**Definition:**

The amount of drug that enters the body from site of administration to the systemic circulation is known as absorption. The rate of absorption affects the onset, duration and intensity of drug action.

Absorption involves several phases. First, the drug needs to be introduced via some route of administration and in a specific dosage form such as a tablet, capsule, and so on.

Absorption is a primary focus in drug development and medicinal chemistry, since the drug must be absorbed before any pharmacological effects can take place.

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**Pharmacokinetics of drug molecule**
Cell Membranes:

**Structure:** Cell membrane consists of a phospholipid bilayer studded with proteins, poly-saccharides, lipids and the lipid bilayer.

It is semipermeable to H2O and some small, uncharged, molecules (O2, CO2) can pass through. Phospholipids have two parts

"Head": hydrophilic → attracts and mixes with H2O

Two "fatty acid tails": hydrophobic

Membrane proteins embedded in the bilayer serve as receptors, ion channels or transporters to transduce electrical or chemical signaling pathways and provide selective targets for drug actions.

**Processes of Absorption:**

**Processes involved in the absorption of drug:**

Following are the processes involved in the transport of drugs:

1. Passive diffusion
2. Specialized transport

1: Passive membrane transport

   a) Simple diffusion
   b) Filtration/aqueous diffusion
   c) Osmosis
   d) Bulk flow

2: Specialized transport

   a) Active membrane transport (primary/secondary)
   b) Facilitated diffusion
   c) Endocytosis (phagocytosis/pinocytosis)
   d) Exocytosis
Absorption

1: Passive membrane transport:

In passive transport, the drug molecule penetrates in the lipid bilayer membrane from higher concentration to the lower concentration of solutes along the concentration gradient without expenditure of energy.

So passive transport mechanism involves following processes.

a) Simple diffusion:

It is characterized by the direct movement of a solute through the semi permeable cell membrane from a phase of higher concentration to the phase of lower concentration without expenditure of energy until the equilibrium is achieved.

Concentration gradient:

The force which directs the movement of solutes toward or against the gradient or the difference in concentration between both sides of membrane is known as concentration gradient. Transfer is directly proportional to the magnitude of the concentration gradient across the membrane.

Fick’s law of diffusion: Rate of diffusion across an exchange surfaces depends upon

- Surface area across within diffusion occurs
- Thickness of cell membrane
- Difference in conc. gradient on both sides

\[
\text{Molecule} = \frac{\text{Difference in conc.}}{\text{Thickness}} \times \text{AREA} \times \text{permeability}
\]

\[
\text{Molecule} = \frac{(C1-C2) \times A \times p}{D}
\]
Absorption

b) Filtration or aqueous diffusion:

It is the passage of a substance through pores in the cell membrane by means of their hydrostatic or osmotic pressure gradient. Water, ions and some polar and non polar molecules of low molecular weight diffuse through membrane indicating the existence of pores or channels.

Glomerular membrane of kidney is a good example of filtration.

c) Osmosis:

Osmosis is a special case of diffusion. In this case, a large molecule of drug like starch is dissolved in water.

The starch molecule is too large to pass through the pores in the cell membrane, so it cannot diffuse from one side of the membrane to the other. The water molecules can do, pass through the membrane. Hence the membrane is said to be semi permeable, since it allows some molecules to pass through but not others.

d) Bulk flow:

It is the movement of drug molecules across the membrane by pores between capillaries endothelial cells.

It is important in regulating the distribution of fluids between the plasma and interstitial fluid, that is important in maintain the blood pressure.
Absorption

2: Specialized transport mechanism

Specialized transport of drug across the cell membrane requires transport mechanisms or carrier protein. It involves various processes of mechanisms.

In these mechanism drug forms a complex with the carrier proteins or transporters at the outer surface of the cell membrane and then transported across the cell membrane to the inner surface when the drug is released from the carrier complex.

a) Active transport mechanism

In active transport, the drug molecule penetrates in the lipid bilayer membrane from lower concentration to the higher concentration of solutes against the concentration gradient with the expenditure of energy and with the help of special carrier proteins.

This process has two types of energy dependent mechanisms.

i. Primary active transport

ii. Secondary active transport

i. Primary active transport:

Primary active transport, also called direct active transport, directly uses energy to transport molecules across a membrane. The energy used in this type of active transport is ATP. The only substances transported by carriers that directly hydrolyze ATP. These include positively-charged ions - Na⁺, K⁺, Ca²⁺ or H⁺.
ii. Secondary active transport

Secondary active transport, also called co-transport, electrochemical potential difference created by pumping ions out of the cell is used to transport molecules across a membrane but there is no direct coupling of ATP. Sodium-proton or Sodium-calcium co transport mechanism involved in this type of absorption mechanism.

b) Facilitated diffusion:

It is a special form of carrier mediated transport in which the movement across cell membrane occurs along with the concentration gradient but with the help of special transporters or carrier proteins without the expenditure of energy.
Absorption

c) Endocytosis:

Endocytosis is a process in which a substance gains entry into a cell by formation of intracellular vesicle by virtue of invagination of plasma membrane and membrane fusion takes place.

i. Phagocytosis

ii. Pinocytosis

iii. Receptor mediated endocytosis

i. Phagocytosis:

The cellular process of engulfing the solid particles e.g. bacterium by vesicular internalization by the cell membrane itself to form the internal phagosome is known as phagocytosis.

ii. Pinocytosis:

The endocytosis in which small particle or liquid material is brought into the cell by forming an invagination or vesicle called lysosomes, is known as pinocytosis. This process requires a lot of energy in the form of ATP.
iii. **Receptor-mediated endocytosis:**

Receptor-mediated endocytosis (RME), also called clathrin-dependent endocytosis, is a process by which cells internalize molecules (endocytosis) by the inward budding of plasma membrane vesicles containing proteins with receptor sites specific to the molecules being internalized.

![Diagram of receptor-mediated endocytosis](image)

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d) **Exocytosis:**

Exocytosis is a process in which a substance removes from the cell by formation of extracellular vesicle by virtue of invagination of plasma membrane itself. Finally the vesicle is discharged with its contents into extracellular space.

![Diagram of exocytosis](image)
Application of Absorption processes:

1: Passive membrane transport

a) Simple diffusion
b) Filtration/ aqueous diffusion
c) Osmosis
d) Bulk flow

2: Specialized transport

a) Active membrane transport (primary/secondary)
b) Facilitated diffusion
c) Endocytosis (phagocytosis/pinocytosis)
d) Exocytosis

1: Passive membrane transport

a) **Simple diffusion:** The entire lipid soluble drugs absorb by simple diffusion. This type of absorption is done in stomach, small intestine and kidney, in both acidic and basic medium.

b) **Filtration/ aqueous diffusion:** The entire hydrophilic (water loving) drugs absorb by this process. These are low molecular weight drugs. This process of absorption is only done in jejunum and proximal tubules of kidney.

c) **Osmosis:** This type of absorption is done when the drug is in liquid or in solution form. This is simplest type of absorption with semi permeable membrane.

d) **Bulk flow:** This passage of absorption is independent to the water or lipid solubility. pKa, pH value, or nature of the medium. Drug absorption is only depending upon the blood flow and blood supply. The drug administers through IM route follow this mechanism of absorption.

2: Specialized transport

a) **Active membrane transport (primary/secondary):** This is special type of absorption in which amino acids, sugar molecules, neurotransmitters or inorganic ions move across the membrane with the help of transporters or carrier proteins.
b) **Facilitated diffusion**: In this type of absorption lipid insoluble become lipid soluble with combining some special type of carrier proteins like catecholamine (epinephrine or nor epinephrine) absorption across the cell membrane.

c) **Endocytosis (phagocytosis/pinocytosis)**: Fat soluble vitamins e.g vit B-12 with intrinsic factor, protein molecules and folic acid follow endocytosis for absorption. LDLP (low density lipoprotein) follow receptor mediated endocytosis for absorption.

d) **Exocytosis**: Anticancer drug follow this type of absorption. In which vesicle discharge at the cell surface to the outside cell. Toxins are also removed by this type of transport from the cell body.

### Tabular form

<table>
<thead>
<tr>
<th></th>
<th>Passive transport</th>
<th>Active transport</th>
<th>Facilitated transport</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conc. gradient</td>
<td>towards</td>
<td>against</td>
<td>towards</td>
</tr>
<tr>
<td>Energy consumption</td>
<td>no</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Carrier protein</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Specificity</td>
<td>Non-specific</td>
<td>Specific</td>
<td>Specific</td>
</tr>
<tr>
<td>Saturability</td>
<td>Non-saturable</td>
<td>Saturable</td>
<td>Saturable</td>
</tr>
<tr>
<td>Drugs nature</td>
<td>Lipid soluble</td>
<td>Lipid insoluble</td>
<td>Non-diffusible</td>
</tr>
<tr>
<td>Example</td>
<td>Aspirin, phenobarbitone etc</td>
<td>Anticancers, neurotransmitters etc</td>
<td>Adrenaline and nor adrenaline etc</td>
</tr>
</tbody>
</table>
## Routes of Drug Administration

<table>
<thead>
<tr>
<th>Route</th>
<th>Bioavailability</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PARENTERAL ROUTES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous bolus (IV)</td>
<td>Complete (100%) systemic absorption</td>
<td>Use for immediate effect</td>
<td>Increased chance for adverse reaction</td>
</tr>
<tr>
<td>Intravenous infusion (IV inf)</td>
<td>Complete (100%) systemic absorption</td>
<td>Plasma drug levels precisely controlled</td>
<td>Requires skill in insertion of infusion set</td>
</tr>
<tr>
<td></td>
<td>Rate of drug absorption controlled by infusion rate.</td>
<td>inject large volumes use for irritate/poor lipid soluble drugs</td>
<td>Tissue damage at site of injection (infiltration, necrosis, or abscess)</td>
</tr>
<tr>
<td>Intramuscular injection (IM)</td>
<td>Rapid from aqueous solution.</td>
<td>Easier to inject than i.v</td>
<td>Irritating drugs may be very painful</td>
</tr>
<tr>
<td></td>
<td>Slow absorption from nonaqueous (oil) solutions.</td>
<td>Larger volumes may use compared to sc. solutions.</td>
<td>Different rates of absorption depending on muscle and blood flow</td>
</tr>
<tr>
<td>Subcutaneous injection (SC)</td>
<td>Prompt from aqueous solution</td>
<td>Generally, used for insulin injection</td>
<td>Rate of drug absorption depends on flow and vol</td>
</tr>
<tr>
<td><strong>ENTERAL ROUTES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buccal or sublingual (SL)</td>
<td>Rapid absorption from lipidsoluble drug</td>
<td>No &quot;first-pass&quot; effects</td>
<td>Some drugs may be swallowed</td>
</tr>
<tr>
<td>Oral (PO)</td>
<td>Generally, slower absorption rate</td>
<td>Safest and easiest route of drug administration.</td>
<td>Drugs unstable in GIT, or be metabolized by liver</td>
</tr>
<tr>
<td>Rectal (PR)</td>
<td>Reliable absorption from enema</td>
<td>Useful when patient cannot swallow</td>
<td>Patient discomfort</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Absorption may be erratic</td>
</tr>
<tr>
<td><strong>OTHER ROUTES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transdermal</td>
<td>Slow absorption</td>
<td>patch is easy to use</td>
<td>Irritation by patch or drug.</td>
</tr>
<tr>
<td></td>
<td>Increased absorption with occlusive dressing</td>
<td>Used for lipid-soluble drugs with low dose and low MW</td>
<td>Permeability of skin variable with condition, site, age, and gender.</td>
</tr>
<tr>
<td>Inhalation and intranasal</td>
<td>Rapid absorption.</td>
<td>used for local or systemic effects</td>
<td>stimulate cough reflex</td>
</tr>
</tbody>
</table>
Absorption

Factors influencing the absorption mechanisms:

These are the factors, influence the diffusion of the drug molecule across the membrane. The rate of absorption determines by

- Onset of absorption
- Duration of absorption
- Intensity of absorption

A. Physiological factor

1. Membrane thickness
2. Membrane surface area
3. pH of gastrointestinal fluids
4. Functional integrity of GIT
5. Gastric emptying time
6. Blood flow

B. Physiochemical factor

1. Lipid solubility
2. pH of the medium
3. Ionization of drug
4. Ionization coefficient
5. Partition coefficient
6. Protonated and Unprotonated form

C. Pharmaceutical factor

1. Particle size of drug
2. Nature of the drug
3. Concentration of drug
4. Formulation
5. Physical state
6. Dosage form
7. Chemical nature of drug
Absorption

A. Physiological factor

1: **Membrane thickness**: Membrane thickness is inversely proportional to the absorption of the drug across the membrane. As the thickness of the lipid bi layer membrane increases the absorption of the drug decreases.

2: **Membrane surface area**: Drugs are better absorbs from large surface area such as pulmonary alveolar epithelium, intestinal mucosa etc. The area of absorbing surface depends to a greater extent on the route of administration.

3: **pH of gastrointestinal fluids**: In the stomach the weak acids e.g aspirin, phenobarbitone will be in the nonionized state hence these are lipid soluble and would be better absorbed than in the alkaline medium of the intestine.

On the other hand weak bases e.g quinidine, ephedrine would be highly ionized in the stomach and poorly absorbed from the stomach while it would be better absorbed in the intestine with alkaline medium.

4: **Functional integrity of GIT**: Increased peristaltic movement as in diarrhea reduces the drug absorption. Gastro intestinal mucosal edema depresses the absorption of drug.

5: **Gastric emptying time**: Enhance the gastric emptying time increase the rate of absorption in the GIT. E.g Metolopramide enhances the gastric emptying time.

6: **Blood flow**: In shock, blood flow to intestine is decreased and absorption from the intestine is reduced.

B. Physiochemical factor

1: **Lipid solubility**: Drugs those are lipid soluble diffuse through the cell membrane more rapidly than the lipid insoluble drugs because the compatibility of the drug with the structure of lipid bi layer membrane.

2: **pH of the medium**: In the stomach the weak acids e.g aspirin, phenobarbitone will be in the nonionized state hence these are lipid soluble and would be better absorbed than in the alkaline medium of the intestine.

On the other hand weak bases e.g quinidine, ephedrine would be highly ionized in the stomach and poorly absorbed from the stomach while it would be better absorbed in the intestine with alkaline medium.
3: Ionization of drug: Most drugs are weak acids or bases and are present in the solution in both ionized and unionized form. The nonionized being the lipid soluble diffuse across the cell membrane while ionized form being the lipid insoluble unable to penetrate the lipid membrane.

The rate of diffusion of weak electrolytes is dependent on their degree of ionization. The greater the nonionized fraction greater will be the rate of diffusion.

For acid in acidic medium: \[ HA \leftrightarrow A^- + H^+ \]

For base in acidic medium: \[ BH^+ \leftrightarrow B + H^+ \]

4: Ionization coefficient: The distribution of weak electrolyte is determined by its ionization coefficient pKa value and pH gradient across the membrane. When pKa of the drug is equal to pH of the medium then 50% of the drug will be ionized and 50% will be in the unionized state.

Dissociation of an acid: \[ K_a = [A^-][H^+]/[HA] \]

Dissociation of an acid: \[ K_a = [B][H^+]/[BH^+] \]

5: Partition coefficient: Partition coefficient deals with motion of molecule across the cell membrane. Greater the ionization coefficient greater will be the partition coefficient and thus greater will be the diffusion.

Relation between pH, pKa and ionized/unionized fractions can be depicted from Henderson Hasselbalch equation:

For an acid: \[ pKa = pH + \log \frac{\text{Molecular conc. of nonionized acid}}{\text{Molecular conc. of ionized acid}} \]

For a base:

\[ pKa = pH + \log \frac{\text{Molecular conc. of ionized base}}{\text{Molecular conc. of nonionized base}} \]

6: Protonated and Unprotonated form: Protonated form of acid is well absorbed and in unionized form while protonated form of base is less absorbed because it is ionized form of base.

For acid: \[ pKa = pH + \log \frac{\text{protonated form}}{\text{unprotonated form}} \]
Protonated form of acid and base: (HA or BH⁺) form

Unprotonated form of acid and base: (A⁻ or B) form

C. Pharmaceutical factor

1. **Particle size of drug:** Small water soluble molecules diffuse more efficiently across cell membrane through pores. The smaller the particle, the faster the rate of diffusion.

2. **Nature of the drug:** The drug administered in different dosage form having different rate of disintegration and dissolution those are limiting factor in absorption of drug particle.

3. **Concentration of drug:** Drug ingested or injected in solution of high concentration are absorbed more rapidly than drug in low concentration.

4. **Formulation:** Substances like sucrose, lactose, starch, are commonly used as excipients in formulating the drugs. These substances may effects the absorption.

5. **Physical state:** liquids are better absorbed than solids and crystalloids are better absorbed than colloids.

6. **Dosage form:** In case of tablet and capsule disintegration time and dissolution rate are important factor affecting the rate and extent of absorption.

7. **Chemical nature of drug:** Inorganic iron preparation is better absorbed from GIT than organic preparations. Ferrous salts are better absorbed than ferric salts.
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