Biopharmaceutical aspects of drug absorption

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

Absorption can be defined as the transfer of a drug from its site of administration to the blood stream. If the drug is intended for systemic activity, the drug should ideally be completely and consistently absorbed. In contrast, if the drug is intended for local activity, then systemic absorption from the application should be minimal to prevent systemic drug exposure and possible systemic side effects. For extended-release drug products, the drug product should remain at or near the application site and then slowly release the drug for the desired period of time.

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

Route of drug administration

Intravenous bolus = Complete (100%) systemic drug absorption and the rate of bioavailability considered instantaneous.

Intravenous infusion = Complete (100%) systemic drug absorption and the rate of drug absorption controlled by infusion rate.

Subcutaneous injection = Rapid absorption from aqueous solution and slow absorption from repository formulations.

Intradermal injection = Drug injected into dermal surface area of skin.

Intramuscular injection = Rapid absorption from aqueous solution and slow absorption from nonaqueous oily solutions.

Intra-arterial and Intrathecal injection = 100% of solution is absorbed.

Intraperitoneal injection = In laboratory animals (eg, rat) and the drug absorption resembles oral absorption.

Buccal or sublingual = Rapid absorption from lipid soluble drugs.

Oral = Slower absorption rate compared to IV bolus or IM injection.

Rectal = Slow absorption from suppository but more reliable absorption from enema (solution).

Transdermal = Slow absorption and its rate may vary. Increased absorption with occlusive dressing.

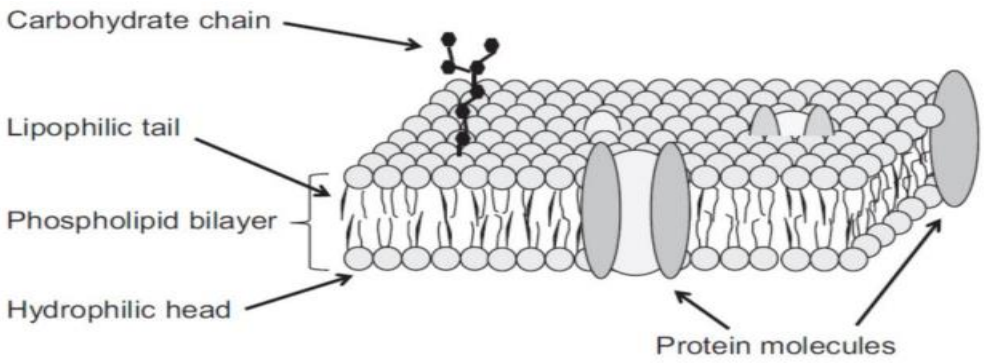
Inhalation and intranasal = Rapid absorption and total dose absorbed is variable.

Nature of cell membrane

Drugs that are administered by extravascular routes (eg, oral, topical, intranasal, inhalation, rectal) are either designed for local effect or designed to be absorbed from the site of administration into the systemic circulation. For systemic drug absorption, the drug has to cross cellular membranes to reach the site of action. The general principles and kinetics of absorption from these extravascular sites follow the same principles as oral dosing, although the physiology of the site of administration differs.

The permeability of a drug at the absorption site into the systemic circulation is mainly related to (1) the molecular structure and properties of the drug and to (2) the physical and biochemical properties of the cell membranes. Therefore, biological membranes represent a significant barrier to drug delivery. Epithelial and endothelial membrane barriers separate the body from its environment and individual body compartments from each other.

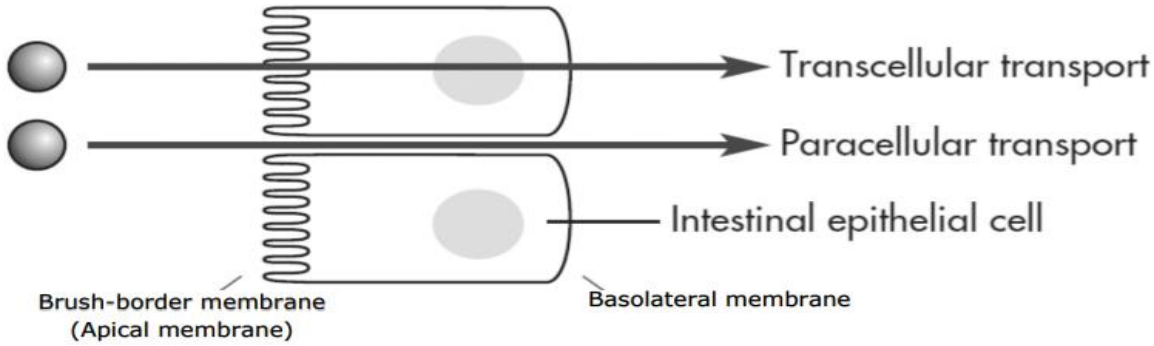
- The epithelium is a membrane tissue that covers almost all body surfaces such as the skin, lungs, nasal cavity, buccal cavity, intestine, and other body cavities. The endothelium consists of thin layer of cells that lines the interior surface of blood vessels.
- The basic structure of cellular membranes is the lipid bilayer, composed of double layer of phospholipids, with occasional proteins, some of these proteins function as channel formers, drug transporters, or drug-metabolizing enzymes



Transport mechanisms of drugs through biomembranes

- Transcellular transport is the process of drug movement across a cell.
- Paracellular transport is the process of drug movement through gaps or tight junctions between intestinal epithelial cells for polar molecules and small molecules (limited to drug molecules smaller than 500 MW).

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



PASSAGE OF DRUGS ACROSS CELL MEMBRANE

1. PASSIVE DIFFUSION: It is the process by which molecules spontaneously diffuse from a region of higher concentration to a region of lower concentration according to Fick's law of diffusion. This process is passive because no external energy is expended. Drug molecules can move forward and back across a membrane; the net movement of molecules depends on the concentration differences on both sides of the membrane. Passive diffusion is the major absorption process for most drugs. The driving force for passive diffusion is higher drug concentrations, typically on the mucosal side compared to the blood as in the case of oral drug absorption.

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

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

Notes:

- Once the drug is absorbed to the blood it distributes rapidly into a large volume. The concentration in the blood will be quite low with respect to the concentration at the site of drug administration. For example, a drug is usually given in milligram doses, whereas plasma concentrations are often in the µg/mL or ng/mL range. If the drug is given orally, then $C_{GI} >> C_p$ and a large concentration gradient is maintained until most of the drug is absorbed.
- Drugs that are more lipid soluble have a larger value of K.
- The surface area, A, of the membrane also influences the rate of absorption. The duodenal area of the small intestine shows the most rapid drug absorption, due to such anatomic features as villi and microvilli, which provide a large surface area. These villi are less abundant in other areas of the gastrointestinal tract.
- The thickness of the membrane, h, affects the diffusion. Drugs usually diffuse very rapidly through capillary plasma membranes in the vascular compartments, in contrast to diffusion through plasma membranes of capillaries in the brain (the brain has a thicker lipid membrane).
- The diffusion constant, D, is specific constant for each drug.
- Because D, A, K, and h are constants under usual conditions for absorption, a combined constant P or permeability coefficient can be used instead.

$P = DAK/h$

- The drug concentration in the plasma, C_p, is extremely small compared to the drug concentration in the gastrointestinal tract, C_{GI}. If C_p is negligible and P is substituted into the equation, the following relationship for Fick's law is obtained: $dQ/dt = P\ (C_{GI})$

Factors affecting the drug diffusion across biomembranes

A. Effect of pH and the extent of ionisation on diffusion

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

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

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

For weak acids,

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

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

For weak bases,

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

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

Example: The extent of ionisation for salicylic acid (pKa = 3.0) in plasma (pH = 7.4) is:

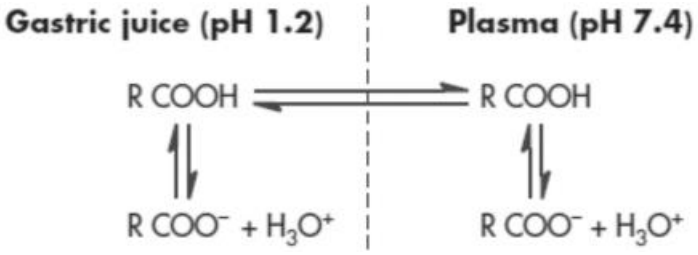
- Ratio = [Salt]/ [Acid] = $10^{(7.4 - 3)}$
- Log [Salt]/ [Acid] = 7.4 – 3 = 4.4
- [Salt]/ [Acid] = 2.51×10^4

At plasma pH, salicylic acid exists mostly in its ionized form.

Note: For nonelectrolyte drugs or drugs that do not ionize, the drug concentrations on either side of the membrane are the same at equilibrium.

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

For example, consider the concentration of salicylic acid (pKa = 3.0) in the stomach (pH 1.2) as opposed to its concentration in the plasma (pH 7.4)



According to the Henderson–Hasselbalch equation for weak acids, at pH 7.4 and at pH 1.2, salicylic acid exists in the different ratios

In the plasma , Ratio = [RCOO−] / [RCOOH] = 2.51×10^{4}

In gastric juice, Ratio = [RCOO−] / [RCOOH] = 1.58×10^{-2}

In this example the total concentration of salicylic acid at equilibrium is ~ 25,000 times greater in the plasma than in the stomach.

The pH–partition hypothesis

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

For these reasons, a weak acid (such as salicylic acid) will be rapidly absorbed from the stomach (pH 1.2), whereas a weak base (such as quinidine) will be poorly absorbed from the stomach.

B. The affinity of the drug for a tissue component

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

Examples of binding include:

1. Binding to plasma or tissue proteins;

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

2. Partitioning to the adipose tissues;

• Chlordane is a very lipid soluble drug and will partition to adipose tissues.

3. Complexation with a tissue component;

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

4. Active transport uptake by the tissue;

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

2. CARRIER-MEDIATED TRANSPORT

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

• Uptake (influx) transporters move drug to the blood and increase plasma concentration.

• Efflux transporters move drug back to the lumen (GIT for example) and decrease plasma concentration.

A. Active Transport: It is a type of carrier mediated transport and it is characterized by the ability to transport drug against a concentration gradient (from regions of low drug concentrations to regions of high drug concentrations)

• The carrier molecule may be highly selective for the drug molecule.

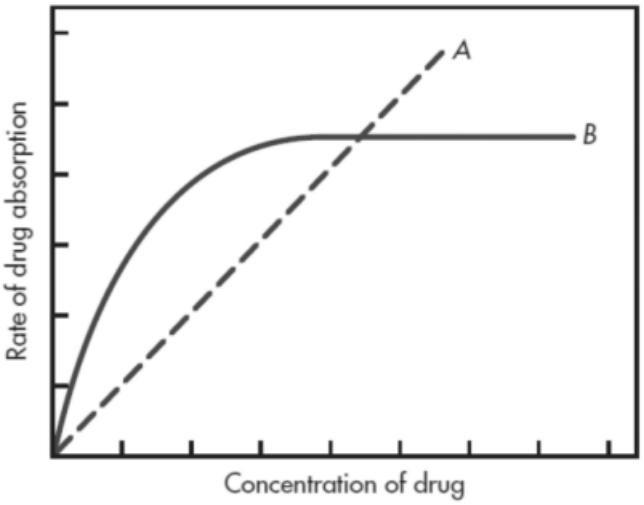
• It is an energy consuming process.

• If a drug is structurally similar to the natural substance that is actively transported by the carrier, it is likely to be transported by the same carrier such as 5-fluorouracil lipid-insoluble drug that is nucleobase analogue resemble to uracil.

• Only a fixed number of carriers are available, the biding sites may become

saturated if high concentration of the drug is applied.

- The rate of drug absorption increases with the increase in the concentration of the drug until all the carrier molecules are saturated. At higher concentrations, the rate of absorption remains constant (zero order).
- For the passive diffuse the rate of absorption is directly related to the concentration of the drug at the site of administration (first order rate).



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

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

- This system does not require energy input.
- It is saturable and structurally selective for the drug and shows competition kinetics for drugs of similar structure.
- In terms of drug absorption, this diffusion seems to play a very minor role.
- Some cephalosporin such as cephalexin undergo facilitated diffusion by an oligopeptide transporter protein located in intestinal epithelial cells.

Transporters and Carrier-Mediated Intestinal Absorption

Both influx and efflux transporters are present in the brush border and

basolateral membrane that will increase drug absorption (influx transporter) or decrease drug absorption (efflux transporter).

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

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

3.VESICULAR TRANSPORT: It is the process of engulfing particles or dissolved materials by the cell.

A. Pinocytosis refers to the engulfment of small solutes or fluid.

B. Phagocytosis refers to the engulfment of larger particles or macromolecules, generally by macrophages.

During pinocytosis and phagocytosis the cell membrane invaginates to surround the material and then engulfs the material, incorporating it inside the cell. Subsequently, the cell membrane containing the material forms a vesicle within the cell.

C. Endocytosis and exocytosis are the processes of moving specific macromolecules into and out of a cell, respectively.

Examples of exocytosis is the transport of a protein such as insulin from insulin-producing cells of the pancreas into the extracellular space. The insulin molecules are first packaged into intracellular vesicles, which then fuse with the plasma membrane to release the insulin outside the cell.

D. Transcytosis is the process by which various macromolecules are transported across the interior of a cell. In transcytosis, vesicles are employed

to intake the macromolecules on one side of the cell, draw them across the cell, and eject them on the other side. Transcytosis (sometimes referred to as vesicular transport) is the proposed process for the absorption of orally administered Sabin polio vaccine and various large proteins.

4. PORE (CONVECTIVE) TRANSPORT

Very small molecules (such as urea, water, and sugars) are able to cross cell membranes rapidly, as if the membrane contained channels or pores. A certain type of protein called a transport protein may form an open channel across the lipid membrane of the cell . Small molecules including drugs move through the channel by diffusion more rapidly than at other parts of the membrane.

5. ION – PAIR FORMATION

Strong electrolyte drugs are highly ionized molecules, such as quaternary nitrogen compounds with extreme pKa values. They maintained their charge at all physiologic pH values and penetrate membranes poorly. When the ionized drug is linked with an oppositely charged ion, an ion pair is formed in which the overall charge of the pair is neutral. This neutral drug complex diffuses more easily across the membrane (e.g.; propranolol with oleic acid, and quinine with hexylsalicylate).An interesting application of ion pairs is the complexation of amphotericin B and DSPG (disteroylphosphatidylglycerol) in some amphotericin B/liposome products. Ion pairing may transiently alter distribution, reduce high plasma free drug conc,entration and reduce renal toxicity.