ABSORPTION

❖PHARMACOKINETICS:

➢*Pharmacokinetics* is the science of the kinetics of drug absorption, distribution, and elimination (i.e., excretion and metabolism).

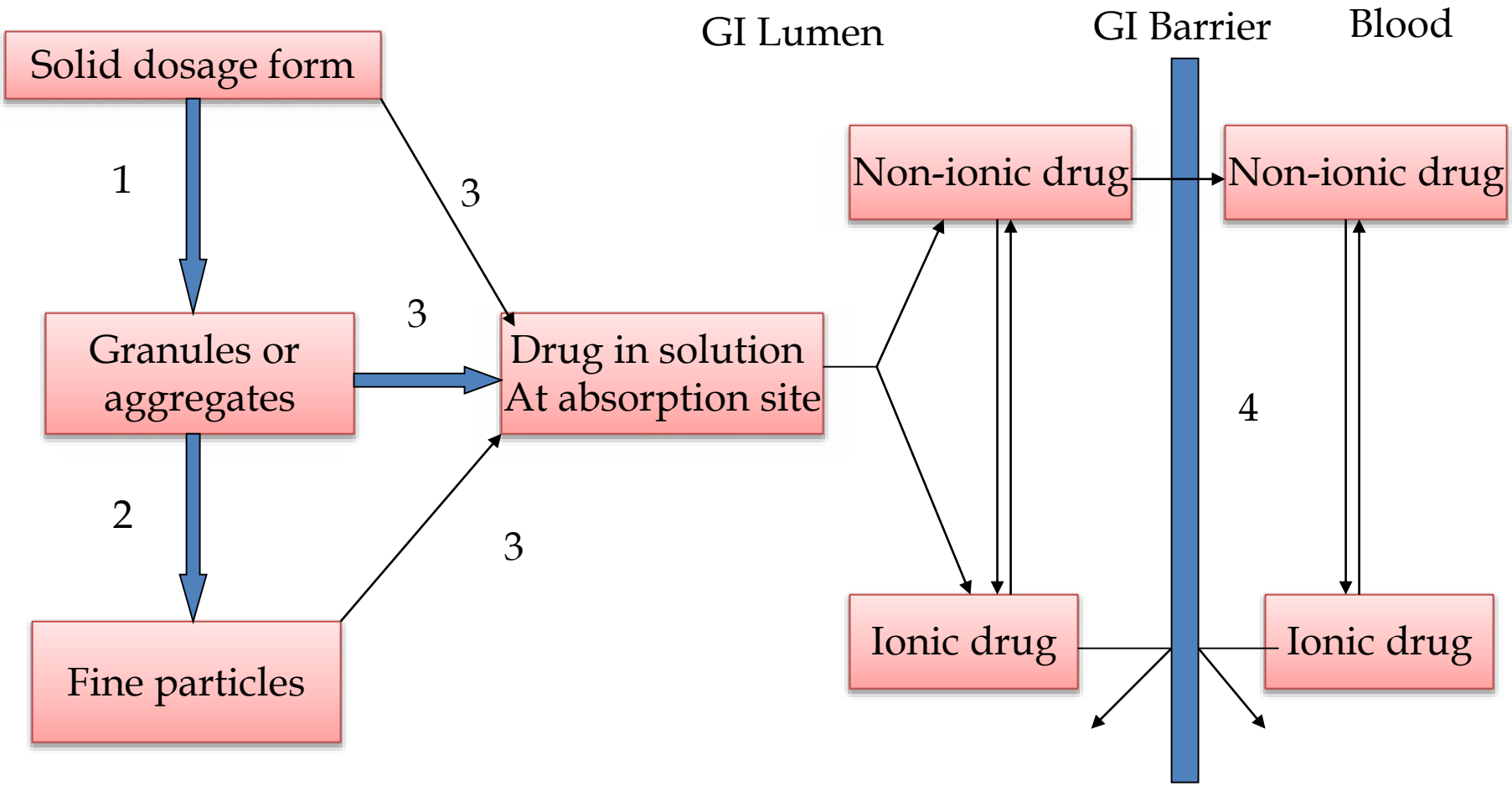
❖PHARMACODYNAMICS:

➢*Pharmacodynamics* refers to the relationship between the drug concentration at the site of action (receptor) and pharmacologic response.

❖ABSORPTION:

➢"The process of movement of unchanged drug from the site of administration to systemic circulation is called as absorption".

➢It can also be defined as the process of movement of unchanged drug from the site of administration to the site of measurement i.e. plasma.



Means of
- 1- Disintegration
- 2- Deaggregation
- 3- Dissolution
- 4- Absorption

Sequence of events in the absorption of drugs from orally administered solid dosage forms

❖FACTORS AFFECTING DRUG ABSORPTION

A. Physicochemical factors:

1) Drug solubility & dissolution rate
2) Particle size & effective surface area
3) Polymorphism & amorphism
4) Pseudoploymorphism (hydrates/solvates)
5) Salt form of the drug
6) Lipophilicity of the drug
7) pKa of drug & gastrointestinal pH

pH- Partition hypothesis

8) Drug stability

B. Pharmaceutical factors :

1) Disintegration time (tablets/capsules)
2) Dissolution time
3) Manufacturing variables
4) Pharmaceutical ingredients (excipients/adjuvants)
5) Nature & type of dosage form
6) Product age & storage condition

C. Patient related factors :

1) Route of administration
2) Membrane physiology
    a) Nature of cell membrane
    b) Transport processes
3) Age
4) Gastric emptying time
5) Intestinal transit time

6) Gastrointestinal pH
7) Disease states
8) Blood flow through the GIT
9) Gastrointestinal contents:
    a) Food- drug interactions
    b) Fluids
    c) Other normal GI contents
10) Presystemic metabolism by:
    a) Luminal enzymes
    b) Gut wall enzymes
    c) Bacterial enzymes
    d) Hepatic enzymes

PHYSICOCHEMICAL FACTORS

1) Drug solubility & dissolution rate :

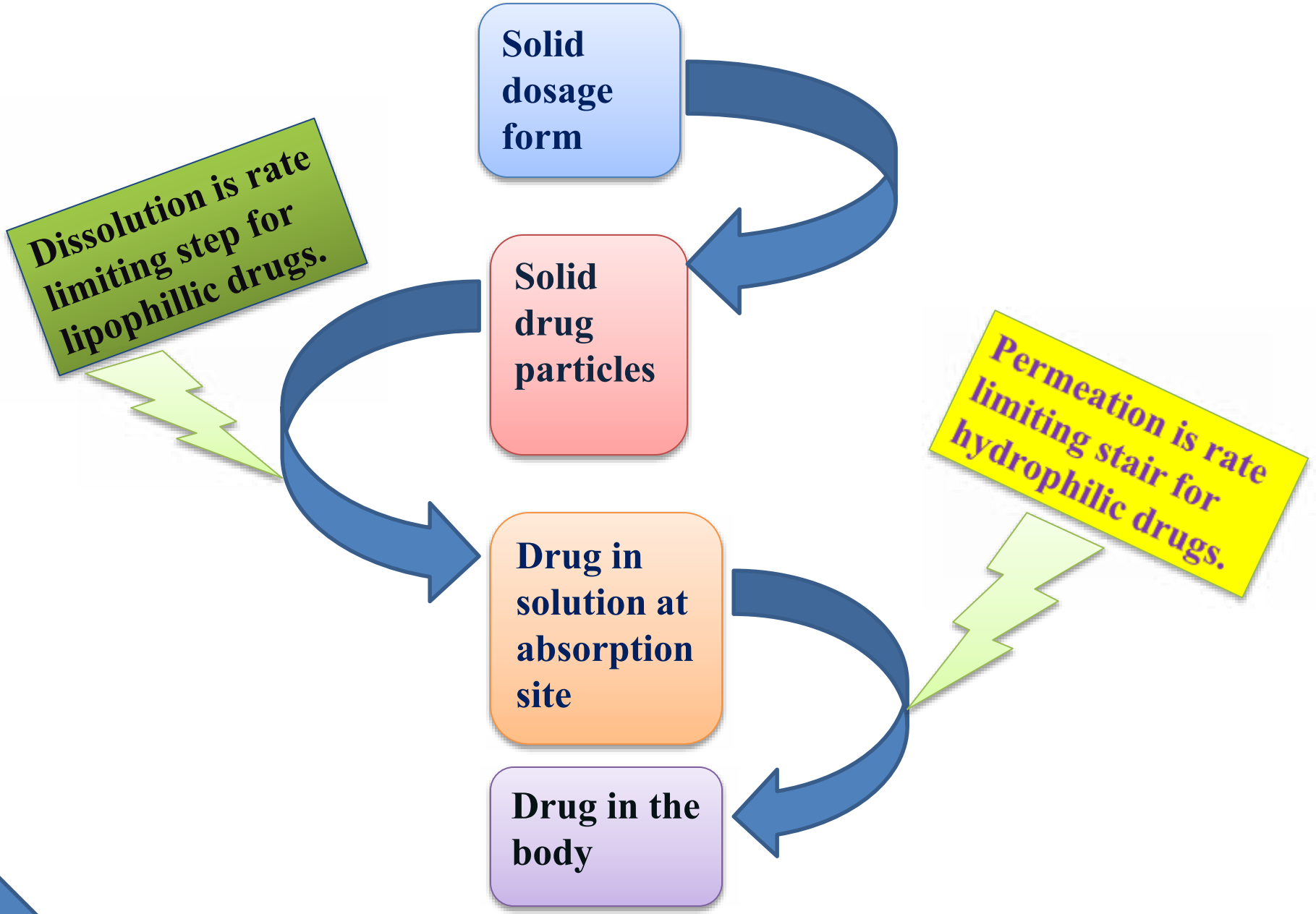
The rate determining steps in absorption of orally administered drugs are:

1. Rate of dissolution
2. Rate of drug permeation through the bio-membrane.

➢Dissolution is rate determining step for hydrophobic & poorly aqueous soluble drugs.
E.g. Griesiofulvin & Spironolactone.

➢Permeation is the rate determining step for hydrophilic & high aqueous soluble drugs.
E.g. cromolyn sodium or Neomycin.

➢Prerequisite for the absorption of a drug is that it must be present in aqueous solution & this is depends on drug's aqueous solubility & its dissolution rate.


Solid dosage form
Solid drug particles
Drug in solution at absorption site
Drug in the body
Dissolution is rate limiting step for lipophillic drugs.
Permeation is rate limiting stair for hydrophilic drugs.

2) Particle size and effective surface area:

- Particle size may play a major role in drug absorption.
- Dissolution rate of solid particles is proportional to surface area.
- Smaller particle size, greater surface area then higher will be dissolution rate, because dissolution is thought to take place at the surface area of the solute (Drug).
- Particle size reduction has been used to increase the absorption of a large number of poorly soluble drugs.
- E.g. Bishydroxycoumarin, digoxin, griseofulvin
- Two types of surface area
  1) Absolute surface area
  2) Effective surface area

- In absorption studies the effective surface area is of much important than absolute.
- To increase the effective surface area, we have to reduce the size of particles up to 0.1 micron. So these can be achieved by "micronisation process".
- But in these case one most important thing to be keep in mind that which type of drug is micronised if it is:

a) HYDROPHILIC OR b) HYDROPHOBIC

a) HYDROPHILIC DRUGS:

- In hydrophilic drugs the small particles have higher energy than the bulk of the solid resulting in an increased interaction with the solvent.

▪Examples,

1.Griesiofulvin – Dose reduced to half due to micronisation.

2.Spironolactone – the dose was decreased to 20 times.

3.Digoxin – the bioavailability was found to be 100% in micronized tablets.

➢After micronisation it was found that the absorption efficiency was highly increased

b) HYDROPHOBIC DRUGS:

➢In this micronisation techniquies results in decreased effective surface area & thus fall in dissolution rate.

REASONs:

1) The hydrophobic surface of the drugs adsorbs air on to their surface which inhibits their wettability.

2) The particles reaggregates to form large particles due to their high surface free energy, which either float on the surface or settle on the bottomof the dissolution medium.
3) Electrically induced agglomeration owing to surface charges prevents intimate contact of the drug with the dissolution medium.

➢Such hydrophobic drugs can be converted to their effective surface area.
a) Use of surfactant as a wetting agent which
- decrease the interfacial tention.
- displace the absorbed air with the solvent. Eg. phenacetin
b) Add hydrophilic diluents like PEG, PVP, dextrose etc. which coat the surface of hydrophobic drug particles.

3) Polymorphism & Amorphism:

➢Depending upon 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.

➢Polymorps are of two types:

1) **Enantiotropic polymorph** is the one which can be reversibly changed into anthor form by altering the temperature or pressure.E.g. Sulfur.

2) **Monotropic polymorph** is the one which is unstable at all the temperature or pressures. E.g. glyceryl strarates.

➢The polymorphs differ from each other with respect to their physical properties such as solubility, melting point, density, hardness and compression characteristics. Thus, these change in physical properties affect the dissolution properties and hence the absorption.

➢E.g. The vitamin riboflavin exists in several polymorphic forms, polymorphic form III of riboflavin is 20 times more water soluble than the form I.

➢ **AMORPHISM:** Some drugs can exist in amorphous form (i.e. having no internal crystal structure). Such drug represents the highest energy state.

➢They have greater aqueous solubility than the crystalline forms because a energy required to transfer a molecule from the crystal lattice is greater than that required for non-crystalline (amorphous form).

➢For example: the amorphous form of Novobiocin is 10 times more soluble than the crystalline form. Thus, the order of different solid dosage forms of the drugs is

Amorphous > Meta-stable > stable

4) Pseudoploymorphism: When the solvent molecules are entrapped in the crystalline structure of the polymorph, it is known as pseudo-polymorphism.

- **Solvates:** the stoichiometric type of adducts where the solvent molecules are incorporated in the crystal lattice of the solid are called as the solvates, and the trapped solvent as solvent of crystallization.

- **Hydrates:** when the solvent in association with the drug is water , the solvate is known as a hydrate.
- Hydrates/Solvates are pseudo-polymorphs where hydrates are less soluble and solvates are more soluble and thus affect the absorption accordingly.
- For example: n-pentanol solvates of fludrocortisone and succinyl-sulfathiazole have greater aqueous solubility than the non-solvates.

(5) Salt form of drug:

- While considering the salt form of drug, pH of the diffusion layer is important not the pH of the bulk of the solution.
- Example of salt of weak acid. - It increases the pH of the diffusion layer, which promotes the solubility and dissolution of a weak acid and absorption is bound to be rapid.
- Other approach to enhance the dissolution and absorption rate of certain drugs is the formation of in – situ salt formation i.e. increasing in pH of microenvironment of drug by incorporation of a buffering agent. E.g. aspirin, penicillin
- But sometimes more soluble salt form of drug may result in poor absorption. e.g. sodium salt of phenobarbitone viz., its tablet swells and did not get disintegrate, thus dissolved slowly and results in poor absorption.

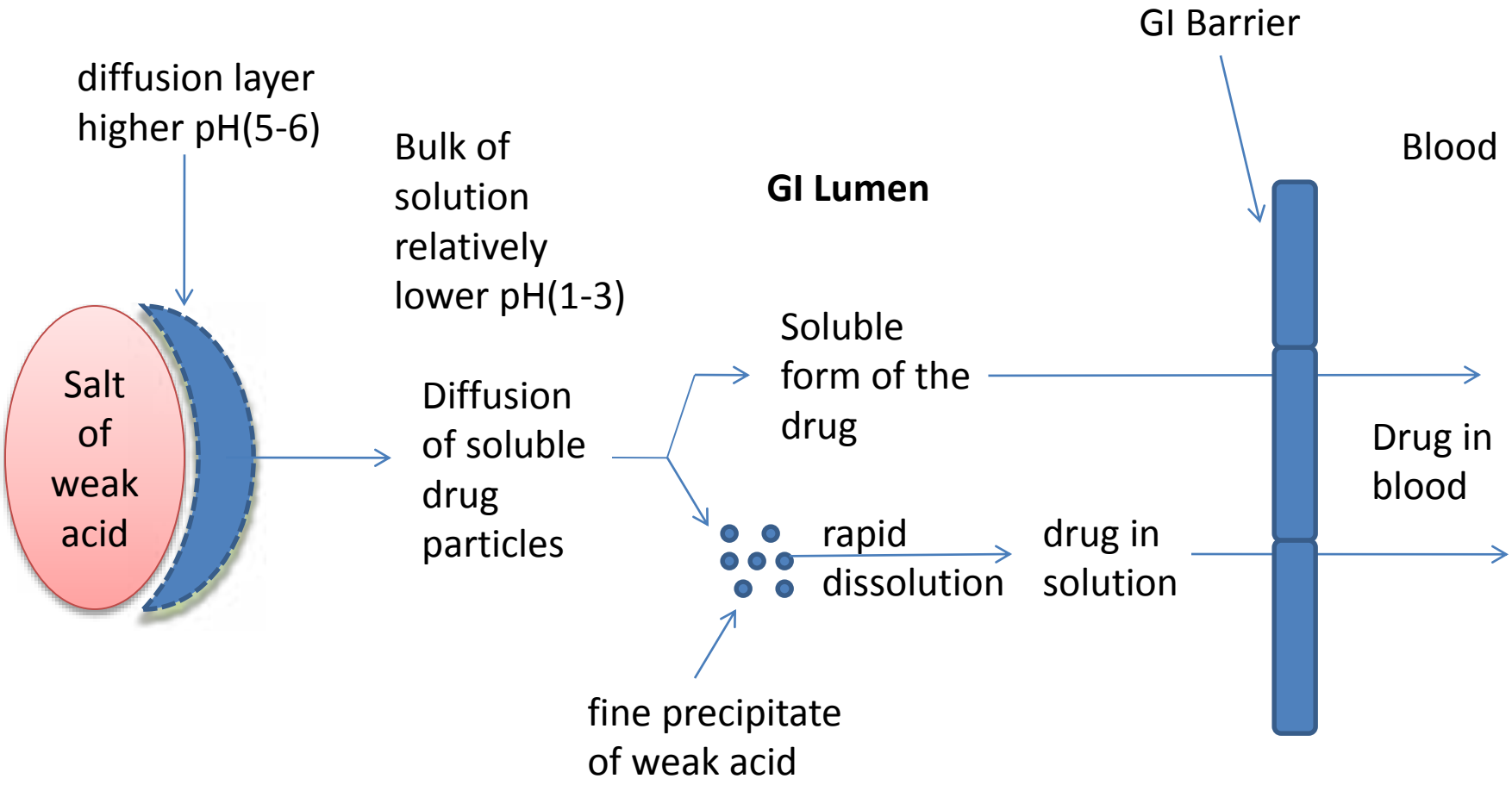


Fig: Dissolution and absorption of an acidic drug administered in a salt form

6 & 7) pH-Partion hypothesis:

➢The theory states that for drug compounds of molecular weight more than 100, which are primarily transported across the bio-membrane by passive diffusion, the process of absorption is governed by:

1. The dissociation constant pKa of the drug.

2. The lipid solubility of the un-ionized drug.

3. The pH at the absorption site.

A) DRUG pKa AND GI pH:

➢Amount of drug that exists in un-ionized form and in ionized form is a function of pKa of drug and pH of the fluid at the absorption site, and it can be determined by Handerson-Hasselbach equation:

•**For weak acids,**

$$pH = pKa + \log \frac{[\text{ionized}]}{[\text{un-ionized}]} \quad ..(1.1)$$

$$\% \text{ Drug ionized} = \frac{10^{pH-pKa}}{1+10^{pH-pKa}} \times 100 \quad \ldots (1.2)$$

•**For weak bases,**

$$pH = pKa + \log \frac{[\text{un-ionized}]}{[\text{ionized}]} \quad \ldots(1.3)$$

$$\% \text{ Drug ionized} = \frac{10^{pKa-pH}}{1+10^{pKa-pH}} \times 100 \quad \ldots(1.4)$$

➢If there is a membrane barrier that separates the aqueous solutions of different pH such as the GIT and the plasma, then the theoretical ratio R of drug concentration on either side of the membrane can be given by the following equations:

- **For weak acids,**

$$R_a = \frac{C_{GIT}}{C_{plasma}} = \frac{1+10^{pHGIT-pKa}}{1+10^{pHplasma-pKa}} \quad \ldots. (1.5)$$

- **For weak bases,**

$$R_b = \frac{C_{GIT}}{C_{plasma}} = \frac{1+10^{pKa-pHGIT}}{1+10^{pKa-pHplasma}} \quad .... (1.6)$$

B) LIPOPHILICITY AND DRUG ABSORPTION:

- The lipid solubility of the drug is determined form its oil/water partition co-efficient (Ko/w) value, whereby the increase in this value indicates the increase in percentage drug absorbed.

- $K_{o/w} = \frac{\text{Distribution of the drug in the organic phase (octanol)}}{\text{Distribution of the drug in the aqueous phase}}$ …… (1.7)

8) 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.

PHARMACEUTICAL FACTORS

1. Disintegration time (tablets/capsules):

- Rapid disintegration is important to have a rapid absorption so lower disintegration time is required.
- Disintegration time of tablet is directly proportional to – amount of binder & Compression force.
- In vitro disintegration test gives no means of a guarantee of drugs bioavailability because if the disintegrated drug particles do not dissolve then absorption is not possible.
- E.g. COATED TABLETS: they have long disintegration time.
- Fast dispersible tablets have short disintegration time.

2) Dissolution time:

- Dissolution is a process in which a solid substance solubilises in a given solvent i.e… mass transfer from the solid surface to the liquid phase.
- Dissolution time is also an important factor which affect the drug absorption.

3) Manufacturing variables:

- Several manufacturing processes influence drug dissolution from solid dosage forms.
- For example: For tablet it is
  - ✓Method of granulation
  - ✓Compression force

▪Method of granulation:

➢The wet granulation process is the most conventional technique

➢The tablets that dissolve faster than those made by other granulation methods.

➢But wet granulation has several limitations like formation of crystal bridge or chemical degradation.

➢The method of direct compression force has been utilized to yield the tablets that dissolve at a faster rate.

▪Compression force:

➢The compression force employed in tableting process influence density, porosity, hardness, disintegration time and dissolution rate of tablets.

➢Higher compression force increases the density and hardness of the tablet, decreases porosity and hence penetrability of the solvent into the tablet and thus in slowing of dissolution and absorption (Fig .A)

➢On the other hand, higher compression force causes deformation, crushing or fracture of drug particles into smaller ones and causes a large increase in effective surface area. This results in an increase in dissolution rate of tablets (Fig B)

➢A combination of both the curves A and B is also possible as shown in curves C & D.

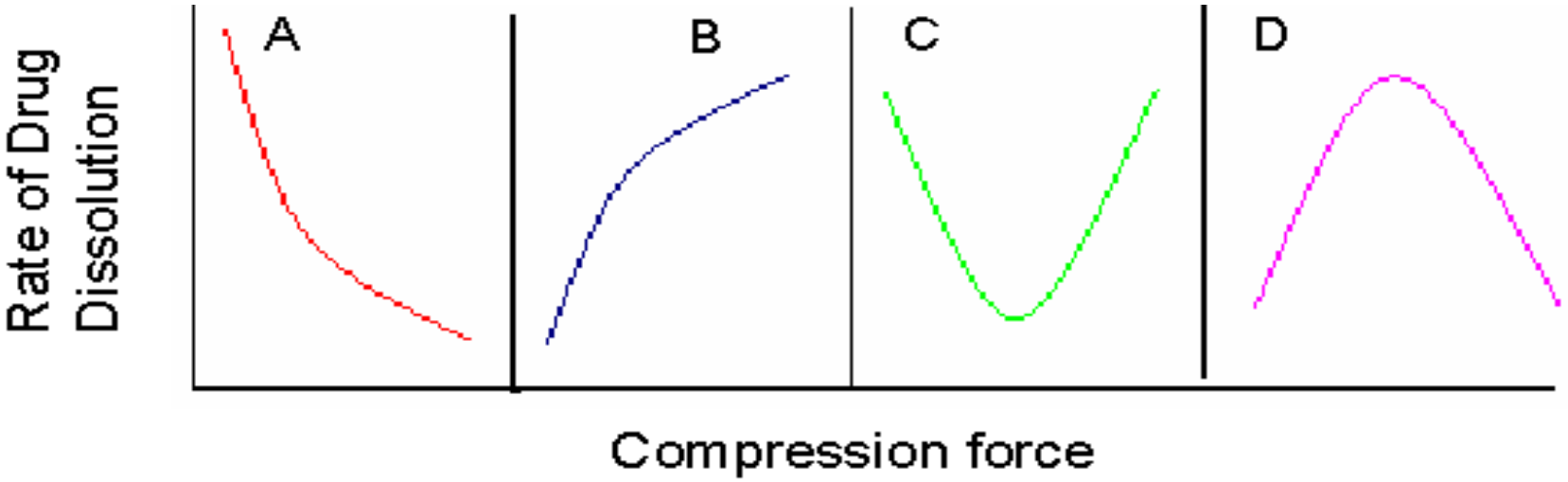


Fig. Influence of compression force on the dissolution rate of tablets

4) Pharmaceutical ingredients (excipients/adjuvants):

- More the number of Excipients in the dosage form, more complex it is & greater the potential for absorption and Bioavailability problems.
- Commonly used excipients in various dosage forms are,

a) Vehicle:

- Rate of absorption – depends on its miscibility with biological fluid
- Miscible vehicles causes rapid absorption e.g. propylene glycol.
- Immiscible vehicles – Absorption depends on its partitioning from oil phase to aqueous body fluid.

b) Diluents:

➢Hydrophilic diluents – Imparts Absorption

Hydrophobic diluents – Retards Absorption

➢Also, there is a drug-diluent interaction, forming insoluble complex and retards the absorption. E.g. Tetracycline-DCP

c) Binders & granulating agent:

➢Hydrophilic binders – Imparts hydrophilic properties to the granule surface – gives better dissolution properties. E.g. Starch, Gelatin. PVP.

➢More amount of binder increases the hardness of the tablet and retards the absorption rate.

d) Disintegrants:

➢Mostly hydrophilic in nature.

➢Decrease in amount of disintegrants – significantly lowers bioavailability.

e) Lubricants:

- Commonly hydrophobic in nature – therefore inhibits penetration of water into tablet and thus dissolution and disintegration.

f) Suspending agents/viscosity agent:

- Stabilized the solid drug particles and thus affect drug absorption.
- Macromolecular gum forms un-absorbable complex with drug e.g. Na CMC.
- Viscosity imparters – act as a mechanical barrier to diffusion of drug from its dosage form and retard GI transit of drug.

g) Surfactants:

- May enhance or retards drug absorption by interacting with drug or membrane or both.
- e.g. Griseofulvin, steroids
- It may decrease absorption when it forms the un-absorbable complex with drug above CMC.

h) Coating:

➢In general, deleterious effects of various coatings on the drug dissolution from a tablet dosage form are in the following order.

Enteric coat > sugar coat > non-enteric coat

➢The dissolution profile of certain coating materials change on aging; e.g. shellac coated tablets, on prolonged storage, dissolve more slowly in the intestine. This can be however, be prevented by incorporating little PVP in the coating formulation.

i) 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 B_2 and sulfanilamide.

j) Colorants:

- Even a low concentration of water soluble dye can have an inhibitory effect on dissolution rate.
- The dye molecules get absorbed onto the crystal faces and inhibit the drug dissolution.
- For example: Brilliant blue retards dissolution of sulfathiazole.

k) Complexing agents:

- Complex formation has been used to alter the physicochemical & biopharmaceutical properties of a drug.

Example

1)Enhanced dissolution through formation of a soluble complex.

- E.g. ergotamine tartarate-caffeine complex & hydroquinone-digoxin complex.

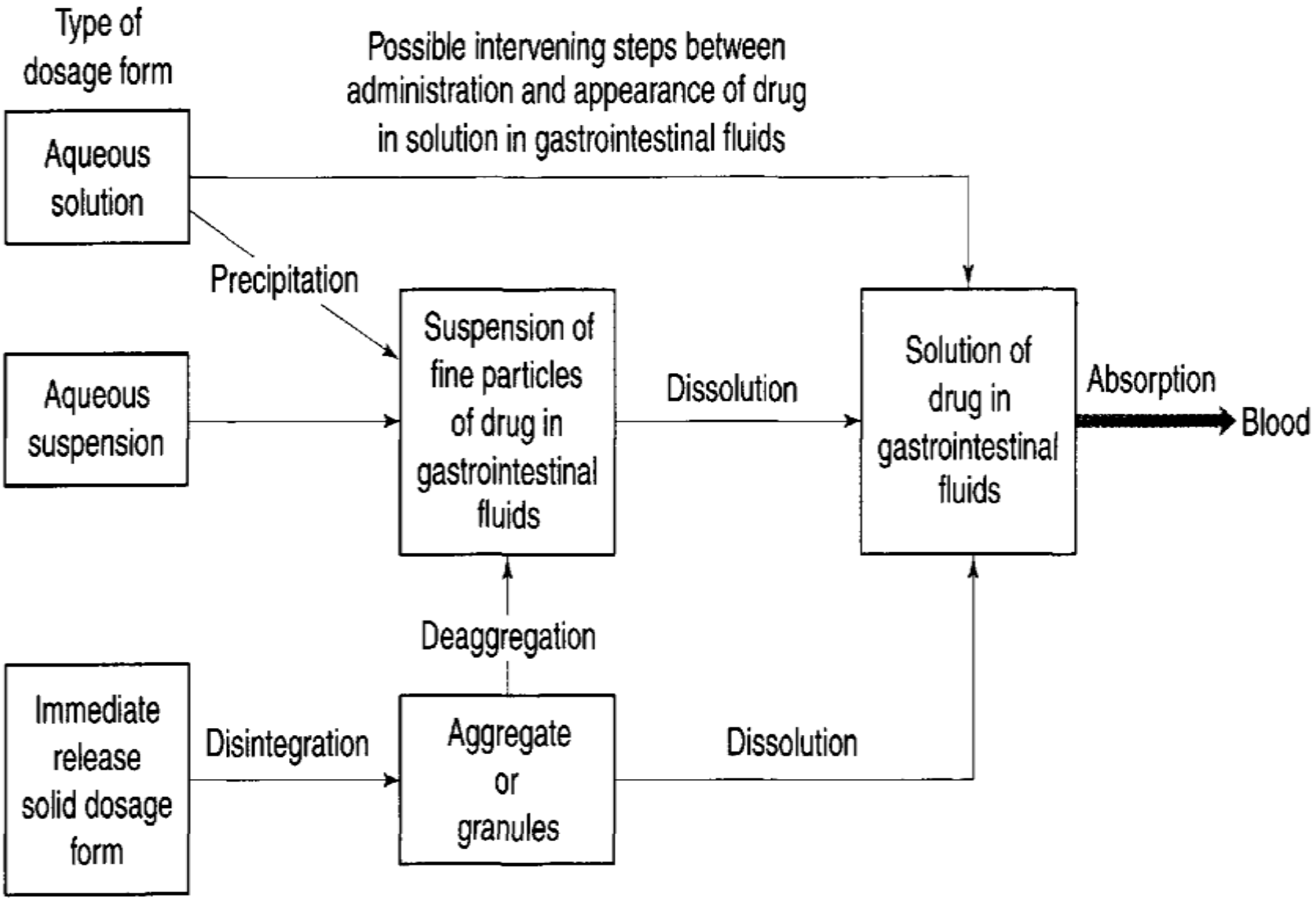
2)Enhanced lipophilicity for better membrane permeability.

- E.g. caffeine-PABA complex.

5) Nature & type of dosage form:

- Apart from the proper selection of the drug, clinical success often depends to a great extent on the proper selection of the dosage form of that drug.
- As a general rule, the bio-availability of a drug form various dosage forms decrease in the following order:

Solutions > Emulsions > Suspensions > Capsules > Tablets > Coated Tablets > Enteric Coated Tablets > Sustained Release Products.



.3 Schematic outline of the influence of the dosage form on the appearance of drug in solution in the gastrointestinal tract.

➢ 6) Product age & storage condition:

➢Product aging and storage conditions can adversely affect the bio-availability by change in especially the physico-chemical properties of the dosage forms.

➢For example:

1.Precipitation of the drug in solution

2.Hardening of tablet

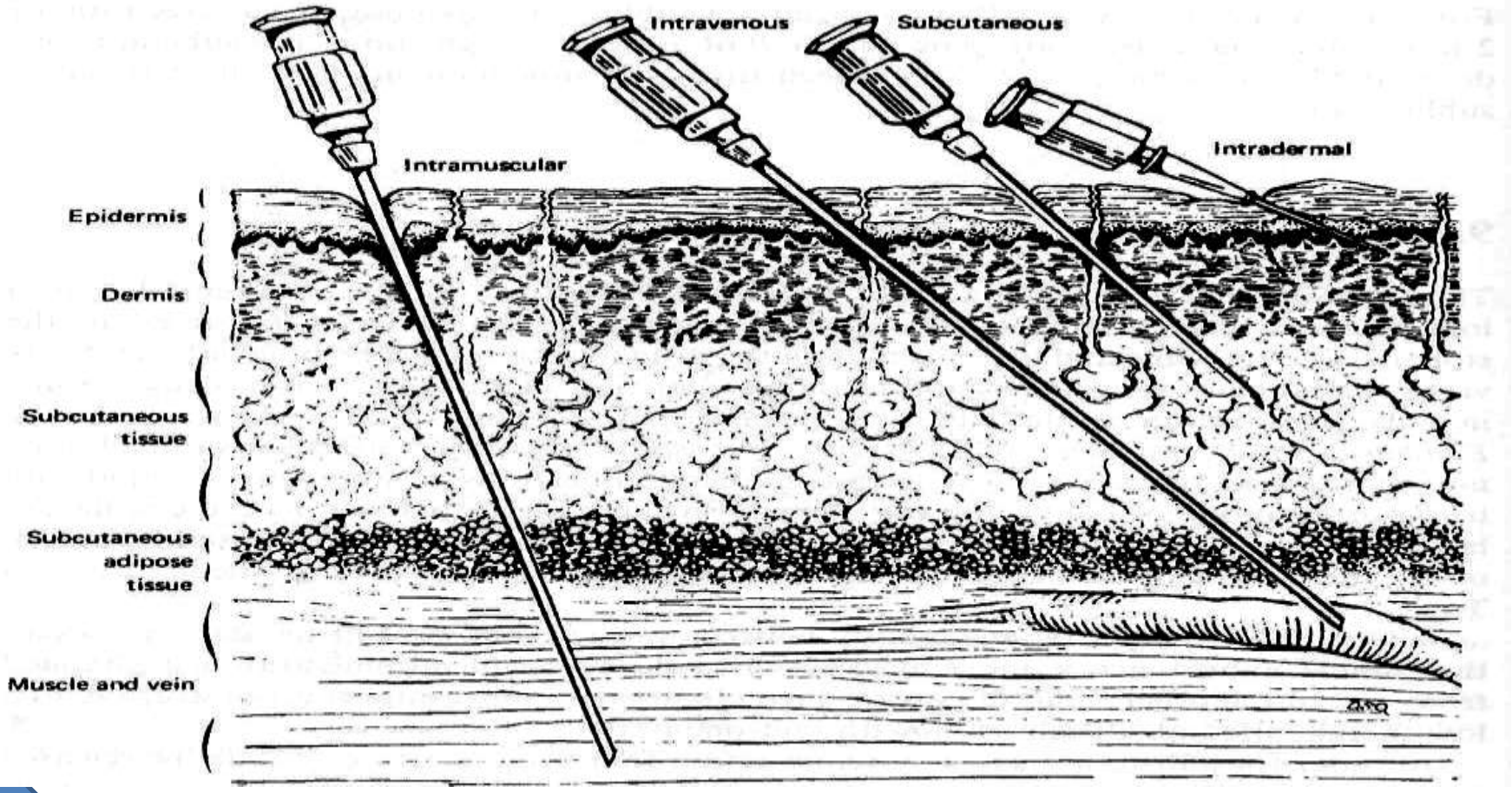
3.Change in particle size of suspension.

PATIENT RELATED FACTORS

1) Route of administration:

❖ ***Parentral route:***

➢ They avoid the possibility of hepatic first-pass metabolism.



•Intra-arterial:

➢Intra-arterial injection is used to deliver drugs directly to organs, for example, in cancer chemotherapy, and in the use of vasopressin for GI bleeding.

• Intrathecal:

➢Injection directly into the cerebrospinal fluid (CFS) ensures complete CNS bioavailability for drugs that can not cross the blood-brain barrier.

➢E.g. Mepivacaine and prilocaine for spinal anesthesia.

•Intravenous (IV):

➢IV administration introduces drug directly into the venous circulation.

➢IV bolus is used for immediate therapeutic effect, typically for general anesthesia and for treatment of cardiac arrhythmia.

•Intramuscular (IM):

➢Intramuscular injection is used mainly for drugs and vaccines that are not absorbed orally, for example, aminoglycosides, insulin, and hepatitis vaccine.

➢The IM route is often used for sustained medication and specialized vehicles, such as aqueous suspensions, oily vehicles

❖***Topical route:***

•Transdermal:

➢This drug delivery route include continuous release of drug over a specified period, low presystemic clearance, and facile drug withdrawal by simply removing the device, and good patient convenience and compliance.

- Some disadvantages relate to barrier properties of the skin, skin reactions, and the relatively large dose size.
- Gnerally small dose is deleverd (<10mg)
- E.gclonidine, estradiol

•Intranasal:

- Intranasal administration may be used for local or systemic effects. Local effects include treatment of nasal allergies, rhinitis, and nasal congestion. Nasal delivery for systemic effects is established for a small number of drugs
- E.g. Vasopressin analogues and oxytocin are commercially available for intranasal dosage.

•Vaginal:

- Vaginal drug delivery is used mostly for local effects, but vaginal absorption can give rise to rapid and efficient systemic delivery.
- E.g. vaginal rings and biodegradable microspheres.

❖***Enteral routes:***

•Rectal:

➢Rectal absorption is generally slower than oral absorption, but for some drugs, rectal absorption exceeds oral absorption presumably due to avoidance of first-pass metabolism after rectal delivery.

➢E.g. Metoclopramide, ergotamine, lidocaine

•Buccal:

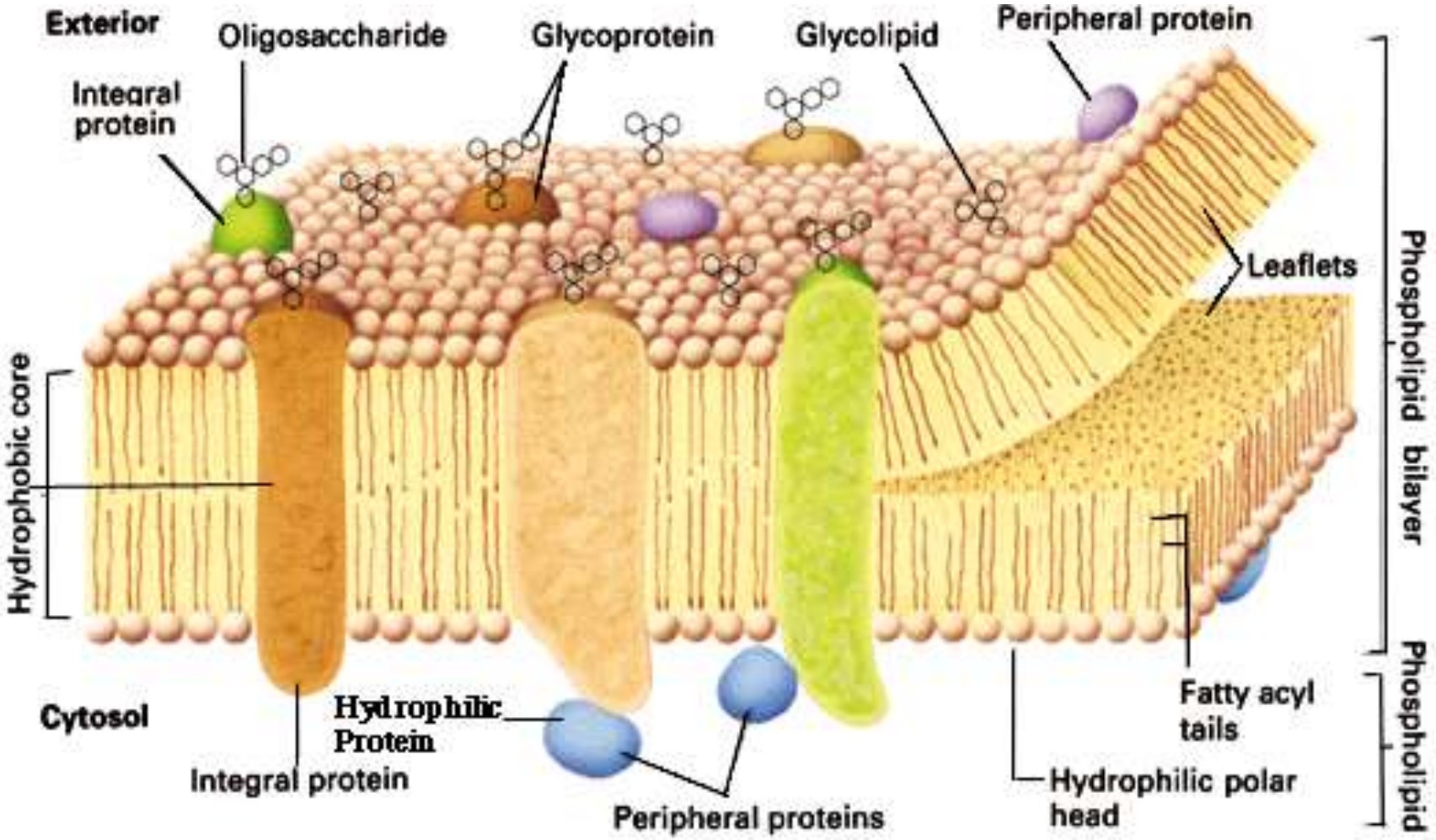
➢Drugs can be absorbed from the oral cavity itself or sublingually. Absorption from either route is rapid, sublingual more so apparently because of greater permeability of sublingual membranes and rich blood supply.

➢The mean pH of saliva is approximately 6 so that drug absorption, predominantly passive in nature, is favored for unchanged molecules, acids with pKa values >3, and bases with pKa values <9.

➢E.g. organic nitrates, barbiturates, papaverine, prochlorperazine, benzodiazepines.

2) Membrane physiology:

a) Nature of cell membrane:



- The cell membrane consists of globular proteins embedded in a dynamic fluid, lipid bilayer matrix
- Cell membranes are generally thin, approximately 70 to 100 Å in thickness.
- Cell membranes are composed primarily of phospholipids in the form of a bilayer interdispersed with carbohydrates and protein groups. The plasma membrane to be composed of two layers of phospholipid between two surface layers of proteins, with the hydrophilic "head" groups of the phospholipids facing the protein layers and the hydrophobic "tail" groups of the phospholipids aligned in the interior.
- lipid-soluble drugs tend to penetrate cell membranes more easily than polar molecules.
- proteins provide a pathway for the selective transfer of certain polar molecules and charged ions through the lipid barrier.

3) 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 compare to adults.
- In elderly persons, gastric emptying altered, decreased intestinal surface area and GI blood flow, higher incidents of achlorhydria so impaired drug absorption.

4) Gastric emptying time:

- The process by which food leaves the stomach and enters the duodenum.
- Rapid gastric emptying is required when the drug is best absorbed from distal part of the small intestine.

- Delayed gastric emptying is required when drugs are absorbed from proximal part of the small intestine and prolonged drug absorption site contact is desired.

- Gastric emptying is a first order process.

- **Gastric emptying rate:** This is the speed at which the stomach contents empty into the intestine.

- **Gastric emptying time:** Which is the time required for the gastric contents to the SMALL INTESTINE.

- **Gastric emptying half-life:** which is the time taken for half the stomach contents to empty.

Volume of Ingested Material	As volume increases initially an increase then a decrease. Bulky material tends to empty more slowly than liquids
Type of Meal	Gastric emptying rate: carbohydrates > proteins > fats
Physical state of gastric contents	Solutions or suspensions of small particles empty more rapidly than do chunks of material that must be reduced in size prior to emptying.
Body Position	Lying on the left side decreases emptying rate and right side promotes it
Drugs Anticholinergics Narcotic analgesics Ethanol	 Reduction in rate of emptying Reduction in rate of emptying Reduction in rate of emptying
Emotional state	Anxiety promotes where as depression retards it
Disease states	gastric ulcer, hypothyroidism retards it, while duodenal ulcer, hyperthyroidism promotes it.

5) Intestinal transit time:

➢Intestinal transit time is the major site of absorption of most of drugs.

➢The mixing movement of the intestine that occurs due to peristaltic contractions promotes drug absorption, firstly, by increasing the drug intestinal membrane contact and secondly by enhancing drug dissolution of especially of poorly soluble drugs, through induced agitation.

➢Delayed intestinal transit is desirable for

A) Drugs that dissolve or release slowly from their dosage form (sustained release products)

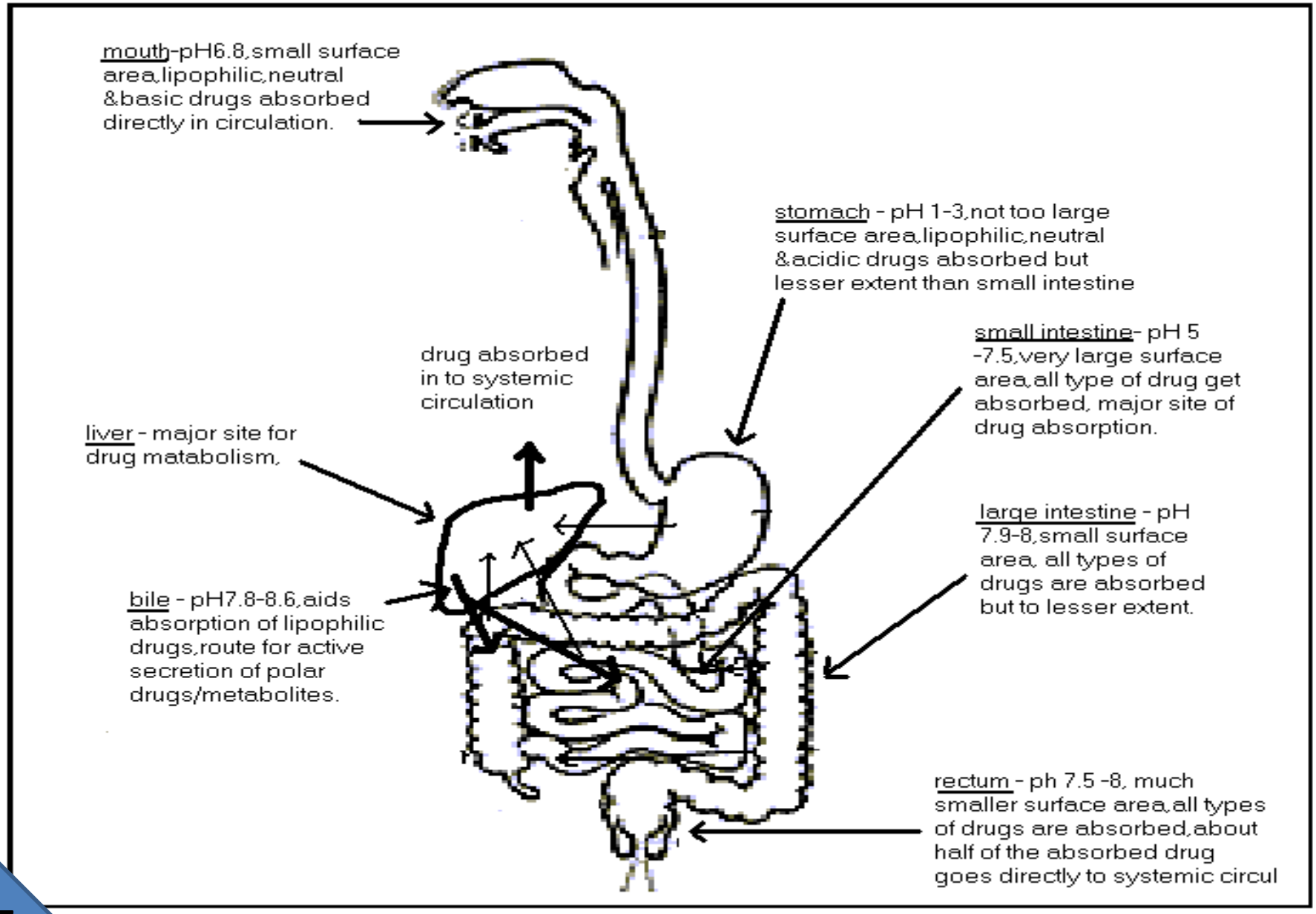
B) Drugs that dissolve only in intestine (enteric coated formulations)

C) Drugs absorbed from specific sites in the intestine (several B vitamins)

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

- Intestinal transit time is influenced by various factors such as food, diseases and drugs
- E.g. metoclopramide which promotes intestinal transit, enhance absorption of rapidly soluble drugs while anticholinergic retards intestinal transit and promotes the absorption of poorly soluble drugs.

6) Gastrointestinal pH:



7) Disease states:

Gastric diseases (Achlorhydric patients):

- They may not have adequate production of acids in the stomach; stomach HCl is essential for solubilizing insoluble free bases.

- Many weak-base drugs that cannot form soluble salts & remain undissolved therefore unabsorbed. Salt forms of these drugs cannot be prepared because the free base readily precipitates out.

- E.g. Dapsone, itraconazole, and ketoconazole .

Cardio-vascular diseases:

- Several changes associated with congestive cardiac failure influence bio-availability of a drug viz., edema of the intestine, decreased blood flow to the GIT and gastric emptying rate and altered GI pH, secretions and microbial flora.

8) Blood flow through the GIT:

- It plays a major role in absorption by continuously maintain the concentrtion gradient across the epithelial membrane.

- The GIT is extensively supplied by blood capillary network.

- Blood flow is imp for actively absorption of drugs.

- Absorption of polar molecules doesn't depends on the blood flow but lipid soluble molecules highly depends on the blood flow.

- Food influences blood flow to the GIT. Perfusion increases after meals & persist for few hours but absorption is not affected.

9) Gastrointestinal contents:

1) **Food- drug interactions**:The presence of food in the GI tract can affect the bioavailability of the drug .

- Digested foods contain amino acids, fatty acids, and many nutrients that may affect intestinal pH and solubility of drugs.

- Some effects of food on the bioavailability of a drug from a drug product include:

Delay in gastric emptying
Stimulation of bile flow
A change in the pH of the GI tract
An increase in splanchnic blood flow

➢Presence of food will affect absorption in following way

a)Decreased absorption: ex. Penicillin, erythromycin, ethanol, tetracycline, levodopa etc.

b)Increased absorption: ex grieseofulvin, diazepam, vitamins etc.

2) Fluid volume:

➢Large fluid volume results in better dissolution, rapid gastric emptying and enhanced absorption-

➢Ex. Erythromycin is better absorbed when taken with a glass of water under fasting condition than when taken with meals.

3) Interaction of drug with normal GI constituents:

➢The GIT contains a number of normal constituents such as mucin which is a protective mucopolysaccharides that lines the GI mucosa, interact with streptomycin.

10) Presystemic metabolism:

➢The loss of drugs through bio-transformation by such eliminating organs during the passage to systemic circulation is called as first-pass or pre-systemic metabolism.

➢complete absence of the drug in plasma after oral administration is indicative of the first-pass effects. The four primary systems which affect the pre-systemic metabolism of a drug

1) Lumenal Enzymes
2) Gut wall enzymes/mucosal enzymes
3) Bacterial enzymes
4) Hepatic enzymes

1) Lumenal Enzymes:

➢The primary enzyme found in gastric juice is pepsin. Lipases, amylases and proteases are secreted from the pancreas into the small intestine in response to ingestion of food.

➢Pepsins and the proteases are responsible for the degradation of protein and peptide drugs in the lumen.

2) Gut wall enzymes:

➢These also called mucosal enzymes, they are present in stomach, intestine and colon. Alcohol dehydroginase (ADH) is an enzyme of stomach mucosa that inactivates ethanol.

➢E.g. sulfation of ethinyl estrdiol & isoprenaline.

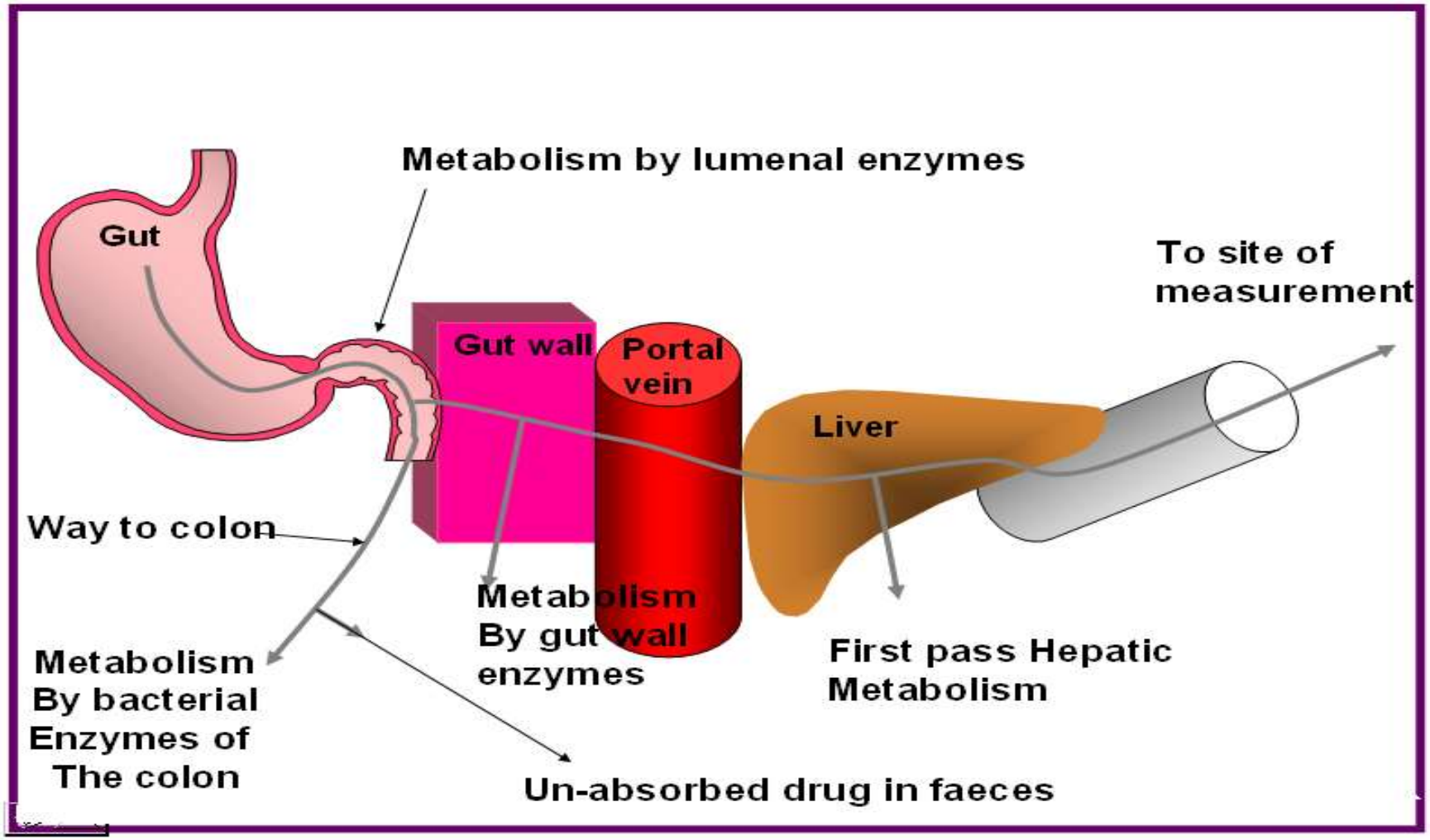
3) Bacterial enzymes:

- Which are mainly localized within the colonic region of the gastrointestinal tract, also secrete enzymes which are capable of a range of reactions.

- E.g. Sulphasalazine, is a prodrug of 5- aminosalicylic acid linked via an azo bond to sulphapyridine.

4) Hepatic enzymes:

➢Several drugs undergo first –pass hepatic metabolism, the highly extracted ones being Isoprenaline, propanolol, diltiazem, etc.



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THANK
YOU….

MEASUREMENT OF BIOAVAILABILITY & CONCEPT OF EQUIVALENCE

CONTENTS

- *Brief introduction to bioavailability*
- *Objectives of bioavailability*
- *Methods of assessing bioavailability*
- *Concept of equivalence*
- *References*

Introduction

- Bioavailability is defined as rate and extent of absorption of unchanged drug from it's dosage form and become available at the site of action.

- Bioavailability of a drug from it's dosage form depends upon 3 major factors:

  - ➢ Pharmaceutical factors
  - ➢ Patient related factors
  - ➢ Route of administration

Objectives

- Development of new formulations.
- Determination of influence of excipients, patient related factors and possible interaction with other drugs on the efficiency of absorption.
- Control of quality of a drug product during the early stages of marketing in order to determine the influence of processing factors, storage, stability on drug absorption.
- Primary stages of the development of a suitable dosage form for a new drug entity.

Absolute bioavailability (F)

•When systemic availability of drug administered orally is determined in comparison to its intravenous administration, is called absolute bioavailability.

•Its determination is used to characterize a drug's inherent absorption properties from the extra vascular site.

$$\text{Absolute bioavailability} = \frac{[\text{AUC}]_{oral}\,(\text{Dose})_{iv}}{[\text{AUC}]_{iv}\,(\text{Dose})_{oral}}$$

Relative Bioavailability (Fr)

- When systemic availability of drug after oral administration is compared with that of an oral standard of same drug (such as an aqueous or non aqueous solution or suspension) it is referred as relative bioavailability.

- It is used to characterize absorption of drug from its formulation.

$$\text{Relative Bioavailability} = \frac{[\text{AUC}]\text{test (Dose)std}}{[\text{AUC}]\text{std (Dose)test}}$$

METHODS OF ASSESSING BIOAVAILABILITY:

PHARMACOKINETIC METHODS

- *Plasma Level- Time Studies*
- *Urinary Excretion Studies*

PHARMACODY NAMIC METHODS

- *Acute Pharmacological Response*
- *Therapeutic Response*

Pharmacokinetic Methods

- Widely used and based on assumption that Pharmacokinetic profile reflects the therapeutic effectiveness of a drug.

Plasma Level- Time Studies:

- Most common type of human bioavailability studies.
- Based on the assumption that there is a direct relationship between the concentration of drug in blood or plasma and the concentration of drug at the site of action.
- Following the administration of a single dose of a medication, blood samples are drawn at specific time intervals and analyzed for drug content.

- A profile is constructed showing the concentration of drug in blood at the specific times the samples were taken.

- Bioavailability (the rate and extent of drug absorption) is generally assessed by the determination of following three parameters.

They are.. C_{max} ***(Peak plasma concentration)***

t_{max}***(time of peak)***

Area under curve

Plasma Drug Concentration- Time Profile

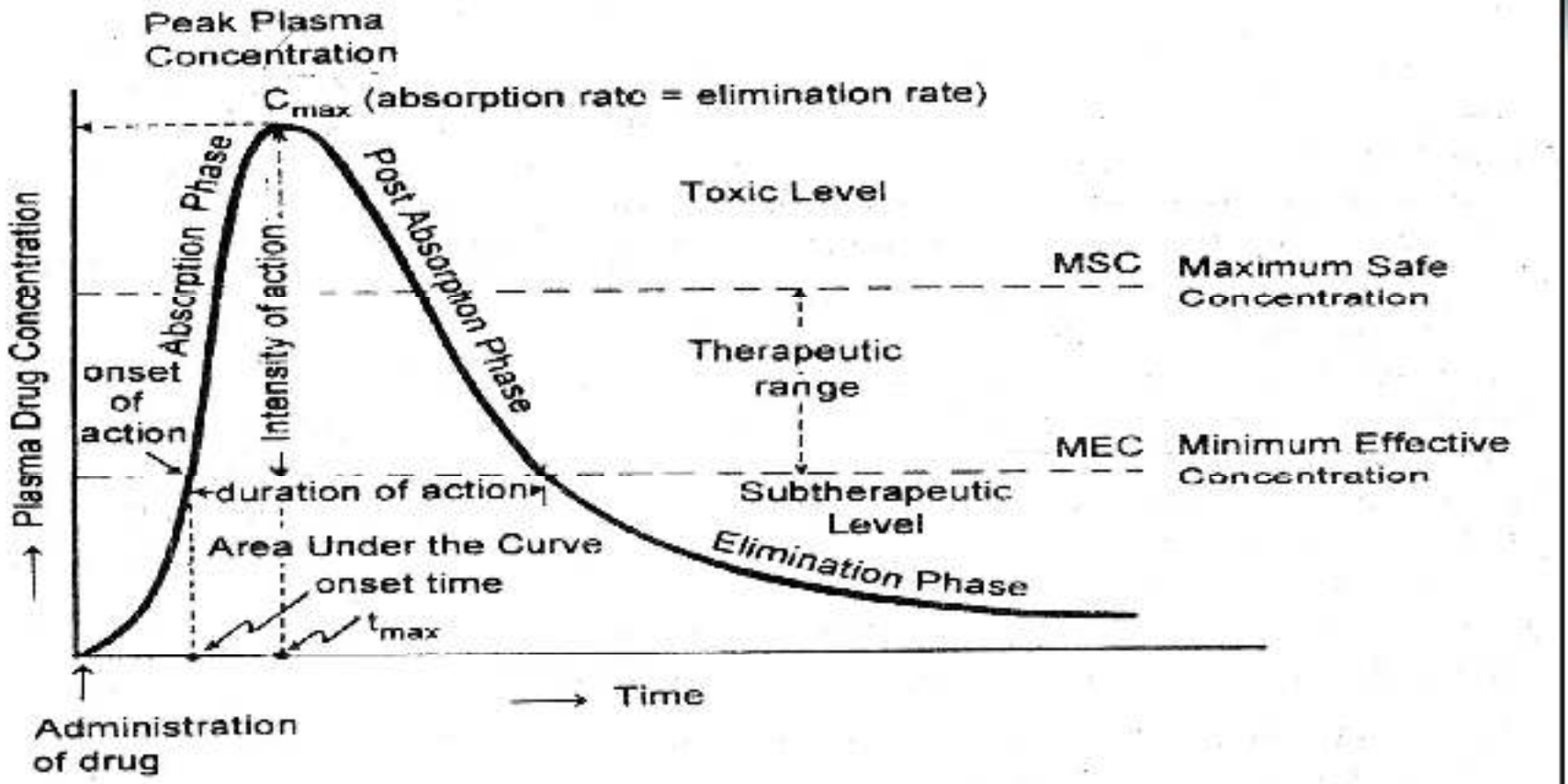


Fig. 9.1 A typical plasma concentration-time profile showing pharmacokinetic and pharmacodynamic parameters, obtained after oral administration of single dose of a drug.

Methods of Bioavailability measurement

Pharmacokinetic methods

1. Plasma level time studies:

most reliable method of choice comparison to urine data method

Single dose: serial blood samples collection – **2-3 half lifes**

Plot concentration vs time

For **I.V.** Sampling started within **5 min** and subsequent samples at **15 min intervals**

For **oral dose** at least **3 points** taken on absorption curve (ascending part)

Parameters considered important in plasma level time studies

➢ **C_{max}:** (Peak plasma drug concentration)

- Maximum concentration of the drug obtained after the administration of single dose of the drug.
- Expressed in terms of μg/ml or mg/ml.

➢ **t_{max}:** (Time of peak plasma conc.)

Time required to achieve peak concentration of the drug after administration.

- Gives indication of the rate of absorption.
- Expressed in terms of hours or minutes.

- The extent of bioavailability can be determined by the following equations:

For single dose study:

$$F = \frac{[AUC]\text{oral Div}}{[\text{AUC}]\text{iv Div}}$$

$$Fr = \frac{[AUC]\text{test Dstd}}{[\text{AUC}]\text{stdDtest}}$$

For multiple dose study:

$$Fr = \frac{[AUC]\text{test Dstd}\tau\text{test}}{[\text{AUC}]\text{stdDtest}\tau\text{std}}$$

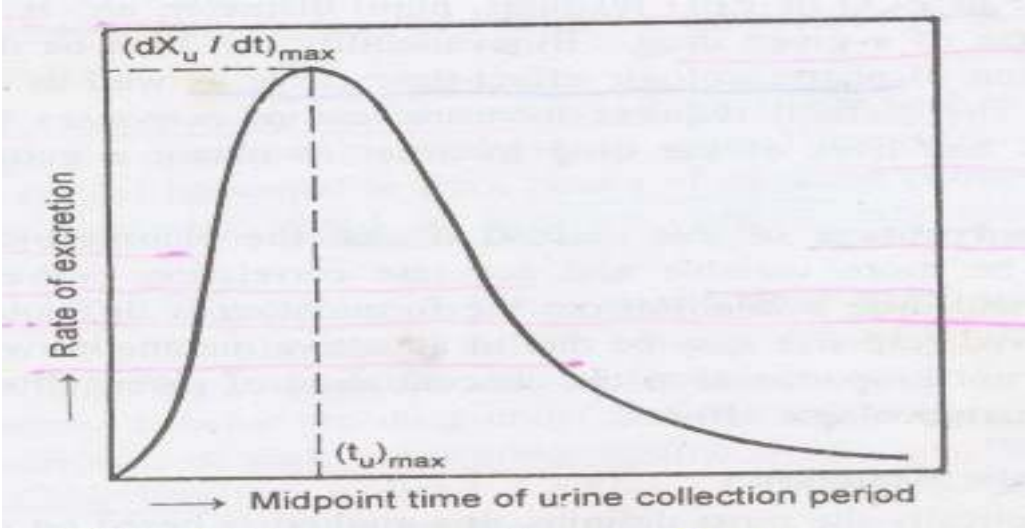
$$Fr = \frac{(\text{Css, max})\text{test Dstd }\tau\text{test}}{[\text{Css, max}]\text{stdDtest}\tau\text{std}}$$

➢ *Three Important Parameters in urine excretion data for single dose study:*

$(dx_u/dt)_{max}$

$(t_u)_{max}$

X_u^{∞}



Plot of urinary excretion rate V_s time

2. Urinary excretion studies:

This method is based on the principle that the **urinary excretion** of unchanged drug is **directly proportional** to the **plasma concentration** of drug.

It can be performed if

-At least **20%** of administered dose is **excreted** unchanged in urine.

The study is useful for

- Drugs that extensively excreted unchanged in urine eg. Thiazide diuetics
- Drugs that have urine as site of action eg. Urinary antiseptics like nitrofurontoin.

Steps involved:

-collection of urine at regular intervals for **7 half lifes.**

- **Analysis** of unchanged drug in collected sample.
- Determination of **amount of drug** at each interval and **cumulative** as well.

Criteria's must be followed

- At each sample collection **total emptying of bladder** is necessary.
- **Frequent sampling** is essential in the **beginning** to compute correct rate of absorption.
- The fraction excreted unchanged in urine must remain constant.

Parameters considered important in Urinary excretion studies

1. **(Dx/dt)max:** Maximun urinary excretion rate
2. **(tu)max:** Time for maximum excretion rate
3. **Xu∞**: Cumulative amount of drug excreted in the urine.

Urinary Excretion Studies:

- Urinary excretion of unchanged drug is directly proportional to plasma concentration of drug.
- Thus, even if a drug is excreted to some extent (at least 10 to 20%) in the urine, bioavailability can be determined.

  eg: Thiazide diuretics, Sulphonamides.
- Method is useful when there is lack of sufficiently sensitive analytical technique to measure drug concentration.
- Noninvasive method, so better patient compliance.

$(dx_u/dt)max$:(Maximum urinary excretion rate)

- Its value increases as rate and/or extent of absorption increases.
- Obtained from peak of plot between rate of excretion versus midpoint time of urine collection period.

(t_u) max:

- Time for maximum excretion rate
- Its value decreases as absorption rate increases.
- Analogues of t_{max} of plasma level data.

$X_{u\infty}$:Cumulative amount of drug excreted in urine

- Related to AUC of plasma level data.
- It increases as the extent of absorption increases.

Pharmacodynamic methods

1. Acute pharmacological response:

When bioavailability measurement by pharmacokinetic methods is difficult, inaccurate or non reproducible this method is used. Such as **ECG, EEG, Pupil diameter** etc.

It can be determined by **dose response graphs**. Responses measure for at least **3 half lifes.**

Disadvantages:

- Pharmacological response is **variable** and accurate correlation drug and formulation is difficult.

-Observed response may be due to **active metabolite.**

2. Therapeutic response:

This method is based on observing **clinical response** in patients.

Drawbacks:

- **Quantitation** of observed response is too **improper.**

-The **physiological status** of subject **assumed** that does **not change** significantly over duration of study.

-If multiple dose protocols are not involved. Patient receive **only single dose** for **few days** or a **week**

-The patient s receiving **more than one drug** treatment may be compromised due to **drug-drug interaction.**

Pharmacodynamic methods

Acute Pharmacologic Response Method:

- When bioavailablity measurement by pharmacokinetic method is difficult, an acute pharmacologic effect such as effect on pupil diameter, EEG & ECG readings related to time course of drug.
- Bioavailability can then be determined by construction of pharmacological effect- time curve as well as dose response graphs.

Disadvantage:

- It tends to be more variable.
- Observed response may be due to an active metabolite whose concentration is not proportional to concentration of parent drug.

Therapeutic Response Method:

- This method based on observing the clinical response to a drug formulation given to patient suffering from disease.

Drawbacks:

The major drawbacks of this method is that quantitation of observed response is too improper to allow for reasonable assessment of relative bioavailability between two dosage forms of the same drug.

E.g.: Anti-inflammatory drugs.

❖ Many patients receive more than one drug

In vitro dissolution studies and bioavailability:

The physicochemical property of most drugs that has greatest influence on absorption from GIT is dissolution rate. However in vitro dissolution is good substitute for in vivo study in terms of saving cost and time. The best available tool today which can at least quantitatively assure about the bioavailability of drug from its formulation is in vitro dissolution test.

In vitro- in vivo correlation (IVIVC):

It is defined as the predictive mathematical model that describes the relationship between in vitro property (rate & extent of dissolution) and in vivo response (plasma drug concentration).

The main objective of developing and evaluating IVIVC is to use dissolution test to serve as alternate for in vivo study in human beings.

IVIVC Levels:

Level A: The highest category of correlation. It represents point to point correlation between in vitro dissolution and in vivo rate of absorption.

Advantages: serves as alternate for in vivo study, change in mfg. Procedure or formula can be justified without human studies.

Level B: The mean in vitro dissolution time is compare with mean in vivo residence time. It is not point to point correlation . Data can be used for quality control standards.

Level C: It is single point correlation. e.g. $t_{50\%,}$ Tmax, Cmax. This level is only useful as guide for formulation development or quality control.

CONCEPT OF EQUIVALENCE:

EQUIVALENCE: Relationship in terms of bioavailability, therapeutic response or a set of established standards of one drug product to another.

Objectives:

- If a new product intended to be a substitute for an approved medical product.
- To ensure clinical performance of drugs.
- Equivalence studies are conducted if there is:
  - a) A risk of bio-inequivalence.
  - b) A risk of pharmacotherapeutic failure or diminished clinical safety.

Equivalence may be defined in several ways:

Chemical equivalence:

✓ If two or more dosage forms of same drug contain same labelled quantities specified in pharmacopoeia.

Eg : Dilantin and Eptoin chemically equivalent as they contain same quantity of Phenytoin on chemical assay.

Bioequivalence:

✓ The drug substance in two or more identical dosage forms, reaches the systemic circulation at the same relative rate and extent i.e. their plasma concentration-time profiles will be identical without significant statistical differences.

Pharmaceutical equivalents:

Drug products in identical dosage forms that contain same active ingredient(s),i.e , the same salt or ester, are of the same dosage form, use the same route of administration, and are identical in strength or concentration.

Eg : Chlordiazepoxide hydrochloride,5mg capsules.

Pharmaceutical equivalent drug products are:

Same in :

- ✓ Active ingredient and it's quantity
- ✓ Dosage form
- ✓ standards like strength, quality , purity and identity.

✓ Disintegration time

✓ Dissolution rates

Differ in:

- Shape
- Release mechanisms
- Packing
- Excipients(including colours , flavours , preservatives)
- labeling

Pharmaceutical alternatives:

✓ Drug product that contain the same therapeutic moiety but as different salts, esters or complexes.

Eg: Tetracyclin phosphate or Tetracyclin hydrochloride equivalent to 250mg Tetracyclin base are consider as pharmaceutical alternatives.

pharmaceutical substitution:

✓ The process of dispensing a pharmaceutical alternative for the prescribed drug product.

Eg: Ampicillin suspension is dispensed in place of Ampicillin capsules.

Tetracyclin hydrochloride is dispensed in place of Tetracyclin phosphate.

NOTE: Pharmaceutical substitution generally requires the physician's approval.

Therapeutic equivalents:

✓ Drug products consider to be therapeutic equivalence only if they are pharmaceutical equivalence and if they can be expected to have a same clinical effect and safety profile when administered to patient specified in the labeling.

✓ FDA classifies as therapeutically equivalent those products that meet the fallowing general criteria:

1)They approved as safe and effective.

2)They are pharmaceutically equivalents.

3)They are bioequivalence.

4)They are adequately labeled .

5)They are manufactured in compliance with current GMP regulations.

Therapeutic alternatives:

✓ Drug products containing different active ingredients that are indicated for the same therapeutic or clinical objectives.

Eg: Ibuprofen is given instead of Aspirin.

Cimetidine instead of Ranitidine.

Therapeutic substitution:

✓ The process of dispensing a therapeutic alternative in place of the prescribed drug product.

Eg: Ampicillin is dispensed instead of Amoxicillin.

Ibuprofen is dispensed instead of Naproxen.

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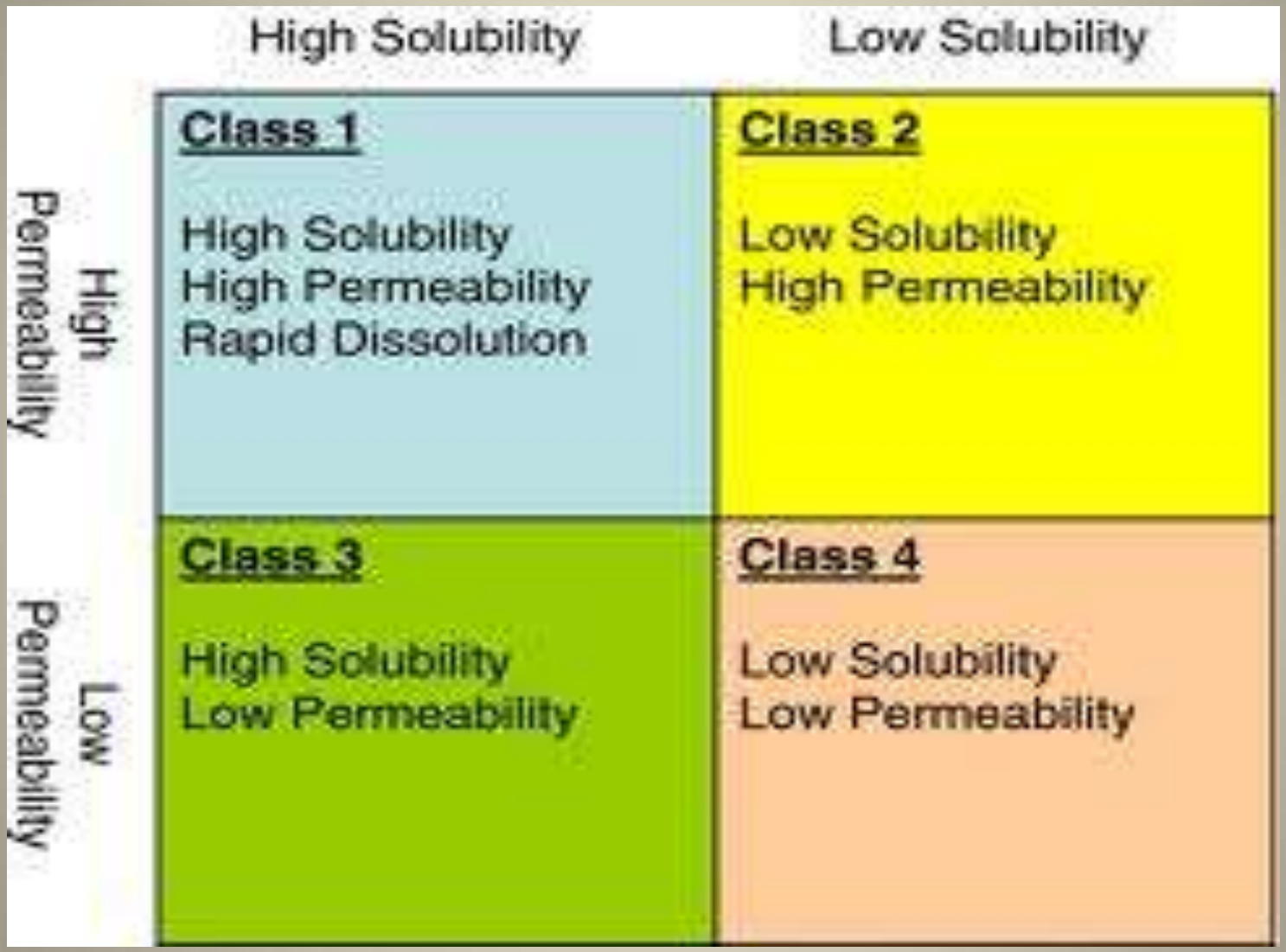
THANK YOU...

INTRODUCTION :

- DEFINITION : Solubility is defined in quantitative terms as concentration of solute in concentrated solution at a certain temperature, and in qualitative way it can be defined as a spontaneous interaction of two or more substances to form a homogenous molecular dispersion.

- Solubilization can be defined as a preparation of thermodynamically stable isotropic solution of a substance normally insoluble or slightly soluble in a given solvent by introduction of an additional component or components.


High Solubility
Low Solubility
Class 1
High Solubility
High Permeability
Rapid Dissolution
Class 2
Low Solubility
High Permeability
Class 3
High Solubility
Low Permeability
Class 4
Low Solubility
Low Permeability
High Permeability
Low Permeability

The biopharmaceutical classification system (BCS)

CLASS	SOLUBILITY	PERMEABILITY	ABSORPTION PATTERN	RATE LIMITING STEP IN ABSORPTION
I	High	High	Well absorb	Gastric emptying
II	Low	High	variable	Dissolution
III	High	Low	Variable	Permeability
IV	Low	Low	Poorly absorb	Case by case

The pharmacopoeia lists solubility in terms of number of milliliters of solvent required to dissolve 1g of solute. The Indian pharmacopoeia provides general terms to describe a given range. These descriptive terms are given as:

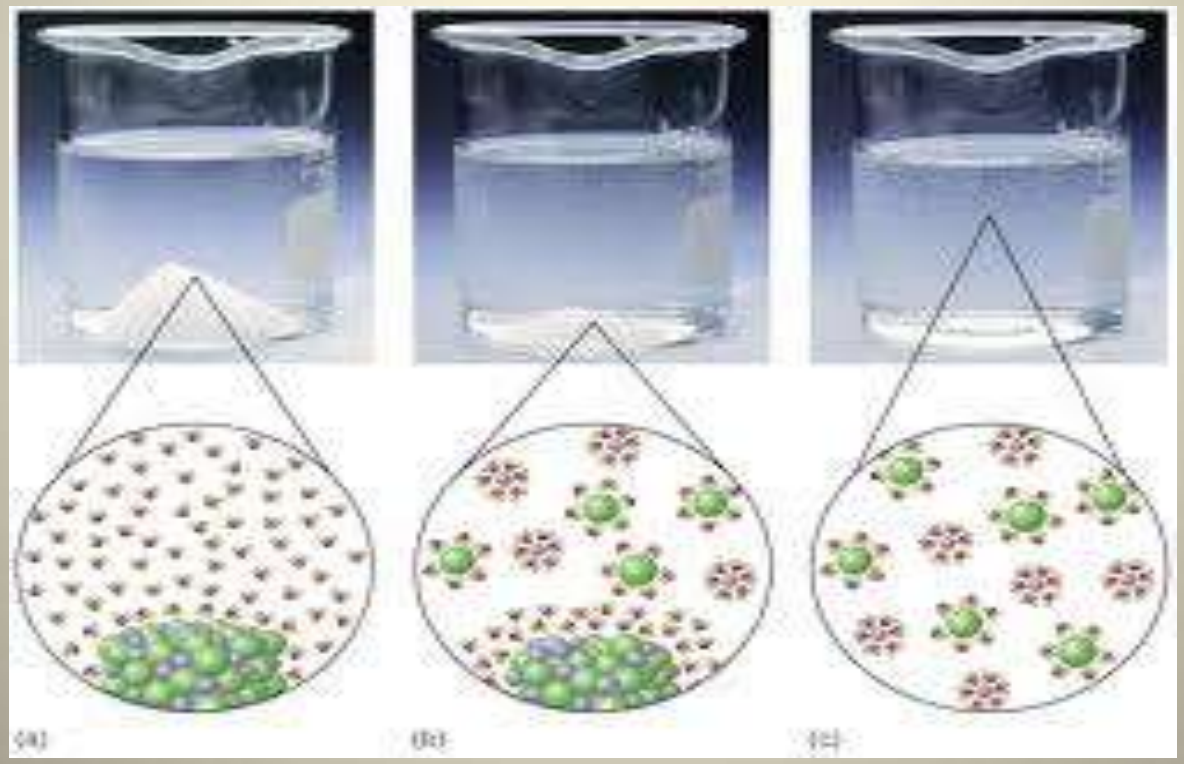
DEFINITION	PARTS OF SOLVENT REQUIRED FOR 1 PART OF SOLUTE
Very soluble	< 1
Freely soluble	1 - 10
Soluble	10 – 30
Sparingly soluble	30 - 100
Slightly soluble	100 - 1000
Very slightly soluble	1000 – 10,000
Insoluble	>10,000

IMPORTANCE OF SOLUBILITY:

- Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules.
- Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown.
- Currently only 8% of new drug candidates have both high solubility and permeability.
- Nearly 40% of the new chemical entities currently being discovered are poorly water soluble.
- More than one-third of the drugs listed in the U.S. Pharmacopoeia fall into the poorly water-soluble or water-insoluble categories.
- Low aqueous solubility is the major problem encountered with formulation development of new chemical entities.
- Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption.

SOLUBILIZATION

The process of solubilization involves the breaking of inter-ionic or intermolecular bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion.

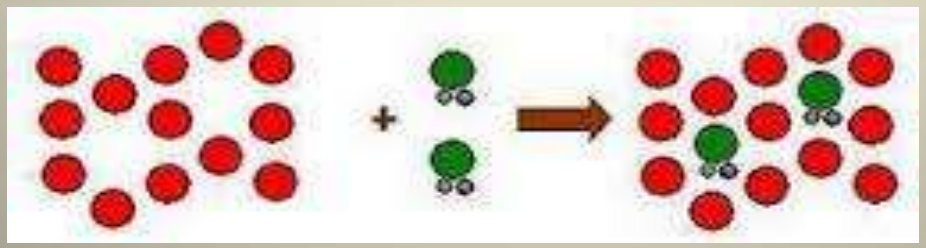


STEPS INVOLVED ARE :

1: Holes opens in the solvent

2. Molecules of the solid breaks away from the bulk.

3. The freed solid molecule is integrated into the hole.



TECHNIQUES OF SOLUBILITY ENHANCEMENT

I. Physical Modifications

A. Particle size reduction

1. Micronization
2. Nanosuspension
3. Sonocrystalisation
4. Supercritical fluid process

B. Modification of the crystal habit

1. Polymorphs
2. Pseudopolymorphs

C. Drug dispersion in carriers

1. Eutectic mixtures
2. Solid dispersions
3. Solid solutions

D. Complexation

Use of complexing agents

E. Solubilization by surfactants

Microemulsions

II. Chemical Modifications

1. Change in the pH
2. Use of buffer
3. Derivatization

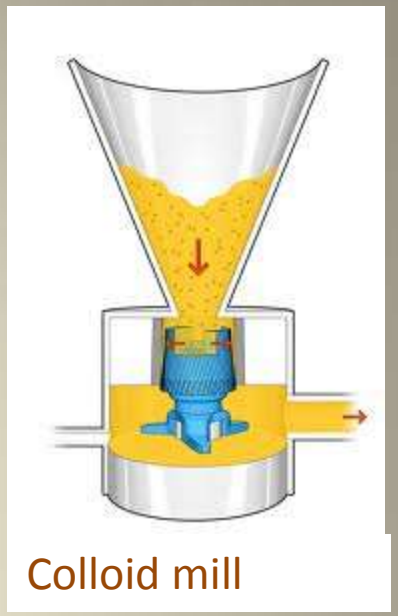
III. Other methods

1.co-crystallisation
2. co-solvency
3.Hydrotrophy
4.Solubilizing agents
5.Selective adsorption on insoluble carrier
6.Solvent deposition
7.Using soluble prodrug
8.Functional polymer technology
9.Precipitation Porous
10.microparticle technology
11.Nanotechnology approaches

A.Particle size reduction:

Particle size reduction can be achieved by

a. Micronization
b. nanosuspension
c. Sonocrystalisation
d.Supercritical fluid process



Colloid mill

1. Micronization:

- Micronization increases the dissolution rate of drugs through increased surface area.
- Micronization of drugs is done by milling techniques using jet mill, rotor stator colloid mills etc.
- Micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug .
- The process involves reducing the size of the solid drug particles to 1 to 10 microns commonly by spray drying or by use of attrition methods. The process is also called micro-milling.

2. Nanosuspension :

Nanosuspensions are sub-micron colloidal dispersion of pure particles of the drug, which are stabilized by surfactants. Nanosuspension technology is used for efficient delivery of hydrophobic drugs . The particle size distribution of the solid particles in nanosuspensions is usually less than one micron with an average particle size ranging between 200 and 600 nm.

Advantage :

Increased dissolution rate due to larger surface area exposed.

Eg., Nanosuspension approach has been employed drugs like paclitaxel, tarazepide, amphotericin B which are still on research stage.

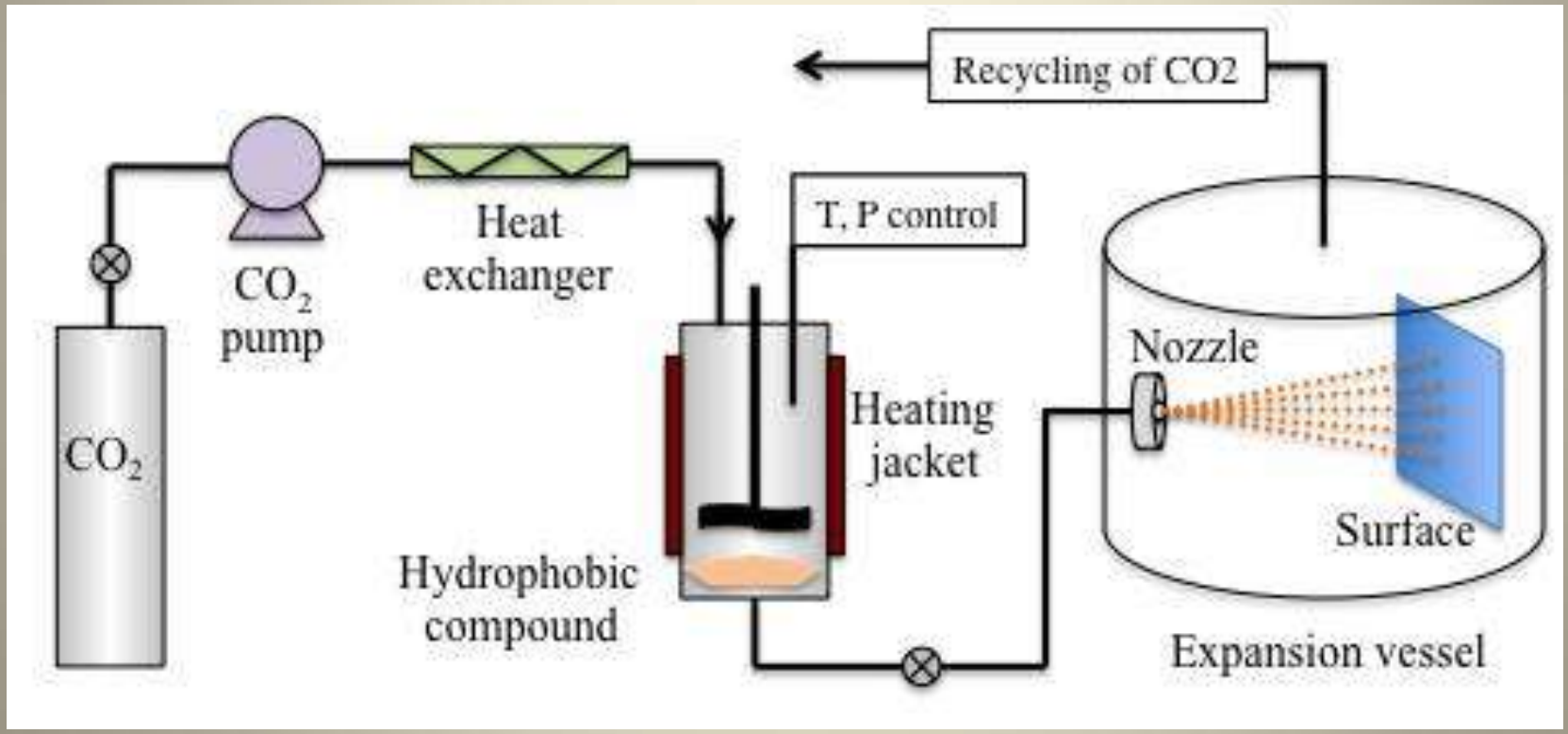
3.Sonocrystallisation :

Particle size reduction on the basis of crystallisation by using ultrasound is Sonocrystallisation . Sonocrystallisation utilizes ultrasound power for inducing crystallisation . It not only enhances the nucleation rate but also an effective means of size reduction and controlling size distribution of the active pharmaceutical ingredients. Most applications use ultrasound in the range 20 kHz-5 MHz.

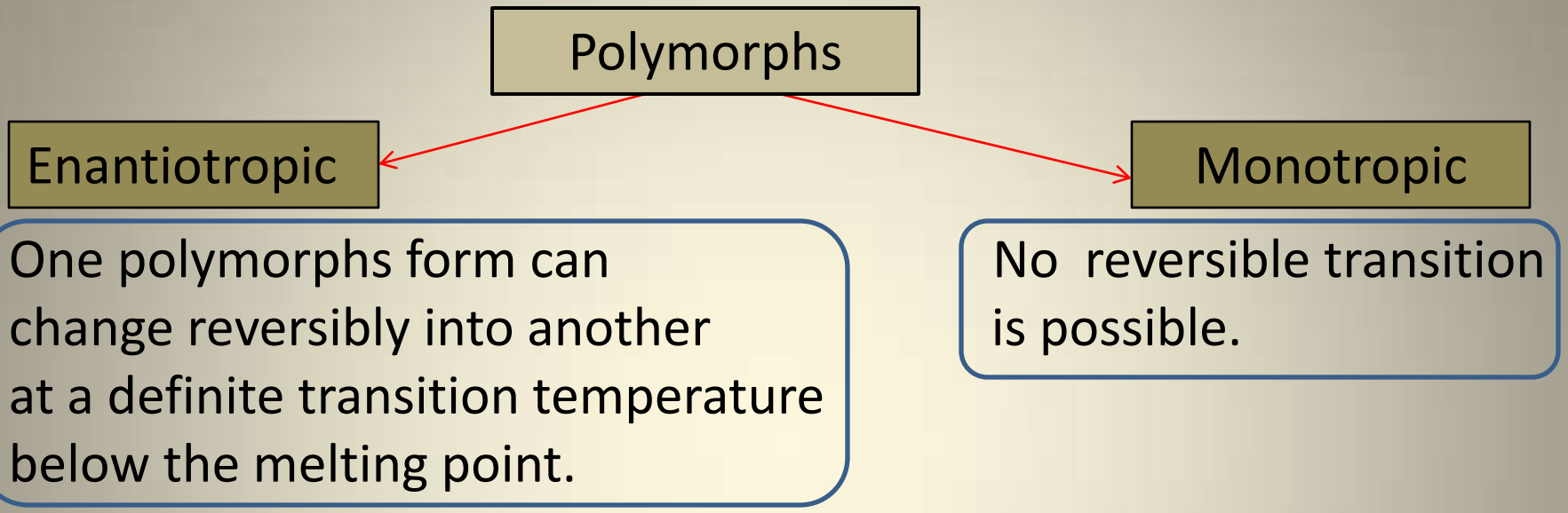
4. Supercritical fluid process :

- A supercritical fluids are dense non-condensable fluid whose temperature and pressure are greater than its critical temperature (Tc) and critical pressure (Tp) allowing it to assume the properties of both a liquid and a gas.
- Through manipulation of the pressure of SCFs, the favourable characteristics of gases – high diffusivity, low viscosity and low surface tension may be imparted upon the liquids to precisely control the solubilisation of a drug with a supercritical fluid.

- Once the drug particles are solubilised within SCFs, they may be recrystalised at greatly reduced particle sizes.
- A SCF process allows micronisation of drug particles within narrow range of particle size, often to sub-micron levels.



B. Modification of the crystal habit:



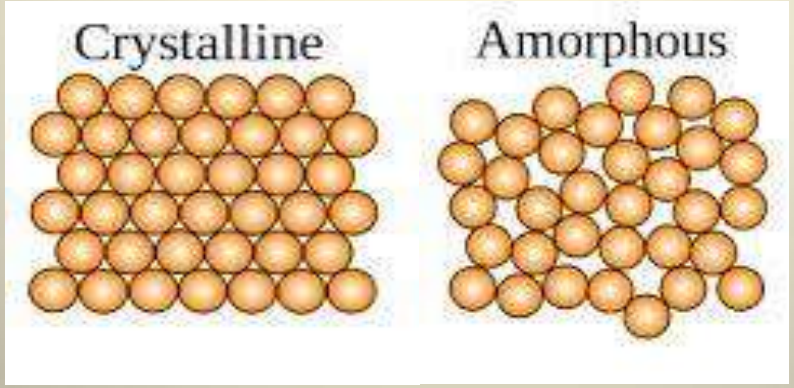
- Metastable forms are associated with higher energy and thus higher solubility. Similarly the amorphous form of drug is always more suited than crystalline form due to higher energy associated and increased surface area.
- The anhydrous form of a drug has greater solubility than the hydrates. This is because the hydrates are already in interaction

with water and therefore have less energy for crystal breakup in comparison to the anhydrates.

- They have greater aqueous solubility than the crystalline forms because they require less energy to transfer a molecule into solvent. Thus, the order for dissolution of different solid forms of drug is

Amorphous > metastable polymorph > stable polymorph

- Melting followed by a rapid cooling or recrystallization from different solvents can produce metastable forms of a drug.



C. Drug dispersion in carriers:

The term “solid dispersions” refers to the dispersion of one or more active ingredients in an inert carrier in a solid state, frequently prepared by the

1. • Hot melt mehod
2. • Solvent evaporation method
3. • Hot melt extrusion method

1. Hot melt method :

Drug + vehicle (m.p low, organic solvent – insoluble)

(heating)

Melting

Freezing quickly

Dosage forms

A molecular dispersion can be achieved or not, depends on the degree of supersaturation and rate of cooling used in the process.

Important requisites :

1. Miscibility of the drug & carrier in the molten form,
2. Thermostability of the drug & carrier.

Suitable to drugs and vehicles with promising heat stability.

2. Solvent evaporation method:

Drug + vehicle (both soluble in solvent)

⇩ organic solvent

solution

⇩

evaporate the solvent

⇩

coprecipitates

⇩

dosage forms

The solvent evaporation can be done by spray drying or freeze drying.

Temperatures used for solvent evaporation generally lie in the range 23-65 C.

suitable to drugs with volatility or poor stability

3.Hot-melt Extrusion:

Hot melt extrusion of miscible components results in amorphous solid solution formation, whereas extrusion of an immiscible component leads to amorphous drug dispersed in crystalline excipient. The process has been useful in the preparation of solid dispersions in a single step.

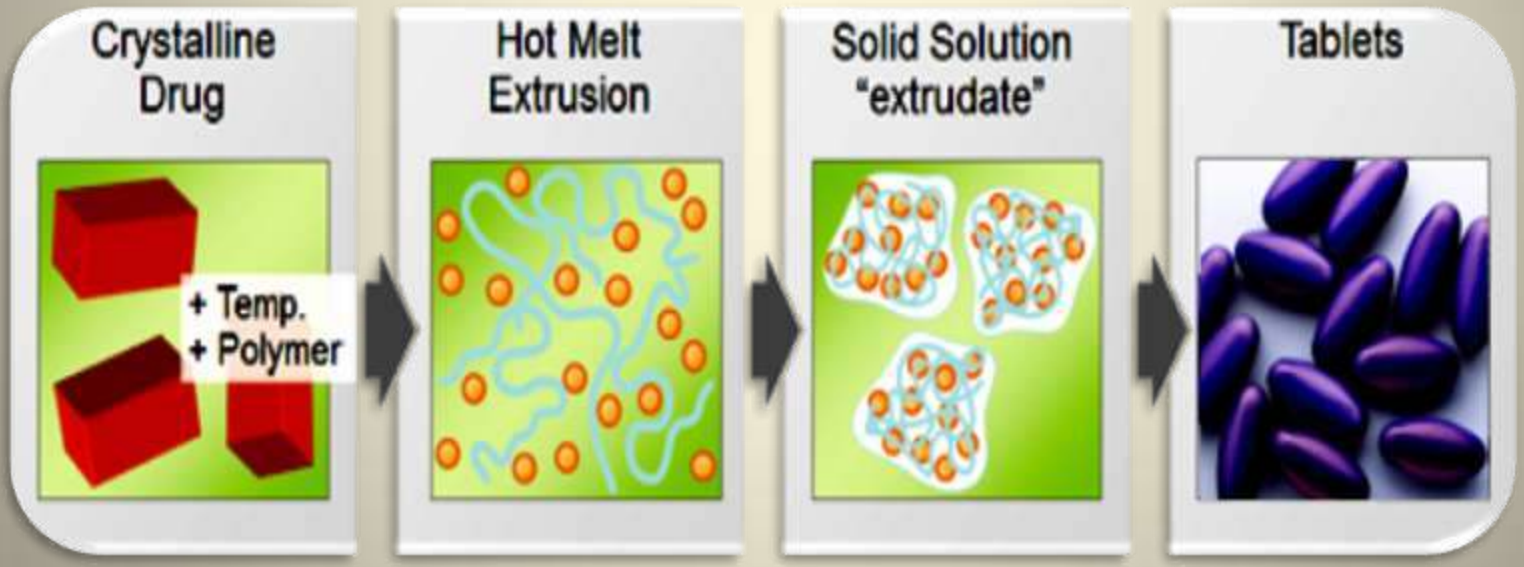
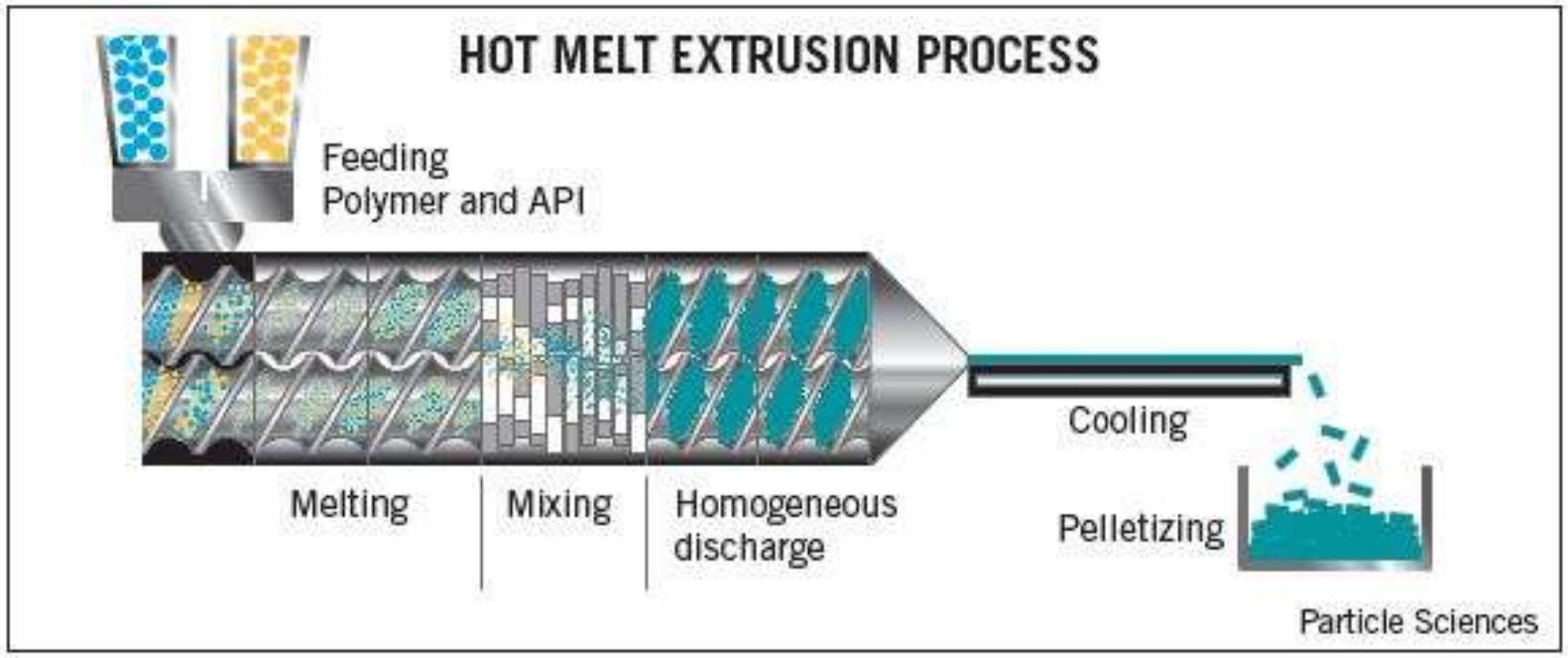


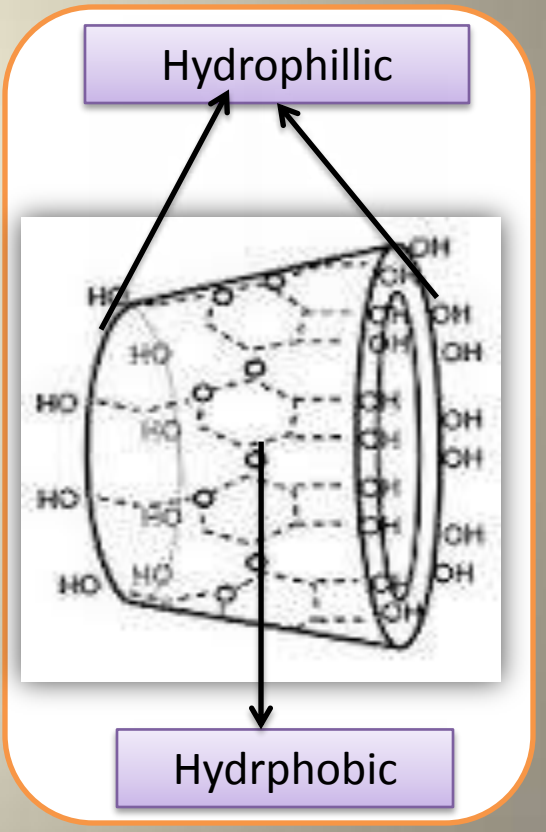
Figure 1


HOT MELT EXTRUSION PROCESS
Feeding
Polymer and API
Cooling
Melting
Mixing
Homogeneous
discharge
Pelletizing
Particle Sciences

D. Complexation :

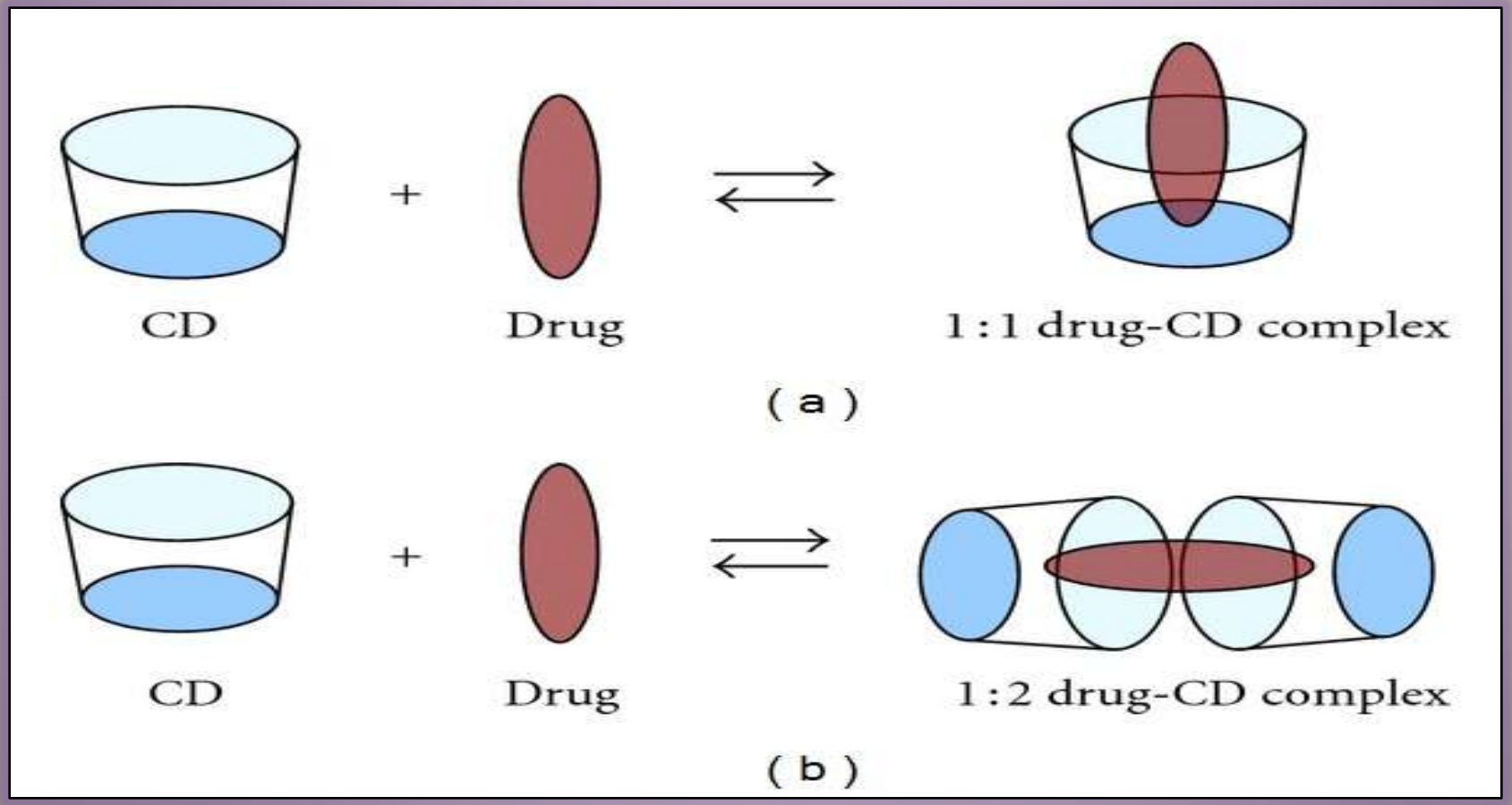
Complexation is the reversible association between two or more molecules to form a nonbonded entity with a well defined stoichiometry . Complexation relies on relatively weak forces such as van-derwaal forces, hydrogen bonding and hydrophobic interactions.

Inclusion complexation: These are formed by the insertion of the nonpolar molecule or the nonpolar region of one molecule into the cavity of another molecule or group of molecules. The most commonly used host molecules are cyclodextrins . Cyclodextrins are non- reducing, crystalline , water soluble, cyclic, oligosaccharides. Cyclodextrins consist of glucose monomers arranged in a donut shape ring.



CYCLODEXTRIN

The surface of the cyclodextrin molecules makes them water soluble, but the hydrophobic cavity provides a microenvironment for appropriately sized non-polar molecules. Based on the structure and properties of drug molecule it can form 1:1 or 1:2 drug cyclodextrin complex. Three naturally occurring CDs are α Cyclodextrin, β Cyclodextrin, and γ Cyclodextrin.



Staching complexation

Organic drug + water → Squeezed out by strong water-water interaction force.

↓

Forms aggregates

↓

Reduces the contact b/w nonpolar hydrocarbon moieties & the polar water molecule

↓

Large nonpolar regions

↓

Opposed by entropy

↓

Random arrangement

↓

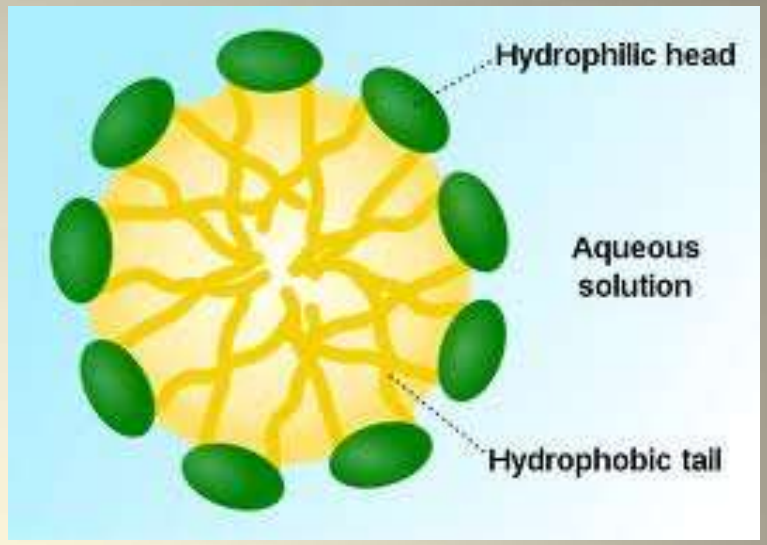
Complexes stached can be homogeneous or mixed

↓

Self association complexation

Eg .,
Nicotinamide,
Anthracene,
Caffeine,
Theobromine.

E. Solubilization by surfactants:



Surfactants are molecules with distinct polar and nonpolar regions. Most surfactants consist of a hydrocarbon segment connected to a polar group. The polar group can be anionic, cationic, zwitter ionic or nonionic. The presence of surfactants may lower the surface tension and increase the solubility of the drug within an organic solvent .

Microemulsion : A microemulsion is a four-component system composed of external phase, internal phase, surfactant and co surfactant . The addition of surfactant, which is predominately soluble in the internal phase unlike the co surfactant , results in the formation of an optically clear, isotropic, thermodynamically stable emulsion. It is termed as microemulsion because of the internal phase is <0.1 micron droplet diameter.

The surfactant and the co surfactant alternate each other and form a mixed film at the interface, which contributes to the stability of the microemulsion .

Non-ionic surfactants, such as Tweens (polysorbates) and Labrafil (polyoxyethylated oleic glycerides), with high hyrophile-lipophile balances are often used to ensure immediate formation of oil-in-water droplets during production.

Advantages :

- Ease of preparation due to spontaneous formation.
- Thermodynamic stability,
- transparent and elegant appearance,
- enhanced penetration through the biological membranes,
- increased bioavailability and
- less inter- and intra-individual variability in drug pharmacokinetics.

II. CHEMICAL MODIFICATIONS

1)By change of pH:

For organic solutes that are ionizable, changing the pH of the system is the simplest and most effective means of increasing aqueous solubility .

For weakly acidic drugs,

LOWER pH → UNIONISED FORM → INSOLUBLE PPT

HIGHER pH → IONISED FORM → MORE SOLUBLE DRUG

For weakly basic drugs,

Lower pH → Ionized form → More soluble drug

Higher pH → UNIONISED FORM → INSOLUBLE PPT

2) Use of buffer: Buffer maintains the pH of the solution overtime and it reduces or eliminate the potential for precipitation upon dilution. On dilution pH alteration occurs that decrease solubility . Change of pH by 1 fold increase solubility by 10 fold If it changes by one pH unit ,that decrease ionization of the drug and solubility decreases by 10 fold.

3) Derivatization : It is a technique used in chemistry which transforms a chemical compound into a product of similar chemical structure, called derivative. Derivatives have different solubility as that of adduct. It is used for quantification of adduct formation of esters and amides via acyl chlorides.

III. OTHER METHODS.

1.Co-crystallization:

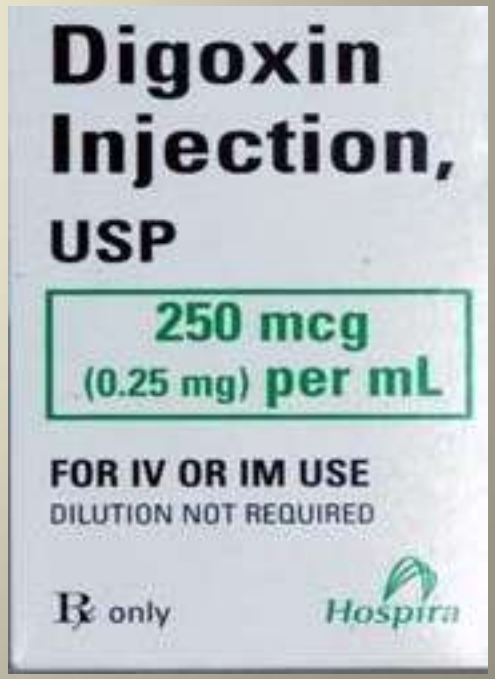
A co-crystal may be defined as a crystalline material that consists of two or more molecular species held together by non-covalent forces.

- Co-crystals are more stable, particularly as the co-crystallizing agents are solids at room temperature.
- Co-crystals can be prepared by evaporation of a heteromeric solution or by grinding the components together.
- Another technique for the preparation of co-crystals includes sublimation, growth from the melt, and slurry preparation.
- Only three of the co-crystallizing agents are classified as generally recognised as safe (GRAS) it includes saccharin, nicotinamide and acetic acid limiting the pharmaceutical applications.

2. Cosolvency : Cosolvents are prepared by mixing miscible or partially miscible solvents. Weak electrolytes and nonpolar molecules have poor water solubility and it can be improved by altering polarity of the solvent. It is well-known that the addition of an organic cosolvent to water can dramatically change the solubility of drugs. Cosolvent system works by reducing the interfacial tension between the aqueous solution and hydrophobic solute.

Aquous solvent - Etahnol, sorbitol, glycerin, propylene glycol.

Non aquous solvent - glycerol dimethyl ketal, glycerol formal, glycofurol, dimethyl acetamide.

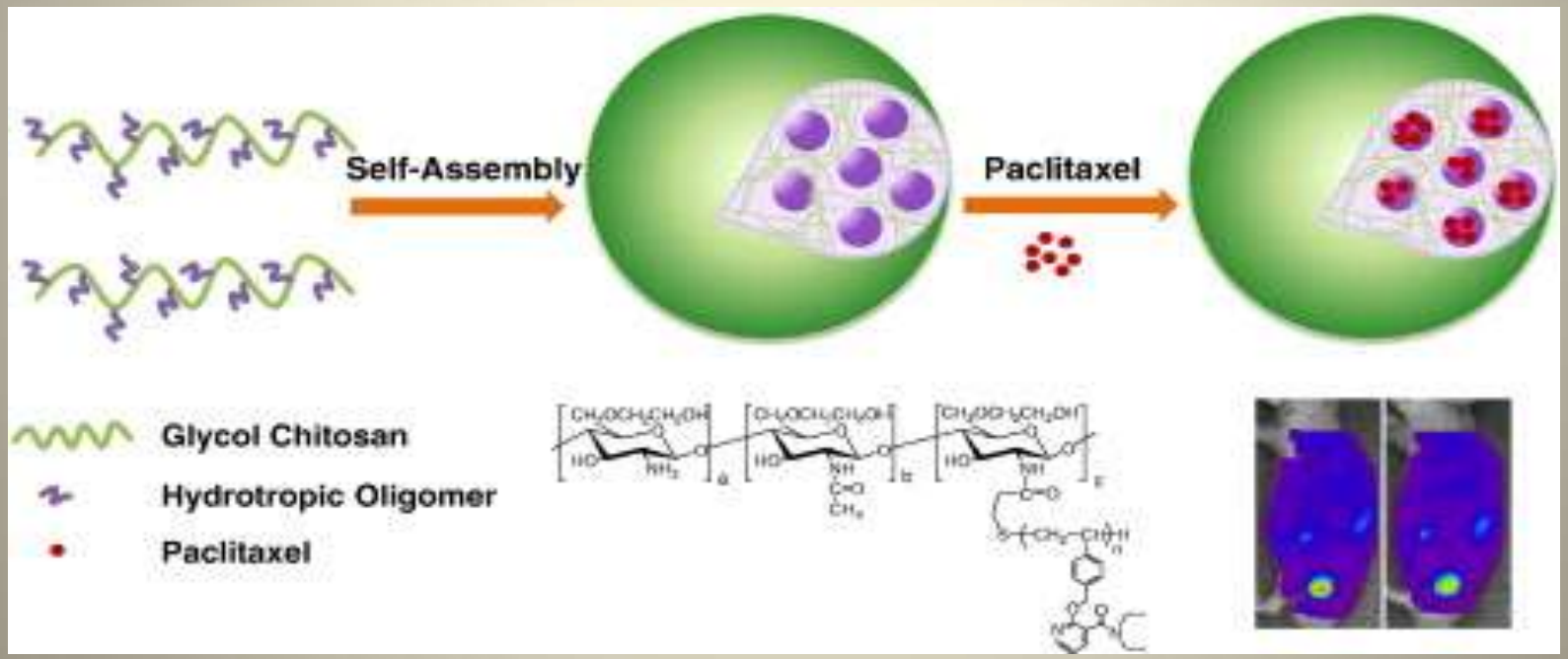


SOME PERANTRALPRODUCT THAT CONTAIN COSOLVENT

1.Diazepam - 10% ethanol + propylene glycol

2.Digoxin - 10% ethanol + propylene glycol

3. Hydrotrophy : Hydrotrophy designate the increase in solubility in water due to the presence of large amount of additives. The mechanism by which it improves solubility is more closely related to complexation involving a weak interaction between the hydrotrophic agents (sodium benzoate, sodium acetate, sodium alginate, and urea).



4. Solubilizing agents: The solubility of poorly soluble drug can also be improved by various solubilizing materials. PEG 400 is improving the solubility of hydrochlorthiazide85. Modified gum karaya (MGK), a recently developed excipient was evaluated as carrier for dissolution enhancement of poorly soluble drug, nimodipine .

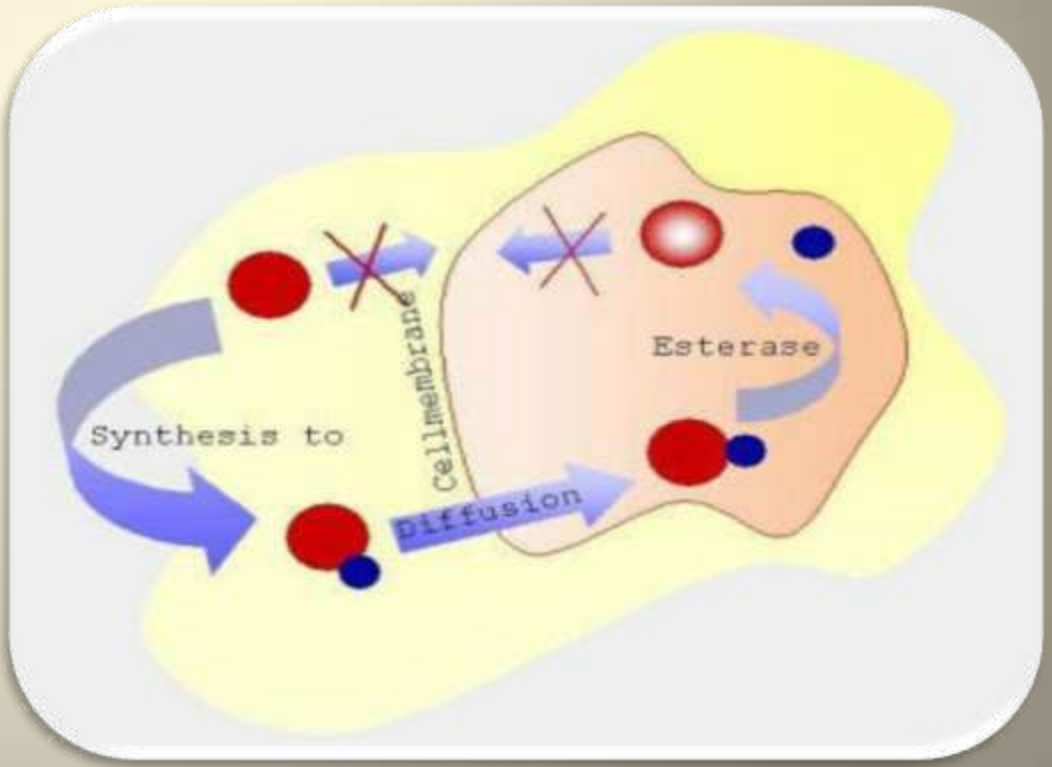
5. Selective adsorption on insoluble carriers: A highly active adsorbent such as inorganic clays like Bentonite can enhance the dissolution rate of poorly water-soluble drugs such as griseofulvin, indomethacin and prednisone by maintaining the concentration gradient at its maximum. 2 reasons suggested for rapid release of drugs from the surface of clays :-

1. weak physical bonding between adsorbate and adsorbent.
2. hydration and swelling of the clay in the aqueous media.

6. Solvent deposition: In this method,the poorly aqueous soluble drug such as Nifedipine is dissolved in an organic solvent like alcohol and deposited on an inert , hydrophilic, solid matrix such as starch or microcrystalline cellulose and evaporation of solvent is done.

7. Use of soluble prodrug :

Prodrug stratergy involves the incorporation of polar or ionizable moiety into the parent compound to improve aqueous solubility. Example : prodrug of established drugs has been successfully used to improve water solubility of corticosteroids benzodiazepines.



8. Functional Polymer Technology : Functional polymer enhances the dissolution rate of poorly soluble drugs by avoiding the lattice energy of the drug crystal, which is the main barrier to rapid dissolution in aqueous media. The dissolution rate of poorly soluble , ionizable drug like cationic, anionic and amphoteric actives can be enhanced by this technology. Applied to heat sensitive materials and oils also.

9. Precipitation: In this method, the poorly aqueous soluble drug such as cyclosporine is dissolved in a suitable organic solvent followed by its rapid mixing with a non-solvent to effect precipitation of drug in nano size particles. The product so prepared is also called as hydrosol.

10. Porous microparticle technology: The poorly water soluble drug is embedded in a microparticle having a porous, water soluble, sponge like matrix, dissolves wetting the drug and leaving a suspension of rapidly dissolving drug particles. These drug particles provide large surface area for increased dissolution rate . This is the core technology applied as HDDS.

11. Nanotechnology approaches : For many new chemical entities of very low solubility ,oral bioavailability enhancement by micronization is not sufficient because micronized product has a tendency of agglomeration, which leads to decreased effective surface area for dissolution . Nanotechnology refers broadly to the study and use of materials and structures at the nanoscale level of approximately 100 nanometers (nm) or less .

NANOCRYSTAL: Size: 1-1000 nm Crystalline material with dimensions measured in nanometers. There are two distinct methods used for producing nanocrystals . 1 . bottom-up. 2. top-down . The top-down methods (i.e. Milling and High pressure homogenization) start milling down from macroscopic level, e.g. from a powder that is micron sized. In bottom-up methods (i.e. Precipitation and Cryo -vacuum method), nanoscale materials are chemically composed from atomic and molecular components.

NanoMorph :

- The NanoMorph technology is to convert drug substances with low water-solubility from a coarse crystalline state into amorphous nanoparticles .
- A suspension of drug substance in solvent is fed into a chamber, where it is rapidly mixed with another solvent. Immediately the drug substance suspension is converted into a true molecular solution. The admixture of an aqueous solution of a polymer induces precipitation of the drug substance. The polymer keeps the drug substance particles in their nanoparticulate state and prevents them from aggregation or growth. Using this technology the coarse crystalline drug substances are transformed into a nanodispersed amorphous state, without any physical milling or grinding procedures. It leads to the preparation of amorphous nanoparticles .

Bioavailability And Bioequivalence

Content

- Objective
- Introduction
- Definition
- Objective
- Signification
- Components
- Measurement of bioavailability
  1. Pharmacokinetic (indirect)
  2. Pharmacodynamic (direct)
- conclusion

Objective

- To study various objective of bioavailability.
- To known significance of bioavailability.
- To study various measurement parameters used in measurement of bioavailability.

Introduction

- Bioavailability (denoted as F and generally expressed as a percentage, F%) quantifies the **proportion of a drug which is absorbed and available to produce systemic effects.**
- Bioavailability is a **fundamental property** of a pharmaceutical product for a given route of administration.
- It should be **known and shown to be reproducible** for all drug products intended to produce a **systemic effect.**

- The **therapeutic effectiveness** of a drug depends upon the ability of the dosage form to deliver the medicament to its **site of action** at a rate and amount sufficient to elicit the desired **pharmacological response.**
- This attribute of the dosage form is referred to as **physiological availability, biological availability** or simply, **bioavailability.**
- For most drugs, the pharmacological response can be related directly to the **plasma levels.**

Definition : Bioavailability

- ✓ "Bioavailability is a term used to indicate the **fractional extent** to which a dose of drug reaches its site of action or a biological fluid from which the drug has access to its site of action." **(Goodman & Gillman).**
- ✓ "The term Bioavailability is defined as a **rate & extent** (amount) of absorption of unchanged drug from its dosage form." **(Brahmankar & Jaiswal)**

Other Definitions

- **Brand-name drug:** A brand-name drug is a drug marketed under a proprietary, trademark-protected name.
- **Generic drug:** A generic drug is the same as a brand- name drug in dosage, safety, strength, how it is taken, quality, performance, and intended use.
- **Pharmaceutical equivalents:** Drug products are con- sidered to be pharmaceutical equivalents if they contain the **same active ingredient(s), have the same dosage form and route of administration, and are identical in strength or concentration.**

- **Pharmaceutical alternatives:** These are drug products that **contain the same active moiety** but contain **different chemical** forms such as esters or salts of the active moiety or they may differ from the innovator's product in the dosage form or strength.
- **Reference listed drug (RLD):** A reference listed drug is an approved drug product to **which new generic versions are compared** to show that they are bioequivalent.

Cont…

- If the size of the dose to be administered is same, then bioavailability of a drug from its dosage form depends upon 3 major factors :

1. Pharmacological factors related to **physicochemical properties** of the drug and characteristics of the dosage form.
2. **Patient** – related factors.
3. **Route of administration.**

- Within the parenteral route, intravenous injection of a drug results in 100% bioavailability as the absorption process is bypassed.
- However, for reason of stability and convenience, most drug are administered orally.

- In such cases, the dose available to the patient, called as the **bio available dose**, is often less than the administered dose.
- The amount of drug that reaches the systemic circulation (i.e. extent of absorption) is called as **systemic availability** or simply **availability.**
- The term **bio available fraction F,** refers to the fraction of administered dose that enters the systemic circulation.

$$F = \frac{\text{Bio available dose}}{\text{Administered dose}}$$

- To exert an optimal therapeutic action an active moiety should be delivered to its site of action in an effective concentration for the desired period.

Objective of bioavailability studies

✓ Bioavailability studies are important in the –

1. Primary stages of development of a suitable dosage form for a new drug entity to obtain evidence of its therapeutic utility.

2. Determination of influence of

   - excipients,

   - patient related factors,

   - possible interaction with other drugs on the efficiency of absorption.

3. Development of new formulations of the existing drugs.

Cont…

4. **Control of quality** of a drug product during the early stages of marketing in order to determine the influence of processing factors, **storage and stability** on drug absorption.
5. Comparison of availability of a drug substance from different dosage forms or form the same dosage form produced by different manufacturers.

Significance of Bioavailability

- Drugs having **low therapeutic index,** e.g. cardiac glycosides, quinidine, phenytoin etc. and **narrow margin of safety** e.g. antiarrythmics, antidiabetics, adrenal steroids, theophylline .
- Drugs whose **peak levels are required** for the effect of drugs, e.g. phenytoin, phenobarbitone, primidone, sodium valporate, anti-hypertensives, antidiabetics and antibiotics.
- Drugs that are absorbed **by an active transport,** e.g. amino acid analogues, purine analogues etc.
- In addition, any **new formulation** has to be tested for its bioavailability profile.

- Drugs which are **disintegrated in the alimentary canal and liver,** e.g.chlorpromazine etc. or those which under go **first pass metabolism.**
- Formulations that give **sustained release of drug,** formulations with smaller disintegration time than dissolution rate and drugs used as **replacement therapy** also warrant bioavailability testing.
- Drugs with **steep dose response relationship** i.e. drugs **obeying zero order kinetics / mixed order elimination kinetics** (e.g. warfarin , phenytoin, digoxin, aspirin at high doses, phenylbutazone)

Components

- **Rate of absorption** – The rapidity with which the drug is absorbed.

  -**Rapid onset :** conditions like acute attack of asthma, intense acute pain

  - **Slower onset :** To prolong duration of action.

    To avoid adverse effects.

- **Extent of absorption** -chronic conditions like Epilepsy.

Absolute Bioavailability (F)

- **Definition**

"When the systemic availability of a drug administered ***orally*** is determined in comparison to its ***intravenous*** administration ,is called as absolute bioavailability".

$$\% \text{ Absorption} = \frac{\text{Dose}_{(iv)} \times \text{AUC}_{(oral)}}{\text{Dose}_{(oral)} \times \text{AUC}_{(iv)}} \times 100$$

- It is denoted by symbol **F.**
- Its determination is used to characterize a **drug's inherent absorption properties from the e.v. Site.**

Relative Bioavailability (Fr)

- **Definition**

  "When the systemic availability of the drug after **oral** administration is compared with that of **oral standard of same drug** (such as aqueous or non aqueous solution or a suspension) is referred as Relative Bioavailability or comparative ".

  e.g. comparison between **cap**. Amox and **susp.** Amox

- It is used to characterize absorption of a drug from its formulation.

- It is denoted by symbol **Fr.**

$$Fr = \frac{AUC\ A}{AUC\ B}$$

Single Dose vs Multiple Dose Studies

- **Single dose study**

Advantages

- More common
- Easy
- less tedious
- Less exposure to drug.

Disadvantages

- Difficult to predict steady state characteristics.

Multiple dose study

Advantages

- ✓ Accurate.
- ✓ Easy to predict the peak & valley characteristics of drug.
- ✓ Few blood samples required.
- ✓ Ethical.
- ✓ Small inter subject variability .
- ✓ Better evaluation of controlled release formulations.
- ✓ Can detect non linearity in pharmacokinetics.
- ✓ Higher blood levels (d/t cumulative effect).
- ✓ Eliminates the need for long wash out period between doses.

Disadvantages

- ✓ Poor subject compliance .
- ✓ Tedious , time consuming.
- ✓ More drug exposure.
- ✓ More difficult and costly.

Human Volunteers

Healthy Subjects vs. Patients

- ✓ **Patients :** used in multiple dose studies.
- ✓ **Advantages**

1. Patient gets benefited from the study.
2. Reflects better therapeutic efficacy.
3. Drug absorption pattern in disease states evaluated.
4. Avoids ethical quandary.

- ✓ **Disadvantages**

1. Disease states , other drugs affects study
2. Difficult to follow stringent study conditions.

❑ Healthy human volunteers

i. Young

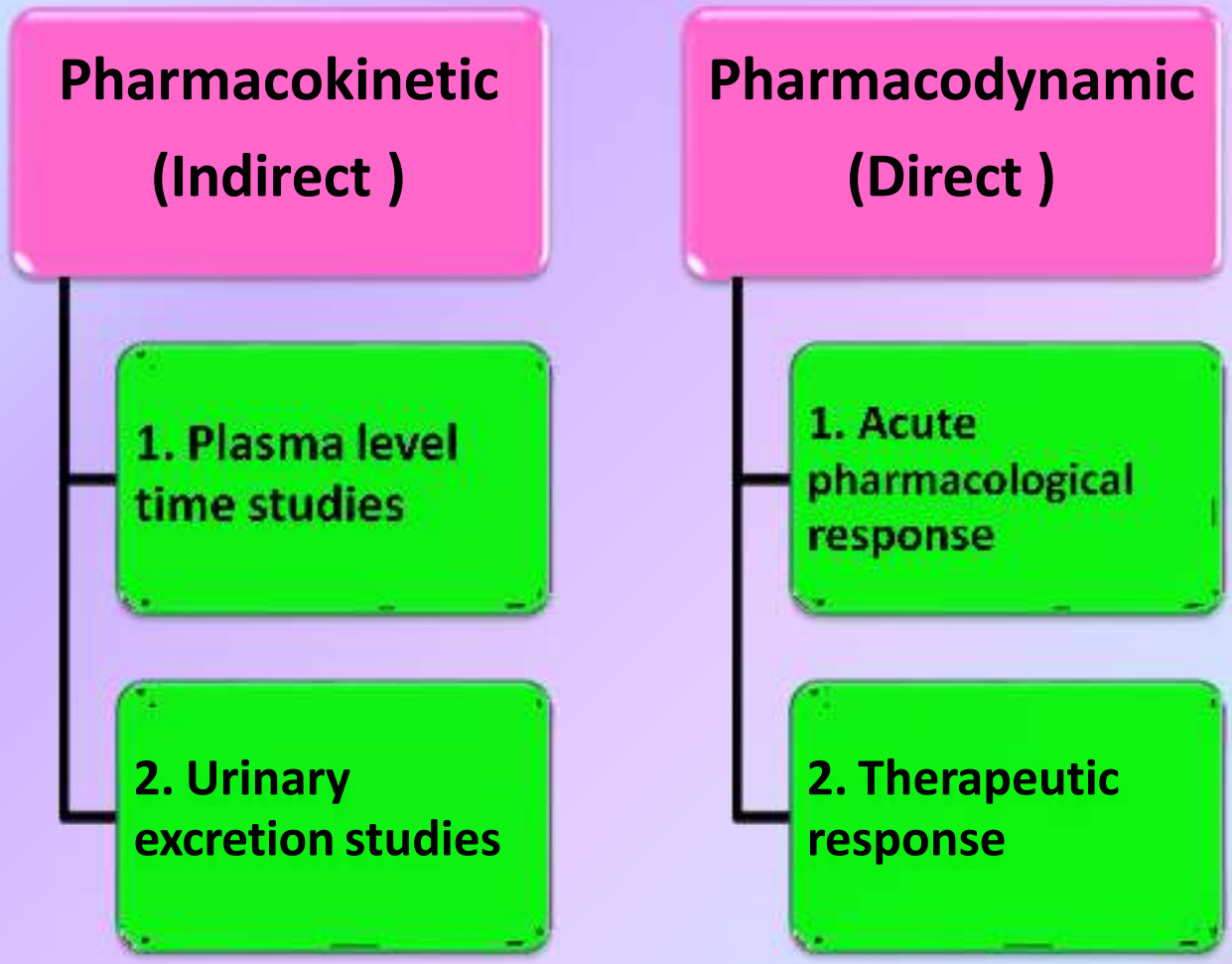
ii. Healthy

iii. Male (females : e.g. OC pills study)

iv. Body wt. within narrow range.

v. Restricted dietary & fixed activity conditions.

Measurement of Bioavailability



- **Pharmacokinetic method**

1. Based on assumption that the pharmacokinetic profile **reflects** the therapeutic effectiveness of drug.
2. These are **indirect** method.

- **Pharmacodynamic method**

1. Involves **direct measurement** of drug effect on a (patho) physiological process as a function of time.
2. It is direct measurement.

1. Plasma level-time studies

✓With single dose study

- The method is based on the **assumption of 2 dosage forms that exhibit superimposable plasma level time profiles** in a group of subject should result in identical therapeutic activity.
- With single does study, the method **requires collection of serial blood samples for a period of 2 to 3 biological half lives** after drug administration, their analysis for drug concentration and making a plot of **concentration versus corresponding time** of sample collection to obtain the plasma level – time profile.
- **With i.v.** Does, **sampling should start within 5 minutes of drug administration** and subsequent samples taken at **15 minute intervals.**

- The three parameters of plasma level time studies which are considered important for determining bioavailability are:

1. **AUC:** The **AUC** is proportional to the **total amount of drug reaching the systemic circulation,** and thus characterizes the extent of absorption.

2. **C_{max}:** Gives indication whether drug is **sufficiently absorbed systemically to provide a therapeutic response.** It is a function of both the rate and extent of absorption**. C_{max} will increase with an increase in the dose, as well as with an increase in the absorption rate.**

3. **T_{max}:** The **T_{max}** reflects the **rate of drug absorption, and decreases as the absorption rate increases**.

- The extent of bioavailability can be determined by following equation:

$$F = \frac{[AUC]_{oral}\, D_{iv}}{[AUC]_{iv}\, D_{oral}}$$

$$Fr = \frac{[AUC]_{test}\, D_{std}}{[AUC]_{test}\, D_{std}}$$

Where, D = dose administered and subscript iv and oral indicates the route of administration.

Subscript **test and std** indicates the test and standard doses of same drug .

✓With multiple dose administration

- The method involves drug administration for atleast 5 biological half lives a dosing interval equal to or greater than the biological half life (i.e. Adminstration of at least 5 doses) to reach the steady state.
- The extent of bioavailability is given as:

$$Fr = \frac{[AUC]_{test}\, D_{std}\, \tau_{test}}{[AUC]_{test}\, D_{std}\, \tau_{std}}$$

where, τ = dosing interval

- Bioavailability can also be determined from peak plasma concentration at steady state Css,max according to following equation:

$$Fr = \frac{[Css,max]_{test}\ D_{std}\ \tau_{test}}{[Css,max]_{test}\ D_{std}\ \tau_{std}}$$

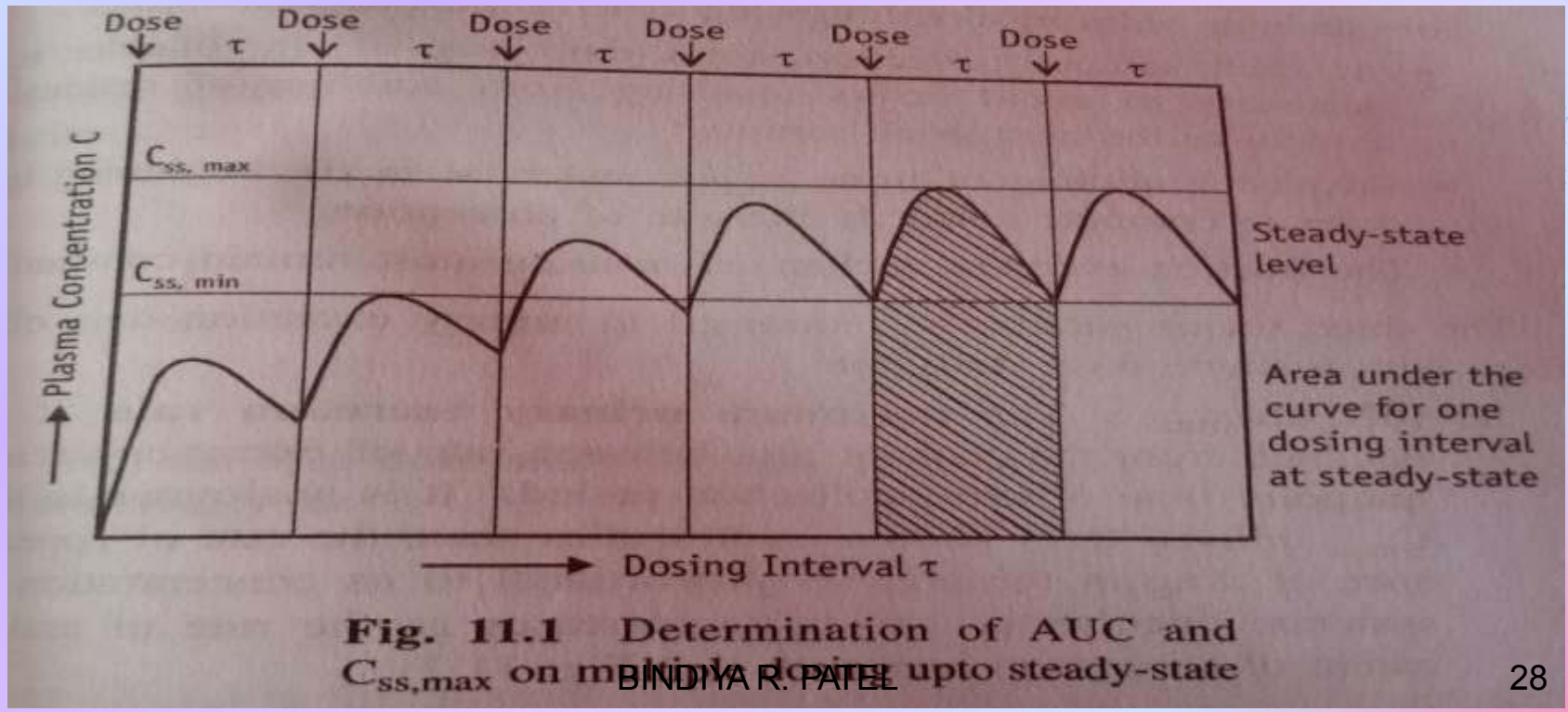


Fig. 11.1 Determination of AUC and $C_{ss,max}$ on multiple dosing upto steady-state

2. Urinary Excretion studies

- These studies are based on the premise that urinary excretion of the **unchanged drug is directly proportional to the plasma concentration of total drug.**
- As a rule of thumb, determination of bioavailability using urinary excretion data should be conducted **only if at least 20% of administered dose is excreted unchanged in the urine.**
- The study is particularly useful for

  1. Drugs that extensively excreted **unchanged** in the urine.

     For example: thiazide diuretics, sulfonamides.

  2. Drug that have **urine as the site of action.**

     For example: Urinary antiseptics : nitrofurantoin, Hexamine.

✓ **The method involves**

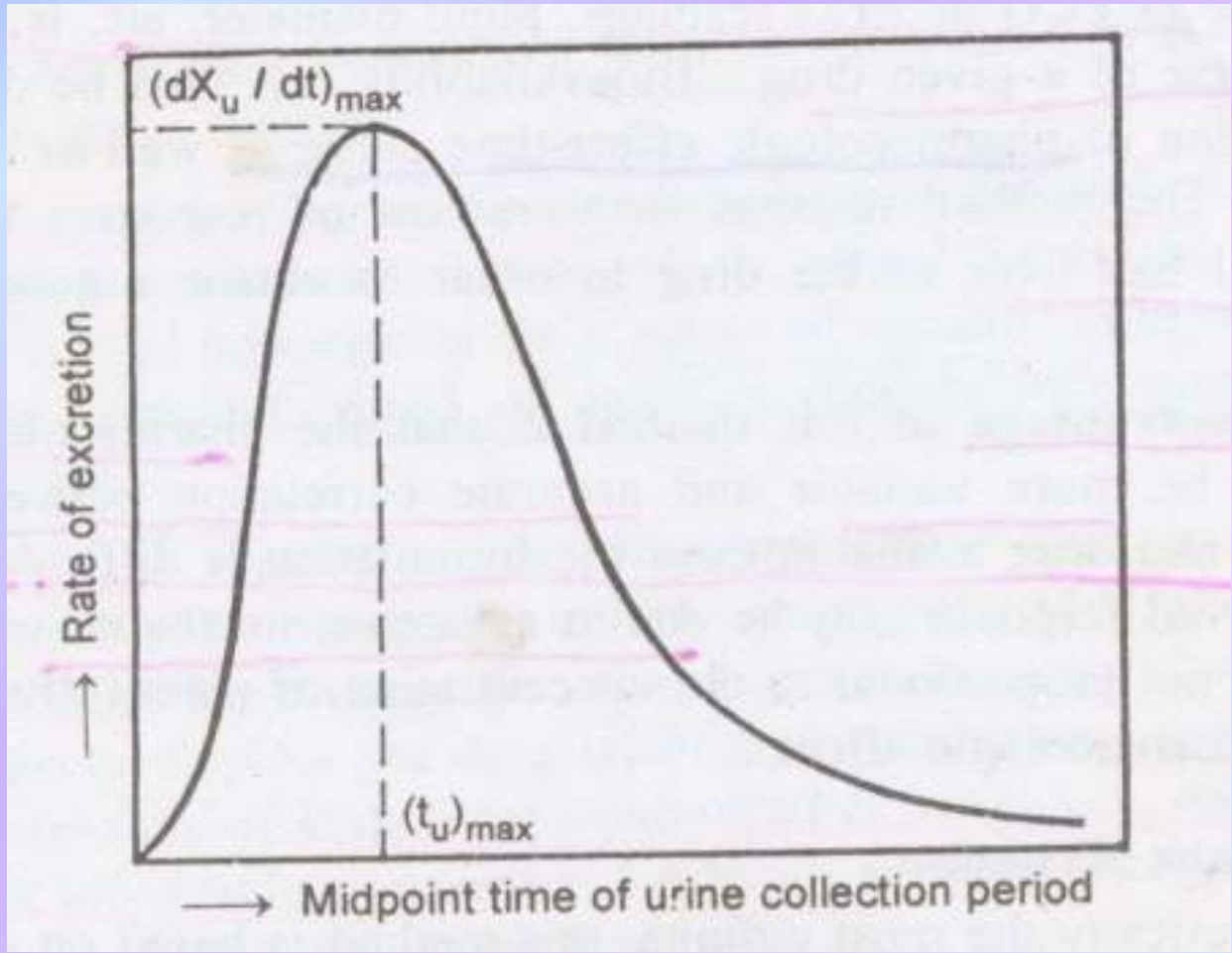
1. Collection of urine at regular intervals for a time **span equal to 7 biological half lives.**
2. Analysis of **unchanged drug** in the collected sample.
3. Determination of the **amount of drug excreted** in each interval and cumulative excreted.

✓ **For obtaining valid result following criteria must be followed**

1. At each sample collection, **total emptying of the bladder** is necessary to avoid errors.
2. **Frequent sampling** of urine is also essential in the beginning.
3. The fraction excreted unchanged in urine must remain **constant**.

- ✓ **The three major parameters examined in urinary excretion data are as follow:**

1. **$(dXu/dt)_{max}$:** It gives the rate of appearance of drug in the urine is **proportional to its concentration in systemic circulation**. Its value increases as the rate of and/or extent of absorption increases
2. **$(tu)_{max}$:** It is analogous to the plasma level data, its value **decreases as the absorption rate increases.**
3. **Xu :** It is related to the **AUC of plasma level data** and increases as the extent of absorption increases.



Plot of urinary excretion rate versus time.

✓ The extent of bioavailability is calculated from equation

$$F = \frac{[Xu\infty]oral \times D\ iv}{[Xu\infty]iv \times D\ oral}$$

$$Fr = \frac{[Xu\infty]test \times D\ std}{[Xu\infty]std \times D\ test}$$

✓ With multiple dose study

$$Fr = \frac{[Xu,ss]test \times D\ std \times \tau_{test}}{[Xu,ss]std \times D\ test \times \tau_{std}}$$

✓Where (Xu,ss) is the **amount of drug excreted unchanged** during a single interval at steady state.

B. Pharmacodynamic methods

1) Acute Pharmacological Response :

✓ Used when pharmacokinetic methods are difficult, inaccurate & non reproducible an acute pharmacological effect such as

- E.g. 1. Change in ECG/EEG readings.

2. Pupil diameter.

<u>Disadvantages</u> :

1. **More variable** and accurate correlation between measured response and available from the formulation is **difficult**.
2. **Active metabolite interferes** with the result.

2) Therapeutic Response :

- ✓ Measurement of clinical response to a drug formulation given to **patients suffering from disease** for which it is intended to be used.

- ✓ **Disadvantages :**

1. Improper quantification of observed response.
2. Bioequivalence studies are usually conducted using a **crossover design.**

LIMITATIONS OF BA/BE STUDIES

- Difficult for drugs with a **long elimination half life.**
- **Highly variable drugs** may require a far greater number of subjects
- Drugs that are administered by **routes other than the oral route** drugs/dosage forms that are intended **for local effects** have minimal systemic bioavailability.

  E.g. ophthalmic, dermal, intranasal and inhalation drug products.
- **Biotransformation** of drugs make it difficult to evaluate the bioequivalence of such drugs: e.g. stereoisomerism

CONCLUSION

- Bioavailability is a key pharmacokinetic parameter which must be systematically estimated for a new drug formulation or a new modality of administration.
- Many possible approaches exist to evaluate both rate and extent of bioavailability, including situations for which intravenous drug admin- istration is not possible.

REFERENCE

- Toutain, P. L., Bousquet-Me ´lou, A. Bioavailability and its assessment. J. vet. Pharmacol. Therap. 27, 455–466.
- Biopharmaceutics and pharmacokinetics A treatise by D. M. Brahmankar , Sunil B. Jaiswal, second edition, Vallabh Prakashan, pg. No. 315 – 363.

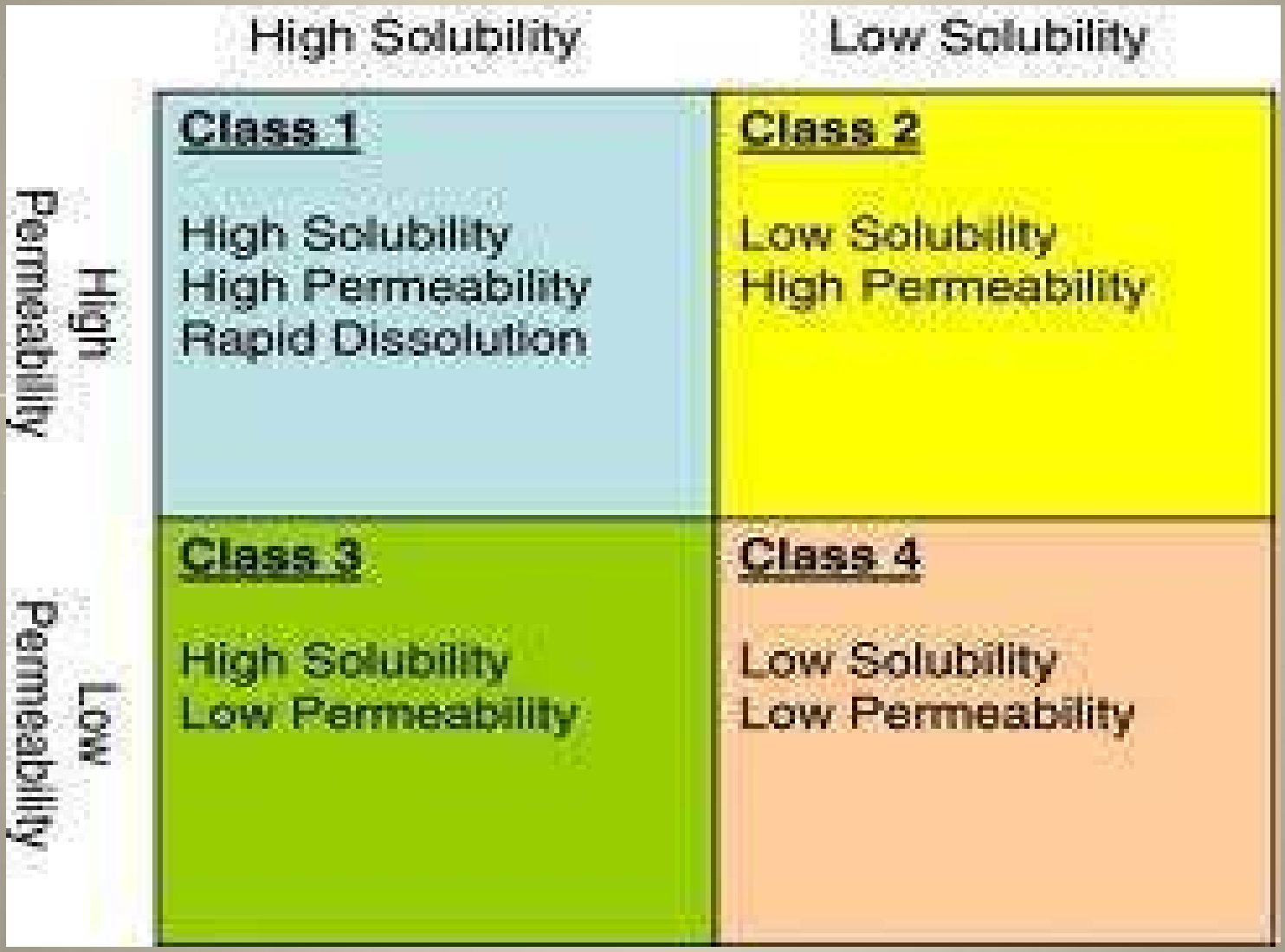

Thank You!

BIOAVAILABILITY ENHANCEMENT TECHNIQUES

INTRODUCTION :

- DEFINITION : Solubility is defined in quantitative terms as concentration of solute in concentrated solution at a certain temperature, and in qualitative way it can be defined as a spontaneous interaction of two or more substances to form a homogenous molecular dispersion.

- Solubilization can be defined as a preparation of thermodynamically stable isotropic solution of a substance normally insoluble or slightly soluble in a given solvent by introduction of an additional component or components.


High Solubility
Low Solubility
High Permeability
Low Permeability
Class 1
High Solubility
High Permeability
Rapid Dissolution
Class 2
Low Solubility
High Permeability
Class 3
High Solubility
Low Permeability
Class 4
Low Solubility
Low Permeability

The biopharmaceutical classification system (BCS)

CLASS	SOLUBILITY	PERMEABILITY	ABSORPTION PATTERN	RATE LIMITING STEP IN ABSORPTION
I	High	High	Well absorb	Gastric emptying
II	Low	High	variable	Dissolution
III	High	Low	Variable	Permeability
IV	Low	Low	Poorly absorb	Case by case

The pharmacopoeia lists solubility in terms of number of milliliters of solvent required to dissolve 1g of solute. The Indian pharmacopoeia provides general terms to describe a given range. These descriptive terms are given as:

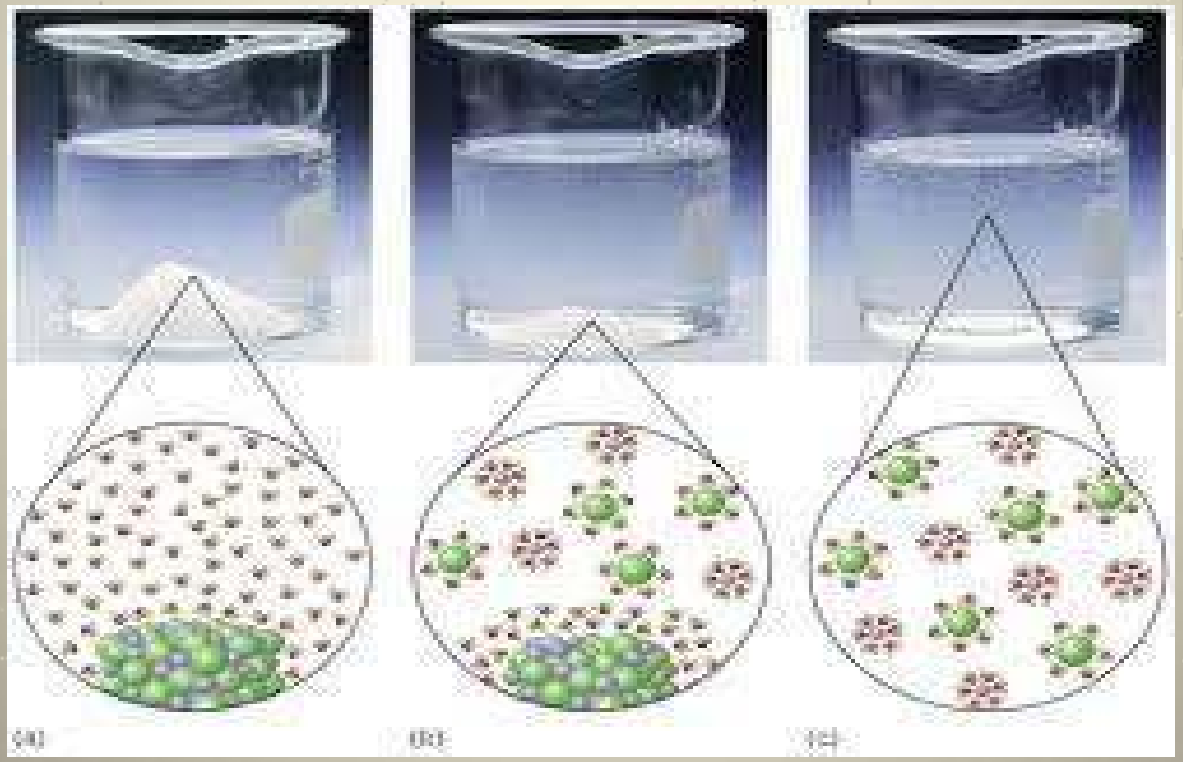
DEFINITION	PARTS OF SOLVENT REQUIRED FOR 1 PART OF SOLUTE
Very soluble	< 1
Freely soluble	1 - 10
Soluble	10 – 30
Sparingly soluble	30 - 100
Slightly soluble	100 - 1000
Very slightly soluble	1000 – 10,000
Insoluble	>10,000

IMPORTANCE OF SOLUBILITY:

- Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules.
- Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown.
- Currently only 8% of new drug candidates have both high solubility and permeability.
- Nearly 40% of the new chemical entities currently being discovered are poorly water soluble.
- More than one-third of the drugs listed in the U.S. Pharmacopoeia fall into the poorly water-soluble or water-insoluble categories.
- Low aqueous solubility is the major problem encountered with formulation development of new chemical entities.
- Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption.

SOLUBILIZATION

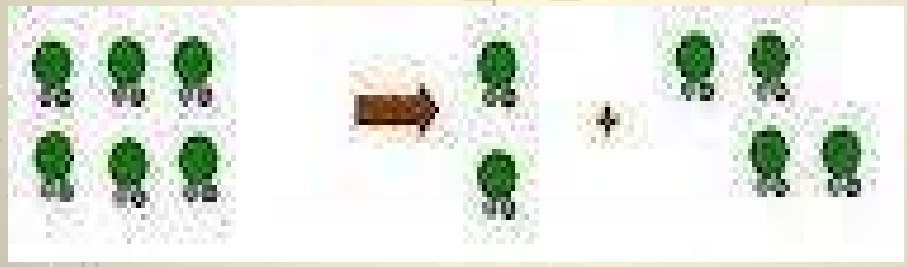
The process of solubilization involves the breaking of inter-ionic or intermolecular bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion.



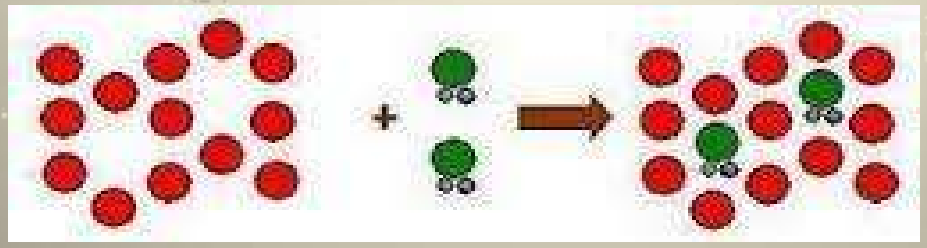
STEPS INVOLVED ARE :

1: Holes opens in the solvent

2. Molecules of the solid breaks away from the bulk.



3. The freed solid molecule is integrated into the hole



TECHNIQUES OF SOLUBILITY ENHANCEMENT

I. Physical Modifications

A. Particle size reduction

1. Micronization
2. Nanosuspension
3. Sonocrystalisation
4. Supercritical fluid process

B. Modification of the crystal habit

1. Polymorphs
2. Pseudopolymorphs

C. Drug dispersion in carriers

1. Eutectic mixtures
2. Solid dispersions
3. Solid solutions

D. Complexation

Use of complexing agents

E. Solubilization by surfactants

Microemulsions

II. Chemical Modifications

1. Change in the pH
2. Use of buffer
3. Derivatization

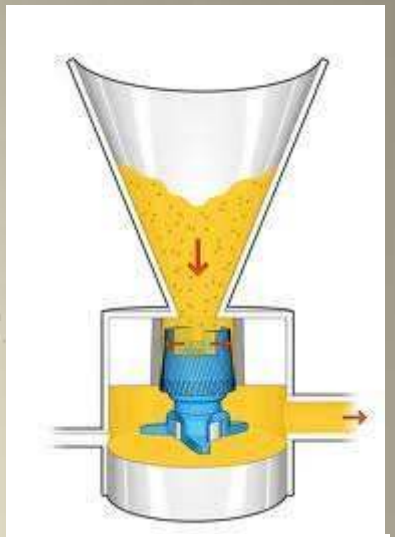
III. Other methods

1. co-crystallisation
2. co-solvency
3. Hydrotrophy
4. Solubilizing agents
5. Selective adsorption on insoluble carrier
6. Solvent deposition
7. Using soluble prodrug
8. Functional polymer technology
9. Precipitation Porous
10. microparticle technology
11. Nanotechnology approaches

A.Particle size reduction:

Particle size reduction can be achieved by

a. Micronization
b. nanosuspension
c.Sonocrystalisation
d.Supercritical fluid process



Colloid mill

1. Micronization:

- Micronization increases the dissolution rate of drugs through increased surface area.
- Micronization of drugs is done by milling techniques using jet mill, rotor stator colloid mills etc.
- Micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug .
- The process involves reducing the size of the solid drug particles to 1 to 10 microns commonly by spray drying or by use of attrition methods. The process is also called micro-milling.

2. Nanosuspension :

Nanosuspensions are sub-micron colloidal dispersion of pure particles of the drug, which are stabilized by surfactants. Nanosuspension technology is used for efficient delivery of hydrophobic drugs . The particle size distribution of the solid particles in nanosuspensions is usually less than one micron with an average particle size ranging between 200 and 600 nm.

Advantage :

Increased dissolution rate due to larger surface area exposed.

Eg., Nanosuspension approach has been employed drugs like paclitaxel, tarazepide, amphotericin B which are still on research stage.

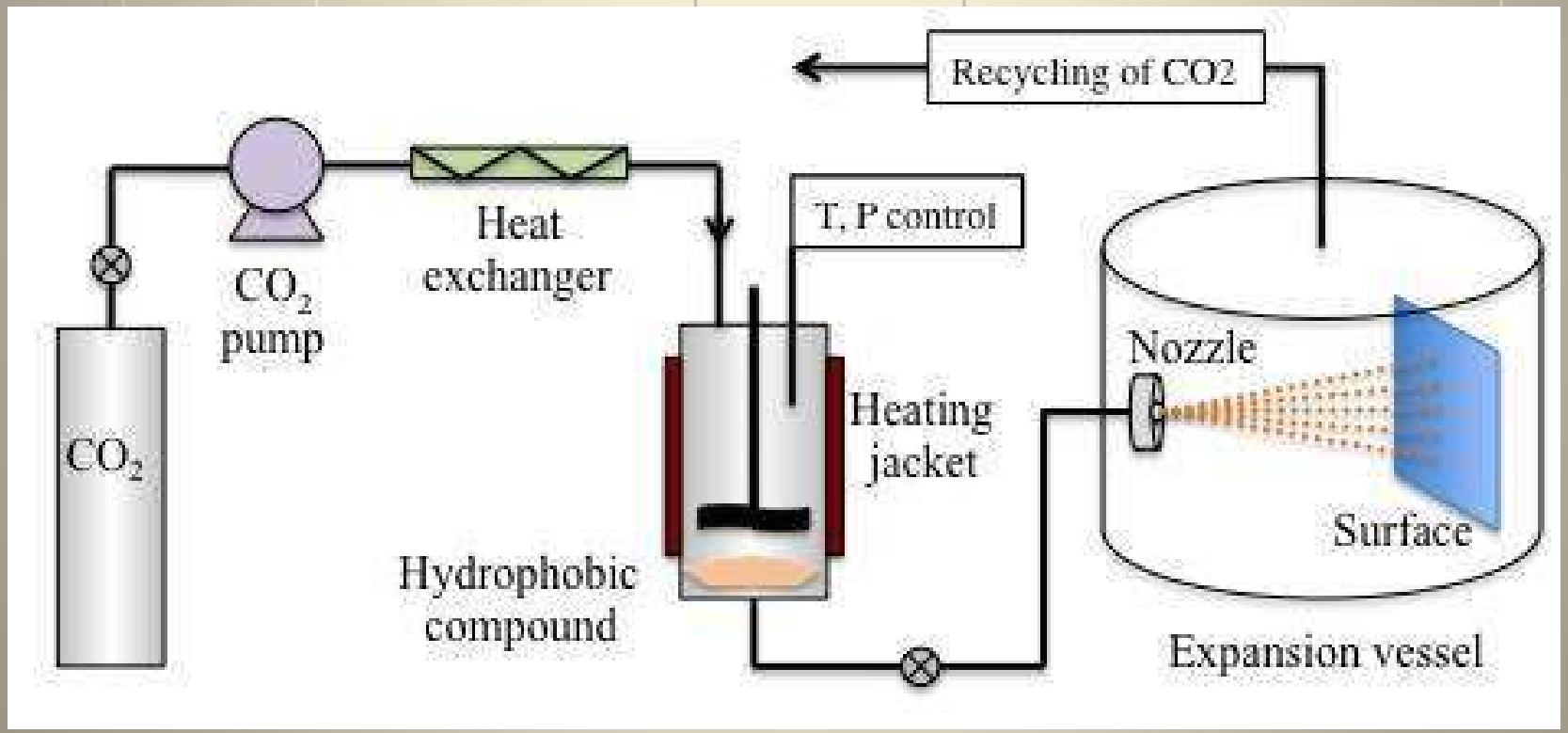
3.Sonocrystallisation :

Particle size reduction on the basis of crystallisation by using ultrasound is Sonocrystallisation . Sonocrystallisation utilizes ultrasound power for inducing crystallisation . It not only enhances the nucleation rate but also an effective means of size reduction and controlling size distribution of the active pharmaceutical ingredients. Most applications use ultrasound in the range 20 kHz-5 MHz.

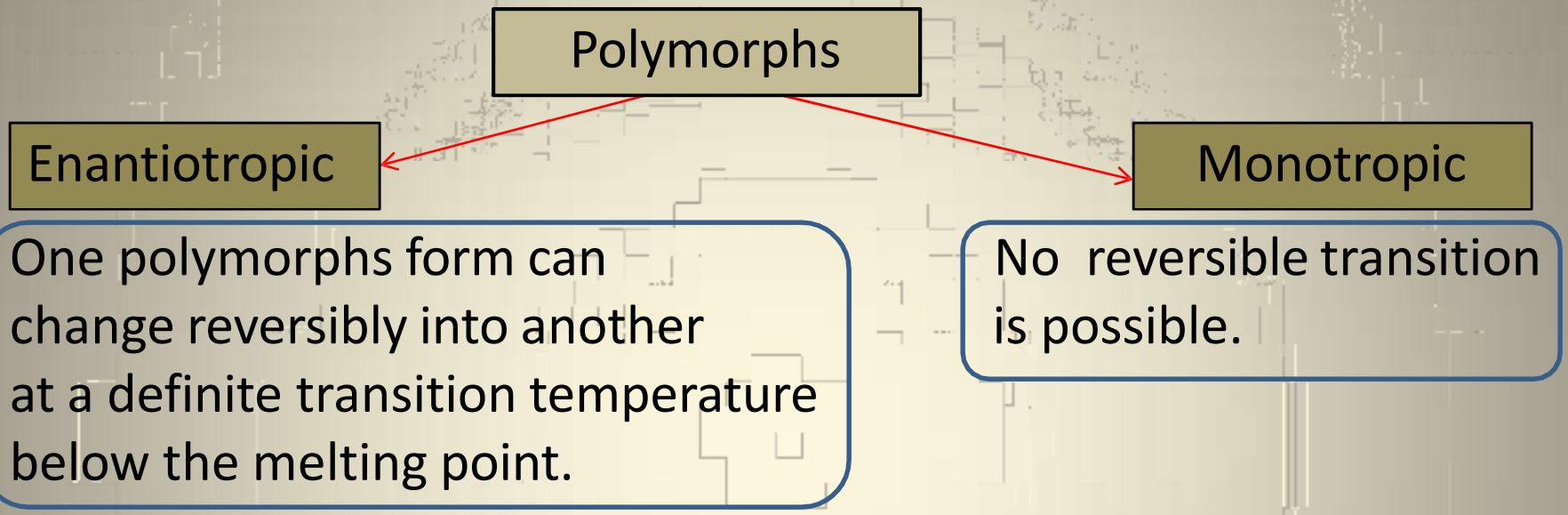
4. Supercritical fluid process :

- A supercritical fluids are dense non-condensable fluid whose temperature and pressure are greater than its critical temperature (Tc) and critical pressure (Tp) allowing it to assume the properties of both a liquid and a gas.
- Through manipulation of the pressure of SCFs, the favourable characteristics of gases – high diffusivity, low viscosity and low surface tension may be imparted upon the liquids to precisely control the solubilisation of a drug with a supercritical fluid.

- Once the drug particles are solubilised within SCFs, they may be recrystalised at greatly reduced particle sizes.
- A SCF process allows micronisation of drug particles within narrow range of particle size, often to sub-micron levels.



B. Modification of the crystal habit:



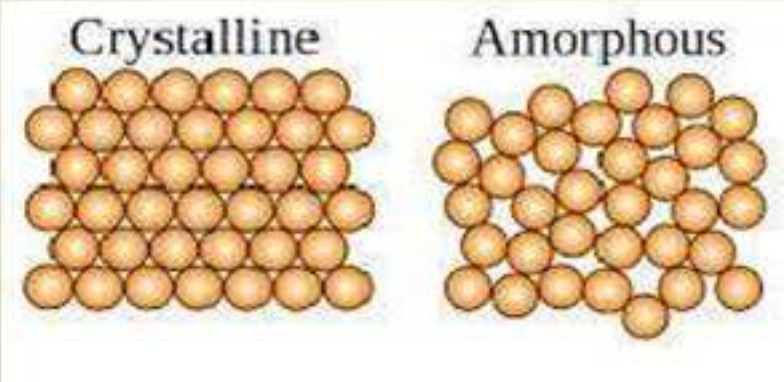
- Metastable forms are associated with higher energy and thus higher solubility. Similarly the amorphous form of drug is always more suited than crystalline form due to higher energy associated and increased surface area.
- The anhydrous form of a drug has greater solubility than the hydrates. This is because the hydrates are already in interaction

with water and therefore have less energy for crystal breakup in comparison to the anhydrates.

- They have greater aqueous solubility than the crystalline forms because they require less energy to transfer a molecule into solvent. Thus, the order for dissolution of different solid forms of drug is

Amorphous > metastable polymorph > stable polymorph

- Melting followed by a rapid cooling or recrystallization from different solvents can produce metastable forms of a drug.



C. Drug dispersion in carriers:

The term “solid dispersions” refers to the dispersion of one or more active ingredients in an inert carrier in a solid state, frequently prepared by the

1. • Hot melt mehod
2. • Solvent evaporation method
3. • Hot melt extrusion method

1. Hot melt method :

Drug + vehicle (m.p low, organic solvent – insoluble)

(heating)

Melting

Freezing quickly

Dosage forms

A molecular dispersion can be achieved or not, depends on the degree of supersaturation and rate of cooling used in the process.

Important requisites :

1. Miscibility of the drug & carrier in the molten form,
2. Thermostability of the drug & carrier.

Suitable to drugs and vehicles with promising heat stability.

2. Solvent evaporation method:

Drug + vehicle (both soluble in solvent)

organic solvent

solution

evaporate the solvent

coprecipitates

dosage forms

The solvent evaporation can be done by spray drying or freeze drying.

Temperatures used for solvent evaporation generally lie in the range 23-65 C.

suitable to drugs with volatility or poor stability

3.Hot-melt Extrusion:

Hot melt extrusion of miscible components results in amorphous solid solution formation, whereas extrusion of an immiscible component leads to amorphous drug dispersed in crystalline excipient. The process has been useful in the preparation of solid dispersions in a single step.

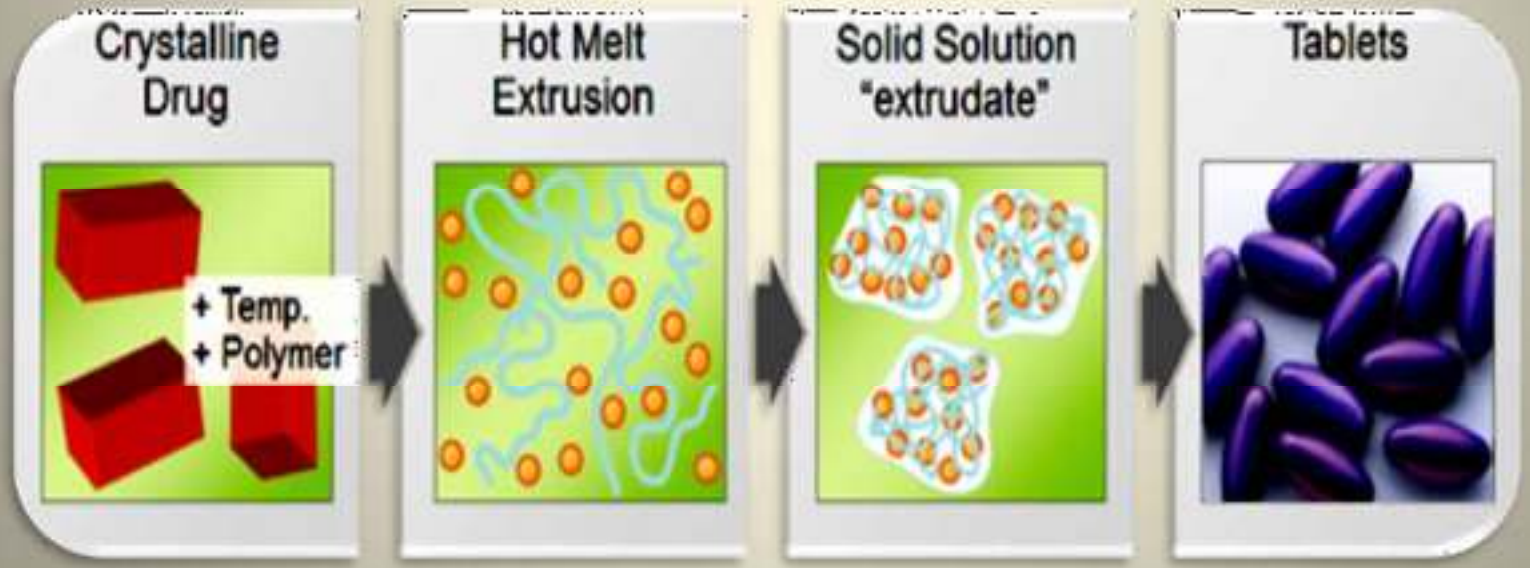
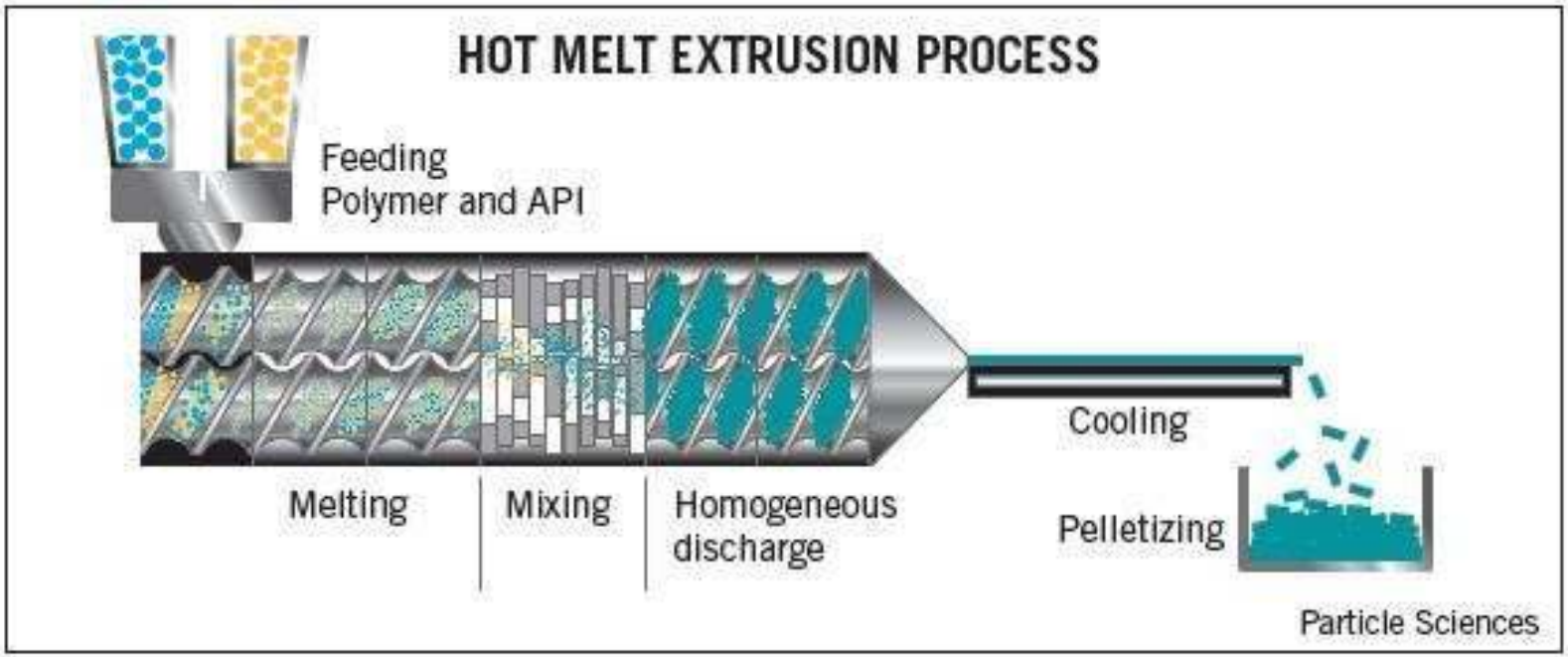


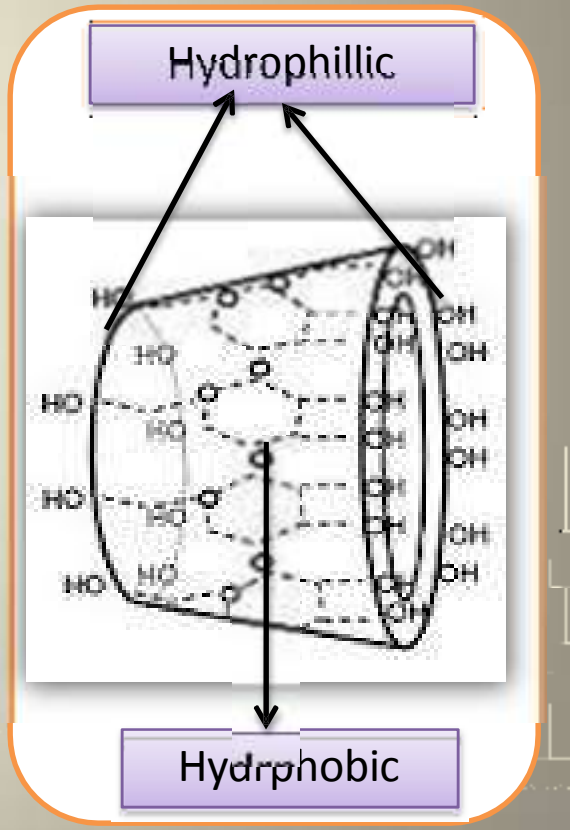
Figure 1


HOT MELT EXTRUSION PROCESS
Feeding
Polymer and API
Melting
Mixing
Homogeneous
discharge
Cooling
Pelletizing
Particle Sciences

D. Complexation :

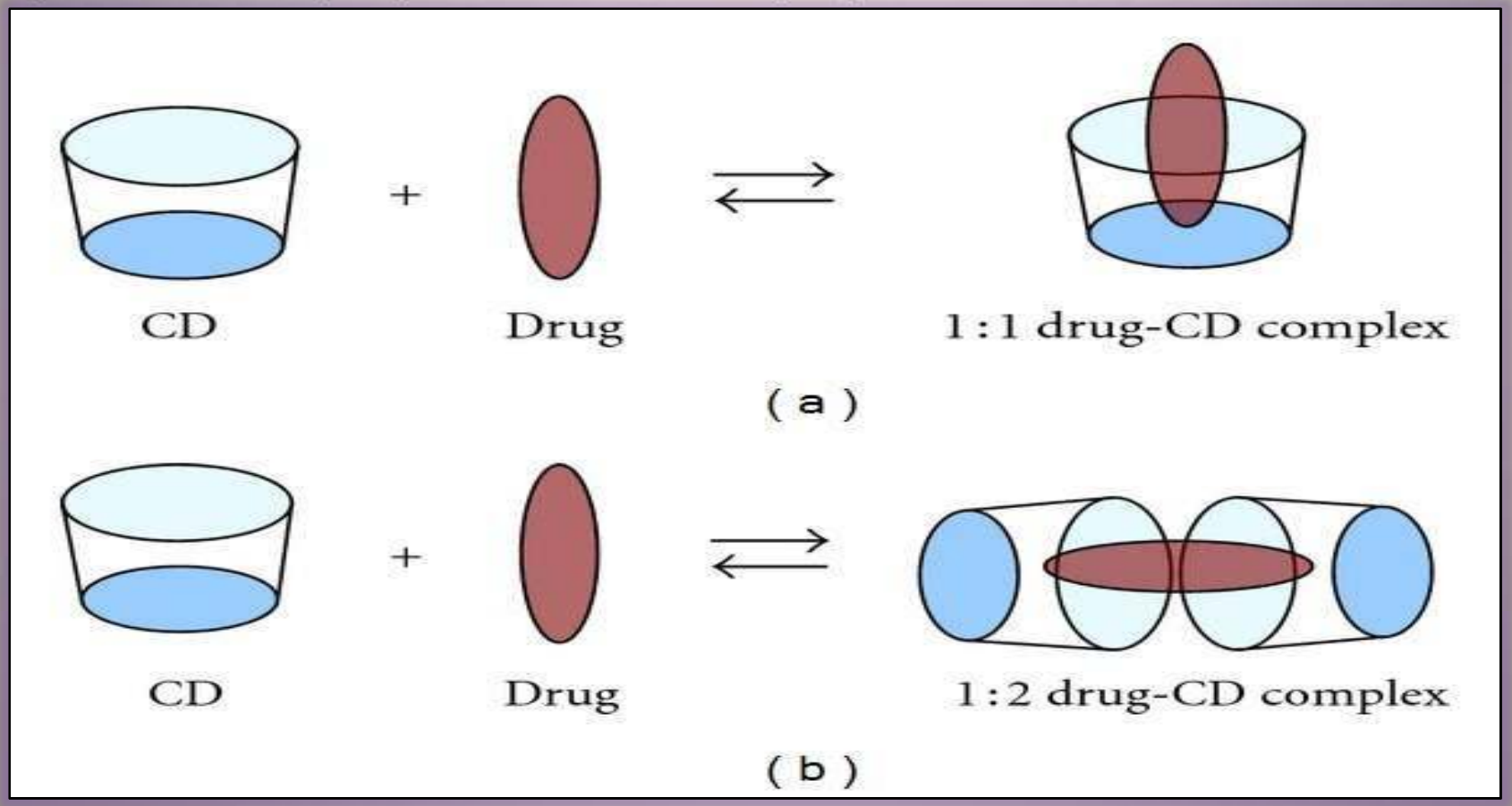
Complexation is the reversible association between two or more molecules to form a nonbonded entity with a well defined stoichiometry . Complexation relies on relatively weak forces such as van-derwaal forces, hydrogen bonding and hydrophobic interactions.

Inclusion complexation: These are formed by the insertion of the nonpolar molecule or the nonpolar region of one molecule into the cavity of another molecule or group of molecules. The most commonly used host molecules are cyclodextrins . Cyclodextrins are non- reducing, crystalline , water soluble, cyclic, oligosaccharides. Cyclodextrins consist of glucose monomers arranged in a donut shape ring.



CYCLODEXTRIN

The surface of the cyclodextrin molecules makes them water soluble, but the hydrophobic cavity provides a microenvironment for appropriately sized non-polar molecules. Based on the structure and properties of drug molecule it can form 1:1 or 1:2 drug cyclodextrin complex. Three naturally occurring CDs are α Cyclodextrin, β Cyclodextrin, and γ Cyclodextrin.



Staching complexation

Organic drug + water → Squeezed out by strong water-water interaction force.

↓

Forms aggregates

↓

Reduces the contact b/w nonpolar hydrocarbon moieties & the polar water molecule

↓

Large nonpolar regions

↓

Opposed by entropy

↓

Random arrangement

↓

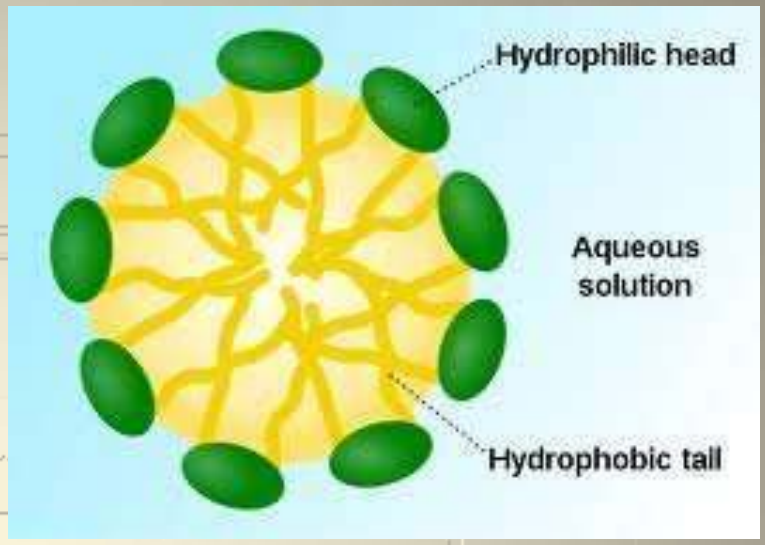
Complexes stached can be homogeneous or mixed

↓

Self association complexation

Eg .,
Nicotinamide,
Anthracene,
Caffeine,
Theobromine.

E. Solubilization by surfactants:



Surfactants are molecules with distinct polar and nonpolar regions. Most surfactants consist of a hydrocarbon segment connected to a polar group. The polar group can be anionic, cationic, zwitter ionic or nonionic. The presence of surfactants may lower the surface tension and increase the solubility of the drug within an organic solvent .

Microemulsion : A microemulsion is a four-component system composed of external phase, internal phase, surfactant and co surfactant . The addition of surfactant, which is predominately soluble in the internal phase unlike the co surfactant , results in the formation of an optically clear, isotropic, thermodynamically stable emulsion. It is termed as microemulsion because of the internal phase is <0.1 micron droplet diameter.

The surfactant and the co surfactant alternate each other and form a mixed film at the interface, which contributes to the stability of the microemulsion .

Non-ionic surfactants, such as Tweens (polysorbates) and Labrafil (polyoxyethylated oleic glycerides), with high hyrophile-lipophile balances are often used to ensure immediate formation of oil-in-water droplets during production.

Advantages :

- Ease of preparation due to spontaneous formation.
- Thermodynamic stability,
- transparent and elegant appearance,
- enhanced penetration through the biological membranes,
- increased bioavailability and
- less inter- and intra-individual variability in drug pharmacokinetics.

II. CHEMICAL MODIFICATIONS

1)By change of pH:

For organic solutes that are ionizable, changing the pH of the system is the simplest and most effective means of increasing aqueous solubility .

For weakly acidic drugs,

LOWER pH	UNIONISED FORM	INSOLUBLE PPT
HIGHER pH	IONISED FORM	MORE SOLUBLE DRUG

For weakly basic drugs,

Lower pH	Ionized form	More soluble drug
Higher pH	UNIONISED FORM	INSOLUBLE PPT

2) Use of buffer: Buffer maintains the pH of the solution overtime and it reduces or eliminate the potential for precipitation upon dilution. On dilution pH alteration occurs that decrease solubility . Change of pH by 1 fold increase solubility by 10 fold If it changes by one pH unit ,that decrease ionization of the drug and solubility decreases by 10 fold.

3) Derivatization : It is a technique used in chemistry which transforms a chemical compound into a product of similar chemical structure, called derivative. Derivatives have different solubility as that of adduct. It is used for quantification of adduct formation of esters and amides via acyl chlorides.

III. OTHER METHODS.

1.Co-crystallization:

A co-crystal may be defined as a crystalline material that consists of two or more molecular species held together by non-covalent forces.

- Co-crystals are more stable, particularly as the co-crystallizing agents are solids at room temperature.
- Co-crystals can be prepared by evaporation of a heteromeric solution or by grinding the components together.
- Another technique for the preparation of co-crystals includes sublimation, growth from the melt, and slurry preparation.
- Only three of the co-crystallizing agents are classified as generally recognised as safe (GRAS) it includes saccharin, nicotinamide and acetic acid limiting the pharmaceutical applications.

2. Cosolvency : Cosolvents are prepared by mixing miscible or partially miscible solvents. Weak electrolytes and nonpolar molecules have poor water solubility and it can be improved by altering polarity of the solvent. It is well-known that the addition of an organic cosolvent to water can dramatically change the solubility of drugs. Cosolvent system works by reducing the interfacial tension between the aqueous solution and hydrophobic solute.

Aquous solvent - Etahnol, sorbitol, glycerin, propylene glycol.

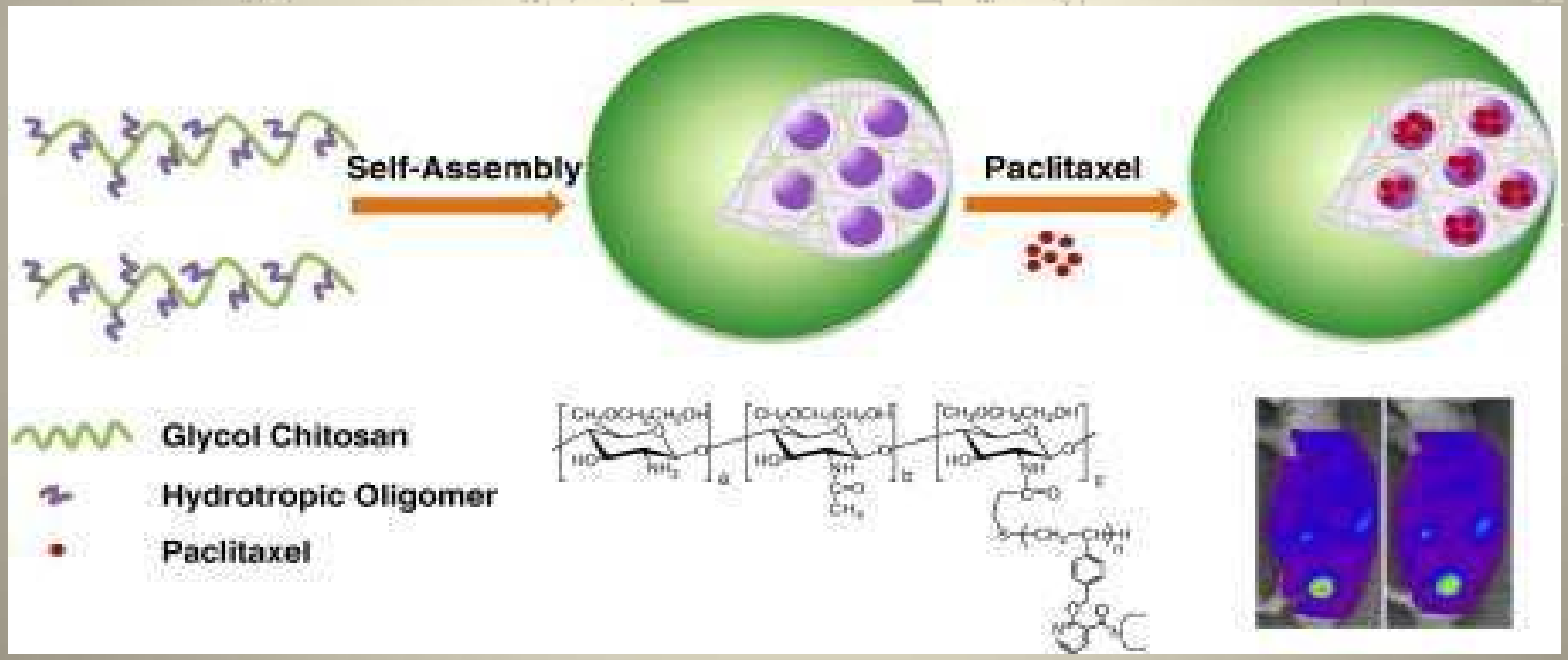
Non aquous solvent - glycerol dimethyl ketal, glycerol formal, glycofurol, dimethyl acetamide.

SOME PERANTRALPRODUCT THAT CONTAIN COSOLVENT

1.Diazepam - 10% ethanol + propylene glycol

2.Digoxin - 10% ethanol + propylene glycol

3. Hydrotrophy : Hydrotrophy designate the increase in solubility in water due to the presence of large amount of additives. The mechanism by which it improves solubility is more closely related to complexation involving a weak interaction between the hydrotrophic agents (sodium benzoate, sodium acetate, sodium alginate, and urea).



4. Solubilizing agents: The solubility of poorly soluble drug can also be improved by various solubilizing materials. PEG 400 is improving the solubility of hydrochlorthiazide85. Modified gum karaya (MGK), a recently developed excipient was evaluated as carrier for dissolution enhancement of poorly soluble drug, nimodipine .

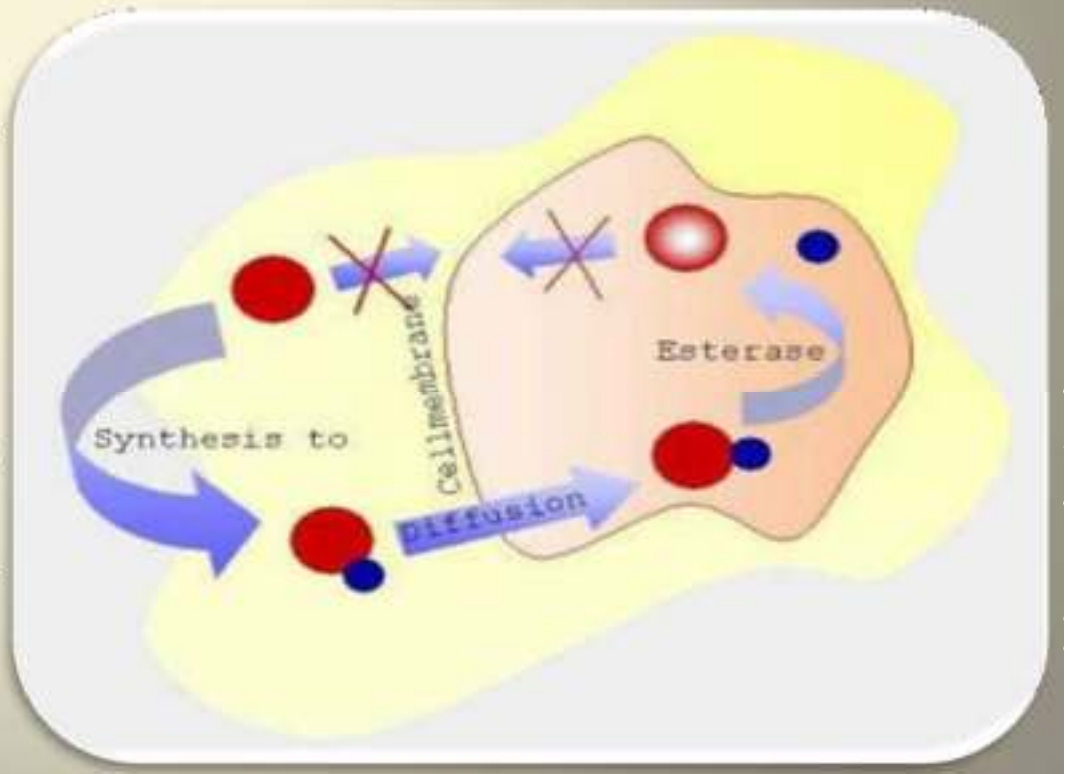
5. Selective adsorption on insoluble carriers: A highly active adsorbent such as inorganic clays like Bentonite can enhance the dissolution rate of poorly water-soluble drugs such as griseofulvin, indomethacin and prednisone by maintaining the concentration gradient at its maximum. 2 reasons suggested for rapid release of drugs from the surface of clays :-

1. weak physical bonding between adsorbate and adsorbent.
2. hydration and swelling of the clay in the aqueous media.

6. Solvent deposition: In this method,the poorly aqueous soluble drug such as Nifedipine is dissolved in an organic solvent like alcohol and deposited on an inert , hydrophilic, solid matrix such as starch or microcrystalline cellulose and evaporation of solvent is done.

7. Use of soluble prodrug :

Prodrug stratergy involves the incorporation of polar or ionizable moiety into the parent compound to improve aqueous solubility. Example : prodrug of established drugs has been successfully used to improve water solubility of corticosteroids benzodiazepines.



8.Functional Polymer Technology : Functional polymer enhances the dissolution rate of poorly soluble drugs by avoiding the lattice energy of the drug crystal, which is the main barrier to rapid dissolution in aqueous media. The dissolution rate of poorly soluble , ionizable drug like cationic, anionic and amphoteric actives can be enhanced by this technology. Applied to heat sensitive materials and oils also.

9. Precipitation: In this method, the poorly aqueous soluble drug such as cyclosporine is dissolved in a suitable organic solvent followed by its rapid mixing with a non-solvent to effect precipitation of drug in nano size particles. The product so prepared is also called as hydrosol.

10. Porous microparticle technology: The poorly water soluble drug is embedded in a microparticle having a porous, water soluble, sponge like matrix, dissolves wetting the drug and leaving a suspension of rapidly dissolving drug particles. These drug particles provide large surface area for increased dissolution rate . This is the core technology applied as HDDS.

11. Nanotechnology approaches : For many new chemical entities of very low solubility ,oral bioavailability enhancement by micronization is not sufficient because micronized product has a tendency of agglomeration, which leads to decreased effective surface area for dissolution . Nanotechnology refers broadly to the study and use of materials and structures at the nanoscale level of approximately 100 nanometers (nm) or less .

NANOCRYSTAL: Size: 1-1000 nm Crystalline material with dimensions measured in nanometers. There are two distinct methods used for producing nanocrystals . 1 . bottom-up. 2. top-down . The top-down methods (i.e. Milling and High pressure homogenization) start milling down from macroscopic level, e.g. from a powder that is micron sized. In bottom-up methods (i.e. Precipitation and Cryo -vacuum method), nanoscale materials are chemically composed from atomic and molecular components.

NanoMorph :

•The NanoMorph technology is to convert drug substances with low water-solubility from a coarse crystalline state into amorphous nanoparticles .

•A suspension of drug substance in solvent is fed into a chamber, where it is rapidly mixed with another solvent. Immediately the drug substance suspension is converted into a true molecular solution. The admixture of an aqueous solution of a polymer induces precipitation of the drug substance. The polymer keeps the drug substance particles in their nanoparticulate state and prevents them from aggregation or growth. Using this technology the coarse crystalline drug substances are transformed into a nanodispersed amorphous state, without any physical milling or grinding procedures. It leads to the preparation of amorphous nanoparticles .

BASIC PHARMACOKINETICS
&
COMPARTMENT MODELLING

Dosage Regimen:

The frequency of administration of a drug in a particular dose is called as **dosage regimen**.

Pharmacokinetics:

Pharmacokinetics *is defined as the kinetics of drug absorption, distribution, metabolism and excretion (KADME) and their relationship with the pharmacological, therapeutic or toxicological response in man and animals*. There are two aspects of pharmacokinetic studies –

Theoretical aspect – which involves development of pharmacokinetic models to predict drug disposition after its administration. Statistical methods are commonly applied to interpret data and assess various parameters.

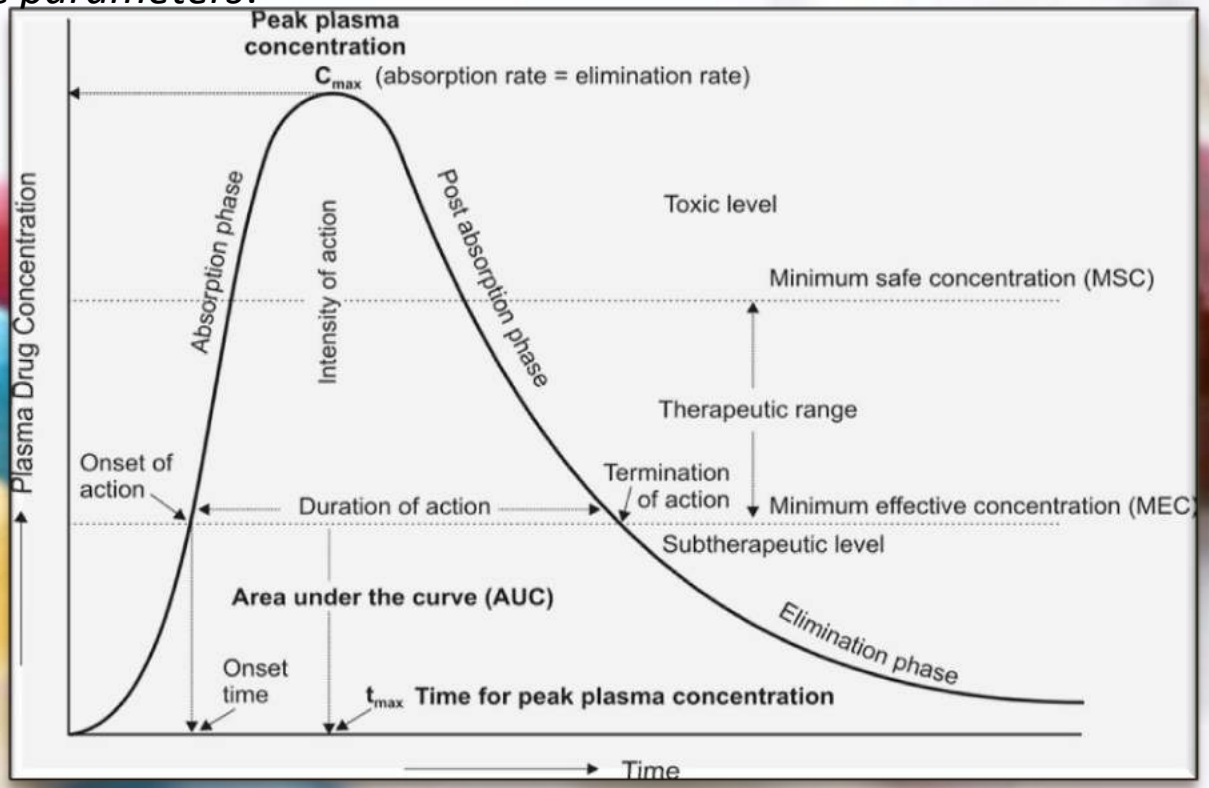
Experimental aspect – which involves development of biological sampling techniques, analytical methods for measurement of drug (and metabolites) concentration in biological samples and data collection and evaluation.

Plasma Drug Concentration-Time Profile

A direct relationship exists between the concentration of drug at the biophase (site of action) and the concentration of drug in plasma. Two categories of parameters can be evaluated from a plasma concentration time profile –

Pharmacokinetic parameters, and

Pharmacodynamic parameters.



Pharmacokinetic Parameters

1. **Peak Plasma Concentration (Cmax)**
   The peak plasma level depends upon –
   The administered dose
   Rate of absorption, and
   Rate of elimination.
2. **Time of Peak Concentration (tmax)**
3. **Area Under the Curve (AUC)**

Pharmacodynamic Parameters

1. **Minimum Effective Concentration (MEC)**
2. **Maximum Safe Concentration (MSC)**
3. **Onset of Action**
4. **Onset Time**
5. **Duration of Action**
6. **Intensity of Action**
7. **Therapeutic Range**
8. **Therapeutic Index**

Rate, Rate Constants and Orders of Reactions

Rate: *The velocity with which a reaction or a process occurs is called as its* **rate**.

Order of reaction: *The manner in which the concentration of drug (or reactants) influences the rate of reaction or process is called as the* **order of reaction** or **order of process**.

Consider the following chemical reaction:

Drug A $\longrightarrow$ Drug B

The rate of forward reaction is expressed as –

$-dA/dt$

Negative sign indicates that the concentration of drug A decreases with time t. As the reaction proceeds, the concentration of drug B increases and the rate of reaction can also be expressed as: dB/dt

$$\mathbf{dC/dt = -KC^n}$$

K = rate constant

n = order of reaction

Zero-Order Kinetics (Constant Rate Processes)

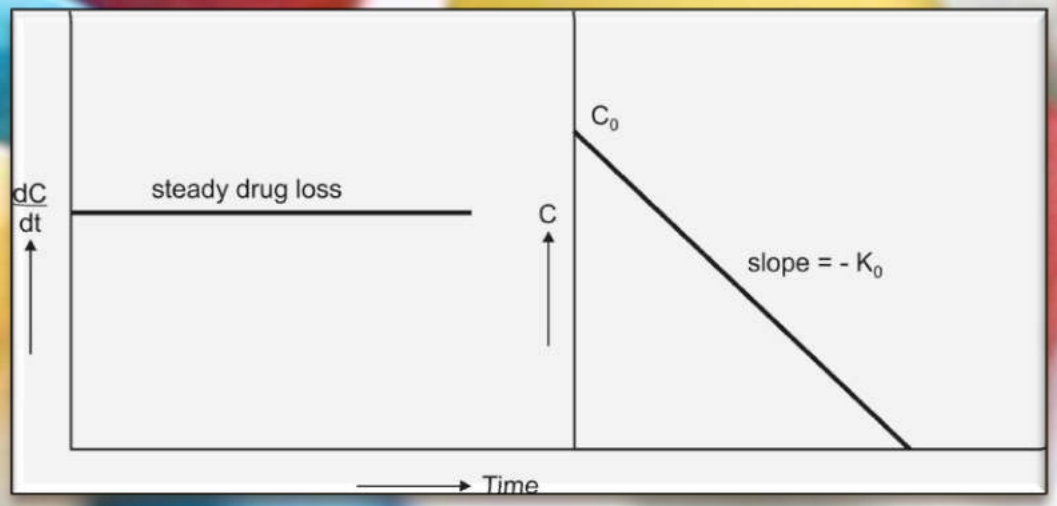
If n = 0, equation becomes:

$$dC/dt = -K_o C^o$$

where Ko = zero-order rate constant (in mg/min)

Zero-order process *can be defined as the one whose rate is independent of the concentration of drug undergoing reaction i.e. the rate of reaction cannot be increased further by increasing the concentration of reactants*.

Finally $C = C_o - K_o t$



Zero-Order Half-Life

Half-life (t½) or **half-time** *is defined as the time period required for the concentration of drug to decrease by one-half*.

$$t_{1/2} = C_o / 2 K_o$$

Examples of zero-order processes are –

1. Metabolism/protein-drug binding/enzyme or carrier-mediated transport under saturated conditions. The rate of metabolism, binding or transport of drug remains constant as long as its concentration is in excess of saturating concentration.
2. Administration of a drug as a constant rate i.v. infusion.
3. Controlled drug delivery such as that from i.m. implants or osmotic pumps.

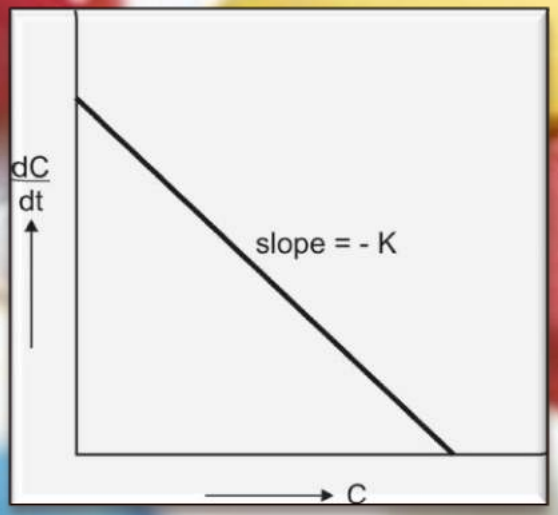
First-Order Kinetics (Linear Kinetics)

If n = 1, equation becomes:

$$dC/dt = - K C$$

where K = first-order rate constant (in time–1 or per hour)

first-order process *is the one whose rate is directly proportional to the concentration of drug undergoing reaction i.e. greater the concentration, faster the reaction*. It is because of such proportionality between rate of reaction and the concentration of drug that a first-order process is said to follow **linear kinetics.**

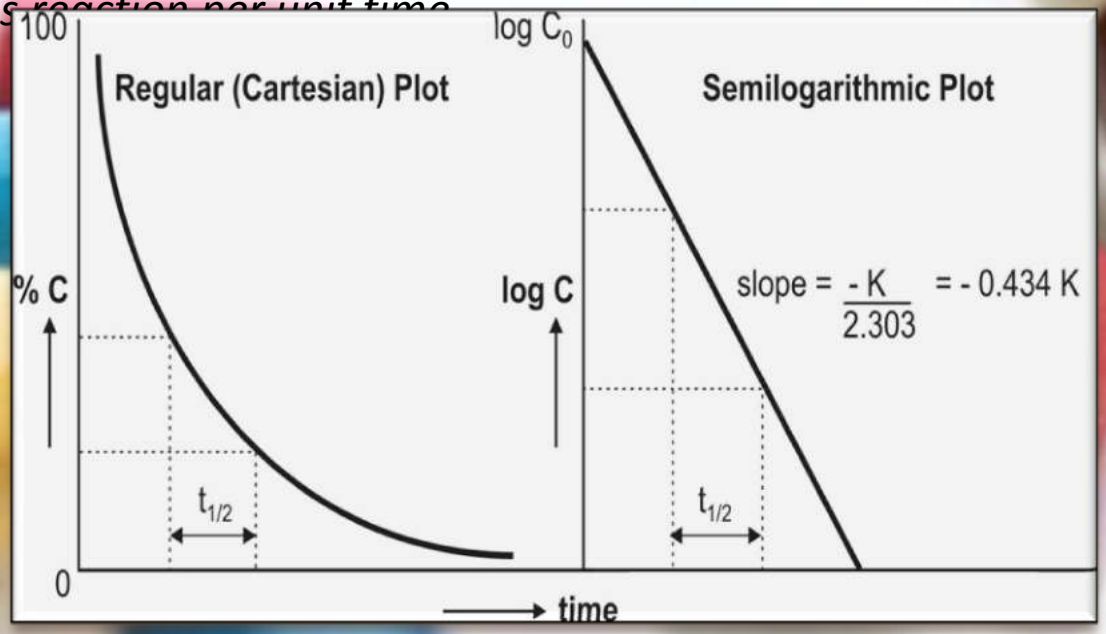


$$\ln C = \ln C_o - K t$$

$$C = C_o - e^{-Kt}$$

$$\log C = \log Co - Kt/2.303$$

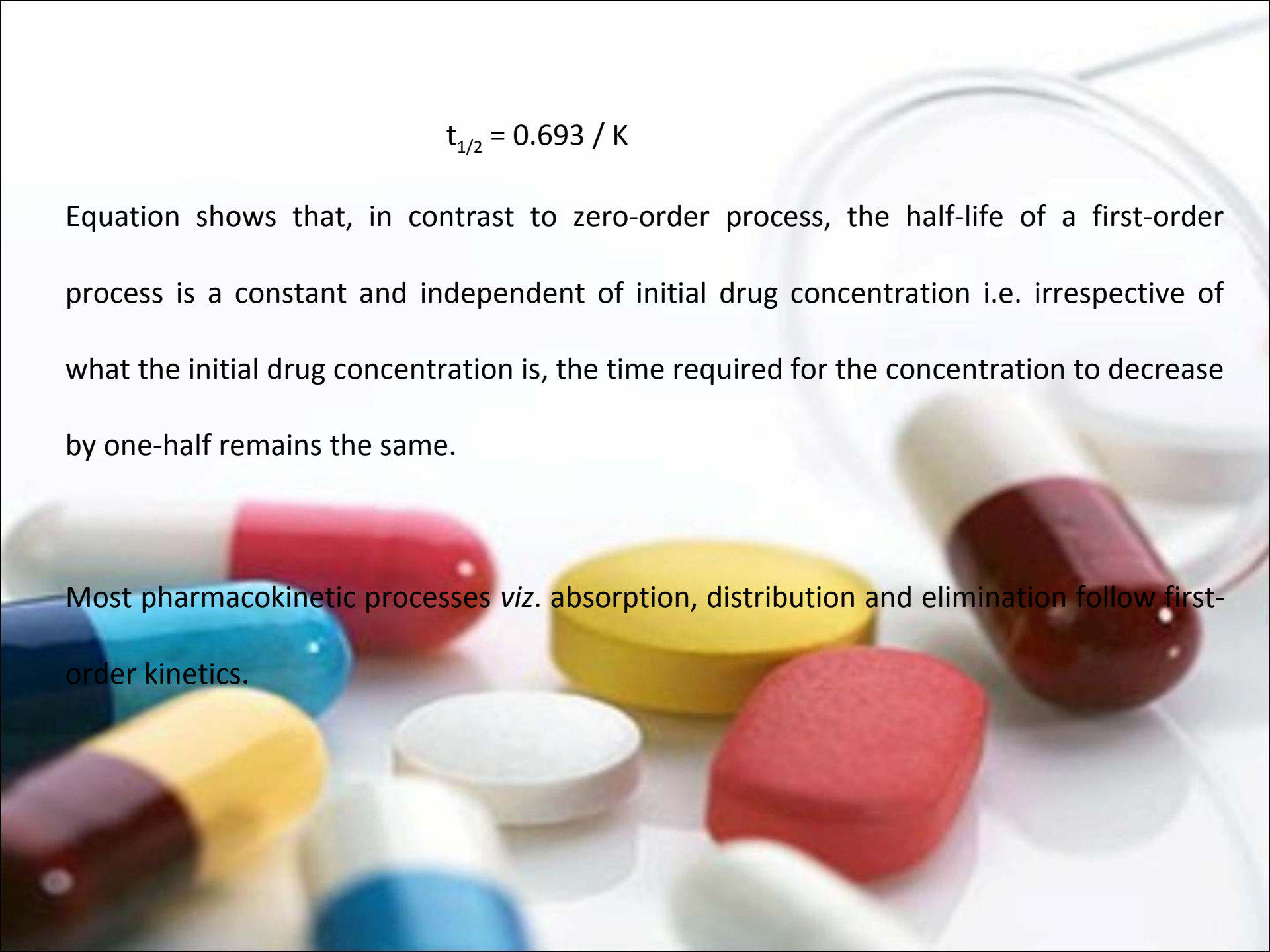
The first-order process is also called as **monoexponential rate process**. Thus, a first-order process is characterized by **logarithmic** or **exponential kinetics** i.e. *a constant fraction of drug undergoes reaction per unit time*



$$t_{1/2} = 0.693 / K$$

Equation shows that, in contrast to zero-order process, the half-life of a first-order process is a constant and independent of initial drug concentration i.e. irrespective of what the initial drug concentration is, the time required for the concentration to decrease by one-half remains the same.

Most pharmacokinetic processes *viz*. absorption, distribution and elimination follow first-order kinetics.



Mixed-Order Kinetics (Nonlinear Kinetics)

A *mixture* of both first-order and zero-order kinetics is said to follow **mixed-order kinetics**. Since deviations from an originally linear pharmacokinetic profile are observed, the rate process of such a drug is called as **nonlinear kinetics**. Mixed order kinetics is also termed as **dose-dependent kinetics** as it is observed at increased or multiple doses of some drugs.

Nonlinearities in pharmacokinetics have been observed in –

Drug absorption (e.g. vitamin C)

Drug distribution (e.g. naproxen), and

Drug elimination (e.g. riboflavin).

The phenomena is seen when a particular pharmacokinetic process involves presence of carriers or enzymes which are substrate specific and have definite capacities and can get saturated at high drug concentrations (i.e. capacity-limited). The kinetics of such capacity-limited processes can be described by the **Michaelis-Menten kinetics**.

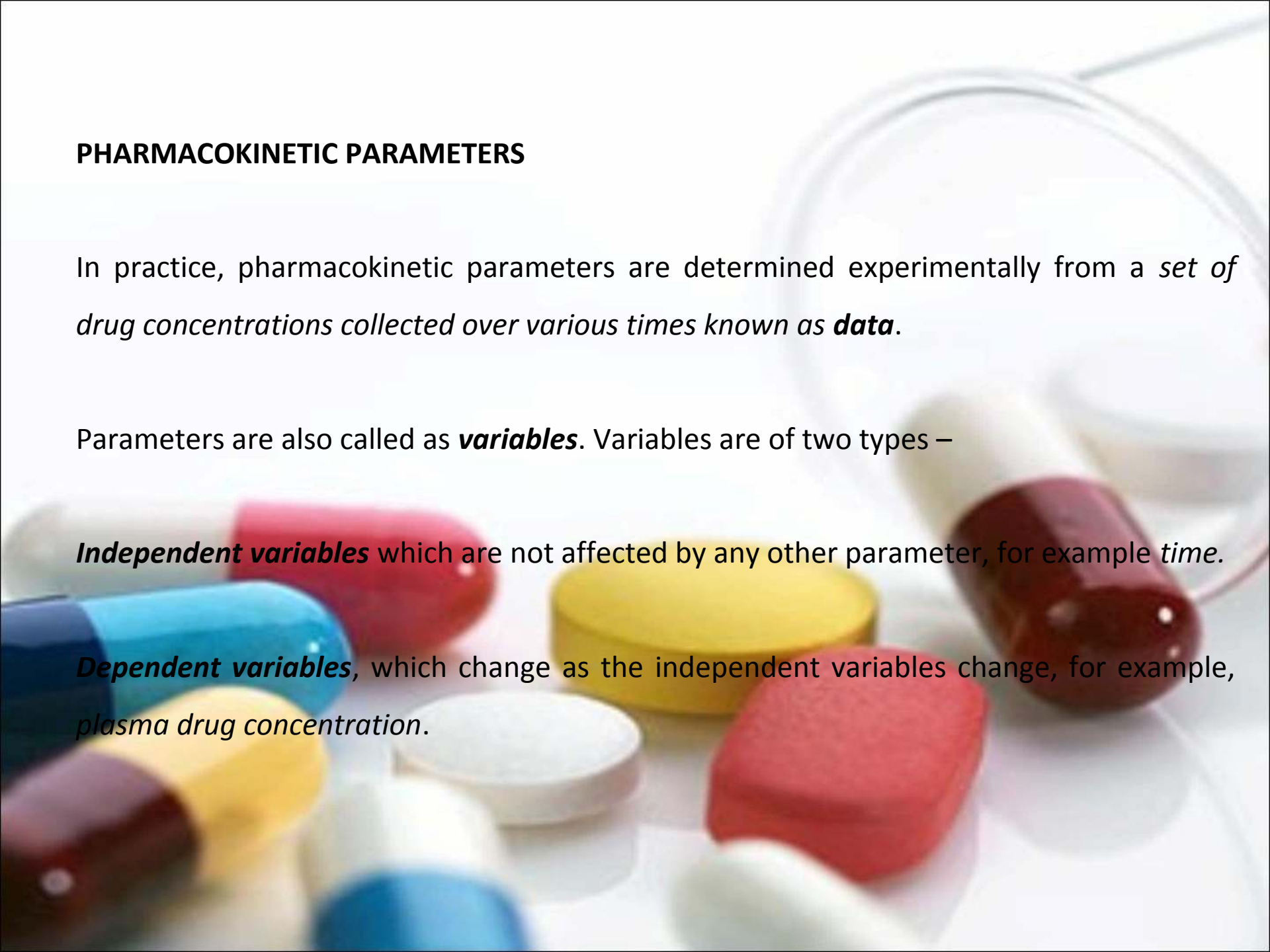
PHARMACOKINETIC PARAMETERS

In practice, pharmacokinetic parameters are determined experimentally from a *set of drug concentrations collected over various times known as* ***data***.

Parameters are also called as ***variables***. Variables are of two types –

Independent variables which are not affected by any other parameter, for example *time.*

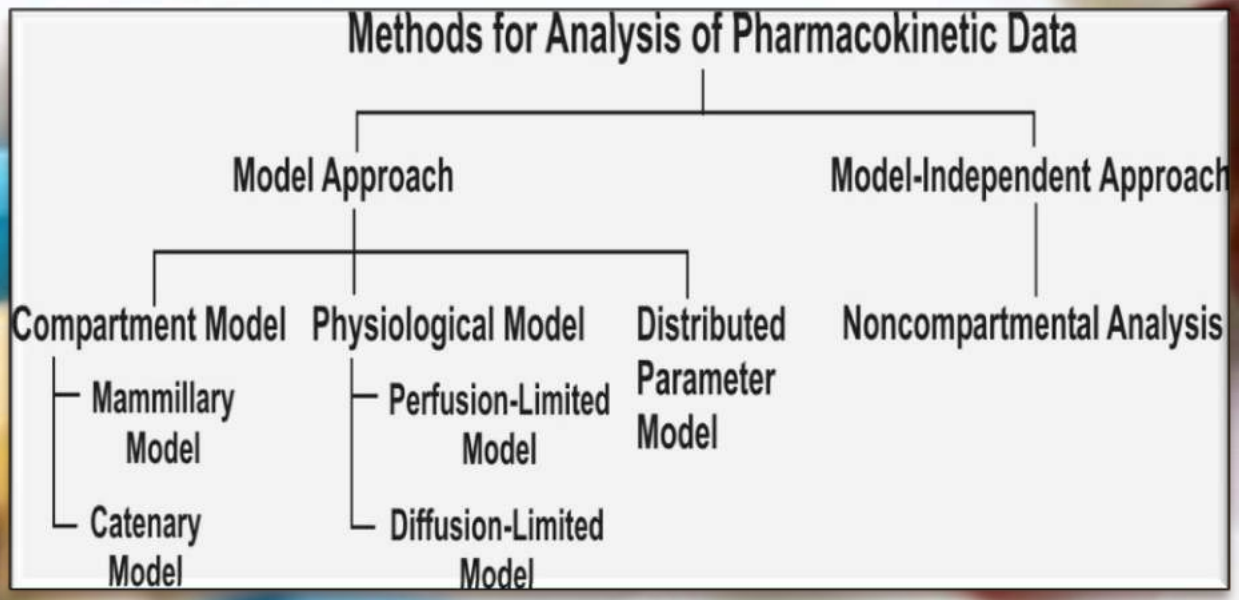
Dependent variables, which change as the independent variables change, for example, *plasma drug concentration*.



PHARMACOKINETIC MODELS

Drug movement within the body is a complex process. The major objective is therefore to develop a generalized and simple approach to describe, analyse and interpret the data obtained during *in vivo* drug disposition studies. The two major approaches in the quantitative study of various kinetic processes of drug disposition in the body are

1. Model approach, and
2. Model-independent approach (also called as non-compartmental analysis).



Pharmacokinetic Model Approach

*A **model** is a hypothesis that employs mathematical terms to concisely describe quantitative relationships*. **Pharmacokinetic models** provide concise means of expressing mathematically or quantitatively, the time course of drug(s) throughout the body and compute meaningful **pharmacokinetic parameters**.

Applications of Pharmacokinetic Models –

1. Characterizing the behaviour of drugs in patients.
2. Predicting the concentration of drug in various body fluids with any dosage regimen.
3. Predicting the multiple-dose concentration curves from single dose experiments.
4. Calculating the optimum dosage regimen for individual patients.
5. Evaluating the risk of toxicity with certain dosage regimens.
6. Correlating plasma drug concentration with pharmacological response.
7. Evaluating the bioequivalence between different formulations of the same drug.
8. Estimating the possibility of drug and/or metabolite(s) accumulation in the body.
9. Determining the influence of altered physiology/disease state on drug ADME.
10. Explaining drug interactions.

Types of Pharmacokinetic Models

Pharmacokinetic models are of three different types –

Compartment models – are also called as ***empirical models***, and

Physiological models – are *realistic models*.

Distributed parameter models – are also *realistic models*.

Compartment Models

Compartmental analysis is the traditional and most commonly used approach to pharmacokinetic characterization of a drug. These models simply interpolate the experimental data and allow an *empirical formula* to estimate the drug concentration with time.

Depending upon whether the compartments are arranged parallel or in a series, compartment models are divided into two categories —

1. Mammillary model
2. Catenary model.

Since compartments are hypothetical in nature, compartment models are based on certain ***assumptions*** –

1. The body is represented as a series of compartments arranged either in series or parallel to each other, that communicate reversibly with each other.

2. Each compartment is not a real physiologic or anatomic region but a fictitious or virtual one and considered as a tissue or group of tissues that have similar drug distribution characteristics (similar blood flow and affinity). This assumption is necessary because if every organ, tissue or body fluid that can get equilibrated with the drug is considered as a separate compartment, the body will comprise of infinite number of compartments and mathematical description of such a model will be too complex.

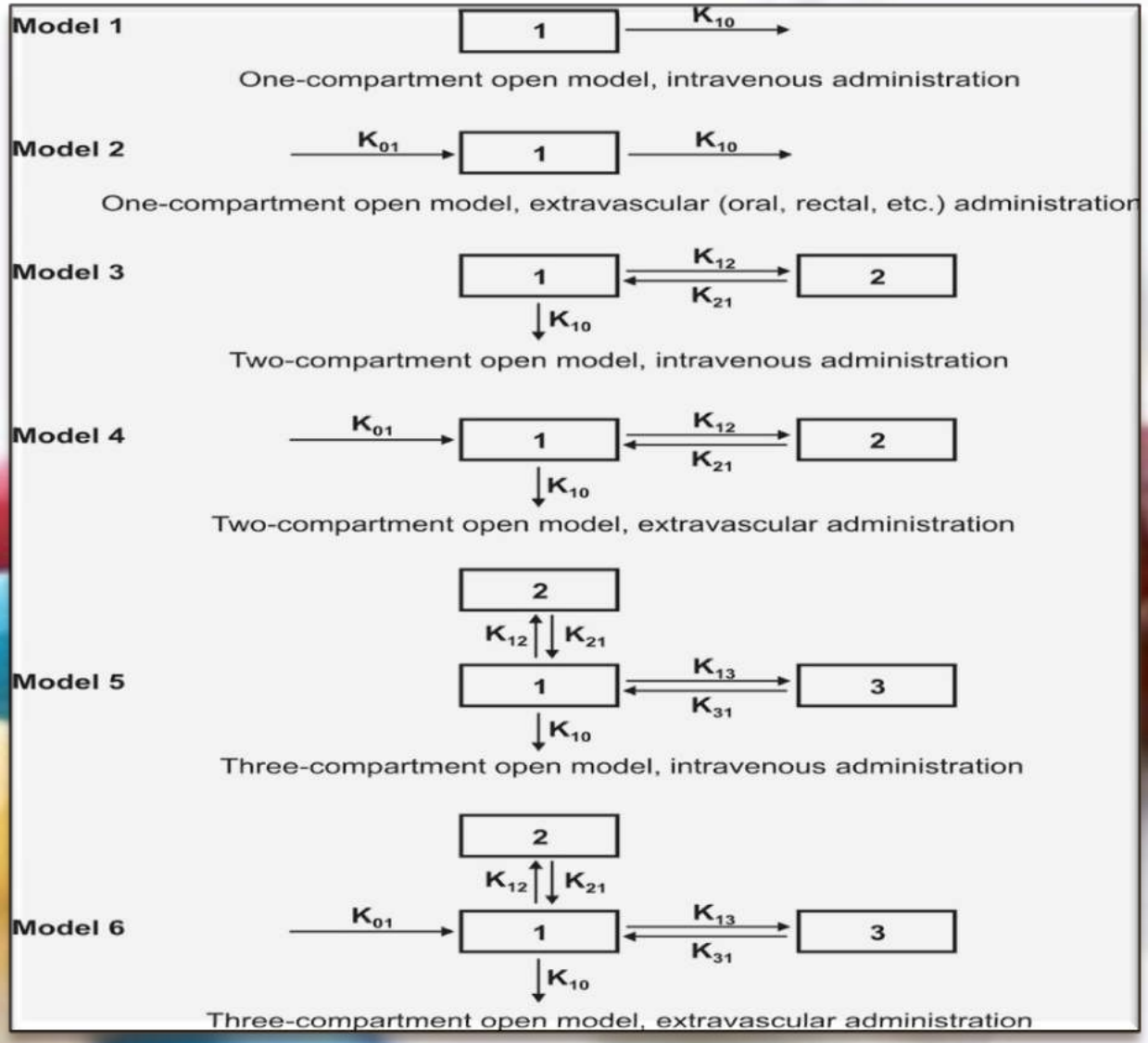
3. Within each compartment, the drug is considered to be rapidly and uniformly distributed i.e. the compartment is *well-stirred*.

4. The rate of drug movement between compartments (i.e. entry and exit) is described by first-order kinetics.

5. Rate constants are used to represent rate of entry into and exit from the compartment.

Mammillary Model

This model is the most common compartment model used in pharmacokinetics.



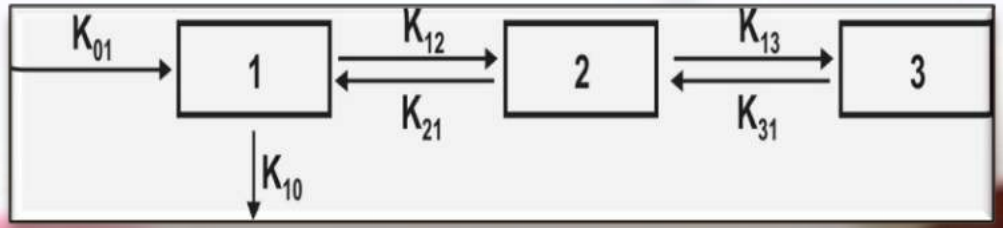
The number of rate constants which will appear in a particular compartment model is given by R.

For intravenous administration, $R = 2n - 1$

For extravascular administration, $R = 2n$

where n = number of compartments.

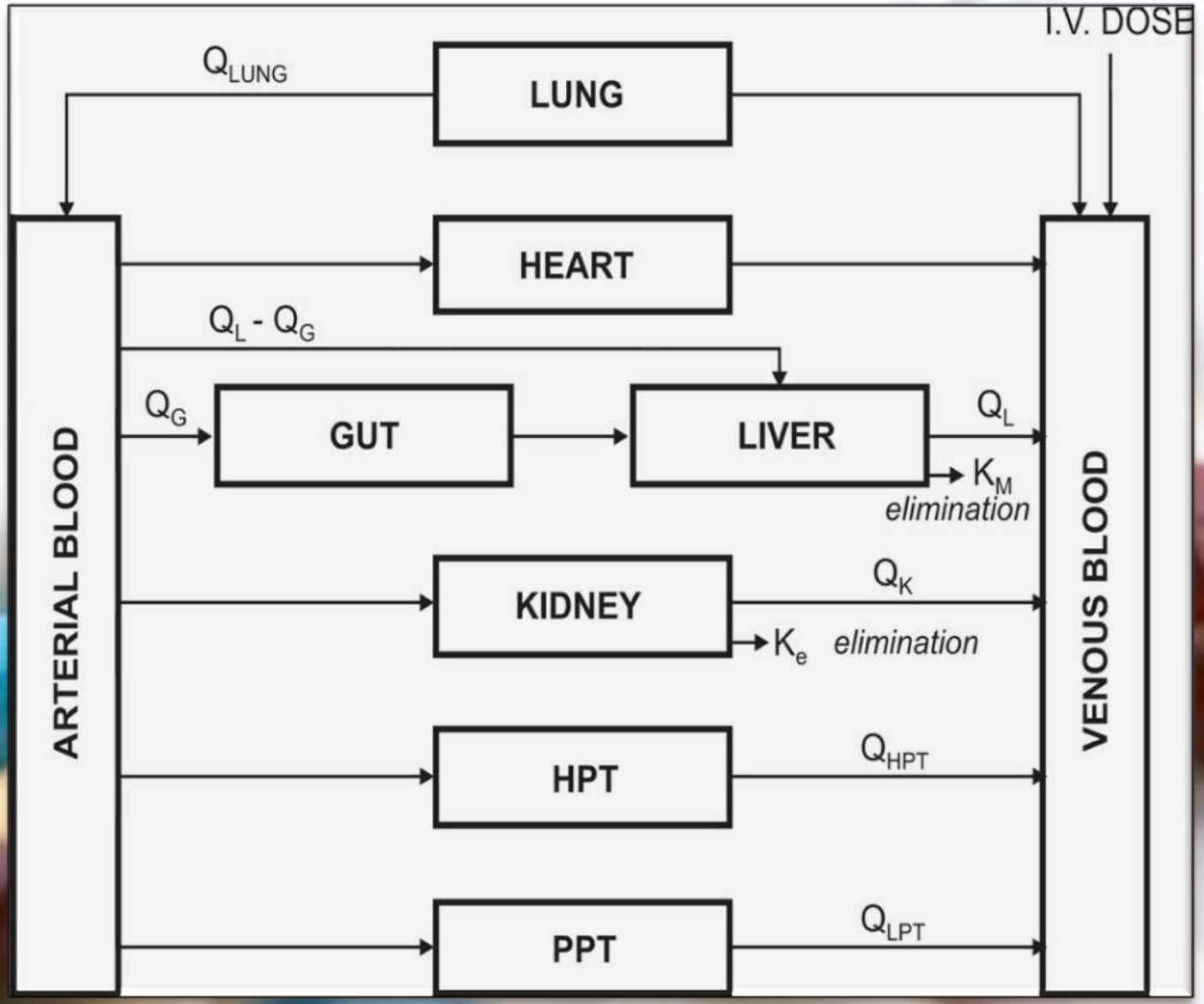
Catenary Model



Physiological Models

These models are also known as *physiologically-based pharmacokinetic models* (***PB-PK models***)

They are drawn on the basis of known anatomic and physiological data and thus present a more realistic picture of drug disposition in various organs and tissues. The number of compartments to be included in the model depends upon the disposition characteristics of the drug. Organs or tissues such as bones that have no drug penetration are excluded.


I.V. DOSE
Q_{LUNG}
LUNG
HEART
$Q_L - Q_G$
Q_G
GUT
LIVER
Q_L
K_M
elimination
ARTERIAL BLOOD
VENOUS BLOOD
KIDNEY
Q_K
K_e
elimination
HPT
Q_{HPT}
PPT
Q_{LPT}

The physiological models are further categorized into two types –

Blood flow rate-limited models – These models are more popular and commonly used than the second type, and are based on the assumption that the drug movement within a body region is much more rapid than its rate of delivery to that region by the perfusing blood. These models are therefore also called as ***perfusion rate-limited models***. This assumption is however applicable only to the highly membrane permeable drugs i.e. low molecular weight, poorly ionised and highly lipophilic drugs, for example, thiopental, lidocaine, etc.

Membrane permeation rate-limited models – These models are more complex and applicable to highly polar, ionised and charged drugs, in which case the cell membrane acts as a barrier for the drug that gradually permeates by diffusion. These models are therefore also called as ***diffusion-limited models***. Owing to the time lag in equilibration between the blood and the tissue, equations for these models are very complicated.

Noncompartmental Analysis

The ***noncompartmental analysis***, also called as the **model-independent method**, does not require the assumption of specific compartment model. This method is, however, *based on the assumption that the drugs or metabolites follow linear kinetics*, and on this basis, this technique can be applied to any compartment model.

The noncompartmental approach, based on the **statistical moments theory**, involves collection of experimental data following a single dose of drug. If one considers the time course of drug concentration in plasma as a statistical distribution curve, then:

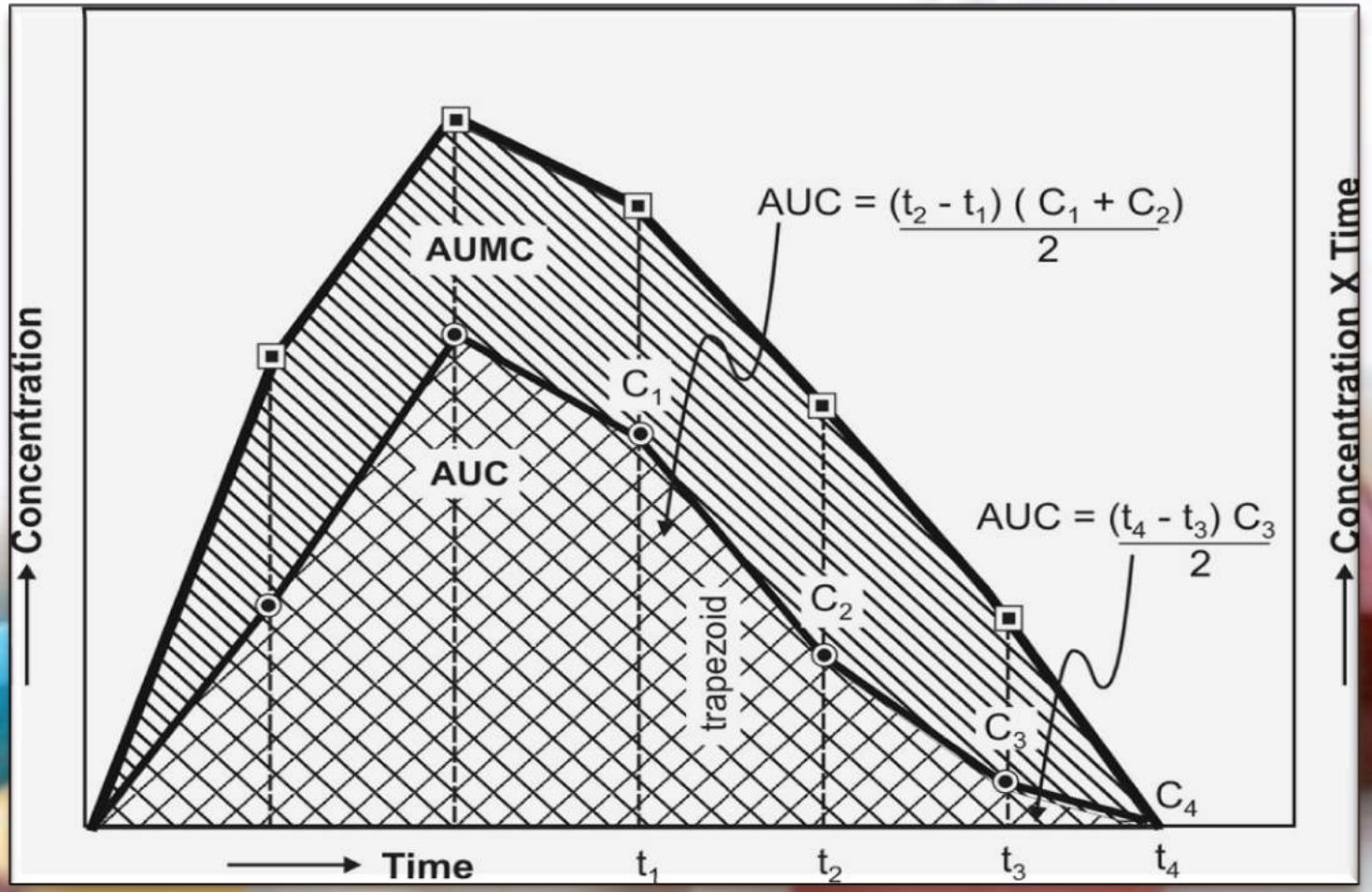
$$MRT = AUMC/AUC$$

where MRT = mean residence time

AUMC = area under the *first-moment curve*

AUC = area under the *zero-moment curve*

MRT *is defined as the average amount of time spent by the drug in the body before being eliminated*.


Concentration
Concentration X Time
AUMC
AUC
AUC = (t2 - t1) (C1 + C2) / 2
AUC = (t4 - t3) C3 / 2
C1
C2
C3
C4
trapezoid
Time
t1
t2
t3
t4

ONE-COMPARTMENT OPEN MODEL

(INSTANTANEOUS DISTRIBUTION MODEL)

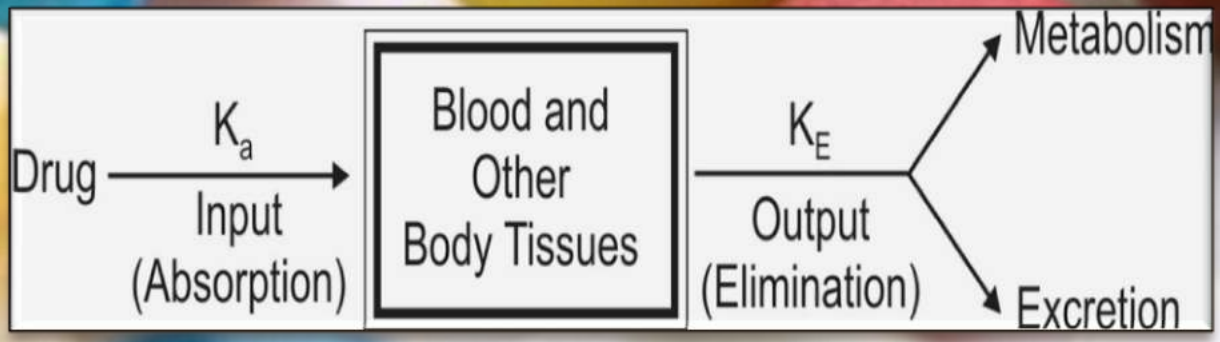
The one-compartment open model is the simplest model.

1. Elimination is a first-order (monoexponential) process with first-order rate constant.

2. Rate of input (absorption) > rate of output (elimination).

3. The anatomical ***reference compartment*** is plasma and concentration of drug in plasma is representative of drug concentration in all body tissues i.e. any change in plasma drug concentration reflects a proportional change in drug concentration throughout the body.

However, the model does not assume that the drug concentration in plasma is equal to that in other body tissues.



One-Compartment Open Model : Intravenous Bolus Administration

The general expression for **rate of drug presentation** to the body is:

$$\frac{dX}{dt} = \text{Rate in (availability)} - \text{Rate out (elimination)}$$

$$\frac{dX}{dt} = -K_E X$$

Estimation of Pharmacokinetic Parameters

Elimination phase can be characterized by 3 parameters—

1. Elimination rate constant
2. Elimination half-life
3. Clearance.

Elimination Rate Constant:

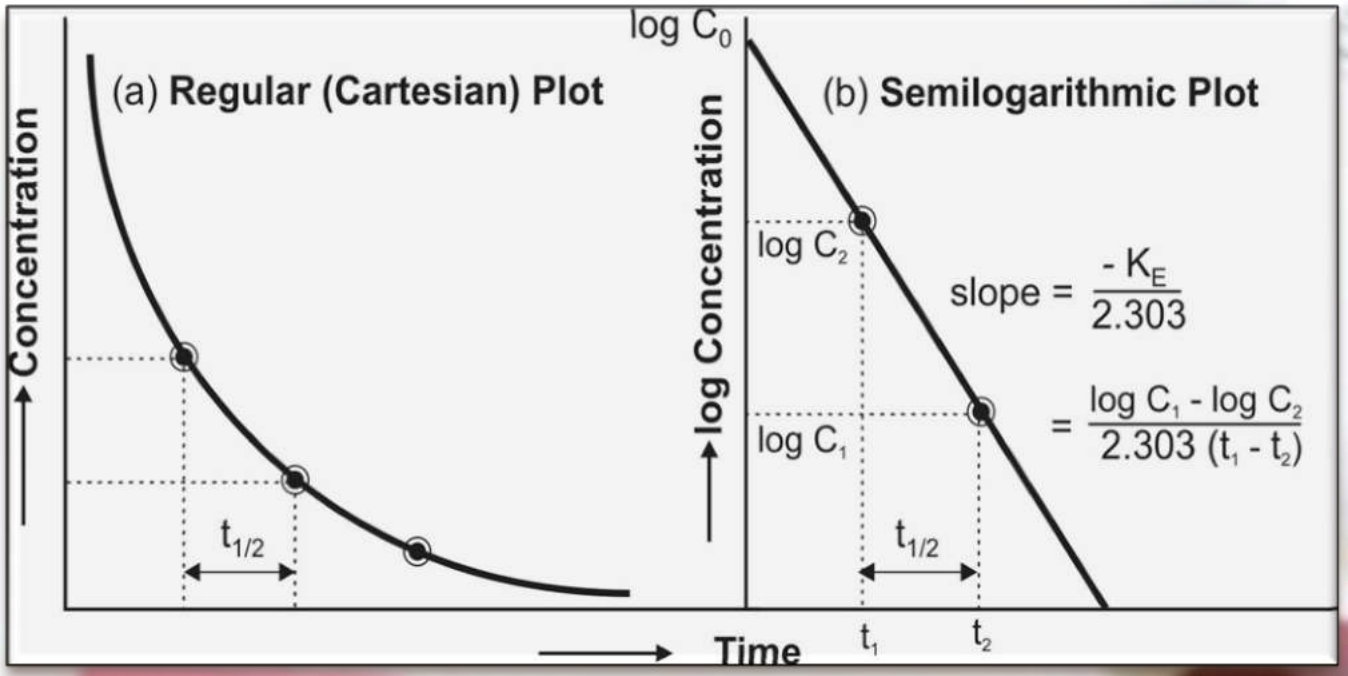
$$\ln X = \ln Xo - KE\ t$$

The above equation shows that *disposition of a drug that follows one-compartment kinetics is* **monoexponential**.

$$X = Xo\ e^{-KEt}$$

$$X = Vd\ C$$

$$\log C = \log C_0 - \frac{K_E\ t}{2.303}$$



$$KE = Ke + Km + Kb + Kl + ...$$

if a drug is eliminated by urinary excretion and metabolism only, then, the fraction of drug

excreted unchanged in urine **Fe** and fraction of drug metabolized **Fm** can be given as:

$$F_e = \frac{K_e}{K_E} \qquad F_m = \frac{K_m}{K_E}$$

Elimination Half-Life:

$$t_{1/2} = \frac{0.693}{K_E}$$

$$t_{1/2} = \frac{0.693\ V_d}{Cl_T}$$

- **Apparent volume of distribution, and**
- **Clearance.**

Since these parameters are closely related with the physiologic mechanisms in the bo

***they are called as* primary parameters.**

$$V_d = \frac{\text{Amount of drug in the body}}{\text{Plasma drug concentration}} = \frac{X}{C}$$

$$V_d = \frac{X_0}{C_0} = \frac{\text{i.v. bolus dose}}{C_0}$$

Clearance *is defined as the theoretical volume of body fluid containing drug* (i.e. that fraction of apparent volume of distribution) *from which the drug is completely removed in a given period of time*. It is expressed in ml/min or liters/hour.

$$Cl_R = \frac{\text{Rate of elimination by kidney}}{C}$$

$$Cl_H = \frac{\text{Rate of elimination by liver}}{C}$$

$$Cl_{Others} = \frac{\text{Rate of elimination by other organs}}{C}$$

$$Cl_T = \frac{0.693\ V_d}{t_{1/2}}$$

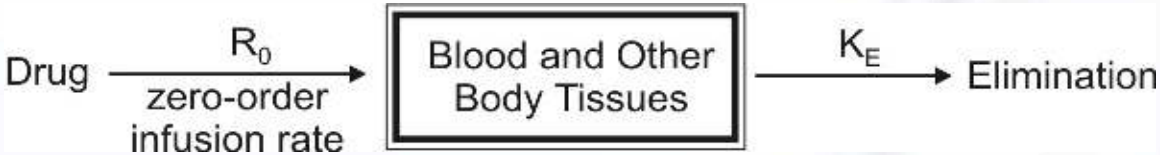
For drugs given as i.v. bolus

$$Cl_T = \frac{X_0}{AUC}$$

For drugs given e.v.

$$Cl_T = \frac{F\ X_0}{AUC}$$

One-Compartment Open Model : Intravenous Infusion



$$\frac{dX}{dt} = R_0 - K_E X$$

$$X = \frac{R_0}{K_E}(1 - e^{-K_E t})$$

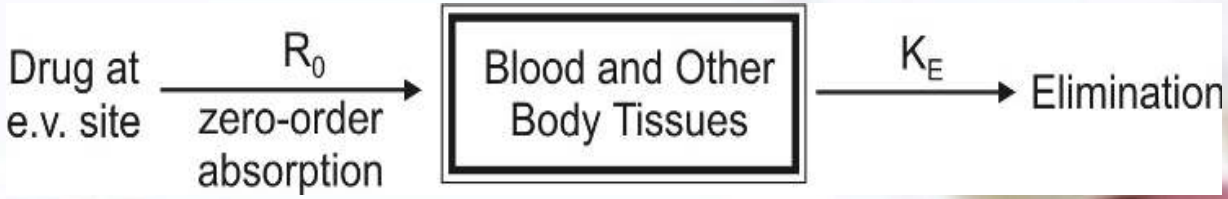
$$C = \frac{R_0}{K_E V_d}(1 - e^{-K_E t}) = \frac{R_0}{Cl_T}(1 - e^{-K_E t})$$

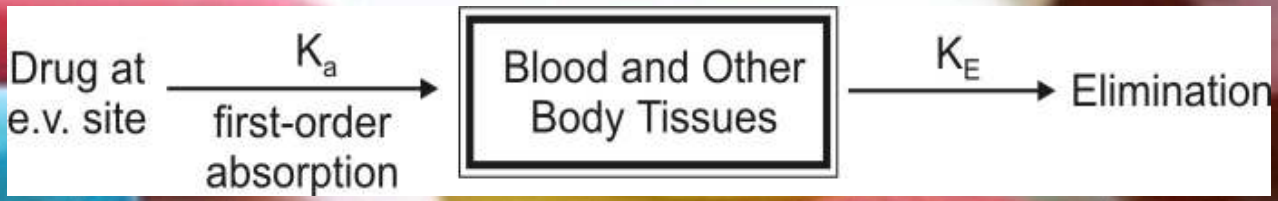
$$C_{ss} = \frac{R_0}{K_E V_d} = \frac{R_0}{Cl_T} \quad \text{i.e.} \quad \frac{\text{Infusion rate}}{\text{Clearance}}$$

One-Compartment Open Model: Extravascular Administration

dX/dt = Rate of absorption – Rate of elimination

$$\frac{dX}{dt} = \frac{dX_{ev}}{dt} - \frac{dX_E}{dt}$$





$$X = \frac{K_a F X_0}{(K_a - K_E)}\left[e^{-K_E t} - e^{-K_a t}\right]$$

$$C = \frac{K_a F X_0}{V_d (K_a - K_E)}\left[e^{-K_E t} - e^{-K_a t}\right]$$

At peak plasma concentration, the rate of absorption equals rate of elimination i.e. KaXa = $K_E X$

$$\frac{dC}{dt} = \frac{K_a F X_0}{V_d (K_a - K_E)} \left[- K_E e^{-K_E t} + K_a e^{-K_a t} \right] \quad = \text{Zero}$$

$$K_E \, e^{-K_E t} = K_a \, e^{-K_a t}$$

$$\log K_E - \frac{K_E t}{2.303} = \log K_a - \frac{K_a t}{2.303}$$

$$t_{max} = \frac{2.303 \log (K_a / K_E)}{K_a - K_E}$$

$$C_{max} = \frac{F X_0}{V_d} e^{-K_E t_{max}}$$

Absorption Rate Constant: It can be calculated by the **method of residuals**. The technique is also known as **feathering**, **peeling** and **stripping**. It is commonly used in pharmacokinetics to resolve a multiexponential curve into its individual components. For a drug that follows one-compartment kinetics and administered e.v., the concentration of drug in plasma is expressed by a biexponential equation.

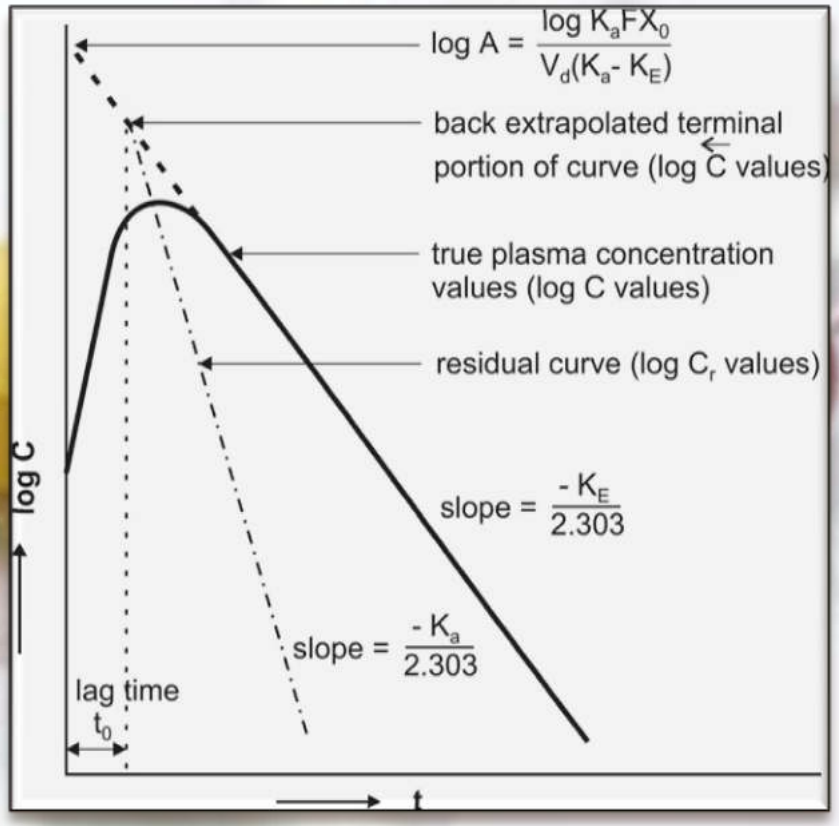
$$C = \frac{K_a F X_0}{V_d (K_a - K_E)} \left[e^{-K_E t} - e^{-K_a t} \right]$$

$$\overleftarrow{C} = A \; e^{-K_E t}$$

$$\log \overleftarrow{C} = \log A - \frac{K_E t}{2.303}$$

$$(\overleftarrow{C} - C) = C_\tau = A \; e^{-K_a t}$$

$$\log C_\tau = \log A - \frac{K_a t}{2.303}$$



Wagner-Nelson Method for Estimation of Ka

The method involves determination of Ka from percent unabsorbed-time plots and does not require the assumption of zero- or first-order absorption.

$$X_A = X + X_E$$

$$X_E = K_E \, V_d \, [AUC]_0^t$$

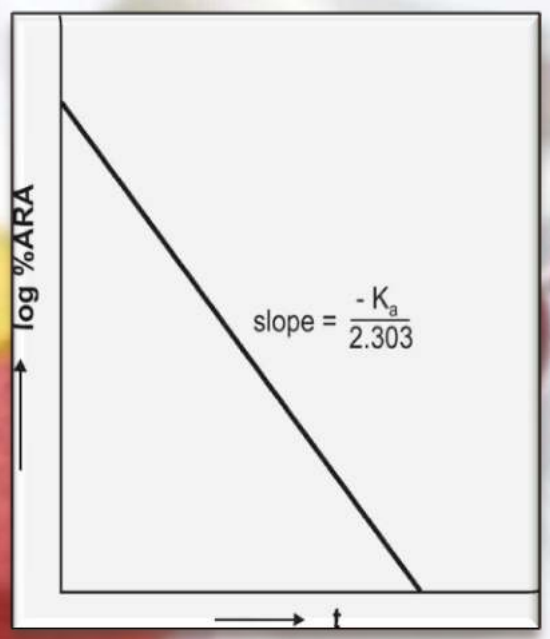
$$X_A = V_d C + K_E \, V_d \, [AUC]_0^t$$

$$X_A^\infty = V_d \, C^\infty + K_E \, V_d \, [AUC]_0^\infty$$

$$X_A^\infty = K_E \, V_d \, [AUC]_0^\infty$$

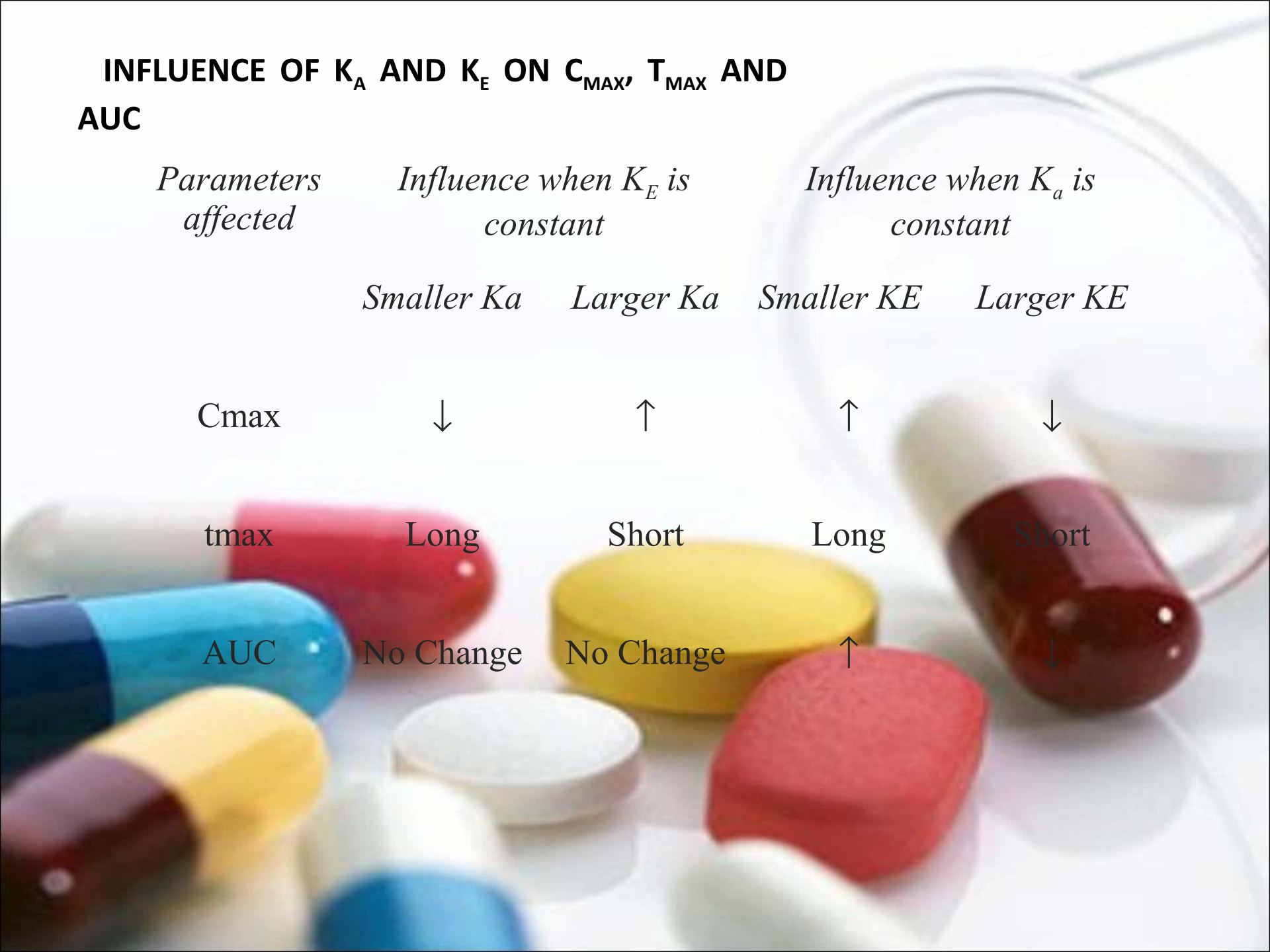
$$\frac{X_A}{X_A^\infty} = \frac{V_d \, C + K_E \, V_d \, [AUC]_0^t}{K_E \, V_d \, [AUC]_0^\infty} = \frac{C + K_E \, [AUC]_0^t}{K_E \, [AUC]_0^\infty}$$

$$\%ARA = \left[1 - \frac{XA}{X_A^\infty}\right] 100 = \left[1 - \frac{C + K_E \, [AUC]_0^t}{K_E \, [AUC]_0^\infty}\right] 100$$



INFLUENCE OF K_A AND K_E ON C_{MAX}, T_{MAX} AND AUC

Parameters affected	*Influence when K_E is constant*		*Influence when K_a is constant*	
	Smaller Ka	*Larger Ka*	*Smaller KE*	*Larger KE*
Cmax	↓	↑	↑	↓
tmax	Long	Short	Long	Short
AUC	No Change	No Change	↑	↓



URINARY EXCRETION DATA

Criteria for Obtaining Valid Urinary Excretion Data

A significant amount of drug must be excreted unchanged in the urine (at least 10%).

1. The analytical method must be specific for the unchanged drug; metabolites should not interfere.

2. Water-loading should be done by taking 400 ml of water after fasting overnight, to promote diuresis and enable collection of sufficient urine samples.

3. Before administration of drug, the bladder must be emptied completely after 1 hour from water-loading and the urine sample taken as blank. The drug should then be administered with 200 ml of water and should be followed by 200 ml given at hourly intervals for the next 4 hours.

4. Volunteers must be instructed to completely empty their bladder while collecting urine samples.

5. Frequent sampling should be done in order to obtain a good curve.

6. During sampling, the exact time and volume of urine excreted should be noted.

7. An individual collection period should not exceed one biological half-life of the drug and ideally should be considerably less.

8. Urine samples must be collected for at least 7 biological half-lives in order to ensure collection of more than 99% of excreted drug.

9. Changes in urine pH and urine volume may alter the urinary excretion rate.

Determination of K_E from Urinary Excretion Data

1. Rate of excretion method, and
2. Sigma-minus method.

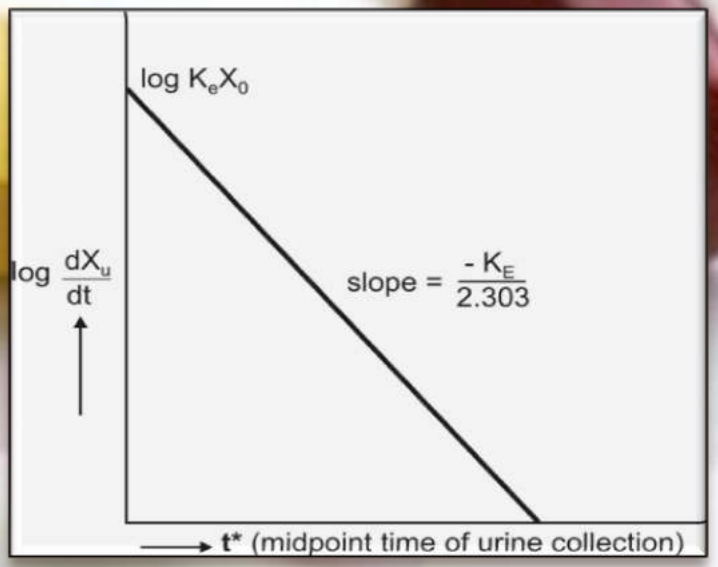
Rate of Excretion Method: The rate of urinary drug excretion dXu/dt is proportional to the amount of drug in the body X and written as:

$$\frac{dX_u}{dt} = K_e X$$

According to first-order disposition kinetics, $X = Xo\ e^{-K_E t}$

$$\frac{dX_u}{dt} = K_e X_0\ e^{-K_E t}$$

$$\log \frac{dX_u}{dt} = \log K_e X_0 - \frac{K_E t}{2.303}$$



Sigma-Minus Method: A *disadvantage of rate of excretion method* in estimating K_E is that fluctuations in the rate of drug elimination are observed to a high degree and in most instances, the data are so scattered that an estimate of half-life is difficult. These problems can be minimized by using the alternative approach called as sigma-minus method.

$$\frac{dX_u}{dt} = K_e X_0 \, e^{-K_E t}$$

$$X_u = \frac{K_E X_0}{K_E}(1 - e^{-K_E t})$$

Xu = cumulative amount of drug excreted unchanged in urine at any time t. As time approaches infinity i.e. after 6 to 7 half-lives, the value e–KE∞ becomes zero and therefore the cumulative amount excreted at infinite time Xu ∞ can be given by equation

$$X_u^{\infty} = \frac{K_e X_0}{K_E}$$

$$X_u^{\infty} - X_u = X_u^{\infty} e^{-K_E t}$$

$$\log (X_u^{\infty} - X_u) = \log X_u^{\infty} - \frac{K_E t}{2.303}$$

$(Xu_\infty - Xu)$ = **amount remaining to be excreted**

i.e. **ARE** at any given time.

A semilog plot of ARE versus t yields a straight line with slope -KE/2.303.

The method is, therefore, also called as **ARE plot method**.

A *disadvantage* of this method is that total urine collection has to be carried out until no unchanged drug can be detected in the urine i.e. upto 7 half-lives, which may be tedious for drugs having long t½.

MULTICOMPARTMENT MODELS: INTRAVENOUS BOLUS ADMINISTRATION

Pharmacokinetic models- represent drug distribution and elimination in the body.

A model should mimic closely the physiologic processes in the body

In compartmental models, drug tissue concentration is assumed to be uniform within a given hypothetical compartment.

All muscle mass and connective tissues may be lumped into one hypothetical tissue compartment that equilibrates with drug from the central (or plasma) compartment.

Multicompartment models were developed to explain and predict plasma and tissue concentrations for the behavior of these drugs.

In contrast, a one-compartment model is used when the drug appears to distribute into tissues instantaneously and uniformly.

Central compartment

These highly perfused tissues and blood make up the central compartment.

Multicompartment drugs

Multicompartment drugs are delivered concurrently to one or more peripheral compartments composed of groups of tissues with lower blood perfusion and different affinity for the drug.

Many drugs given in a single intravenous bolus dose demonstrate a plasma level–time curve that does not decline as a single exponential (first-order) process.

The plasma level–time curve for a drug that follows a two-compartment model shows that the plasma drug concentration declines *biexponentially as the sum of two first-order processes—distribution and elimination.*

TWO COMPARTMENT OPEN MODEL

A drug that follows the pharmacokinetics of a two-compartment model does not equilibrate rapidly throughout the body, as is assumed for a one-compartment model.

In this model, the drug distributes into two compartments, the central compartment and the tissue, or peripheral compartment.

Central compartment:

Represents the blood, extracellular fluid, and highly perfused tissues. The drug distributes rapidly and uniformly in the central compartment.

Second compartment,

Known as the tissue or peripheral compartment, contains tissues in which the drug equilibrates more slowly.

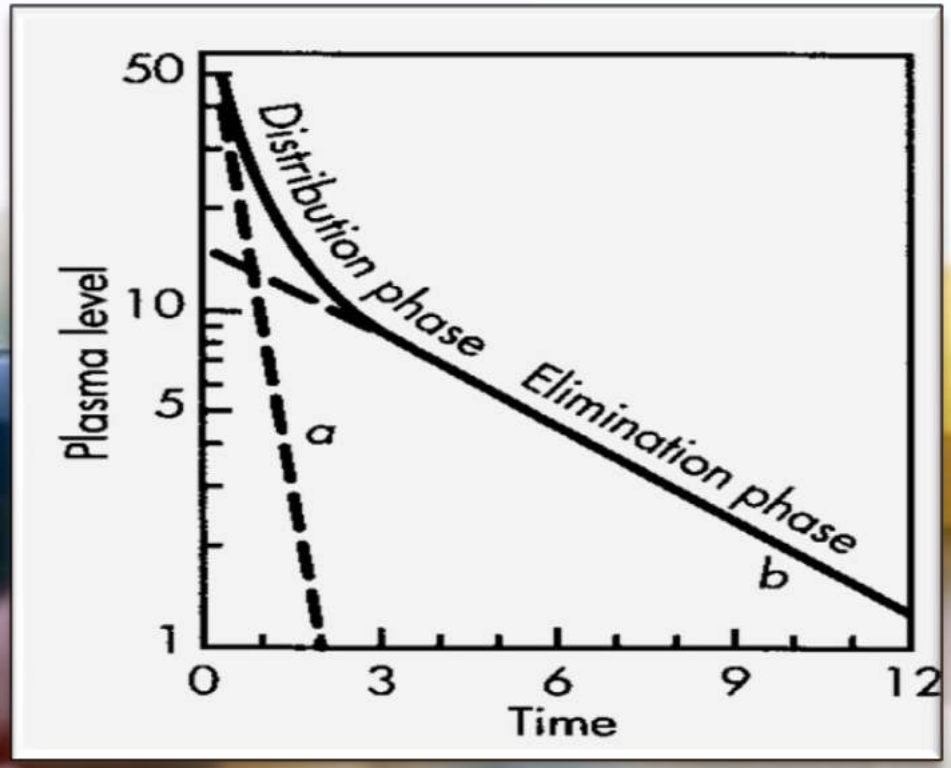
Drug transfer between the two compartments is assumed to take place by first-order processes.

GENERAL GROUPING OF TISSUE ACCORDING TO BLOOD SUPPLY

TABLE 4.2 General Grouping of Tissues According to Blood Supply[a]

BLOOD SUPPLY	TISSUE GROUP	PERCENT BODY WEIGHT
Highly perfused	Heart, brain, hepatic-portal system, kidney, and endocrine glands	9
	Skin and muscle	50
	Adipose (fat) tissue and marrow	19
Slowly perfused	Bone, ligaments, tendons, cartilage, teeth, and hair	22

Distribution phase- represents the initial, more rapid decline of drug from the central compartment into tissue compartment (line *a*)
The decline is 1st order process and called **elimination phase** or β phase (line *b*)



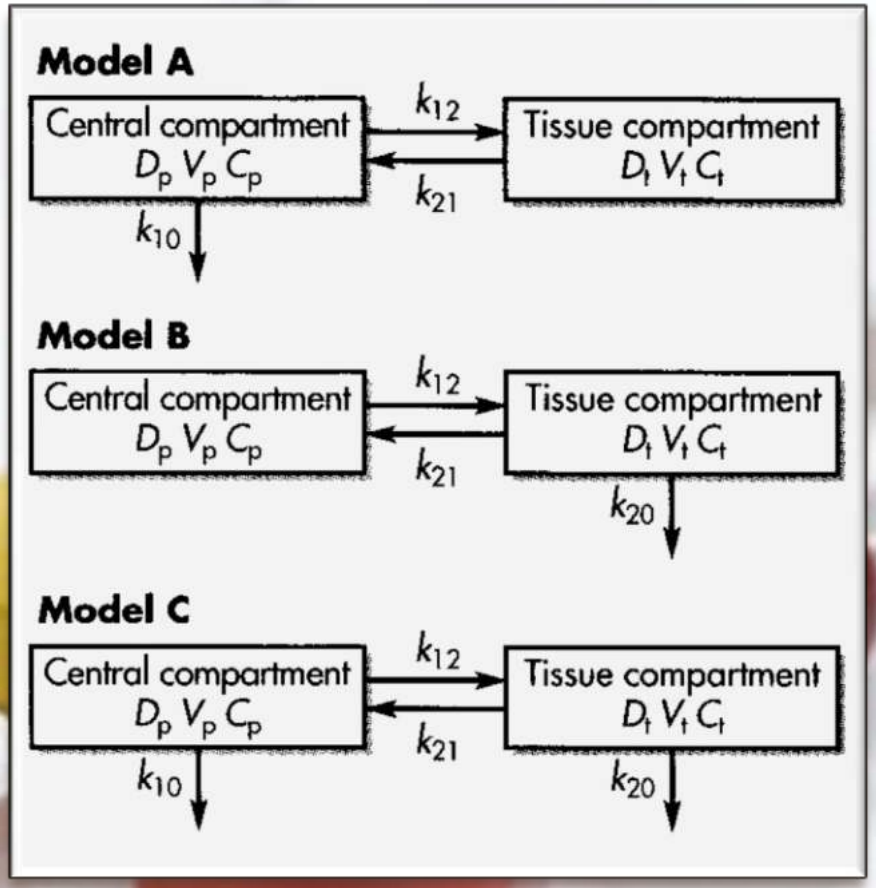
- Distribution phase- drug elimination and distribution occur concurrently
- Net transfer of drug from central to tissue compartment
- Fraction of drug in the tissue compartment during distribution phase increases to max.
- At max. tissue conc. – rate of drug entry into tissue = rate of drug exit from tissue.
- Drug in tissue compartment- equilibrium with drug in central compartment (distribution equilibrium)
- Drug conc in both compartment decline in parallel and more slowly compared to distribution phase

TWO COMPARTMENT MODELS

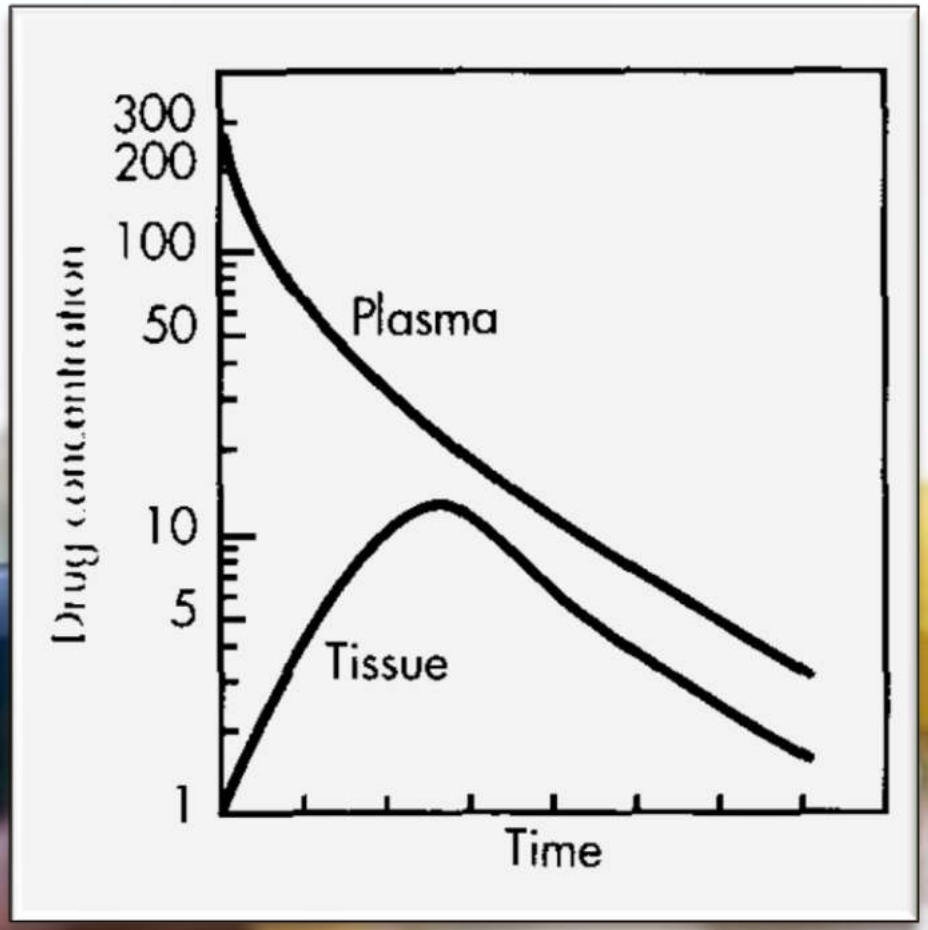
There are several possible two-compartment models

- compartment 1 is the central compartment and compartment 2 is the tissue compartment.

- The rate constants k_{12} and k_{21} represent the first-order rate transfer constants for the movement of drug from compartment 1 to compartment 2 (k_{12}) and from compartment 2 to compartment 1 (k_{21}).



RELATIONSHIP BETWEEN DRUG CONCENTRATIONS IN TISSUE AND PLASMA



The maximum tissue drug concentration may be greater or less than the plasma drug concentration.

The rate of drug change in and out of the tissues:

$$\frac{dC_t}{dt} = k_{12}C_p - k_{21}C_t$$

The relationship between the amount of drug in each compartment and the concentration of drug in that compartment is shown by:

$$C_p = \frac{D_p}{V_p} \qquad C_t = \frac{D_t}{V_t}$$

where,

D_p = *amount of drug in the central compartment,*

D_t = *amount of drug in the tissue compartment,*

V_p = *volume of drug in the central compartment, and*

V_t = *volume of drug in the tissue compartment.*

Rate equation:

$$-\frac{dC_p}{dt} = k_{21}\frac{D_t}{V_t} - k_{12}\frac{D_p}{V_p} - k\frac{D_p}{V_p}$$

$$\frac{dC_t}{dt} = k_{12}\frac{D_p}{V_p} - k_{21}\frac{D_t}{V_t}$$

Drug concentration in blood and tissue

$$C_p = \frac{D_p^0}{V_p}\left(\frac{k_{21}}{b} - \frac{a}{a}e^{-at} + \frac{k_{21} - b}{a - b}e^{-bt}\right)$$

$$C_t = \frac{D_p^0}{V_t}\left(\frac{k_{12}}{b} - \frac{a}{a}e^{-at} - \frac{k_{12}}{a - b}e^{-bt}\right)$$

Amount of drug in blood and tissue

$$D_p = D_p^0\left(\frac{k_{21} - a}{b} - \frac{a}{a}e^{-at} + \frac{k_{21} - b}{a - b}e^{-bt}\right)$$

$$D_t = D_p^0\left(\frac{k_{12}a}{b} - \frac{a}{a}e^{-at} + \frac{k_{12}}{a - b}e^{-bt}\right)$$

The rate constants for the transfer of drug between compartments are referred to as *microconstants* or *transfer constants,* and relate the amount of drug being transferred per unit time from one compartment to the other.

The constants *a* and *b* are hybrid first-order rate constants for the distribution phase and elimination phase, respectively.

$$a + b = k_{12} + k_{21} + k$$

$$ab = k_{21}k$$

Equation

$$C_p = \frac{D_0^0}{V_p}\left(\frac{k_{21} - a}{b - a}e^{-at} + \frac{k_{21} - b}{a - b}e^{-bt}\right)$$

Constants a and b- rate constant for distribution phase and elimination phase

Can be write as

$$C_p = Ae^{-at} + Be^{-bt}$$

The constants *A* and *B* are intercepts on the *y* axis for each exponential segment of the curve

$$A = \frac{D_0(a - k_{21})}{V_p(a - b)}$$

$$B = \frac{D_0(k_{21} - b)}{V_p(a - b)}$$

Intercepts *A* and *B* are hybrid constants

METHOD OF RESIDUALS

Method of residual- feathering or peeling, useful for fitting a curve to the experimental data of drug when drug does not follow one compartment model.

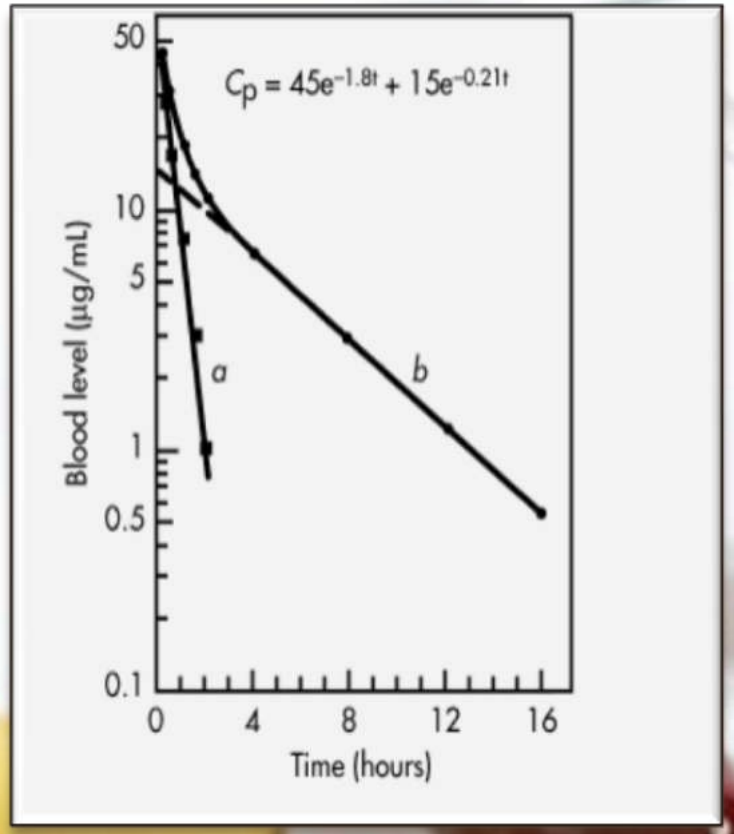
E.g: 100 mg of drug administered by rapid IV injection to a 70-kg healthy adult male. Blood sample were taken periodically and the following data were obtained:

Time (hr)	Plasma Concentration (μg/mL)
0.25	43.00
0.5	32.00
1.0	20.00
1.5	14.00
2.0	11.00
4.0	6.50
8.0	2.80
12.0	1.20
16.0	0.52

When data is plotted, a curved line is observed. The curved-line relationship between logarithm of the plasma conc and time indicates that drug is distributed in more than one compartment. From these data, biexponential equation, may be derived

$$C_p = Ae^{-at} + Be^{-bt}$$

As shown in biexponential curve, the decline in initial distribution phase is more rapid than elimination phase.
Rapid distribution phase confirmed with constant *a* being larger than constant *b*.
at some later time Ae^{-at} will approach 0, while Be^{-bt} still have value.



The rate constant and intercepts were calculated by method of residuals

Therefore, $C_P = Be^{-bt}$

In common logarithms,

$$\log C_P = \frac{-bt}{2.3} + \log B$$

From equation above, rate constant can be obtained from the slope (-*b*/2.3) of a straight line representing the terminal exponential phase.

The t1/2 for elimination phase (beta half life) can be derived from the following relationship:

$$t_{1/2_\beta} = \frac{0.693}{b}$$

From Eg. *b* was found to be 0.21 hr^{-1}. from this info the regression line for terminal exponential or *b* phase is extrapolated to the y axis; y intercept = *B* or 15um/mL.

Table 4.3 Application of the Method of Residuals			
TIME (hr)	C_p Observed Plasma Level	C'_p Extrapolated Plasma Concentration	$C_p - C'_p$ Residual Plasma Concentration
0.25	43.0	14.5	28.5
0.5	32.0	13.5	18.5
1.0	20.0	12.3	7.7
1.5	14.0	11.0	3.0
2.0	11.0	10.0	1.0
4.0	6.5		
8.0	2.8		
12.0	1.2		
16.0	0.52		

•Values from the extrapolated line are then substracted from the original experimental data points and a straight line is obtained. This line represents the rapidly distributed phase.

•The new line obtained by graphing the logarithm of residual plasma conc (Cp- C'p) against time represents the a phase. The value for *a* is 1.8 hr^{-1} and y intercept is 45ug/mL. elimination half life, $t_{1/2}$ computed from *b*, has the value of 3.3 hr.

A no of pharmacokinetic parameters may be derived by proper substitution of rate constants *a* and *b* and y intercepts *A* and *B* to following equations:

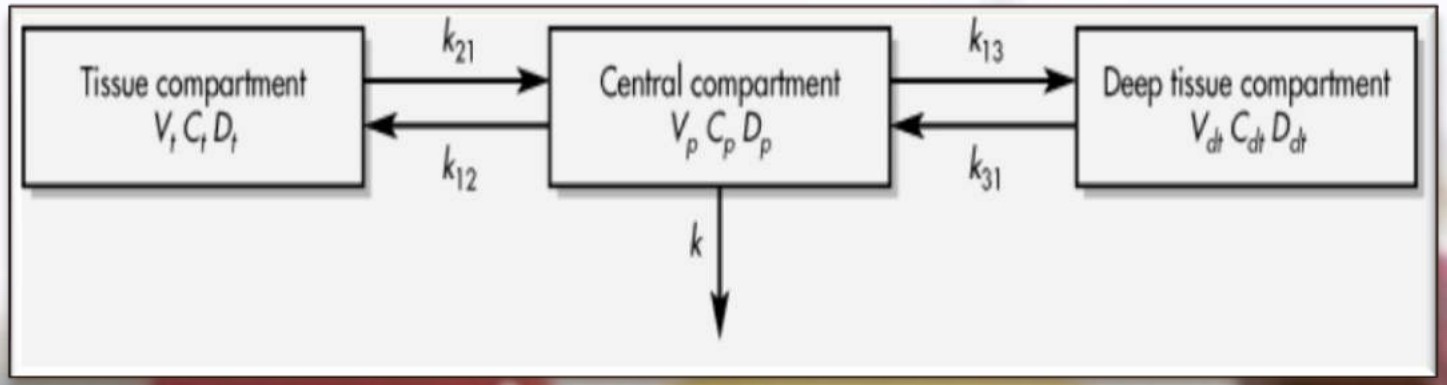
$$k = \frac{ab(A + B)}{Ab + Ba}$$

$$k_{12} = \frac{AB(b - a)^2}{(A + B)(Ab + Ba)}$$

$$k_{21} = \frac{Ab + Ba}{A + B}$$

THREE COMPARTMENT OPEN MODEL

Three compartment- two compartment model + deep tissue compartment



Central compartment- distributed most rapidly- highly perfused tissues

Compartment 2- distributed less rapidly

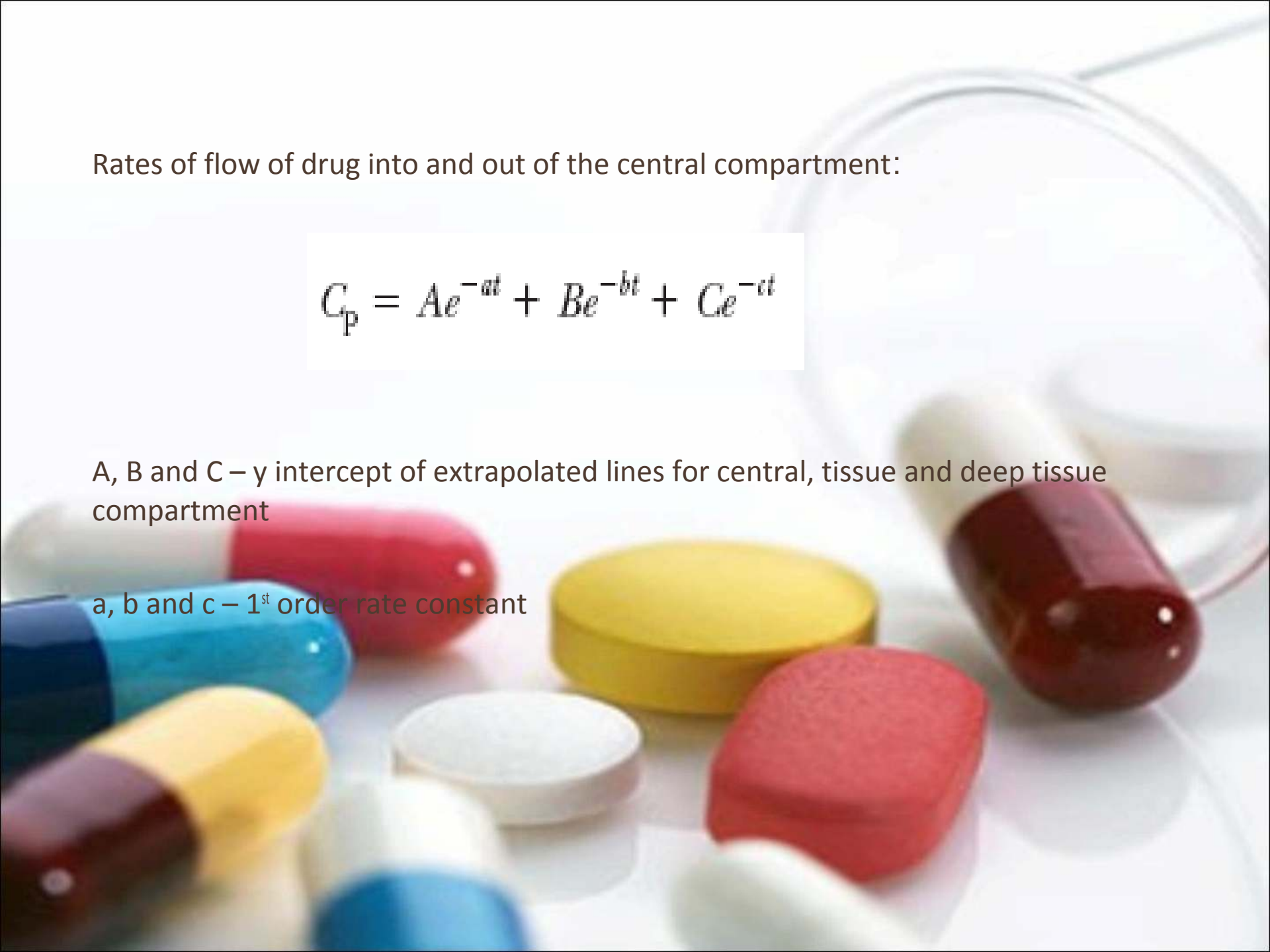
Compartment 3- distributed very slowly- poorly perfused tissues, i.e. bone/ fat

Rates of flow of drug into and out of the central compartment:

$$C_p = Ae^{-at} + Be^{-bt} + Ce^{-ct}$$

A, B and C – y intercept of extrapolated lines for central, tissue and deep tissue compartment

a, b and c – 1st order rate constant



Elimination rate constant, k

$$k = \frac{(A + B + C)abc}{Abc + Bac + Cab}$$

Volume of central compartment

$$V_P = \frac{D_0}{A + B + C}$$

Area

$$[\mathrm{AUC}] = \frac{A}{a} + \frac{B}{b} + \frac{C}{c}$$

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THANK YOU

DISSOLUTION TESTING

12/08/12

IN-VITRO DISSOLUTION TESTING MODELS

12/08/12

OFFICIAL METHODS

12/08/12

CLASSIFICATION

- There are basically three general categories of dissolution apparatus :

1. Beaker methods
2. Open flow-through compartment system
3. Dialysis concept

1. BEAKER METHODS

ROTATING BASKET APPARATUS(APPARATUS 1)

- It is basically a closed-compartment, beaker type apparatus.
- It comprising of a cylindrical glass vessel with hemispherical bottom of one litre capacity partially immersed in a water bath.
- A cylindrical basket made of #22 mesh is located centrally in the vessel at a distance of 2 cm from the bottom and rotated by a variable speed motor through a shaft.

- All metal parts like basket and shaft are made of stainless steel 316.

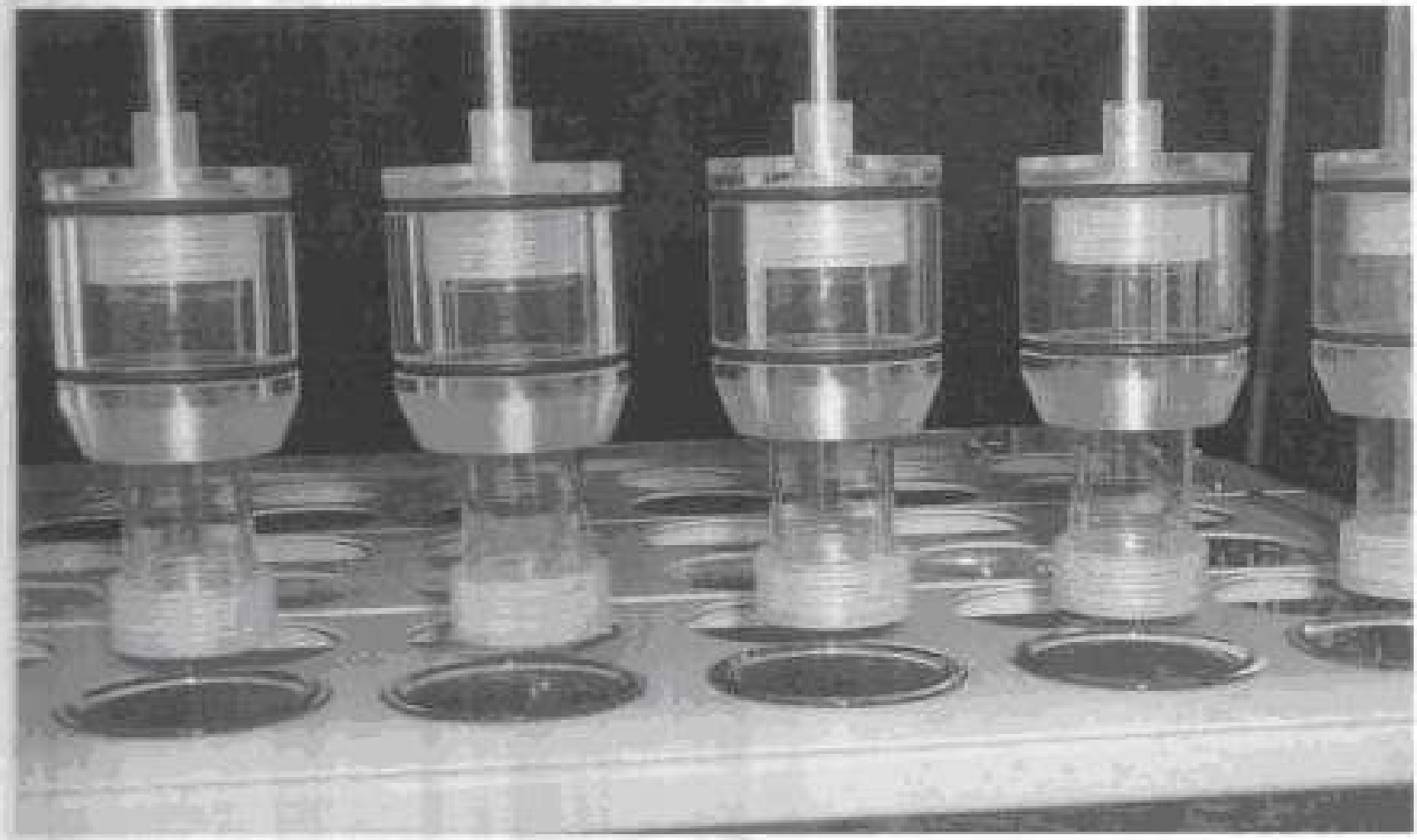
ROTATING PADDLE APPARATUS(APPARATUS 2)

- Here, basket is replaced with a stirrer.
- A small, loose, wire helix may be attached to the dosage form that would otherwise float.
- The position and alignment of the paddle are specified in the official books.

CYLINDER METHOD (APPARATUS 3)

- This method adopts the USP disintegration "basket and rack" assembly for the dissolution test.
- The disks are not used.
- This method is less suitable for precise dissolution testing due to the amount of agitation and vibration involved.
- E.g. Chlorpheniramine ER tablets, Carbamazepine chewable tablet

(c) The reciprocating cylinder (USP III) dissolution apparatus.



(APPARATUS 5)

- Modification of Apparatus 2.
- Here, stainless steel disk designed for holding transdermal system at the bottom of the vessel.
- The disk/device should not , react with, or interfere with the specimen being tested.
- The disk holds the system flat and is positioned such that the release surface is parallel with the bottom of the paddle blade.

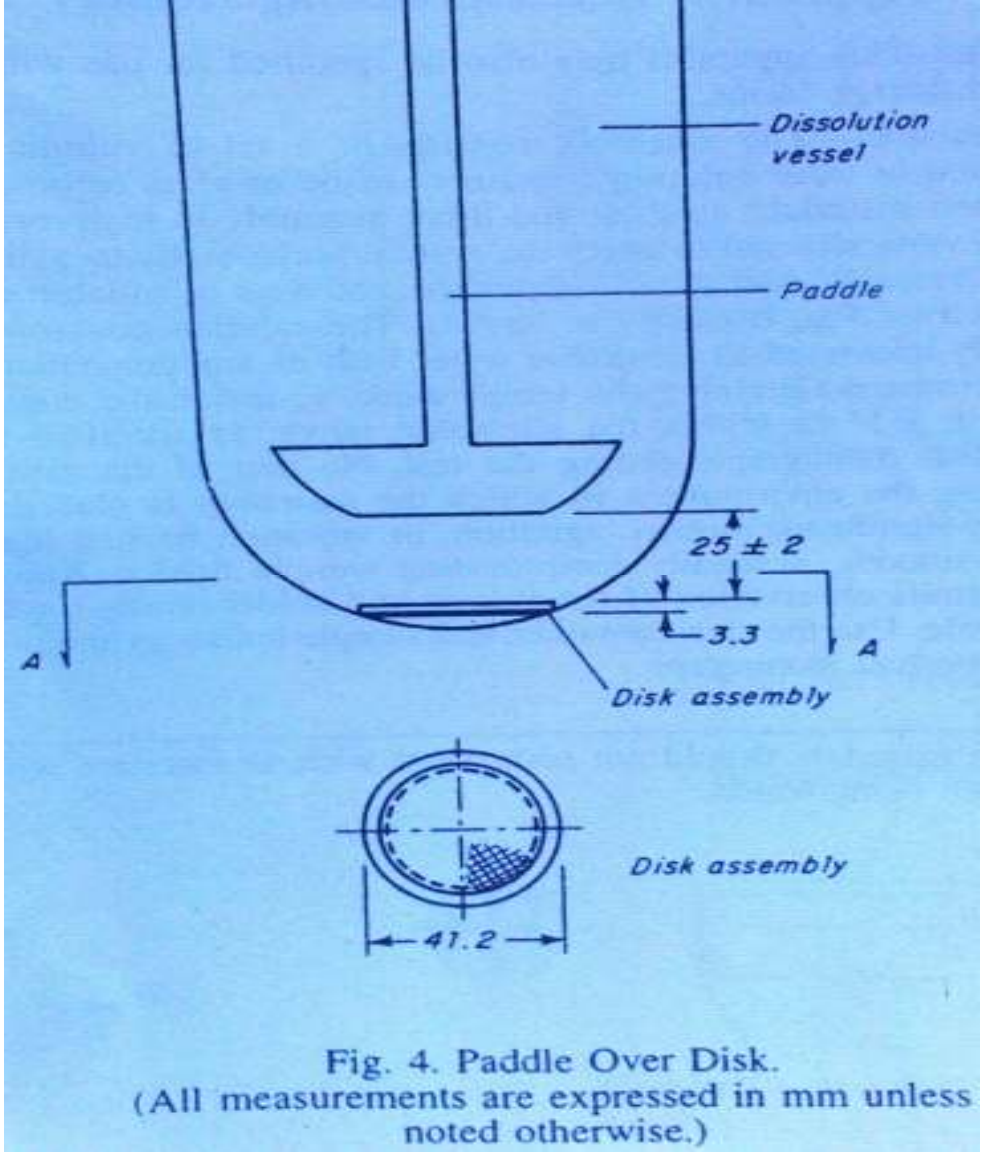


Fig. 4. Paddle Over Disk.
(All measurements are expressed in mm unless noted otherwise.)

CYLINDER METHOD (APPARATUS 6)

- Same as apparatus 1,except to replace the basket and shaft with a S.S. cylinder stirring element.
- Temperature - 32 ± 0.5°
- The dosage unit is placed on the cylinder.
- Distance between the inside bottom of the vessel and cylinder is maintained at 25 ± 2 mm.

METHOD (APPARATUS 7)

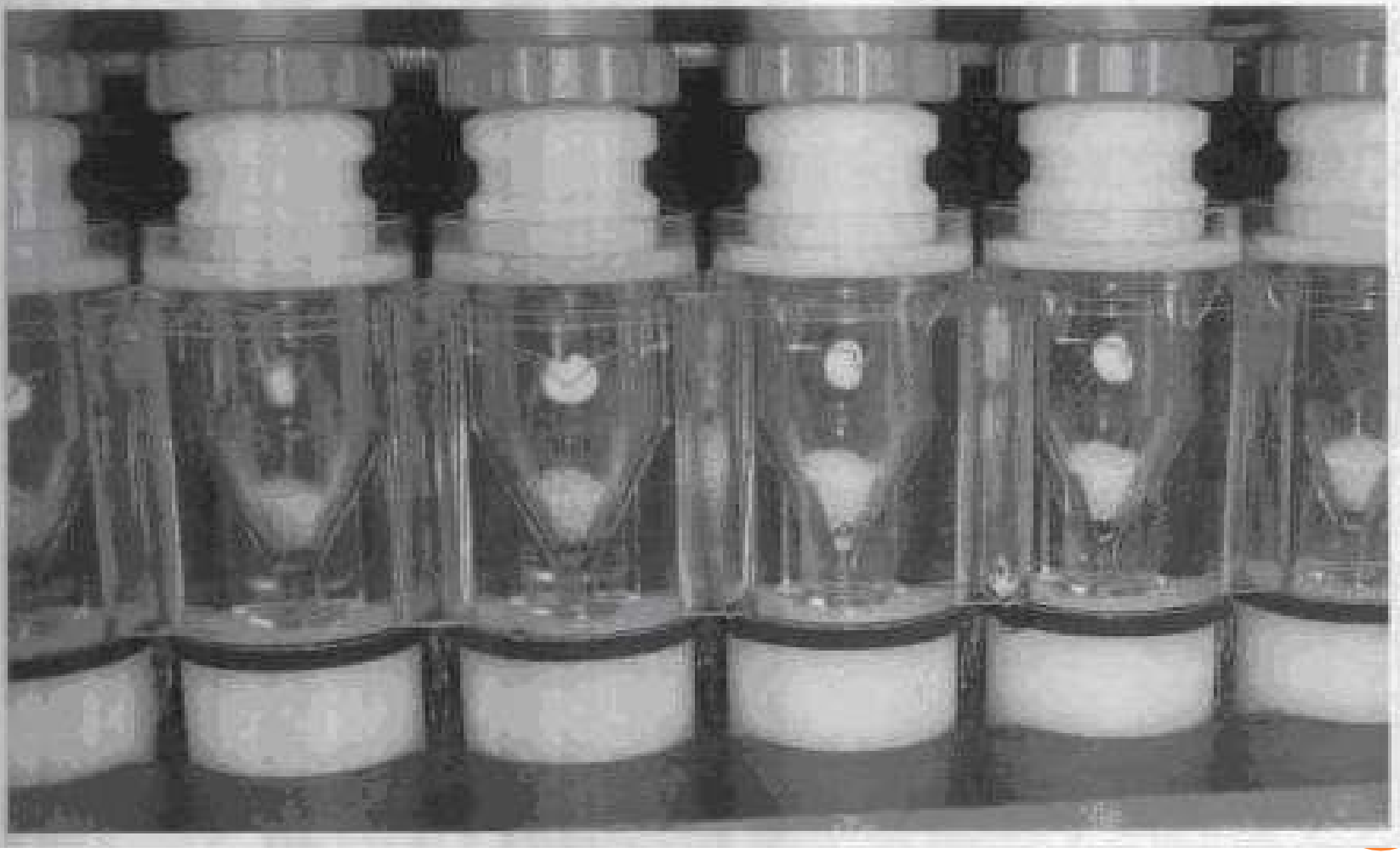
- The assembly consists of a set of calibrated solution containers, a motor and drive assembly to reciprocate the system vertically.

- Various type of sample holder are used.

2. OPEN FLOW-THROUGH COMPARTMENT SYSTEM

- The dosage form is contained in a small vertical glass column with built in filter through which a continuous flow of the dissolution medium is circulated upward at a specific rate from an outside reservoir using a peristaltic or centrifugal pump.
- Dissolution fluid is collected in a separate reservoir.
- E.g. lipid filled soft Gelatin capsule

(d) Flow-through cell (USP IV).



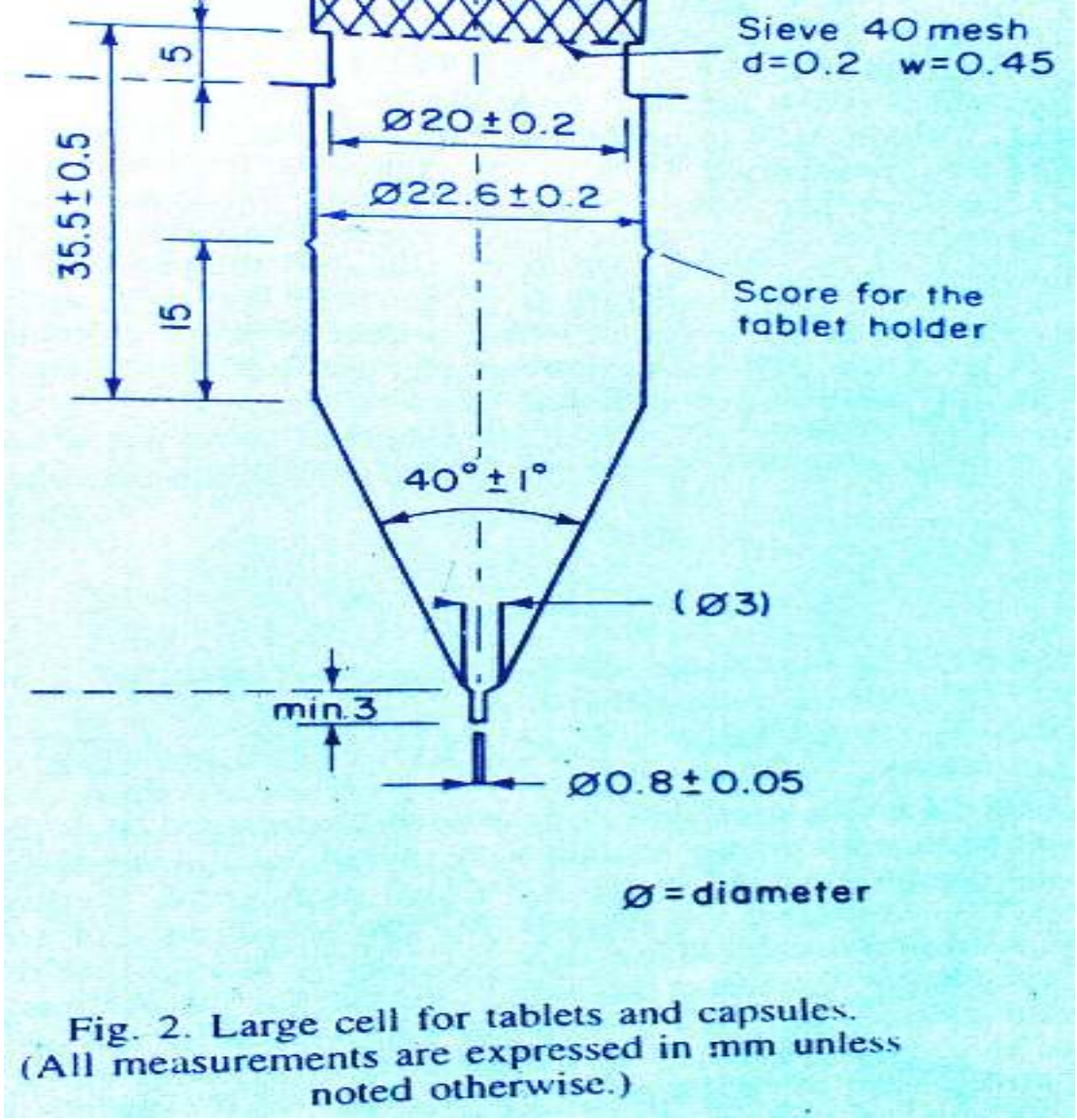


Fig. 2. Large cell for tablets and capsules. (All measurements are expressed in mm unless noted otherwise.)

ADVANTAGES

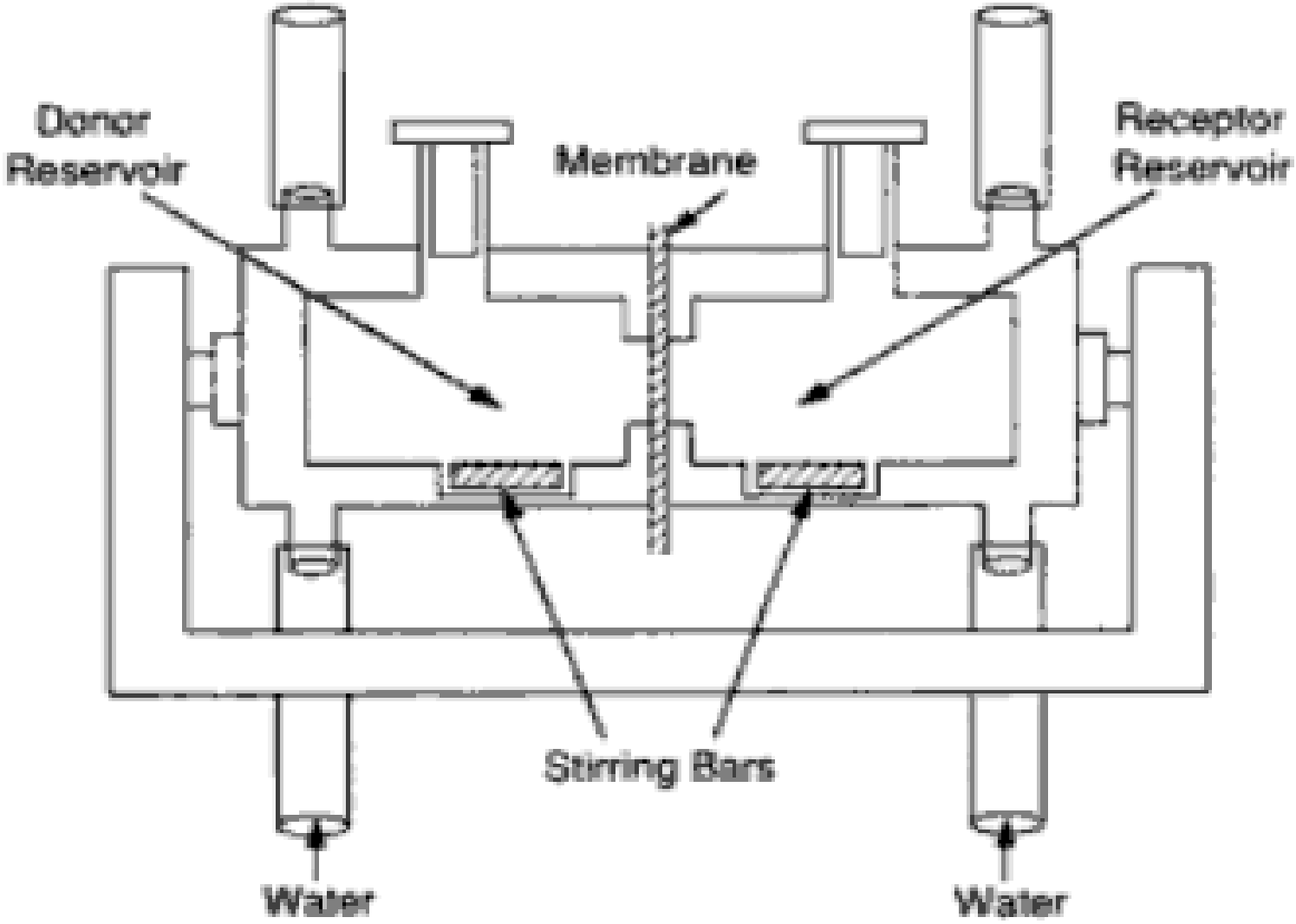
- No stirring and drug particles are exposed to homogeneous, laminar flow that can be precisely controlled. All the problems of wobbling, shaft eccentricity, vibration, stirrer position don't exist.
- There is no physical abrasion of solids.
- Perfect sink conditions can be maintained.

DISADVANTAGES

- Tendency of the filter to clog because of the unidirectional flow.
- Different types of pumps, such as peristaltic and centrifugal, have been shown to give different dissolution results.
- Temperature control is also much more difficult to achieve in column type flow through system than in the conventional stirred vessel type.

3. DIALYSIS SYSTEM

- Here, dialysis membrane used as a selective barrier between fresh solvent compartment and the cell compartment containing dosage form.
- It can be used in case of very poorly soluble drugs and dosage form such as ointments, creams and suspensions.


Donor
Reservoir
Membrane
Receptor
Reservoir
Stirring Bars
Water
Water

TYPE OF DOSAGE FORM	APPARATUS
Recommended	
Oral suspensions	Paddle
Orally disintegrating tablets	Paddle
Chewable tablets	Basket, paddle, or reciprocating cylinder with glass beads
Transdermals—patches	Paddle over disk
Topicals—semisolids	Franz cell diffusion system
Suppositories	Paddle, modified basket, or dual chamber flow-through cell
More work needed	
Chewing gum	Special apparatus (PhEur)
Powders and granules	Flow-through cell (powder/granule sample cell)
Microparticulate formulations	Modified flow-through cell
Implants	Special apparatus, modified flow-through cell
Drug-Device combination Products (i.e. Drug eluting stents and steroid eluting pacemaker-leads)	Special apparatus, modified flow-through cell, modified reciprocating cylinder, etc.

OCULAR DRUG DELIVERY SYSTEMS

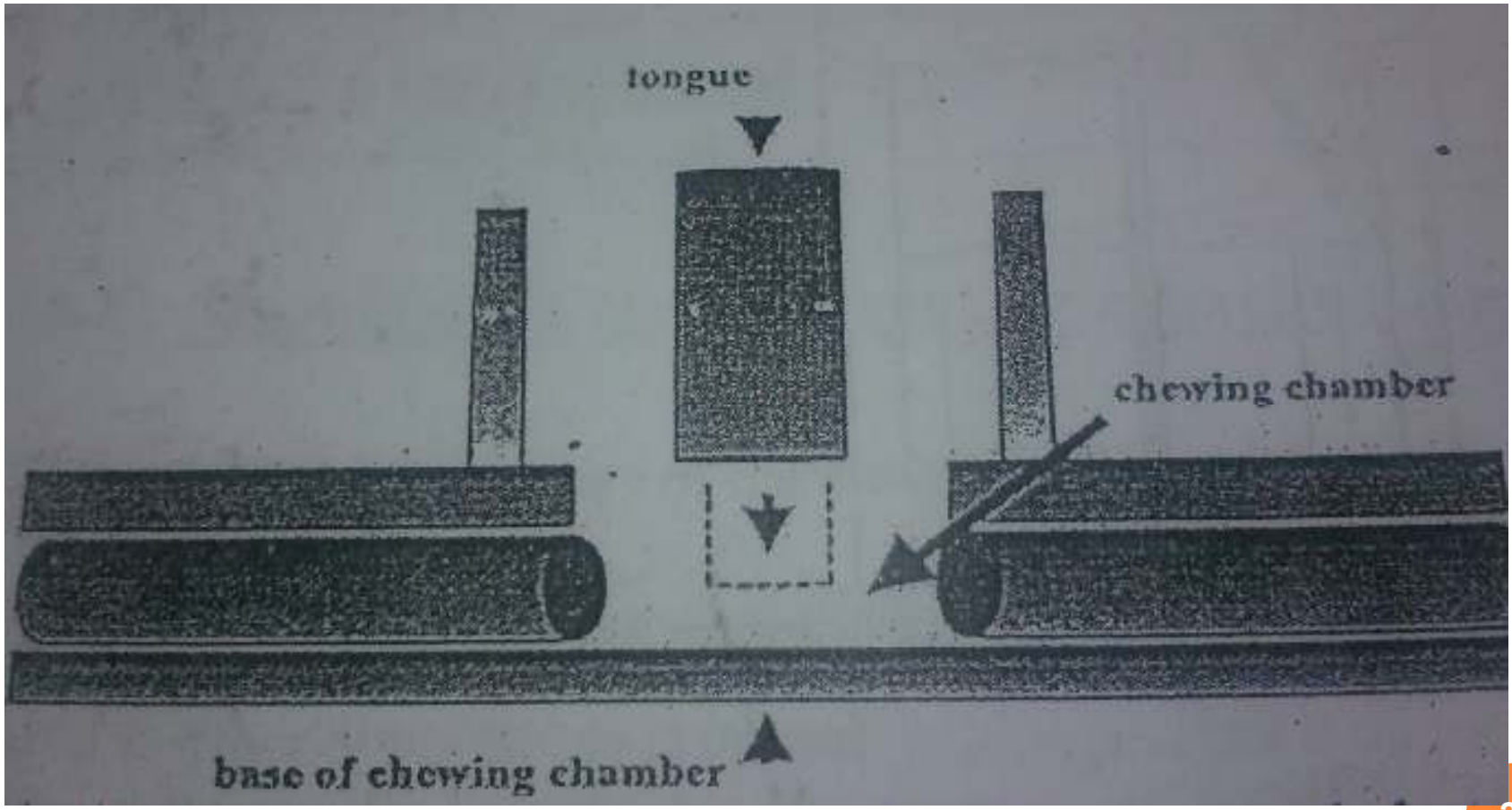
- A number of methods are used to conduct in-vitro evaluation of controlled ocular drug delivery systems.
- **(a) Bottle method**
- In this method, dosage forms are placed in the culture bottles containing phosphate buffer at pH 7.4.
- The culture bottles are shaken in a thermostatic water bath at 37°C.
- A sample of medium is taken out at appropriate intervals and analyzed for drug contents.

- **b) Modified rotating basket method**
- In this method, dosage form is placed in a basket assembly connected to a stirrer. The assembly is lowered into a jacketed beaker containing buffer medium.
- The temperature of system is maintained at 37°C. A sample of medium is taken out at appropriate time

MICROSPHERES

- **Beaker method**
- The dosage form in this method is made to adhere at the bottom of the beaker containing the medium and stirred uniformly using over head stirrer.
- Volume of the medium used for the studies varies from 50-500 ml and the stirrer speed form 60-300 rpm.
- **Modified Keshary Chien Cell**
- A specialized apparatus was designed in the laboratory.
- It comprised of a Keshary Chien cell containing distilled water (50ml) at 37^0 c as dissolution medium.
- TMDDS (Trans Membrane Drug Delivery System) was placed in a glass tube fitted with a 10# sieve at the bottom which reciprocated in the medium at 30 strokes per min.
- Samples are removed at appropriate time intervals and analyzed for drug content.

DOSAGE FORM



- TEMP-37.c
- Chew Rate-60 chew/min.
- Unspecified buffer (ph close to 6)-20 ml

CRITRIA

- **Q –Value –**

- Define as a percentage of drug conten dissolved in a given time period.

CRITRIA

STAGE	No. of Dosage units tested	Acceptance criteria
S1	6	No Dosage unit is less then Q+5%
S2	6	Average Of 12 dosage units (S1+S2) and no dosage unit is less then Q-15%
S3	12(6+6+12=24)	Average of 24 dosage units >- And not more than two dosage units are less than Q-15% and No dosage unit is less than Q-25%

OF DISSOLUTION PROFILE

- Difference factor (F1 Value)-
- Define as calculate the % Difference between 2 curves at each time point and is a measurement of the relative error between 2 curves.
- $f1 = \{[\Sigma\ t=1n\ |\ Rt-Tt|\ ]\ /[\Sigma\ t=1n\ Rt]\} \times 100.$
- Values range from 0 to 15

- Similarity Factor (F 2 value)-define as measurement of similarity in % Dissolution between two curve.

$$f_2 = 50 \log\{[1 + 1/n \sum_{t=1}^{n} (Rt - Tt)^2]^{-0.5} \times 100\}$$

- Where R_t and T_t = cumulative % dissolved for reference and test
- Values range from 50 to 100

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Thank you

DRUG DISTRIBUTION

Once a drug enter in to the blood stream,
the drug is subjected to a number of processes
called as Disposition Processes that tend to lower
the plasma concentration.

1. **Distribution** which involves **reversible** transfer of a drug between compartments.

2.Elimination which involves **irreversible loss** of drug from the body. It comprises of **biotransformation and excretion.**

CONTENTS

DEFINITION

Drug Distribution is defined as the Reversible transfer of drug between one compartment (blood) to another (extra vascular tissue)

Significance :-

Pharmacological action of drug depends upon its concentration at the site of action

Thus distribution plays important role in

- Onset of Action
- Intensity of Action
- Duration of Action

STEPS IN DRUG DISTRIBUTION

- **Permeation of Free Drug through capillary wall & entry in to ECF.**
- **Permeation of drugs from ECF to ICF through membrane of tissue cell.**

Rate Limiting Steps

- Rate of Perfusion to the ECF
- Membrane Permeability of the Drug

DISTRIBUTION PROCESS

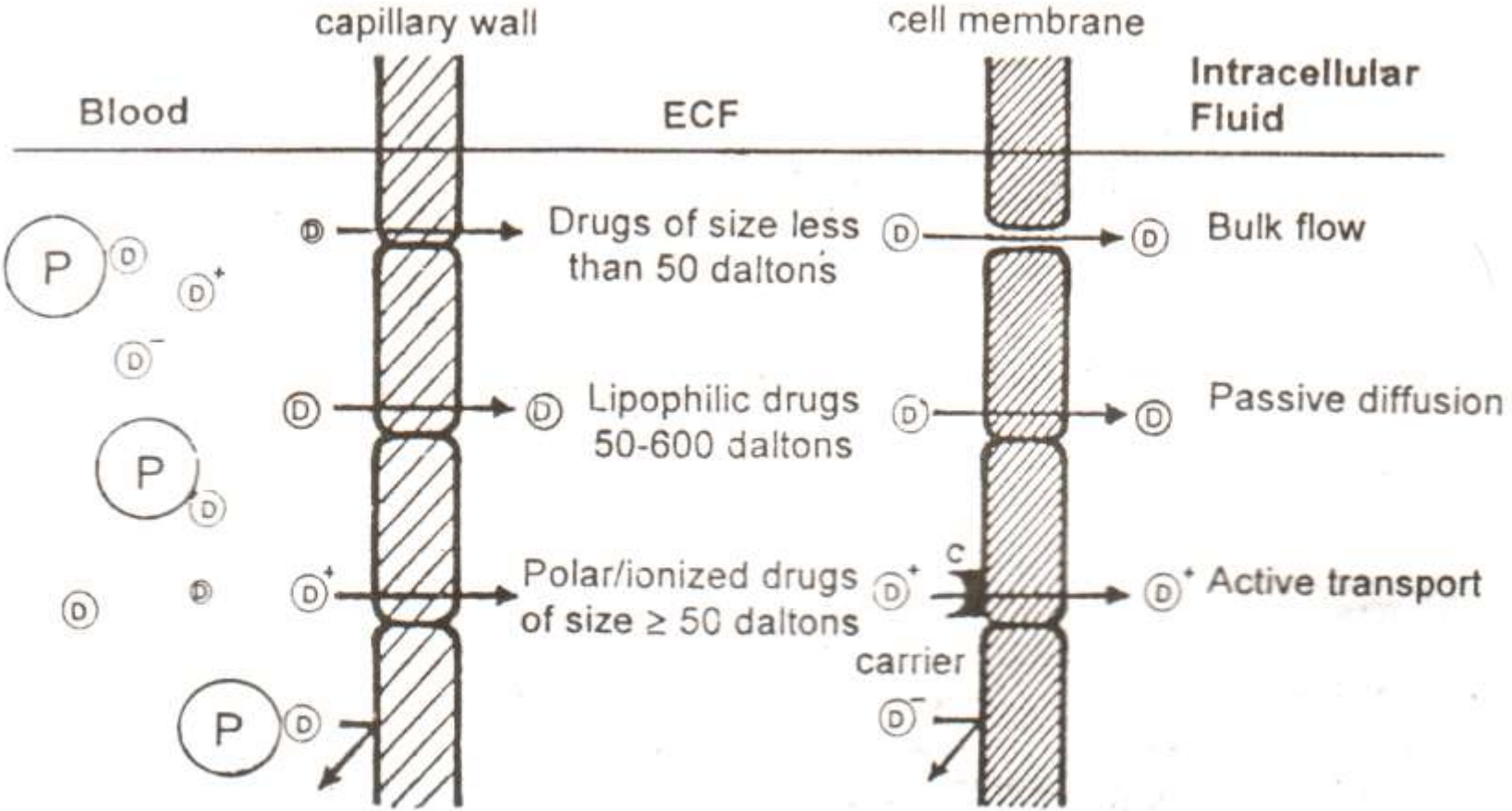


Fig. 3.3 Plasma membrane barrier and drug diffusion across it

Distribution is a **Passive Process**,

for which the

Driving Force is the Conc. Gradient between the Blood and Extravascular Tissues

- The Process occurs by the Diffusion of Free Drug until equilibrium is established

DISTRIBUTION OF DRUG IS NOT UNIFORM THROUGH OUT THE BODY---- WHY ?

Because tissue receive the drug from plasma at different rates & different extents.

Organ perfused	Blood flow (mL/min)	Organ mass (kg)	Normalized blood flow (mL/min/kg)
Liver	1700	2.5	680
Kidney	1000	0.3	3333
CNS	800	1.3	615
Myocardium	250	0.3	833
Fat	250	10	25
Other (muscle...)	1400	55.6	25
total	5400	70	

FACTORS AFFECTING DISTRIBUTION OF DRUGS

1. **Tissue Permeability of Drugs**
   - ❖ **Physicochemical Properties of drug like**

     Mol.size, pK_a, o/w Partition Coefficient
   - ❖ **Physiological barriers to diffusion of drugs**

2. **Organ/tissue size and perfusion rate**

3. **Binding of drugs to tissue components.**
   - ❖ **binding of drug to blood components**
   - ❖ **binding of drug to extra cellular components**

4. **Miscellaneous**

TISSUE PERMEABILITY OF DRUGS

Physicochemical Properties of drug

- Molecular size,
- pKa
- o/w Partition Co Efficient.

Physiological barriers to Diffusion of Drugs

- Simple Capillary Endothelial Barrier
- Simple Cell Membrane Barrier
- Blood Brain Barrier
- Blood – CSF Barrier
- Blood Placental Barrier
- Blood Testis Barrier

1). TISSUE PERMEABILITY OF DRUG

a. physicochemical property:

I) Molecular Size;

Mol wt less then 500 to 600 Dalton easily pass capillary membrane to extra cellular fluid.

Penetration of drug from ECF to cells is function of Mol size, ionization constant & lipophilicity of drug

From extra cellular fluid to cross cell membrane through aqueous filled channels need particle size less then 50 Dalton (small) with hydrophilic property .

Large mol size restricted or require specialized transport system

1). TISSUE PERMEABILITY OF DRUG

a. Physicochemical Property

ii) Degree of Ionization (pKa)

♫ The pH at which half of a drug is unionized is called pKa

A weak acid becomes unionized in a strong acidic environment.

A weak acid becomes ionized in a neutral or basic environment.

&

A weak base becomes unionized in a strong basic environment.

A weak base becomes ionized in a neutral or acidic environment.

BUT

The PH of Blood plasma, extra cellular fluid and CSF is 7.4(constant)

Except in acidosis and alkalosis

All the drugs ionize at plasma pH (i.e. Polar , Hydrophilic Drugs)

Can not penetrate the Lipoidal cell membrane

1). TISSUE PERMEABILITY OF DRUG

a. Physicochemical Property

iii) o/w permiability

- Polar and hydrophilic drugs are less likely to cross the cell membrane

Where,,,,,,,,

- **Nonpolar and hydrophobic drugs are more likely to cross the cell membrane**

EFFECTIVE $K_{o/w}$ = Fraction unionized at pH 7.4 x $K_{o/w}$ of unionized drug

In case of polar drugs where permeability is the rate- limiting step in the distribution , the driving force is the *effective partition coefficient* of drug ……..that can be calculated by above formula

- **Lipoidal drug penetrate the tissue rapidly. Among Drugs with same Ko/w but diff in ionization of blood pH.**

- **One which has less ionization show better distribution.**

  E.g. Phenobarbital > salicylic acid

  Both are having same Ko/w but phenobarbitol have more unionized at blood pH

- **highly specialized and less permeable to water soluble drugs.**

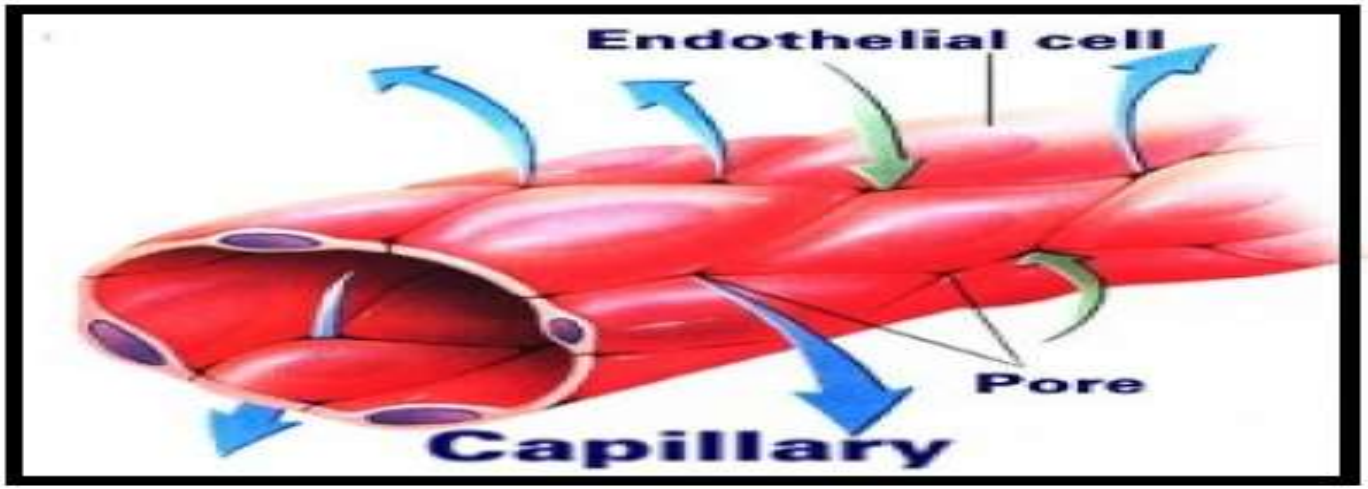
B. PHYSIOLOGICAL BARRIERS

1) The simple capillary endothelial barrier

Capillary supply the blood to the most inner tissue

All drugs ionized or unionized molecular size less than 600dalton diffuse through the capillary endothelium to interstitial fluid

Only drugs that bound to that blood components can't pass through this barrier Because of larger size of complex



B. PHYSIOLOGICAL BARRIERS

2. Simple cell membrane barrier

once the drug diffuse through capillary to extracellular fluid ,its further entry in to cells of most tissue is limited.

Simple cell Membrane is similar to the lipoidal barrier (absorption)

Non polar & hydrophillic drugs will passes through it (passively).

Lipophilic drugs with 50-600 dalton mol size &

Hydrophilic, Polar drugs with <50dalton will pass this membrane

B. PHYSIOLOGICAL BARRIERS

3) Blood brain barrier

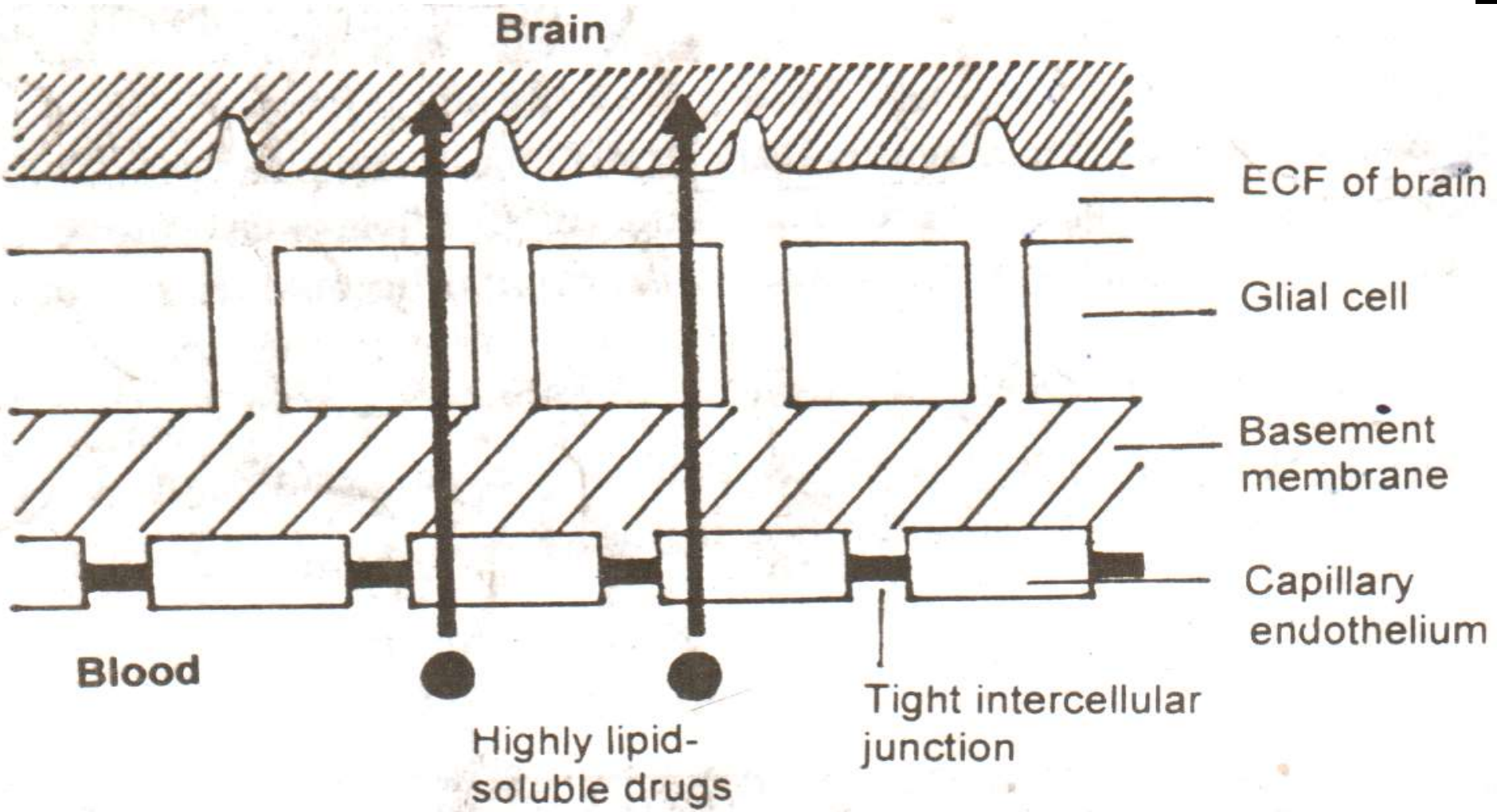


Fig. 3.4 Blood-brain barrier

B. PHYSIOLOGICAL BARRIERS

3) Blood brain barrier

Capillary in brain is highly specialized & much less permeable to water soluble drugs

ENDOTHELIAL CELLS ;- Tightly bonded with each other by intracellular junctions

ASTROCYTES :- present @ the base of endothelial tissue and act as supporting materials

& it Form Envelop around the capillary thus intercellular passage get blocked.

BBB is lipoidal barrier, thus drugs with high o/w partition coefficient diffuse passively others (moderately lipid soluble and partially ionised molecules passes slowly.

Polar natural substance (sugar & amino acid) transported to brain actively thus structurally similar drug can pass easily to BBB.

DIFFERENT APPROACHES TO CROSS BBB

A) Permeation Enhancers ;- Dymethyl Sulfoxide

B) Pro- Drug Approach ;- Dopamine---- Levodopa (Parkinsonism)

and osmatic disruption of the BBB BY infusing internal carotid artery with mannitol

C) carrier system ;- Dihydropyridine (Lipid soluble) moiety redox system (highly lipophilic & cross the BBB)

Complex formation (DRUG-DHP). After entering in brain DHP gets metabolize by (CNS) enzyme in brain and drug gets trapped in side the brain.

Polar pyridinium ion can not diffuse back out of the brain.

Ex. Steroidal drug

B. PHYSIOLOGICAL BARRIERS

4) Cerebral spinal fluid barrier ;-

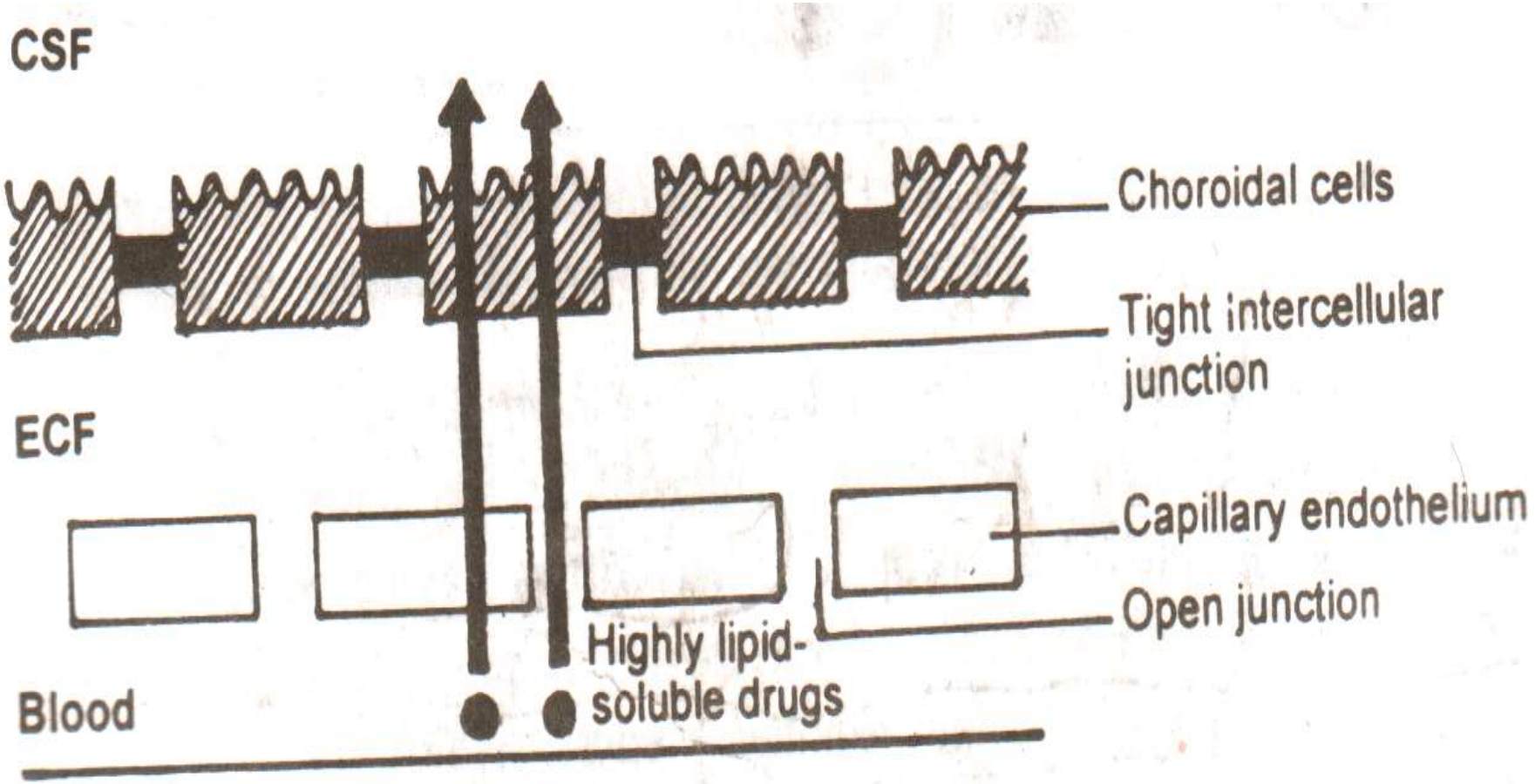


Fig. 3.5 The blood-CSF barrier

B. PHYSIOLOGICAL BARRIERS

4) Cerebral Spinal Fluid Barrier;-

Capillary endothelial cells;- have open junction or gaps so…. Drugs can flow freely b/w capillary wall & choroidal cells.

Choroids plexus;- major components of CSF barriers is choroidal cells which are joined with each other by tight junctions forming the blood-CSF barrier (similar permeability to BBB)

Highly lipid soluble drugs can easily cross the blood-CSF Barrier but moderatly soluble & ionize drugs permeate slowly.

Mechanism of drug transport is similar to CNS &CSF

but the Degree of uptake may vary significantly.

B. PHYSIOLOGICAL BARRIERS

5) Placenta barriers ;-

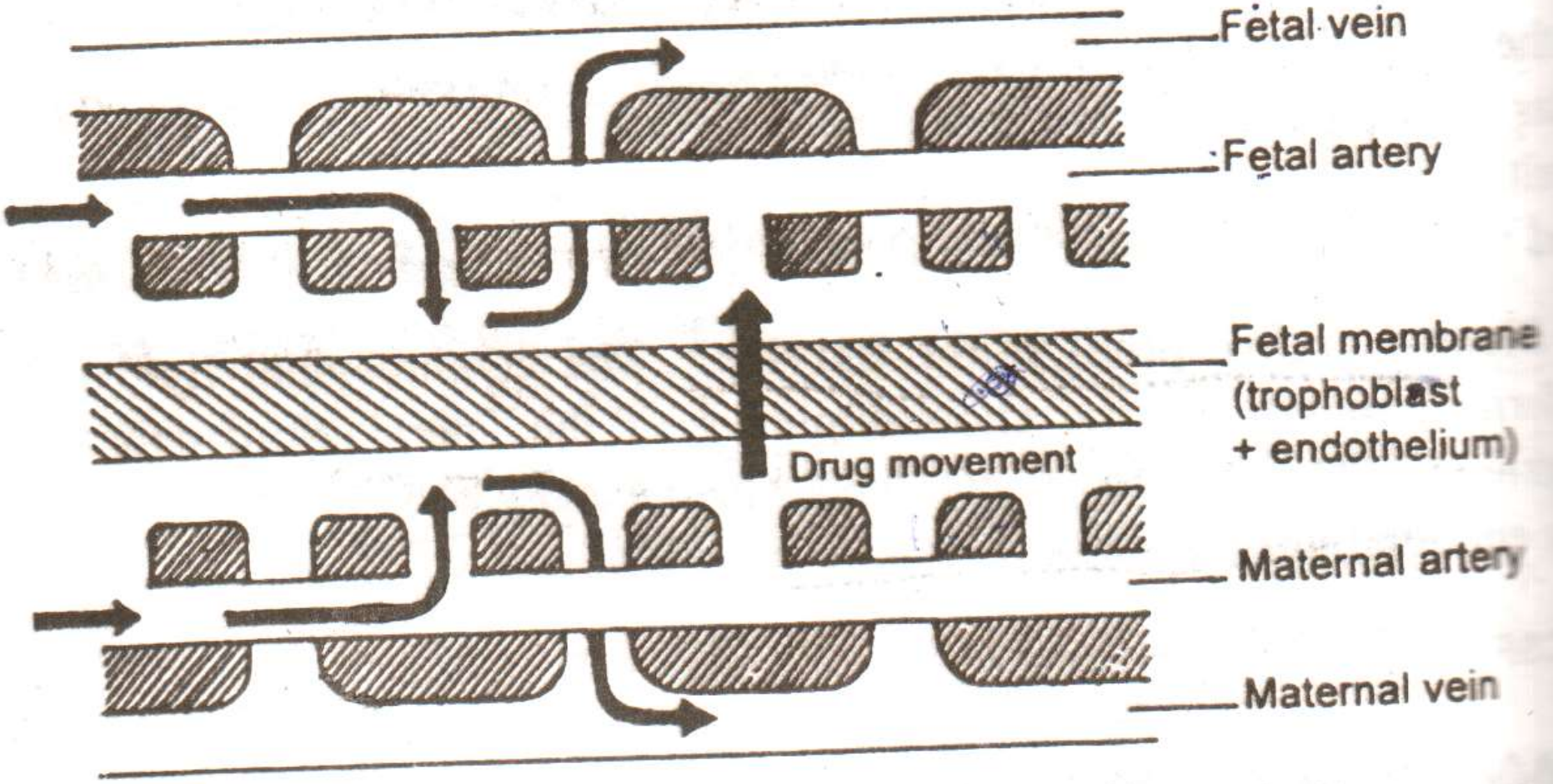


Fig. 3.6 Placental barrier and blood flow across it

B. PHYSIOLOGICAL BARRIERS

- 5) Placenta barriers ;-
- It's the barrier b/w Maternal & Fetal blood vessels
- Both are separated by fetal trofoblast basement membrane & endothelium .
- Thickness *25μ @ early pregnancy* later reduce up to *2μ* (even its effectiveness remain unchanged)
- Mol wt <1000 Dalton & moderate to high lipid solubility drugs like….. (Sulfonamides, Barbiturets, Steroids, Narcotic some Antibiotics) cross the barrier by Simple Diffusion rapidly
- Essential Nutrients for fetal growth transported by carrier-mediated processes.
- Immunoglobulines are transported by endocytosis.
- Drugs dangerous to fetus at Two stages
- Its advisable to avoid drugs during 1st trimester (fetal organ development) some drugs produce teratogenic effect ex. Phenytoin, methotrexate
- later stage pregnancy affect physiological functions like respiratory depression ex. morphine
- Better to restrict all drugs during pregnancy.

B. PHYSIOLOGICAL BARRIERS

6) Blood - Testis Barrier :-

This barrier not located @ capillary endothelium level.

But at sertoli - sertoli cell junction.

It is the tight junction / barrier b/w neighboring sertoli cells that act as blood-testis barrier .

This barrier restrict the passage of drugs to spermatocytes & spermatids.

2). ORGAN TISSUE SIZE AND PERFUSION RATE

Perfusion Rate :- *is defined as the volume of blood that flows per unit time per unit volume of the tissue (ml/min/ml)*

Perfusion rate – limited *when.....*

1) Drug is highly lipophilic

2) Membrane across which the drug is supposed to diffuse

Above both the cases Greater the blood flow , Faster the distribution

Organ perfused	Blood flow (mL/min)	Organ mass (kg)	Normalized blood flow (mL/min/kg)
Liver	1700	2.5	680
Kidney	1000	0.3	3333
CNS	800	1.3	615
Myocardium	250	0.3	833
Fat	250	10	25
Other (muscle...)	1400	55.6	25
total	5400	70	

- **Distribution is permeability rate - limited in following cases**
  - **When the drug is ionic/polar/water soluble**
  - **Where the highly selective physiology barrier restrict the diffusion of such drugs to the inside of cell.**

- **Distribution will be perfusion rate - limited**
  - **When the drug is highly lipohilic**
  - **When the membrane is highly permeable.**

It is defined as the volume of the blood that flows per unit time per unit volume of the tissue.

Unit: ml/min/ml

(Distribution Rate Constant) Kt = perfusion rate / $K_{t/b}$

Distribution half life = 0.693/Kt

=0.693$K_{t/b}$/perfusion rate

$K_{t/b}$ tissue/blood partition coefficient

Highly lipophilic drugs can cross most selective barrier like BBB, ex. thiopental,

Highly permeable capillary wall permits passage of almost all drugs (except those bound to plasma protein).

Highly perfused tissues Lungs, Kidneys, Liver, Heart, Brain are rapidly equlibriated with lipid soluble drugs

Drug is distributed in a particular tissue or organ depends upon the **size of tissue** (Volume) & **Tissue/blood** partition coefficient

Ex.Thiopental i.v (liphopillic drug) & high tissue/blood partition coefficient towards brain & adipose tissue

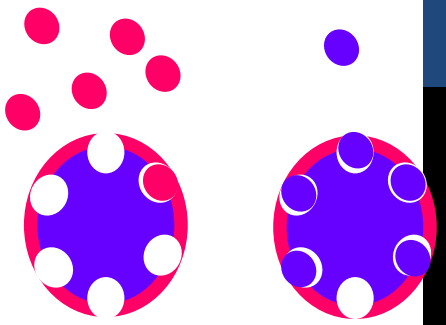
But brain is **highly perfused organ** so drug is distributed **fast** and shows **rapid onset of action than** poorly perfused adipose tissue.

3)Binding of drug to blood and other tissue components

- Binding of drugs to blood components
  - Blood cells
  - Plasma proteins
- Binding of drugs to extra vascular tissues

3).BINDING OF DRUG TO TISSUE COMPONENTS

a) Binding of drug to blood components;-



i) Plasma protein bindings

- **Human serum albumin**:-all types drug
- **α_1- acid glycoprotein** :-basic drugs(impr)
- **Lipoproteins** :-basic,lipophilic drugs(chlorpromazin)
- **α_1-Globuline** :-steroids like corticosterone ,vit-B12
- **α_2-Globuline** :-vit-A,D,E,K,cupric ions.
- **Hemoglobin** :-Phenytoin, phenothiazines.

ii) Blood cells bindings:-

RBC : 40% of blood comprise of blood cells

out of that 95% cells are RBC (RBC comprise of hemoglobin)

drugs like, phenytoin,phenobarbiton binds with Hb

,imipramine,chlorpromazine binds with RBC Cell wall

The major component of blood is RBC

The RBC comprises of 3 components each of which can bind to drugs:

- **Hemoglobin**
- **Carbonic Anhydrase**
- **Cell Membrane**

BINDING OF DRUGS TO PLASMA PROTEINS

- The binding of drug to plasma protein is reversible
  - The extent or order of binding of drugs to various plasma proteins is:

Albumin >α_1-Acid Glycoprotein> Lipoproteins > Globulins

Human Serum Albumin

- Most abundant plasma protein with large drug binding capacity
- Both endogenous compounds and drugs bind to HSA
- Four different sites on HSA:

  Site I: warfarin and azapropazone binding site

  Site II: diazepam binding site

  Site III: digitoxin binding site

  Site IV: tamxifen binding site

3).BINDING OF DRUG TO TISSUE COMPONENTS

B. Extra Vascular Tissue proteins

- 40% of total body weight comprise of vascular tissues
- Tissue-drug binding result in localization of drug at specific site in body and serve as reservoir
- As binding increases it also increase bio-logical half life.
- Irreversible binding leads to drug toxicity. (carbamazepin-autoinduction)
- liver>kidney>lungs>muscle>skin>eye>bone>Hair, nail

4). Miscellaneous Factors

- **Age:**
  - a) Total body water
  - b) Fat content
  - c) Skeletal muscles
  - d) Organ composition
  - e) Plasma protein content
- **Pregnancy**
- **Obesity**
- **Diet**
- **Disease states**

4). MISCELLANEOUS FACTORS

a) AGE:-

Difference in distribution pattern is mainly due to

Total body water –(both ICF &ECF) greater in infants

Fat content – higher in infants & elderly

Skeletal muscle – lesser in infants & elderly

organ composition – BBB is poorly developed in infants & myelin content is low & cerebral blood flow is high, hence greater penetration of drug in brain

plasma protein content– low albumin in both infants & elderly

b) PREGNANCY:-

During Pregnancy, due to growth of UTERUS,PLECENTA,FETUS…

Increases the volume available for distribution drug.

fetus have separate compartment for drug distribution, plasma & ECF Volume also increase but albumin content is low.

C) OBECITY :-

In obese persons, high adipose (fatty acid) tissue so high distribution of lipophilic drugs

4). MISCELLANEOUS FACTORS

d) DIET:- A diet high in fats will increases free fatty acid levels in circulation thereby affecting binding of acidic drugs (NSAIDs to albumin)

e) DISEASE STATES:- mechanism involved in alteration of drug distribution in disease states.

i) Altered albumin & other drug-binding protein concentration.

ii) Alteration or reduced perfusion to organ or tissue

iii) Altered tissue pH.

iv) Alteration of permeability of physiological barrier (BBB)

EX- BBB (in meningitis & encephalities) BBB becomes more permeable polar antibiotics ampicilin, penicilin G. &

patient affect CCF, Perfusion rate to entire body decreases it affect distribution.

f) DRUG INTERACTION:-Displacement interaction occurs when two drugs administered which having similar binding site affinity.

Ex.A.Warfarin (Displaced Drug)&B.Phenylbutabutazone (Displacer)HSA

Apparent Volume Of Distribution

The apparent volume of distribution is a proportionality constant relating the plasma concentration to the total amount of drug in the body.

$$X \alpha C$$

$$X = Vd.C$$

$$Vd = X/C$$

Apparent volume of distribution = amount of drug in the body/ plasma drug concentration

Apparent volume of distribution is dependent on concentration of drug in plasma.

Drugs with a large apparent volume are more concentrated in extra vascular tissues and less concentrated intravascular.

In certain pathological cases, the Vd for the drug may be altered if the distribution of the drug is changed.

$Vd = X/C$

$Vd = X_0 / C_o$

=i.v. bolus dose/concentration of drug in plasma

for drugs given as i.v. bolus:

$$Vd_{(area)} = X0/K_E(AUC)$$

For drugs administered extravascularly:

$$Vd_{(area)} = FXo/K_E(AUC)$$

Reference:-

Applied Biopharmaceutics and Pharmacokinetics by *Leon Shargel*

Clinical biopharmaceutics and pharmacokinetics by *Gibaldi*

Biopharmaceutics and Pharmacokinetics by *Brahmankar*


THANK
YOU

EXCRETION OF DRUGS

EXCRETION OF DRUGS

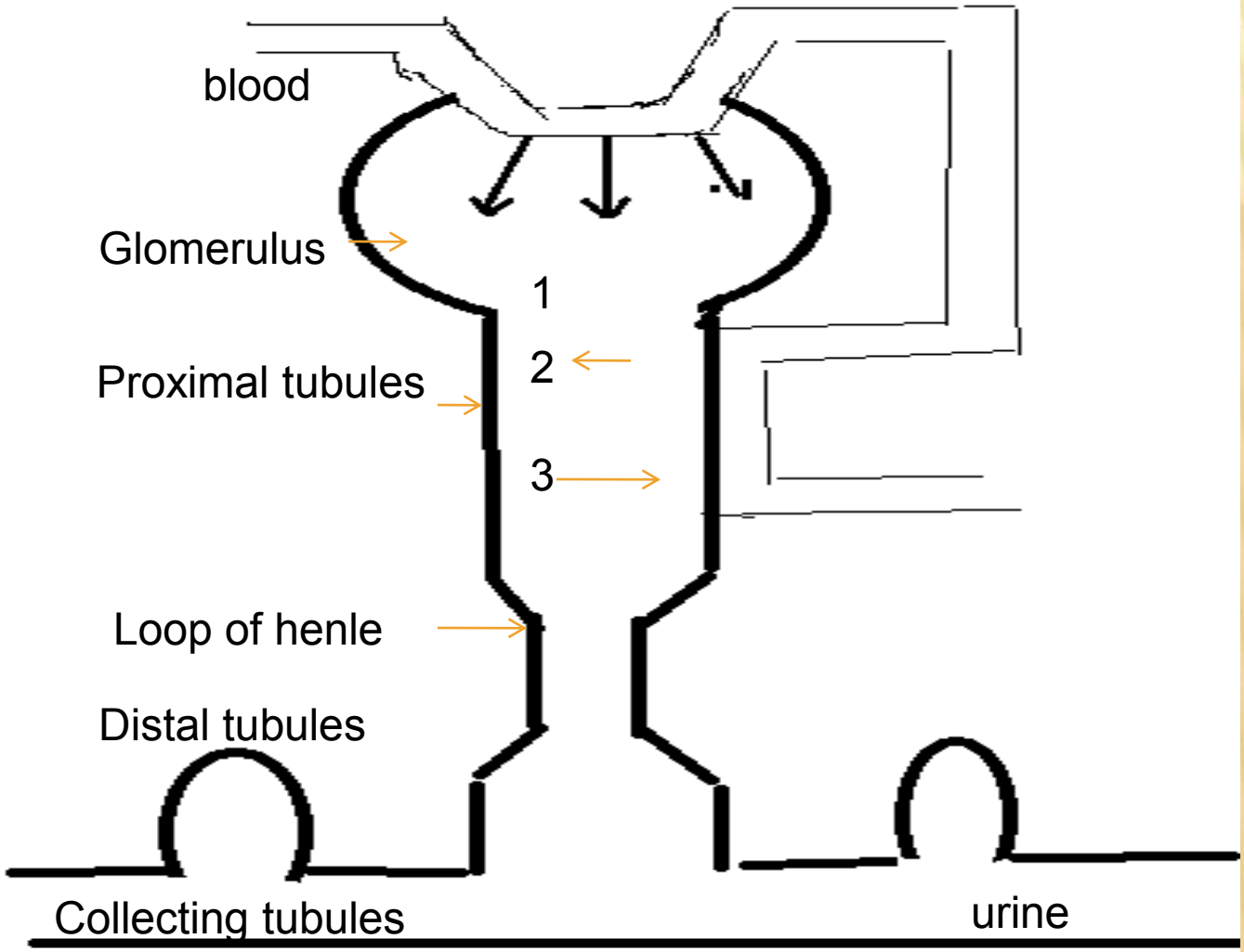
Excretion is defined as the process where by drugs or metabolites are irreversibly transferred from internal to external environment through renal or non renal route.

Excretion of unchanged or intact drug is needed in termination of its pharmacological action.

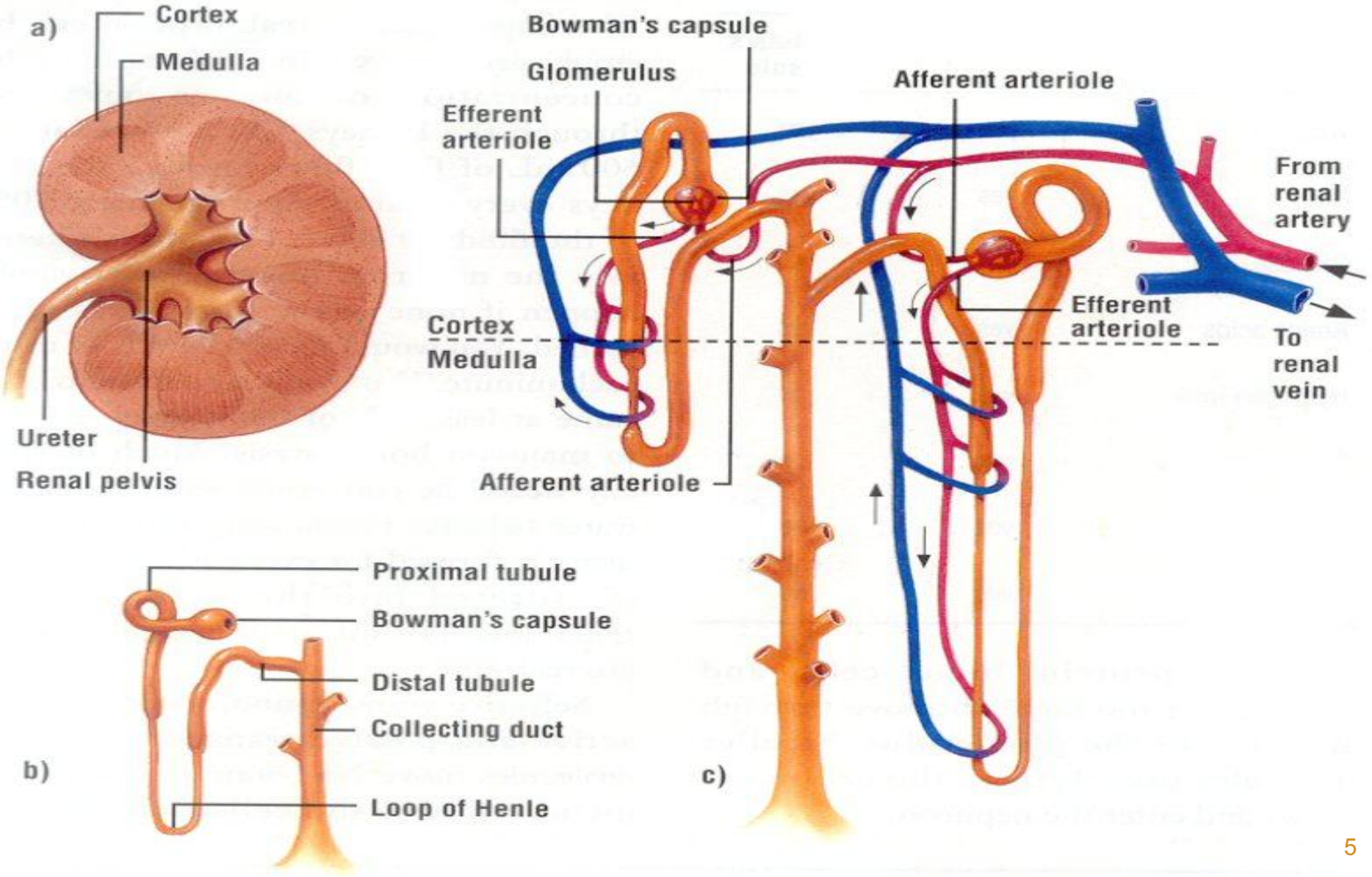
The principal organ of excretion are kidneys.

TYPES OF EXCRETION

1. **RENAL EXCRETION**
2. **NON RENAL EXCRETION**
   - **Biliary excretion.**
   - **Pulmonary excretion.**
   - **Salivary excretion.**
   - **Mammary excretion.**
   - **Skin / Dermal excretion.**
   - **Gastrointestinal excretion.**
   - **Genital excretion.**


blood
Glomerulus
1
2
Proximal tubules
3
Loop of henle
Distal tubules
Collecting tubules
urine

ANATOMY OF NEPHRON



GLOMERULAR FILTRATION

- It Is non selective , unidirectional process
- Ionized or unionized drugs are filtered, except those that are bound to plasma proteins.
- Driving force for GF is hydrostatic pressure of blood flowing in capillaries.
- **GLOMERULAR FILTRATION RATE:**

  Out of 25% of cardiac out put or 1.2 liters of blood/min that goes to the kidney via renal artery only 10% or 120 to 130ml/min is filtered through glomeruli. The rate being called as glomerular filtration rate (GFR).

e.g. creatinine, inulin.

ACTIVE TUBULAR SECRETION

- This mainly occurs in proximal tubule.
- It is carrier mediated process which requires energy for transportation of compounds against conc. gradient

Two secretion mechanisms are identified.

- System for secretion of organic acids/anions
  E.g. Penicillin, salicylates etc uric acid secreted
- System for organic base / cations
  E.g. morphine, mecamylamine hexamethonium
- Active secretion is Unaffected by change in pH and protein binding.
- Drug undergoes active secretion have excretion rate values greater than normal GFR e.g. Penicillin.

TUBULAR REABSORPTION

- It occurs after the glomerular filtration of drugs. It takes place all along the renal tubules.
- Reabsorption of drugs indicated when the excretion rate value are less than the GFR 130ml/min.e.g. Glucose
- TR can be active or passive processes.
- Reabsorption results in increase in the half life of the drug.

- **Active Tubular Reabsorption:**

  Its commonly seen with endogenous substances or nutrients that the body needs to conserve e.g. electrolytes, glucose, vitamins.

- **Passive Tubular Reabsorption:**

  It is common for many exogenous substances including drugs. The driving force is Conc. Gradient which is due to re-absorption of water, sodium and inorganic ions. If a drug is neither excreted or re-absorbed its conc. In urine will be 100 times that of free drug in plasma.

pH OF THE URINE

- It varies between 4.5 to 7.5
- It depends upon diet, drug intake and pathophysiology of the patient .
- Acetazolamide and antacids produce alkaline urine, while ascorbic acid makes it acidic.
- IV infusion of sodium and ammonium chloride used in treatment of acid base imbalance shows alteration in urine pH.
- Relative amount of ionized ,unionized drug in the urine at particular pH & % drug ionized at this pH can be given by " HENDERSON-HESSELBACH" equation.

HENDERSON-HESSELBACH EQUATION

1)FOR WEAK ACIDS

$$pH = pKa + \log \frac{[\text{ionized}]}{[\text{unionized}]}$$

$$\% \text{ of drug ionized} = \frac{10^{pH - pKa}}{1 + 10^{pH - pKa}} \times 100$$

HENDERSON-HESSELBACH EQUATION

2)FOR WEAK BASE

$$pH = pKa + \log \frac{[\text{unionized}]}{[\text{ionized}]}$$

$$\% \text{ of drug ionized} = \frac{10^{pH - pKa}}{1 + 10^{pH - pKa}} \times 100$$

FACTORS AFFECTING RENAL EXCRETION

- Physicochemical properties of drug
- Plasma concentration of the drug
- Distribution and binding characteristics of the drug
- Urine pH
- Blood flow to the kidney
- Biological factor
- Drug interaction
- Disease state

PHYSICOCHEMICAL PROPERTIES OF DRUG

- **Molecular size**

Drugs with Mol.wt <300, water soluble are excreted in kidney. Mol.wt 300 to 500 Dalton are excreted both through urine and bile.

PLASMA CONCENTRATION OF THE DRUG

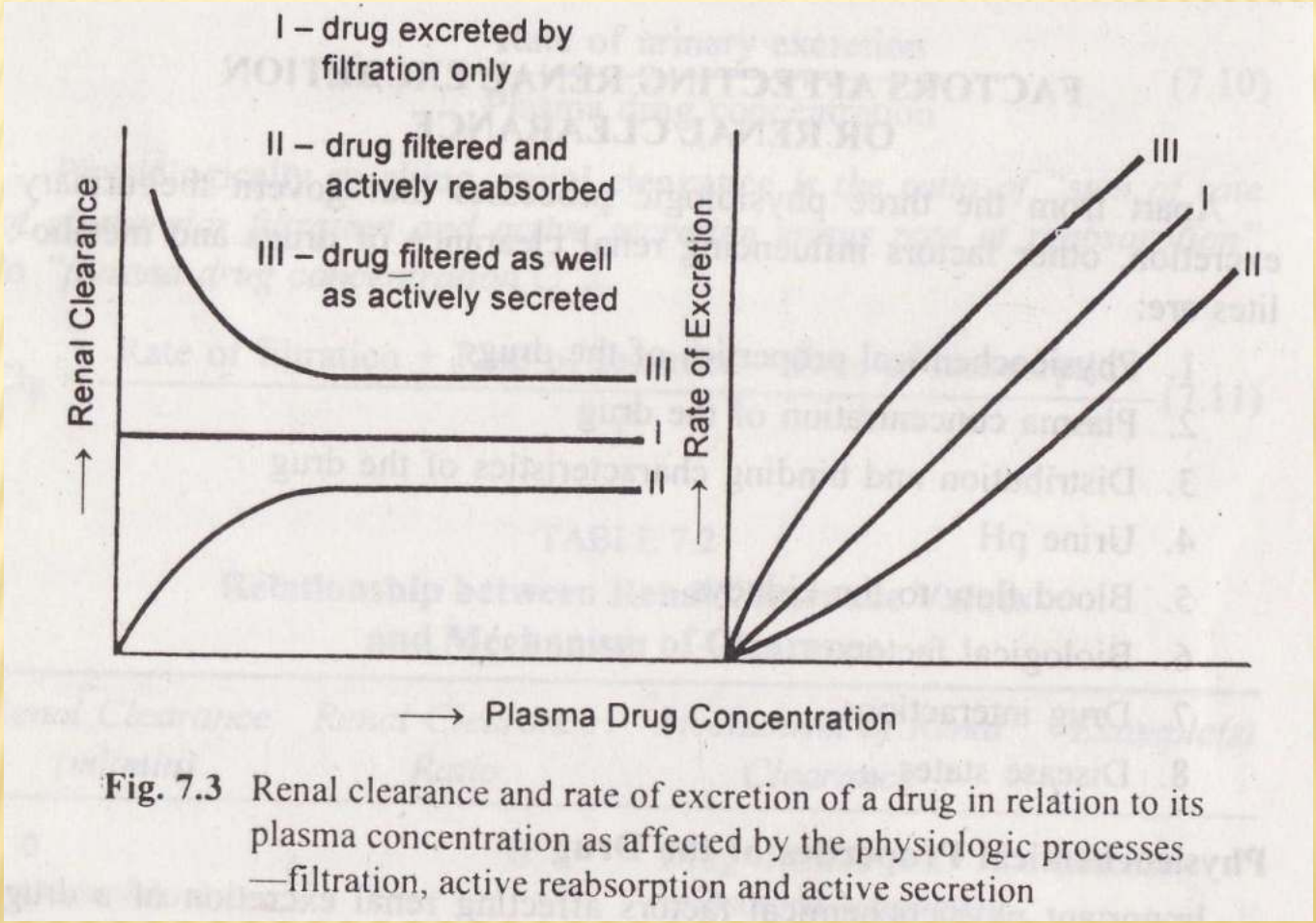


Fig. 7.3 Renal clearance and rate of excretion of a drug in relation to its plasma concentration as affected by the physiologic processes —filtration, active reabsorption and active secretion

DISTRIBUTION AND BINDING CHARACTERISTICS OF THE DRUG

Drugs that are bound to plasma proteins behave as macromolecules and cannot be filtered through glomerulus. Only unbound or free drug appear in glomerular filtrate. Protein bound drug has long half lives.

BIOLOGICAL FACTORS

- Age, sex, species, strain difference etc alter the excretion of the drug.
- **Sex** – Renal excretion is 10% lower in female than in males.
- **Age** – The renal excretion in newborn is 30-40 % less in comparison to adults.
- **Old age** – The GFR is reduced and tubular function is altered which results in slow excretion of drugs and prolonged half lives.

DRUG INTERACTION

Any drug interaction that result in alteration of binding characteristics, renal blood flow, active secretion, urine pH, intrinsic clearance and forced diuresis would alter renal clearance of drug.

Renal clearance of a drug highly bound to plasma proteins is increased after it is displaced with other drug e.g. Gentamicin induced nephrotoxicity by furosemide.

Alkalinization of urine with citrates and bicarbonates promote excretion of acidic drugs.

DISEASE STATE

- **RENAL DYSFUNCTION**

Greatly impairs the elimination of drugs especially those that are primarily excreted by kidney. Some of the causes of renal failure are B.P, Diabetes, Pyelonephritis.

- **UREMIA**

Characterized by Impaired GFR , accumulation of fluids & protein metabolites, also impairs the excretion of the drugs. Half life is increased resulting in drug accumulation and increased toxicity.

NON-RENAL ROUTE OF DRUG EXCRETION

Various routes are

- Biliary Excretion
- Pulmonary Excretion
- Salivary Excretion
- Mammary Excretion
- Skin/dermal Excretion
- Gastrointestinal Excretion
- Genital Excretion

BILIARY EXCRETION

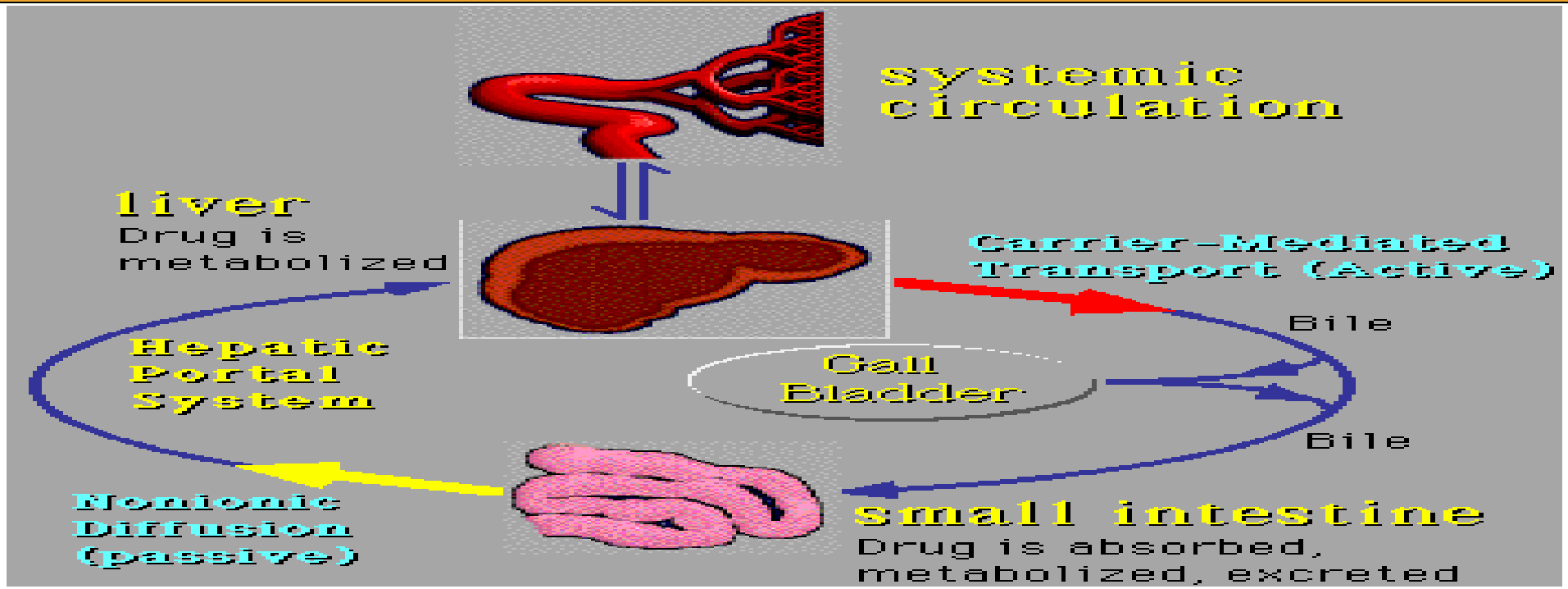
Bile juice is secreted by hepatic cells of the liver. The flow is steady-0.5 to 1ml /min. Its important in the digestion and absorption of fats.90% of bile acid is reabsorbed from intestine and transported back to the liver for resecretion. Compounds excreted by this route are sodium, potassium, glucose, bilirubin, Glucuronide, sucrose, Inulin, muco-proteins etc. Greater the polarity better the excretion. The metabolites are more excreted in bile than parent drugs due to increased polarity.

Nature of bio transformation process:

Phase-II reactions mainly glucuronidation and conjugation with glutathione result in metabolites with increased tendency for biliary excretion. Drugs excreted in the bile are chloromphenicol, morphine and indomethacin. Glutathione conjugates have larger molecular weight and so not observed in the urine. For a drug to be excreted in bile must have polar groups like –COOH, $-SO_3H$. Clomiphene citrate, ovulation inducer is completely removed from the body by BE.

ENTERO-HEPATIC CIRCULATION

Some drugs which are excreted as glucuronides/ as glutathione conjugates are hydrolyzed by intestinal/ bacterial enzymes to the parent drugs which are reabsorbed. The reabsorbed drugs are again carried to the liver for resecretion via bile into the intestine. This phenomenon of drug cycling between the intestine & the liver is called Enterohepatic circulation



THE ENTEROHEPATIC CIRCULATION

EC is important in conservation of Vitamins, Folic acid and hormones. This process results in prolongation of half lives of drugs like DDT, Carbenoxolone. Some drugs undergoing EC are cardiac glycosides, rifampicin and chlorpromazine. The principle of adsorption onto the resins in GIT is used to treat pesticide poisoning by promoting fecal excretion.

OTHER FACTORS

The efficacy of drug excretion by biliary system can be tested by an agent i.e. completely eliminated in bile. Example sulfobromophthalein. This marker is excreted in half an hour in intestine at normal hepatic functioning. Delay in its excretion indicates hepatic and biliary mal function.

$$\textbf{Biliary clearance} = \frac{\text{Biliary excretion rate}}{\text{Plasma drug concentration}}$$

The ability of liver to excrete the drug in the bile is expressed as **Biliary clearance**.

PULMONARY EXCRETION

Gaseous and volatile substances such as general anesthetics (Halothane) are absorbed through lungs by simple diffusion. Pulmonary blood flow, rate of respiration and solubility of substance effect PE. Intact gaseous drugs are excreted but not metabolites. Alcohol which has high solubility in blood and tissues are excreted slowly by lungs.

MAMMARY EXCRETION

Milk consists of lactic secretions which is rich in fats and proteins. 0.5 to one liter of milk is secreted per day in lactating mothers. Excretion of drug in milk is important as it gains entry in breast feeding infants. pH of milk varies from 6.4 to 7.6. Free un-ionized and lipid soluble drugs diffuse passively. Highly plasma bound drug like Diazepam is less secreted in milk. Since milk contains proteins. Drugs excreted can bind to it.

SALIVARY EXCRETION

The pH of saliva varies from 5.8 to 8.4. Unionized lipid soluble drugs are excreted passively. The bitter after taste in the mouth of a patient is indication of drug excreted. Some basic drugs inhibit saliva secretion and are responsible for mouth dryness. Compounds excreted in saliva are Caffeine, Phenytoin, Theophylline.

MAMMARY EXCRETION

Amount of drug excreted in milk is less than 1% and fraction consumed by infant is too less to produce toxic effects. Some potent drugs like barbiturates and morphine may induce toxicity.

ADVERSE EFFECTS

Discoloration of teeth with tetracycline and jaundice due to interaction of bilirubin with sulfonamides. Nicotine is secreted in the milk of mothers who smoke.

SKIN EXCRETION

Drugs excreted through skin via sweat follows pH partition hypothesis. Excretion of drugs through skin may lead to urticaria and dermatitis. Compounds like benzoic acid, salicylic acid, alcohol and heavy metals like lead, mercury and arsenic are excreted in sweat.

GASTROINTESTINAL EXCRETION

Excretion of drugs through GIT usually occurs after parenteral administration. Water soluble and ionized from of weakly acidic and basic drugs are excreted in GIT. Example are nicotine and quinine are excreted in stomach. Drugs excreted in GIT are reabsorbed into systemic circulation & undergo recycling.

EXCRETION PATHWAYS, TRANSPORT MECHANISMS & DRUG EXCRETED.

Excretory route	Mechanism	Drug Excreted
Urine	GF/ ATS/ ATR, PTR	Free, hydrophilic, unchanged drugs/ metabolites of MW< 500
Bile	Active secretion	Hydrophilic, unchanged drugs/ metabolites/ conjugates of MW >500
Lung	Passive diffusion	Gaseous &volatile, blood & tissue insoluble drugs
Saliva	Passive diffusion Active transport	Free, unionized, lipophilic drugs. Some polar drugs
Milk	Passive diffusion	Free, unionized, lipophilic drugs (basic)
Sweat/ skin	Passive diffusion	Free, unionized lipophilic drugs
Intestine	Passive diffusion	Water soluble. Ionized drugs

CONCEPT OF CLEARANCE

CLEARANCE:-

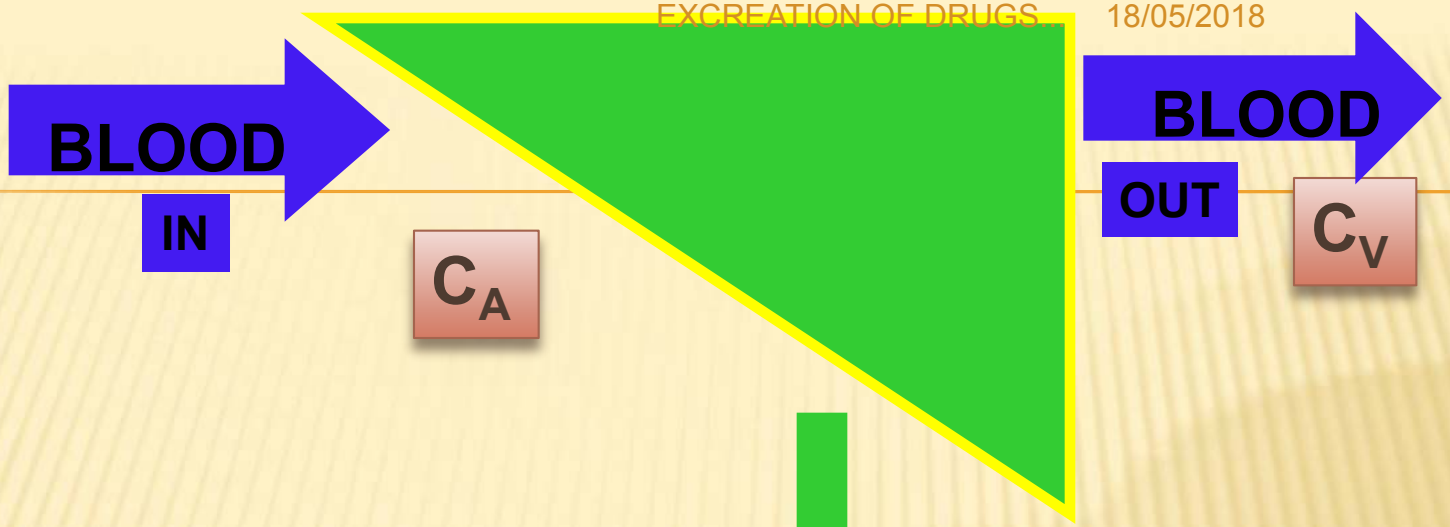
Is defined as the hypothetical volume of body fluids containing drug from which the drug is removed/ cleared completely in a specific period of time. Expressed in ml/min.

Clearance = Rate of elimination ÷plasma conc.

TOTAL BODY CLEARANCE:-

Is defined as the sum of individual clearances by all eliminating organs is called total body clearance/ total systemic clearance.

Total Body Clearance = $CL_{liver} + CL_{kidney} + CL_{lungs} + CL_x$



ELIMINATED

Rate of Elimination = $QC_A - QC_V = Q(C_A - C_V)$

Liver Clearance = $Q(C_A - C_V)/C_A$ = $Q \times ER$

SIMILARLY FOR OTHER ORGANS

Total Body Clearance = $CL_{liver} + CL_{kidney} + CL_{lungs} + CL_x$

RENAL CLEARANCE

Major organ for elimination of almost all drugs & their metabolites.

Water soluble, Nonvolatile, Low molecular weight/ slowly metabolized drugs by liver are eliminated by kidneys.
Drugs like Gentamycin- exclusively eliminated by kidneys.
Basic functional unit of kidney involved in excretion is *NEPHRON.*

The principle processes that determine the urinary excretion of drugs are:-

- ✓Glomerular filtration
- ✓Active tubular secretion
- ✓ Active/ passive tubular reabsorption
- ✓ RE = RF + RS - RRA

RENAL CLEARANCE:- is defined as the volume of blood/ plasma which is completely cleared of the unchanged drug by the kidney/unit time

Cl_R = rate of urinary excretion ÷ plasma drug concentration

Or

$$Cl_R = \frac{\text{rate of filtration + rate of secretion – rate reabsorption}}{C}$$

$$Cl_R = \frac{dX/dt}{C}$$

Where Cl_R = renal clearance
dX/dt = elimination rate constant
C= concentration of drug in plasma

$$Cl_R = \frac{K_e X}{C}$$

Where K_e = first order elimination rate constant
X = amount of drug in the body remaining to be eliminated at time t

$$Cl_R = \frac{Cl_{RF} + Cl_{RS} - Cl_{FR}}{C}$$

Cl_{RF} = renal filtration clearance
Cl_{RS} = renal secretion clearance
Cl_{FR}= fraction of drug absorbed

$$Cl_R = (Cl_{RF} + Cl_{RS})(1 - Cl_{FR})$$

$1 - Cl_{FR}$ = fraction of drug filtered & secreted that is reabsorbed

RENAL CLEARANCE:-

$$Cl_R = \frac{K_e X}{C} \quad \ldots\ldots\ldots\ldots \text{I}$$

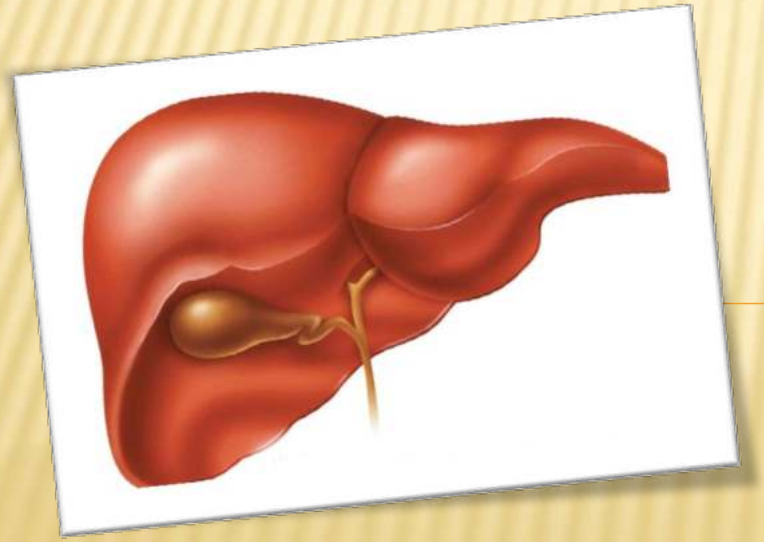
where $X/C = V_d$ then above eqn becomes:

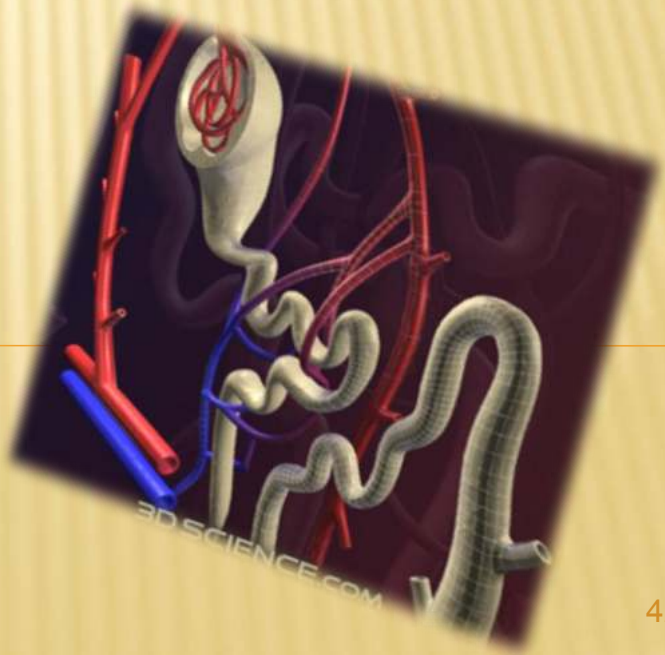
$$Cl_R = K_e V_d \quad \ldots\ldots\ldots\ldots \text{II}$$

for non compartmental method the renal clearance is computed as (When given in i.v.bolus)

$$Cl_R = \frac{X_u^{\infty}}{AUC} \quad \ldots\ldots\ldots\ldots \text{III}$$

HEPATIC CLEARANCE & ORGAN CLEARANCE





ELIMINATION

IRREVERSIBLE REMOVAL OF DRUG FROM THE BODY BY ALL ROUTES OF ELIMINATION

Excretion

Metabolism

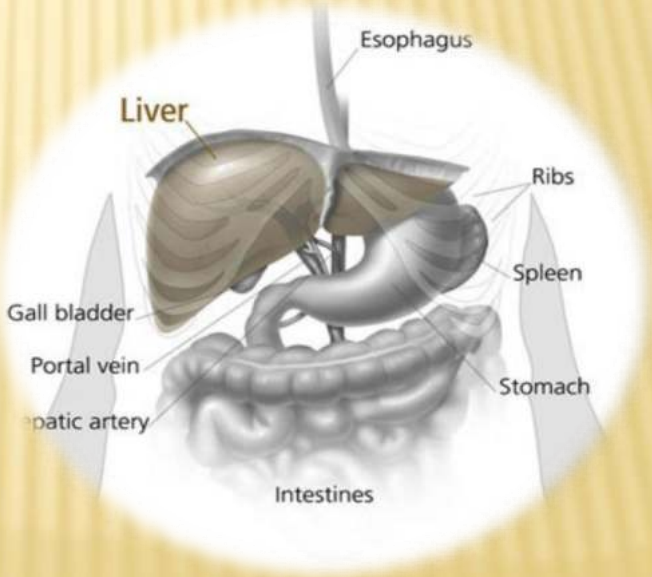
- Metabolism mainly by liver-oxidation, reduction, hydolysiconjugation

CLEARANCE

CLEARANCE IS THE LOSS OF DRUG ACROSS AN ORGAN OF ELIMINATION.

CLEARANCE IS DEFINED AS THE HYPOTHETICAL VOLUME OF BODY FLUIDS CONTAINING DRUG FROM WHICH DRUG IS COMPLETELY REMOVED OR CLEARED COMPLETELY IN A SPECIFIC PERIOD OF TIME

HEPATIC CLEARANCE



FOR CERTAIN DRUGS , THE NON-RENAL CLEARANCE CAN BE ASSUMED AS EQUAL TO HEPATIC CLEARANCE Cl_H

IT IS GIVEN AS :

$$Cl_H = Cl_T - Cl_R$$

Where ,

Q_H = HEPATIC BLOOD FLOW (about 1.5 liters/min)
ER_H = HEPATIC EXTRACTION RATION

THE HEPATIC CLEARANCE OF DRUG CAN BE DIVIDED INTO 2 GROUPS

1. DRUG WITH HEPATIC FLOW RATE-LIMITED CLEARANCE
2. DRUGS WITH INTRINSIC CAPACITY-LIMITED CLEARANCE

1. HEPATIC BLOOD FLOW :

WHEN ER_H IS ONE, Cl_H APPROACHES ITS MAXIMUM VALUE i.e. HEPATIC BLOOD FLOW. IN SUCH A SITUATION, HEPATIC CLEARANCE IS SAID TO BE perfusion rate-limited OR flow dependent.

ALTERATION IN HEPATIC BLOOD FLOW SIGNIFICANTLY AFFECTS THE ELIMINATION OF DRUGS WITH HIGH ER_H.
Eg. Propranolol , lidocaine etc….

SUCH DRUGS ARE REMOVED FROM THE BLOOD AS RAPIDLY AS THEY ARE PRESENTED TO THE LIVER

INDOCYANINE GREEN IS SO RAPIDLY ELIMINATED BY THE HUMAN LIVER THAT ITS CLEARANCE IS OFTEN USED AS AN INDICATOR.

FIRST-PASS HEPATIC EXTRATION IS SUSPECTED WHEN THERE IS LACK OF UNCHANGED DRUG IN SYSTEMIC CIRCULATION AFTER ORAL ADMINISTRATION

MAXIMUM ORAL AVAILABILITY

$$F = 1 - ER_H = \frac{AUC_{ORAL}}{AUC_{i.v}}$$

- Hepatic blood flow has very little or no effect on drugs with low ER_H eg. Theophylline.

- For such drugs, what ever concentration of drug present in the blood perfuses liver, is more than what the liver can eliminate.

- Hepatic clearance of a drug with high ER is independent of protein binding

2. INTRINSIC CAPACITY CLEARANCE (Cl_{INT})

IT IS DEFINED AS THE ABILITY OF AN ORGAN TO IRREVERSIBLY REMOVE A DRUG IN THE ABSENCE OF ANY FLOW LIMITATION

DRUG WITH LOW ER_H AND WITH ELIMINATION PRIMARILY BY METABOLISM ARE GREATLY AFFECTED BY CHANGE IN ENZYME ACTIVITY

HEPATIC CLEARANCE OF SUCH DRUGS IS SAID TO BE capacity-limited Eg. THEOPHYLINE
THE $t_{1/2}$ OF SUCH DRUGS SHOW GREAT INTERSUBJECT VARIABILITY.

HEPATIC CLEARANCE OF DRUGS WITH LOW ER IS INDEPENDENT OF BLOOD FLOW RATE BUT SENSITIVE TO CHANGE IN PROTEIN BINDING

HEPATIC AND RENAL EXTRATION RATIO OF SOME DRUG AND METABOLITES

	Extraction ratio		
	High	Intermediate	Low
Hepatic extraction	Propranolol Lidocaine Nitroglycerine Morphine	Aspirine Codeine Nortriptyline Quinidine	Diazepam Phenobarbital Phenytoin Theophylline
Renal extraction	Some - penicilline Hippuric acid Several - sulphates	Some - penicilline Procainamide Cimetidine	Digoxin Furosemide Atenolol Tetracycline

ORGEN CLEARANCE

•IT IS THE BEST WAY OF UNDERSTANDING CLEARANCE IS AT INDIVIDUAL ORGAN LEVEL.

SUCH A PHYSIOLOGIC APPROCH IS ADVANTAGEOUS IN PREDICTING AND EVALUATING THE INFLUENCE OF PATHOLOGY , BLOOD FLOW , P-D BINDING , ENZYME ACTIVITY , ETC ON DRUG ELIMINATION

AT ORGAN LEVEL , THE RATE OF ELIMINATION CAN BE WRITTEN AS :

RATE OF ELIMINATION BY ORGAN = RATE OF PRESENTATION TO THE ORGAN − RATE OF EXIT FROM THE ORGAN

RATE OF PRESENTATION TO THE ORGAN(INPUT) = ORGAN BLOOD FLOW $(Q.C_{IN})$ X ENTERING CONC.

RATE OF EXIT = ORGAN BLOOD FLOW $(Q.C_{OUT})$ X EXITING CONC.

$$\text{RATE OF ELIMINATION} = Q.C_{IN} - Q.C_{OUT}$$
$$Q\ (C_{IN} - C_{OUT})$$

DIVISION OF ABOVE EQUATION BY CONC OF DRUG THAT ENTERS THE ORGAN OF ELIMINATION C_{IN} YIELDS AN EXPRESSION FOR CLEARENCE OF DRUG BY THE ORGAN UNDER CONSIDERATION

$$\frac{\text{RATE OF EXTRACTION}}{C_{IN}} = Cl_{ORGAN} = \frac{Q\ (C_{IN} - C_{OUT})}{C_{IN}} = Q.ER$$

WHERE $ER = (C_{IN} - C_{OUT}) / C_{IN}$ IS CALLED AS EXTRATION RATION. IT HAS NO UNITS AND ITS VALUE RANGES FROM 0 (NO ELIMINATION) TO 1 (COMPLETE ELIMINATION).

BASED ON ER VALUES DRUGS CAN BE CLASSIFIED INTO 3 GROUPS :

DRUGS WITH HIGH ER (ABOVE 0.7)

DRUGS WITH INTERMEDIATE ER (BETWEEN 0.7 TO 0.3)

DRUGS WITH LOW ER (BELOW 0.3)

ER IS AN INDEX OF HOW EFFICIENTLY THE ELIMINATING ORGAN CLEARS THE BLOOD FLOWING THROUGH IT OF DRUG

THE FRACTION OF DRUG THAT ESCAPES REMOVAL BY THE ORGAN IS EXPRESSED AS :

$$F = 1 - ER$$

WHERE ,

F = SYSTEMIC AVAILABILITY WHEN THE ELIMINATING ORGAN IS LIVER

REFERENCES

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Brahmankar MD,Jaiswal S.,Biopharmaceutics & Pharmacokinetics- A teratise;

Shargel L.,Susanna W., Applied Biopharmaceutics and Pharmacokinetics.

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THANK YOU

BIOTRANSFORMATION

❑Contents:-

- ✓*Introduction*
- ✓*Phase I reaction*
- ✓*Phase II reaction*
- ✓*Factors affecting Biotransformation*
- ✓*Reference*

INTRODUCTION

ELIMINATION: It is defined as the irreversible loss of drug from body.

Elimination occur by two process

Biotransformation (Metabolism) :- It is defined as the conversion from one chemical form to another,

Definition exclude chemical instability of drug within the body Ex: Penicillin to Penicilloic acid (Metabolism) Penicillin degradation to penicillenic acid (Chemical instability)

❑*Definition:*

- "Biotransformation of drug is defined as the **conversion from one chemical form to another".**

the term is used synonymously with ***metabolism***.

All chemical substances that are not nutrient for the body and enter the body through, ingestion, inhalation, absorption are called as ***xenobiotics*** **or** ***exogenous compounds.***

Biotransformation normally leads to

1. Pharmacologic inactivation of drugs, (phenytoin to p-hydroxy phenytoin)
2. No change in pharmacological activity. (Phenyl butazone to oxy phenyl butazone)
3. Toxicological activation (Paracetamol).

TABLE 5.1 **Metabolites and Relative Activity of Drugs**

Drugs	*Metabolites*
Pharmacologic Inactivation	
Active	*Inactive*
Amphetamine	Phenylacetone
Phenobarbital	Hydroxyphenobarbital
Phenytoin	p-Hydroxy phenytoin
Salicylic acid	Salicyluric acid
No Change in Pharmacologic Activity	
Active	*Active*
Amitriptyline	Nortriptyline
Imipramine	Desipramine
Codeine	Morphine
Phenylbutazone	Oxyphenbutazone
Diazepam	Temazepam
Digitoxin	Digoxin
Toxicologic Activation	
Active	*Reactive Intermediates*
Isoniazid	Tissue acylating intermediate
Paracetamol	Imidoquinone of N-hydroxylated metabolite
Pharmacologic Activation	
Inactive (Prodrugs)	*Active*
Aspirin	Salicylic acid
Phenacetin	Paracetamol
Sulfasalazine	Mesalamine and Sulfapyridine
Pivampicillin	Ampicillin
Enalapril	Enalaprilat
Chloramphenicol palmitate	Chloramphenicol
Change in Pharmacologic Activity	
Iproniazid (antidepressant)	Isoniazid (antitubercular)
Diazepam (tranquilizer)	Oxazepam (anticonvulsant)

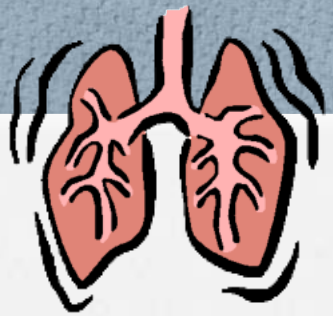
Drug metabolizing organs

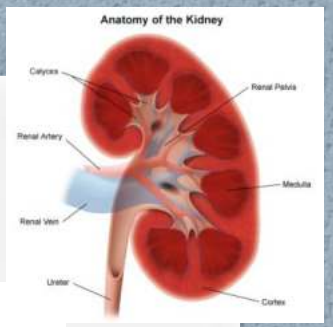
- Liver is the heart of metabolism
- Because of its relative richness of enzymes in large amount.
- Schematic chart of metabolizing organ (decreasing order)
- Liver > lungs > Kidney > Intestine > Placenta > Skin > Brain > Testes > Muscle > Spleen

Drug Metabolizing Enzymes

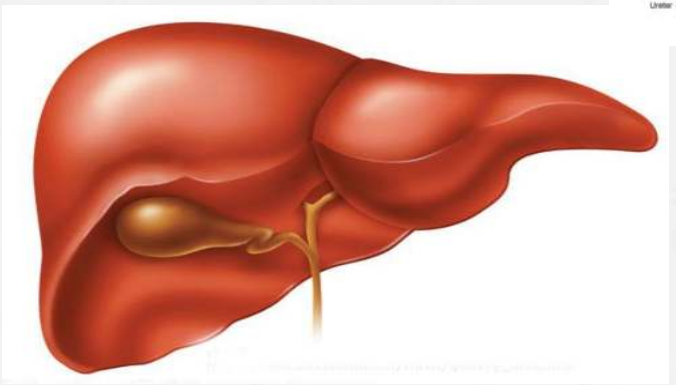
- *Microsomal*
- *Non - Microsomal*

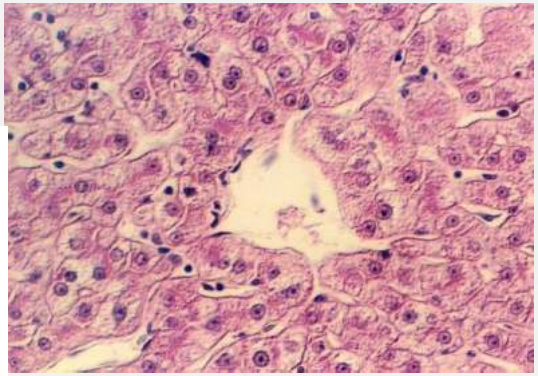
Microsomal Enzymes

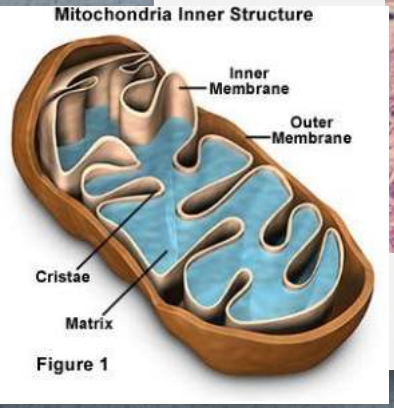




- *Found predominately in the smooth Endoplasmic Reticulum of liver*
- *Other areas:*
  - *Kidney*
  - *Lungs*
  - *Intestinal mucosa*







Non-microsomal enzymes

- *Found in the cytoplasm and mitochondria of hepatic cells*
- *Other tissues including plasma*

Microsomal Enzymes

- *Non-synthetic/ Phase I reactions*
  - *Most oxidation and reduction*
  - *Some hydrolysis*
- *Synthetic/ Phase II reactions*
  - *ONLY Glucuronide conjugation*

Non-microsomal enzymes

- *Non-synthetic/ Phase I reactions*
  - *Most hydrolysis*
  - *Some oxidation and reduction*
- Synthetic/ Phase II reactions
  - *ALL except Glucuronide conjugation*

Microsomal Enzymes

- *Inducible*
  - Drugs, diet, etc.

Non-microsomal enzymes

- *Not inducible*

Why Biotransformation?

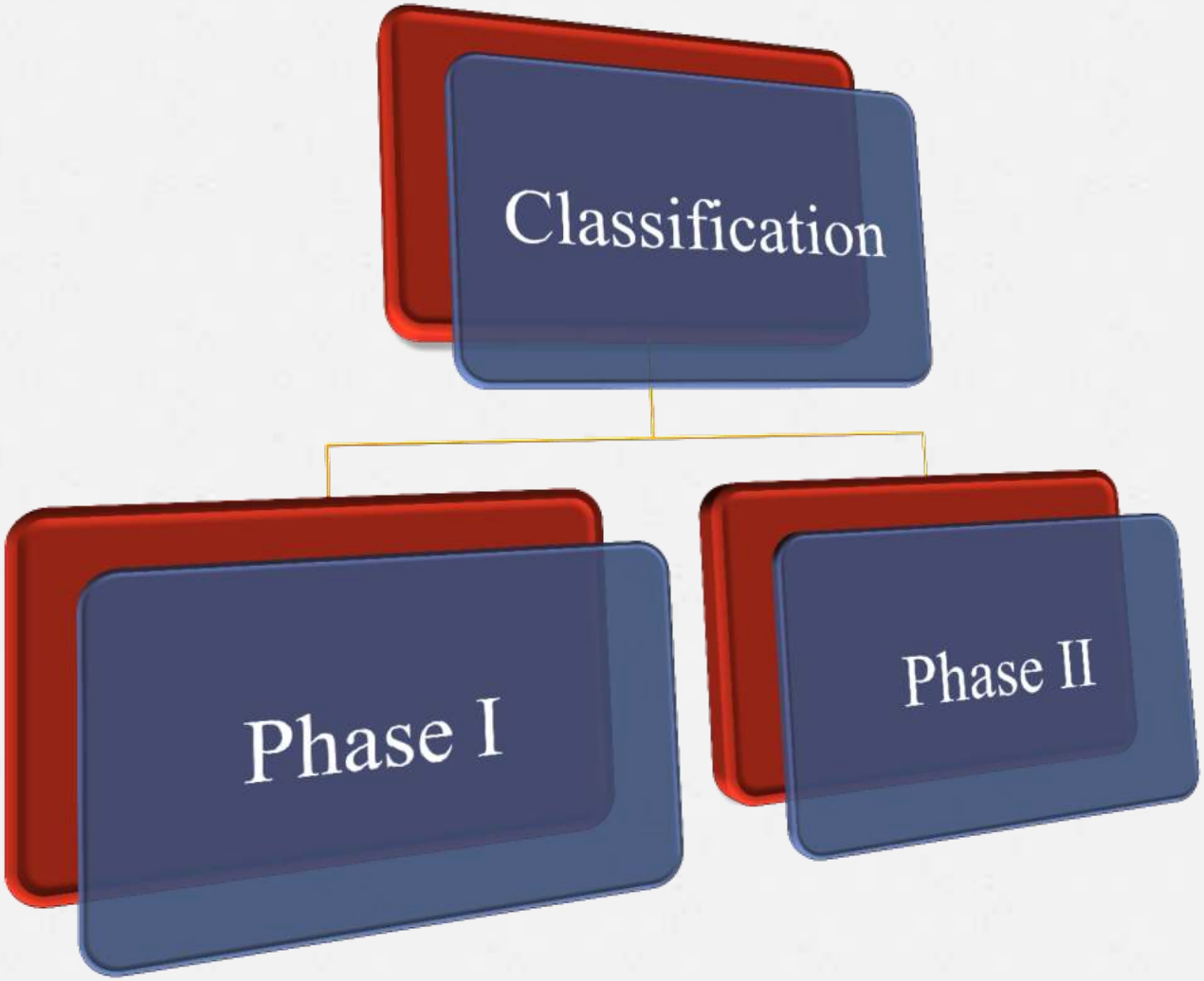
- Most drugs are excreted by the kidneys.
- For renal excretion drugs should:

– have small molecular mass

– be polar in nature

- Most drugs are complex and do not have these properties and thus have to be broken down to simpler products.
- Drugs are lipophilic in nature.

- Strongly bound to plasma proteins.
- This property also stops them from getting eliminated.
- They have to be converted to simpler hydrophilic compounds so that they are eliminated and their action is terminated.


Classification
Phase I
Phase II

❖*Metabolic reaction:*

❖*Phase I reaction*

- ✓Oxidation
- ✓Reduction
- ✓Hydrolysis

❖*Phase II reaction*

- ✓Conjugation

❑ *Phase I:*

- A polar functional group is either introduced or unmasked if already present on the otherwise lipid soluble Substrate,
- ✓ ***E.g***. **–OH, -COOH, -NH2 and –SH.**
- Thus, phase I reactions are called as ***functionalization reactions***.
- Phase I reactions are Non-synthetic in nature.
- The majority of Phase I metabolites are generated by a common hydroxylating enzyme system known as cytochrome P450.

❑ *Oxidative reaction:*

1) Oxidation of aromatic carbon atoms

2) Oxidation of olefins (C=C bonds)

3) Oxidation of Benzylic, Allylic carbon atoms & carbon atoms alpha to carbonyl & imines

4) Oxidation of aliphatic carbon atoms

5) Oxidation of alicyclic carbon atoms

6) Oxidation of carbon-heteroatom systems:

A. Carbon-Nitrogen system

- N- Dealkylation.
- Oxidative deamination
- N-Oxide formation
- N-Hydroxylation

B. Carbon-Sulfur system

- S- Dealkylation
- Desulfuration
- S-oxidation

C. Carbon-Oxygen systems(O- Dealkylation)

7) Oxidation of Alcohol, Carbonyl and Acid functions.

8) Miscellaneous oxidative reactions.

❑ *Reductive reactions:*

1) Reduction of Carbonyl functions.(aldehydes/ketones)

2) Reduction of alcohols and C=C bonds

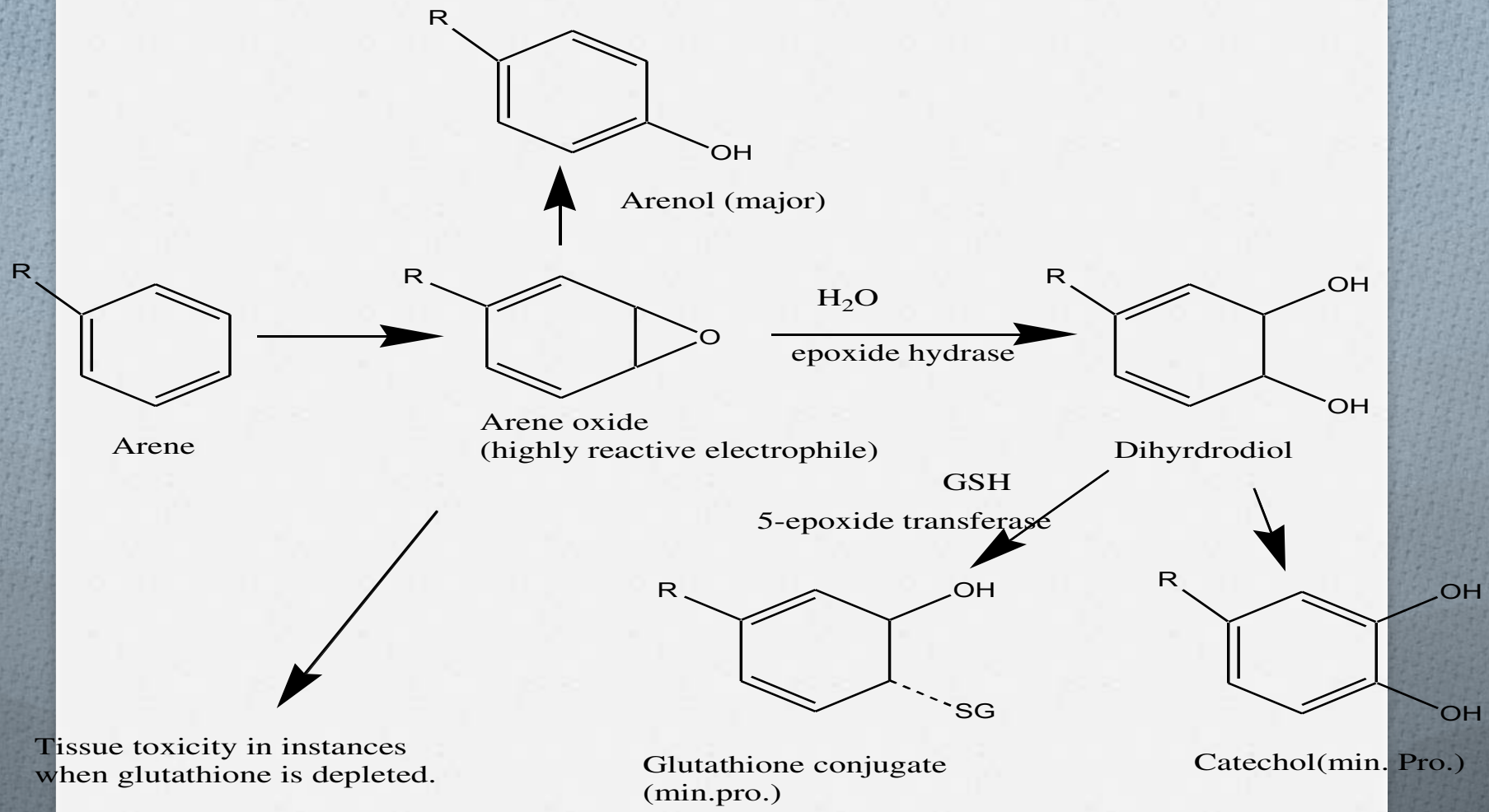
3) Reduction of N-compounds (nitro,azo & N-oxide)

4) Miscellaneous Reductive reactions.

❑ *Hydrolytic reactions*

1) Hydrolysis of Esters and Ethers
2) Hydrolysis of Amides.
3) Hydrolytic cleavage of non aromatic heterocycles
4) Hydrolytic Dehalogination
5) Miscellaneous hydrolytic reactions.

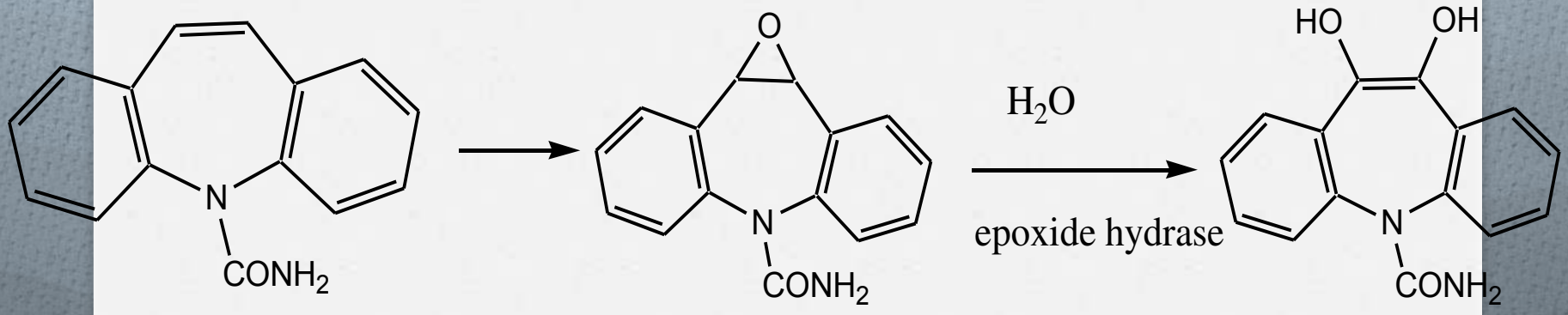
❖ *Oxidation of aromatic carbon atoms (aromatic hydroxylation):*



- **E.g. Epoxides of Bromobenzene and Benzopyrene.**

❖ *Oxidation of olefins (C=C bonds):*

- Oxidation of non-aromatic C=C bonds is analogous to aromatic hydroxylation. i.e. it proceeds via formation of epoxides to yield 1,2-dihydrodiols.



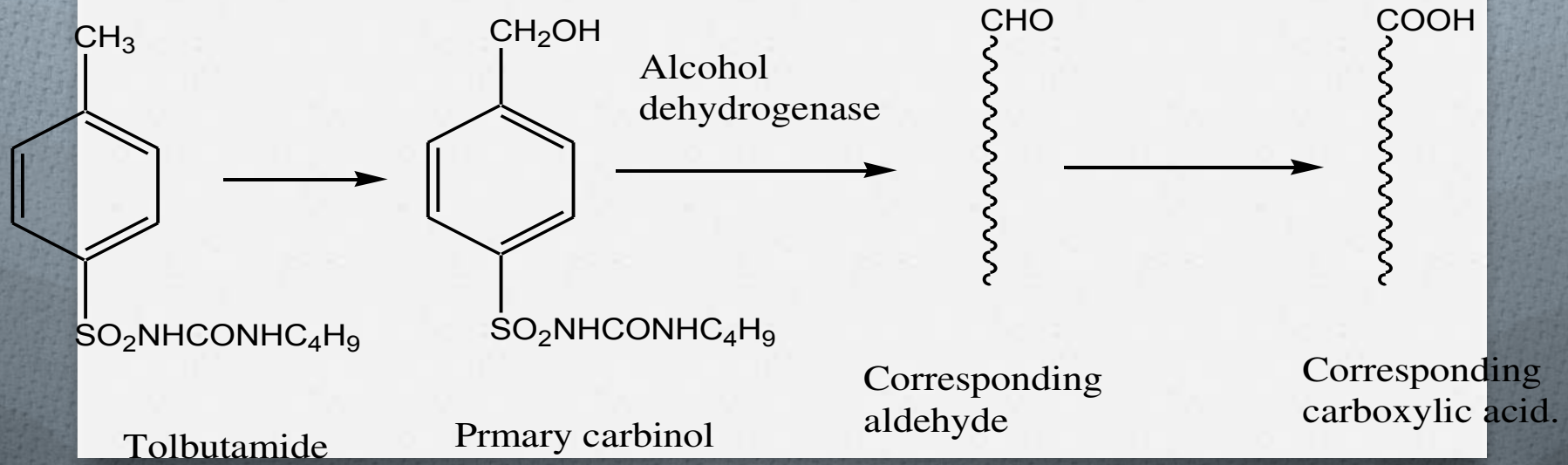
Carbamazepine

Carbamazepine-10,11 epoxide

Trans-10,11 dihydroxy carbamazepine

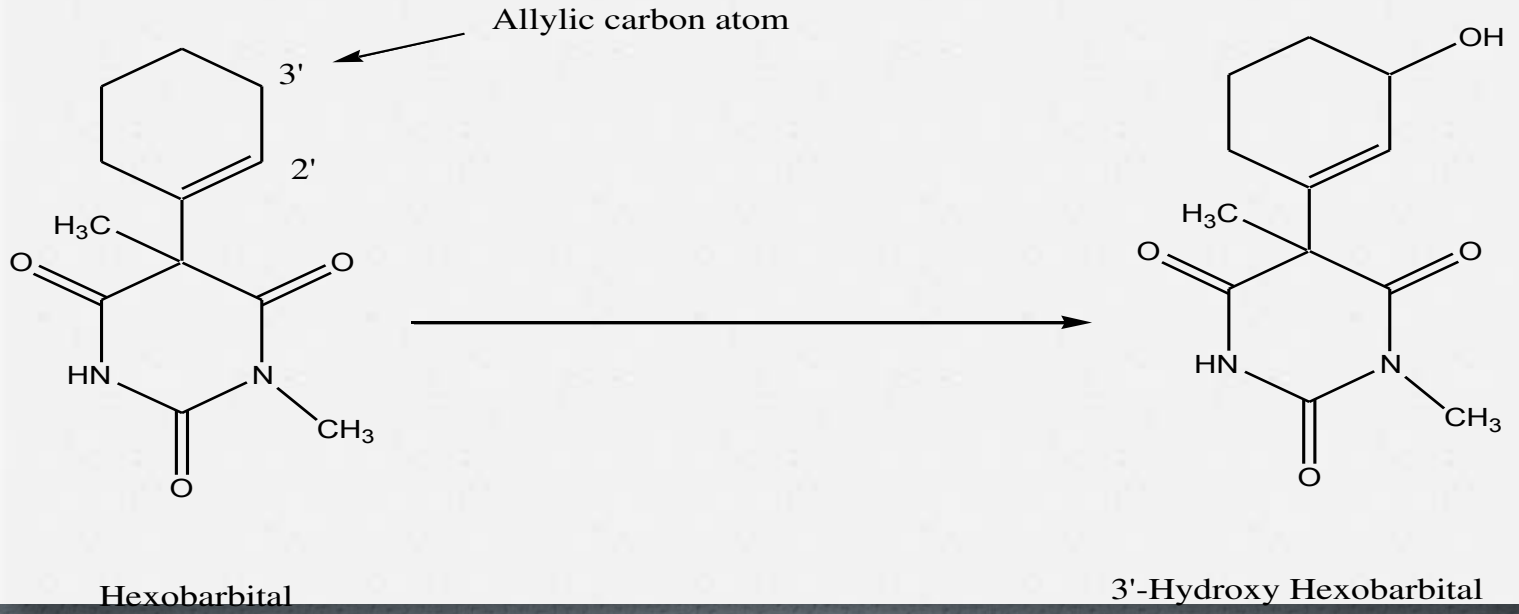
❖ *Oxidation of Benzylic Carbon Atoms:*

- Carbon atoms attached directly to the aromatic ring are hydroxylated to corresponding Carbinols.
- If the product is a primary carbinol, it is further oxidized to aldehydes and then to carboxylic acids,
  - ✓ **E.g.Tolbutamide**
- A secondary Carbinol is converted to Ketone.



❖ *Oxidation of Allylic carbon Atoms:*

- Carbon atoms adjacent to Olefinic double bonds (are allylic carbon atoms) also undergo hydroxylation in a manner similar to Benzylic Carbons.
- **E.g. Hydroxylation of Hexobarbital to 3`-hydroxy Hexobarbital.**



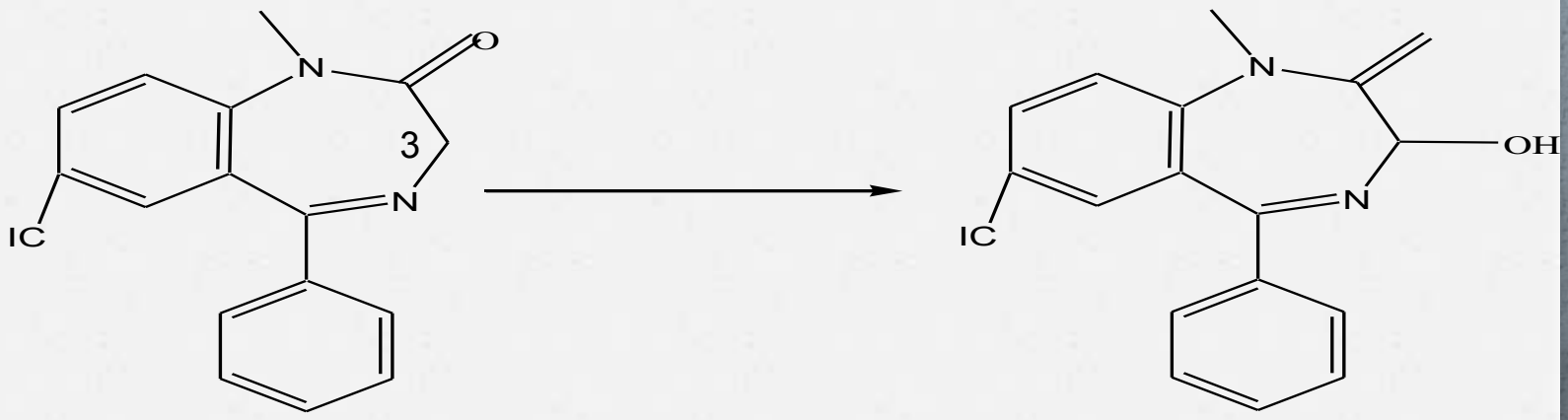
Hexobarbital

3'-Hydroxy Hexobarbital

❖ *Oxidation of Carbon Atoms Alpha to Carbonyls and Imines:*

- Several Benzodiazepines contain a carbon atom (C-3) alpha to both Carbonyl (C=0) and imino (C=N) function which readily undergoes Hydroxylation.

- ✓ **E.g. Diazepam**



Diazepam

3-Hydroxy diazepam

❖ *Oxidation of Aliphatic Carbon Atoms (Aliphatic Hydroxylation):*

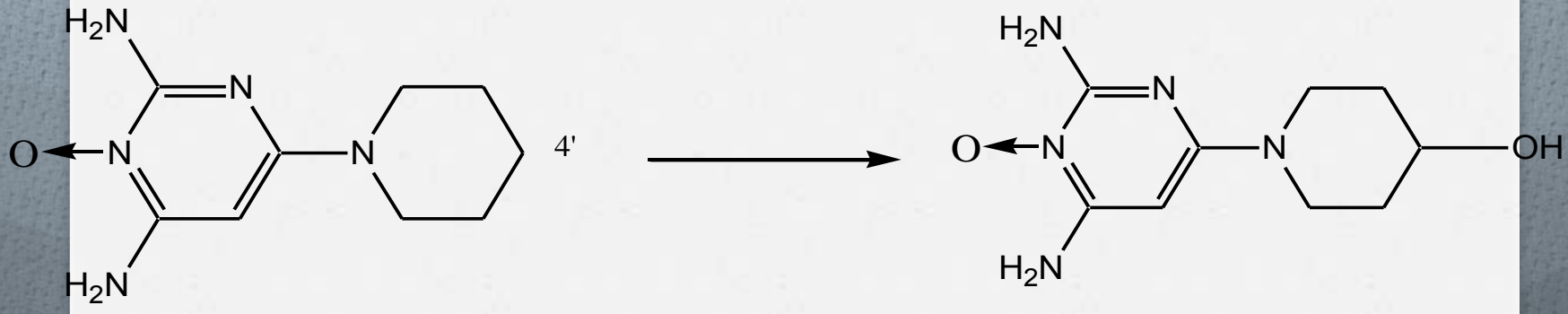
- Terminal hydroxylation of methyl group yields primary alcohols which undergoes further oxidation to aldehydes and then to carboxylic acid.

Ibuprofen

Tertiary alcohol metabolite

❖ *Oxidation of Alicyclic Carbon Atoms (Alicyclic Hydroxylation):*

- Cyclohexane (alicyclic) and piperidine (non-aromatic heterocyclic) rings are commonly found in a number of molecules.
- ✓ **E.g. Acetohexamide and minoxidil respectively.**
- Such rings are generally hydroxylated at C-3 or C-4 positions.



Minoxidil

4'-Hydroxy Minoxidil

❖ *Oxidation of Carbon-Heteroatom Systems:*

- Biotransformation of C-N, C-0 and C-S system proceed in one of the two way:

1. Hydroxylation of carbon atom attached to the heteroatom and subsequent cleavage at carbon-heteroatom bond.

✓**E.g. N-, O- and S- dealkylation, oxidative deamination and desulfuration.**

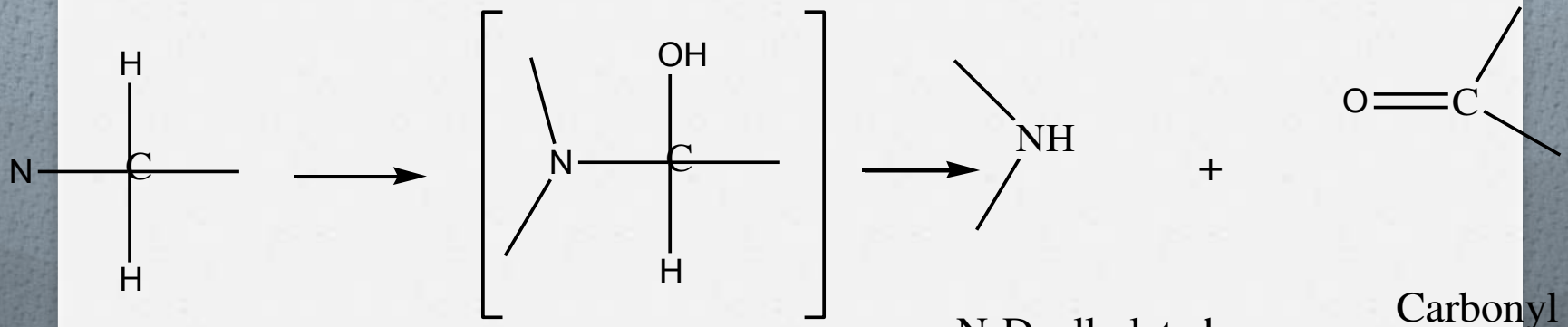
2. Oxidation of the heteroatom itself.

✓ **E.g. N- and S- oxidation.**

❖ *Oxidation of Carbon-Nitrogen System:*

❑ N-Dealkylation:

- Mechanism of N-dealkylation involve oxidation of α-carbon to generate an intermediate carbinolamine which rearranges by cleavage of C-N bond to yield the N dealkylated product and the corresponding carbonyl of the alkyl group.



Carbinolamine Intermediate

N-Dealkylated metabolite

Carbonyl

- A tertiary nitrogen attached to different alkyl groups undergoes dealkylation by removal of smaller alkyl group first.

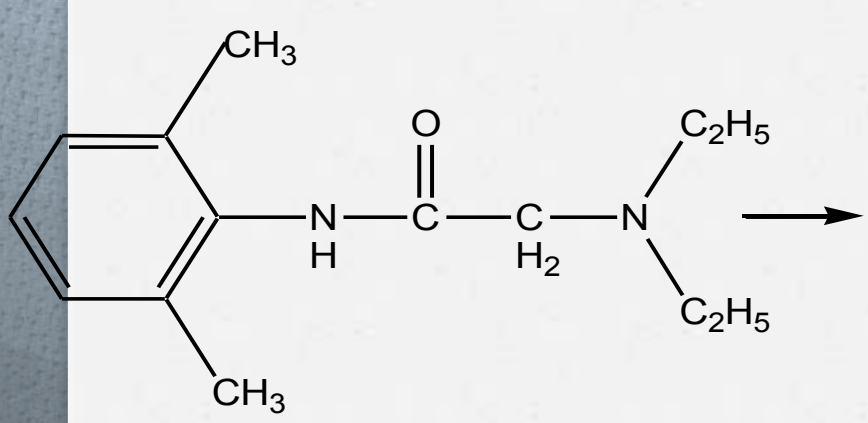
- **Example:**

- ✓ Secondary aliphatic amine ***E.g.*** **Methamphetamine.**
- ✓ Tertiary aliphatic amine ***E.g.*** **imipramine**
- ✓ Tertiary alicyclic amine ***E.g.*** **hexobarbital**
- ✓ Amides ***E.g.*** **Diazepam**

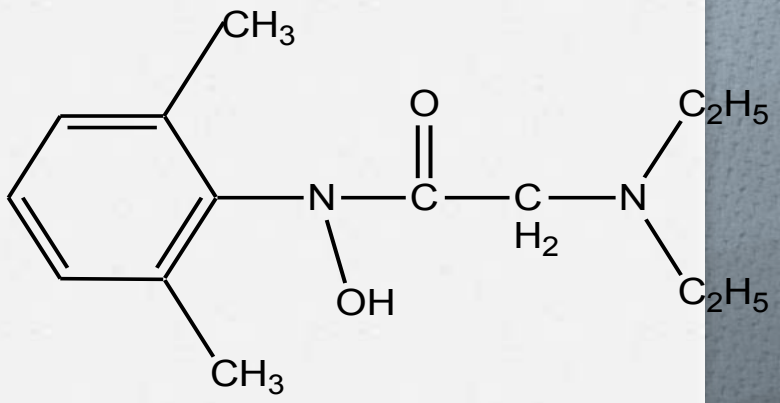
N-Hydroxylation:-

- Converse to basic compounds that form N-oxide, N-hydroxy formation is usually displayed by non-basic nitrogen atoms such as amide Nitrogen.

- **E.g. Lidocaine**



Lidocaine

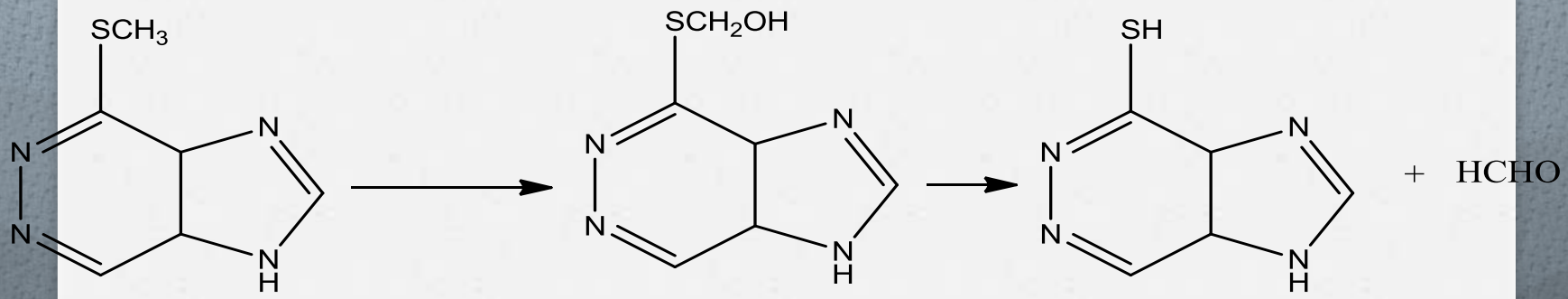


N- Hydroxy Lidocaine

❖ *Oxidation of Carbon-Sulfur Systems:*

❑ S-Dealkylation:

- The mechanism of S-Dealkylation of thioethers is analogous to N-dealkylation. It proceed via α-carbon hydroxylation.
- The C-S bond cleavage results in formation of a thiol and a carbonyl product.
- ✓ ***E.g.*** **6-Methyl mercaptopurine.**



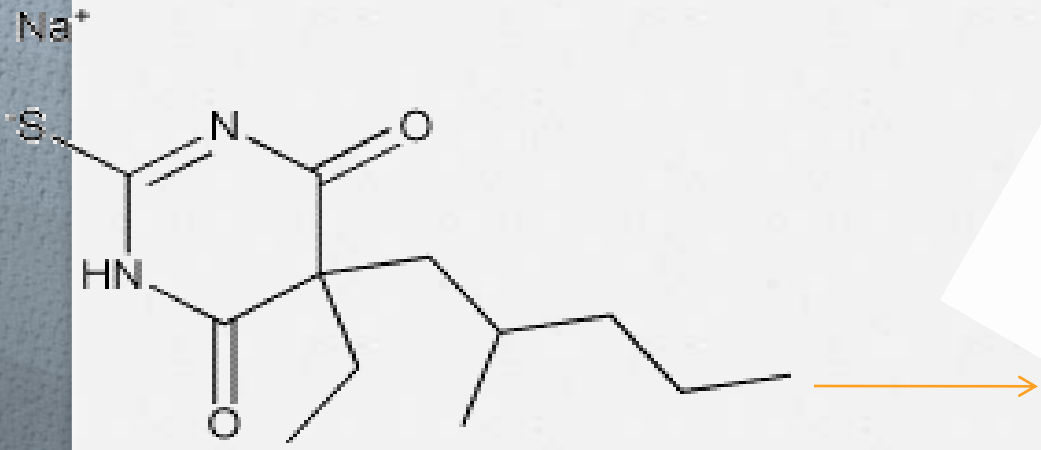
6-Methyl Mercaptopurine

Hydroxylated intermediate

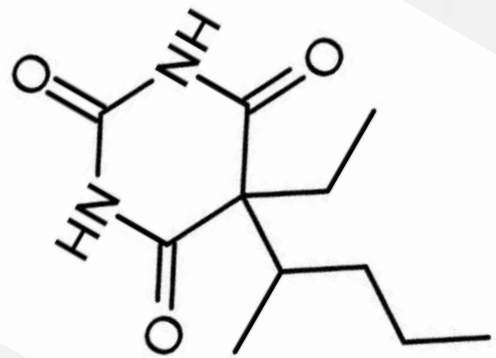
6-Mercaptopurine

❑ Desulfuration:

- This reaction also involves cleavage of carbon-sulfur bond (C=S).
- The product is the one with C=0 bond. Such a desulfuration reaction is commonly observed in thioamides such as thiopental.



Thiopental



Pentobarbital

❑ S-Oxidation:

- Apart from S-dealkylation, thioethers can also undergo S-oxidation reaction to yield sulfoxides which may be further oxidized to sulfones several phenothiazines.

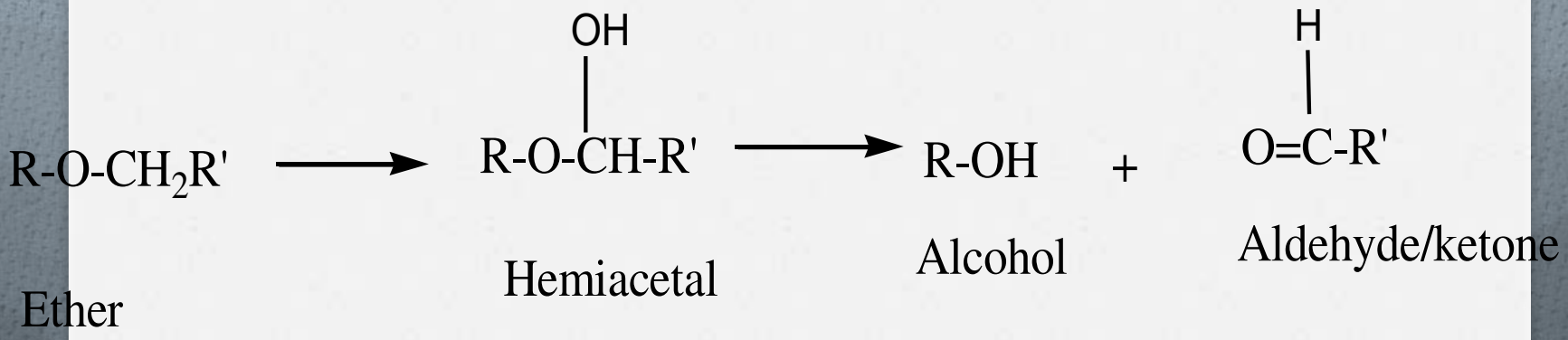
- ✓ **E.g**. Chlorpromazine undergo S-oxidation**.**

❖ *Oxidation of Carbon-Oxygen Systems:*

❑ O-Dealkylation:

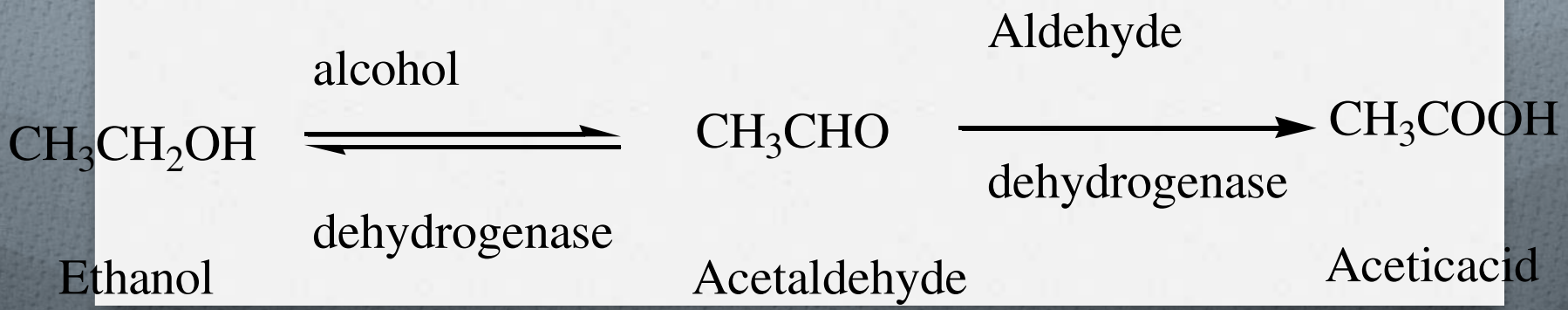
- This reaction is also similar to N-Dealkylation and proceeds by α-carbon hydroxylation to form an unstable hemiacetal or hemiketal intermediate.

- Which spontaneously undergoes C-0 bond cleavage to form alcohol and a carbonyl moiety.



❖ *Oxidation of Alcohol, Carbonyl and Carboxylic Acid*

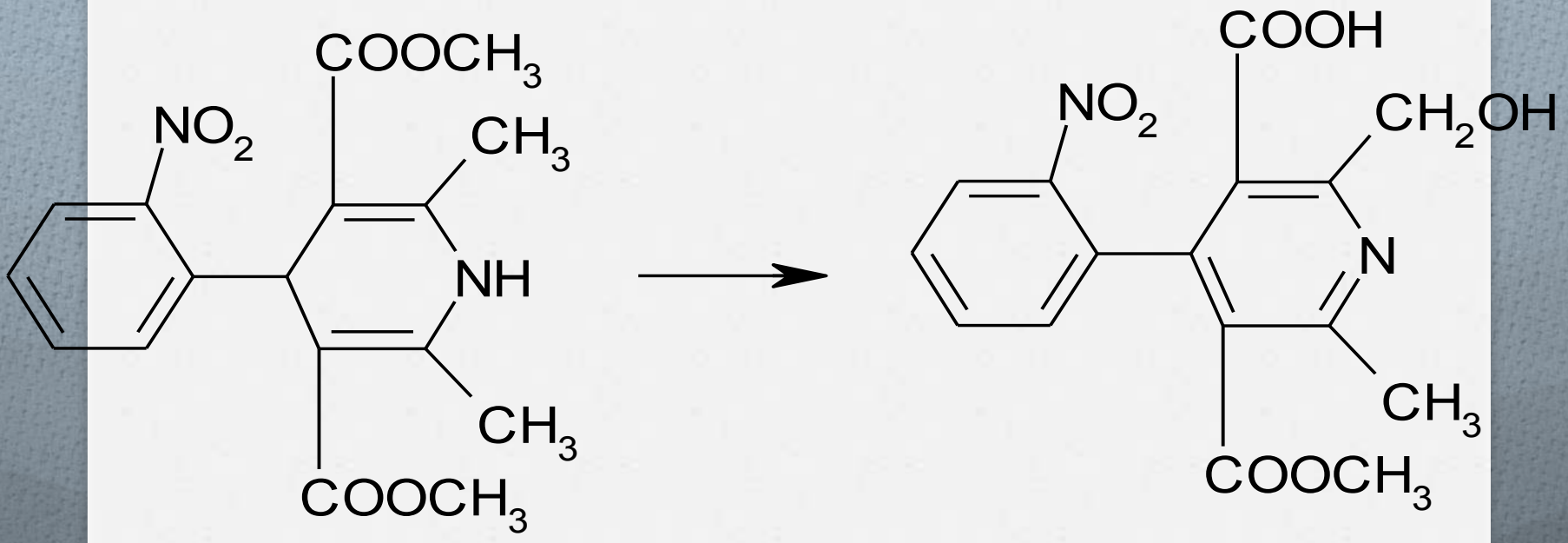
- In case of ethanol, Oxidation to acetaldehyde is reversible and further oxidation of the latter to acetic acid is very rapid since Acetaldehyde is highly toxic and should not accumulate in body.



❖ *Miscellaneous oxidative reactions:*

❑ Oxidative aromatization /dehydrogenation:

✓ E.g. Metabolic aromatization of drug nifedipine.

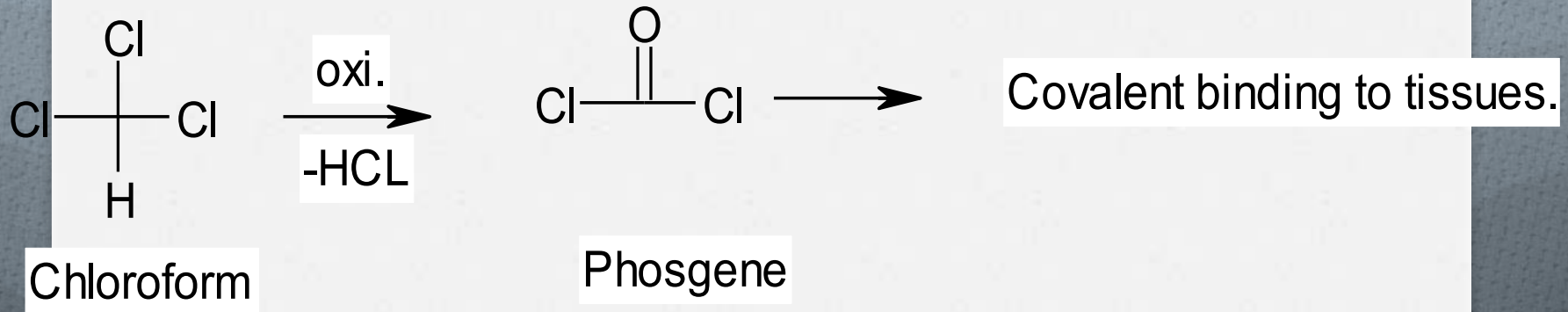


Nitedipine

Pyridine metabolite

❑ Oxidative Dehalogenation:

- This reaction is common with halogen containing drugs such as chloroform.
- Dehalogenation of this drug yields phosgene which may results in electrophiles capable of covalent binding to tissue.



❖ *Reductive reaction:*

- Bioreductions are also capable of generating polar functional group such as hydroxy and amino which can undergo further biotransformation or conjugation.

❑ Reduction of carbonyls:

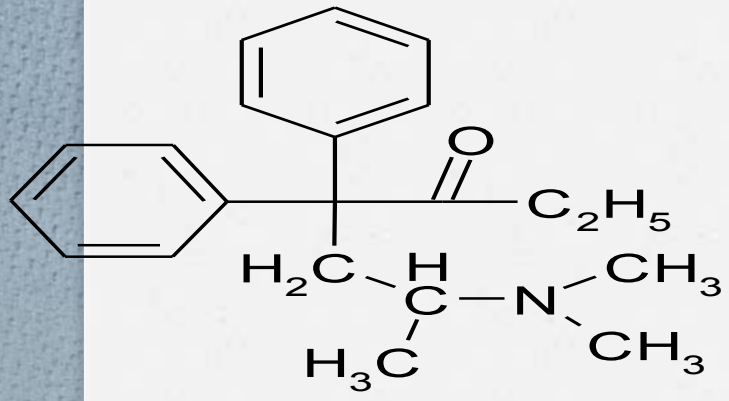
- Aliphatic aldehydes :

✓**E.g. Chloral hydrate**

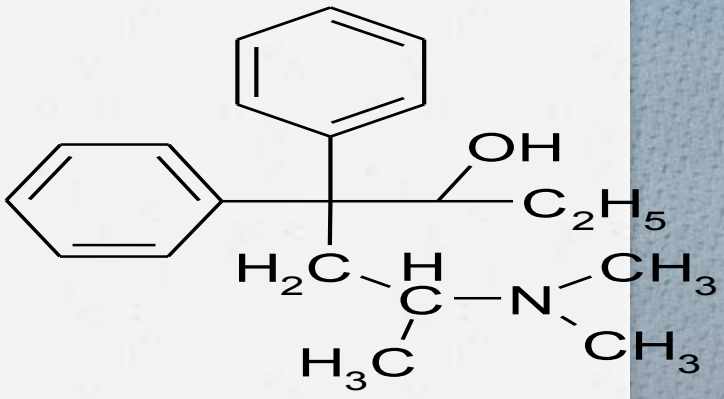
Chloral hydrate Trichloroethan

❑Aliphatic ketones:

E.g. Methadone.



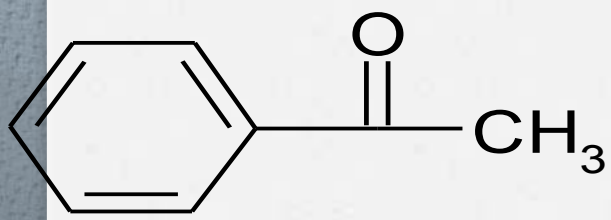
Methadone



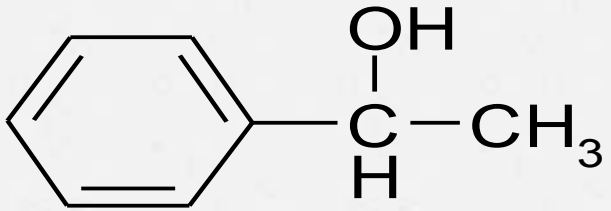
Methadol

❑Aromatic Ketone:

E.g. Acetophenone.



Acetophenone

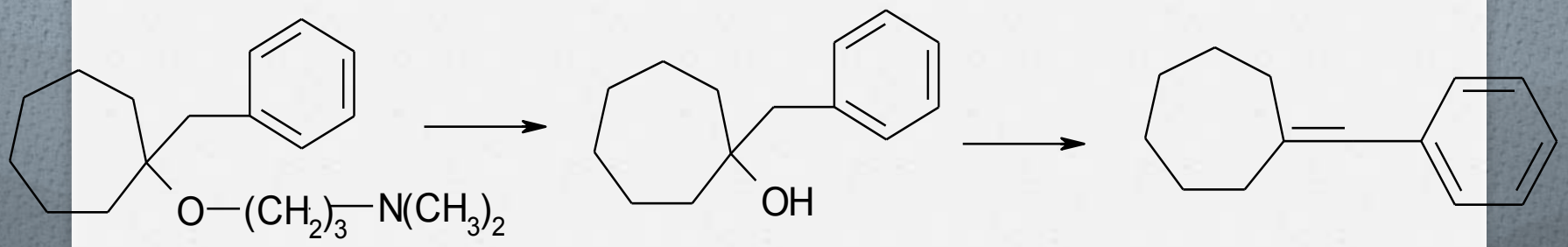


Methyl phenyl carbinol

❑ *Reduction of alcohols and C=C:*

- These two reductions are considered together because the groups are interconvertible by simple addition or loss of a water molecule. Before an alcohol is reduced it is dehydrated to C=C bond.

✓ **Example – bencyclane .** (antispasmodic)



Bencyclane → Bencyclanol → Benzylidine cycloheptane

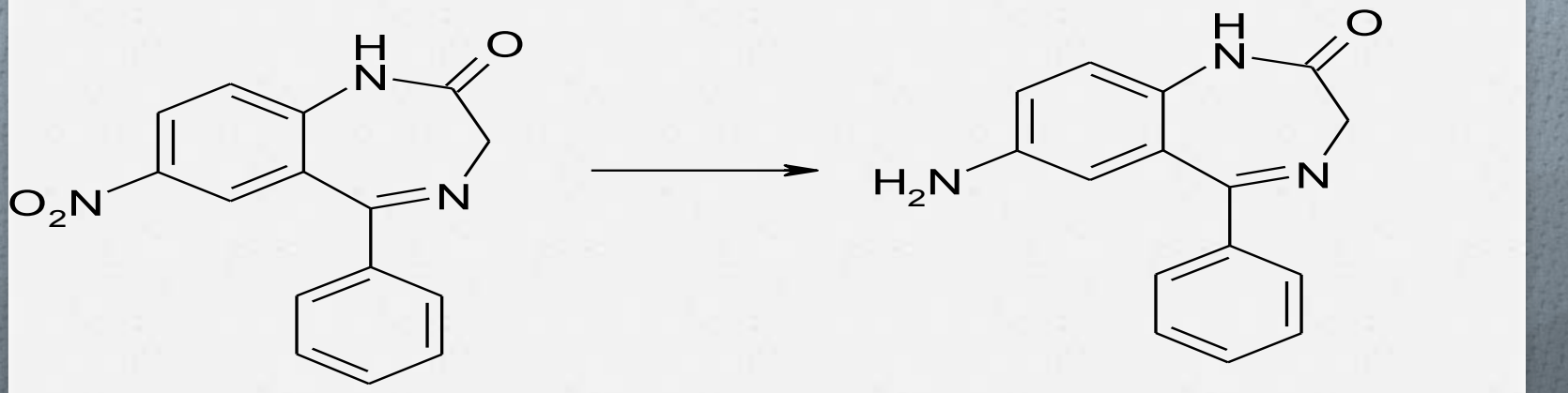
❖ *Reduction of N-compounds:*

- Reduction of nitro groups proceeds via formation of nitro so and hydroxyl amine intermediates to yield amines.

$$RNO_2 \longrightarrow R\text{-}N{=}O \longrightarrow R\text{-}NHOH \longrightarrow RNH_2$$

Nitro Nitroso Hydroxylamine Am

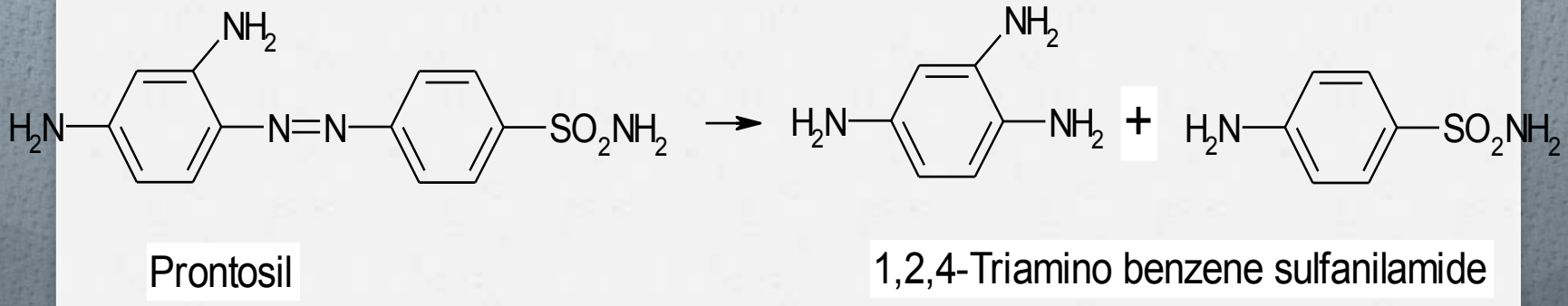
- ✓ For **E.g. Reduction of Nitrazepam.**



Nitrazepam 7-Amino metabolite.

- Reduction of azo compounds yield primary amines via formation of hydrazo intermediate which undergo cleavage at N-N bond.

- ✓ **E.g. Prontosil.**

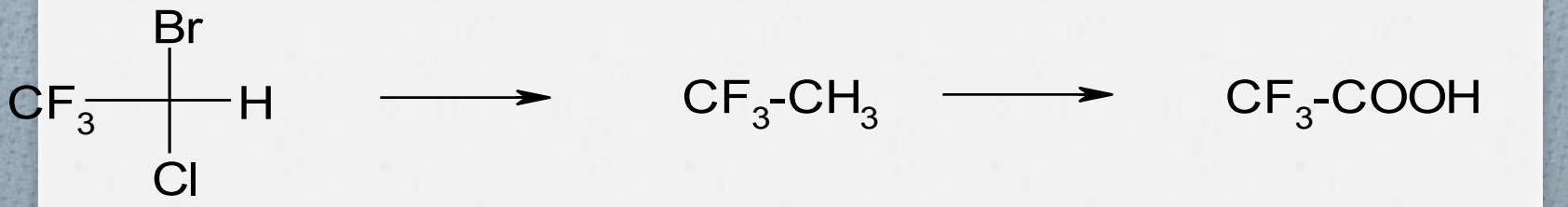


- It is reduced to active Sulfanilamide.

❖ *Miscellaneous reductive reactions:*

❑ Reductive Dehalogenation:

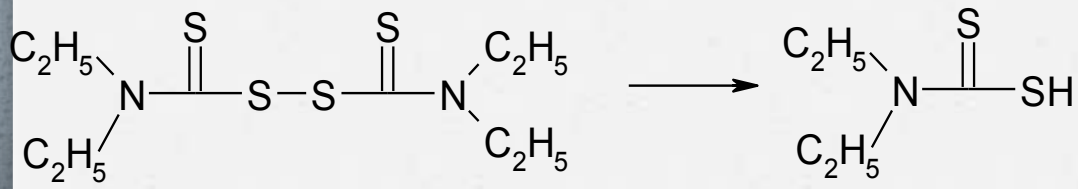
➢This reaction involves replacement of halogen attached to the carbon with the H-atom. **E.g. Halothane.**



Halothane 1,1,1- Trifluroethane Trifluroacetic a

❑ Reduction of sulfur containing functional groups:

E.g. Disulfuram



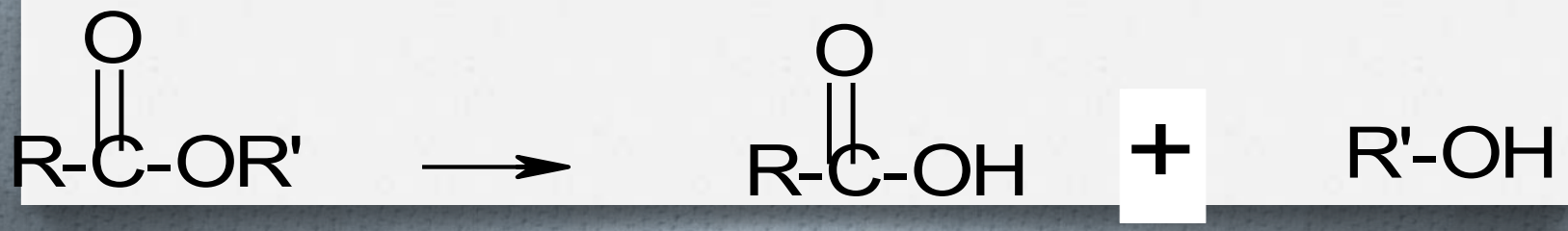
Dsulfiram Diethyldithiocarbamic acid

❖ *Hydrolytic reactions:*

1. The reaction does not involve change in the state of oxidation of substrate.
2. The reaction results in a large chemical chain in the substrate brought about by loss of relatively large fragments of the molecule.

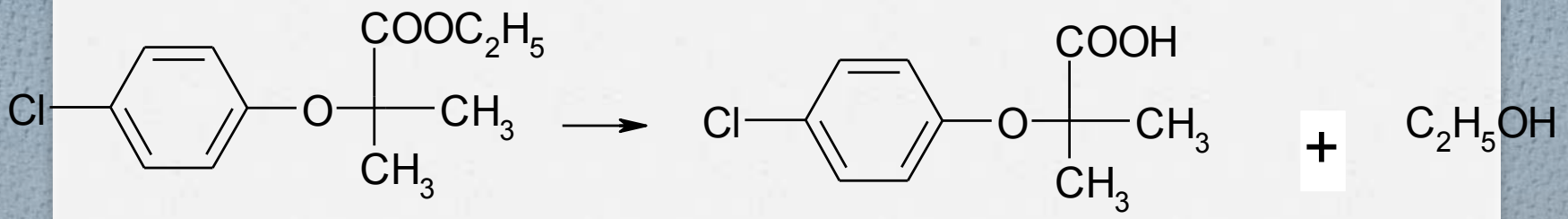
❑ Hydrolysis of esters and ethers:

➢Esters on hydrolyisis yield alcohol and carboxylic acid. The reaction is catalyzed by esterases.



❑ *Organic acid esters:*

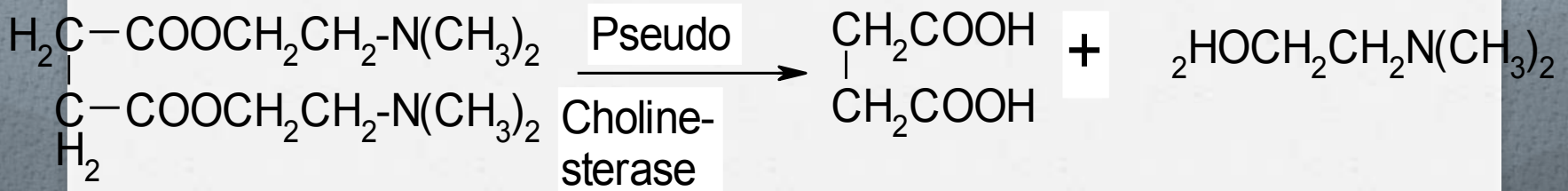
➢ Esters with a large acidic group : **E.g. Clofibrate**



Clofibrate — Free acid metan

➢ Esters with a large acidic and alcoholic group:

E.g. Succinylcholine

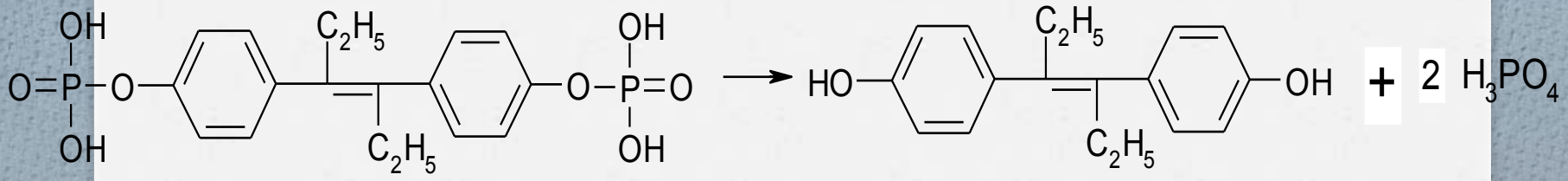


Suceinylcholine — succinic acid — choline

❖ *Inorganic acid esters:*

❑ Phosphates:

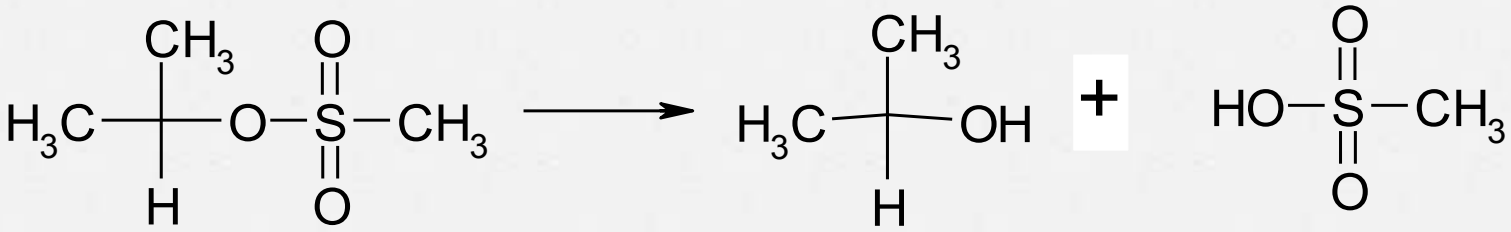
E.g. Stilbestrol diphosphate



Stilbestrol diphosphate stilbestrol

❑ Sulfates:

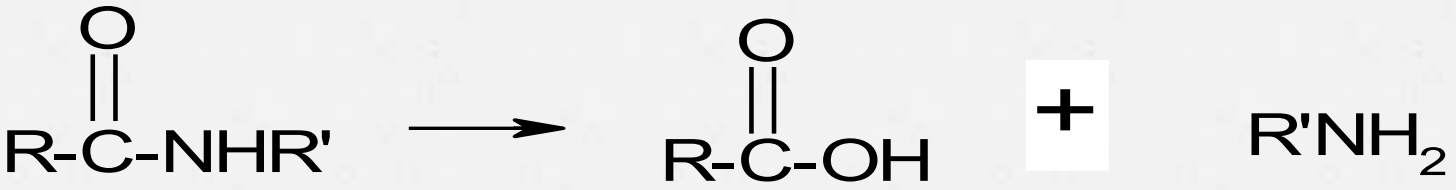
E.g. Isopropyl methanesulfonate



Isopropyl methnesulfonate isopropanol methanesulfonic ac

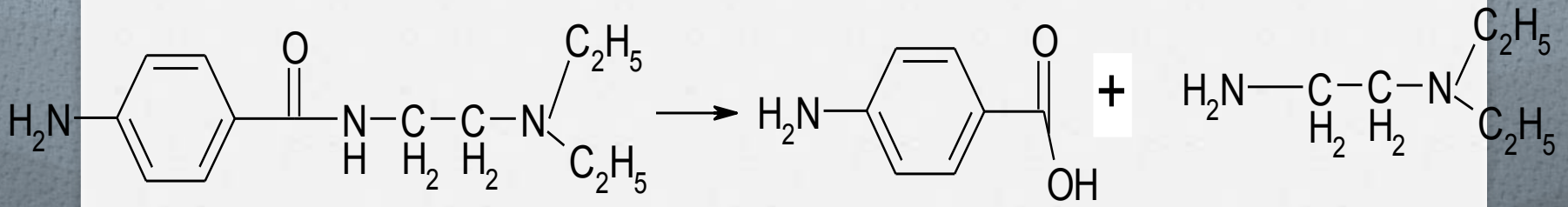
❖ *Hydrolysis of amides:*

➢ The reactions catalyzed by amides, involves C-N cleavage to yield carboxylic acid and amine.



❑ **primary amide with aliphatic substituent on N-atom:**

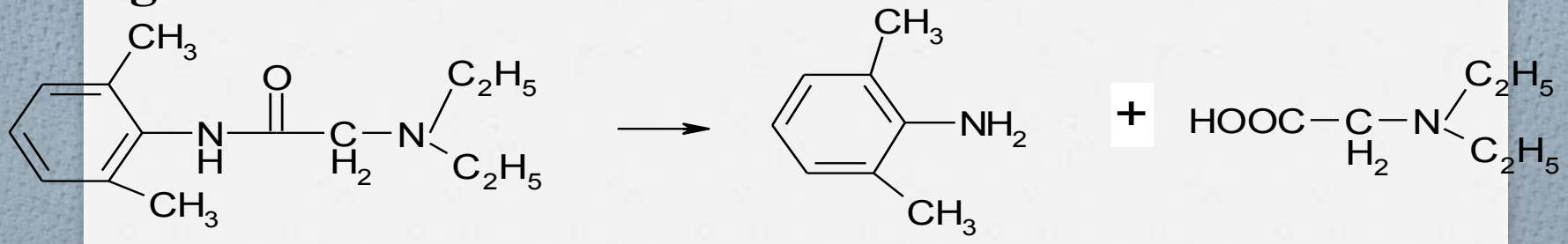
E.g. Procainamide



Procanamide PABA

❑ Secondary amide with aromatic Substituent on N-atom:

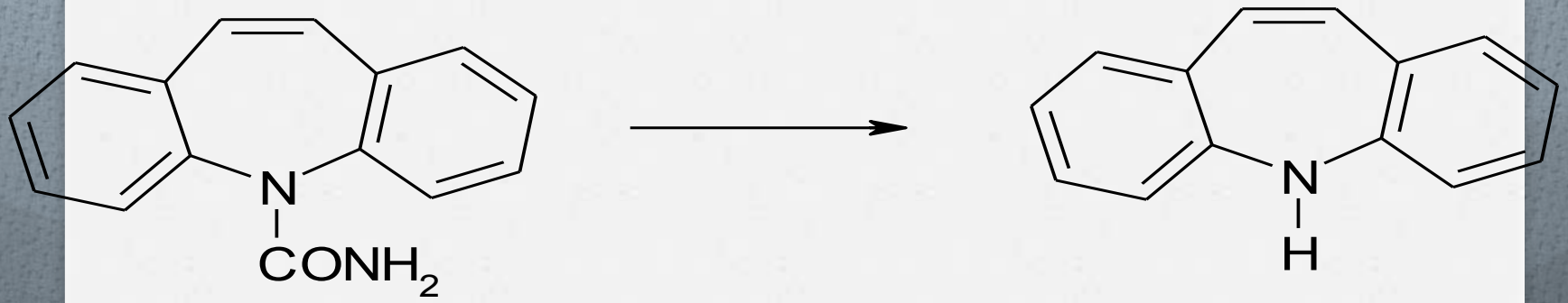
E.g. Lidocaine



Lidocaine 2,6 Xylidine N, N- Diethylglyc

❑ Tertiary amide:

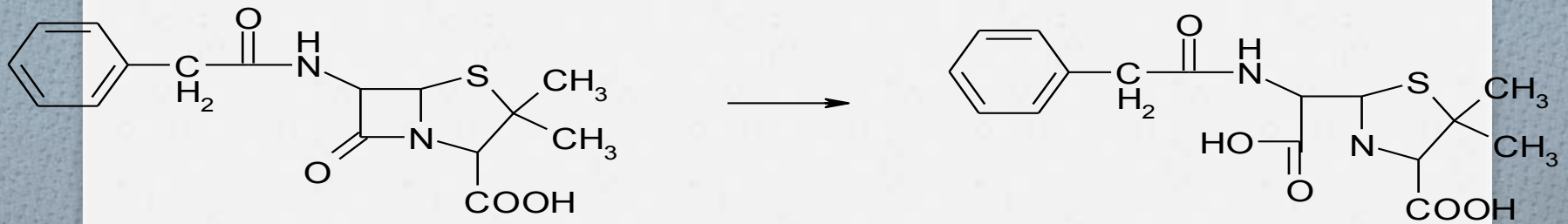
E.g. Carbamazepine



Carbamazepine Iminostilbene

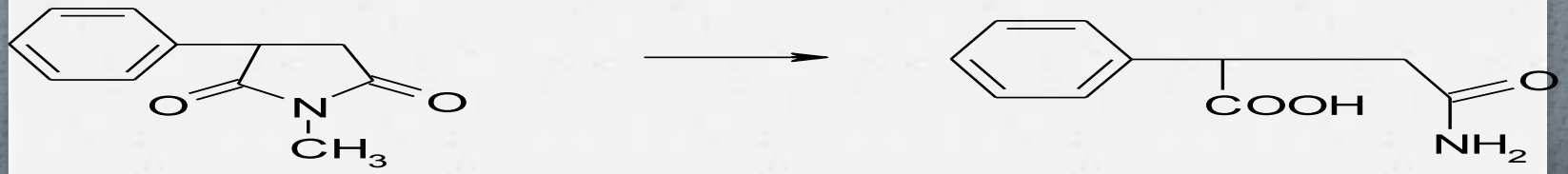
❖ *Hydrolytic cleavage of non aromatic heterocyclics:*

- **Four – membered lactams:** **E.g. Penicillins**



Penicillin G — Penicinoic acid metabolite

- **Five – member lactams:** **E.g. Succinimides**

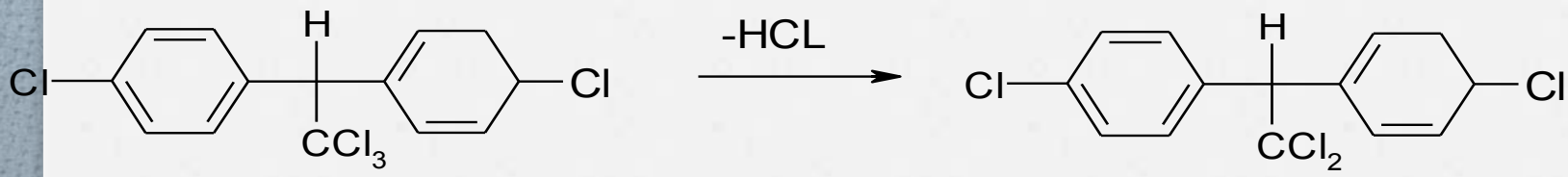


Phensuximide — Phenyl succinamic acid

❖ *Hydrolytic dehalogenation:*

➢Chlorine atoms attached to aliphatic carbons are dehalogenated easily.

✓ **E.g. Dichloro diphenyl trichloro ethane**



DDT DDE

❖ *Miscellaneous hydrolytic reactions:*

➢Include hydration of epoxides and arene oxides, hydrolysis of Sulfonylureas, Carbamates, Hydroxamates and alpha Glucuronide and sulfate conjugates

Phase 2 Reactions

Synthetic Conjugation

Phase II

- Phase II - combines functional group of compound with endogenous substance

E.g. Glucuronicacid, Sulfuric acid, Amino Acid, Acetyl.

- Products usually very hydrophilic
- The final compounds have a larger molecular weight.

Enzymes

- Glucuronosyl Transferases
- Sulfotransferases (ST)
- Acetyltransferase
- Methylases

How We Get To Phase 2

- Most of the drugs do not become polar upon phase 1 reactions.
- The Body is left with a plan to further metabolize the Drugs
- ***Goal of Phase 2 :*** Make substances more soluble that couldn't be done in the Phase 1 reactions.

Synthetic Reactions / Phase II

- These reactions usually involves covalent attachments of small polar endogenous molecules such as Glucoronic acid, Sulfate, Glycine to either unchanged drugs or Phase I product having suitable functional groups as COOH,-OH,-NH_2,- SH.
- Thus is called as Conjugation reactions.
- Since the product formed is having high molecular weight so called as synthetic reactions.
- The product formed is hydrophilic in nature with total loss of pharmacologic activity so called as a true detoxification reaction

Phase II

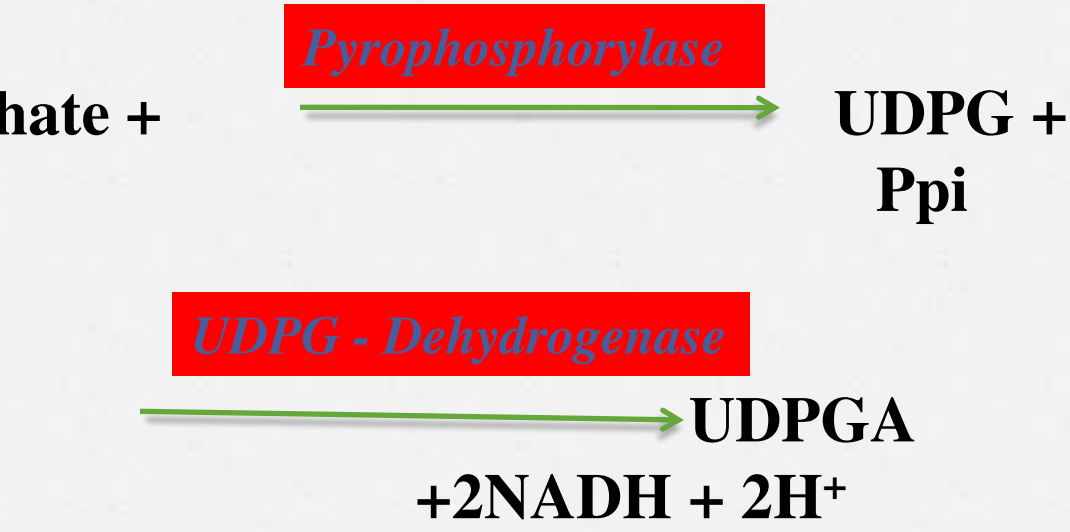
- Glucuronide Conjugation
- Methylation
- Acetylation
- Sulfate Conjugation
- Conjugation With Alpha Amino Acids
- Glutathione Conjugation
- Glycine Conjugation
- Cyanide Conjugation

Glucuronide Conjugation

- Very important Synthetic reactions carried out by Uredine Di Phosphate Glucuronosyl Transferase.
- Hydroxyl and Carboxylic acid groups are easily combined with Glucuronic acid.

✓ *Glucuronide formation occurs in 2 steps:-*

1. Synthesis of an activated coenzyme uridine-5'- diphospho -alpha-D- Glucuronic acid (UDPGA) from UDP- glucose (UDPG).



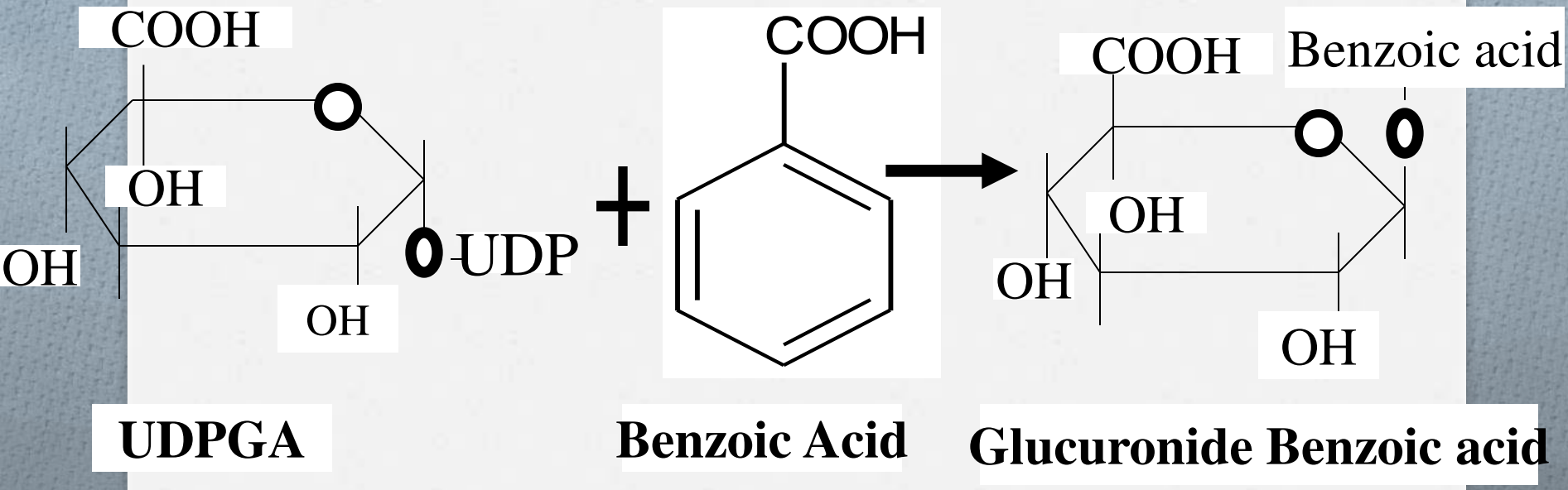
2. Transfer of the glucuronyl moiety from UDPGA to the substrate RXH in presence of enzyme UDP-glucuronyl transferase to form the conjugate.

UDPGA + RXH → **RX**

Glucuronic Acid +UDP

Where,

X = O, COO, NH or S



UDPGA **Benzoic Acid** **Glucuronide Benzoic acid**

Ex.

Chloramphenicol, Morphine, Salicylic Acid, Paracetamol

Methylation

- Common, minor pathway.
- Methyltransferases
  - -CH_3 transfer to *O*, *N*, *S*, *C*

1. Synthesis of an activated coenzyme S- adenosyl methionine(SAM), the donor of methyl group, from L-methionine and ATP.

L – Methionine + ATP —*Methionine Adenosyl Transferase*→ **SAM + PPi + Pi**

2. Transfer of the methyl group from SAM to the substrate in presence of nonmicrosomal enzyme methyl transferase.

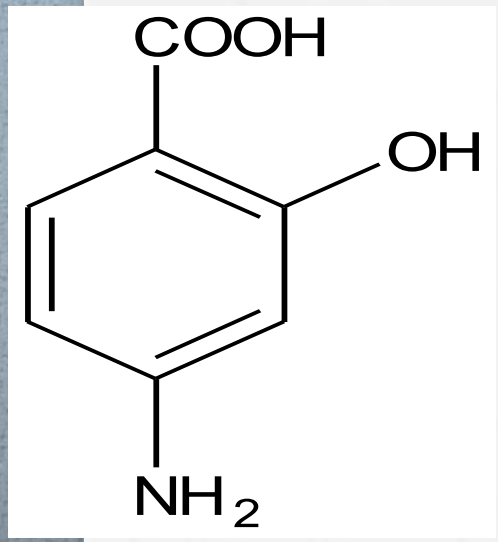
RXH + SAM —*Methyl Transferase*→ **RX-CH3 + S – Adenosyl Homocysteine**

Ex.

Morphine, Nicotine, Histamine

Acetylation reaction

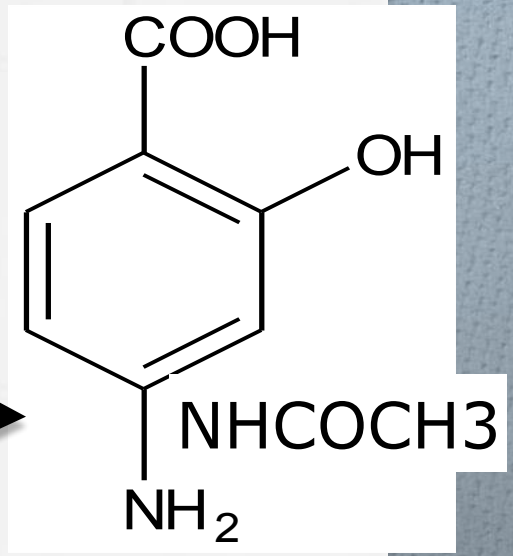
- Major route of biotransformation for aromatic amines, hydrazine.
- Generally decreases water solubility
- Enzyme: - N- Acetyltransferase (NAT)



Paraaminosalicyclic Acid

+ CH_3COS-COA

Acetyl Co enzyme



N- Acetylated PAS

Ex.

Histamine, PAS, PABA

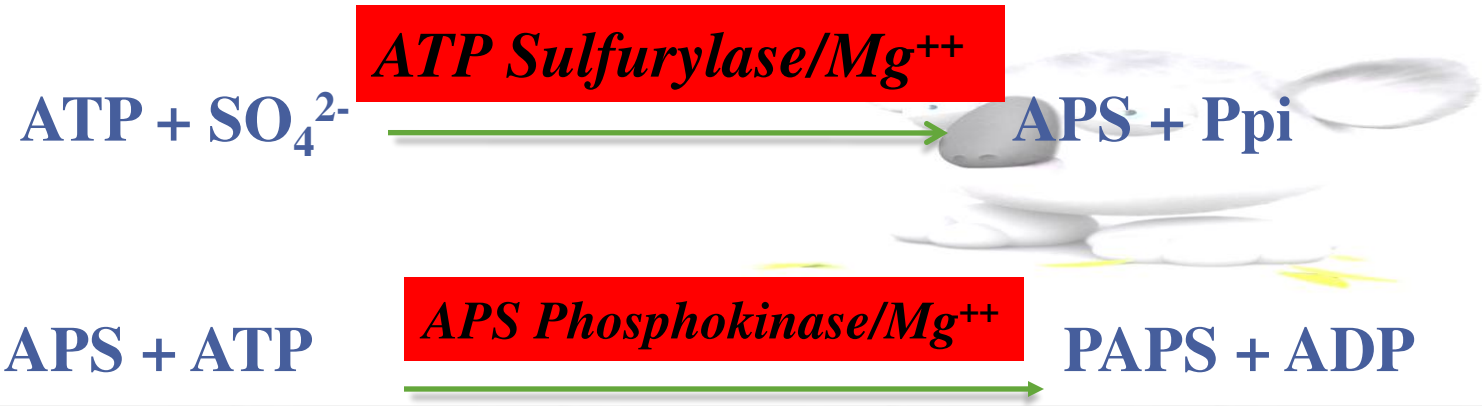
Sulfation

- Sulfotransferases are widely-distributed enzymes
- Cofactor is 3'-phosphoadenosine-5'-phosphosulfate (PAPS)
- Produce highly water-soluble sulfate esters, eliminated in urine, bile

- R – OH R – O – SO_3

1. Synthesis of an activated coenzyme 3’-phosphoadenosine-5’-phosphosulfate (PAPS) which acts as a donor of sulfate to the substrate.

✓ This also occurs in two steps- an initial interaction between the sulfate and the adenosine triphosphate (ATP) to yield adenosine-5’-phosphosulfate (APS) followed by activation of latter to PAPS.



2. Transfer of sulfate group from PAPS to the substrate RXH in presence of enzyme Sulfotransferase and subsequent liberation of 3'- phosphoadenosine-5'-phosphate(PAP).

PAPS + RxH —***Sulfotransferase***→ $Rx\text{-}SO_3$ + PAP

X= O,NH

Examples of compounds undergoing sulfation are:

- ✓ Phenol — Paracetamol , Salbutamol
- ✓ Alcohols — Aliphatics C-1 to C-5
- ✓ Arylamines — Aniline

Conjugation With Alpha Amino Acids

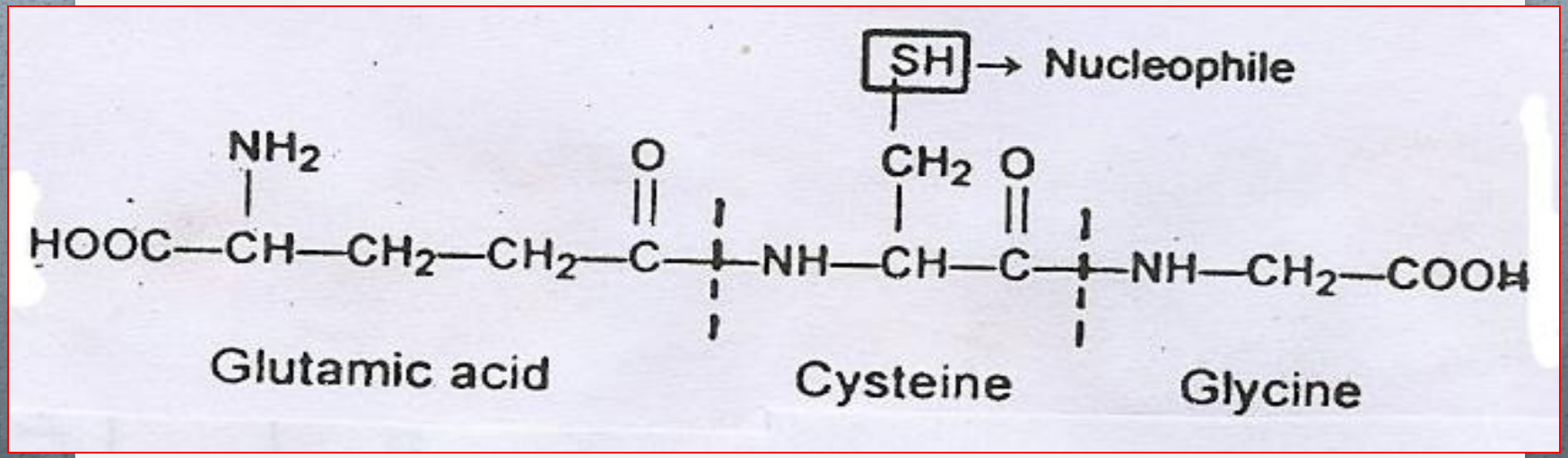
- Alternative to glucuronidation
- Two principle pathways
  - -COOH group of substrate conjugated with -NH_2 of Glycine, Serine, Glutamine, requiring CoA activation
    - ***E.g.*** conjugation of benzoic acid with Glycine to form Hippuric acid
  - Aromatic -NH_2 or NHOH conjugated with -COOH of Serine, Proline, requiring ATP activation

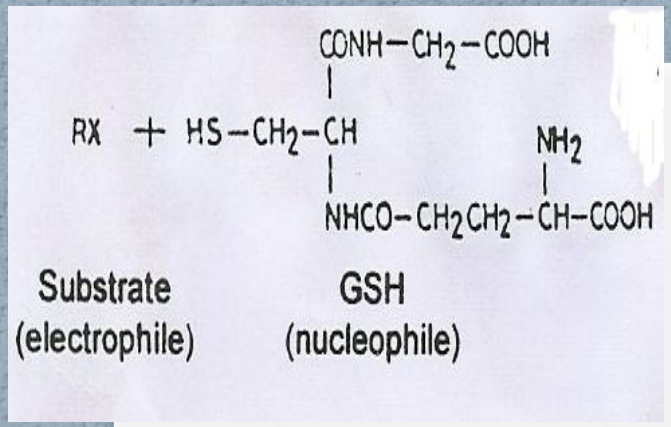
1. Activation of carboxylic acid drug substrate with ATP and coenzyme A (CoA) to form an acyl CoA intermediate. Thus, the reaction is a contrast of glucuronidation and sulfation where the donor coenzyme is activated and not the substrate.

2. Acylation of the alpha- amino acid by the acyl CoA in presence of enzyme N-acyl transferase.

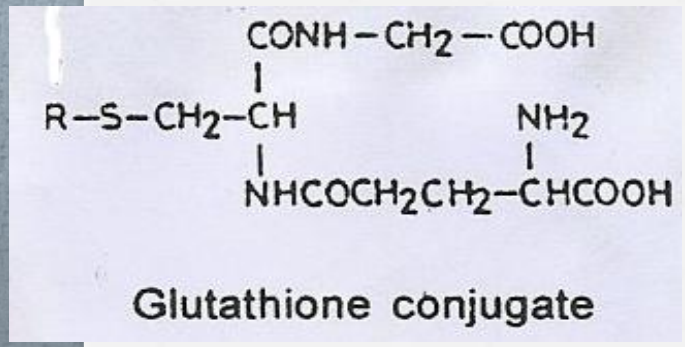
Glutathione Conjugation

- Glutathione-*S*-transferase catalyzes conjugation with glutathione
- Glutathione is tripeptide of Glycine, Cysteine, Glutamic acid



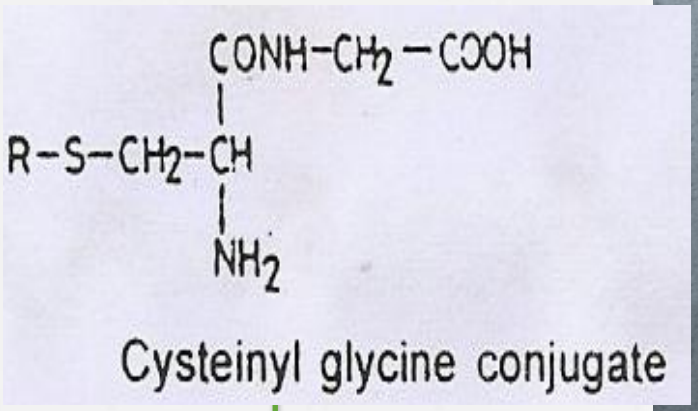


Glutathione-S-transferase



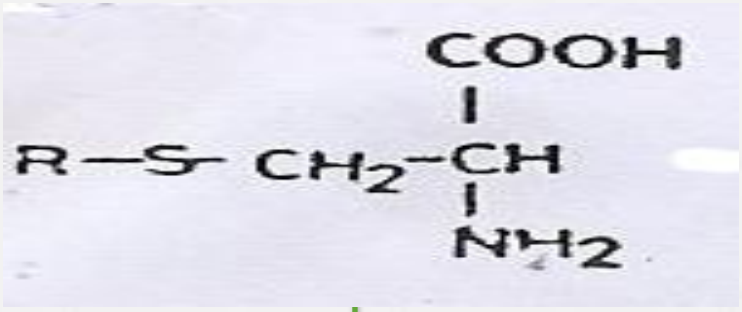
Glutamine

γ-Glutamyl transferase

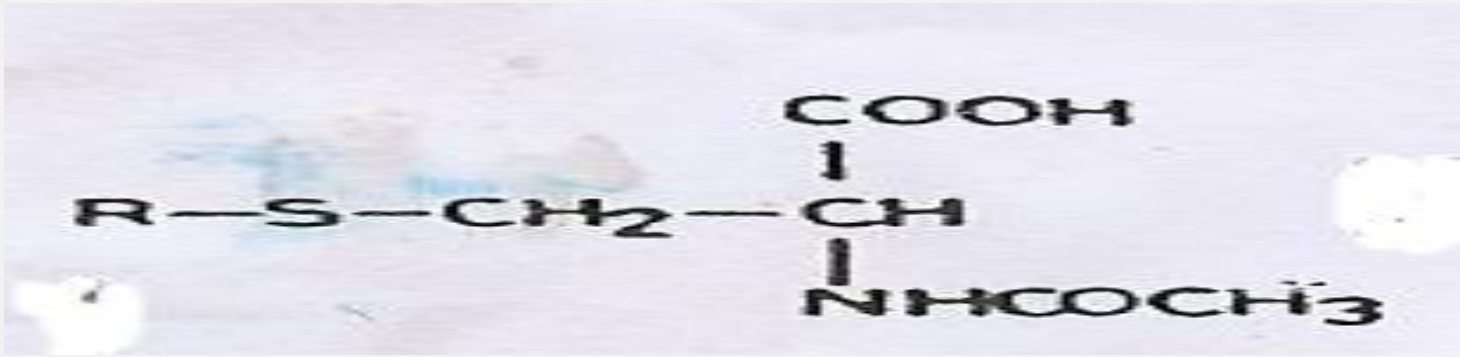


Glycine

Cysteinyl glycinase



N- acetylase



Mercapturic Acid Derivative

Glycine Conjugation

- ✓ Salicylates and other drugs having carboxylic acid group are conjugated with Glycine.
- ✓ Not a major pathway of metabolism

Cyanide Conjugation

- ✓ Conjugation of cyanide ion involves transfer of sulfur atom from thiosulfate to the cyanide ion in presence of enzyme rhodanese to form inactive thiocyanate.

Biotransformation-Conclusion

- Change the Xenobiotics to a form that can be eliminated from the body
- Change the Xenobiotics to a less biologically active form
- Bioactivation to more toxic forms can also occur
- Synthetic Phase II reactions are carried out by other enzymes.

❖ *Factor affection of Biotransformation of drug:*

➢The Therapeutic efficacy, Toxicity and Biological half life of drug depends on metabolic rate and the factor that influence metabolic rate are:

1) **Physicochemical property of drug.**

2) **chemical factors:**

- ✓ a. Induction of drug metabolizing enzyme.
- ✓ b. Inhibition of drug metabolizing enzyme
- ✓ c. Environmental chemicals.

3) **Biological factors.**

- ✓ A. Species differences.
- ✓ B. Strain differences.
- ✓ C. Sex differences.

- D. **Age.**
- E. **Diet.**
- F. **Altered pharmacologic factors:**

✓ i Pregnancy.
✓ ii Hormonal imbalance.
✓ iii Disease state.

- G. **Temporal factors:**
- I Circadian rhythm.

References

- Biopharmaceutics & Pharmacokinetics by D.M. Brahmankar, S. B. Jaswal, Vallabh Prakashan, Pg-111-158.
- Biopharmaceutics & Pharmacokinetics by Milo Gibaldi, 4th edition, Pg.no. 203.
- Text book of Biopharmaceutics & pharmacokinetics, Dr.Sobha Rani R. Hiremath, Prism Books Pvt Ltd, Bangalore, 2000 Pg.no. 157-166.
- www.google.com
- www.vadlo.com

Thank you

BASIC PHARMACOKINETICS
&
COMPARTMENT MODELLING

Dosage Regimen:

The frequency of administration of a drug in a particular dose is called as **dosage regimen**.

Pharmacokinetics:

Pharmacokinetics *is defined as the kinetics of drug absorption, distribution, metabolism and excretion (KADME) and their relationship with the pharmacological, therapeutic or toxicological response in man and animals*. There are two aspects of pharmacokinetic studies –

Theoretical aspect – which involves development of pharmacokinetic models to predict drug disposition after its administration. Statistical methods are commonly applied to interpret data and assess various parameters.

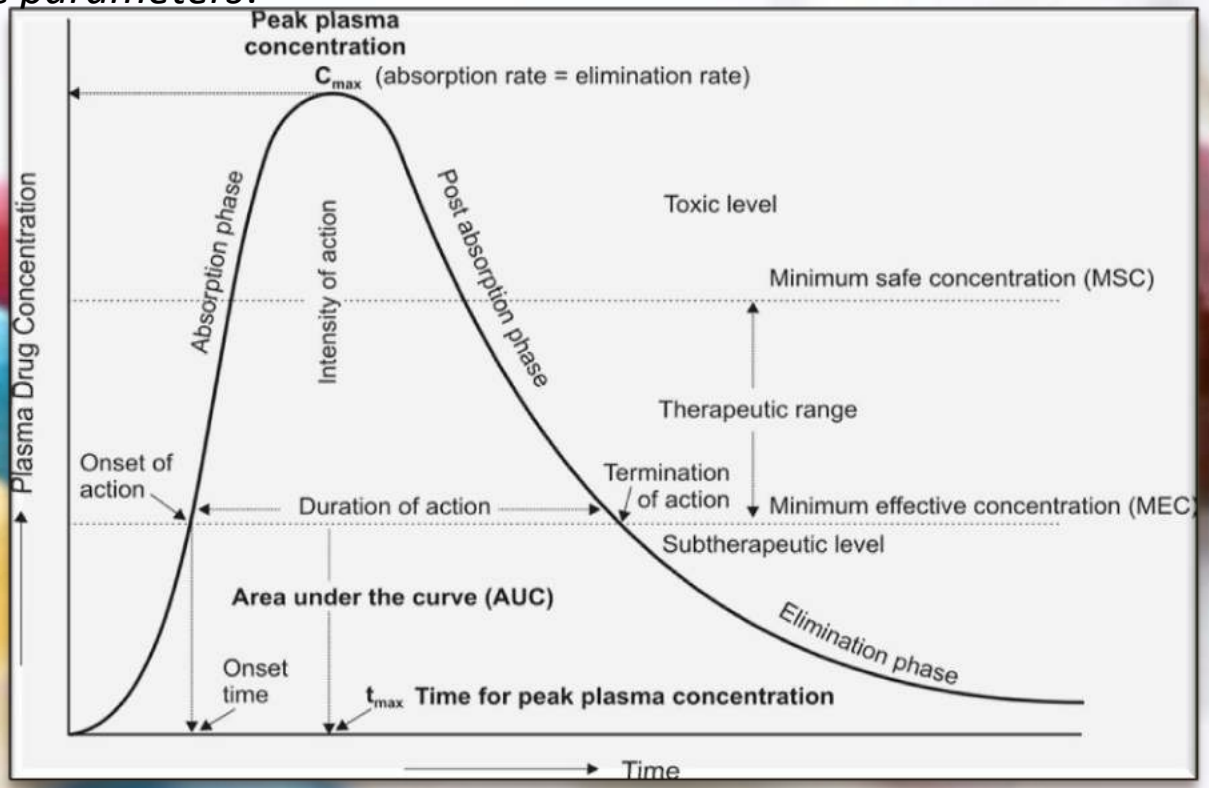
Experimental aspect – which involves development of biological sampling techniques, analytical methods for measurement of drug (and metabolites) concentration in biological samples and data collection and evaluation.

Plasma Drug Concentration-Time Profile

A direct relationship exists between the concentration of drug at the biophase (site of action) and the concentration of drug in plasma. Two categories of parameters can be evaluated from a plasma concentration time profile –

Pharmacokinetic parameters, and

Pharmacodynamic parameters.



Pharmacokinetic Parameters

1. **Peak Plasma Concentration (Cmax)**
   The peak plasma level depends upon –
   The administered dose
   Rate of absorption, and
   Rate of elimination.
2. **Time of Peak Concentration (tmax)**
3. **Area Under the Curve (AUC)**

Pharmacodynamic Parameters

1. **Minimum Effective Concentration (MEC)**
2. **Maximum Safe Concentration (MSC)**
3. **Onset of Action**
4. **Onset Time**
5. **Duration of Action**
6. **Intensity of Action**
7. **Therapeutic Range**
8. **Therapeutic Index**

Rate, Rate Constants and Orders of Reactions

Rate: *The velocity with which a reaction or a process occurs is called as its* **rate**.

Order of reaction: *The manner in which the concentration of drug (or reactants) influences the rate of reaction or process is called as the* **order of reaction** or **order of process**.

Consider the following chemical reaction:

Drug A $\longrightarrow$ Drug B

The rate of forward reaction is expressed as –

$-dA/dt$

Negative sign indicates that the concentration of drug A decreases with time t. As the reaction proceeds, the concentration of drug B increases and the rate of reaction can also be expressed as: dB/dt

$$\mathbf{dC/dt = -KC^n}$$

K = rate constant

n = order of reaction

Zero-Order Kinetics (Constant Rate Processes)

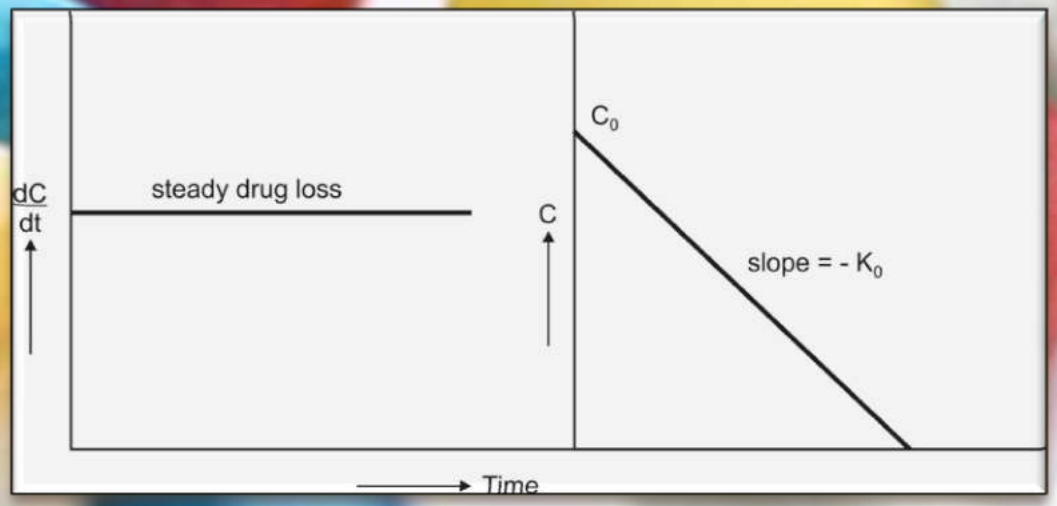
If n = 0, equation becomes:

$$dC/dt = -K_o C^o$$

where Ko = zero-order rate constant (in mg/min)

Zero-order process *can be defined as the one whose rate is independent of the concentration of drug undergoing reaction i.e. the rate of reaction cannot be increased further by increasing the concentration of reactants*.

Finally $C = C_o - K_o t$



Zero-Order Half-Life

Half-life (t½) or **half-time** *is defined as the time period required for the concentration of drug to decrease by one-half*.

$$t_{1/2} = C_o / 2 K_o$$

Examples of zero-order processes are –

1. Metabolism/protein-drug binding/enzyme or carrier-mediated transport under saturated conditions. The rate of metabolism, binding or transport of drug remains constant as long as its concentration is in excess of saturating concentration.
2. Administration of a drug as a constant rate i.v. infusion.
3. Controlled drug delivery such as that from i.m. implants or osmotic pumps.

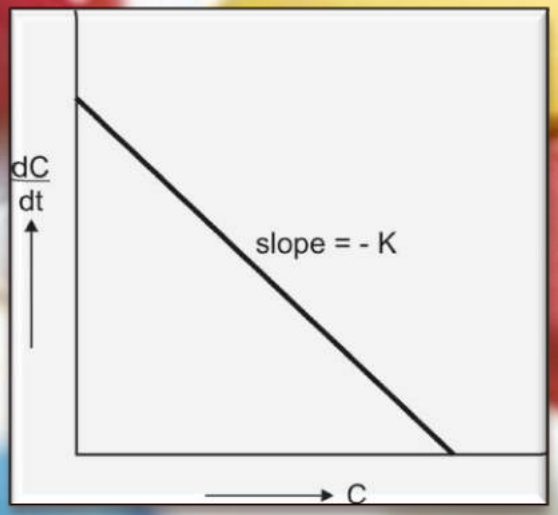
First-Order Kinetics (Linear Kinetics)

If n = 1, equation becomes:

$$dC/dt = - K C$$

where K = first-order rate constant (in time–1 or per hour)

first-order process *is the one whose rate is directly proportional to the concentration of drug undergoing reaction i.e. greater the concentration, faster the reaction*. It is because of such proportionality between rate of reaction and the concentration of drug that a first-order process is said to follow **linear kinetics.**

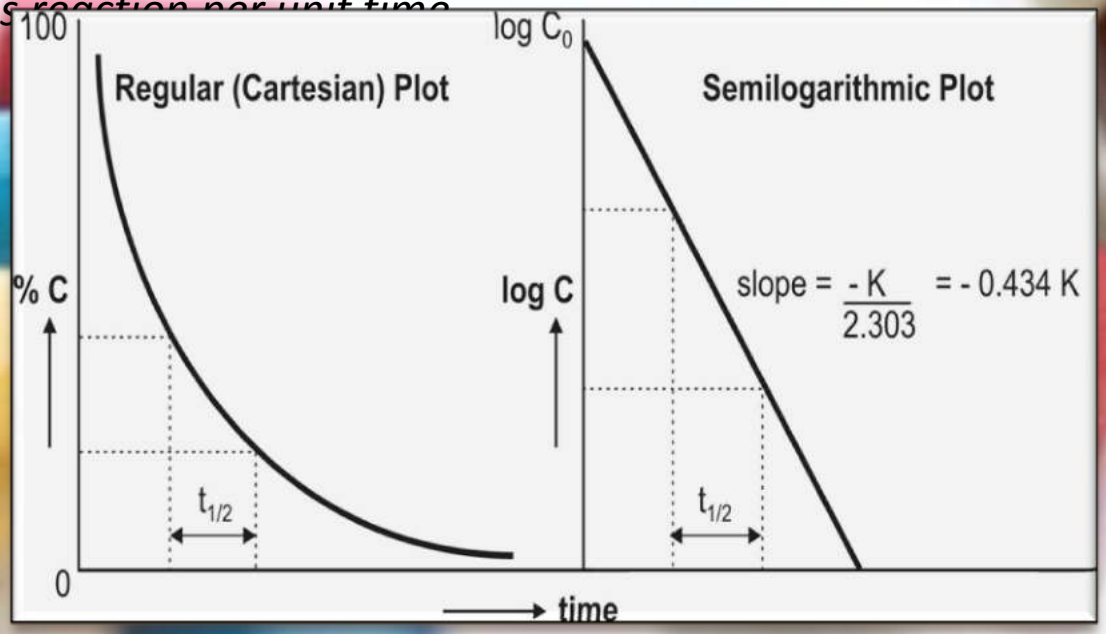


$$\ln C = \ln C_o - K t$$

$$C = C_o - e^{-Kt}$$

$$\log C = \log Co - Kt/2.303$$

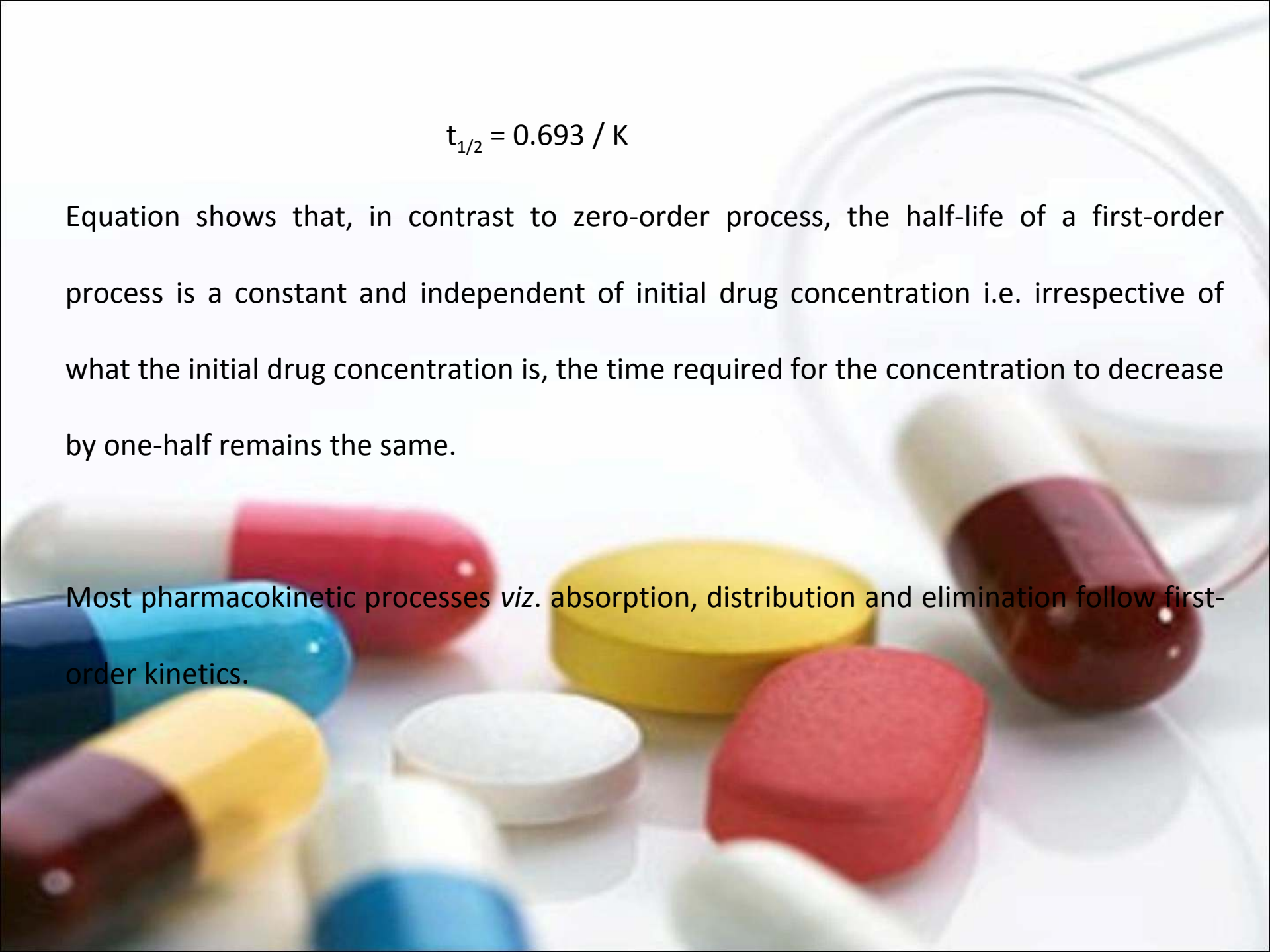
The first-order process is also called as **monoexponential rate process**. Thus, a first-order process is characterized by **logarithmic** or **exponential kinetics** i.e. *a constant fraction of drug undergoes reaction per unit time*



$$t_{1/2} = 0.693 / K$$

Equation shows that, in contrast to zero-order process, the half-life of a first-order process is a constant and independent of initial drug concentration i.e. irrespective of what the initial drug concentration is, the time required for the concentration to decrease by one-half remains the same.

Most pharmacokinetic processes *viz*. absorption, distribution and elimination follow first-order kinetics.



Mixed-Order Kinetics (Nonlinear Kinetics)

A *mixture* of both first-order and zero-order kinetics is said to follow **mixed-order kinetics**. Since deviations from an originally linear pharmacokinetic profile are observed, the rate process of such a drug is called as **nonlinear kinetics**. Mixed order kinetics is also termed as **dose-dependent kinetics** as it is observed at increased or multiple doses of some drugs.

Nonlinearities in pharmacokinetics have been observed in –

Drug absorption (e.g. vitamin C)

Drug distribution (e.g. naproxen), and

Drug elimination (e.g. riboflavin).

The phenomena is seen when a particular pharmacokinetic process involves presence of carriers or enzymes which are substrate specific and have definite capacities and can get saturated at high drug concentrations (i.e. capacity-limited). The kinetics of such capacity-limited processes can be described by the **Michaelis-Menten kinetics**.

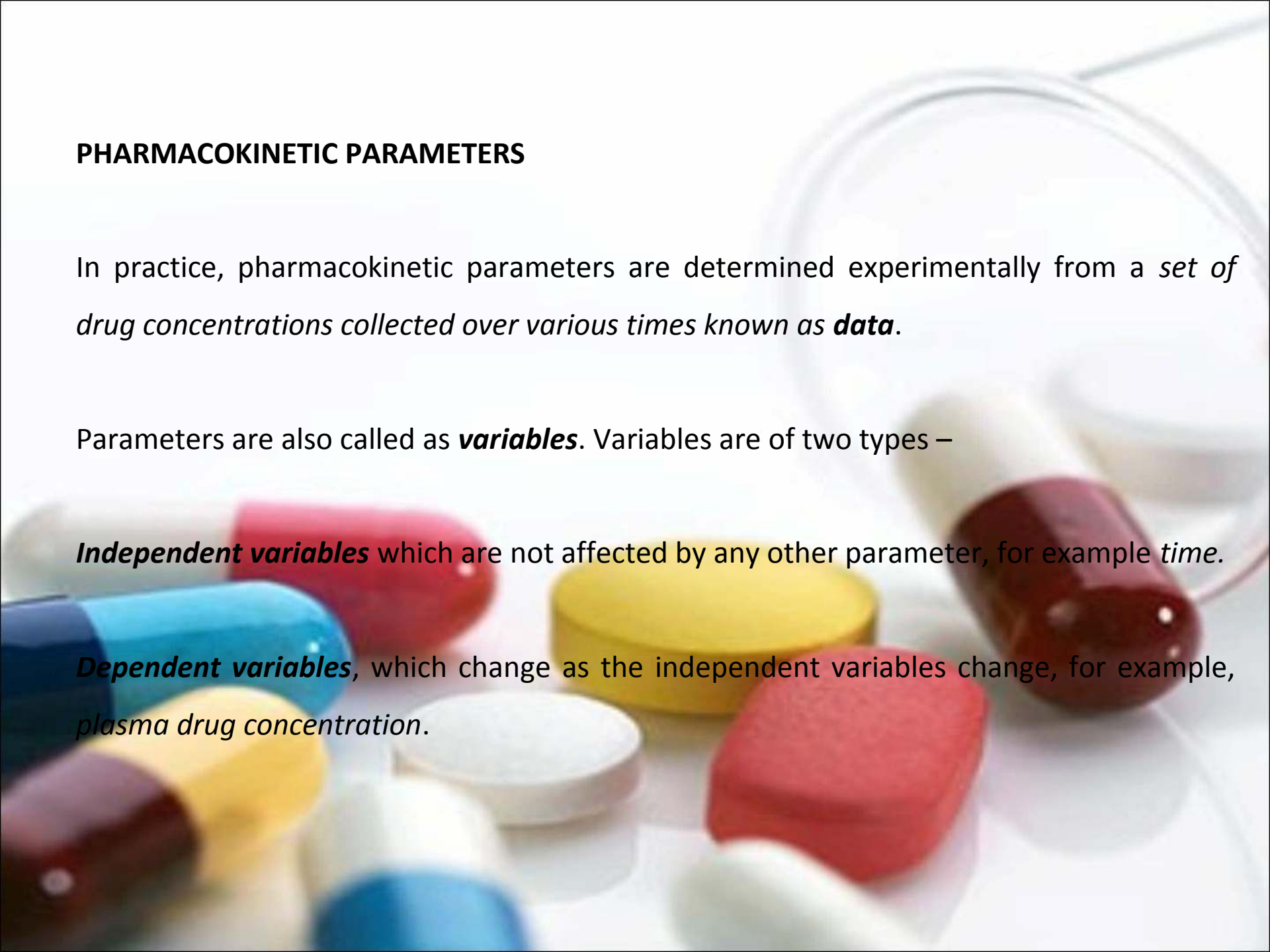
PHARMACOKINETIC PARAMETERS

In practice, pharmacokinetic parameters are determined experimentally from a *set of drug concentrations collected over various times known as* ***data***.

Parameters are also called as ***variables***. Variables are of two types –

Independent variables which are not affected by any other parameter, for example *time.*

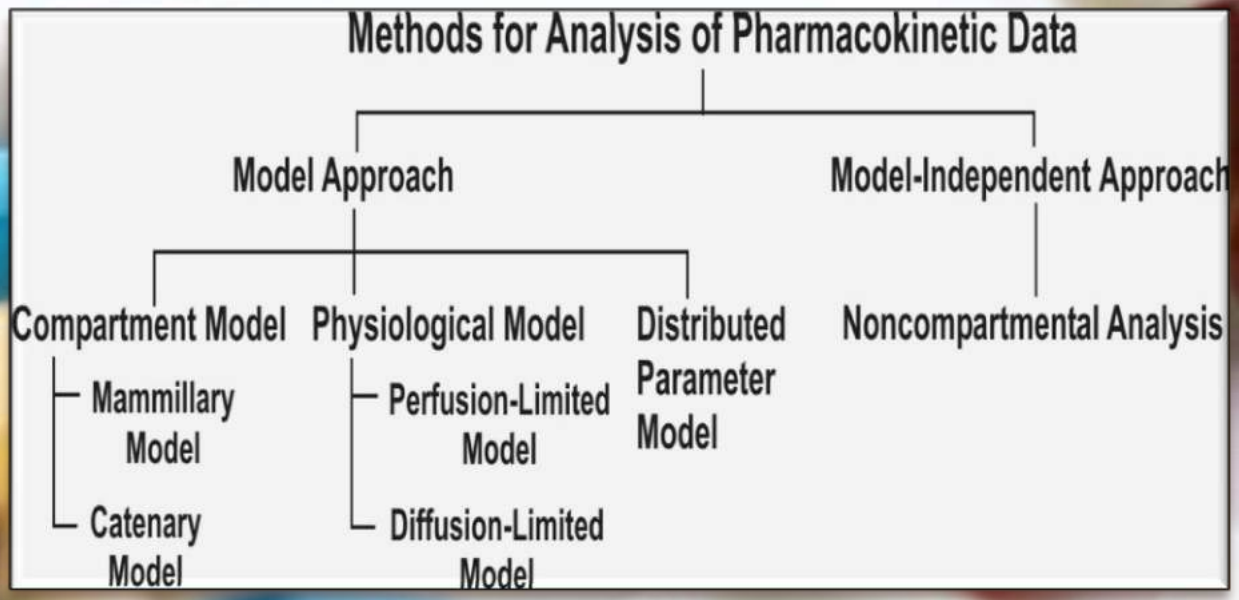
Dependent variables, which change as the independent variables change, for example, *plasma drug concentration*.



PHARMACOKINETIC MODELS

Drug movement within the body is a complex process. The major objective is therefore to develop a generalized and simple approach to describe, analyse and interpret the data obtained during *in vivo* drug disposition studies. The two major approaches in the quantitative study of various kinetic processes of drug disposition in the body are

1. Model approach, and
2. Model-independent approach (also called as non-compartmental analysis).



Pharmacokinetic Model Approach

*A **model** is a hypothesis that employs mathematical terms to concisely describe quantitative relationships*. **Pharmacokinetic models** provide concise means of expressing mathematically or quantitatively, the time course of drug(s) throughout the body and compute meaningful **pharmacokinetic parameters**.

Applications of Pharmacokinetic Models –

1. Characterizing the behaviour of drugs in patients.
2. Predicting the concentration of drug in various body fluids with any dosage regimen.
3. Predicting the multiple-dose concentration curves from single dose experiments.
4. Calculating the optimum dosage regimen for individual patients.
5. Evaluating the risk of toxicity with certain dosage regimens.
6. Correlating plasma drug concentration with pharmacological response.
7. Evaluating the bioequivalence between different formulations of the same drug.
8. Estimating the possibility of drug and/or metabolite(s) accumulation in the body.
9. Determining the influence of altered physiology/disease state on drug ADME.
10. Explaining drug interactions.

Types of Pharmacokinetic Models

Pharmacokinetic models are of three different types –

Compartment models – are also called as ***empirical models***, and

Physiological models – are *realistic models*.

Distributed parameter models – are also *realistic models*.

Compartment Models

Compartmental analysis is the traditional and most commonly used approach to pharmacokinetic characterization of a drug. These models simply interpolate the experimental data and allow an *empirical formula* to estimate the drug concentration with time.

Depending upon whether the compartments are arranged parallel or in a series, compartment models are divided into two categories —

1. Mammillary model
2. Catenary model.

Since compartments are hypothetical in nature, compartment models are based on certain ***assumptions*** –

1. The body is represented as a series of compartments arranged either in series or parallel to each other, that communicate reversibly with each other.

2. Each compartment is not a real physiologic or anatomic region but a fictitious or virtual one and considered as a tissue or group of tissues that have similar drug distribution characteristics (similar blood flow and affinity). This assumption is necessary because if every organ, tissue or body fluid that can get equilibrated with the drug is considered as a separate compartment, the body will comprise of infinite number of compartments and mathematical description of such a model will be too complex.

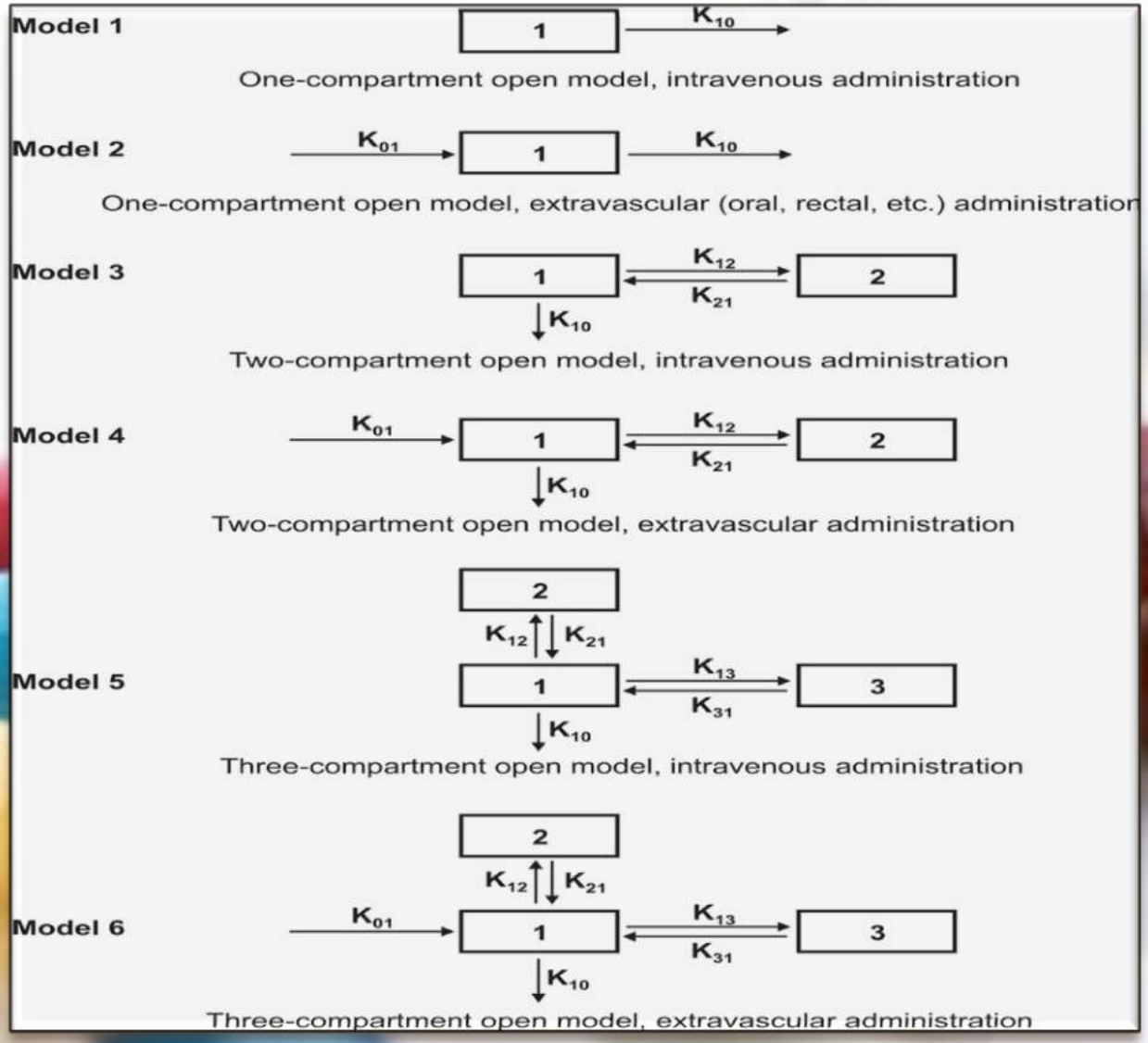
3. Within each compartment, the drug is considered to be rapidly and uniformly distributed i.e. the compartment is *well-stirred*.

4. The rate of drug movement between compartments (i.e. entry and exit) is described by first-order kinetics.

5. Rate constants are used to represent rate of entry into and exit from the compartment.

Mammillary Model

This model is the most common compartment model used in pharmacokinetics.



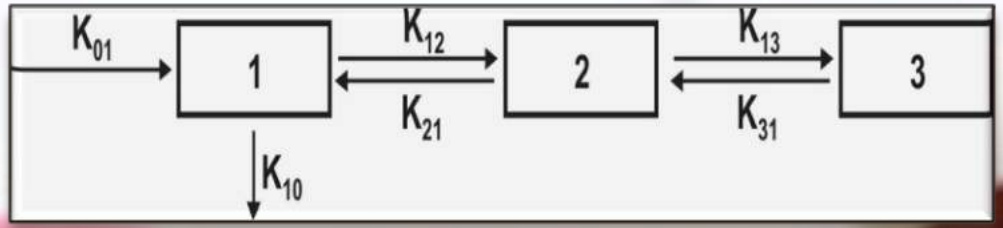
The number of rate constants which will appear in a particular compartment model is given by R.

For intravenous administration, $R = 2n - 1$

For extravascular administration, $R = 2n$

where n = number of compartments.

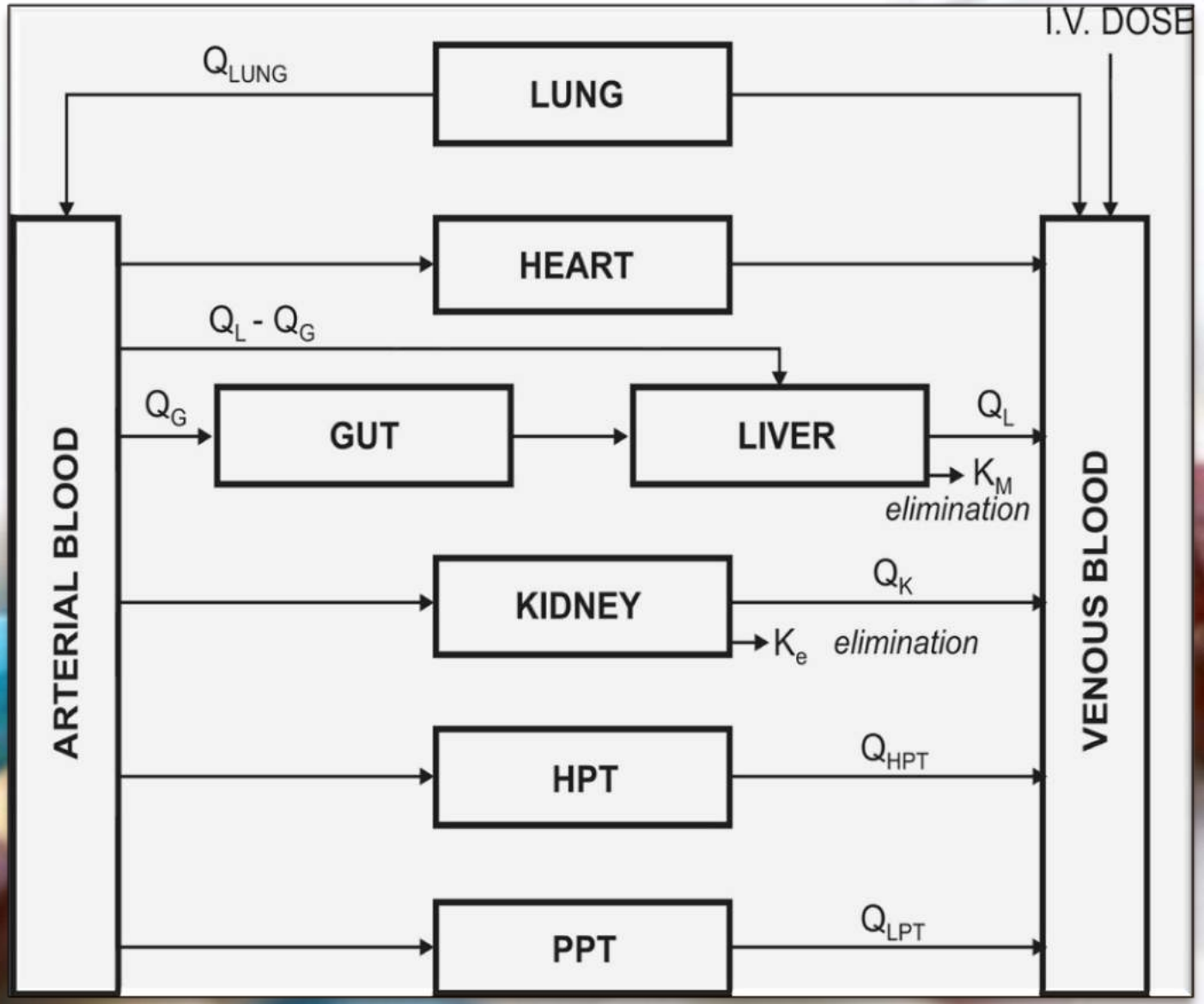
Catenary Model



Physiological Models

These models are also known as *physiologically-based pharmacokinetic models* (***PB-PK models***)

They are drawn on the basis of known anatomic and physiological data and thus present a more realistic picture of drug disposition in various organs and tissues. The number of compartments to be included in the model depends upon the disposition characteristics of the drug. Organs or tissues such as bones that have no drug penetration are excluded.


I.V. DOSE
Q_{LUNG}
LUNG
HEART
$Q_L - Q_G$
Q_G
GUT
LIVER
Q_L
K_M
elimination
ARTERIAL BLOOD
VENOUS BLOOD
KIDNEY
Q_K
K_e
elimination
HPT
Q_{HPT}
PPT
Q_{LPT}

The physiological models are further categorized into two types –

Blood flow rate-limited models – These models are more popular and commonly used than the second type, and are based on the assumption that the drug movement within a body region is much more rapid than its rate of delivery to that region by the perfusing blood. These models are therefore also called as ***perfusion rate-limited models***. This assumption is however applicable only to the highly membrane permeable drugs i.e. low molecular weight, poorly ionised and highly lipophilic drugs, for example, thiopental, lidocaine, etc.

Membrane permeation rate-limited models – These models are more complex and applicable to highly polar, ionised and charged drugs, in which case the cell membrane acts as a barrier for the drug that gradually permeates by diffusion. These models are therefore also called as ***diffusion-limited models***. Owing to the time lag in equilibration between the blood and the tissue, equations for these models are very complicated.

Noncompartmental Analysis

The ***noncompartmental analysis***, also called as the **model-independent method**, does not require the assumption of specific compartment model. This method is, however, *based on the assumption that the drugs or metabolites follow linear kinetics*, and on this basis, this technique can be applied to any compartment model.

The noncompartmental approach, based on the **statistical moments theory**, involves collection of experimental data following a single dose of drug. If one considers the time course of drug concentration in plasma as a statistical distribution curve, then:

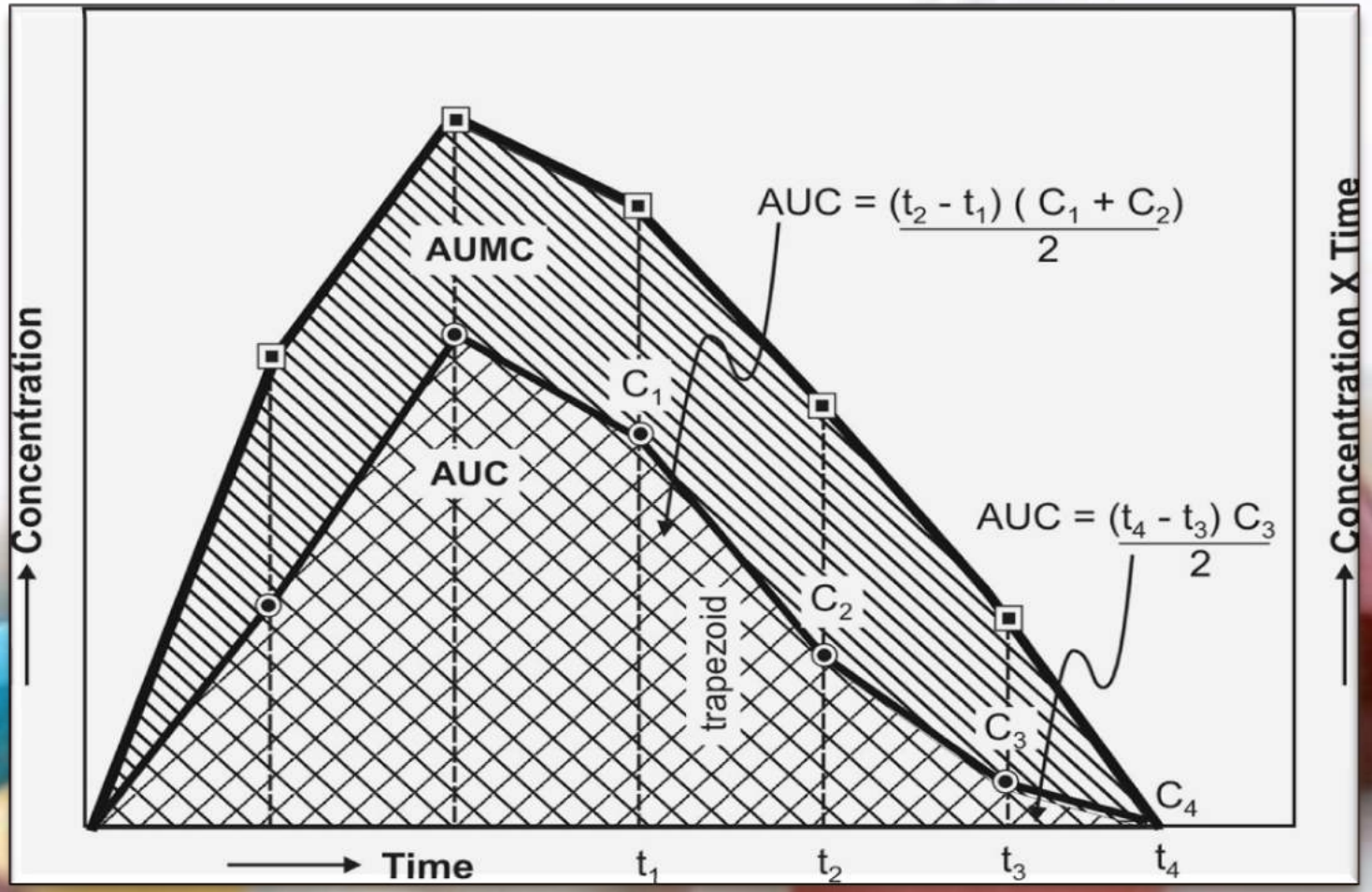
$$MRT = AUMC/AUC$$

where MRT = mean residence time

AUMC = area under the *first-moment curve*

AUC = area under the *zero-moment curve*

MRT *is defined as the average amount of time spent by the drug in the body before being eliminated*.


Concentration
Concentration X Time
AUMC
AUC
AUC = (t2 - t1) (C1 + C2) / 2
AUC = (t4 - t3) C3 / 2
C1
C2
C3
C4
trapezoid
Time
t1
t2
t3
t4

ONE-COMPARTMENT OPEN MODEL

(INSTANTANEOUS DISTRIBUTION MODEL)

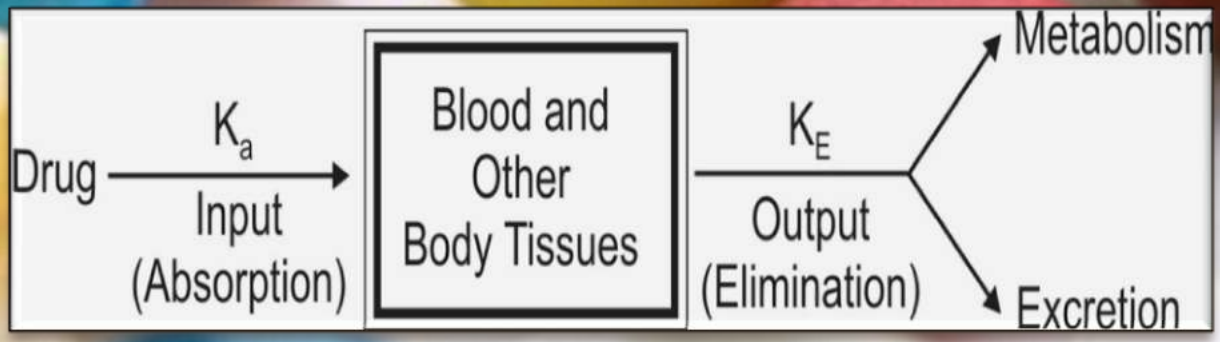
The one-compartment open model is the simplest model.

1. Elimination is a first-order (monoexponential) process with first-order rate constant.

2. Rate of input (absorption) > rate of output (elimination).

3. The anatomical ***reference compartment*** is plasma and concentration of drug in plasma is representative of drug concentration in all body tissues i.e. any change in plasma drug concentration reflects a proportional change in drug concentration throughout the body.

However, the model does not assume that the drug concentration in plasma is equal to that in other body tissues.



One-Compartment Open Model : Intravenous Bolus Administration

The general expression for **rate of drug presentation** to the body is:

$$\frac{dX}{dt} = \text{Rate in (availability)} - \text{Rate out (elimination)}$$

$$\frac{dX}{dt} = -K_E X$$

Estimation of Pharmacokinetic Parameters

Elimination phase can be characterized by 3 parameters—

1. Elimination rate constant
2. Elimination half-life
3. Clearance.

Elimination Rate Constant:

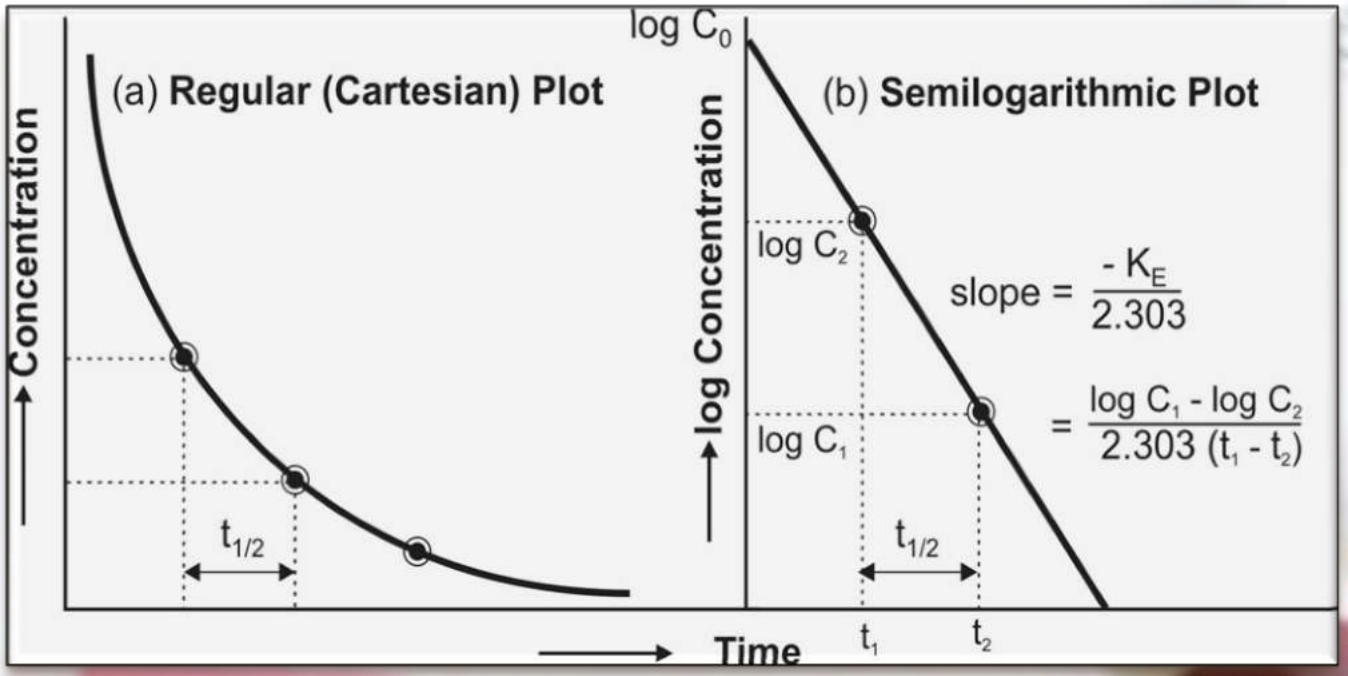
$$\ln X = \ln Xo - KE\ t$$

The above equation shows that *disposition of a drug that follows one-compartment kinetics is* **monoexponential**.

$$X = Xo\ e^{-KEt}$$

$$X = Vd\ C$$

$$\log C = \log C_0 - \frac{K_E\ t}{2.303}$$



$$KE = Ke + Km + Kb + Kl + ...$$

if a drug is eliminated by urinary excretion and metabolism only, then, the fraction of drug

excreted unchanged in urine **Fe** and fraction of drug metabolized **Fm** can be given as:

$$F_e = \frac{K_e}{K_E} \qquad F_m = \frac{K_m}{K_E}$$

Elimination Half-Life:

$$t_{1/2} = \frac{0.693}{K_E}$$

$$t_{1/2} = \frac{0.693\ V_d}{Cl_T}$$

- **Apparent volume of distribution, and**
- **Clearance.**

Since these parameters are closely related with the physiologic mechanisms in the bo

***they are called as* primary parameters.**

$$V_d = \frac{\text{Amount of drug in the body}}{\text{Plasma drug concentration}} = \frac{X}{C}$$

$$V_d = \frac{X_0}{C_0} = \frac{\text{i.v. bolus dose}}{C_0}$$

Clearance *is defined as the theoretical volume of body fluid containing drug* (i.e. that fraction of apparent volume of distribution) *from which the drug is completely removed in a given period of time*. It is expressed in ml/min or liters/hour.

$$Cl_R = \frac{\text{Rate of elimination by kidney}}{C}$$

$$Cl_H = \frac{\text{Rate of elimination by liver}}{C}$$

$$Cl_{Others} = \frac{\text{Rate of elimination by other organs}}{C}$$

$$Cl_T = \frac{0.693\ V_d}{t_{1/2}}$$

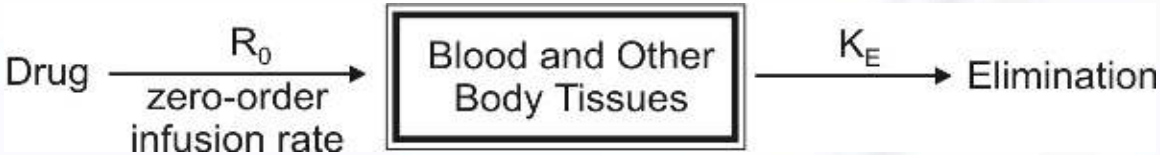
For drugs given as i.v. bolus

$$Cl_T = \frac{X_0}{AUC}$$

For drugs given e.v.

$$Cl_T = \frac{F\ X_0}{AUC}$$

One-Compartment Open Model : Intravenous Infusion



$$\frac{dX}{dt} = R_0 - K_E X$$

$$X = \frac{R_0}{K_E}(1 - e^{-K_E t})$$

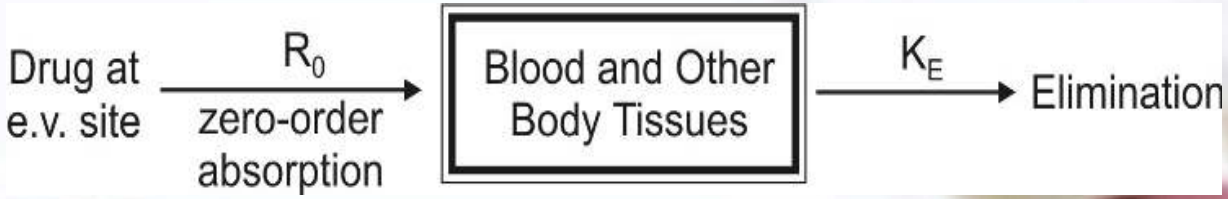
$$C = \frac{R_0}{K_E V_d}(1 - e^{-K_E t}) = \frac{R_0}{Cl_T}(1 - e^{-K_E t})$$

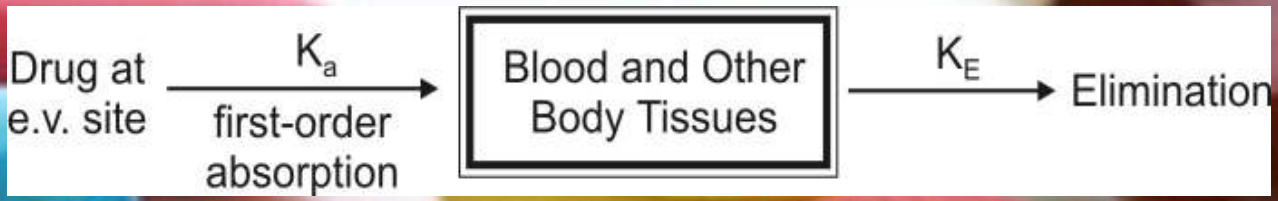
$$C_{ss} = \frac{R_0}{K_E V_d} = \frac{R_0}{Cl_T} \quad \text{i.e.} \quad \frac{\text{Infusion rate}}{\text{Clearance}}$$

One-Compartment Open Model: Extravascular Administration

dX/dt = Rate of absorption – Rate of elimination

$$\frac{dX}{dt} = \frac{dX_{ev}}{dt} - \frac{dX_E}{dt}$$





$$X = \frac{K_a F X_0}{(K_a - K_E)}\left[e^{-K_E t} - e^{-K_a t}\right]$$

$$C = \frac{K_a F X_0}{V_d (K_a - K_E)}\left[e^{-K_E t} - e^{-K_a t}\right]$$

At peak plasma concentration, the rate of absorption equals rate of elimination i.e. KaXa = $K_E X$

$$\frac{dC}{dt} = \frac{K_a F X_0}{V_d (K_a - K_E)} \left[- K_E e^{-K_E t} + K_a e^{-K_a t} \right] \quad = \text{Zero}$$

$$K_E \, e^{-K_E t} = K_a \, e^{-K_a t}$$

$$\log K_E - \frac{K_E t}{2.303} = \log K_a - \frac{K_a t}{2.303}$$

$$t_{max} = \frac{2.303 \log (K_a / K_E)}{K_a - K_E}$$

$$C_{max} = \frac{F X_0}{V_d} e^{-K_E t_{max}}$$

Absorption Rate Constant: It can be calculated by the **method of residuals**. The technique is also known as **feathering**, **peeling** and **stripping**. It is commonly used in pharmacokinetics to resolve a multiexponential curve into its individual components. For a drug that follows one-compartment kinetics and administered e.v., the concentration of drug in plasma is expressed by a biexponential equation.

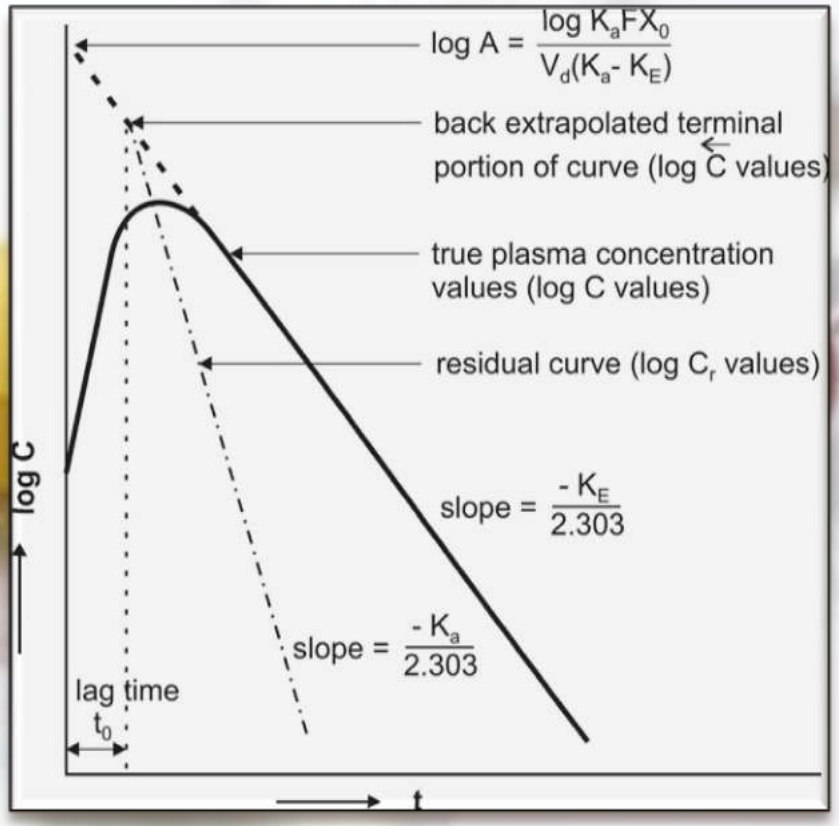
$$C = \frac{K_a F X_0}{V_d (K_a - K_E)} \left[e^{-K_E t} - e^{-K_a t} \right]$$

$$\overleftarrow{C} = A \; e^{-K_E t}$$

$$\log \overleftarrow{C} = \log A - \frac{K_E t}{2.303}$$

$$(\overleftarrow{C} - C) = C_\tau = A \; e^{-K_a t}$$

$$\log C_\tau = \log A - \frac{K_a t}{2.303}$$



Wagner-Nelson Method for Estimation of Ka

The method involves determination of Ka from percent unabsorbed-time plots and does not require the assumption of zero- or first-order absorption.

$$X_A = X + X_E$$

$$X_E = K_E \, V_d \, [AUC]_0^t$$

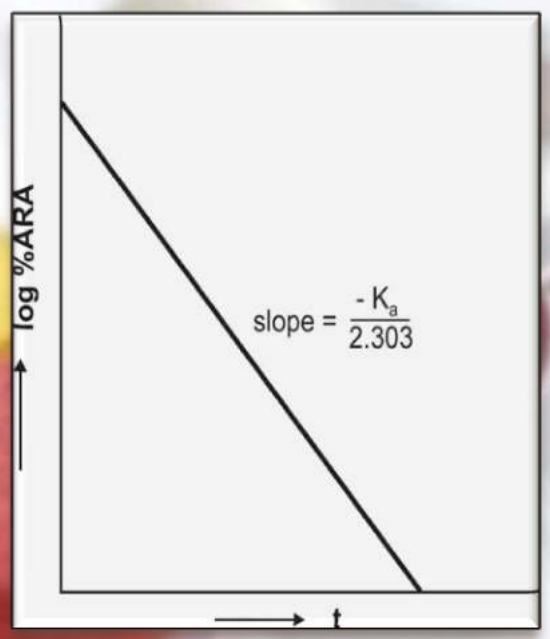
$$X_A = V_d C + K_E \, V_d \, [AUC]_0^t$$

$$X_A^\infty = V_d \, C^\infty + K_E \, V_d \, [AUC]_0^\infty$$

$$X_A^\infty = K_E \, V_d \, [AUC]_0^\infty$$

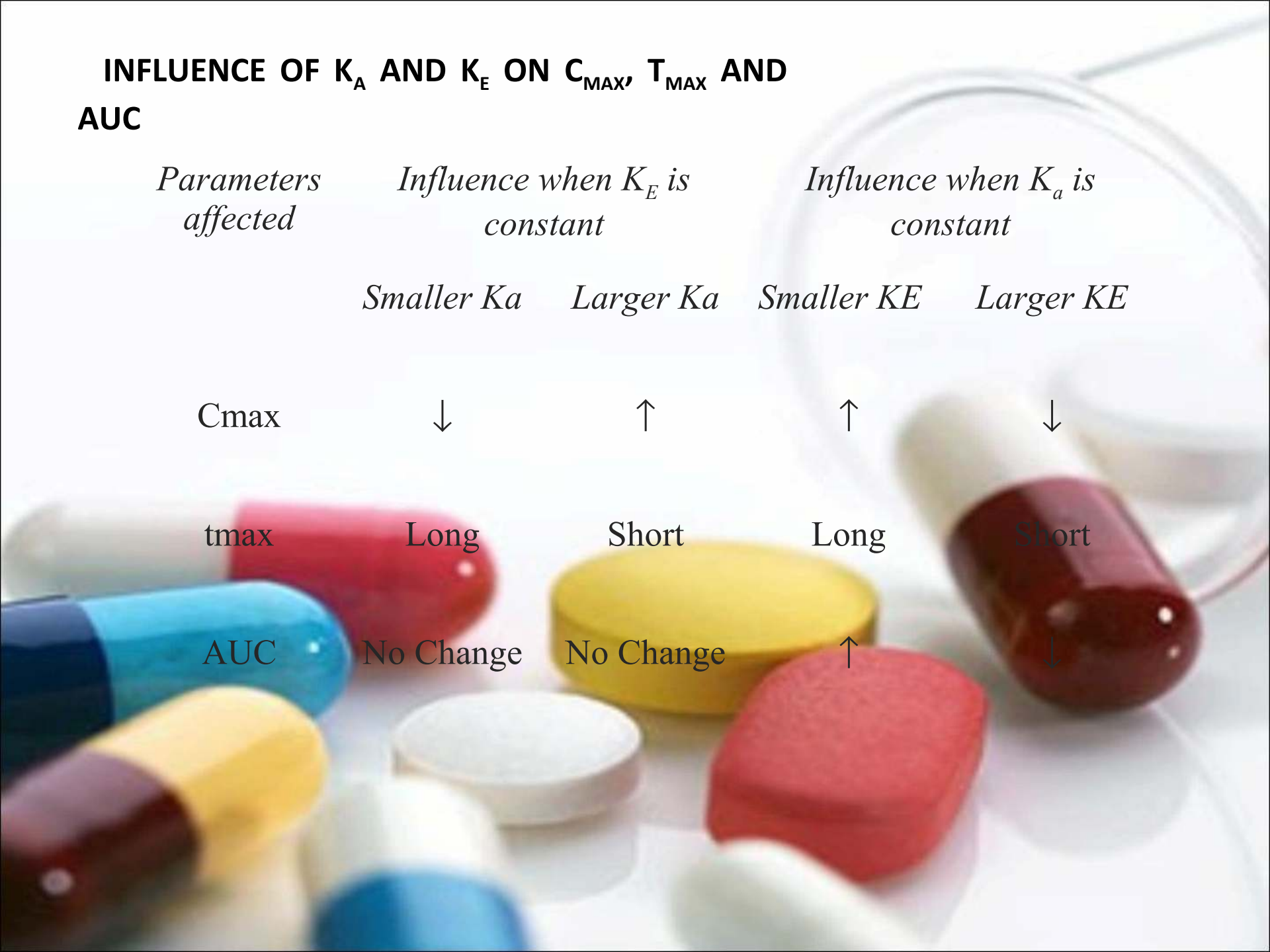
$$\frac{X_A}{X_A^\infty} = \frac{V_d \, C + K_E \, V_d \, [AUC]_0^t}{K_E \, V_d \, [AUC]_0^\infty} = \frac{C + K_E \, [AUC]_0^t}{K_E \, [AUC]_0^\infty}$$

$$\%ARA = \left[1 - \frac{XA}{X_A^\infty}\right] 100 = \left[1 - \frac{C + K_E \, [AUC]_0^t}{K_E \, [AUC]_0^\infty}\right] 100$$



INFLUENCE OF K_A AND K_E ON C_{MAX}, T_{MAX} AND AUC

Parameters affected	*Influence when K_E is constant*		*Influence when K_a is constant*	
	Smaller Ka	*Larger Ka*	*Smaller KE*	*Larger KE*
Cmax	↓	↑	↑	↓
tmax	Long	Short	Long	Short
AUC	No Change	No Change	↑	↓



URINARY EXCRETION DATA

Criteria for Obtaining Valid Urinary Excretion Data

A significant amount of drug must be excreted unchanged in the urine (at least 10%).

1. The analytical method must be specific for the unchanged drug; metabolites should not interfere.

2. Water-loading should be done by taking 400 ml of water after fasting overnight, to promote diuresis and enable collection of sufficient urine samples.

3. Before administration of drug, the bladder must be emptied completely after 1 hour from water-loading and the urine sample taken as blank. The drug should then be administered with 200 ml of water and should be followed by 200 ml given at hourly intervals for the next 4 hours.

4. Volunteers must be instructed to completely empty their bladder while collecting urine samples.

5. Frequent sampling should be done in order to obtain a good curve.

6. During sampling, the exact time and volume of urine excreted should be noted.

7. An individual collection period should not exceed one biological half-life of the drug and ideally should be considerably less.

8. Urine samples must be collected for at least 7 biological half-lives in order to ensure collection of more than 99% of excreted drug.

9. Changes in urine pH and urine volume may alter the urinary excretion rate.

Determination of K_E from Urinary Excretion Data

1. Rate of excretion method, and
2. Sigma-minus method.

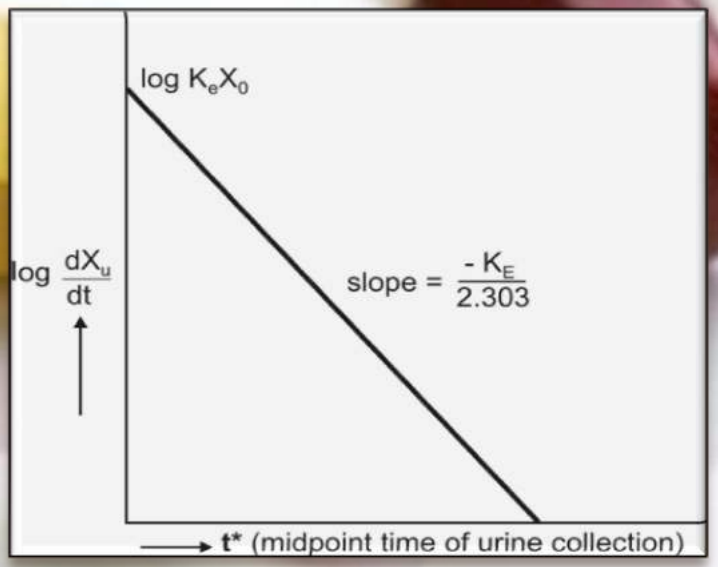
Rate of Excretion Method: The rate of urinary drug excretion dXu/dt is proportional to the amount of drug in the body X and written as:

$$\frac{dX_u}{dt} = K_e X$$

According to first-order disposition kinetics, $X = Xo\ e^{-K_E t}$

$$\frac{dX_u}{dt} = K_e X_0\ e^{-K_E t}$$

$$\log \frac{dX_u}{dt} = \log K_e X_0 - \frac{K_E t}{2.303}$$



Sigma-Minus Method: A *disadvantage of rate of excretion method* in estimating K_E is that fluctuations in the rate of drug elimination are observed to a high degree and in most instances, the data are so scattered that an estimate of half-life is difficult. These problems can be minimized by using the alternative approach called as sigma-minus method.

$$\frac{dX_u}{dt} = K_e X_0 \, e^{-K_E t}$$

$$X_u = \frac{K_E X_0}{K_E}(1 - e^{-K_E t})$$

Xu = cumulative amount of drug excreted unchanged in urine at any time t. As time approaches infinity i.e. after 6 to 7 half-lives, the value e–KE∞ becomes zero and therefore the cumulative amount excreted at infinite time Xu ∞ can be given by equation

$$X_u^{\infty} = \frac{K_e X_0}{K_E}$$

$$X_u^{\infty} - X_u = X_u^{\infty} e^{-K_E t}$$

$$\log (X_u^{\infty} - X_u) = \log X_u^{\infty} - \frac{K_E t}{2.303}$$

$(Xu_\infty - Xu)$ = **amount remaining to be excreted**

i.e. **ARE** at any given time.

A semilog plot of ARE versus t yields a straight line with slope -KE/2.303.

The method is, therefore, also called as **ARE plot method**.

A *disadvantage* of this method is that total urine collection has to be carried out until no unchanged drug can be detected in the urine i.e. upto 7 half-lives, which may be tedious for drugs having long t½.

MULTICOMPARTMENT MODELS: INTRAVENOUS BOLUS ADMINISTRATION

Pharmacokinetic models- represent drug distribution and elimination in the body.

A model should mimic closely the physiologic processes in the body

In compartmental models, drug tissue concentration is assumed to be uniform within a given hypothetical compartment.

All muscle mass and connective tissues may be lumped into one hypothetical tissue compartment that equilibrates with drug from the central (or plasma) compartment.

Multicompartment models were developed to explain and predict plasma and tissue concentrations for the behavior of these drugs.

In contrast, a one-compartment model is used when the drug appears to distribute into tissues instantaneously and uniformly.

Central compartment

These highly perfused tissues and blood make up the central compartment.

Multicompartment drugs

Multicompartment drugs are delivered concurrently to one or more peripheral compartments composed of groups of tissues with lower blood perfusion and different affinity for the drug.

Many drugs given in a single intravenous bolus dose demonstrate a plasma level–time curve that does not decline as a single exponential (first-order) process.

The plasma level–time curve for a drug that follows a two-compartment model shows that the plasma drug concentration declines *biexponentially as the sum of two first-order processes—distribution and elimination.*

TWO COMPARTMENT OPEN MODEL

A drug that follows the pharmacokinetics of a two-compartment model does not equilibrate rapidly throughout the body, as is assumed for a one-compartment model.

In this model, the drug distributes into two compartments, the central compartment and the tissue, or peripheral compartment.

Central compartment:

Represents the blood, extracellular fluid, and highly perfused tissues. The drug distributes rapidly and uniformly in the central compartment.

Second compartment,

Known as the tissue or peripheral compartment, contains tissues in which the drug equilibrates more slowly.

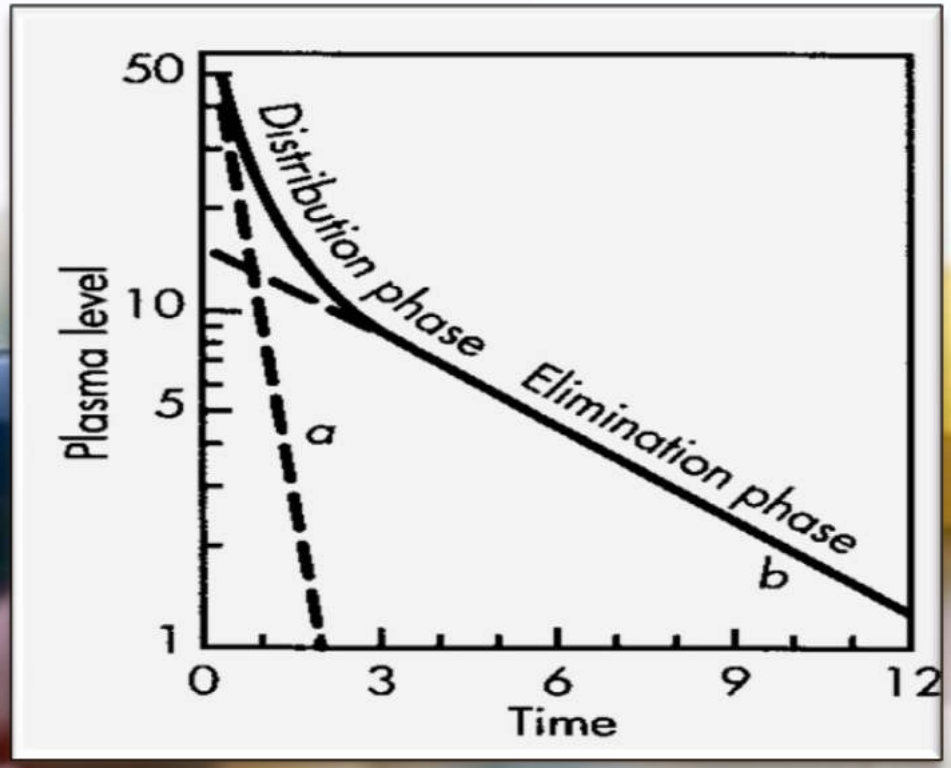
Drug transfer between the two compartments is assumed to take place by first-order processes.

GENERAL GROUPING OF TISSUE ACCORDING TO BLOOD SUPPLY

TABLE 4.2 General Grouping of Tissues According to Blood Supply[a]

BLOOD SUPPLY	TISSUE GROUP	PERCENT BODY WEIGHT
Highly perfused	Heart, brain, hepatic-portal system, kidney, and endocrine glands	9
	Skin and muscle	50
	Adipose (fat) tissue and marrow	19
Slowly perfused	Bone, ligaments, tendons, cartilage, teeth, and hair	22

Distribution phase- represents the initial, more rapid decline of drug from the central compartment into tissue compartment (line *a*)
The decline is 1st order process and called **elimination phase** or β phase (line *b*)



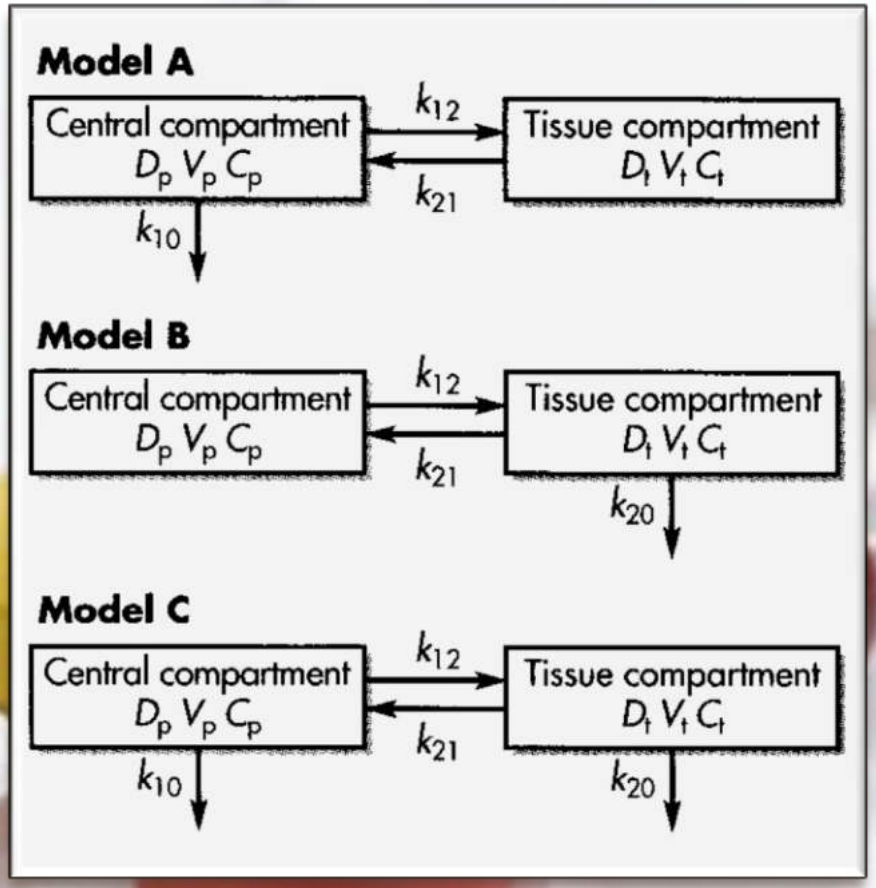
- Distribution phase- drug elimination and distribution occur concurrently
- Net transfer of drug from central to tissue compartment
- Fraction of drug in the tissue compartment during distribution phase increases to max.
- At max. tissue conc. – rate of drug entry into tissue = rate of drug exit from tissue.
- Drug in tissue compartment- equilibrium with drug in central compartment (distribution equilibrium)
- Drug conc in both compartment decline in parallel and more slowly compared to distribution phase

TWO COMPARTMENT MODELS

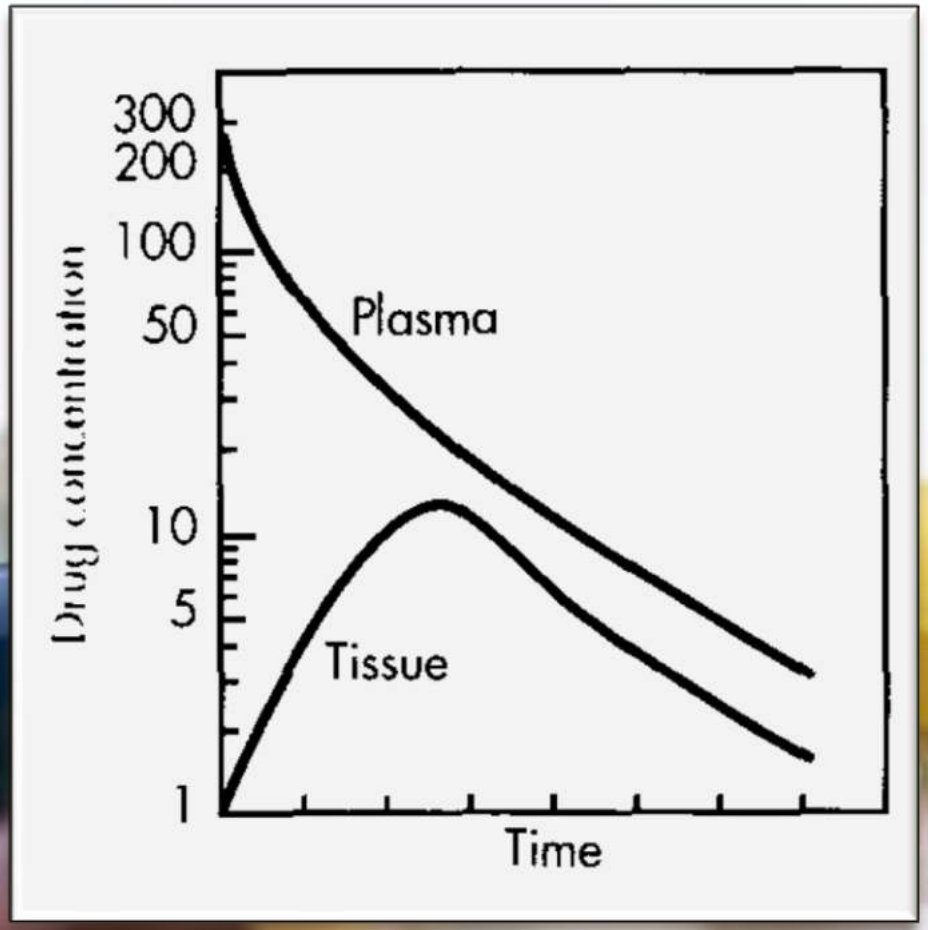
There are several possible two-compartment models

- compartment 1 is the central compartment and compartment 2 is the tissue compartment.

- The rate constants k_{12} and k_{21} represent the first-order rate transfer constants for the movement of drug from compartment 1 to compartment 2 (k_{12}) and from compartment 2 to compartment 1 (k_{21}).



RELATIONSHIP BETWEEN DRUG CONCENTRATIONS IN TISSUE AND PLASMA



The maximum tissue drug concentration may be greater or less than the plasma drug concentration.

The rate of drug change in and out of the tissues:

$$\frac{dC_t}{dt} = k_{12}C_p - k_{21}C_t$$

The relationship between the amount of drug in each compartment and the concentration of drug in that compartment is shown by:

$$C_p = \frac{D_p}{V_p} \qquad C_t = \frac{D_t}{V_t}$$

where,

D_p = *amount of drug in the central compartment,*

D_t = *amount of drug in the tissue compartment,*

V_p = *volume of drug in the central compartment, and*

V_t = *volume of drug in the tissue compartment.*

Rate equation:

$$-\frac{dC_p}{dt} = k_{21}\frac{D_t}{V_t} - k_{12}\frac{D_p}{V_p} - k\frac{D_p}{V_p}$$

$$\frac{dC_t}{dt} = k_{12}\frac{D_p}{V_p} - k_{21}\frac{D_t}{V_t}$$

Drug concentration in blood and tissue

$$C_p = \frac{D_p^0}{V_p}\left(\frac{k_{21}}{b} - \frac{a}{a}e^{-at} + \frac{k_{21} - b}{a - b}e^{-bt}\right)$$

$$C_t = \frac{D_p^0}{V_t}\left(\frac{k_{12}}{b} - \frac{a}{a}e^{-at} - \frac{k_{12}}{a - b}e^{-bt}\right)$$

Amount of drug in blood and tissue

$$D_p = D_p^0\left(\frac{k_{21} - a}{b} - \frac{a}{a}e^{-at} + \frac{k_{21} - b}{a - b}e^{-bt}\right)$$

$$D_t = D_p^0\left(\frac{k_{12}a}{b} - \frac{a}{a}e^{-at} + \frac{k_{12}}{a - b}e^{-bt}\right)$$

The rate constants for the transfer of drug between compartments are referred to as *microconstants* or *transfer constants,* and relate the amount of drug being transferred per unit time from one compartment to the other.

The constants *a* and *b* are hybrid first-order rate constants for the distribution phase and elimination phase, respectively.

$$a + b = k_{12} + k_{21} + k$$

$$ab = k_{21}k$$

Equation

$$C_p = \frac{D_0^0}{V_p}\left(\frac{k_{21} - a}{b - a}e^{-at} + \frac{k_{21} - b}{a - b}e^{-bt}\right)$$

Constants a and b- rate constant for distribution phase and elimination phase

Can be write as

$$C_p = Ae^{-at} + Be^{-bt}$$

The constants *A* and *B* are intercepts on the *y* axis for each exponential segment of the curve

$$A = \frac{D_0(a - k_{21})}{V_p(a - b)}$$

$$B = \frac{D_0(k_{21} - b)}{V_p(a - b)}$$

Intercepts *A* and *B* are hybrid constants

METHOD OF RESIDUALS

Method of residual- feathering or peeling, useful for fitting a curve to the experimental data of drug when drug does not follow one compartment model.

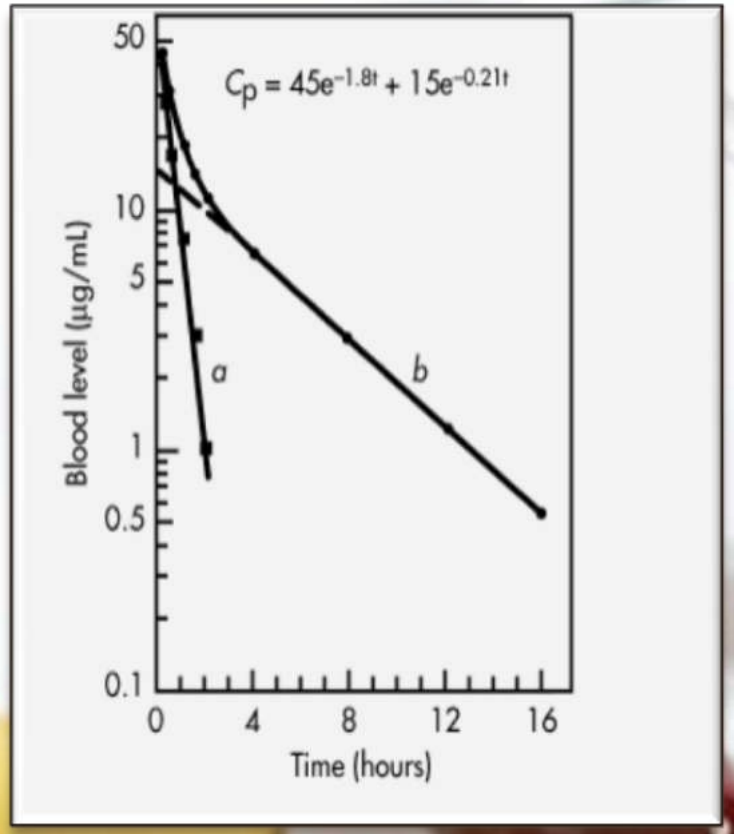
E.g: 100 mg of drug administered by rapid IV injection to a 70-kg healthy adult male. Blood sample were taken periodically and the following data were obtained:

Time (hr)	Plasma Concentration (μg/mL)
0.25	43.00
0.5	32.00
1.0	20.00
1.5	14.00
2.0	11.00
4.0	6.50
8.0	2.80
12.0	1.20
16.0	0.52

When data is plotted, a curved line is observed. The curved-line relationship between logarithm of the plasma conc and time indicates that drug is distributed in more than one compartment. From these data, biexponential equation, may be derived

$$C_p = Ae^{-at} + Be^{-bt}$$

As shown in biexponential curve, the decline in initial distribution phase is more rapid than elimination phase.
Rapid distribution phase confirmed with constant *a* being larger than constant *b*.
at some later time Ae^{-at} will approach 0, while Be^{-bt} still have value.



The rate constant and intercepts were calculated by method of residuals

Therefore, $C_P = Be^{-bt}$

In common logarithms,

$$\log C_P = \frac{-bt}{2.3} + \log B$$

From equation above, rate constant can be obtained from the slope (-*b*/2.3) of a straight line representing the terminal exponential phase.

The t1/2 for elimination phase (beta half life) can be derived from the following relationship:

$$t_{1/2_\beta} = \frac{0.693}{b}$$

From Eg. *b* was found to be 0.21 hr^{-1}. from this info the regression line for terminal exponential or *b* phase is extrapolated to the y axis; y intercept = *B* or 15um/mL.

Table 4.3 Application of the Method of Residuals			
TIME (hr)	C_p Observed Plasma Level	C'_p Extrapolated Plasma Concentration	$C_p - C'_p$ Residual Plasma Concentration
0.25	43.0	14.5	28.5
0.5	32.0	13.5	18.5
1.0	20.0	12.3	7.7
1.5	14.0	11.0	3.0
2.0	11.0	10.0	1.0
4.0	6.5		
8.0	2.8		
12.0	1.2		
16.0	0.52		

•Values from the extrapolated line are then substracted from the original experimental data points and a straight line is obtained. This line represents the rapidly distributed phase.

•The new line obtained by graphing the logarithm of residual plasma conc (Cp- C'p) against time represents the a phase. The value for *a* is 1.8 hr^{-1} and y intercept is 45ug/mL. elimination half life, $t_{1/2}$ computed from *b*, has the value of 3.3 hr.

A no of pharmacokinetic parameters may be derived by proper substitution of rate constants *a* and *b* and y intercepts *A* and *B* to following equations:

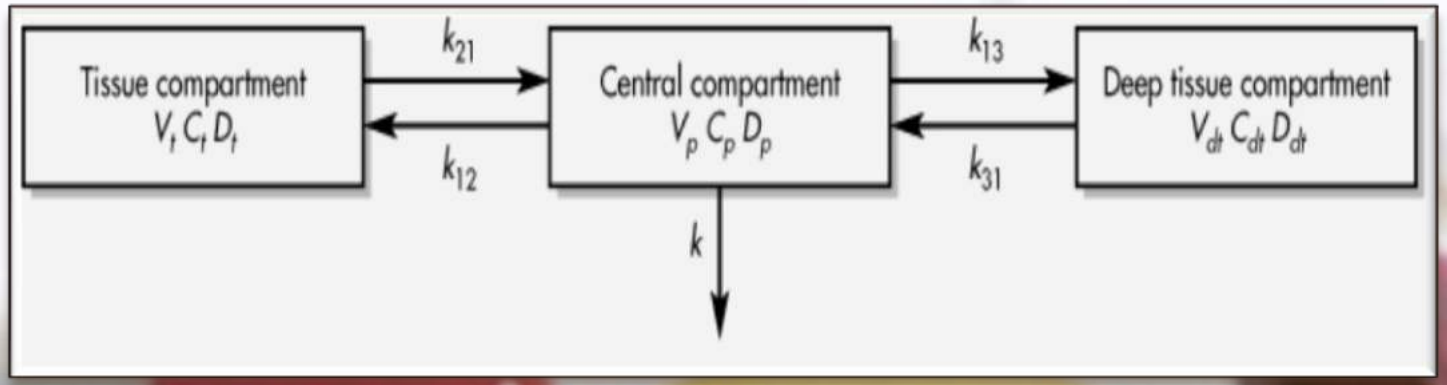
$$k = \frac{ab(A + B)}{Ab + Ba}$$

$$k_{12} = \frac{AB(b - a)^2}{(A + B)(Ab + Ba)}$$

$$k_{21} = \frac{Ab + Ba}{A + B}$$

THREE COMPARTMENT OPEN MODEL

Three compartment- two compartment model + deep tissue compartment



Central compartment- distributed most rapidly- highly perfused tissues

Compartment 2- distributed less rapidly

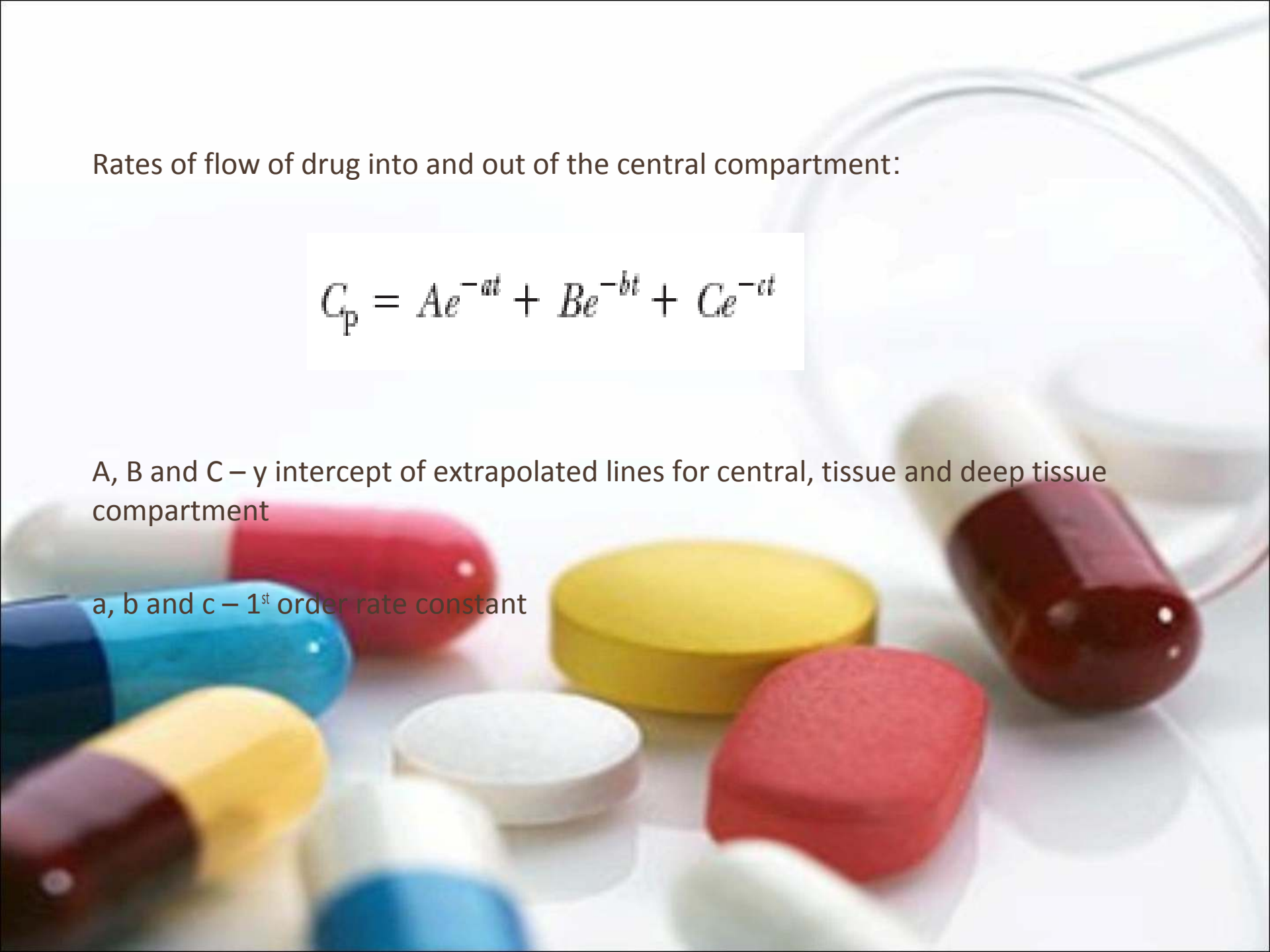
Compartment 3- distributed very slowly- poorly perfused tissues, i.e. bone/ fat

Rates of flow of drug into and out of the central compartment:

$$C_p = Ae^{-at} + Be^{-bt} + Ce^{-ct}$$

A, B and C – y intercept of extrapolated lines for central, tissue and deep tissue compartment

a, b and c – 1st order rate constant



Elimination rate constant, k

$$k = \frac{(A + B + C)abc}{Abc + Bac + Cab}$$

Volume of central compartment

$$V_P = \frac{D_0}{A + B + C}$$

Area

$$[\mathrm{AUC}] = \frac{A}{a} + \frac{B}{b} + \frac{C}{c}$$

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THANK YOU