SECTION

1

Biopharmaceutics and Pharmacokinetics

1. Biopharmaceutics
2. Bioavailability and Bioequivalence
3. Biopharmaceutical Statistics

1. Biopharmaceutics

Biopharmaceutics examines the inter-relationship of the physical/chemical properties of the drug, the dosage form (drug product) in which the drug is given, and the route of administration on the rate and extent of systemic drug absorption.

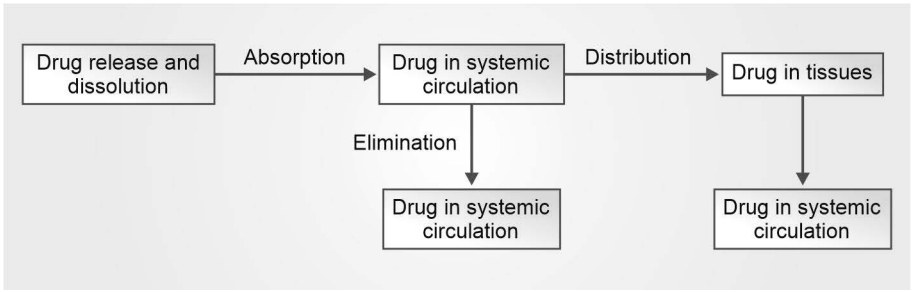

Fig. 1.1: Relationship between the drug, the drug product and the pharmacologic effect

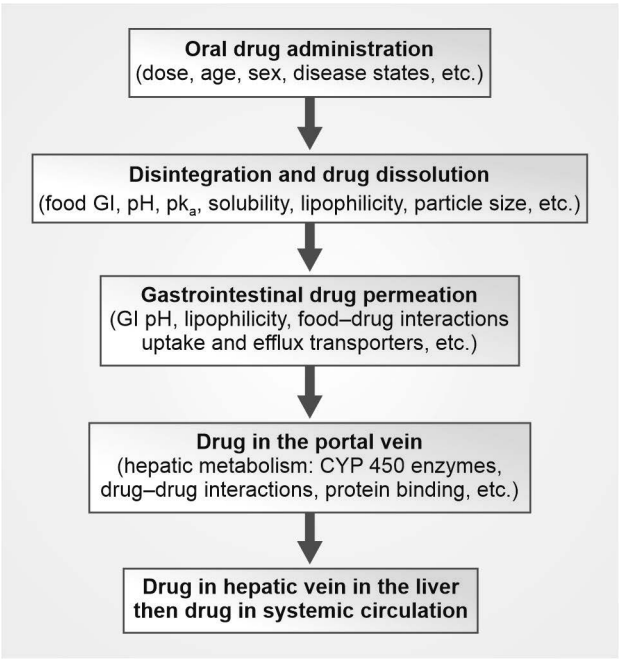

Fig. 1.2: Pharmacokinetics of drug and drug product

Biopharmaceutic Considerations in Drug Product Design

Products	*Considerations*
Therapeutic objective	Drug may be intended for rapid relief of symptoms, slow extended action given once per day, or longer for chronic use; some drugs may be intended for local action or systemic action
Drug (active pharmaceutical ingredient, API)	Physical and chemical properties of API, including solubility, polymorphic form, particle size; impurities
Route of administration	Oral, topical, parenteral, transdermal, inhalation, etc.
Drug dosage and dosage regimen	Large or small drug dose, frequency of doses, patient acceptance of drug product, patient compliance

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Products	*Considerations*
Type of drug product	Orally disintegrating tablets, immediate release tablets, extended release tablets, transdermal, topical, parenteral, implant, etc.
Excipients	Although very little pharmacodynamic activity, excipients may affect drug product performance including release of drug from drug product
Method of manufacture	Variables in manufacturing processes, including weighing accuracy, blending uniformity, release tests, and product sterility for parenteral

Comparison of Zero-order and First-order Reactions

Criteria	*Zero-order reaction*	*First-order reaction*
Equation	$-dC/dt = k_0$	$-dC/dt = kC$
Rate constant—units	(mg/L)/h	1/h
Half-life, $t_{½}$ (units = time)	$t_{½} = 0.5C/k_0$ (not constant)	$t_{½} = 0.693/k$ (constant)
Effect of time on rate	Zero-order rate is constant with respect to time	First-order rate will change with respect to time as concentration changes
Effect of time on rate constant	Rate constant with respect to time changes as the concentration changes	Rate constant remains constant with respect to time
Drug concentrations versus time—plotted on rectangular coordinates	Drug concentrations decline linearly for a zero-order rate process	Drug concentrations decline nonlinearly for a first-order rate process

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Criteria	*Zero-order reaction*	*First-order reaction*
Drug concentrations versus time—plotted on a semi-logarithmic graph	Drug concentrations decline nonlinearly for a zero-order rate process	Drug concentrations decline linearly for a single first-order rate process

Absorption in the Gastrointestinal Tract

The gastrointestinal (GI) tract is a muscular tube around 6 meters long with varying diameters, extending from the mouth to the anus. It consists of four main anatomical sections: The esophagus, stomach, small intestine, and large intestine (colon). The inner surface of the GI tract is rough, increasing the surface area for absorption. The GI tract wall comprises four principal histological layers:

1. **Serosa:** The outermost layer, consisting of epithelial cells and connective tissues continuous with the peritoneum.
2. **Muscularis Externa:** This layer contains three layers of smooth muscle. The outer layer has longitudinally oriented fibers, while the two inner layers have circularly oriented fibers. These muscles facilitate the movement and physical breakdown of food through contractions.
3. **Submucosa:** A connective tissue layer that houses some secretory tissues, blood vessels, lymphatic vessels, and a network of nerve cells known as the submucous plexus.
4. **Mucosa:** Composed of three layers—the muscularis mucosae, which alters the mucosa's shape, the lamina propria (a connective tissue layer), and the epithelial layer.

A significant portion of the GI epithelium is covered with mucus, a viscoelastic, translucent aqueous gel. Mucus serves as a protective layer and mechanical barrier, continuously changing with various secretions and exfoliated epithelial cells. It consists mainly of water (~95%) and large glycosylated proteins called mucins. Mucins have a protein backbone about 800 amino acids long and oligosaccharide side chains up to 18 residues in length. The mucus layer's thickness varies from 5 µm to 500 µm, averaging around 80 µm. Mucus is constantly removed by abrasion and breakdown from acids and enzymes and is continually replenished, with an estimated turnover time of 4 to 5 hours, which may vary along the GI tract.

The gastrointestinal tract comprises the mouth, pharynx, esophagus, stomach, small intestine, large intestine, and anus. The degree of drug absorption in any part of the gastrointestinal tract is influenced by the absorption rate, the surface area exposed, and the duration available for absorption.

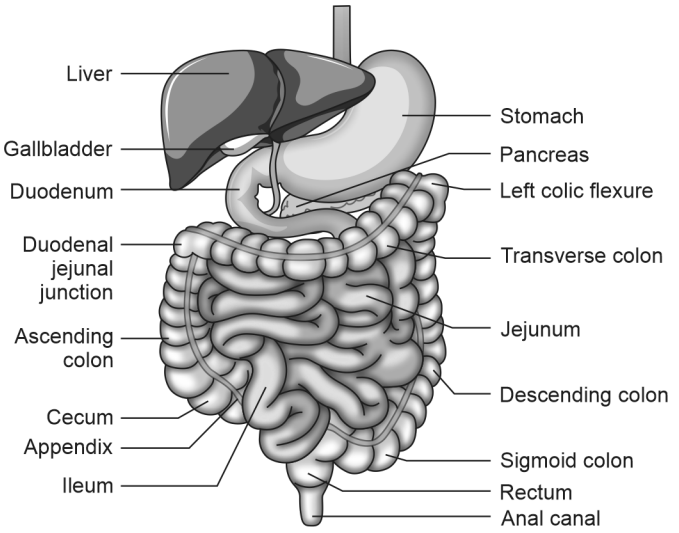


Fig. 1.3: Anatomy of GIT

Mechanism of Drug Absorption

There are three main categories of drug transport mechanisms involved in absorption:

1. Transcellular/Intracellular transport
2. Paracellular/Intercellular transport
3. Vesicular transport

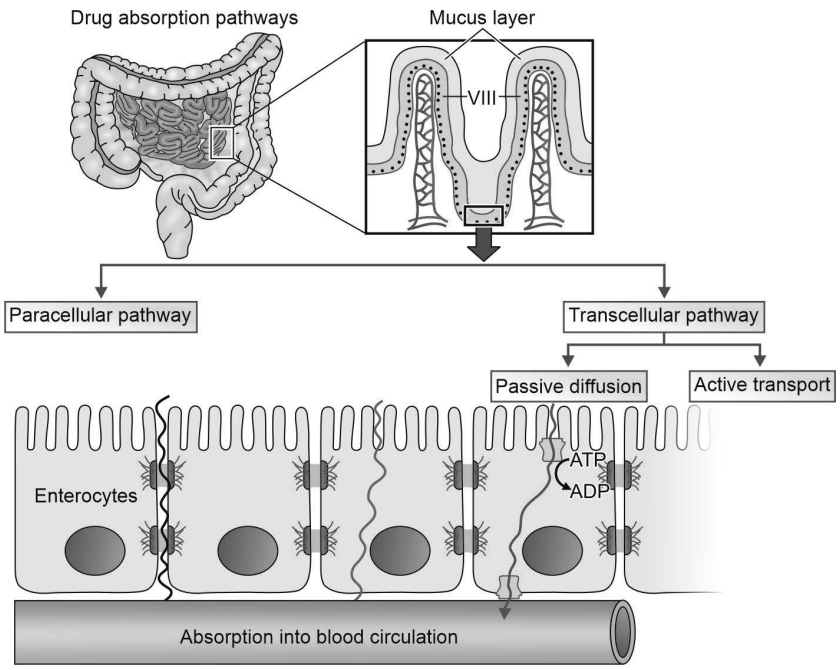


Fig. 1.4: Drug absorption pathway

A. Transcellular/Intracellular Transport

This mechanism involves the passage of drugs across the gastrointestinal (GI) epithelium and is the most common pathway for drug transport. The steps involved in transcellular transport include:

- **Permeation of the GI epithelial cell membrane:** This lipid barrier is the primary obstacle to drug absorption.
- **Movement through the intracellular space (cytosol).**
- **Permeation of the lateral or basolateral membrane:** This step is of secondary importance.

Various processes involved in transcellular drug transport include:

1. **Passive Transport Processes:** These do not require energy beyond molecular motion (Brownian motion) to pass through the lipid bilayer and are further classified into:
   - Passive diffusion
   - Pore transport
   - Ion-pair transport
   - Facilitated or mediated diffusion
2. **Active Transport Processes:** These require energy from ATP to move drug molecules from the extracellular to intracellular environment and are divided into:
   - Primary active transport
   - Secondary active transport, which includes:
     - Symport (co-transport)
     - Antiport (counter-transport)

B. Paracellular/Intercellular Transport

This involves the transport of drugs through the junctions between GI epithelial cells and is of minor importance in drug absorption. The mechanisms include:

- **Permeation through tight junctions of epithelial cells:** Occurs through openings slightly larger than aqueous pores, allowing compounds like insulin and cardiac glycosides to be absorbed.
- **Persorption:** Drug permeation through temporary openings formed by the shedding of adjacent epithelial cells into the lumen. Paracellular transport differs from pore transport in that it involves transfer across the epithelium through cellular junctions, whereas pore transport involves movement into the cell through pores in the cell membrane.

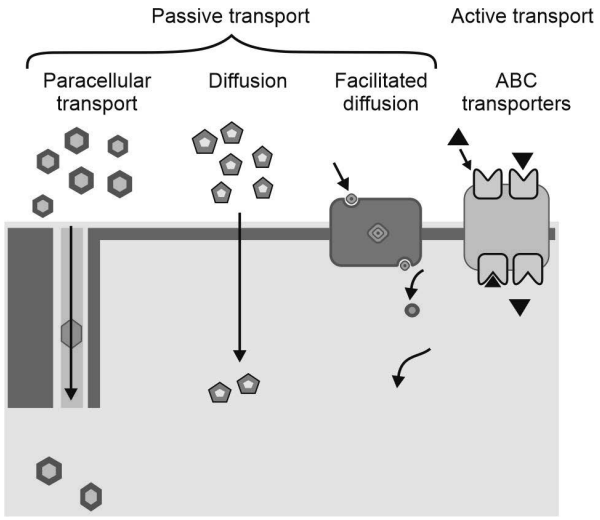


Fig. 1.5: Transportation of drug

C. Vesicular or Corpuscular Transport (Endocytosis)

Similar to active transport, vesicular transport is energy-dependent but involves substances being transported within vesicles into a cell. This process, which can also be classified as transcellular due to its mechanism, includes:

- **Pinocytosis**
- **Phagocytosis**

Passive Diffusion

Also known as nonionic diffusion, passive diffusion is the primary process for the absorption of over 90% of drugs. The driving force behind this process is the concentration or electrochemical gradient, defined as the difference in drug concentration on either side of the membrane. Drug movement results from the kinetic energy of molecules. Because no external energy source is required, this process is termed passive diffusion. During passive diffusion, the drug in the aqueous solution at the absorption site partitions into and dissolves within the lipid membrane, eventually leaving by dissolving again in the aqueous medium on the membrane's interior side.

Passive diffusion is best explained by Fick's first law of diffusion, which states that drug molecules diffuse from a region of higher concentration to a region of lower concentration until equilibrium is reached. The rate of diffusion is directly proportional to the concentration gradient across the membrane. Mathematically, it is expressed as:

dQ/dt = Rate of drug diffusion (amount/time). It also represents the rate of appearance of drug in blood.

D = Diffusion coefficient of the drug through the membrane (area/time)

A = Surface area of the absorbing membrane for drug diffusion (area)

$K_{m/w}$ = Partition coefficient of the drug between the lipoidal membrane and the aqueous GI fluids (no units) (C_{GIT} – C) = difference in the concentration of drug in the GI fluids and the plasma, called the concentration gradient (amount/volume)

h = Thickness of the membrane (length)

Fick's 1st Law of Diffusion

$$dQ/dt = \frac{DAK_{m/w}(C_{GIT}-C)}{h}$$

dQ/dt = Rate of drug diffusion (amount/time).

D = Diffusion coefficient of the drug through the membrane.

A = Surface area of the absorbing membrane for drug diffusion.

$K_{m/w}$ = Partition coefficient of the drug b/w the lipoidal membrane and aqs GIT.

(C_{GIT}–C) = Difference in concentration of the drug in the GI fluid and the plasma

h = Thickness of the membrane

Based on this equation, certain characteristics of passive diffusion include:

1. **Downhill Transport:** Drugs move down the concentration gradient.
2. **Energy-independent and Nonsaturable:** No energy source is needed.
3. **Proportional Rate:** The rate of drug transfer is directly proportional to the concentration gradient between GI fluids and blood.

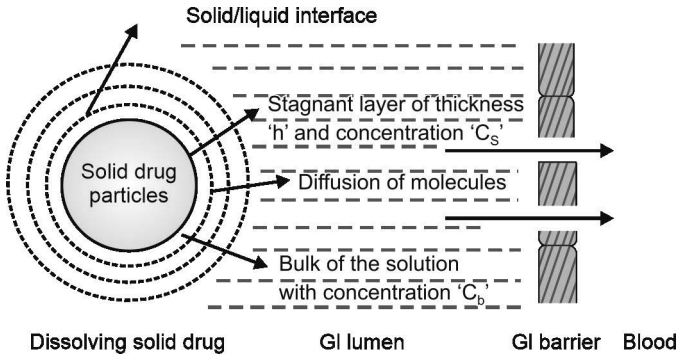


Fig. 1.6: Diffusion layer model for drug dissolution

4. **Surface Area and Thickness:** Greater surface area and thinner membranes enhance diffusion, making drug absorption faster from the intestine than the stomach.
5. **Distance Impact:** The process is rapid over short distances and slower over long distances.
6. Passive diffusion process is energy independent but depends more or less on the square root of the molecular size of the drugs.
7. The mol. wt. of the most drugs lie between 100 to 400 Daltons which can be effectively absorbed passively.

Pore Transport

Also known as convective transport, bulk flow, or filtration, pore transport involves the movement of molecules through protein channels in the cell membrane. Characteristics of pore transport include:

1. **Driving Force:** Hydrostatic pressure or osmotic differences across the membrane drives bulk water flow, along with small solid molecules, through aqueous channels. This water flux is known as solvent drag.
2. **Small Molecule Absorption:** This process is crucial for absorbing low molecular weight (less than 100), small size, and generally water-soluble drugs through narrow, water-filled channels or pores, such as urea, water, and sugars.
3. **Filtration of Larger Molecules:** Chain-like or linear compounds with molecular weights up to 400 Daltons can be absorbed by filtration.

Pore transport is particularly important in renal excretion, drug removal from cerebrospinal fluid, and drug entry into the liver.

Ion-pair Transport

Ion-pair transport explains the absorption of drugs like quaternary ammonium compounds and sulfonic acids, which ionize under all pH conditions. Despite their low oil/water partition coefficient values, these agents penetrate the membrane by forming reversible neutral complexes with endogenous GI ions, like mucin. These neutral complexes possess the necessary lipophilicity and aqueous solubility for passive diffusion. This phenomenon is known as ion-pair transport. Propranolol, a basic drug that forms an ion pair with oleic acid, is absorbed by this mechanism.

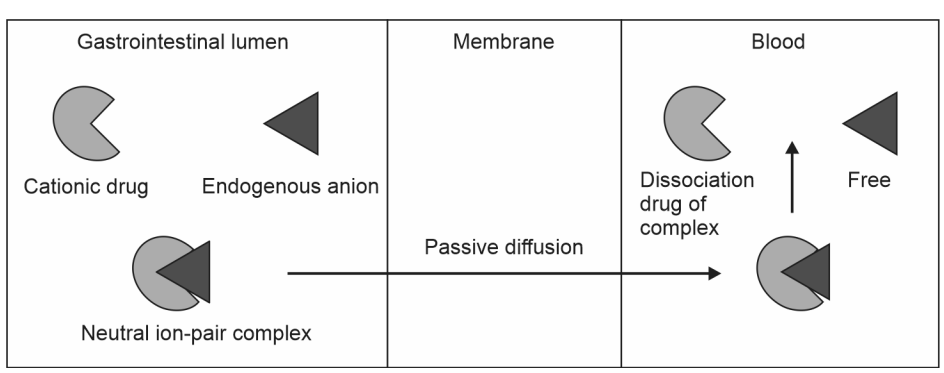


Fig. 1.7: Ion-pair transport of a cationic drug

Carrier-mediated Transport

Certain polar drugs cross cell membranes more efficiently than their concentration gradients and partition coefficients would predict, suggesting the presence of specialized transport mechanisms. These mechanisms are essential for the absorption of many water-soluble nutrients such as monosaccharides, amino acids, and vitamins. Carrier-mediated transport involves membrane components known as carriers that bind reversibly or noncovalently to the solute molecules being transported. The carrier-solute complex traverses the membrane, dissociates on the other side to release the solute, and then the carrier returns to its original position to transport another solute molecule. Carriers are transport proteins, often enzymes, embedded in the lipid bilayer of the membrane.

Key characteristics of carrier-mediated transport include:

1. **Solubility:** Carrier proteins have a nonpolar outer surface, making them soluble within the membrane lipid.
2. **Bidirectional Function:** Carriers operate with equal efficiency in both directions.
3. **Structure-specific:** The process is specific to the chemical structure of the drug, similar to a lock and key mechanism, usually favoring essential nutrients.
4. **False Nutrients:** Drugs with structures similar to essential nutrients can be absorbed by the same carriers, which is crucial for the absorption of certain antineoplastic agents like 5-fluorouracil and 5-bromouracil.
5. **Competition:** Due to the limited number of carriers, there is competition between molecules with similar structures.

There are two types of carrier-mediated transport systems: facilitated diffusion and active transport.

Facilitated Diffusion

Facilitated diffusion is a carrier-mediated process that operates down the concentration gradient (downhill transport) but at a faster rate than simple passive diffusion. The driving force is the concentration gradient, making it a passive process without energy expenditure, hence not inhibited by metabolic poisons. Facilitated diffusion is less significant for drug absorption but notable examples include glucose entry into red blood cells and the intestinal absorption of vitamins B_1 and B_2. A classic example is the GI absorption of vitamin B_{12}, where an intrinsic factor (IF), a glycoprotein produced by gastric parietal cells, forms a complex with vitamin B_{12}, facilitating its transport across the intestinal membrane via a carrier system.

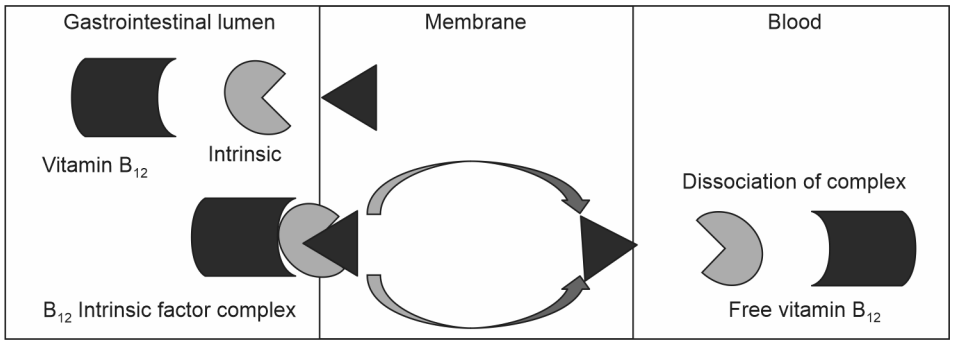


Fig. 1.8: Facilitated diffusion of vitamin B_{12}

Active Transport

Active transport requires energy in the form of ATP and can be divided into two main types:

Primary Active Transport

This process involves the direct use of ATP to transfer ions or molecules in a single direction (uniporter). For example, glucose absorption. Carrier proteins involved in primary active transport are of two types:

1. **Ion Transporters:** These transport ions into or out of cells. A classic example is the proton pump, which acidifies intracellular compartments. Important ion transporters for intestinal drug absorption include:
   - **Organic Anion Transporter:** Assists in the absorption of drugs such as pravastatin and atorvastatin.
   - **Organic Cation Transporter:** Aids in the absorption of drugs such as diphenhydramine.
2. **ABC (ATP-binding cassette) Transporters:** These transport small foreign molecules (like drugs and toxins) out of cells, functioning as efflux pumps. A notable example is P-glycoprotein (P-gp), which pumps hydrophobic drugs, especially anticancer drugs, out of cells. High levels of P-gp in cells lead to resistance to various cancer drugs, known as multi-drug resistance (MDR). ABC transporters in brain capillaries also pump a wide range of drugs out of the brain.

Secondary Active Transport

This process does not directly require ATP. Instead, it utilizes the energy from an existing concentration gradient to transport another ion or molecule. This co-transport can move substances in the same direction (symport) or opposite directions (antiport):

1. **Symport (Co-transport):** Both molecules move in the same direction. For example, the Na^+-glucose symporter uses the potential energy of the Na^+ concentration gradient to move glucose against its gradient. A notable symporter is the H^+-coupled peptide transporter (PEPT1), which is involved in the intestinal absorption of peptide-like drugs such as β-lactam antibiotics.
2. **Antiport** (counter-transport)–involves movement of molecules in the opposite direction, e.g. expulsion of H^+ ions using the Na^+ gradient in the kidneys.

Active transport plays a crucial role in the absorption of nutrients and drugs, differing from facilitated diffusion in several key aspects:

1. **Against the Gradient:** Drugs are transported from a lower to a higher concentration region (against the concentration gradient) or against an electrochemical gradient (uphill transport), without aiming for equilibrium.
2. **Speed:** The process is faster than passive diffusion.
3. **Energy Requirement:** Energy is required for the work done by the carrier, as the process is uphill.
4. **Inhibition by Metabolic Poisons:** Since the process requires energy expenditure, it can be inhibited by metabolic poisons that interfere with energy production, such as fluorides, cyanide, dinitrophenol, and lack of oxygen.

Endogenous substances actively transported include sodium, potassium, calcium, iron, glucose, certain amino acids, and vitamins like niacin, pyridoxine, and ascorbic acid. Drugs structurally similar to these agents are also actively absorbed, particularly those used in cancer chemotherapy. Examples include:

- **Pyrimidine Transport System:** Absorption of 5-fluorouracil and 5-bromouracil.
- **L-amino Acid Transport System:** Absorption of methyldopa and levodopa.
- **Small Peptide Carrier System:** Absorption of ACE inhibitor enalapril.

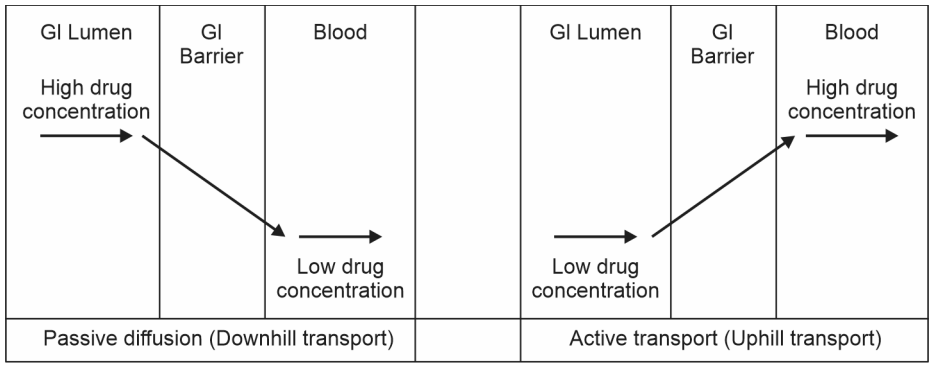


Fig. 1.9: Comparison of active and passive transport

A notable example of competitive inhibition of drug absorption via active transport is the impaired absorption of levodopa when ingested with protein-rich meals. Active transport is also significant in the renal and biliary excretion of many drugs and their metabolites, as well as in the secretion of certain acids out of the CNS.

THEORIES OF DISSOLUTION

1. Diffusion layer model (film theory)
2. Danckwert's model (penetration or surface renewal theory)
3. Interfacial barrier model (double barrier mechanism or limited solvation theory)

Diffusion Layer Model (Film Theory)

It is a simplest model where dissolution of crystal, immersed in liquid takes place without involving reactive or electrical forces.

It consists of two consecutive steps:

- Solution of the solid to form a thin film or layer at the solid/liquid interface called as stagnant film or diffusion layer which is saturated with the drug this step is usually rapid (instantaneous).
- Diffusion of the soluble solute is from the stagnant layer to the bulk of the solution. This step is slower and is therefore the rate determining step in the drug dissolution.

Equation (A) is based on Fick's first law of diffusion and constant surface area

$$\frac{dC}{dt} = k\,(C_s - C_b) \qquad \text{... (A)}$$

where,

$\frac{dC}{dt}$ = Dissolution rate of the drug

k = Dissolution rate constant

C_s = Concentration of drug in stagnant layer (saturation or maximum drug solubility)

C_b = Concentration of drug in bulk of the solution in time t

Brunner incorporated Fick's first law of diffusion and modification of the Noyes–Whitney's equation to

$$\frac{dC}{dt} = \frac{DAK_{W/O}(C_s - C_b)}{Vh} \qquad \text{... (B)}$$

where,

D = Diffusion coefficient of the drug

A = Surface are of dissolving solid

$K_{W/O}$ = Water/Oil partition coefficient of the drug considering the fact that dissolution body fluid is aqueous since the rapidity with which a drug dissolved depends on the $K_{W/O}$, it is also called the intrinsic dissolution rate constant.

V = Volume of dissolution medium

h = Thickness of stagnant layer

$(C_s - C_b)$ = Concentration gradient of diffusion

Sink condition: *In vivo* condition, there is no conc. build up in the bulk of the solution and hence no retarding effect on the dissolution rate of the drug, i.e. $C_s >> C_b$ and sink condition maintain.

- Sink condition can be achieved by:
  - Bathing the dissolving solid in fresh solvent from time to time.
  - Increase the volume of dissolution fluid.
  - Removing the dissolved drug by the organic phase, e.g. hexane or chloroform.
  - Adding a water miscible solvent such as alcohol
  - By adding selected adsorbents to remove the dissolution drug.

Noyes Whitney's equation assumes that surface area should remain constant during the dissolution.

Hixson and Crowell's cubic root low of dissolution for change in surface area on dissolution due to decrease in particle and decrease in surface area.

$$W_0^{1/3} - W^{1/3} = kt$$

where,

W_0 = Original mass of drug

W = Mass of drug remaining to dissolve at time t

K = Dissolution rate constant

Danckwert's Model (Penetration or Surface Renewal Theory)

This model assume that transport of solute away from the solid surface is achieve by means the agitated fluid consisting of macroscopic mass of eddies or packets reach the solid/liquid interface in a random fashion due to eddy currents.

Interfacial Barrier Model (double barrier or limited salvation theory

According to interfacial barrier model, an intermediate conc. C_s can exist at the interface as a result of salvation mechanism and is a function of solubility rather than diffusion. When considering the dissolution, the crystal will have a different interfacial barrier given by following equation,

$$G = K_i (C_s - C_b)$$

where,

G = Dissolution per unit area

K_i = Effective interfacial transport constant

In this theory, the diffusivity D may not be independent of saturation conc. C_s. The interfacial barrier model can be extended to both diffusion layer model and the Danckwert's model.

Types of Models of Mechanism of Drug Release

Types	*Special feature*	*Graph plotted*
Zero-order	Drug release rate is independent of concentration of dissolved substance $Q_t = Q_0 + K_0 t$	Cumulative % of drug release *vs* time (h) Straight line comes
First-order	Drug release rate depends on concentration of dissolved substance $\log Q_t = \log Q_0 + Kt/2.303$	Log cumulative % of drug remaining to be dissolved *vs* time (h) Straight line comes
Higuchi model	Describe drug release by dissolution and with change in surface area and diameter of dissolved particles $Q = k_H t_{½}$	Cumulative % of drug release *vs* square root of time (h) Straight line comes
Hixon-Crowell	It suggests drug release by diffusion mechanism $Q_0^{1/3} - Q_t^{1/3} = K_{HC}^t$	Cube root of initial concentration minus cube root of % remaining *vs* time (h) Straight line comes
Korsmeyer Peppas	Equation – $M_t/M = K_m t^n$(release exponent) value: 1. n = 0.45—Fickian diffusion 2. 0.45 < n < 0.89—anomalous or non-Fickian diffusion means both diffusion and erosion controlled release 3. n = 0.89 or above—Case-II relaxation or Super Case-II transport; drug release is mainly controlled by polymer relaxation, and when n >0.89 it additionally involves polymer chain erosion/disentanglement	Log cumulative % of drug remaining to be dissolved *vs* log time (h) Straight line comes

Factors Affecting Drug Absorption

Pharmaceutical Factors:

1. **Physicochemical Properties of the Drug:**
   - **Drug Solubility and Dissolution Rate:** Essential for drug absorption; poor solubility can limit absorption.
   - **Particle Size and Effective Surface Area:** Smaller particles with a larger surface area can enhance absorption.
   - **Polymorphism and Amorphism:** Different crystal forms can affect solubility and dissolution.
   - **Pseudopolymorphism (Hydrates or Solvates):** Water or solvent molecules within the drug crystal can alter its properties.
   - **Salt Form of the Drug:** Salts can improve solubility and absorption.
   - **Lipophilicity of the Drug:** Lipophilic drugs may cross cell membranes more easily.
   - **Drug Stability:** Stability in the gastrointestinal environment is crucial.
   - **Stereochemical Nature of the Drug:** Different isomers may have different absorption rates.
2. **Formulation Factors:**
   - **Disintegration Time:** Faster disintegration can lead to quicker absorption.
   - **Manufacturing Variables:** Techniques and processes can affect drug release and absorption.
   - **Nature and Type of Dosage Form:** Different forms (tablets, solutions, etc.) affect absorption rates.
   - **Pharmaceutical Ingredients (Excipients):** Can influence drug release and absorption.
   - **Product Age and Storage Conditions:** Stability over time and under various conditions is important.

Patient-related Factors:

1. Age: Can influence metabolic rate and gastrointestinal function.

2. Gastric Emptying Time: Slower emptying can delay drug absorption.
3. Intestinal Transit Time: Affects the duration drugs stay in absorption sites.
4. Gastrointestinal pH: Influences drug solubility and stability.
5. Diseased States: Conditions like gastrointestinal diseases can affect absorption.
6. Blood Flow Through the GIT: Higher blood flow can enhance absorption.
7. Gastrointestinal Contents: Food, fluids, and other contents can interact with the drug.
8. Presystemic Metabolism: Metabolism before the drug reaches systemic circulation can reduce availability.

Pharmaceutical Factors

For optimal drug formulation, pharmacists must consider:

1. **Physicochemical Properties of the Drug**
2. **Type of Formulation** (e.g. solution, suspension, tablet)
3. **Nature of Excipients in the Formulation**

Physicochemical Factors Affecting Drug Absorption

Drug Solubility and Dissolution Rate: For well-formulated dosage forms, disintegration and deaggregation occur quickly. Thus, the two critical, slower, rate-determining steps for orally administered drugs are:

1. **Rate of Dissolution:** Particularly important for hydrophobic, poorly soluble drugs like griseofulvin and spironolactone, where absorption is often limited by the dissolution rate.
2. **Rate of Drug Permeation Through the Biomembrane:** For hydrophilic drugs with high aqueous solubility, such as cromolyn sodium or neomycin, the dissolution rate is rapid. In these cases, the rate-limiting step for absorption is the permeation through the biomembrane, known as permeation rate-limited or transmembrane rate-limited absorption.

Route	*Absorption pattern*	*Special utility*	*Limitations and precaution*
Intravenous	Absorption circumvented potentially immediate effects suitable for large volumes, irritating subtancce, or complex mixtures	▪ Valuable for emergency use Permits titration of dosage ▪ Usually required for high molecular weight drugs (peptides, proteins)	▪ Increased risk of adverse effect ▪ Must inject solutions slowly as a rule ▪ Not suitable for oily solution of poorly soluble substances
Subcutaneous	▪ Prompt from aqueous solution ▪ Slow and sustained from repository preparation	Suitable for some poorly soluble suspensions and slow release implants	▪ Not suitable for large volumes ▪ Possible pain or necrosis from irritants
Intramuscular	▪ Prompt from aqueous solution ▪ Slow and sustained from repository preparation	Suitable for moderate volumes, oily vehicles and some irritants appropriate for self administration	▪ Precluded during anticoagulants therapy ▪ May interfere with interpretation of certain diagnosis tests
Oral ingestion	Variable, depends on many factors	Most convenient and economical; usually more safe	▪ Requires patients compliance ▪ Bioavailability erratic and incomplete

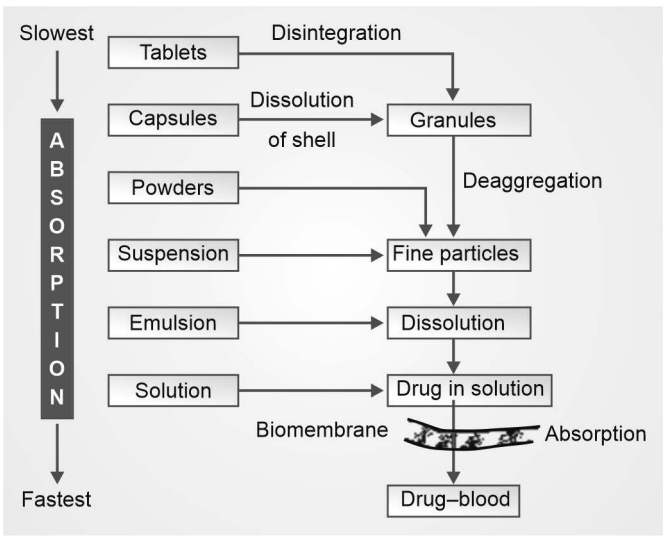
Absorption Pattern of Dosage Form

Dosage form consideration for gastrointestinal absorption

Drug formulations are designed to provide an attractive, stable, and convenient method to use products. Conventional dosage forms may be broadly characterized in order of decreasing dissolution rate as solutions, solid solutions, suspensions, capsules and tablets, coated capsules and tablets, and controlled release formulations.

Capsules and Tablets

- These formulations differ from each other in that material in capsules is less impacted than in compressed tablets. Once a capsule dissolves, the contents generally disperse quickly.
- Although water soluble, can impede drug dissolution by interacting with the drug, but this is uncommon.
- Tablets generally disintegrate in stages, first into granules and then into primary particles. As particle size decreases, dissolution rate increases due to of increased surface area.



- Tablet disintegration was once considered a sufficient criterion to predict *in vivo* absorption.

- As a general rule, the bioavailability of a drug from various dosage forms decreases in the following order: Solutions > emulsions > suspensions > capsules > tablets > coated tablets > enteric-coated tablets > sustained release products.

Solutions

Aqueous solutions, syrups, elixirs, and emulsions do not present a dissolution problem and generally result in fast and often complete absorption as compared to solid dosage forms. Due to their generally good systemic availability, solutions are frequently used as bioavailability standards against which other dosage forms are compared.

Solid solutions

The solid solution is a formulation in which drug is trapped as a solid solution or monomolecular dispersion in a water-soluble matrix. Although the solid solution is an attractive approach to increase drug absorption, only one drug, griseofulvin, is currently marketed in this form.

Suspensions

- A drug in a suspension is in solid form, but is finely divided and has a large surface area. Drug particles can diffuse readily between the stomach and small intestine so that absorption is relatively insensitive to stomach emptying rate.
- Adjusting the dose to a patient's needs is easier with solutions and suspensions than with solid dosage forms. Liquid dosage forms, therefore, have several practical advantages besides simple dissolution rate.
- However, they also have some disadvantages, including greater bulk, difficulty in handling, and perhaps reduced stability.

Factors Influencing Drug Dissolution and Dissolution Rate

Factors that influence drug dissolution and absorption can be divided into two main categories:

1. Physicochemical properties of the drug
2. Dosage form factors

Physicochemical Properties of the Drug

Key physicochemical properties affecting drug dissolution and its rate include solubility, particle size, polymorphism, salt form, pseudopolymorphism, complexation, wettability, among others.

Particle Size and Effective Surface Area

- Particle size and surface area are inversely proportional: Smaller particles have a larger surface area.
- Absolute surface area is the total area of a particle's solid surface.
- Effective surface area is the area of the solid surface exposed to the dissolution medium.

Polymorphism and Amorphism

- Solids can exist in crystalline or amorphous forms.
- A substance that exists in more than one crystalline form has polymorphs, a phenomenon known as polymorphism.
  - Enantiotropic polymorphs can reversibly change form with temperature or pressure changes (e.g. sulfur).
  - Monotropic polymorphs are unstable at all temperatures and pressures (e.g. glyceryl stearates).
- Polymorphs have different physical properties like solubility, melting point, density, hardness, and compression characteristics.
- Polymorphs are prepared by crystallizing the drug from various solvents under different conditions and identified using techniques like optical crystallography, X-ray diffraction, and differential scanning calorimetry.
- The most stable polymorph has the highest melting point and the lowest aqueous solubility, while metastable forms have higher solubility and lower melting points. Metastable forms tend to convert to the stable form over time.
- Drugs in amorphous form have no internal crystal structure, representing the highest energy state and greater aqueous solubility compared to crystalline forms. For example, amorphous novobiocin is ten times more soluble than its crystalline counterpart.

Hydrates/Solvates (Pseudopolymorphism)

- Drugs can form crystalline adducts with solvent molecules, known as solvates, which are a type of pseudopolymorph.
- Hydrates are solvates where the solvent is water.

Salt Form of the Drug

- Converting weak acids or bases into their salt forms can enhance solubility and dissolution rates.

Drug pKa, Lipophilicity, and GI pH—pH Partition Hypothesis

- The pH partition theory explains drug absorption from the GIT and distribution across biological membranes for drugs with molecular weights above 100 that passively diffuse across membranes.
- Absorption is influenced by:
  1. The drug's dissociation constant (pKa).
  2. The lipid solubility of the unionized drug (determined by its partition coefficient, $K_{O/W}$).
  3. The pH at the absorption site.
- For acidic drugs, lower pKa means stronger acid and a higher proportion of ionized form at a given pH. For basic drugs, higher pKa indicates a stronger base.

The ratio of unionized to ionized drug forms, determined by the drug's pKa and the absorption site's pH, can be calculated using the Henderson-Hasselbalch equation.

For acidic drug

$$pH = pKa + \log [\text{ionized form}]/[\text{Unionized form}]$$

For basic drug

$$pH = pKa + \log [\text{unionized form}]/[\text{Ionized form}]$$

Lipophilicity and Drug Absorption

The pKa of a drug determines its degree of ionization at a given pH, and only the unionized form of the drug, if it is sufficiently lipid-soluble, is absorbed into the systemic circulation. Therefore, even if the drug is in its unionized form, it will have poor absorption if it lacks lipid solubility (or has a low partition coefficient, $K_{O/W}$). In other words, the drug must have a perfect hydrophilic-lipophilic balance (HLB) for optimal bioavailability.

DOSAGE FORM (PHARMACO-TECHNICAL) FACTORS

Disintegration time (DT) is crucial for solid dosage forms like tablets and capsules. An *in vitro* disintegration test does not guarantee a drug's bioavailability because, if the disintegrated particles do not dissolve, absorption cannot occur. However, if a solid dosage form fails to meet the DT standard, it indicates potential bioavailability issues because dissolution will be slower, leading to insufficient absorption. Coated tablets, particularly sugar-coated ones, have long DTs. Rapid disintegration is vital for the therapeutic success of solid dosage forms. The DT of a tablet is directly related to the amount of binder used and the compression force applied (tablet hardness). A harder tablet with a large amount of binder has a longer DT. Disintegration can be improved by incorporating suitable amounts of disintegrants during formulation. After a solid dosage form disintegrates into granules, these granules must deaggregate into fine particles, as dissolution from tiny particles is faster than from granules.

Manufacturing/Processing variables drug dissolution is the most crucial factor in drug absorption, especially from conventional solid dosage forms like tablets and capsules. Factors related to dosage form that influence dissolution and absorption include:

- Excipients (formulation ingredients apart from the active principles)
- Manufacturing processes

Pharmaceutical ingredients/excipients (formulation factors): A drug is rarely administered in its original form. Typically, it is formulated into a convenient dosage form for a suitable route of administration, containing various excipients (nondrug components). Excipients are added to ensure acceptability, physicochemical stability during shelf life, uniformity of composition and dosage, and optimal bioavailability and functionality of the drug product. Despite their inertness and utility, excipients can affect drug absorption. The more excipients in a dosage form, the more complex it is, increasing the potential for absorption and bioavailability issues. Generally, the bioavailability of a drug from different dosage forms decreases in the following order: Solutions > Emulsions > Suspensions > Capsules > Tablets > Coated Tablets > Enteric Coated Tablets > Sustained Release Products.

PATIENT-RELATED FACTORS AFFECTING DRUG ABSORPTION

Age

- **Infants:** Higher gastric pH, reduced intestinal surface area, and lower blood flow to the gastrointestinal tract (GIT) result in different absorption patterns compared to adults.
- **Elderly:** Impaired drug absorption due to altered gastric emptying, decreased intestinal surface area and GI blood flow, increased incidence of achlorhydria, and bacterial overgrowth in the small intestine.

Gastric Emptying: The process of moving contents from the stomach to the small intestine, known as gastric emptying, can be a rate-limiting step in drug absorption since the small intestine is the primary site of drug absorption. Generally, rapid gastric emptying enhances a drug's bioavailability. Rapid gastric emptying is preferred when:

1. A rapid onset of action is needed, such as with sedatives.
2. The drug dissolves in the intestine, such as enteric-coated formulations.
3. The drug is unstable in gastric fluids, such as penicillin G and erythromycin.
4. The drug is best absorbed from the distal small intestine, such as vitamin B_{12}.

Intestinal Transit: Since the small intestine is the main site for the absorption of most drugs, a longer intestinal transit time is desirable for complete drug absorption.

Gastrointestinal pH: There is a significant variation (10^7-fold difference) in hydrogen ion concentration from the stomach to the colon. GI pH generally increases from the stomach to the colon and rectum. GI pH affects drug absorption in several ways:

1. **Disintegration:** Some dosage forms are pH-sensitive, like enteric-coated formulations that only dissolve in the intestine.
2. **Dissolution:** The solubility of many drugs, which are often weak acids or bases, is significantly affected by pH. A pH that promotes the formation of the drug's salt enhances its dissolution, which is a critical step in drug absorption. Weakly acidic drugs dissolve quickly in the alkaline pH of the intestine, while basic drugs dissolve in the acidic pH of the stomach. Since most drugs are primarily absorbed in the small intestine, poorly water-soluble basic drugs must first dissolve in the acidic stomach before reaching the intestine.

Absorption of Drugs from Nonoral Extravascular Routes: Nonoral routes bypass the GIT and reach systemic circulation directly. Noninvasive transmucosal and transdermal routes, such as nasal, buccal, and rectal, offer greater systemic availability and are effective for delivering peptide and protein drugs.

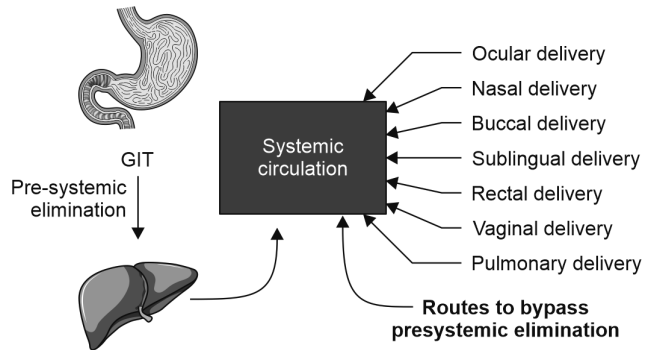


Fig. 1.10: Various transmucosal noninvasive routes of drug administration to bypass presystemic elimination in GIT/liver

Buccal/Sublingual Administration

Sublingual Route: The drug is placed under the tongue to dissolve.

Buccal Route: The drug is placed between the cheek and gum.

The epithelium of the oral mucosa acts as the barrier to drug absorption in these routes. Most drugs are absorbed

through passive diffusion, though nutrients may utilize carrier-mediated processes.

Rectal Administration

While less popular, the rectal route remains important for children and elderly patients. Drugs can be administered as solutions (microenemas) or suppositories. Absorption from solutions is faster than from suppositories but is more variable compared to the oral route. Irritating suppository bases, like PEG, can promote defecation and drug loss, and the presence of fecal matter can slow drug absorption. Despite being highly vascularized, absorption is slower due to limited surface area.

Topical Administration

Apart from the respiratory tract's interaction with inhaled air, the skin is the main surface interfacing the body with the external environment. It is the largest organ, weighing about 2 kg and covering 2 m^2, receiving about one-third of the body's blood flow. Topically applied drugs usually have local effects. When systemic effects are intended, the administration is termed percutaneous or transdermal. Percutaneous absorption occurs when the drug permeates dermal capillaries and enters the bloodstream.

Intramuscular Administration

Drug absorption from intramuscular (IM) sites is relatively rapid but slower than intravenous (IV) injections. Factors influencing absorption from IM sites include:

1. **Vascularity of the Injection Site:** Blood flow rate decreases in the order: Arm (deltoid) > Thigh (vastus lateralis) > Buttocks (gluteus maximus).
2. **Blood Flow Rate:** Often the rate-limiting step; most rapid absorption is from the deltoid muscles, slowest from the gluteal region, and decreases in circulatory disorders like hypotension.
3. **Lipid Solubility and Ionization:** Highly lipophilic drugs are absorbed rapidly by passive diffusion, whereas hydrophilic and ionized drugs are absorbed slowly through capillary pores.
4. **Molecular Size:** Small molecules and ions enter capillaries directly through pores, while macromolecules are absorbed by the lymphatic system. Small peptides and fluids can cross endothelial tissues via vesicular transport, a process known as cytopemphis.

Subcutaneous Administration

Factors influencing intramuscular drug absorption also apply to subcutaneous (SC) sites. Absorption from SC sites is slower due to poor perfusion, which is useful for drugs requiring a slower response or that degrade orally, such as insulin and sodium heparin. Absorption rate from SC sites can be increased by:

1. Enhancing Blood Flow: Massage, heat application, local vasodilators, or exercise.
2. Increasing Drug–Tissue Contact Area: Co-administering hyaluronidase, which breaks down connective tissue, spreading the drug solution over a wider area.

Pulmonary Administration

Inhalation can be used for systemic effects due to the large alveolar surface area, high permeability of the alveolar epithelium, and rich perfusion, allowing rapid absorption similar to gas exchange. However, it is mainly used for pulmonary drugs like bronchodilators (salbutamol), anti-inflammatory steroids (beclomethasone), and antiallergics (cromolyn).

Intranasal Administration

The nasal route is increasingly popular for systemic delivery of some peptide and protein drugs. Absorption from the nasal mucosa is rapid due to its rich vasculature and high permeability, comparable to parenteral administration. It is also used for treating local symptoms like nasal congestion and rhinitis. Drug transport across the nasal mucosa involves:

- **Rapid Rate:** Dependent on drug lipophilicity.
- **Slower Rate:** Dependent on drug molecular weight. Lipophilic drugs show rapid absorption by diffusion up to 400 Daltons, with satisfactory absorption up to 1000 Daltons.

Intraocular Administration

Topical drug application to the eyes is primarily for local effects such as mydriatics, mitosis, anaesthesia, or treatment of infections and glaucoma. Sterile aqueous solutions are commonly used and administered in the conjunctival sac. The cornea, with both hydrophilic and lipophilic properties, acts as the barrier to intraocular drug penetration. For optimal permeation, drugs should have biphasic solubility. The pH of lachrymal fluid influences the absorption of weak electrolytes like pilocarpine. Formulation pH affects lachrymal output—higher pH decreases tear flow and enhances drug absorption, whereas lower pH increases lachrymation and subsequent drug loss. Blinking rate also affects drainage loss.

DISTRIBUTION

Introduction

Once a drug enters the systemic circulation, either via intravascular injection or absorption from extravascular sites, it undergoes various disposition processes. Disposition refers to the processes that reduce the drug's plasma concentration. The two primary disposition processes are:

1. Distribution: The reversible transfer of a drug between compartments.
2. Elimination: The irreversible removal of the drug from the body, which is further divided into:
   - Biotransformation (metabolism)
   - Excretion

Distribution involves the reversible transfer of a drug between compartments, primarily between the blood (or plasma) and extravascular fluids and tissues. This process is driven by the concentration gradient between the blood and extravascular tissues and occurs through the diffusion

of free drug until equilibrium is reached. Since a drug's pharmacological effect depends on its concentration at the action site, distribution significantly influences the onset, intensity, and sometimes duration of drug action.

Steps in Drug Distribution

The distribution of a drug from the systemic circulation to extravascular tissues involves the following steps:

1. **Permeation of Free or Unbound Drug:** The drug in the blood permeates through the capillary wall into the interstitial/extracellular fluid (ECF), a process that occurs rapidly.
2. **Permeation into Tissue Cells:** The drug in the ECF permeates through the tissue cell membrane into the intracellular fluid. This rate-limiting step depends on:
   - The rate of perfusion to the extracellular tissue.
   - The membrane permeability of the drug.

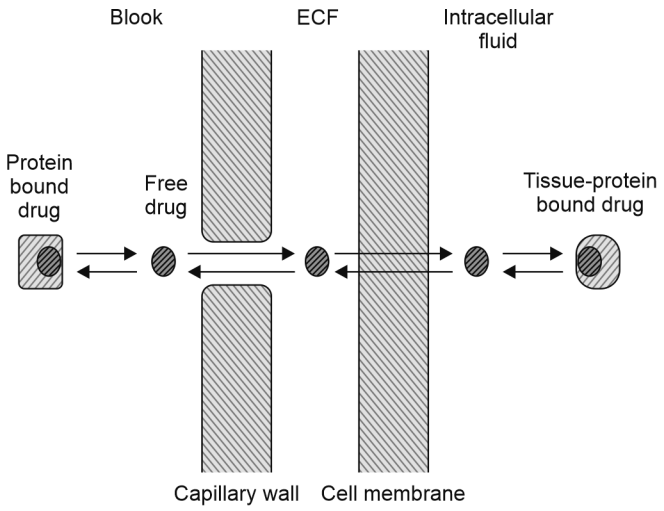


Fig. 1.11: Schematic of the steps involved in drug distribution

Tissue Permeability of Drugs

Two key factors determine the rate of drug distribution:

1. **Rate of tissue permeation:** How quickly a drug can pass through tissue membranes.
2. **Rate of blood perfusion:** How efficiently blood circulates through tissues.

If blood flow to all tissues were uniformly rapid, differences in drug distribution among tissues would primarily reflect variations in tissue permeability, making tissue permeation rate-limited. This permeability depends on the drug's physicochemical properties and the physiological barriers it encounters.

Physicochemical Properties of the Drug: Key physicochemical properties influencing drug distribution include molecular size, degree of ionization, partition coefficient, and stereochemical nature.

- **Molecular Size:** Drugs with molecular weights below 500 to 600 Daltons can easily cross capillary membranes into extracellular interstitial fluids. However, their penetration into cells depends on their size, ionization constant, and lipophilicity. Only small, water-soluble molecules and ions under 50 Daltons can enter cells via aqueous channels; larger molecules require specialized transport systems.
- **Degree of Ionization:** The ionization of a drug significantly affects its ability to penetrate tissues. The pH of blood and extravascular fluid influences drug ionization and diffusion into cells. Drugs that remain unionized at physiological pH (7.4) can permeate cells more easily. Although this pH generally remains stable, conditions like systemic acidosis or alkalosis can alter drug diffusion.
- **pKa and Ionization at Plasma pH:** Most drugs are weak acids or bases, and their ionization at plasma or ECF pH depends on their pKa. Drugs that ionize at plasma pH (polar, hydrophilic drugs) cannot penetrate the lipid cell membrane easily, making tissue permeability the rate-limiting step in their distribution. Conversely, unionized, lipophilic drugs can rapidly cross cell membranes.

Physiological Barriers to Drug Distribution: Certain membranes have structural features that restrict drug permeability. Important physiological barriers include:

1. Simple capillary endothelial barrier
2. Simple cell membrane barrier
3. Blood–brain barrier
4. Blood–CSF barrier
5. Blood–placental barrier
6. Blood–testis barrier

Volume of Distribution

The volume of distribution (V_d) is the theoretical volume in which the total drug amount would need to be uniformly distributed to achieve the same concentration as in plasma. It is termed "apparent" because drug concentrations vary across different body compartments.

Apparent volume of distribution = Amount of drug in body/Plasma drug concentration drug

Protein Binding of Drugs

Drugs in the body interact with various tissue components, primarily:

1. **Blood components**
2. **Extravascular tissues**

These interactions typically involve macromolecules like proteins, DNA, or adipose tissue, with proteins being the main binding partners. Drug–protein interactions, known as protein binding, can be:

1. **Intracellular binding:** The drug binds to a cellular protein, often a receptor, eliciting a pharmacological response. These are primary receptors.
2. **Extracellular binding:** The drug binds to an extracellular protein without triggering a pharmacological response. These are secondary or silent receptors.

Mechanisms of Protein–Drug Binding: Drug–protein binding is usually reversible, involving weak chemical bonds such as:

1. Hydrogen bonds
2. Hydrophobic interactions
3. Ionic bonds
4. van der Waals forces

Irreversible binding, though rare, occurs via covalent bonds and can lead to drug toxicity or carcinogenicity.

For instance, the covalent binding of chloroform and paracetamol metabolites to liver proteins causes hepatotoxicity.

Classes of Drug Binding:

1. **Binding to blood components:**
   - Plasma proteins
   - Blood cells
2. **Binding to extravascular tissue:**
   - Proteins, fats, bones, etc.

Binding of Drugs to Blood Components

Plasma Protein–Drug Binding

Once a drug enters the systemic circulation, it can interact with various blood components such as plasma proteins, blood cells, and hemoglobin. The primary interaction occurs with plasma proteins, which are abundant and diverse in the bloodstream. This binding is reversible, and the hierarchy of drug binding to different plasma proteins is:

Albumin > α1-Acid Glycoprotein > Lipoproteins > Globulins

Tissue Binding of Drugs (Tissue Localization of Drugs)

Body tissues, excluding human serum albumin (HSA), make up about 40% of body weight, which is significantly more than HSA alone. Thus, tissue-drug binding plays a crucial role in drug distribution. A drug can bind to multiple tissue components, and these binding impacts distribution in two main ways:

1. **Increases Apparent Volume of Distribution:** Tissue binding increases the apparent volume of distribution of drugs, unlike plasma protein binding which decreases it. This is because the apparent volume of distribution depends on the ratio of the amount of drug in the body to the concentration of free drug in the plasma, which is lowered by extensive tissue binding.
2. **Drug Localization and Prolonged Biological Half-life:** Tissue binding leads to drug localization at specific body sites, increasing the drug's biological half-life. This is particularly relevant for drugs that bind irreversibly to tissues, such as the oxidation products of paracetamol, phenacetin, chloroform, carbon tetrachloride, and bromobenzene, which bind covalently to hepatic tissues.

Factors influencing drug localization in tissues include the drug's lipophilicity, structural features, perfusion rate, and pH differences. Extensive tissue binding suggests that tissues can serve as drug storage sites, leading to competition between tissue and plasma binding sites.

For most drugs that bind to extravascular tissues, the binding order is:

Liver > Kidney > Lung > Muscles

Examples of Extravascular Tissue-Drug Binding

1. **Liver:** Epoxides of several halogenated hydrocarbons and paracetamol bind irreversibly to liver tissues, causing hepatotoxicity.
2. **Lungs:** Basic drugs like imipramine, chlorpromazine, and antihistamines accumulate in the lungs.
3. **Kidneys:** Metallothionein, a kidney protein, binds to heavy metals like lead, mercury, and cadmium, leading to renal accumulation and toxicity.
4. **Skin:** Drugs such as chloroquine and phenothiazines accumulate in the skin by interacting with melanin.
5. **Eyes:** Retinal pigments in the eye contain melanin, which binds to chloroquine and phenothiazines, causing retinopathy.
6. **Hair:** Arsenicals, chloroquine, and phenothiazines are known to deposit in hair shafts.
7. **Bones:** Tetracycline binds to bones and teeth, causing permanent brown-yellow discolouration of teeth when administered during odontogenesis. Lead can replace calcium in bones, making them brittle.

Factors Affecting Protein–Drug Binding

Factors influencing protein–drug binding can be broadly categorized into:

1. Drug-related factors
2. Protein/Tissue-related factors
3. Drug interactions
4. Patient-related factors

Drug-related Factors

Physicochemical Characteristics of the Drug

- Protein binding is directly related to a drug's lipophilicity. Higher lipophilicity increases binding extent. For instance, cloxacillin is more lipophilic and binds more extensively (95%) to proteins compared to ampicillin, which is less lipophilic and only 20% bound.
- Lipophilic drugs like thiopental tend to localize in adipose tissues. Anionic (acidic) drugs such as penicillins and sulfonamides bind more to HSA, while cationic (basic) drugs like imipramine and alprenolol bind more to AAG. Neutral drugs often bind more to lipoproteins.

Concentration of Drug in the Body

- Protein–drug binding extent can vary with changes in drug and protein concentrations. Drugs binding to HSA are usually not saturated at therapeutic levels, but drugs like lidocaine can saturate AAG due to its lower concentration compared to HSA.

Drug–Protein/Tissue Affinity

- Different drugs have varying affinities for binding components. For example, lidocaine has a higher affinity for AAG than HSA. Digoxin has a higher affinity for cardiac muscle proteins than skeletal muscle or plasma proteins. Iophenoxic acid has such a high affinity for plasma proteins that its half-life is 2½ years.

Protein/Tissue-related Factors

Physicochemical Properties of the Protein-binding Component

- Lipophilic drugs are often bound by lipoproteins and adipose tissues through dissolution in their lipid cores. The physiological pH determines the presence of active anionic and cationic groups on albumin, facilitating drug binding.

Concentration of Protein-binding Component

- Albumin is the predominant plasma protein for binding due to its high concentration. The levels of binding proteins and tissue components can change during disease states, affecting drug binding.

Number of Binding Sites on the Protein

- Albumin has numerous binding sites compared to other proteins, making it a high-capacity binding component. Some drugs can bind at multiple sites on albumin. For instance, flucloxacillin, flurbiprofen, ketoprofen, tamoxifen, and dicoumarol bind to both primary and secondary sites. Indomethacin binds to three different sites. AAG, having a lower concentration and molecular size, has limited binding capacity. Though it has only one binding site for lidocaine, the presence of HSA can create two binding sites due to interactions between HSA and AAG.

Drug Interactions

Competition between Drugs for Binding Sites (Displacement Interactions)

- When multiple drugs bind to the same site, they compete, leading to displacement interactions. For instance, if drug A is bound to a site and drug B, which has affinity for the same site, is administered, drug B will displace drug A. This displacement interaction can lead to increased levels of free drug A, potentially causing adverse effects. For example, phenylbutazone displaces warfarin from its binding site on HSA, increasing free warfarin levels and risk of haemorrhagic reactions. Phenylbutazone can also displace sulphonamides from HSA.

Patient-related Factors

Age

- **Neonates:** Lower albumin content results in higher unbound drug concentrations (e.g. phenytoin, diazepam).
- **Young Infants:** Infants with congestive cardiac failure require higher digoxin doses due to greater drug binding and increased renal clearance.
- **Elderly:** Reduced albumin levels increase free drug concentrations that bind to albumin. Elevated AAG levels decrease free concentrations of drugs binding to AAG. Drugs binding to both HSA and AAG, like lidocaine and propranolol, show complex binding patterns.

Intersubject Variations

- Variability in drug binding between individuals is generally small (no more than two-fold) and is attributed to genetic and environmental factors.

Elimination

Drug Elimination and Metabolism

The decline in peak plasma concentrations of a drug after administration results from the body's elimination processes, which involve both metabolism (biotransformation) and renal excretion. While the liver is the primary site for drug metabolism, other tissues or organs—particularly those at entry points into the body—also contribute. These include the lungs, skin, gastrointestinal mucosal cells, microbial flora in the distal ileum, large intestine, and sometimes the kidneys.

Changes in drug elimination due to renal disease, hepatic disease, or drug interactions can be predicted by assessing the fraction of the drug eliminated through metabolism or excretion. Drugs that are highly metabolized (e.g. phenytoin, theophylline, and lidocaine) show significant variability in elimination half-lives due to differences in enzyme activity, influenced by genetic and environmental factors. In contrast, drugs primarily excreted by the kidneys show less variability, as renal drug excretion relies on the glomerular filtration rate (GFR) and kidney blood flow, which are relatively constant among individuals with normal renal function.

Biotransformation of Drugs

Biotransformation, synonymous with metabolism, refers to the chemical conversion of a drug into another form, typically facilitated by enzymes in the body. This process excludes chemical instability, such as the degradation of penicillin by stomach acid, which is not considered metabolism.

Outcomes of Biotransformation

1. **Pharmacological Inactivation:** Most commonly, biotransformation inactivates drugs, producing metabolites with little or no pharmacological activity (e.g. conversion of phenytoin to p-hydroxy phenytoin).
2. **Active Metabolites:** Occasionally, biotransformation produces metabolites with similar activity to the parent drug (e.g. conversion of phenylbutazone to oxyphenbutazone).
3. **Toxicological Activation:** Rarely, it leads to the formation of toxic metabolites with high tissue reactivity (e.g. conversion of paracetamol to reactive metabolites causing hepatic necrosis).
4. **Prodrug Activation:** Inactive drugs (prodrugs) rely on biotransformation for activation, termed pharmacological activation (e.g. conversion of enalapril to enalaprilat).

Drug-metabolizing Organs

The liver is the main site for the metabolism of most drugs and other xenobiotics due to its abundance of various enzymes. Extrahepatic metabolism (metabolism by organs other than the liver) is less significant because these tissues have lower levels of drug-metabolizing enzymes. The ability of various organs to metabolize drugs decreases in the following order: Liver > Lungs > Kidneys > Intestine > Placenta > Adrenals > Skin.

Other organs, such as the brain, testes, muscles, and spleen, also metabolize drugs but to a much lesser extent.

Chemical Pathways of Drug Biotransformation

RT Williams, a pioneer in drug biotransformation research, categorized drug metabolism reactions into two main types:

Phase I Reactions

Phase I reactions typically precede phase II reactions and encompass oxidative, reductive, and hydrolytic processes. These reactions introduce or unmask polar functional groups (–OH, –COOH, $–NH_2$, –SH) on lipid-soluble substrates. They are also known as functionalization

reactions or nonsynthetic reactions. The resulting products from phase I reactions are primed for phase II reactions.

Phase II Reactions

Phase II reactions involve the covalent attachment of small polar endogenous molecules such as glucuronic acid, sulfate, glycine, etc., to unchanged drugs or phase I metabolites containing suitable functional groups (–OH, –COOH, $–NH_2$, –SH). This forms highly water-soluble conjugates that are easily excreted by the kidneys or bile. These reactions are termed conjugation reactions or synthetic reactions because they increase molecular size and alter physicochemical properties of the compounds. Phase II reactions are commonly referred to as true detoxification reactions because they typically result in metabolites that are pharmacologically inert and highly polar. Enzymes responsible for these reactions are called transferases due to their role in transferring moieties to the substrate for conjugation.

Renal Excretion of Drugs

Excretion refers to the process where drugs and their metabolites are irreversibly transferred from the internal environment to the external environment. This process is crucial for terminating the pharmacological action of a drug. The kidneys are the primary organs responsible for drug excretion, known as renal excretion.

Most drugs and their metabolites are partially excreted by the kidneys. Some drugs, like gentamicin, are exclusively eliminated through the renal route. Drugs excreted in urine generally share the following characteristics:

1. Water-soluble
2. Nonvolatile
3. Small molecular size (less than 500 Daltons)
4. Slowly metabolized.

The nephron, the kidney's basic functional unit, is involved in drug excretion. Each kidney contains about one million nephrons, which consist of the glomerulus, proximal tubule, loop of Henle, distal tubule, and collecting tubule.

The primary processes influencing urinary excretion of a drug include:

1. Glomerular filtration.
2. Active tubular secretion.
3. Active or passive tubular reabsorption.

Factors Affecting Renal Excretion of Drugs

Glomerular Filtration: Glomerular filtration is a nonselective, unidirectional process where most compounds, whether ionized or unionized, are filtered. However, compounds bound to plasma proteins or blood cells, behaving as macromolecules, are not filtered. The glomerulus acts as a negatively charged selective barrier that promotes the retention of anionic compounds. The driving force for filtration is the hydrostatic pressure of blood in the capillaries. Out of the 25% of cardiac output (1.2 liters per minute) that goes to the kidneys, only 10% (120–130 ml/min) is filtered through the glomeruli, known as the glomerular filtration rate (GFR). Although approximately 180 liters of protein and cell-free ultrafiltrate pass through the glomeruli daily, only about 1.5 liters is excreted as urine, with the rest reabsorbed from the tubules.

The GFR can be measured using agents that are exclusively excreted by filtration and are neither secreted nor reabsorbed in the tubules, with an excretion rate value of 120–130 ml/min. Creatinine and inulin are commonly used to estimate GFR, and hence renal function.

Active Tubular Secretion: This process is carrier-mediated and requires energy to transport compounds against the concentration gradient. It is capacity-limited and saturable. Two primary mechanisms to active tubular secretion are identified:

1. Secretion of organic acids/anions (e.g. penicillins, salicylates, glucuronides, sulfates), sharing the system with endogenous acids like uric acid.
2. Secretion of organic bases/cations (e.g. morphine, mecamylamine, hexamethonium) along with endogenous amines such as catecholamines, choline, and histamine.

These systems are relatively nonselective and operate independently, but both can be bidirectional, meaning agents can be secreted and reabsorbed actively (e.g. uric acid).

Tubular Reabsorption: Following glomerular filtration, tubular reabsorption occurs along the renal tubule. Reabsorption is indicated when excretion rate values are less than the GFR of 130 ml/min. Agents like glucose, which are completely reabsorbed, have a clearance value of zero. Reabsorption increases a drug's half-life and can occur actively or passively.

Active reabsorption is common for high-threshold substances the body needs to conserve, such as electrolytes, glucose, vitamins, and amino acids. Uric acid is also actively reabsorbed, a process inhibited by uricosuric agents. Very few drugs undergo active reabsorption (e.g. oxopurinol).

Passive reabsorption is common for many drugs and depends on the concentration gradient established by the reabsorption of water and sodium. If a drug is neither secreted nor reabsorbed, its urine concentration will be about 100 times that of the free drug in plasma due to water reabsorption.

The primary factor in passive reabsorption is a drug's lipophilicity. Lipophilic substances are extensively reabsorbed, whereas polar molecules are not. The degree of ionization, influenced by urine pH, drug pKa, and urine flow rate, affects the diffusion of weak electrolytes through the tubular membrane.

Urine pH: Urine pH, which varies from 4.5 to 7.5, depends on diet, drug intake, and patient pathophysiology. Carbohydrate-rich foods increase urinary pH, while proteins lower it. Drugs like acetazolamide and antacids (e.g. sodium bicarbonate) alkalize urine, whereas ascorbic acid acidifies it. Significant urine pH changes can result from intravenous infusions of sodium bicarbonate or ammonium chloride, used in acid–base imbalance treatments. Conditions like respiratory and metabolic acidosis and alkalosis also alter urine pH.

Renal Clearance: Renal clearance refers to the volume of blood or plasma

$$Cl_R = \frac{\text{Rate of urinary excretion}}{\text{Plasma drug concentration}}$$

completely cleared of unchanged drug by the kidneys per unit time, mathematically expressed as:

$$Cl_R = \frac{\text{Rate of filtration} + \text{Rate of secretion} - \text{Rate of reabsorption}}{C}$$

Nonrenal Routes of Drug Excretion

Drugs and their metabolites can be excreted through routes other than the kidneys, known as extrarenal or nonrenal routes of drug excretion. These routes include:

1. Biliary excretion
2. Pulmonary excretion
3. Salivary excretion
4. Mammary excretion
5. Skin/dermal excretion
6. Gastrointestinal excretion
7. Genital excretion

Biliary Excretion of Drugs: Enterohepatic Cycling

The hepatic cells lining the bile canaliculi produce bile through active processes. After production and storage in the gall bladder, bile is secreted into the duodenum. The bile flow rate in humans is about 0.5 to 1 ml/min. Bile aids in the digestion and absorption of fats, with about 90% of secreted bile acids reabsorbed from the intestine and transported back to the liver for resecretion; the remainder is excreted in feces.

Bile secretion, being an active process, is capacity-limited and subject to saturation, similar to active renal secretion. Different transport mechanisms are involved in the secretion of organic anions, cations, and neutral polar compounds. A drug with a lower biliary concentration compared to plasma has a small biliary clearance, and vice versa. In some cases, the bile-to-plasma concentration ratio of a drug can be as high as 1000, resulting in biliary clearance rates of 500 ml/min or more.

Compounds excreted in bile are categorized based on their bile/plasma concentration ratios:

- **Group A:** Ratio is approximately 1 (e.g. sodium, potassium, chloride ions, glucose).
- **Group B:** Ratio is >1, usually from 10 to 1000 (e.g. bile salts, bilirubin glucuronide, creatinine, sulphobromophthalein conjugates).
- **Group C:** Ratio is <1 (e.g. sucrose, inulin, phosphates, phospholipids, mucoproteins).

Drugs can fall into any of these categories. Several factors influence the secretion of drugs in bile:

Physicochemical Properties of the Drug: The primary factor influencing biliary excretion is molecular weight. Polarity also plays a significant role; higher polarity enhances biliary excretion. Thus, metabolites, being more polar than parent drugs, are more likely to be excreted in bile. The molecular weight threshold for biliary excretion varies with polarity: A threshold of 300 Daltons is necessary for organic cations, while for organic anions, it is greater than 300 Daltons. Nonionic compounds need to be highly polar to be excreted in bile, such as cardiac glycosides.

Pulmonary Excretion

Gaseous and volatile substances, such as general anaesthetics (e.g. halothane), are absorbed through the lungs by simple diffusion. Similarly, they are excreted by diffusion into expired air. Factors influencing the pulmonary excretion of a drug include pulmonary blood flow, respiration rate, and the solubility of the volatile substance. Gaseous anaesthetics like nitrous oxide, which are not very soluble in blood, are excreted rapidly. Typically, intact gaseous drugs are excreted, but not their metabolites. Substances like alcohol, with high solubility in blood and tissues, are excreted slowly by the lungs. The principle of pulmonary excretion for compounds like benzene and halobenzenes is similar to steam distillation.

Salivary Excretion

The excretion of drugs in saliva occurs through passive diffusion and can be predicted based on the pH-partition hypothesis. Saliva pH ranges from 5.8 to 8.4, with a mean pH of 6.4. At this pH, unionized, lipid-soluble drugs are passively excreted into the saliva.

Mammary Excretion

The excretion of drugs in milk is significant as it can transfer drugs to a breast-feeding infant. Milk, derived from extracellular fluid, is rich in fats and proteins, with lactating mothers secreting about 0.5 to 1 litre per day. Drug excretion in milk is a passive process dependent on pH-partition behaviour, molecular weight, lipid solubility, and the degree of ionization. Milk pH varies from 6.4 to 7.6, with a mean of 7.0. Free, unionized, lipid-soluble drugs diffuse passively into mammary alveolar cells. The extent of drug excretion in milk can be measured by the milk/plasma drug concentration ratio (M/P). Since milk is more acidic than plasma, weakly basic drugs tend to concentrate in milk, resulting in an M/P ratio greater than 1, while weakly acidic drugs show the opposite trend. For acidic drugs, excretion in milk is inversely related to molecular weight and partition coefficient, whereas for basic drugs, it is inversely related to the degree of ionization and partition coefficient.

MULTIPLE CHOICE QUESTIONS

1. **Fick's law is used for the study of:**
   - **A.** Dissolution rate
   - **B.** Disintegration rate
   - **C.** Dissociation rate
   - **D.** Diffusion rate

2. **Which of the following is not a mechanism of drug absorption through GIT?**
   - **A.** Pore transport
   - **B.** Active transport
   - **C.** Endocytosis
   - **D.** Metastasis

3. **Which of the following processes is also called "cell drinking"?**
   - **A.** Pinocytosis
   - **B.** Phagocytosis
   - **C.** Convective transport
   - **D.** Active transfer

4. **The absorption of drugs like (quaternary ammonium compounds, sulphonic acid) are explained by:**
   - **A.** Ion-pair transport
   - **B.** Convective transport
   - **C.** Active transport
   - **D.** Facilitated diffusion

5. **The initial distribution of drug into the tissue is determined chiefly by:**
   - **A.** Rate of blood flow to tissue
   - **B.** Plasma protein binding of drug
   - **C.** Affinity for tissue
   - **D.** Gastric emptying time

6. **Nonlinear pharmacokinetics is also known as _____.**
   - **A.** Dose dependent
   - **B.** Enzyme capacity limited
   - **C.** Saturation pharmacokinetics
   - **D.** All of the above

7. **The characteristic of nonlinear pharmacokinetics include _____.**
   - **A.** Area under the curve is proportional to the dose
   - **B.** Elimination half-life remains constant
   - **C.** Area under the curve is not proportional to the dose
   - **D.** Amount of drug excreted through remains constant

8. **Which of following drugs shows nonlinearity in hepatic excretion?**
   - **A.** Carbamazepine
   - **B.** Propranolol
   - **C.** Penicillin
   - **D.** Thiopental

9. **The intensity of pharmacological effect is normally a function of the:**
   - **A.** pH of the drug
   - **B.** Solubility
   - **C.** Concentration of drug achieved in the circulation
   - **D.** None of above

10. **Change in pharmacokinetics parameters depends upon _____ of dose administered.**
    - **A.** Size
    - **B.** Route
    - **C.** Both of free above
    - **D.** None of the above

11. **Linear pharmacokinetics is _____ .**
    - **A.** Dose-dependent
    - **B.** Dose-independent
    - **C.** Both of the above
    - **D.** None of the above

12. **_____ is the ratio of the mean residence time to the absorption time.**
    - **A.** Absorption number
    - **B.** Dissolution number
    - **C.** Dose number
    - **D.** Intrinsic dissolution

13. **USP Apparatus 5 is _____.**
    - **A.** Flow through cell
    - **B.** Paddle over disk
    - **C.** Cylinder
    - **D.** Paddle

14. **Which of the following methods is/are used to determine area under curve?**
    - **A.** Cut and weigh method
    - **B.** Trapezoidal method
    - **C.** Integration method
    - **D.** All of the above

15. **Which route of drug administration shows 100% bioavailability?**
    - **A.** Oral
    - **B.** Intravenous
    - **C.** Rectal
    - **D.** Topical

16. **The concentration of drug in plasma above which toxic effects are precipitated is known as:**
    - **A.** Maximum safe concentration
    - **B.** Minimum effective concentration
    - **C.** Intensity of action
    - **D.** Duration of action

17. **When rate is independent of the reactant concentration, then it is called:**
    - **A.** Zero-order reaction
    - **B.** Pseudo zero-order reaction
    - **C.** First-order reaction
    - **D.** Second-order reaction

18. **Movement of ions through the pores in cell membrane can be controlled by:**
    - **A.** Counter ion transport
    - **B.** Expenditure of intracellular energy
    - **C.** Both A and B
    - **D.** None of the above

19. **The unit of k for zero order reaction is _____.**
    - **A.** Moles/Litre/Second
    - **B.** Moles
    - **C.** Moles/Second
    - **D.** Moles/Litre

20. **Which of the following is not a pharmacokinetic parameter that describe the plasma level time curve?**
    - **A.** t_{max}
    - **B.** C_{max}
    - **C.** Area under curve
    - **D.** Minimum effective concentration

21. **The main features of this transport system are:**
    - **A.** Transport occurs along the concentration gradient
    - **B.** No energy expenditure is involved
    - **C.** Transport is saturable, and competition occurs between isomers
    - **D.** All of these

22. **The onset of drug action depends on the rate of _____.**
    - **A.** Drug absorption
    - **B.** Drug dissociation
    - **C.** Both A and B
    - **D.** None of the these

23. **The drug concentration between minimum effective concentration and maximum safe concentration is called _____.**
    - **A.** Therapeutic range
    - **B.** Area under curve
    - **C.** Peak response
    - **D.** Pharmacological response

24. **After complete absorption of drug it moves into the various processes such as:**
    - **A.** Distribution and protein binding
    - **B.** Biotransformation of drug and excretion
    - **C.** Both A and B
    - **D.** None of these

ANSWER KEY

1. D 2. D 3. A 4. A 5. A 6. D 7. C 8. A 9. C 10. A 11. A 12. A 13. B 14. D
15. B 16. A 17. A 18. C 19. A 20. D 21. D 22. A 23. A 24. C

2. Bioavailability and Bioequivalence

BIOAVAILABILITY

Bioavailability refers to the rate and extent to which the active ingredient or moiety of a drug is absorbed from a product and becomes available at the site of action. It provides an estimate of the fraction of the drug absorbed from the formulation and informs about the drug's pharmacokinetics. Bioavailability studies assess drug product performance, revealing the effects of changes in the drug's physicochemical properties, formulation, and manufacturing process.

As a key indicator of drug absorption, bioavailability represents the fraction of the administered dose that successfully reaches systemic circulation when given orally or by any extravascular route. Intravenous administration is considered 100% bioavailable as the drug directly enters the bloodstream (systemic circulation). Conversely, drugs administered via other routes, especially orally, may have limited bioavailability due to first-pass metabolism by the liver and incomplete absorption in the gut. Bioavailability is thus a crucial pharmacokinetic tool for determining dosages for various administration routes.

BIOEQUIVALENCE

Bioequivalence studies compare the bioavailability of the same drug (in the same salt or ester form) from different drug products. Both bioavailability and bioequivalence serve as *in vivo* performance measures of drug products. If drug products are pharmaceutically equivalent, bioequivalent, and therapeutically equivalent (as defined by regulatory agencies like the FDA), they are assumed to have similar clinical efficacy and safety profiles and can be used interchangeably.

Absolute versus Relative Bioavailability

Absolute bioavailability compares the bioavailability of a drug following extravascular administration with that of the same drug given intravenously, which is considered 100% absorbed. Extravascular administration routes include inhalation, intramuscular, oral, rectal, subcutaneous, sublingual, topical, and transdermal. Absolute bioavailability is calculated by the dose-corrected area under the curve (AUC) of the drug administered extravascularly divided by the AUC of the drug given intravenously.