole***) that are acid labile, and for drugs that are irritating to the stomach (***aspirin***).



Types of oral preparations available

B. Extended-release preparations (sustained)

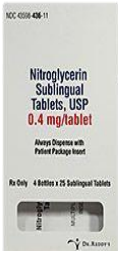


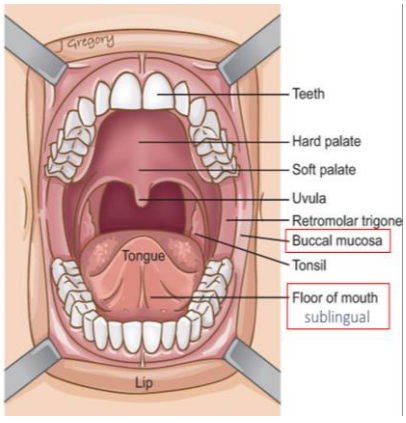
Extended-release (abbreviated ER, XR, XL, SR, etc.) medications have special coatings or ingredients that control drug release, thereby

1. Allowing for **slower absorption and prolonged duration of action**.
2. **Dosed less frequently** which Improve patient **compliance**.
3. **Maintain concentrations** within the therapeutic range **over a longer duration**, as opposed to immediate-release dosage forms, which may result in larger peaks and troughs in plasma concentration.
4. **Used for drugs with short half-lives**. E,g, the oral *morphine* is (**$T_{1/2}$ 2 to 4 hours**), and it dose six times daily to provide continuous pain relief. However, only **two doses needed when extended-release tablets are used**.

2. Sublingual/buccal

- ❑The **sublingual route** involves placement of drug under the tongue.
- ❑The **buccal route** involves placement of drug between the cheek and gum.





➢ **Advantages of this routes of absorption:**

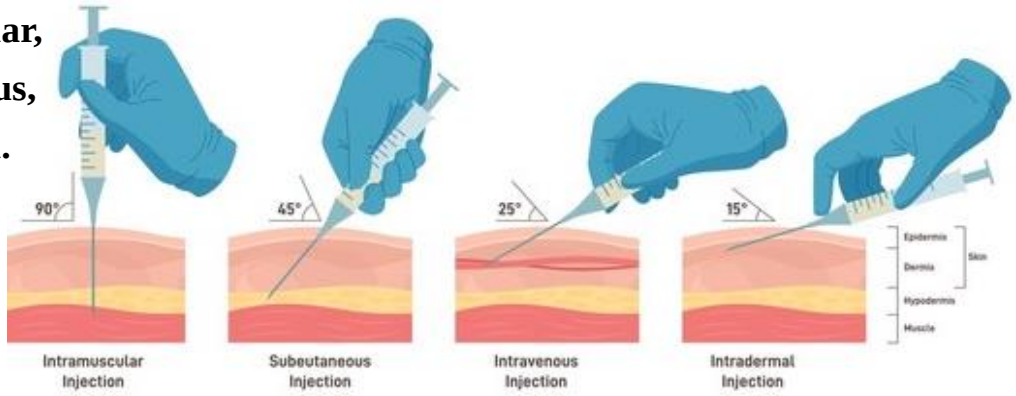
1. Ease of administration,
2. Rapid absorption,
3. Bypass of the harsh gastrointestinal (GI) environment
4. Avoidance of first-pass metabolism

ROUTE OF ADMINISTRATION	ABSORPTION PATTERN	ADVANTAGES	DISADVANTAGES	EXAMPLES
Sublingual	• Depends on the drug: Few drugs (for example, *nitroglycerin*) have rapid, direct systemic absorption Most drugs erratically or incompletely absorbed	• Bypasses first-pass effect • Bypasses destruction by stomach acid • Drug stability maintained because the pH of saliva relatively neutral • May cause immediate pharmacological effects	• Limited to certain types of drugs • Limited to drugs that can be taken in small doses • May lose part of the drug dose if swallowed	• *Nitroglycerin* • *Buprenorphine*

Parenteral administrations

- This route introduces drugs directly into the systemic circulation.
- The four major parenteral routes are

1. **Intravascular (intravenous or intraarterial),**
2. **Intramuscular,**
3. **Subcutaneous,**
4. **Intradermal.**



Indication of parenteral administrations

❑ **The indication of parenteral administrations; it is used for :**

1. Drugs that are **poorly absorbed from the GI tract** (*heparin*)
2. **Drugs are unstable in the GI tract** (*insulin*).
3. Patients **unable to take oral medications** (unconscious patients)
4. Circumstances that require **a rapid onset of action**.
5. **Highest bioavailability**
6. **Avoid first-pass metabolism** or **harsh GI environment.**
7. It provides **control over the dose of drug delivered to the body**.

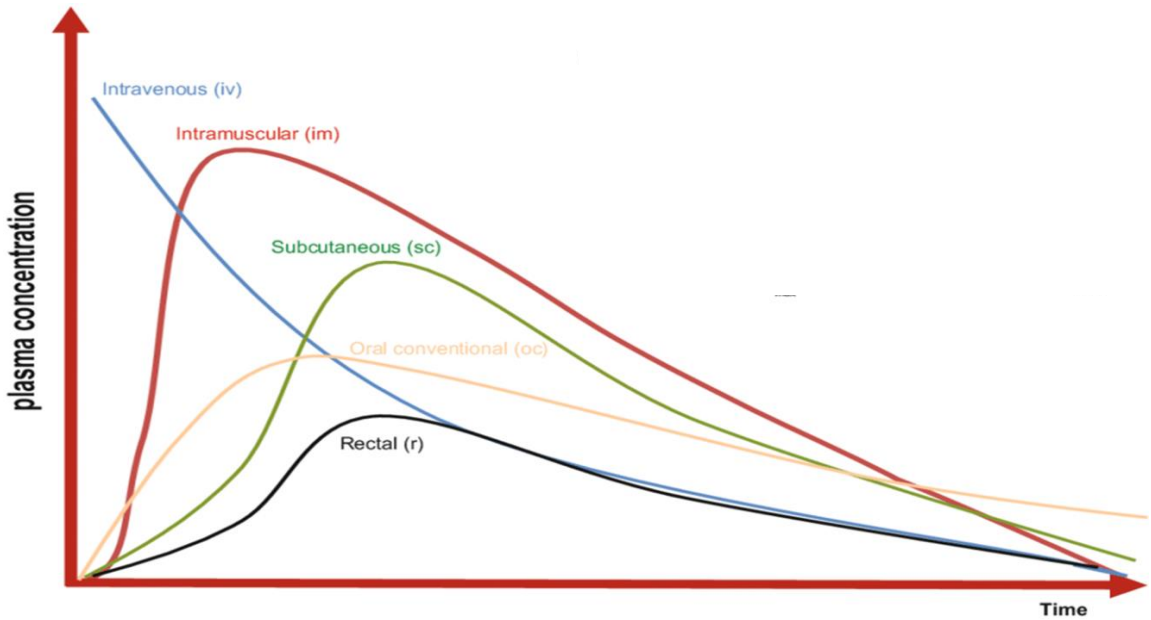
The disadvantage of parenteral

- **However, the disadvantage of parenteral route is**

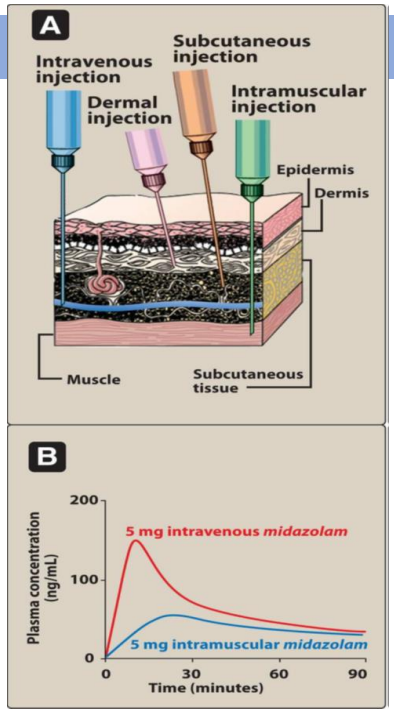
1. **Irreversible**
2. **May cause pain and fear**
3. **Local tissue damage**
4. **Infections**

- The major parenteral routes are intravascular (intravenous or intra-arterial), intramuscular, and subcutaneous.

Dose Response Curve



1. Intravenous (IV)



- IV injection is the **most common** parenteral route.

1. It is useful for **drugs that are not absorbed orally**, such as the neuromuscular blocker *rocuronium*.
2. IV **permits a rapid effect** and a **maximum degree of control** over the amount of drug delivered.
3. IV **bolus**, the **full amount of drug** is delivered to the systemic circulation almost **immediately**.
4. **IV infusion**, the drug is infused over a longer period, resulting in lower peak plasma concentrations and an increased duration of circulating drug.

ROUTE OF ADMINISTRATION	ABSORPTION PATTERN	ADVANTAGES	DISADVANTAGES	EXAMPLES
Intravenous	• Absorption not required	• Can have immediate effects • Ideal if dosed in large volumes • Suitable for irritating substances and complex mixtures • Valuable in emergency situations • Dosage titration permissible • Ideal for high molecular weight proteins and peptide drugs	• Unsuitable for oily substances • Bolus injection may result in adverse effects • Most substances must be slowly injected • Strict aseptic techniques needed	• *Vancomycin* • *Heparin*

2. Intramuscular (IM)

❑ Drugs administered IM can be

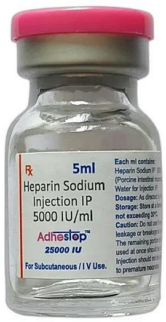
➢ In **aqueous solutions**, which are absorbed rapidly,

➢ In specialized **depot preparations**, which are absorbed slowly.

❑ **Depot preparations** often consist of a **suspension** of drug in a **non-aqueous** vehicle, such as **polyethylene glycol**. As the vehicle diffuses out of the muscle, drug precipitates at the site of injection. The drug then dissolves slowly, providing a sustained dose over an extended interval.

ROUTE OF ADMINISTRATION	ABSORPTION PATTERN	ADVANTAGES	DISADVANTAGES	EXAMPLES
Intramuscular	• Depends on drug diluents: Aqueus solution: prompt Depot preparations: slow and sustained	• Suitable if drug volume is moderate • Suitable for oily vehicles and certain irritating substances • Preferable to intravenous if patient must self-administer	• Affects certain lab tests (creatine kinase) • Can be painful • Can cause intramuscular hemorrhage (precluded during anticoagulation therapy)	• *Haloperidol* • *Depot medroxy-progesterone*

3. Subcutaneous (SC)

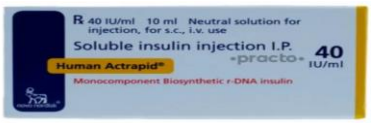


❑ SC injection provides absorption via **simple diffusion** and **is slower than the IV route.**

❑ SC injection *minimizes the risks of hemolysis or thrombosis associated with IV injection* and **may provide constant, slow, and sustained effects**.

❑ This route should not be used with drugs that cause tissue irritation, because severe pain and necrosis may occur.

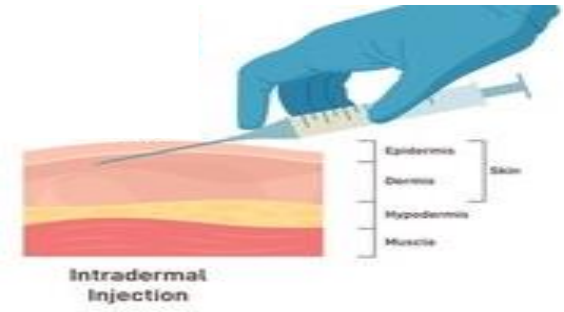
❑Drugs administered SC include insulin and heparin.



ROUTE OF ADMINISTRATION	ABSORPTION PATTERN	ADVANTAGES	DISADVANTAGES	EXAMPLES
Subcutaneous	• Depends on drug diluents: Aqueous solution: prompt Depot preparations: slow and sustained	• Suitable for slow-release drugs • Ideal for some poorly soluble suspensions	• Pain or necrosis if drug is irritating • Unsuitable for drugs administered in large volumes	• *Epinephrine* • *Insulin* • *Heparin*

4. Intradermal (ID)

- The **intradermal (ID)** route involves injection into the **dermis**, the more vascular layer of skin under the epidermis.
- Agents for **diagnostic determination** and **desensitization** are usually administered by this route.



Other routes of administration

1. Oral inhalation and nasal preparations:
2. Intrathecal/intraventricular
3. Topical
4. Transdermal
5. Rectal

1-Oral inhalation and nasal preparations

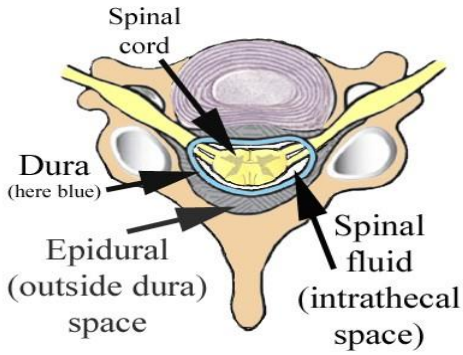
- ❑ Both routes of administration provide **rapid delivery** of drug across the **large surface area of mucous membranes** of the respiratory tract and pulmonary epithelium.
- ❑ The effects are **rapid** as IV bolus.
- ❑ Drugs that are **gases** (e.g, some anesthetics) and those that can be dispersed in an aerosol are administered via **inhalation**.
- ❑This route is **effective and convenient** for patients **with respiratory disorders such as asthma or chronic obstructive pulmonary disease**, **because** drug is delivered directly to the site of action, thereby minimizing systemic side effects.
- ❑ The **nasal route** involves topical administration of drugs directly into the nose, and it is often used for patients with **allergic rhinitis**.

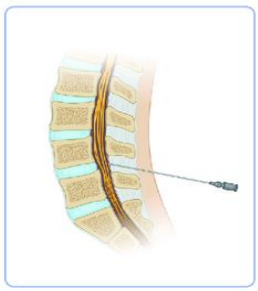
1-Oral inhalation and nasal preparations

ROUTE OF ADMINISTRATION	ABSORPTION PATTERN	ADVANTAGES	DISADVANTAGES	EXAMPLES
Inhalation	• Systemic absorption may occur; this is not always desirable	• Absorption is rapid; can have immediate effects • Ideal for gases • Effective for patients with respiratory problems • Dose can be titrated • Localized effect to target lungs; lower doses used compared to that with oral or parenteral administration • Fewer systemic side effects	• Most addictive route (drug can enter the brain quickly) • Patient may have difficulty regulating dose • Some patients may have difficulty using inhalers	• *Albuterol* • *Fluticasone*

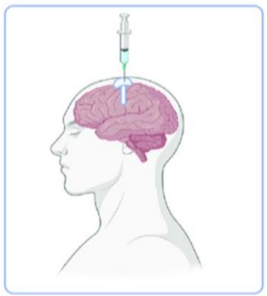
2-Intrathecal/intracerebroventricular

- The blood–brain barrier (BBB) typically **delays or prevents the absorption of drugs** into the central nervous system (CNS).
- **Intrathecal drug administration** is the introduction of a drug into the CSF by injection into the **subarachnoid space** of the spinal cord to bypass the BBB.
- When local, rapid effects are needed, it is necessary to introduce drugs directly into the cerebrospinal fluid.





Intrathecal injection



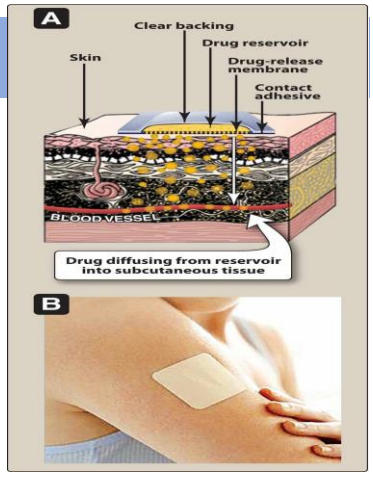
Intracerebroventricular injection

3-Topical

- Topical application is used when a local effect of the drug is desired.

ROUTE OF ADMINISTRATION	ABSORPTION PATTERN	ADVANTAGES	DISADVANTAGES	EXAMPLES
Topical	• Variable; affected by skin condition, area of skin, and other factors	• Suitable when local effect of drug is desired • May be used for skin, eye, intravaginal, and intranasal products • Minimizes systemic absorption • Easy for patient	• Some systemic absorption can occur • Unsuitable for drugs with high molecular weight or poor lipid solubility	• *Clotrimazole* cream • *Hydrocortisone* cream • *Timolol* eye drops
Rectal	• Erratic and variable	• Partially bypasses first-pass effect	• Drugs may irritate the rectal	• *Bisacodyl*

4-Transdermal



- ❑ This route achieves systemic effects by application of drugs to the skin, usually via a transdermal patch.
- ❑The rate of absorption can vary markedly, depending on (1) the **physical characteristics of the skin at the site of application**, as well as (2) **the lipid solubility of the drug**.

ROUTE OF ADMINISTRATION	ABSORPTION PATTERN	ADVANTAGES	DISADVANTAGES	EXAMPLES
Transdermal (patch)	• Slow and sustained	• Bypasses the first-pass effect • Convenient and painless • Ideal for drugs that are lipophilic and have poor oral bioavailability • Ideal for drugs that are quickly eliminated from the body	• Some patients are allergic to patches, which can cause irritation • Drug must be highly lipophilic • May cause delayed delivery of drug to pharmacological site of action • Limited to drugs that can be taken in small daily doses	• *Nitroglycerin* • *Nicotine* • *Scopolamine*

5-Rectal

❑ **The advantages of this route are**

1. Because 50% of the drainage of the rectal region **bypasses the portal circulation**, **the biotransformation of drugs by the liver is minimized** with rectal administration.
2. Preventing the **destruction** of the drug in the GI environment.
3. Useful for **drug induces vomiting** when given orally, if the patient is already **vomiting**, or if the patient is **unconscious**.

❑ **The disadvantages of this route are**

1. **Rectal absorption** is often **erratic** and **incomplete**, and
2. Many drugs **irritate the rectal mucosa**.

ROUTE OF ADMINISTRATION	ABSORPTION PATTERN	ADVANTAGES	DISADVANTAGES	EXAMPLES
Rectal	• Erratic and variable	• Partially bypasses first-pass effect • Bypasses destruction by stomach acid • Ideal if drug causes vomiting • Ideal in patients who are vomiting, or comatose	• Drugs may irritate the rectal mucosa • Not a well-accepted route	• *Bisacodyl* • *Promethazine*

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Oral	• Variable; affected by many factors	• Safest and most common, convenient, and economical route of administration	• Limited absorption of some drugs • Food may affect absorption • Patient compliance is necessary • Drugs may be metabolized before systemic absorption	• *Acetaminophen* tablets • *Amoxicillin* suspension
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Intravenous	• Absorption not required	• Can have immediate effects • Ideal if dosed in large volumes • Suitable for irritating substances and complex mixtures • Valuable in emergency situations • Dosage titration permissible • Ideal for high molecular weight proteins and peptide drugs	• Unsuitable for oily substances • Bolus injection may result in adverse effects • Most substances must be slowly injected • Strict aseptic techniques needed	• *Vancomycin* • *Heparin*
Intramuscular	• Depends on drug diluents: Aqueus solution: prompt Depot preparations: slow and sustained	• Suitable if drug volume is moderate • Suitable for oily vehicles and certain irritating substances • Preferable to intravenous if patient must self-administer	• Affects certain lab tests (creatine kinase) • Can be painful • Can cause intramuscular hemorrhage (precluded during anticoagulation therapy)	• *Haloperidol* • *Depot medroxy-progesterone*
Subcutaneous	• Depends on drug diluents: Aqueous solution: prompt Depot preparations: slow and sustained	• Suitable for slow-release drugs • Ideal for some poorly soluble suspensions	• Pain or necrosis if drug is irritating • Unsuitable for drugs administered in large volumes	• *Epinephrine* • *Insulin* • *Heparin*
Inhalation	• Systemic absorption may occur; this is not always desirable	• Absorption is rapid; can have immediate effects • Ideal for gases • Effective for patients with respiratory problems • Dose can be titrated • Localized effect to target lungs; lower doses used compared to that with oral or parenteral administration • Fewer systemic side effects	• Most addictive route (drug can enter the brain quickly) • Patient may have difficulty regulating dose • Some patients may have difficulty using inhalers	• *Albuterol* • *Fluticasone*
Topical	• Variable; affected by skin condition, area of skin, and other factors	• Suitable when local effect of drug is desired • May be used for skin, eye, intra-vaginal, and intranasal products • Minimizes systemic absorption • Easy for patient	• Some systemic absorption can occur • Unsuitable for drugs with high molecular weight or poor lipid solubility	• *Clotrimazole* cream • *Hydrocortisone* cream • *Timolol* eye drops
Transdermal (patch)	• Slow and sustained	• Bypasses the first-pass effect • Convenient and painless • Ideal for drugs that are lipophilic and have poor oral bioavailability • Ideal for drugs that are quickly eliminated from the body	• Some patients are allergic to patches, which can cause irritation • Drug must be highly lipophilic • May cause delayed delivery of drug to pharmacological site of action • Limited to drugs that can be taken in small daily doses	• *Nitroglycerin* • *Nicotine* • *Scopolamine*
Rectal	• Erratic and variable	• Partially bypasses first-pass effect • Bypasses destruction by stomach acid • Ideal if drug causes vomiting • Ideal in patients who are vomiting, or comatose	• Drugs may irritate the rectal mucosa • Not a well-accepted route	• *Bisacodyl* • *Promethazine*

Absorption of Drugs

❑ Absorption is the transfer of a drug from the site of administration to the bloodstream.

❑The rate and extent of absorption depend on

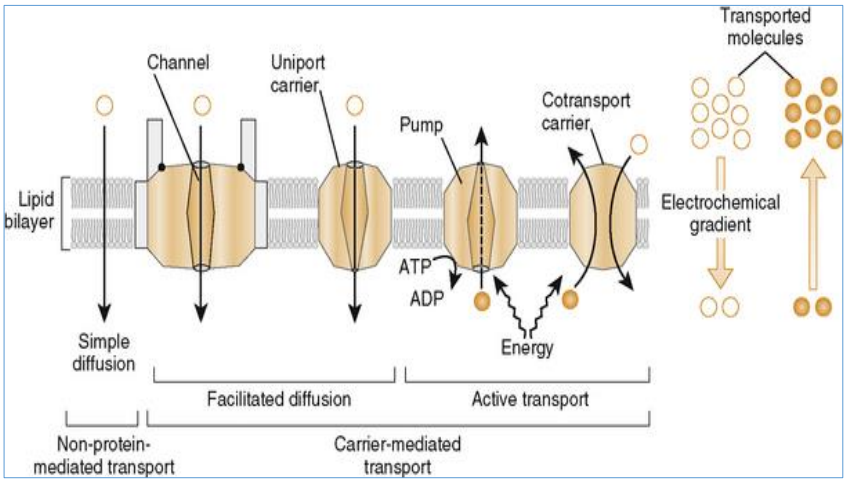
1. The **environment** where the drug is absorbed,
2. **Chemical** characteristics of the drug,
3. The **route of administration** (which influences bioavailability).

✓ Routes of administration other than intravenous may result in partial absorption and lower bioavailability.

A. Mechanisms of absorption of drugs from the GI tract

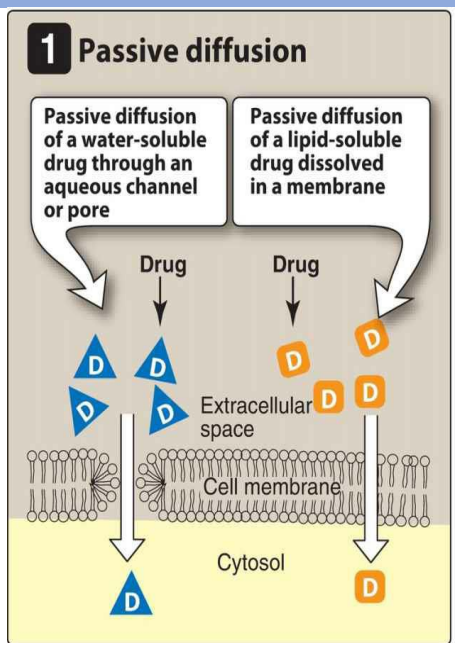
❑ Depending on their chemical properties, drugs may be absorbed from the GI tract by :

1. **Passive diffusion**
2. **Facilitated diffusion**
3. **Active transport**
4. **Endocytosis**



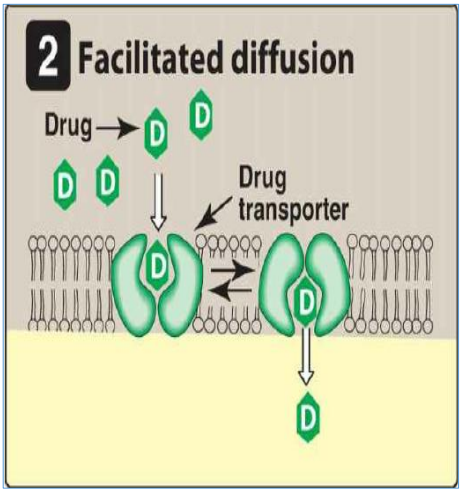
Passive diffusion (PD)

- The driving force for PD of a drug is the **concentration gradient** across a membrane separating two body compartments.
- The drug moves from an area of **high concentration** to one of **lower concentration**.
- PD **does not involve a carrier**, is **not saturable**, and shows low structural specificity.
- **The vast majority of drugs are absorbed by this mechanism.**
- **Water-soluble drugs** penetrate the cell membrane through **aqueous channels or pores**,
- **Lipid-soluble drugs** readily move across most biologic membranes due to **solubility in the membrane lipid bilayers**.



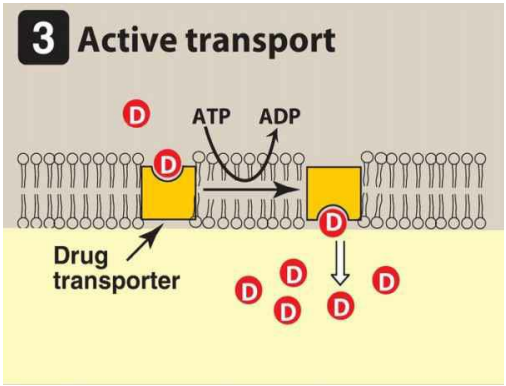
Facilitated diffusion

- Some agents can enter the cell through **specialized transmembrane carrier proteins** that facilitate the passage of **large molecules**.
- These carrier **proteins undergo conformational changes**, allowing the passage of drugs or endogenous molecules into the interior of cells.
- This process is known as **facilitated diffusion**. It does **not require energy**, can be **saturated**, and may be inhibited by compounds that compete for the carrier.



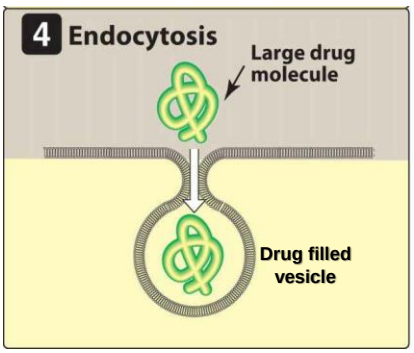
Active transport

- This mode of drug entry also involves **specific carrier proteins** that span the membrane.
- However, active transport is **energy dependent**, driven by the hydrolysis of adenosine triphosphate (ATP).
- It is capable of moving drugs **against a concentration gradient**, from a region of low drug concentration to one of higher concentration.
- The process is **saturable**.
- Active transport systems are selective and may be **competitively inhibited** by other co-transported substances.



Endocytosis and exocytosis

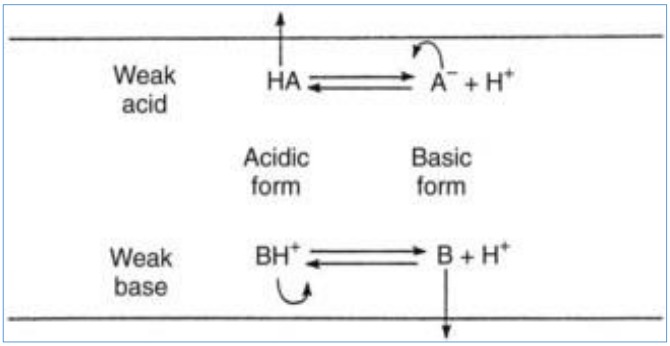
- It is used to transport drugs of **exceptionally large size** across the cell membrane.
- Endocytosis involves **engulfment** of a drug by the cell membrane and transport into the cell by pinching off the drug-filled vesicle.
- **Exocytosis** is the reverse of **endocytosis**. Many cells use exocytosis to secrete substances out of the cell through a similar process of vesicle formation.
- **Vitamin B_{12}** is transported across the gut wall by endocytosis, whereas certain neurotransmitters (e.g. **norepinephrine**) are stored in intracellular vesicles in the nerve terminal and released by exocytosis.



Factors influencing Absorption

1. Effect of **pH** on drug absorption
2. **Blood flow** to the absorption site
3. **Total surface area** available for absorption
4. **Contact time** at the absorption surface
5. **Expression of P-glycoprotein**

Effect of pH on drug absorption



Therefore, ***the effective concentration of the permeable form of each drug at its absorption site is determined by the relative concentrations of the charged and uncharged forms***.

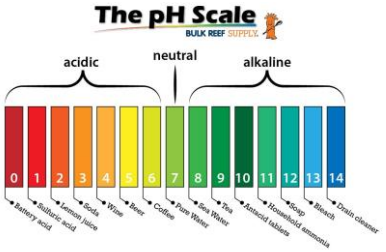
Effect of pH on drug absorption

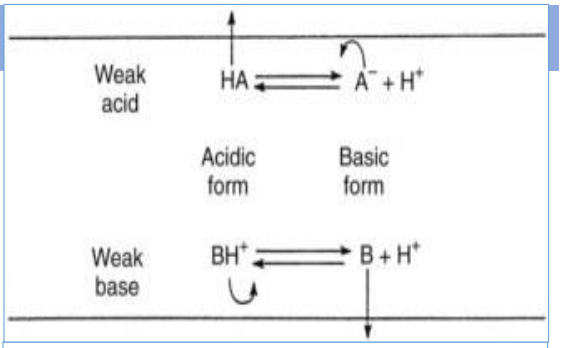
- Most drugs are either **weak acids** or **weak bases**.
- ***Acidic drugs (HA)*** release a proton (H+), causing a charged anion (A−) to form:

$$HA \leftrightarrows H^+ + A^-$$

- **Weak bases (BH+)** can also release an H+. However, the protonated form of basic drugs is usually charged, and loss of a proton produces the **uncharged base** (B):

$$BH^+ \leftrightarrows B + H^+$$





Membrane penetration by weak electrolytes.

- ✓ The **nonionic drugs (uncharged)** *(HA, B)* permeate membranes much more efficiently than do the **ionic; charged forms** *(A^-, BH^+)*.
- ✓ **Acidic conditions** shift the dissociation curves to the left, favoring the diffusion of weak acids.
- ✓ An increase in pH favors the loss of hydrogen *(H^+)* and the diffusion of weak bases.

Effect of pH on drug absorption

- **For a weak acid**, the uncharged, protonated HA can permeate through membranes, and A− cannot.

$$C_8H_7O_2COOH \rightleftharpoons C_8H_7O_2COO^- + H^+$$

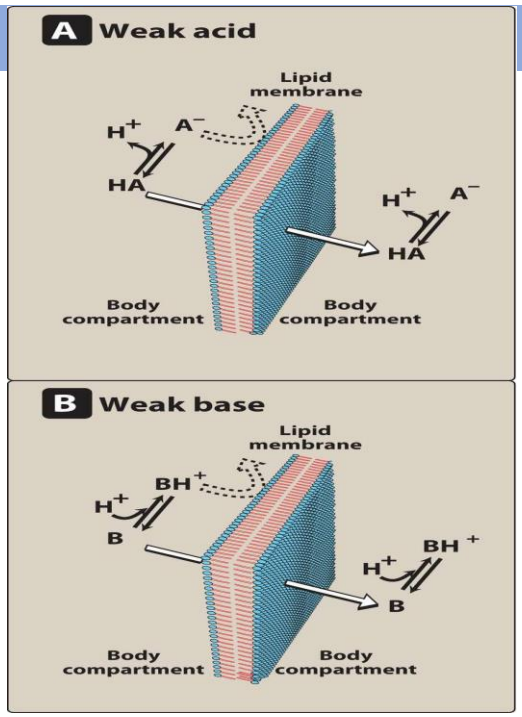
Neutral aspirin — Aspirin anion — Proton

- **For a weak base**, the uncharged form B penetrates through the cell membrane, but the protonated form BH+ does not.

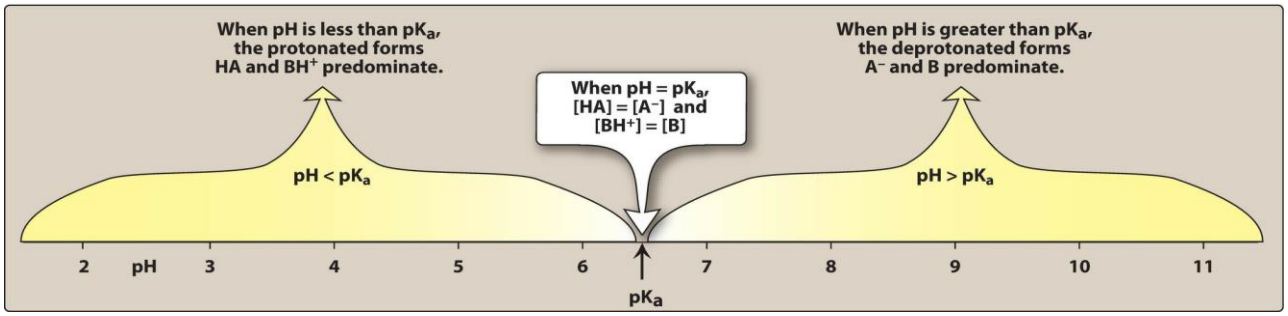
$$C_{12}H_{11}ClN_3NH_3^+ \rightleftharpoons C_{12}H_{11}ClN_3NH_2 + H^+$$

Pyrimethamine cation — Neutral pyrimethamine — Proton

- Therefore, ***the effective concentration of the permeable form of each drug at its absorption site is determined by the relative concentrations of the charged and uncharged forms***.

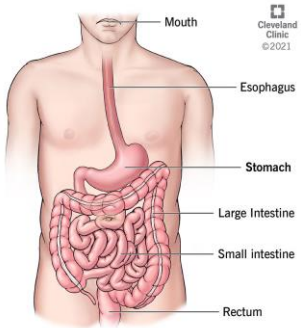


- The ratio between the charged and uncharged forms is determined by (1) **the pH** at the site of absorption and (2) **by the strength of the weak acid or base**, which is represented by the **Ionization Constant, pKa**.
- [Note: The pKa is a measure of the strength of the interaction of a compound with a proton. **The lower the pKa of a drug, the more acidic it is**. Conversely, **the higher the pKa, the more basic is the drug**.]
- **Distribution equilibrium** is achieved when the permeable form of a drug achieves an equal concentration in all body water spaces.



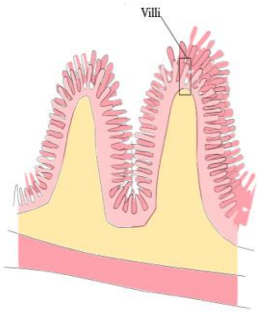
Blood flow to the absorption site

- The **intestines** receive much **more blood flow** than does the stomach, so absorption from the intestine is favored over the stomach.
- [Note: **Shock** severely **reduces blood flow** to **cutaneous tissues**, thereby minimizing absorption from **SC administration**]



Total surface area available for absorption

❑With a surface rich in brush borders containing microvilli, the **intestine** has a surface area about 1000-fold that of the **stomach**, making absorption of the drug across the intestine more efficient.

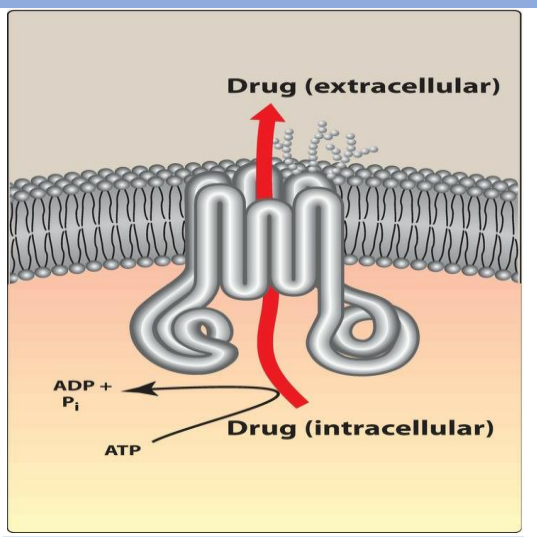


Contact time at the absorption surface

- If a drug moves through the GI tract very quickly, as can happen with severe **diarrhea**, it is **not well absorbed**.
- Conversely, anything that delays the transport of the drug from the stomach to the intestine **delays** the **rate of absorption**.
- [Note: The presence of food in the stomach **both dilutes the drug** and **slows gastric emptying.** Therefore, a drug taken with a meal is generally absorbed **more slowly**.]

Expression of P-glycoprotein

- P-glycoprotein is **a transmembrane transporter protein** responsible for transporting various molecules, including drugs, across cell membranes.
- It is expressed in tissues throughout the body, including the **liver, kidneys, placenta, intestines, and brain capillaries**, and is involved in **transportation of drugs from tissues to blood**.
- It "pumps" drugs out of cells. Thus, in areas of high expression, **P-glycoprotein reduces drug absorption**.
- In addition to transporting many drugs out of cells, It is also associated with **multidrug resistance**.
- Also known as **multidrug resistance protein**.



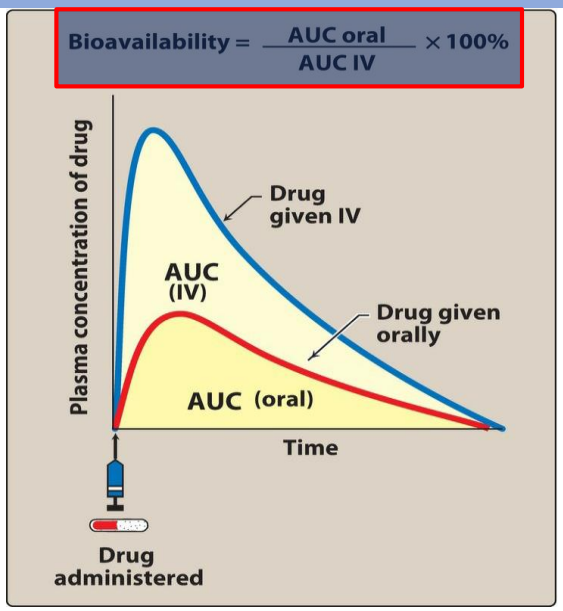
The six membrane-spanning loops of the P-glycoprotein form a central channel for the ATP-dependent pumping of drugs from the cell.

Bioavailability

- **Bioavailability** is the **rate** and **extent** to which an administered drug reaches the **systemic circulation**.
- For example, if 100 mg of a drug is administered orally and 70 mg is absorbed unchanged, the bioavailability is 0.7 or 70%.
- Determining bioavailability is important for calculating drug dosages for **non-intravenous routes** of administration.

Determination of bioavailability

- Bioavailability is determined by **comparing plasma levels** of a drug after a particular **route of administration** (for example, oral administration) with levels achieved by **IV administration**.
- After IV administration, 100% of the drug rapidly enters the circulation.
- When the drug is given orally, only part of the administered dose appears in the plasma.
- By plotting plasma concentrations of the drug versus time, the area under the curve (AUC) can be measured.



Factors that influence bioavailability

❑In contrast to IV administration, which confers 100% bioavailability, orally administered drugs often undergo **first pass metabolism**.

❑This biotransformation, in addition to **chemical and physical characteristics of the drug**, determines the rate and extent to which the agent reaches the systemic circulation.

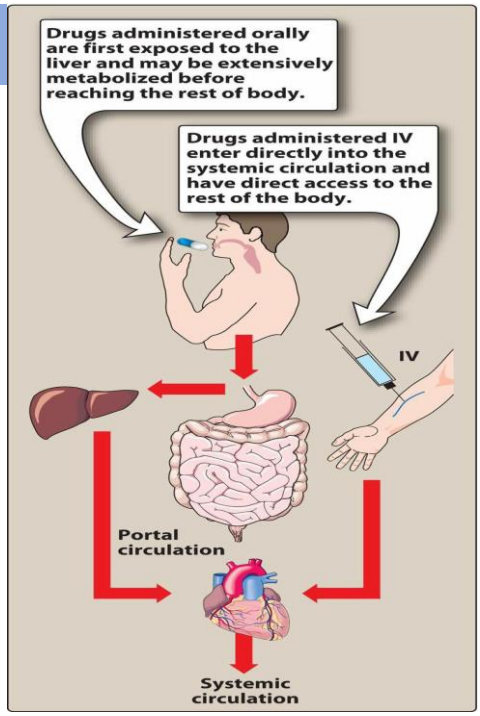
1. **First-pass hepatic metabolism**
2. **Solubility of the drug**
3. **Chemical instability**
4. **Nature of the drug formulation**

1-First-pass hepatic metabolism

❑ When a drug is absorbed from the GI tract, it enters the **portal circulation** before entering the systemic circulation. If the drug is rapidly metabolized in the liver or gut wall during this initial passage, the amount of unchanged drug entering the systemic circulation is **decreased**. This is referred to as **first-pass metabolism**.

❑[Note: First-pass metabolism by the **intestine** or **liver** limits the efficacy of many oral medications, more than **90% of *nitroglycerin*** is cleared during first-pass metabolism. Hence, it is primarily administered via the **sublingual**, **transdermal**, or **intravenous route**.]

❑Drugs with **high first-pass metabolism** should be given in **doses sufficient** to ensure that enough active drug reaches the desired site of action.



2-Solubility of the drug

- **Very hydrophilic drugs** are **poorly absorbed** because of the inability to cross lipid-rich cell membranes.
- **Paradoxically**, drugs that are **extremely lipophilic** are also **poorly absorbed**, because they are insoluble in aqueous body fluids and, therefore, cannot gain access to the surface of cells.
- For a drug to be readily absorbed, it must be ***largely lipophilic, yet have some solubility in aqueous solutions.*** This is one reason why many drugs are either weak acids or weak bases.

3-Chemical instability

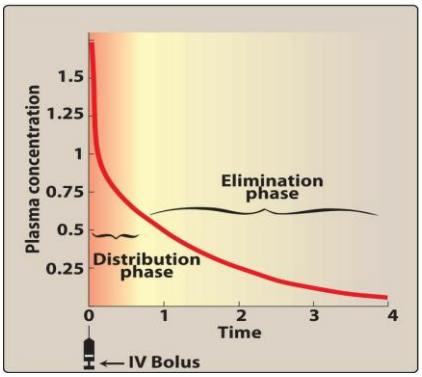
- Some drugs, such as ***penicillin G***, are unstable in the pH of gastric contents.
- Others, such **as *insulin***, are destroyed in the GI tract by degradative enzymes.

4-Nature of the drug formulation

- Drug absorption may be altered by factors unrelated to the chemistry of the drug.
- For example, **particle size**, **salt form, crystal polymorphism**, **enteric coatings**, and the **presence of excipients** (such as binders and dispersing agents) can influence the ease of dissolution and, therefore, alter the rate of absorption.

Drug Distribution

- **Drug distribution** is the process by which a drug ***reversibly*** leaves the **bloodstream** and enters the **extracellular** fluid and tissues.
- For IV drug, absorption is not a factor, and the initial phase immediately following administration represents the **distribution phase**, during which the drug rapidly leaves the circulation and enters the tissues.



Drug Distribution

- **Distribution of a drug from the plasma to the interstitium depends on:**

1. **Cardiac output** and **local blood flow**
2. Capillary **permeability**
3. Tissue **volume**
4. Degree of **binding** of the drug to **plasma and tissue proteins**
5. Relative **lipophilicity of the drug**.

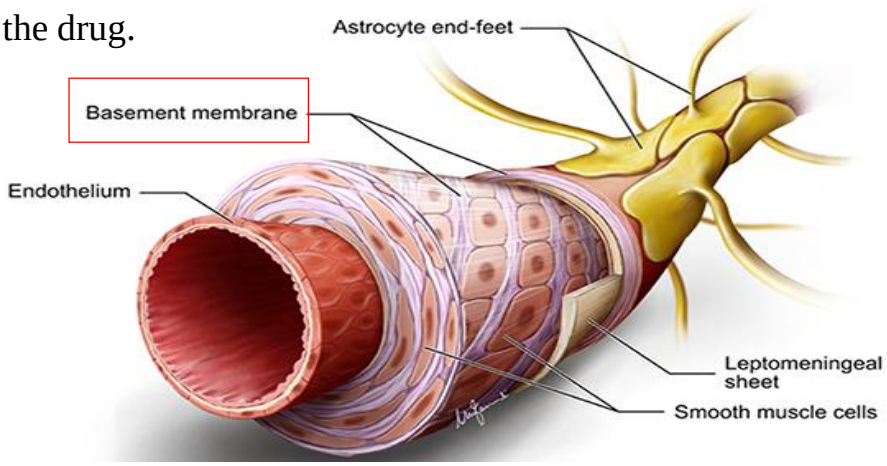
Blood flow

- The rate of blood flow to the tissue capillaries varies widely.
- For instance, blood flow to "vessel-rich organs" (**brain, liver, and kidney**) is greater than that to the skeletal muscles.
- Adipose tissue, skin, and viscera have still lower rates of blood flow.
- Variation in blood flow partly explains the **short duration of hypnosis** produced by an IV bolus of ***propofol***.
- ***High blood flow***, ***together with high lipophilicity*** of *propofol*, permits rapid distribution into the CNS and produces anesthesia.
- A subsequent **slower distribution** to **skeletal muscle and adipose tissue** lowers the **plasma concentration** so that the drug diffuses out of the CNS, down the concentration gradient, and **consciousness** is regained.

Capillary permeability

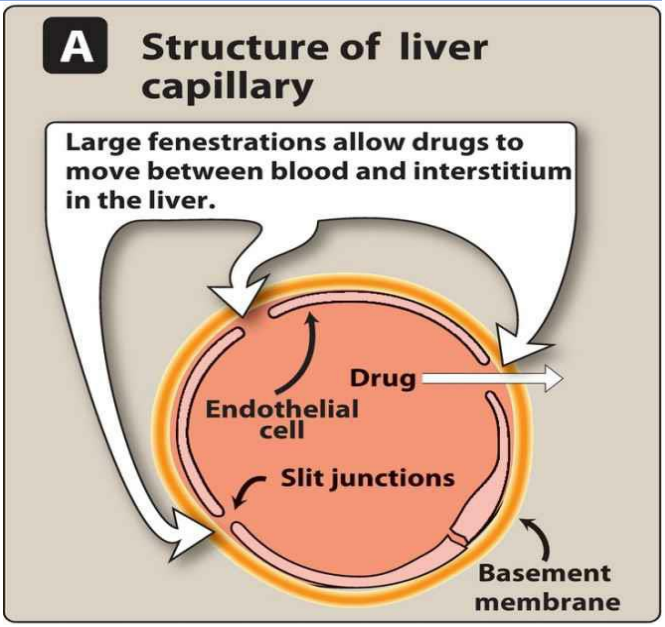
- **Capillary permeability is determined by**

1. Capillary structure
2. Chemical nature of the drug.



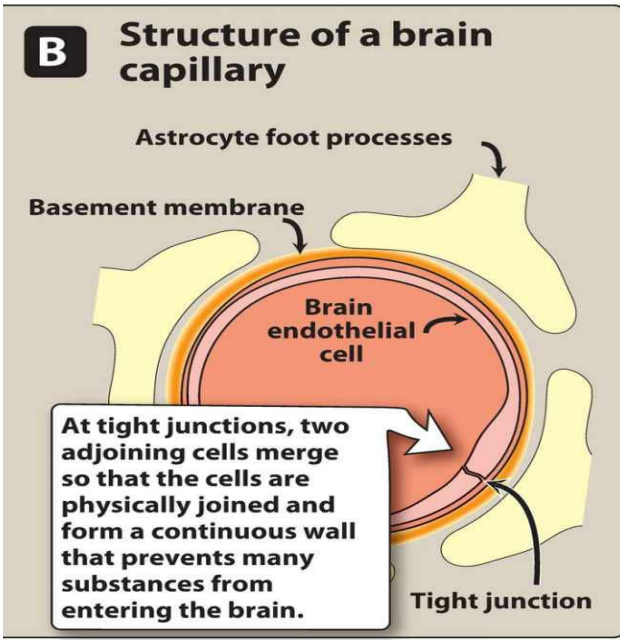
Capillary structure

- Capillary structure **varies** in terms of the **fraction of the basement membrane *exposed*** by slit junctions between endothelial cells.
- **In the liver and spleen**, a significant portion of the basement membrane is exposed due to large, discontinuous capillaries through which large plasma proteins can pass (A).



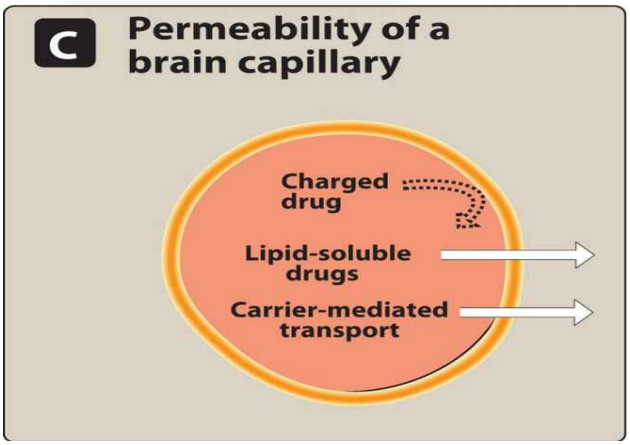
Capillary structure

- **In the brain**, the capillary structure is continuous, and there are no slit junctions (B). To enter the brain, **drugs must pass through the endothelial cells of the CNS capillaries** or **undergo active transport**. For example, a specific transporter carries ***levodopa*** into the brain.
- **Lipid-soluble drugs** readily **penetrate** the CNS because they **dissolve** in the endothelial cell membrane.



Capillary structure

- By contrast, **ionized or polar drugs generally fail to enter the CNS** because they cannot pass through the endothelial cells that have no slit junctions (C). These closely juxtaposed cells form tight junctions that constitute the blood–brain barrier.



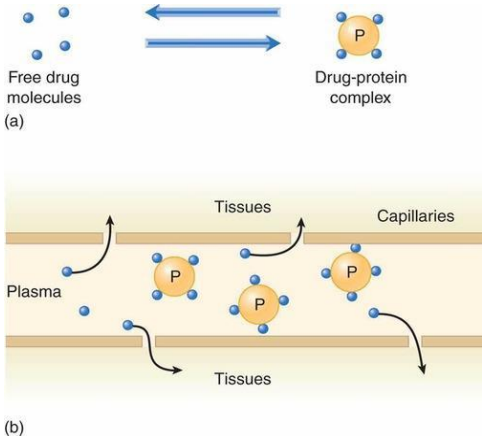
Binding of drugs to proteins

1. **Binding to plasma proteins**
2. **Binding to tissue proteins**

Binding of drugs to plasma proteins and tissues

1. Binding to plasma proteins

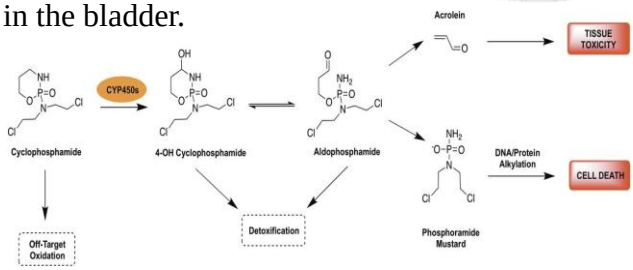
- Reversible binding to plasma proteins sequesters drugs in a **nondiffusible** form and **slows transfer** out of the vascular compartment.
- **Albumin** is the major drug-binding protein, and it may act as a **drug reservoir.** As the concentration of free drug decreases due to elimination, the bound drug dissociates from albumin. This maintains the free-drug concentration as a constant fraction of the total drug in the plasma.



Binding of drugs to plasma proteins and tissues

2. Binding to tissue proteins

- Many drugs **accumulate** in tissues, leading to higher concentrations in tissues than in interstitial fluid and blood. Drugs may accumulate because of **binding to lipids, proteins, or nucleic acids**. Drugs may also undergo active transport into tissues.
- **Tissue reservoirs** may serve as a major **source** of the drug and **prolong** its actions or cause local drug **toxicity**.
- For example, acrolein, the metabolite of ***cyclophosphamide***, can cause **haemorrhagic cystitis** because it accumulates in the bladder.



Lipophilicity

- The chemical nature of a drug strongly influences its ability to cross cell membranes.
- Lipophilic drugs readily move across most biologic membranes. These drugs dissolve in the lipid membranes and penetrate the entire cell surface.
- ***The major factor influencing the distribution of lipophilic drugs*** is **blood flow to the area**. By contrast, **hydrophilic** drugs do not readily penetrate cell membranes and **must pass through slit junctions**.

Volume of distribution

- **The apparent volume of distribution**, Vd, is defined as the fluid volume that is required to contain the entire drug in the body at the same concentration measured in the plasma. It is calculated by dividing the dose that ultimately gets into the systemic circulation by the plasma concentration at time zero (C0).

$$V_d = \frac{\text{Amount of drug in the body}}{C_0}$$

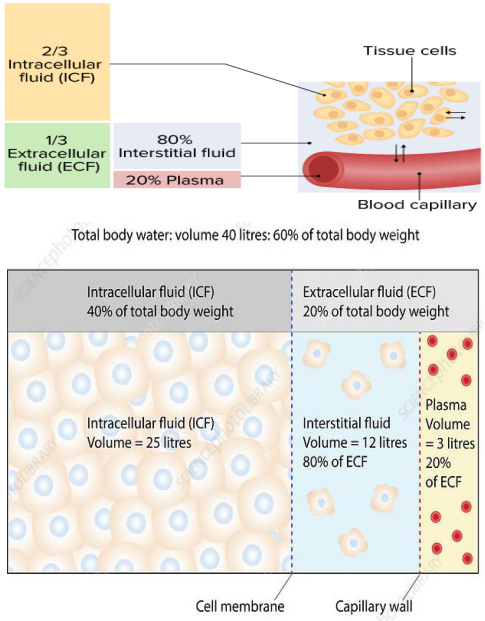
- Although Vd has no physiologic or physical basis, **it can be useful to compare the distribution of a drug with the volumes of the water compartments in the body**.

1-Distribution into the water compartments in the body

- Drug distribute into any one of the three functionally compartments of body water and/ or a cellular site.

A. Plasma compartment

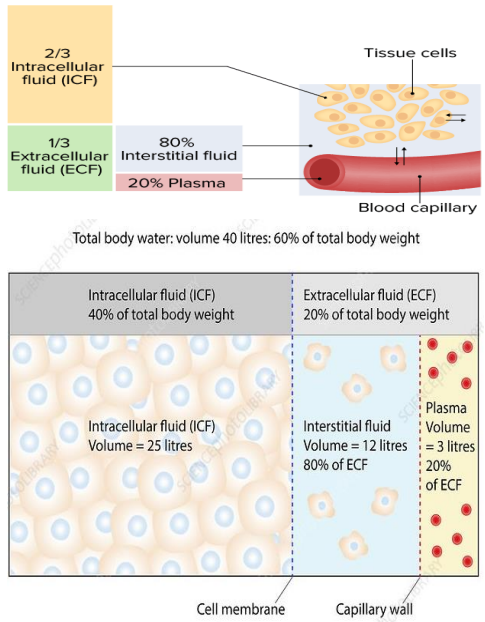
- Drug has a **high molecular weight** or is extensively **protein bound**, it is too large to pass through junctions of the capillaries and is trapped within **the plasma**. These drugs has a **low Vd** that approximates the plasma volume, (4 L in a 70-kg) e.g. *Heparin*



1-Distribution into the water compartments in the body

B. Extracellular fluid

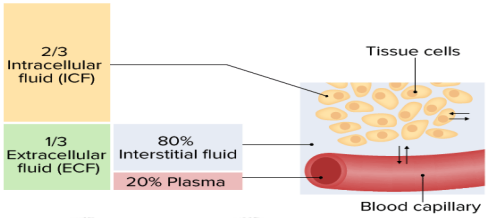
- Drug has a **low molecular weight** but is **hydrophilic**, it can pass through junctions of the capillaries into **the interstitial fluid**. However, hydrophilic drugs ***cannot move across the lipid membranes of cells to enter the intracellular fluid***. Therefore, these drugs distribute into a volume that ***is the sum of the plasma volume and the interstitial fluid***, which together constitute the **extracellular fluid** (~ 20% of body weight or 14 L in a 70-kg). E.g. Aminoglycoside antibiotics



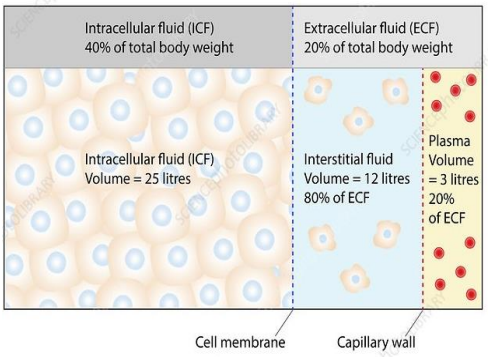
1-Distribution into the water compartments in the body

C-Total body water

- Drugs has a **low molecular weight** and **lipophilic**, it can move into the interstitium through the slit junctions and pass the cell membranes into the **intracellular fluid**. These drugs distribute into a volume of about 60% of body weight (42 L in a 70-kg). e.g, *Ethanol*.
- **Note: In general**,
- **A larger vd** indicates **greater distribution into tissues**;
- **A smaller vd** suggests **confinement to plasma or extracellular fluid.**]

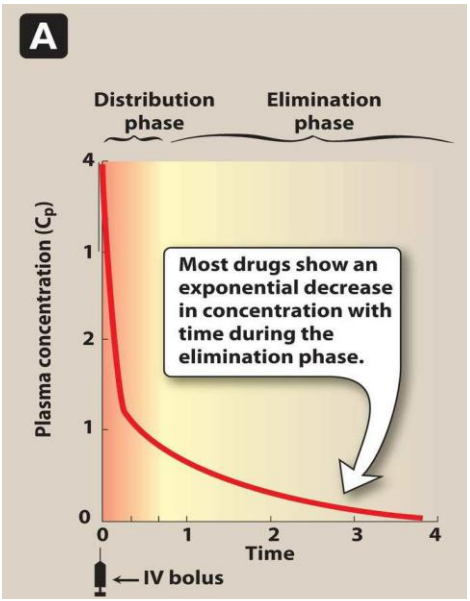


Total body water: volume 40 litres: 60% of total body weight



2. Determination of Vd

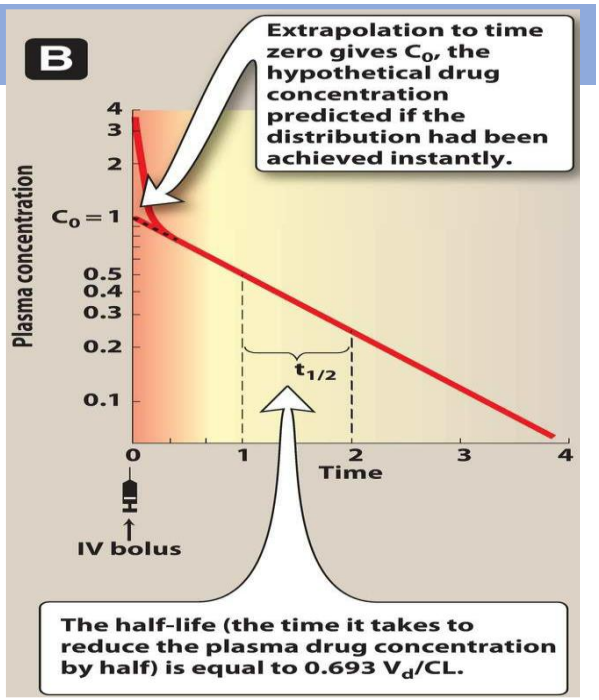
- Drug clearance is usually **First order process which** means ***that a constant fraction of the drug is eliminated per unit of time.***
- It can be analyzed by plotting the log of the plasma drug concentration (Cp) versus time (A).
- drug conc. In plasma can be extrapolated back to time zero (the time of IV bolus) on the Y axis to determine C_0, **which is the concentration of drug that would have been achieved if the distribution phase had occurred instantly**. This allows calculation of Vd as



2. Determination of Vd

$$V_d = \frac{\text{Dose}}{C_0}$$

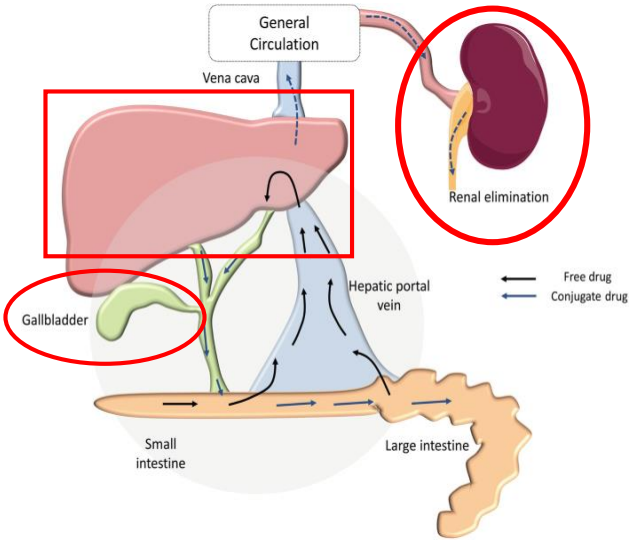
- For example, if 10 mg of drug is injected into a patient and the plasma concentration is extrapolated back to time zero, and C_0 = 1 mg/L (graph B),
- then Vd $= \frac{10\ mg}{1 mg/l}$ = 10 L.



Drug Clearance Through Metabolism

- Once a drug enters the body, the process of elimination begins. The three major routes of elimination are

1. **Hepatic metabolism,**
2. **Biliary elimination,**
3. **Urinary excretion.**



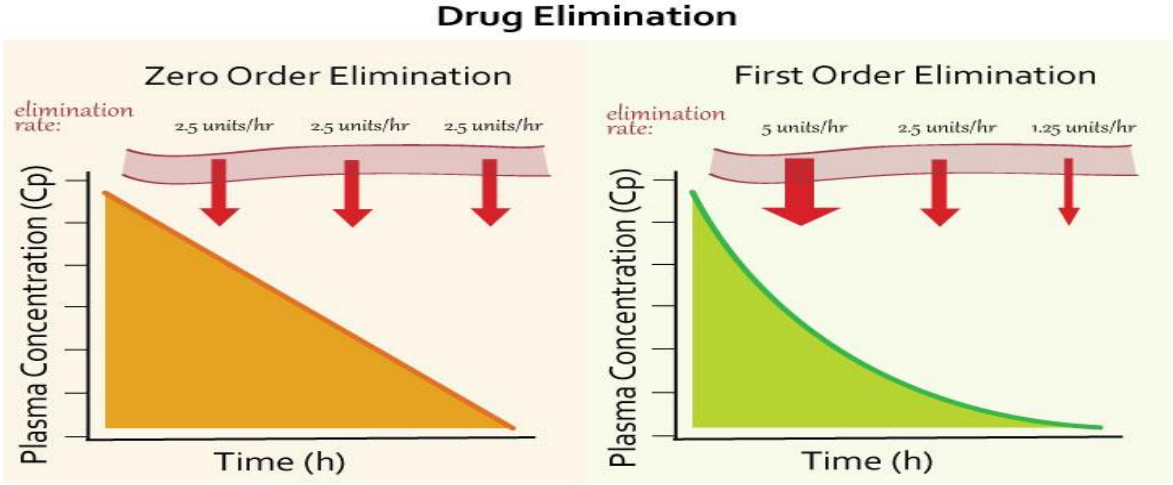
- Note: **Elimination** is irreversible removal of drug from the body. It involves biotransformation (drug metabolism) and excretion.
- **Excretion** is removal of intact drug from the body.

Drug Clearance Through Metabolism

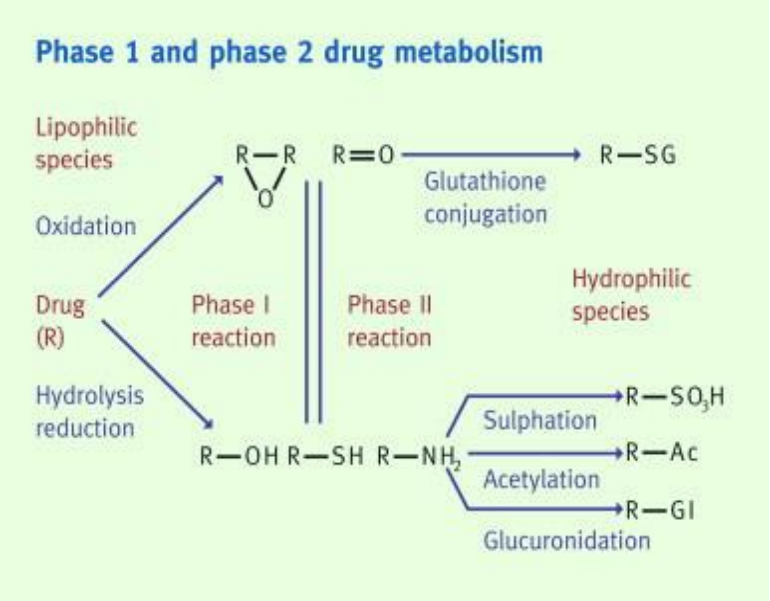
- The elimination processes decrease the plasma concentration exponentially. That is a constant fraction of the drug is eliminated in a given unit of time.
- Most drugs are eliminated according to **first-order kinetics**, although some, such as aspirin in high doses, are eliminated according to **zero-order or nonlinear kinetics**.
- ***Metabolism*** *results in products with increased* ***polarity****, which allows the drug to be eliminated.*
- Clearance (CL) estimates the volume of blood from which the drug is cleared per unit of time.

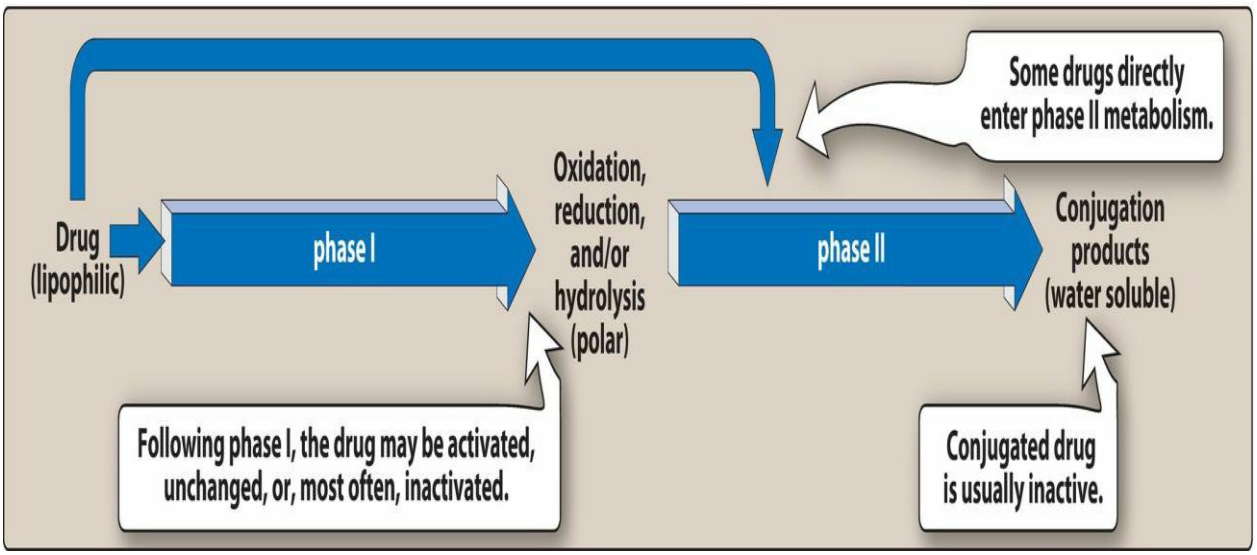
A. Kinetics of metabolism

1. **First-order kinetics**
2. **Zero-order kinetics**



- The kidney cannot efficiently excrete lipophilic drugs that readily cross cell membranes and are reabsorbed in the distal convoluted tubules. Therefore, lipid-soluble agents are first metabolized into more polar (hydrophilic) substances in the liver via two general sets of reactions, called **phase I and phase II**.





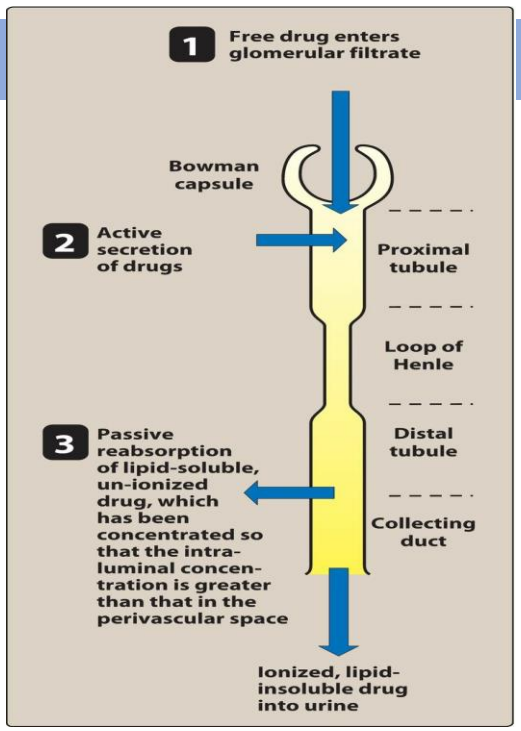
VI. Drug Clearance by the Kidney

- Drugs must be sufficiently **polar** to be eliminated from the body.
- Removal of drugs from the body occurs via a number of routes; the most important is elimination through the kidney into the urine.
- Patients with renal dysfunction may be unable to excrete drugs and are at risk for drug accumulation and adverse effects.

A. Renal elimination of a drug

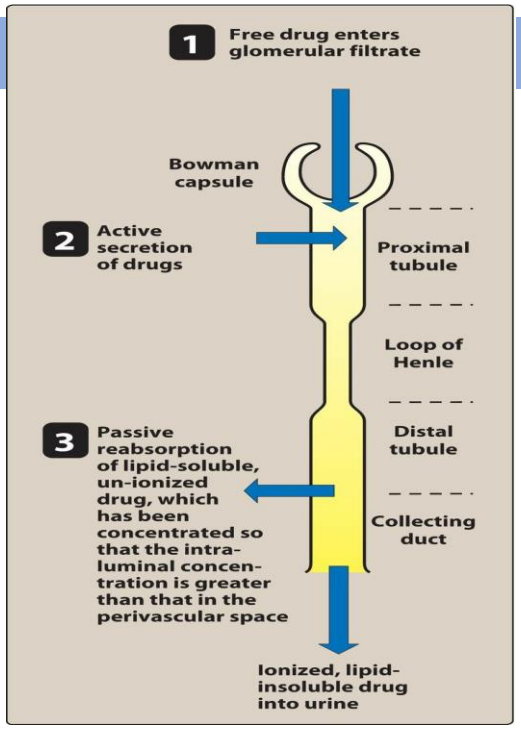
- A drug passes through several processes in the kidney before elimination:

1. **Glomerular filtration,**
2. **Active tubular secretion,**
3. **Passive tubular reabsorption.**



1. Glomerular filtration rate (GFR)

- Drugs enter the kidney through renal arteries, which divide to form a glomerular capillary plexus. Free drug (not bound to albumin) flows through the capillary slits into the Bowman space as part of the glomerular filtrate.
- GFR is normally about 120 mL/min/1.73m2 but may diminish significantly in renal disease.
- **Lipid solubility and pH does not influence** the passage of drugs into the glomerular filtrate.
- However, **variations in GFR** and **protein binding** of drugs do affect this process.

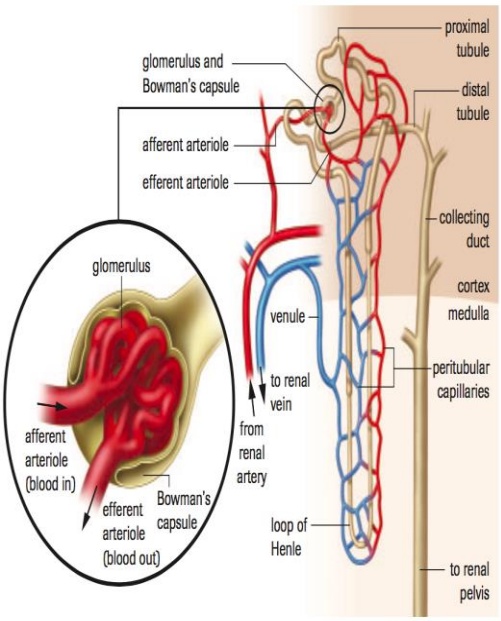


2. Proximal tubular secretion

- Drugs that were not transferred into the glomerular filtrate leave the glomeruli through **efferent arterioles**, which divide to form a capillary plexus surrounding the nephric lumen in the proximal tubule.
- Secretion primarily occurs in the proximal tubules by two energy-requiring active transport systems:

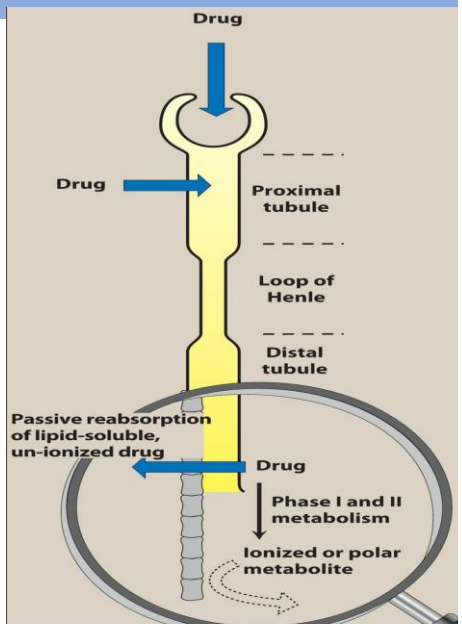
1. **One for anions** (deprotonated forms of weak acids)
2. **One for cations** (protonated forms of weak bases).

- These transport systems shows low specificity. Thus, competition between drugs can occur within each transport system.



3. Distal tubular reabsorption

- As a drug moves toward the distal convoluted tubule, its concentration increases and exceeds that of the perivascular space.
- Uncharged drug diffuse out of the nephric lumen, back into the systemic circulation.
- **Manipulating the urine pH** to increase the fraction of ionized drug in the lumen may be done to minimize the amount of back diffusion and increase the clearance of an undesirable drug.
- **Weak acids** can be eliminated by **alkalinization of the urine**, whereas elimination of **weak bases** may be increased by **acidification of the urine**.
- This process is called "**ion trapping**." For example, a patient presenting with ***phenobarbital*** **(weak acid)** overdose can be given ***bicarbonate***, which **alkalinizes** the urine and keeps the drug ionized, thereby decreasing its reabsorption.



VII. Excretion by Other Routes

- Drug excretion may also occur via **the intestines, bile, lungs, and breast milk, among others.**
- Drugs that are not absorbed after oral administration or drugs that are secreted directly into the intestines or into bile are **excreted in the feces**.
- **The lungs** are primarily involved in the elimination of anesthetic gases (*desflurane*).
- **Elimination of drugs in breast milk** may expose the breast-feeding infant to medications and/or metabolites being taken by the mother and is a potential source of undesirable side effects to the infant.
- **Excretion of most drugs into sweat, saliva, tears, hair, and skin** occurs only to a small extent.
- Total body clearance and drug half-life are important measures of drug clearance that are used to optimize drug therapy and minimize toxicity.

A. Total body clearance

- The total body (systemic) clearance, (CL_{total}), is the sum of all clearances from the drug-metabolizing and drug eliminating organs.
- **The kidney** is often the major organ of excretion**. The liver** also contributes to drug clearance through metabolism and/or excretion into the bile.
- Total clearance is calculated using the following equation: where $CL_{hepatic}$ + CL_{renal} are typically the most important

$$CL_{total} = CL_{hepatic} + CL_{renal} + CL_{pulmonary} + CL_{other}$$

B. Clinical situations resulting in changes in drug half-life

- When a patient has an abnormality that alters the half-life of a drug, adjustment in dosage is required. Patients who may have an increase in drug half-life include those with:

1) **Diminished renal or hepatic blood flow**, for example, in cardiogenic shock, heart failure, or hemorrhage;

2) **Decreased ability to extract drug from plasma**, for example, in renal disease;

3) **Decreased metabolism**, for example, when a concomitant drug inhibits metabolism or in hepatic insufficiency, as with cirrhosis.

- These patients may require a decrease in dosage or less frequent dosing intervals.
- **In contrast**, the half-life of a drug may be decreased by increased hepatic blood flow, decreased protein binding, or increased metabolism. This may necessitate higher doses or more frequent dosing intervals.