BP-604T.BIOPHARMACEUTICS AND PHARMACOKENICTS (Theory)

UNIT-ONE (Part 1)

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UNIT ONE ,Part-1 5 Hours

- **Introduction to Biopharmaceutics,**
- **Absorption: Mechanisms of drugs absorption through GIT,**
- **Factors influencing drug absorption through GIT,**

- **Biopharmaceutics :** is the branch of pharmaceutical sciences in which we study about physicochemical properties of drugs, dosage forms and routes of administration affect the rate and extent of the drug absorption
- Pharmacokinetics: is the branch of Pharmacology in which we study about the absorption, distribution, metabolism, and excretion of drugs *"what the body does to a drug",*
  - Absorption: is the process of a drugs entering the body.
  - Distribution : is the dispersion of drugs through out the fluids and tissues of the body
  - Metabolism: is the irreversible transformation of parent compounds into daughter metabolites.
  - Excretion: is the elimination of the Drugs from the body.
- **Absorption:** absorption is the process of movement of drugs form its site of administration to the blood stream ,the therapeutics response of the drug depends on the rate as extent of drug absorption on and its concentration at the site of action

❖ TRANSPORT OF DRUG ACROSS BIOLOGICAL BARRIERS

For systemic absorption, a drug must pass from the absorption site through one or more layers of cells to gain access into the general circulation. For absorption into the cells, a drug must traverse the cell membrane.

❖ STRUCTURE OF CELL MEMBRANE

Cell membrane surrounds the entire cells and acts as a boundary between cell and interstitial fluid. Cell membrane acts as a selective barrier to the passage of molecules. Water, some small molecules, and lipid-soluble molecules pass through such membrane;

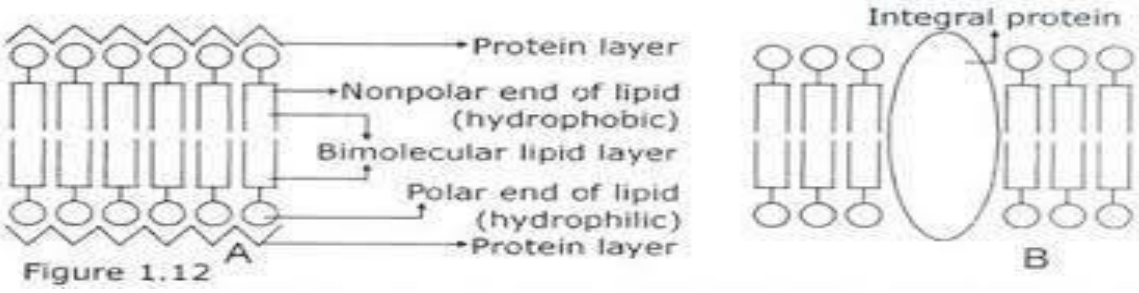
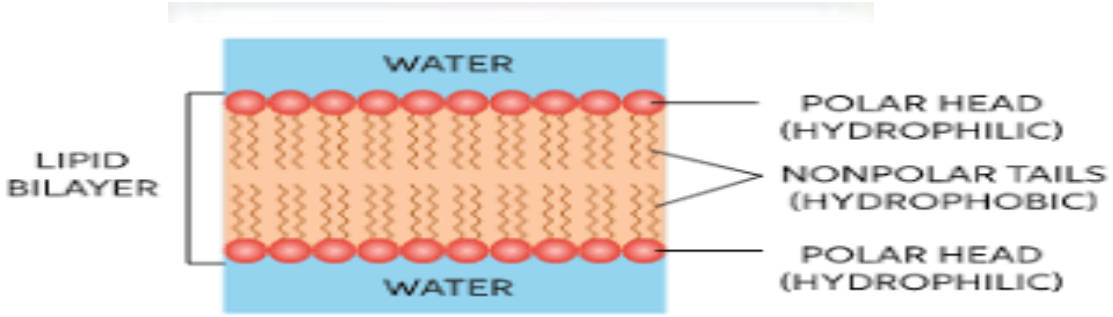


Figure 1.12

❖ Structure

Cell membranes are generally thin, approximately 70 to 100 A in thickness. They are primarily composed of phospholipids in the form of bilayer. Some carbohydrates and proteins are inter dispersed within this lipid bilayer.

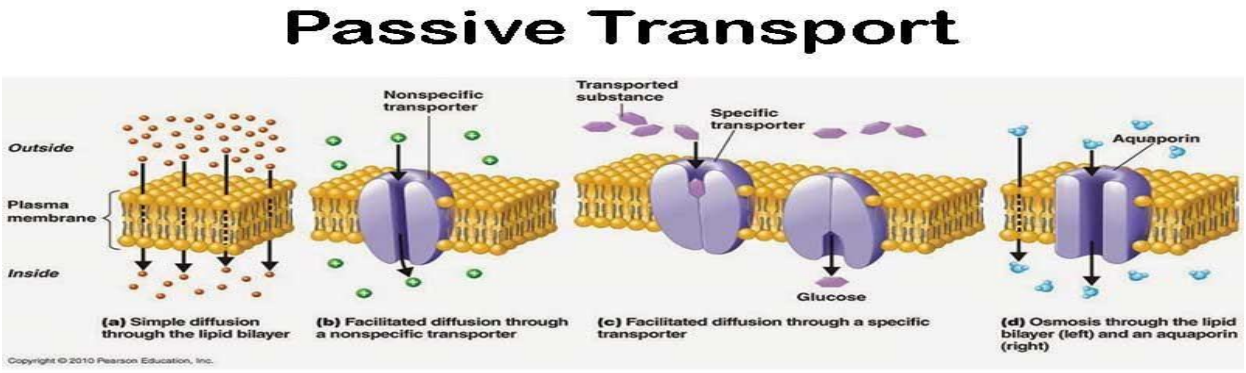


❖ **The principal mechanisms of transport of drug molecules across the cell membrane are :**

1. Passive diffusion
2. Carrier mediated transport
   (a) Active transport
   (b) Facilitated transport
3. Vesicular transport
   (a) Pinocytosis
   (b) Phagocytosis
4. Pore transport
5. Ion pair formation Pore transport

PASSIVE TRANSPORT

Passive diffusion is the process by which molecules spontaneously diffuse from a region of higher concentration to a region of lower concentration. This process is passive because no external energy is expended.



❖ **Characteristics of passive transport:**

✓ Drug molecules moves from a region of relatively high concentration to one of lower concentration.

✓ The rate of transfer is proportional to the concentration gradient between the compartments involved in thetransfer.

✓ The transfer process achieves equilibrium when the concentration of the *transferable species* is equal on both sides of the membrane

2. CARRIER MEDIATED TRANSPORT

Some polar molecules cross the membrane more readily than can be predicted from their concentration gradient and partition coefficient values. This suggests the presence of some specialized transport mechanisms without which many essential water-soluble nutrients like monosaccharide's, amino acids and vitamins will be poorly absorbed. The mechanism is thought to involve a component of the membrane called as the *carrier* that binds reversibly with the solute molecules to be transported. This carrier-solute complex traverses across the membrane to the other side where it dissociates and discharges the solute molecule. The carrier then returns to its original site to complete the cycle by accepting a fresh molecule of solute. The carrier may be an enzyme or some other component of the membrane.

- **Facilitated transport**: The process of the movement of molecules across the cell membrane via special transport proteins that are embedded within the cellular membrane is known as facilitated diffusion or called carrier-mediated diffusion.many large molecules, such as glucose, are insoluble in lipids and too large to fit into the proton therefore, it will bind with its specific carrier proteins, and the complex will then be bonded to a receptor site and moved through the cellular membrane

- **Active transport:** Active transport is the movement of a substance against its concentration gradient (i.e. from low to high concentration). It is an endergonic process that, in most cases, is coupled to the hydrolysis of ATP Active transport:

  It is an endergonic process that, in most cases, is coupled to the hydrolysis

❖ Types of active transport:

1.Primary active transport: it is also called direct active transport, directly uses energy to transport molecules across a membrane. Example: Sodium-potassium pump, which helps to maintain the cell potential.

2.Secondary active transport: Secondary active transport or co-transport, also uses energy to transport molecules across a membrane; however, in contrast to primary active transport, there is no direct coupling of ATP; instead, the electrochemical potential difference created by pumping ions out of the cell is instrumental.

❖ **The two main forms of active transport are antiport and symport**

(a)Antiport: In antiport two species of ion or solutes are pumped in opposite directions across a membrane. One of these species is allowed to flow from high to low concentration which yields the entropic energy to drive the transport of the other solute from a low concentration region to a high one. Example: the sodium-calcium exchanger or antiporter, which allows three sodium ions into the cell to transport one calcium out.

(b) Symport: Symport: uses the downhill movement of one solute species from high to low concentration to move another molecule uphill from low concentration to high concentration (against its electrochemical gradient). Example: glucose symporter SGLT1, which co-transports one glucose (or galactose) molecule into the cell for every two sodium ions it imports into the cell.

❖ VESICULAR TRANSPORT

Vesicular transport is the process of engulfing particles or dissolved materials by the cell.particles or dissolved materials by the cell.

There are two types of vesicular transport –

Phagocytosis: Phagocytosis is the process in which certain living cells called phagocytes engulf larger solid particles such as bacteria, debris or intact cells. Certain unicellular organisms ,"cell eating," is a mechanism whereby the cell can ingest solid particles.

Pinocytosis, "cell drinking," allows the cell to consume solutions. An infant's intestinal lining ingestsbreast milk by pinocytosis, allowing the mother's protective antibodies to enter the baby's bloodstream.

❖ PORE TRANSPORT

Very small molecules (such as urea, water, and sugars) are able to rapidly cross cell membranes as if the membrane contains channels or pores.

A certain type of protein called transport protein may form an open channel across the lipid membrane of the cell.

e.g.

- Drug permeation through aqueous pores is used to explain the renal excretion of drugs and the uptake of drugs intothe liver.

ION PAIR FORMATION

Strong electrolyte drugs are highly ionized or charged molecules, such as quaternary nitrogen compounds with extreme pKa values. Strong electrolyte drugs maintain their charge at all physiologic pH values and penetrate the membrane very poorly.

When ionized drugs is linked up 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.

Example:

- Propranolol, a basic drug, forms an ion pair with oleic acid.

Propranolol-oleic acid ion-pair

FACTORS INFLUENCING GI ABSORPTION OF A DRUG:

(A) PHARMACEUTICAL FACTORS:it include factores relating to the physicochemical properties of drug and dosage form characteristics and pharmaceutical ingredients

Physico-chemical Properties of Drug substances

- Drug solubility and dissolution rate
- Particle size and effective surface area
- Polymorphism and amorphism
- Pseudo polymorphism (hydrates / solvates)
- Salt form of the drug
- Lipophilicity of the drug – (pH partition hypothesis)
- pKa of the drug and pH – (pH partition hypothesis)
- Drug stability

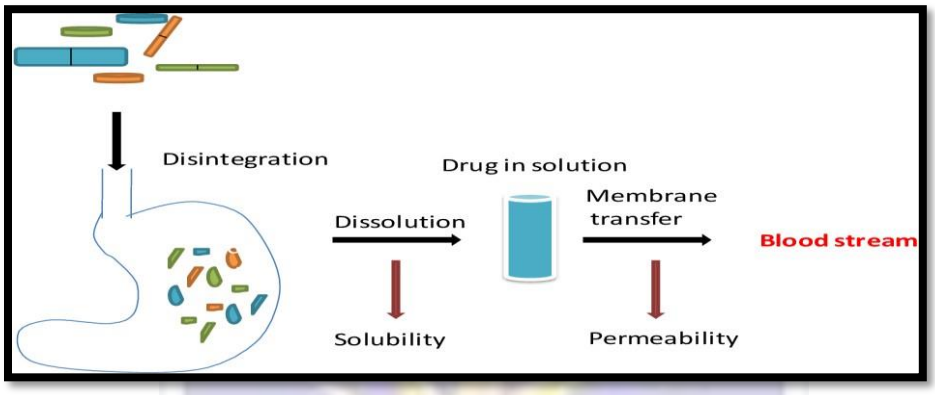
Pharmaco- technical factors

- Disintegration time (tablets / capsules)
- Dissolution time
- Manufacturing variables
- Pharmaceutical ingredients (excipients / adjutants)
- Nature and type of dosage form
- Product age and storage conditions

Patient –related factors :

- Age
- Gastric emptying time
- Intestinal transit time
- Gastrointestinal pH
- Disease states
- Blood flow through the GIT
- Gastrointestinal contents: (a) Other drugs (b) Food (c) Fluids (d) Other normal GI contents
- Pre-systemic metabolism by (a) Luminal enzymes (b) Gut wall enzymes (c) Bacterial enzymes (d) Hepatic enzymes

Drug solubility and dissolution rate: Orally administered solid dosage formare first disintegrated or deaggregated, then the solid particles are dissolved drugs in solution then permeate across biomembrane to be absorbed in the body.



- Their are two critical processes in which the absorption of orallyadministered drugs are:
  1. Rate of dissolution,
  2. Rate of drug permeation through the biomembrane ..
- **Dissolution : is a process in which a solid substance solubilises in agiven solvent**

➢ Their are several theories to explain drug dissolution they are following

- **Diffusion layer model**
- **Danckwert^ model**
- **Interfacial barrier model**

- **Diffusion layer model :it involves two steps**

(1) Solution of the solid to form stagament film or diffusion layer which is saturated with the drug

(2)Diffusion of the soluble solute form the stagment layer to the bulk of the solution this is rate determine step in drug dissolution

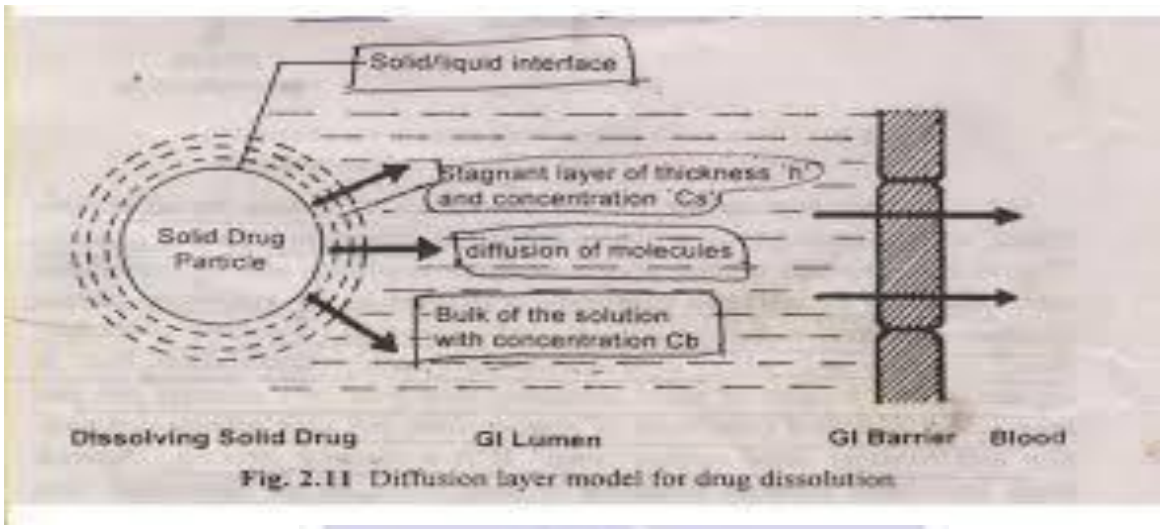


Fig. 2.11 Diffusion layer model for drug dissolution

The rate of dissolution is given by Noyes –Whitney s

$$Dc/dt=(Cs-Cb) \qquad (1)$$

Where

, dc/dt= dissolution rate of drugK= dissolution constant

Cs=Concentration of drug in stamgent layer

Cb= Concentration of drug in the bulk of the soln at time t

Equation (1) was based on ficks second law of diffusion Nernst and brinier incorporated ficks First law of diffusion and modified the Noyes-Whitney

Noyes-Whitney's equation of dissolution:

$$\frac{dc}{dt} = \frac{DAK_{w/o}(C_s - C_b)}{vh}$$

where, D = diffusion coefficient or diffusivity of the drug molecule

A = surface area of the dissolving solid exposed to the dissolution medium

Ko/w = water/oil partition coefficient of the drug

V= volume of dissolution medium

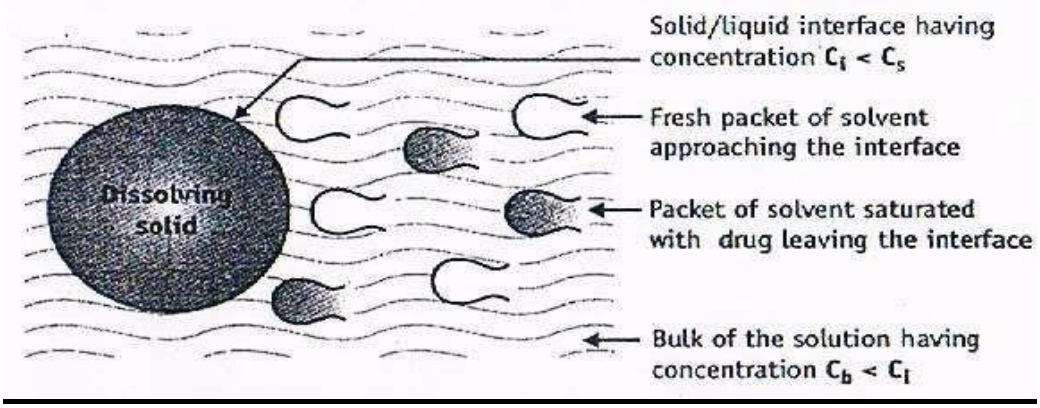
h= thickness of the stagnant layer

Cs – CB = concentration gradient of the diffusing drug molecule

- This equation repent first order dissolution

Danckwert's model

- Danckwert takes into account the eddies or packets that are present in the agitated fluid which reach the solid-liquid interface, absorb the solute by diffusion and carry it into the bulk of solution.
- These packets get continuously replaced by new ones and expose to new solid surface each time, thus the theory is called as surface renewal theory.



Danckwert's model is expressed by equation:

$$V.\ dC/dt = dm/dt = A\ (C_s - C_b).\ \sqrt{(\gamma.D)} \qquad (4)$$

where,

m =mass of solid dissolved
γ=rate of surface renewal

Interfacial barrier model

- According to the interfacial barrier model, an intermediate concentration can exist at the interface as a result of solvation mechanism and is a function of solubility rather than diffusion.
- When considering the dissolution of a crystal, each face of crystal will have a different interfacial barrier.

Interfacial barrier model is expressed by equation

$$G = K_i (C_s - C_b) \ldots\ldots\ldots (5)$$

where,

G=dissolution rate per unit area

K_i =effective interfacial transport constant

Particle size and effective surface area of the drug particles.

From Noyes-Whitney's equation of dissolution:

where, D = diffusion coefficient or diffusivity of the drug molecule

A = surface area of the dissolving solid exposed to the dissolution medium

KO/W= water/oil partition coefficient of the drug

V = volume of dissolution medium

h = thickness of the stagnant layer

$C_S - C_B$ = concentration gradient of the diffusing drug molecule.

- From this equation it can be concluded that the greater the surface area, A, faster the distribution.
- When the particle size of a certain mass of a drug is reduced the surface area is increased, hence, if particle size is reduced dissolution rate increases.

Two types of surface area can be defined:

- Absolute surface area: Which is the total area of solid surface of any particle
- Effective surface area: Which is the area of solid surface exposed to the dissolution medium.

e.g. Micronization of poorly water soluble drugs like griseofulvin, chloramphenicol and several salts of tetracycline results in superior dissolution rates.

- Size reduction has some limitation. In case of hydrophobic drugs like aspirin, phenacetin and phenobarbital micronization actually results in a decrease in effective surface area due to the following reasons.

(i) The hydrophobic surface of the drugs absorb air onto their surface which inhibit their wett ability, such powders float on the dissolution medium.

(ii) The particle reaggregate to form larger particles due to their high surface free energy.

Extreme particle size reduction may impart surface charges that may prevent wetting; moreover electrically induced agglomeration may prevent intimate contact of the drug with the dissolution medium

Polymorphism and amorphism

Depending on the internal structure, a solid can exist either in a crystalline or amorphous form.

- When, a substance exists in more than one crystalline form, the different forms are designated as polymorphs and the phenomenon as polymorphism.

Various polymorphs can be prepared by crystallizing the drug from different solvents under diverse conditions.

- Depending on their relative stability, one of the several polymorphic forms will be physically more stable than the others. Such a stable polymorph represents the lowest energy state, has highest melting point and least aqueous solubility.
- The remaining polymorphs are called metastable forms which represents higher energy state, the metastable forms have a thermodynamic tendency to convert to the stable form.
- A metastable form cannot be called unstable because if it is kept dry, it will remain stable for years.

- So the metastable forms have higher aqueous solubility and hence higher bioavailability than the stable polymorphs.

  e.g. Chloramphenicol palmitate has three polymorphs A, B and C. The B -form shows best bioavailability and A form is virtually inactive biologically.

  e.g. Polymorphic form-III of riboflavin is 20 times more water soluble than the form-I.

  - Due to aging of dosage forms containing metastable forms of the drug results in the formation of less soluble, stable polymorph.

Salt form of the drug

Most drugs are either weak acids or weak bases. One of the easiest approach to enhance the solubility and dissolution rate of such drugs is to convert them into their salt forms.

- Weak acid HA is more soluble in basic pH and weak base B is more soluble in acidic pH by the formation of salt.
- Some time *in-situ* salt formation can be utilized, e.g. certain drugs like aspirin and penicillin are prepared as buffered alkaline tablets.
- When the tablets are put into water the pH of the microenvironment of the drug is increased which promotes the dissolution rate.
- Buffered aspirin tablets have two advantages

(i) the gastric irritation and ulcerogenic tendency of the drug is greatly reduced

(ii) In dry form the hydrolytic stability is better.

pKa of the drug and pH

Drug pKa and lipophilicity and GI pH (pH partition theory)

The pH partition theory (Brodie et.al.) states that for drug compounds of molecular weight greater than 100, which are primarily transported across the biomembrane by passive diffusion.

- The process of absorption is governed by
  - ✓ dissociation constant (Ka) of the drug
  - ✓ lipid solubility of the unionized drug (Ko/w)
  - ✓ the pH at the absorption site

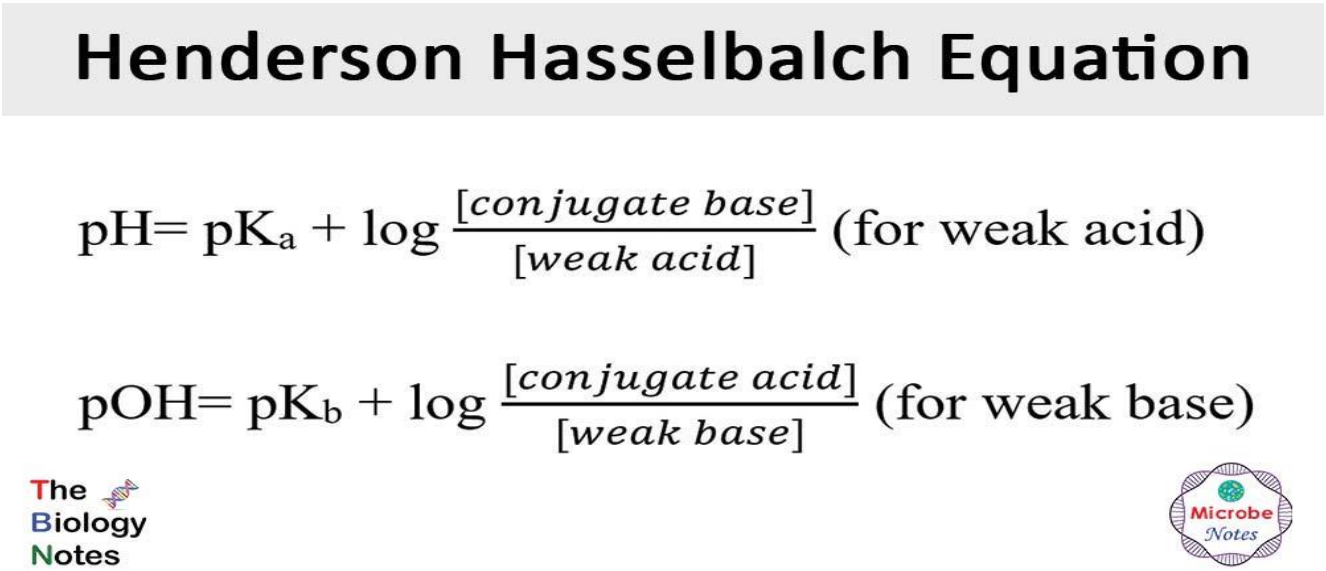
The above statement of the hypothesis was based on the assumptions that:

- ❖ The GIT is simple lipoidal barrier to the transport of drug.
- ❖ Larger the fraction of unionized drug, faster the absorption.
- ❖ Greater the lipophilicity (Ko/w) of the unionized drug, better the absorption.

Handerson-Hasselbach equation

The amount of drug that exists in unionized form is a function of dissociation constant (pKa) of the drug and pH of the fluid at the absorption site.

Handerson-Hasselbach equation:



Drugs	pKa	pH at the site of absorption
Very weak bases Theophyline Caffeine Oxazepam Diazepam	(pKa < 5.0) 0.7 0.8 1.7 3.7	Unionized at all pH values: absorbedalong the entire length of GIT.
Moderately weak bases Reserpine Heroin Codeine Amitriptyline	(5 < pKa < 11) 6.6 7.8 8.2 9.4	Ionized at gastric pH, relatively unionized at intestinal pH better absorbed from intestine.
Stronger base Mecamylamine Guanethidine	(pKa > 11.0) 11.2 11.7	Ionized at all pH values: poorly absorbed form GIT.

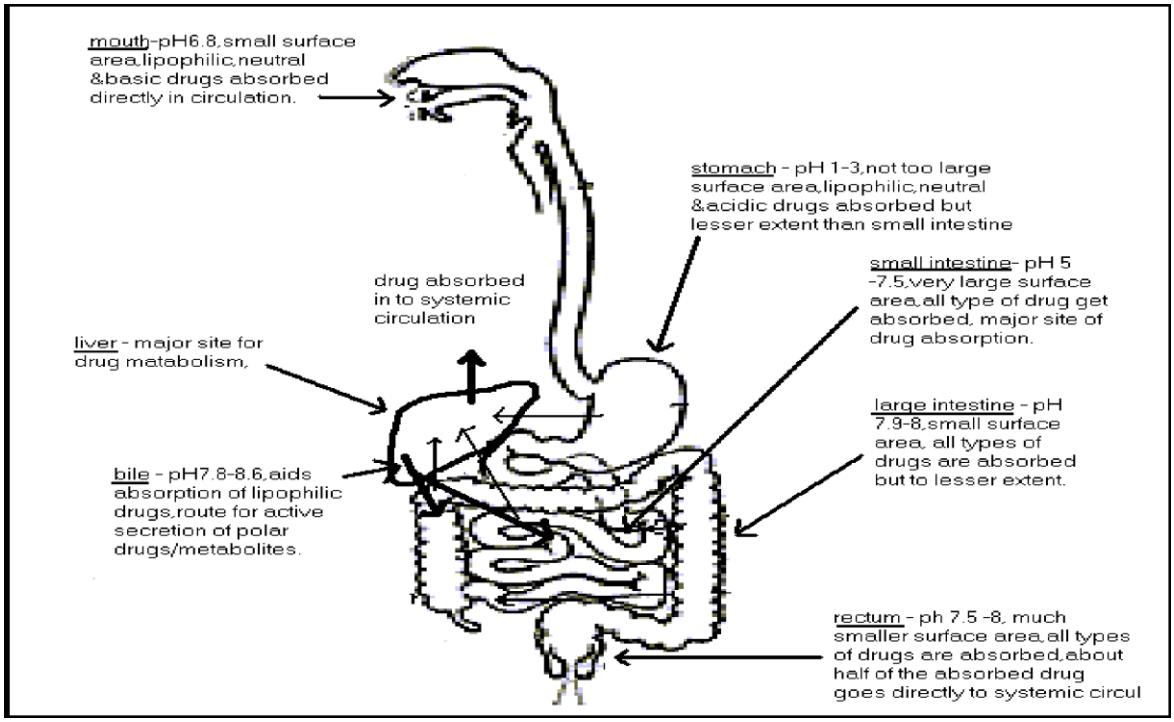
- It is the pKa of the drug that determines the degree of ionization at a particular pH and that only the unionized drug, if sufficiently lipid soluble, is absorbed into the systemic circulation.
- Ideally, for optimum absorption, a drug should have sufficient aqueous solubility to dissolve in the fluids at the absorption site and lipid solubility ($K_{o/w}$) in the lipoidal biomembrane and into the systemic circulation.
- In other words, a perfect hydrophilic-lipophilic balance (HLB) should be there in the structure of the drug for optimum bioavailability.

Patient related factors:

- Gastric emptying: apart from the dissolution of drug and its permeation through the bio membrane,the passage from stomach to small intestine, called as *gastric emptying*,can also be a rate limiting step in absorption because the major site of drug absorption is intestine.

It is advisable where:

- ✓ Rapid onset of drug is desired eg:sedatives
- ✓ Drug not stable in gastric fluids eg:pencillin G
- ✓ Dissolution occuring in intestine eg:enteric coated forms



- **Gastrointestinal pH**

Gastric emptying is retarded at low stomach pH and is promoted at alkaline highe alkile p

- **Electrolyte and osmotic pressure**

Water, isotonic, and solutions of low salt concentration empty the stomach rapidly whereas higher electrolyte concentration decreases gastric emptying rate.

Body posture

Gastric emptying is favoured while standing and while lying on the right side; while lying on the left side or insupine position retards it.

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Disease states

Diseases like gastroenteritis, gastric ulcer, pyloric stenosis, diabetes and hypothyroidism retard gastricemptying.

. Effect of GI pH on drug absorption

GI fluid pH influence drug absorption in several ways:

Disintegration

- ✓ The disintegration of some dosage forms is pH sensitive. With enteric coated formulations, the coat dissolvesonly in the intestinal pH, followed by disintegration of the tablet.

Dissolution

- ✓ A large number of drugs are either weakly acidic or weakly basic whose solubility is greatly affected by pH. A pH that favours the formation of salt of the drug enhances the dissolution rate.
- ✓ e.g. Weakly acidic drugs dissolve rapidly in the alkaline pH of the intestine whereas basic drugs dissolves in the acidic pH of the stomach.

Absorption

- ✓ Depending upon the pKa of the drug and the pH of the GI fluid some amount of the drug remain in ionized state and some in unionized state. The unionized form will be absorbed through GIT quickly than the ionized form.

Stability

- ✓ GI pH influences the chemical stability of drugs.
- ✓ e.g. The acidic stomach pH is known to affect degradation of Penicillin-G and erythromycin.