Biopharmaceutics

Manas Bhowmik

Introduction to Biopharmaceutics

- What is Biopharmaceutics?

  Study of factors influencing the rate and extent of drug that reaches to the systemic circulation and the use of this information to optimize the therapeutic efficacy of drug products.

Introduction to Biopharmaceutics

- What is absorption?

  The process of movement of drug from its site of administration to the systemic circulation.

Introduction to Biopharmaceutics

- What is Bioavailability?

  The rate and extent of drug absorption.

Introduction to Biopharmaceutics

- What is drug disposition?

  The processes other than absorption that play a role in the therapeutic activity of a drug.

  It includes distribution and elimination.

Introduction to Biopharmaceutics

- What is drug distribution?

  The process of movement of drug between one compartment to other.

  The compartment includes blood and extravascular tissues.

Introduction to Biopharmaceutics

- What is elimination?

  The process of removal of drug from the body and termination of its action.

  It includes biotransformation (metabolism) and excretion.

Introduction to Biopharmaceutics

- What is biotransformation (metabolism)?

  The process of chemical conversation of drug which usually inactivates the drug.

Introduction to Biopharmaceutics

- What is excretion?

  The process of removal of drug and metabolites from the body.

Introduction to Biopharmaceutics

- What is pharmacokinetics?

  The study of rate of drug absorption, distribution, metabolism and excretion and their relationship with therapeutic and toxic effects of drug.

  Kinetics of ADME.

Introduction to Biopharmaceutics

- What is clinical pharmacokinetics?

  The Brach of pharmacokinetic that involves in optimization of dose that suit individual patient needs for achieving maximum therapeutic utility.

Absorption

The process of movement of unchanged drug from the site of administration to systemic circulation is drug absorption. This definition emphasized on first pass metabolism.

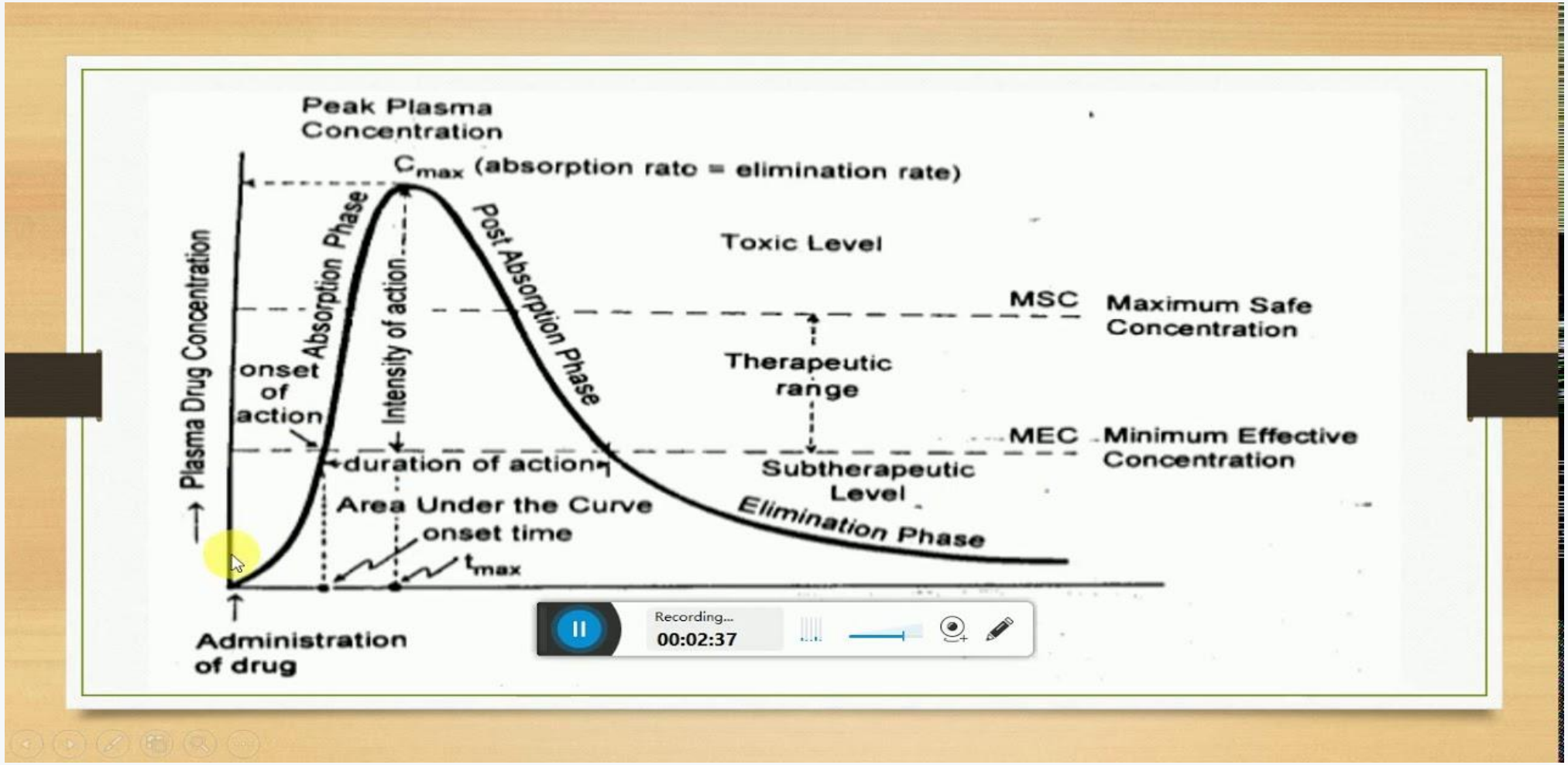
Effectiveness of a drug can be assessed by its concentration at the site of action.

It is difficult to measure the concentration at the site of action.

Plasma drug concentration can be measured easily.

Relationship exist between plasma drug concentration and therapeutic responses.

Absorption


Peak Plasma Concentration
C_{max} (absorption rate = elimination rate)
Toxic Level
MSC
Maximum Safe Concentration
Therapeutic range
MEC
Minimum Effective Concentration
Subtherapeutic Level
Plasma Drug Concentration
Absorption Phase
Post Absorption Phase
Intensity of action
onset of action
duration of action
Area Under the Curve
onset time
t_{max}
Elimination Phase
Administration of drug
Recording...
00:02:37

Mechanism of drug absorption

- Trans-cellular or intracellular transport
- Para-cellular or intercellular transport
- Vesicular or corpuscular transport or endocytosis

Trans-cellular or intracellular transport

The process of passage of drug through the GI epithelium.

Steps:

- Permeation of GI epithelium cell membrane (lipid barrier)
- Movement across the intracellular space (cytosol)
- Permeation of lateral or basolateral membrane

Trans-cellular or intracellular transport

The various Trans-cellular process:

- Passive transport (Do not require energy other than molecular motion)

  1. Passive diffusion 2. Pore transport 3. Ion-pair transport 4. Facilitated or mediated diffusion

- Active transport (Require energy)

  1. Primary active transport 2. Secondary active transport

- Secondary active transport

  i. Symport (Co-transport)

  ii. Antiport (Counter-transport)

Para-cellular or intercellular transport

The process of transportation of drug through the cellular junction between GI epithelium.

This route of transport is less important.

The various paracellular process:

- Permeation through the tight junctions of epithelium cells (openings are involved, insulin, cardiac glycosides)
- Persorption (Permeation of drug through temporary openings made by shedding of two epithelium cells into lumen)

Vesicular or corpuscular transport or endocytosis

It is energy dependent active transport but transport involves formation of vesicles into the cell. In this process drug does not go to solution for absorption. Fats, starch, vit-A, D, E, K, B12 and insulin are absorbed by this process.

The various process:

- Pinocytosis (cell drinking) (Oral polio vaccine, large protein molecule, botulism toxin)
- Phagocytosis (cell eating)

Transportation of Endocytic vesicle from one extracellular compartment to another is called transcytosis.

Passive diffusion

It is also known as non-ionic diffusion. It is the major process of drug absorption (90%). The driving force is concentration or electrochemical gradient.

Concentration or electrochemical gradient is the difference between concentration on either side of the membrane.

Fick's first law of diffusion: The drug molecules diffuse from a region of higher concentration to one of lower concentration until an equilibrium is attained and the rate of diffusion is directly proportional to the concentration gradient across the membrane.

Passive diffusion

Fick's first law of diffusion: $\frac{dQ}{dt} = \frac{A\ D\ K\ (Cgit - Cp)}{h}$

A= Surface area of absorbing membrane

D= Diffusion coefficient

K= Partition coefficient

$(Cgit - Cp)$ = Concentration gradient

h= Thickness of the membrane

Passive diffusion

$$\frac{dQ}{dt} = \frac{A\ D\ K\ (Cgit - Cp)}{h}$$

1. Downhill process

2. Process is energy independent and non-saturable

When D, A, K and h are constant and due to sink condition plasma drug concentration become negligible and $\frac{dQ}{dt} = PCgit$

P is permeability. It is the process of diffusion or permeation of drug through a membrane.

It is a first order process.

Pore Transport

It is also known as convective transport, bulk flow or filtration.

Drug molecules transported through protein channels of the cell membrane.

Driving force is hydrostatic pressure or osmotic pressure across the membrane.

Bulk flow of water along with small solid molecules occurs through the channels.

Water flux that promotes such transport is called solvent drag.

Characteristics of drug:

- Molecular weight <100 Da (linear compounds up to 400 Da)
- Molecular size less than pore diameter
- Water soluble (urea, sugars, water)

This process is associated with renal excretion, removal from CSF, drug entry into the liver.

Ion-pair Transport

It is associated with the drugs which ionize under all pH.

Drug forms reversible neutral complex with endogenous ions like mucin.

This neutral complex has both hydrophilicity and hydrophobicity for passive diffusion.

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

Quaternary ammonium compounds and sulphonic acid also forms ion-pair.

Carrier Mediated Transport

Carriers are transport proteins, enzymes or other component present in cell membrane.

Carriers must dissolved in the lipid bilayer of the membrane.

Carriers can bind reversibly or non-covalently with soluble drug to be transported.

The carrier-drug complex transverses across the membrane, dissociates and release the drug.

Carriers then returns to the original site and again forms new complex.

Characteristics of Carrier Mediated Transport

Carrier has an uncharged non-polar surface for being dissolved in the lipid bilayer of the membrane.

Carriers have no directionality, they work efficiently in both the direction.

Carriers have special affinity for essential nutrients for special chemical structure.

Transport process is structure specific.

Drug molecules having similar structure with essential nutrients binds to carriers as false nutrients (anticancer drugs like 5-flurouracil and 5-bromouracil).

Number of carriers is limited, the transport is subject to competition between agents having similar structure.

Characteristics of Carrier Mediated Transport

Number of carriers is limited, the transport is concentration dependent until the saturation of carriers. Initially it is first order kinetic.

After saturation the transport is concentration independent and follow zero order kinetic.

This capacity limited process is described by mixed-order kinetics, Michaelis-Menten equation or non-linear kinetics.

Bioavailability of such process decreases with increase concentration (Vit B1, B2, B12)

Carrier mediated absorption is occurs from specific site of the intestinal tract where carrier system is most dense is called absorption window.

Drug absorbed through this site is a poor candidate for controlled release formulations.

Carrier Mediated Transport

Types of Carrier Mediated Transport

1. Facilitate Diffusion: It is a carrier mediated transport and faster than simple passive diffusion. Here driving force is concentration gradient (Downhill process). No energy is required. In poisoning situation where energy production is hampered this process can operate. An intrinsic factor which is a glycoprotein forms a complex with drug and then associated with carrier.

Carrier Mediated Transport

Types of Carrier Mediated Transport

2. Active transport: It is a carrier mediated transport and energy is required in the form of ATP.

a) Primary active transport: Direct ATP is required. It transport one ion or molecule in one direction, called as uniporter (glucose). Carrier proteins involved are:

i) Ion transporters: It transport ions in or out of cells (proton pump) are:

(a) Organic anion transporter (Pravastatin, atorvastati)

(b) Organic cation transporter (diphenhydramine)

Carrier Mediated Transport

b) ABC (ATP-Binding Cassette) Transporters: Responsible for transporting small molecular drugs and toxins out of cells (exsorption). It is known as efflux pump.

Ex. P-glycoprotein is responsible for pumping hydrophobic drugs like anticancer drugs out of cells and develop drug resistance. P-glycoprotein is known as multi drug resistance protein.

ABC Transporters are present in brain capillaries.

Carrier Mediated Transport

b) Secondary active transport: Direct ATP is not required. Energy is required in transporting an ion that facilitate the transport of other ions or molecules (co-transpot) either same or opposite direction.

The process are:

(a) Symport (Co-transport): Transport occurs in same direction. Na+-glucose syporter uses potential energy of Na+ concentration gradient to transport glucose in the same direction. H+-coupled peptide transporter for beta lactam antibiotics.

(b) Antiport (Counter-transport): Transport occurs in opposite direction. H+ expulsion with Na+ concentration gradient in kidney.

Active Transport

Characters:

1. Drug is transported against the concentration gradient, Uphill process.

2. Process is faster than passive diffusion.

3. Energy is required.

4. Metabolic poisons can inhibit the process by interfering with energy production.

5. Na+, K+, Ca++, Iron, glucose, amino acids, vit-C, niacin, pyridoxine are absorbed by active transport.

Methyldopa and levodopa absorption occurs via L-amino acid transport system and absorption is impaired by simultaneous ingestion of high protein meal.

Combined absorption mechanism

A drug may be absorbed by more than one mechanism.

Cardiac glycosides are absorbed by both passive diffusion and active transport.

Vitamin B12 is absorbed by both passive diffusion, facilitated diffusion and endocytosis.

Phases of drug absorption

1. Pre-uptake phase

i) Dissolution of drug in the GI tract

ii) Metabolism of drug in the GI tract by digestive enzyme or bacterial enzyme in the colon

2. Uptake phase

i) Delivery of drug to the absorption site

ii) Metabolism of drug by enzyme in the GI epithelium

iii) Passage of drug through the GI epithelium

3. Post uptake phase

i) Metabolism of drug by the liver (first pass metabolism)

ii) Entero-hepatic circulation of drug (From liver drug may excreted in the bile, re-enter into the GIT via gall bladder and gets reabsorbed into the blod)

iii) Transfer the drug into the systemic circulation

Routes of drug absorption (GIT to blood)

1. Splanchnic circulation

i) It is the network of blood vessels that supply the GIT

ii) Major route of absorption into the systemic circulation

iii) Drug undergo first pass metabolism

iv) Drug absorption from stomach, small and large intestine into the systemic circulation via splanchnic circulation

2. Lymphatic circulation (fat, fat soluble vitamins, lipophilic drugs are absorbed)

i) It is less accessible than capillaries

ii) The lymph flow is slow

iii) Avoid first pass metabolism

iv) High molecular weight compound (above 16000) can be absorbed

v) Targeted delivery of drug to lymphatic system in case of cancer is possible

Factors affecting drug absorption

The rate at which drug reaches to the systemic circulation is determined by the slowest step involved in the rate process is known as **rate limiting or rate determining step**.

1. Pharmaceutical Factors

i) Physicochemical properties of drug

ii) Dosage form characteristics

2. Patient related factors

Factors affecting drug absorption: Pharmaceutical Factors

Physicochemical properties of drug:

1. Drug solubility and dissolution rate

Dissolution is the rate determining step for hydrophobic, poorly water soluble drugs (griseofulvin, spironolactone).

Permeation is the rate determining step for hydrophilic, water soluble drugs (neomycin).

Correlation between therapeutic dose and desired solubility

Dose (mg/kg)	Desired solubility (mg/ml) for drug with		
	High permeability (10 times of dose)	Medium permeability (50 times of dose)	Low permeability (210 times of dose)
0.1	1	5	21
1	10	52	207
10	100	520	2100

Factors affecting drug absorption: Drug solubility and dissolution rate

Maximum absorbable dose (MAD)=$K_a S_{GI} V_{GI} t_r$

K_a is intrinsic absorption rate constant

S_{GI} is the solubility of the drug in GI fluid

V_{GI} is the volume of GI fluid

t_r is the residential time of drug in GI

Solubility is the ability of a solid, liquid, or gaseous chemical substance to dissolve in solvent and form a solution.

Intrinsic or absolute solubility is defined as the maximum amount of solute dissolved in a given solvent under standard condition of temperature, pressure and pH.

BCS Classification

Type-III (L-P/H-S)	Type-I (H-P/H-S)
Type-IV (L-P/L-S)	Type-II (H-P/L-S)

Theories of Dissolution

Dissolution is a process in which a solid substance solubilizes in a given solvent.

1. Diffusion layer model or film theory:

i) Non-reactive or non-chemical process

ii) Rapid formation of saturated diffusion or stagnant layer at the solid-liquid interface

iii) Slow diffusion of soluble solute from the stagnant layer to bulk. This is the rate limiting stem.

Rate of dissolution is expressed by Noyes-Whitney equation:

$\frac{dC}{dt}$ =K $(C_s - C_b)$, it is based o Fick's second law of diffusion states the rate of change of concentration in a region is proportional to the curvature of the concentration.

Nernst and Bruner incorporate the Fick's first law of diffusion and modified the Noyes-Whitney's equation to $\frac{dC}{dt} = \frac{\text{D A K } (C_s - C_b)}{Vh}$

Theories of Dissolution

$$\frac{dC}{dt} = \frac{\mathrm{D\ A\ K}\,(C_s - C_b)}{Vh}$$

It is represented by first-order kinetic. This is under non-sink condition in in-vitro dissolution where drug concentration in the bulk may interfere further dissolution.

In in-vivo condition C_b become zero and C_s>>C_b and sink condition is maintained. In this situation if volume and surface area of solid are kept constant than $\frac{dC}{dt} = \mathrm{K}'$, zero order kinetic.

In in-vitro study C_b is always less than 10% of C_s

Noyes-Whitney's equation assume that the surface area remain constant for dissolving solids which is impractical and Hixson and Crowell's cube root law is used $W_0^{\frac{1}{3}} - W^{\frac{1}{3}} = Kt$

W_0 - original mass of drug, W- mass of drug remaining to be dissolved

Theories of Dissolution

2. Danckwert's model (Penetration or Surface renewal theory):

i) No existence of stagnant layer

ii) Turbulence exists at the solid-liquid interface

iii) Mass of eddies or packets are formed and reaches to the solid-liquid interface in a random fashion

iv) Absorb solute by diffusion and carry it to the bulk

v) Solute containing pockets are replaced by fresh pockets and exposed to new surface

$$v\frac{dC}{dt} = \frac{dm}{dt} = A(C_s - C_b)\sqrt{\gamma D}$$

m is the mass of solid dissolve, D is the solid diameter, γ *is the solid* $-$ *liquid surface tension*

Theories of Dissolution

3. Interfacial barrier model (Double barrier or Limited solvation theory):

i) Intermediate concentration can exist at the interface due to solvation mechanism due to solubility

ii) Each face of a crystal will have a different interfacial barrier

$$\mathrm{G} = \mathrm{k}\,(C_s - C_b)$$

G is the dissolution rate per unit area, k is the effective interfacial transport constant.

This theory may be extended to film theory and Surface renewal theory

Particle size and effective surface area

Absolute surface area: Total area of solid surface.

Effective surface area: Area of solid surface exposed to the dissolution medium.

Effective surface area is proportional to the rate of dissolution.

Size reduction of particles <0.1µm increases solubility for non-hydrophobic drugs (griseofulvin, chloramphenicol, tetracycline). Dose of griseofulvin may reduce to half and for spironolactone it is 20 times.

For hydrophobic drugs like aspirin, phenacetin, pentobarbital, effective surface area is reduced after micronization.

Hydrophobic surface absorb air and inhibit wettability.

Particles re-aggregate to larger particle due to high surface free energy (at long distance it is attractive).

Electrically induced agglomeration.

Particle size and effective surface area

The absolute surface area of hydrophobic drugs can be converted to the effective surface area by addition of surfactant to reduce interfacial tension and displacement of air (Polysorobate 80) and addition of hydrophilic diluents (PEG, PVP, dextrose).

Particle size reduction is not recommended when-

1. Drugs are unstable (Penicillin-G, erythromycin)
2. Drug produce undesirable effects (gastric irritation caused by nitrofuratoin)
3. Sustained effect

Polymorphism

Different powder has different habits and internal structure.

Habit is the description of outer appearance and internal structure is the arrangement of the molecules within the solid.

Depending on these properties the shape of different crystals are different. Physical form is directly related to the solubility of any compound.

Polymorphism

Polymorphism is the ability of any compound to crystallize as more than one crystalline form with different physicochemical properties. Generally solubility and stability are different.

All the powders under microscope with cross polarized light are either isotropic or anisotropic.

Isotropic are amorphous having single refractive index and do not transmit light and looks like black.

Anisotropic are crystalline having more than one refractive indices and looks like bright and brilliant colour.

Types of Polymorphs

1. Enantiotropic are crystals that reversibly changed into other form as a function of temperature or pressure. Here one polymorph is stable over a temperature range and pressure but other is stable in other condition.

2. Monotropic are irreversibly changed crystals that are unstable at any temperature and pressure. Here only one stable form is existing at all temperature below melting point.

Polymorph having less free energy below solid melting point is stable and less soluble.

Whereas higher free energy with more soluble crystals are in metastable form, they irreversibly change to another stable form.

At transition temperature the two forms has identical free energy and solubility in different solvent at any vapor pressure.

Polymorphs

Metastable forms have greater solubility than stable forms. Chloramphenicol palmitate can exists as A, B and C form and B is the metastable form having greater solubility and bioavailability.

Polymorphic form of riboflavin (III) is 20 times more soluble than I.

Transformation of metastable to a stable form may be inhibited by dehydrating the molecular environment and by adding viscosity building agents that absorb at the surface of the crystals (PVP, CMC, Pectin, gelatin).

40% of organic compounds can exist as polymorphic forms.

70% of barbiturates can exist as polymorphic forms.

65% of sulphonamides can exist as polymorphic forms.

Barbital, Methyl parabe, Sulphapyridine can exist as 6 polymorphic forms.

Cortisone acetate can exist as 8 polymorphic forms.

Pseudo-polymorphism

The crystalline forms of a drug can either be a polymorph or a molecular adduct (is a product of a direct addition of two or more distinct molecules, resulting in a single reaction product containing all atoms of all components) or both.

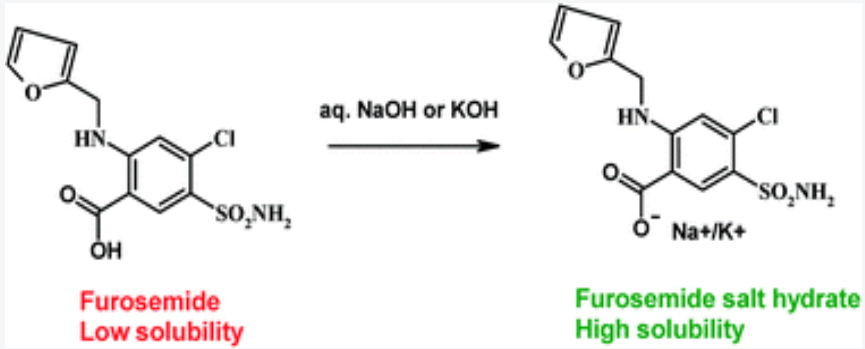
The stoichiometric(is a branch of chemistry that deals with the relative quantities of reactants and products in chemical reactions) type of adducts where the solvent molecules are incorporated in the crystal lattice of solid are called as the solvates.

The solvates can exist in different crystalline forms called pseudo-polymorphs.

When the solvent is water, the solvate is known as hydrate. Hydrates are most common solvate forms of drugs. Generally anhydrous form of drug has greater solubility than hydrates, e.g., theophylline, ampicillin. Organic solvates has greater solubility than amorphous form, e.g., chloroform solvate of griseofulvin, n-pentanol solvate of fludrocortisone. Amorphous form of a drug shows greater solubility than crystalline forms. Amorphous novobiocin is 10 times more soluble than crystalline forms.

Salt form of the drug

- ❖ Most drugs are weakly acidic or basic in nature
- ❖ An easy approach for solubility enhancement is to convert them to their salt form
- ❖ For weakly acidic drugs, a strong base salt is prepared (sodium or potassium salts)
- ❖ For weakly basic drugs, a strong acid salt is prepared (hydrochloride or sulfate salts)
- ❖ The influence of salt formation on drug solubility, rate of dissolution and absorption can be explained by considering the pH of the diffusion layer and not the pH of bulk solution



Contd.

- *For salts of weak acids,* $[H^+]_d < [H^+]_b$
- *For salts of weak bases,* $[H^+]_d > [H^+]_b$

Where, $[H^+]_d$ = hydrogen ion concentration of diffusion layer

$[H^+]_b$ = hydrogen ion concentration of bulk of the solution

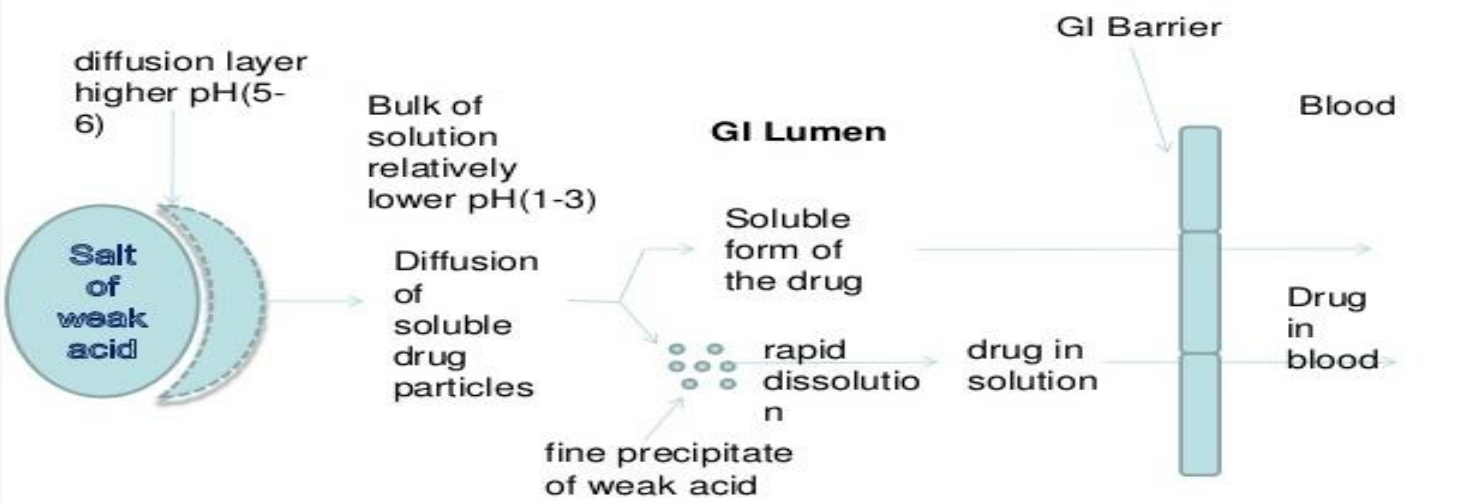


Fig: Dissolution and absorption of an acidic drug administered in a salt form

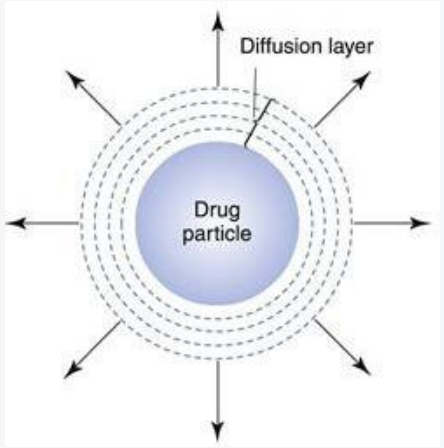
Contd.

❖ Another reason for enhanced solubility of salts of weakly acidic drugs, is the precipitation of the drugs as very fine particles

❖ When, the soluble drug diffuses through the stagnant diffusion layer into bulk solution of low pH, it is transformed into free acid form having lesser aqueous solubility and finally precipitate out as fine particles

❖ The *in situ* salt formation has been utilized to enhance the dissolution and absorption of drugs like aspirin and penicillin from buffered alkaline tablets

❖ The pH of microenvironment is increased by buffering agents to promote dissolution rate



Contd.

- ❖ The size of the counter ion can influence the solubility of salt form
- ❖ Smaller the size of counter ion greater the solubility of salt
- ❖ In some exceptional cases, a more soluble salt form shows poor bioavailability (sodium phenobarbital)
- ❖ Similar results are observed with hydrochloride salts of tetracycline analogs and papaverine demonstrating better dissolution and bioavailability with free bases due to suppression action of common ion effect

Dissociation constant

Henderson-Hasselbalch Equation:

For week acids, $\mathrm{pH} = \mathrm{pK_a} + \log \frac{[\mathrm{Ionizeddrug}]}{[\mathrm{Unionizeddrug}]}$

For week bases, $\mathrm{pH} = \mathrm{pK_a} + \log \frac{[\mathrm{Unionizeddrug}]}{[\mathrm{Ionizeddrug}]}$

$\%\ \text{drug ionization} = \frac{1}{1+e^{x(\mathrm{pH}-\mathrm{pKa})}} \times 100$ [x= -1 for acid & +1 for base]

Acidic drug: Ionization starts at pH below 2 of pKa and 100% at pH above 2 of pKa

Basic drug: Ionization starts at pH above 2 of pKa and 100% at pH below 2 of pKa

pH Partition Hypothesis

❖ The pH partition theory explains the process of drug absorption from GIT and its distribution across all biological membrane

❖ *The theory states that 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-*

a) The dissociation constant of the drug

b) The lipid solubility of unionized drug (a function of drug Ko/w)

c) pH at the site of absorption

Drug pKa & GI pH

❖ The fraction of drug in solution that exist in the unionized form is a function of both dissociation constant of the drug and the pH of the solution.

❖ The dissociation constant is often expressed for both acids and bases as pKa (the basic logarithm of the acidic dissociation constant).

❖ It is customary to express the dissociation constants of both acidic and basic drugs by pKa values.

❖ The lower the pKa of an acidic drug, the stronger the acid i.e., greater the proportion of ionized form at a particular pH. The higher the pKa of a basic drug, the stronger the base.

Contd.

❖ Thus from the knowledge of pKa of the drug and pH at the absorption site (or biological fluid), the relative amount of ionized and unionized drug in solution at a particular pH and the percent of drug in solution at this pH can be determined by Henderson-Hasselbach equation,

❖ *For an acid: pH = pKa + log(ionized drug concentration/ unionized drug concentration)*

❖ *For a base: pH= pKa + log(unionized drug concentration / ionized drug concentration)*

❖ If the concentration of ionized & unionized drug becomes equal, the above two equation becomes pH = pKa (since log 1 = 0)

❖ pKa is considered as a characteristics of drug

Contd.

❖ A barrier that separates the aqueous solutions of different pH such as GIT and plasma then the theoretical ratio R of drug concentration on either side of the membrane can be given by the equation,

❖ For weak acids: $Ra=C_{GIT}/C_{Plasma} = 1+10^{pHGIT-pKa}/1+10^{pH\ plasma-pKa}$

❖ For weak bases: $Rb=C_{GIT}/C_{Plasma} = 1+10^{pka-pHGIT}/1+10^{pka-pH\ plasma}$

❖ The pH range in GIT from 1-8, that of the stomach is from 1-3 and of the intestine (from duodenum to colon) 5-8, then certain generalization regarding ionization and absorption of drugs can be made, as predicted from pH partition hypothesis.

Contd.

❖ ***For weak acids:***

✓ Very weak acids (pKa > 8), are unionized at all pH, hence absorption is rapid and independent of GI pH (phenytoin, barbiturates etc.)

✓ Drugs having pKa between 2.5 to 7.5 are greatly affected by pH change, hence absorption is pH dependent (NSAIDS like aspirin, ibuprofen etc.)

✓ Stronger acids (pKa < 2.5), are ionized in entire pH range in GIT, hence remain poorly absorbed (cromolyn sodium)

Contd.

❖ ***For basic drugs:***

✓ Very weak bases (pKa < 5.0), are unionized at all pH, hence absorption is rapid and independent of GI pH (caffeine, theophylline, diazepam etc.)

✓ Drugs having pKa between 5 to 11.0 are greatly affected by pH change, hence absorption is pH dependent (Morphine analogs, chloroquine etc.)

✓ Stronger bases (pKa > 11), are ionized in entire pH range in GIT, hence remain poorly absorbed (guanethidine, mecamylaamine etc.)

Contd.

Influence of drug pKa and GI pH on drug absorption

Drugs	Site of absorption
Very weak acids (pKa > 8.0)	Unionized at all pH values Absorbed along entire length of GIT
Moderately weak acids (pKa 2.5 – 7.5)	Unionized in gastric pH Ionized in intestinal pH Better absorbed from stomach
Strong acids (pKa <2.5)	Ionized at all pH values Poorly absorbed from GIT
Very weak bases (pKa < 5)	Unionized at all pH values Absorbed along entire length of GIT
Moderately weak bases (pKa 5 – 11)	Ionized in gastric pH Unionized in intestinal pH Better absorbed from intestine
Strong bases (pKa >11)	Ionized at all pH values Poorly Absorbed from GIT

Contd.

Influence of drug pka and GI pH on drug absorption

Drugs	pka	pH/site of absorption
Very weak acids (pka>8)		
Phenobarbital Phenytoin	8.1 8.3	Unionized at all pH values
Moderately weak acids (pka 2.5-7.5)		
Aspirin Ibuprofen	3.5 4.4	Unionized at gastric pH, ionized at intestinal pH
Strong acids (pka<2.5)		
Di sodium cromoglycate	2.0	Ionized at all pH values

Lipophilicity and Drug Absorption

❖ pKa of a drug can determine the degree of ionization at certain pH, the unionized fraction of a lipid soluble drug can become bioavailable

❖ A low lipid soluble drug, eventually results poor absorption

❖ Ideally, a drug should have good aqueous solubility for solubilization with considerable lipid solubility for partitioning into lipoidal biomembrane

❖ A perfect **hydrophilic- lipophilic balance (HLB)** should be there for optimum bioavailability

❖ The lipid solubility of a drug is generally determined by oil/water partition coefficient (Ko/w) value

Limitation of pH- Partition Hypothesis

❖ The limitations of pH partition hypothesis are-

✓ Presence of virtual membrane pH

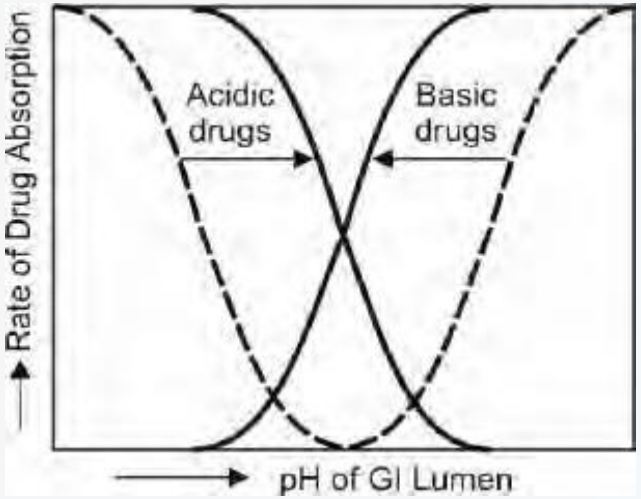
✓Absorption of ionised drug

✓Influence of GI surface area and residence time of drug

✓Presence of aqueous unstirred diffusion layer

Contd.

Presence of Virtual Membrane pH: The pH-partition hypothesis suggested that only the unionised drug at a given GI lumen pH is absorbed. An S-shaped curve, called as the pH-absorption curve denoting the dissociation of drug, is obtained when pH is plotted versus rate of drug absorption.



pH-absorption curve for acidic and basic drugs. Dotted lines indicate curves predicted by pH-partition hypothesis and bold lines indicate the practical curves.

➢ A virtual pH, also called as the microclimate pH, different from the luminal pH exists at the membrane surface which determines the extent of drug ionisation and thus, drug absorption

Contd.

Absorption of Ionised Drugs: An important assumption of the theory was that only unionised form of the drug is absorbed and permeation of the ionised drug is negligible since its rate of absorption is 3 to 4 times less.

This is called as *principle of non-ionic diffusion,* which is true to a large extent as ionised drugs have low lipid solubility and relatively poor permeability.

However, the pH-absorption curve shift suggested that ionised forms of some drugs also get absorbed to a considerable extent. If such drugs have a large lipophilic group in their structure, despite their ionisation, they will be absorbed passively—for example, morphinan derivatives.

Other mechanisms are also involved in the absorption of ionised drugs such as active transport, ion-pair transport and convective flow.

Contd.

Influence of GI Surface Area and Residence Time of Drug: According to the pH-partition theory, acidic drugs are best absorbed from stomach (acidic pH) and basic drugs from intestine (alkaline pH) where they are majorly unionised. This could be true under conditions where the surface area of stomach and intestine are same.

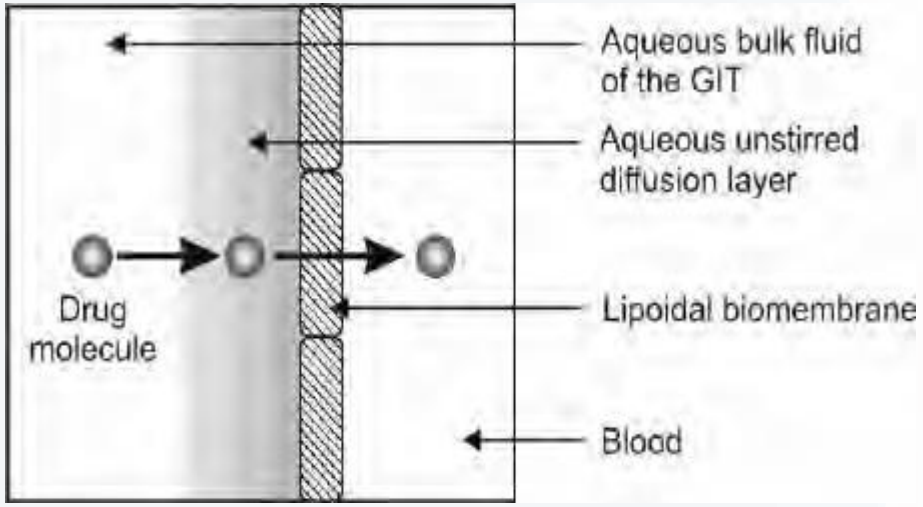
It suggests that once an acidic drug reaches intestine, the remaining fraction will be poorly absorbed and that unless a basic drug reaches the intestine and gets absorbed considerably, it may not be able to attain its therapeutic level.

But, irrespective of the GI pH and the degree of ionisation, both acidic and basic drugs are more rapidly absorbed from the intestine, primarily because of its large surface area and secondly, because of long residence time of the drug in the intestine.

Contd.

Presence of Virtual Membrane pH: The pH-shift in the absorption of acidic and basic drugs, accounts that the bulk of the luminal fluid is not in direct contact with the membrane but a barrier called as aqueous unstirred diffusion layer is interposed between them.

➢The layer has a real thickness and is a barrier to absorption of drugs. Drugs having large partition coefficient can rapidly penetrate the lipid membrane but diffusion through unstirred water layer is the rate-limiting step in their absorption.



Presence of aqueous unstirred diffusion layer on the membrane surface

Drug Permeability and Absorption

Most orally administered drugs enter the systemic circulation by passive diffusion and their absorption is expressed mathematically by equation –

$$M = P_{eff} A C_{app} t_{res}$$

Where, M = amount of drug absorbed

P_{eff} = effective membrane permeability

A = surface area available for absorption

C_{app} = apparent luminal drug concentration

t_{res} = residence time of drug in GI lumen.

Contd.

Since it is difficult to alter or control surface area and residence time of drug, promoting absorption depends on enhancing permeability of drug or drug concentration at absorption site.

The *three major drug characteristics that determine the passive* transport or permeability of drugs across intestinal epithelium are –

✓ Lipophilicity of drug expressed as log P

✓ Polarity of drug which is measured by the number of H-bond acceptors and number of H-bond donors on the drug molecule

✓ Molecular size

Drug Stability

✓ A drug for oral use may destabilize either during its shelf-life or in the GIT.

✓ Two major stability problems resulting in poor bioavailability of an orally administered drug are —

❖ degradation of the drug into inactive form, and

❖ interaction with one or more different component(s) either of the dosage form or those present in the GIT to form a complex that is poorly soluble or is unabsorbable.

Stereochemical Nature of Drug

- Chiral drugs constitute approximately 60% of the drugs in current use
- Chirality can have an impact on pharmacokinetic processes like absorption, distribution and elimination

- Enantiomers possess identical physical and chemical properties despite significant differences in spatial configuration
- Thus, biological processes which are passive in nature do not display selectively for one isomer over another
- However, biological processes such as protein binding which require interaction of a drug with a macromolecule may exhibit stereoselectivity.

- As majority of drugs are absorbed passively, they do not display stereoselectivity.
- Conversely, demonstration of stereoselective absorption would be strong evidence that a drug is absorbed by a carrier-mediated process.

DOSAGE FORM (PHARMACO-TECHNICAL) FACTORS

- Disintegration Time
- Dissolution time
- Manufacturing variables
- Pharmaceutical ingredients
- Nature and types of dosage forms
- Product age and storage condition

DOSAGE FORM (PHARMACO-TECHNICAL) FACTORS

❖ **Disintegration Time**

❖ **Manufacturing / Processing Variables**

The dosage form related factors that influence dissolution and hence absorption of a drug from such formulations are:

a) Excipients (formulation ingredients apart from the active principles), and

b) Manufacturing processes -

✓ Method of granulation &

✓ Compression force

Contd.

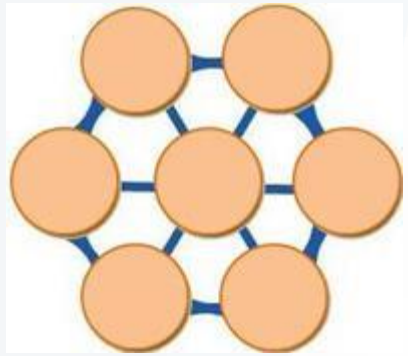
Method of Granulation: The wet granulation process is the most conventional technique in the manufacture of tablets and was once thought to yield tablets that dissolve faster than those made by other granulation methods.

The limitations of this method include—

(i) Formation of crystal bridge by the presence of liquid,

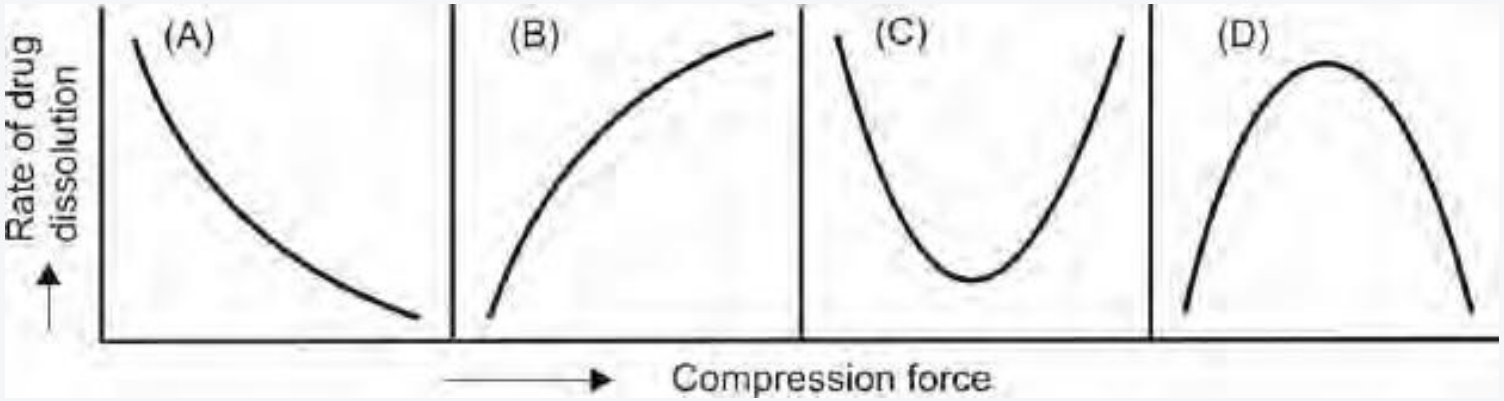
(ii) The liquid may act as a medium for affecting chemical reactions such as hydrolysis, and

(iii) The drying step may harm the thermolabile drugs.



Contd.

Compression Force: The compression force employed in tableting process influence density, porosity, hardness, disintegration time and dissolution of tablets.



Contd.

Intensity of Packing of Capsule Contents

- Like the compression force for tablets, packing density in case of capsule dosage form can either inhibit or promote dissolution.
- Diffusion of GI fluids into the tightly filled capsules creates a high pressure within the capsule resulting in rapid bursting and dissolution of contents.
- Opposite is also possible. It has been shown that capsules with finer particles and intense packing have poor drug release and dissolution rate due to a decrease in pore size of the compact and poor penetrability by the GI fluids.

Contd.

Pharmaceutical Ingredients/Excipients (Formulation factors)

- **Vehicle:** The 3 categories of vehicles in use are—aqueous vehicles (water, syrup, etc.), nonaqueous water miscible vehicles (propylene glycol, glycerol, sorbitol) and nonaqueous water immiscible vehicles (vegetable oils)

- **Diluents:**

Organic diluents: Starch, Lactose, microcrystalline cellulose, etc.

Inorganic diluents: Dicalcium phosphate (DCP) is most commonly used inorganic diluent

Contd.

- **Binders and Granulating Agents:** These materials are used to hold powders together to form granules or promote cohesive compacts for directly compressible materials and to ensure that the tablet remains intact after compression. e.g. starch, cellulose derivatives, acacia, PVP, gelatin, sucrose etc.

- **Disintegrants:** These agents overcome the cohesive strength of tablet and break them up on contact with water which is an important prerequisite to tablet dissolution. Almost all the disintegrants are hydrophilic in nature. e.g. MCC

Contd.

- **Lubricants/Anti-frictional Agents:** These agents are added to tablet formulations to aid flow of granules, to reduce interparticle friction and sticking or adhesion of particles to dies and punches

- **Coatings:** In general, the deleterious effect of various coatings on drug dissolution from a tablet dosage form is in the following order:

Enteric coat > Sugar coat > Non-enteric film coat.

Contd.

- **Suspending Agents/ Viscosity Imparters: e.g.** vegetable gums (acacia, tragacanth, etc.), semi-synthetic gums (CMC, MC) and synthetic gums which primarily stabilize the solid drug particles by reducing their rate of settling through an increase in the viscosity of the medium.

- **Surfactants:** Surfactants are widely used in formulations as wetting agents, solubilisers, emulsifiers, etc. Their influence on drug absorption is very complex. They may enhance or retard drug absorption either by interacting with the drug or the membrane or both.

Contd.

- **Buffers:** Buffers are sometimes useful in creating the right atmosphere for drug dissolution as was observed for buffered aspirin tablets. However, certain buffer systems containing potassium cations inhibit the drug absorption as seen with vitamin B2 and sulphanilamide.

- **Complexing Agents:** Complex formation has been used to alter the physicochemical and biopharmaceutical properties of a drug. A complexed drug may have altered stability, solubility, molecular size, partition coefficient and diffusion coefficient.

Contd.

- **Colorants:** Even a very low concentration of water-soluble dye can have an inhibitory effect on dissolution rate of several crystalline drugs. The dye molecules get adsorbed onto the crystal faces and inhibit drug dissolution— for example, brilliant blue retards dissolution of sulphathiazole. Dyes have also been found to inhibit micellar solubilisation effect of bile acids which may impair the absorption of hydrophobic drugs like steroids. Cationic dyes are more reactive than the anionic ones due to their greater power for adsorption on primary particles.

Contd.

➢ **Precipitation/ Crystal Growth Inhibitors:** When a significant increase in *free drug concentration above saturation or equilibrium solubility occurs, it* results in supersaturation which in turn lead to drug precipitation or crystallization. Precipitation or crystal growth inhibitors such as PVP, HPMC, PEG, PVA (polyvinyl alcohol) and similar such hydrophilic polymers prevent or prolong supersaturation thus preventing precipitation or crystallization by –

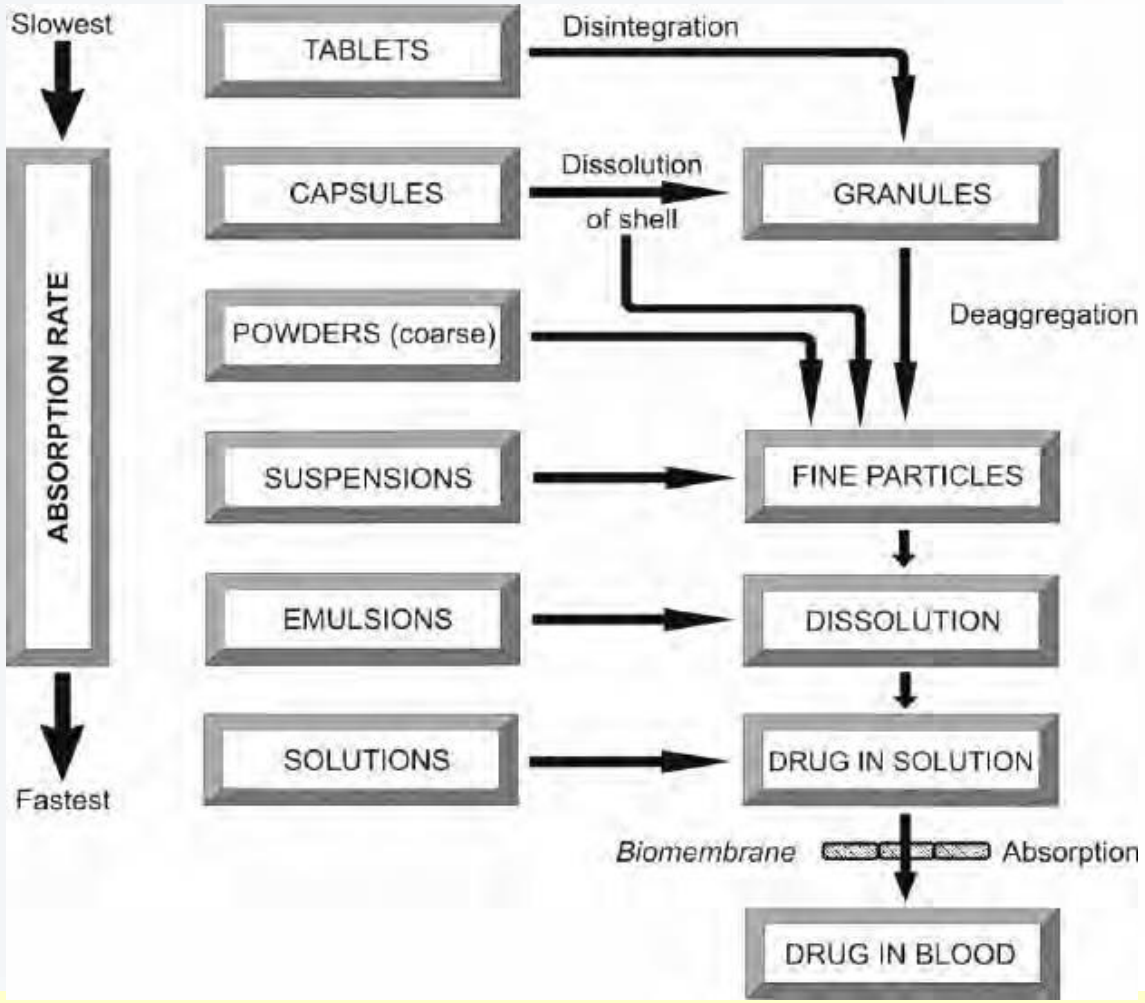
1. Increasing the viscosity of vehicle.
2. Prevent conversion of a high-energy metastable polymorph into stable, less soluble polymorph.
3. Adsorbing on the faces of crystal and reduce crystal growth.

Contd.

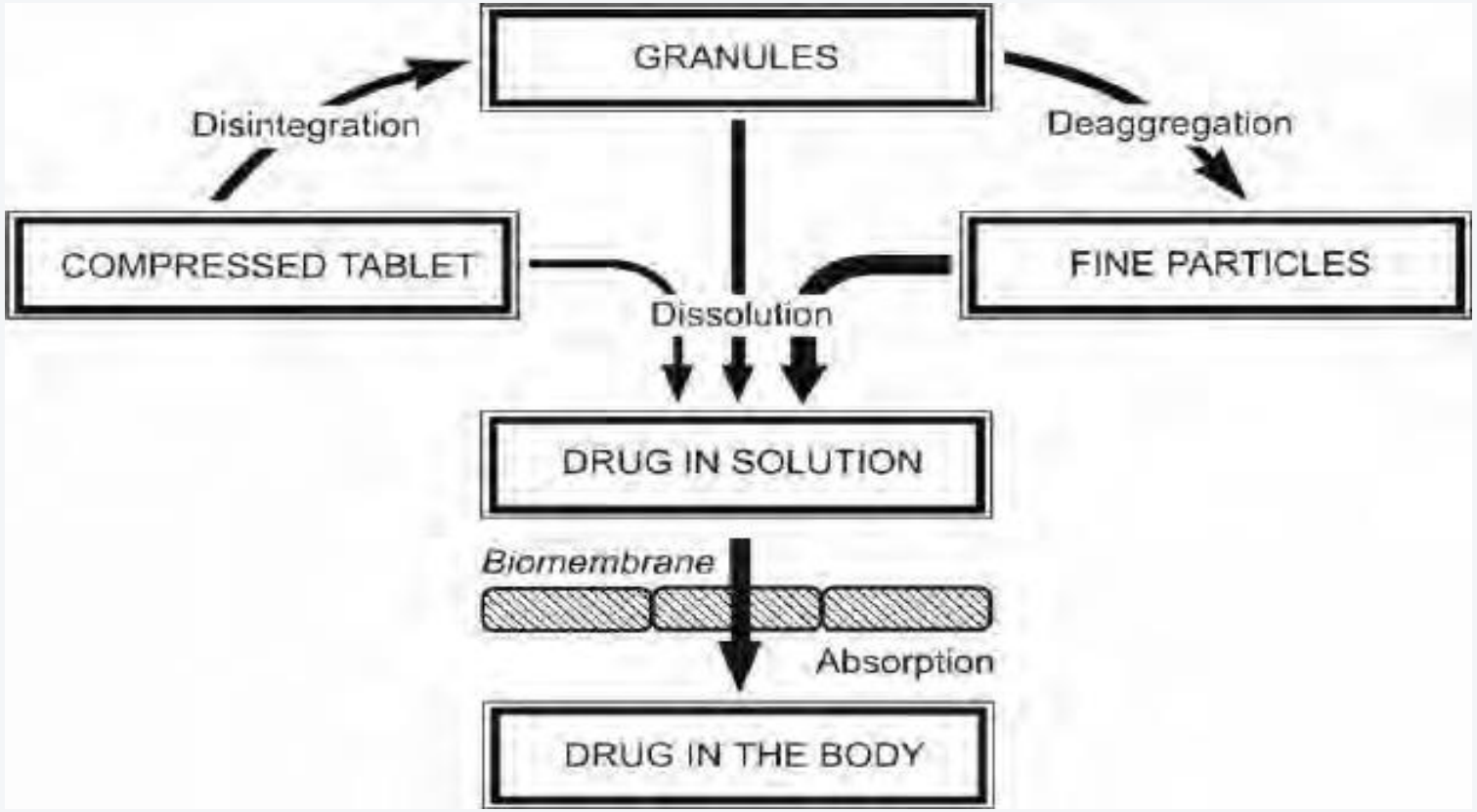
- **Nature and Type of Dosage Form:**

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.



Contd.



Sequence of events in the absorption of a drug from tablet dosage form

Contd.

➢ **Product Age and Storage Conditions:** A number of changes, especially in the physicochemical properties of a drug in dosage form, can result due to aging and alterations in storage conditions which can adversely affect bioavailability.

Changes that occur during the shelf-life of a dosage form are affected mainly by large variations in temperature and humidity. In one of the studies conducted on prednisone tablets containing lactose as the filler, high temperature and high humidity resulted in harder tablets that disintegrated and dissolved slowly.

Patient Related Factors Affecting Drug Absorption

- Age
- Gastric emptying time
- Intestinal emptying time
- GIT pH
- Disease state
- GIT blood flow
- GIT content
- Fast pass metabolism

Patient Related Factors Affecting Drug Absorption

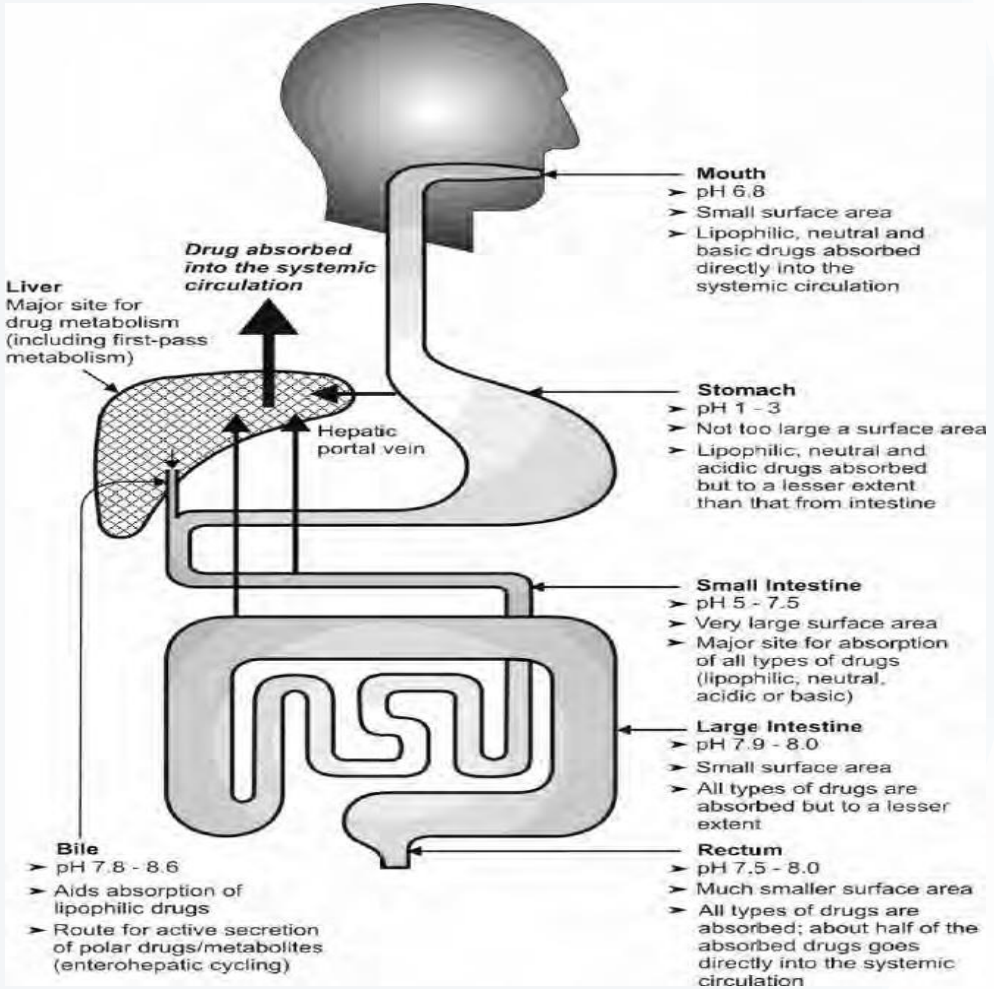
- **GI Tract:**

✓ **Stomach:** *stomach is not the principal region for drug absorption because –*

1. The total mucosal area is small.

2. The epithelium is dominated by mucus-secreting cells rather than absorptive cells.

3. The gastric residence time is limited due to which there is limited opportunity for gastric uptake of drug.



Contd.

- ✓ **Small Intestine:** *It is the major site for absorption of most drugs due to its-*

1. *Large surface area*
2. *Great length of small intestine*
3. *Greater blood flow*
4. *Favourable pH range*
5. *Slow peristaltic movement*
6. *High permeability*

Contd.

✓ **Large Intestine:** Its length and mucosal surface area is very small (villi and microvilli are absent) in comparison to small intestine and thus absorption of drugs from this region is insignificant. Its contents are neutral or alkaline. The main role of large intestine is in the absorption of water and electrolytes. However, because of the long residence time (6 to 12 hours), colonic transit may be important in the absorption of some poorly soluble drugs and sustained release dosage forms.

Patient Related Factors

- **Age**

In infants, the gastric pH is high and intestinal surface and blood flow to the GIT is low resulting in altered absorption pattern in comparison to adults. In elderly persons, causes of impaired drug absorption include altered gastric emptying, decreased intestinal surface area and GI blood flow, higher incidents of achlorhydria and bacterial overgrowth in small intestine.

Contd.

Apart from dissolution of a drug and its permeation through the biomembrane, *the passage from stomach to the small intestine, called as* ***gastric emptying,*** can also be a rate-limiting step in drug absorption because the major site of drug absorption is intestine. Thus, generally speaking, rapid gastric emptying increases bioavailability of a drug.

Rapid gastric emptying is advisable where:

1. A rapid onset of action is desired e.g. sedatives.
2. Dissolution of drug occurs in the intestine e.g. enteric-coated dosage forms.
3. The drugs are not stable in the gastric fluids e.g. penicillin G and erythromycin.
4. The drug is best absorbed from the distal part of the small intestine e.g. vitamin B12.

Contd.

Delay in gastric emptying is recommended in particular where:

1. The food promotes drug dissolution and absorption e.g. griseofulvin.
2. Disintegration and dissolution of dosage form is promoted by gastric fluids.
3. The drugs dissolve slowly e.g. griseofulvin.
4. The drugs irritate the gastric mucosa e.g. aspirin, phenylbutazone and nitrofurantoin.
5. The drugs are absorbed from the proximal part of the small intestine and prolonged drug-absorption site contact is desired e.g. vitamin B2 and vitamin C

Contd.

Gastric emptying is a first-order process. Several parameters are used to quantify gastric emptying:

1. Gastric emptying rate *is the speed at which the stomach contents empty into the intestine.*

2. Gastric emptying time *is the time required for the gastric contents to empty into the small intestine. Longer the gastric emptying time, lesser* the gastric emptying rate.

3. Gastric emptying t½ *is the time taken for half the stomach contents to empty.*

Contd.

The *factors influencing gastric emptying are listed below.*

1. **Volume of meal:** Larger the bulk of the meals, longer the gastric emptying time. However, an initial rapid rate of emptying is observed with a large meal volume and an initial lag phase in emptying of a small volume meal.
2. **Composition of meal:** Predictably, the rate of gastric emptying for various food materials is in the following order: *carbohydrates > proteins > fats. Fats promote secretion of bile which too has an* inhibitory effect on gastric emptying. Delayed gastric emptying as observed with fatty meals, is beneficial for the absorption of poorly soluble drugs like griseofulvin.

Contd.

3. **Physical state and viscosity of meal:** Liquid meals take less than an hour to empty whereas a solid meal may take as long as 6 to 7 h. Viscous materials empty at a slow rate in comparison to less viscous materials.

4. **Temperature of the meal:** High or low temperature of the ingested fluid (in comparison to body temperature) reduce the gastric emptying rate.

5. Gastrointestinal pH: Gastric emptying is retarded at low stomach pH and promoted at higher or alkaline pH.

Contd.

6. Electrolytes and osmotic pressure: Water, isotonic solutions, and solutions of low salt concentration empty the stomach rapidly whereas a higher electrolyte concentration decreases gastric emptying rate.

7. **Body posture:** Gastric emptying is favoured while standing and by lying on the right side since the normal curvature of the stomach provides a *downhill path whereas lying on the left side or in supine* position retards it.

8. **Emotional state:** Stress and anxiety promote gastric motility whereas depression retards it.

Contd.

9. **Exercise:** Vigorous physical training retards gastric emptying.

10. **Disease states:** Diseases like gastroenteritis, gastric ulcer, pyloric stenosis, diabetes and hypothyroidism retard gastric emptying. Partial or total gastrectomy, duodenal ulcer and hyperthyroidism promote gastric emptying rate.

11. **Drugs:** Drugs that retard gastric emptying include poorly soluble antacids (aluminium hydroxide), anticholinergics (atropine, propantheline), narcotic analgesics (morphine) and tricyclic antidepressants (imipramine, amitriptyline). Metoclopramide, domperidone and cisapride (prokinetic agents) stimulate gastric emptying.

Contd.

Intestinal Transit: Since small intestine is the major site for absorption of most drugs, long intestinal transit time is desirable for complete drug absorption

Intestinal region	Transit time
Duodenum	5 minutes
Jejunum	2 hours
Ileum	3 to 6 hours
Caecum	0.5 to 1 hour
Colon	6 to 12 hours

Contd.

Delayed intestinal transit is desirable for:

1. Drugs that dissolve or release slowly from their dosage form (sustained-release products) or when the ratio of dose to solubility is high e.g. chlorothiazide.

2. Drugs that dissolve only in the intestine (enteric-coated formulations).

3. Drugs which are absorbed from specific sites in the intestine (several B vitamins, lithium carbonate, etc.).

4. When the drug penetrates the intestinal mucosa very slowly e.g. acyclovir.

5. When absorption of drug from the colon is minimal.

Contd.

- **Gastrointestinal pH**

1. Disintegration:
2. Dissolution:
3. Absorption:
4. Stability:

- **Disease States**

1. Gastrointestinal diseases,
2. Cardiovascular diseases, and
3. Hepatic diseases.

Contd.

- **Blood flow to GIT**
- **Gastrointestinal Contents**
  - Food drug interaction
  - Fluid volume
  - Interaction of drug with normal GI constituents
  - Drug-Drug interactions in the GIT

Thank you