SS INSTITUTE OF PHARMACY

Approved by Pharmacy Council of India (PCI), New Delhi
Affiliated to The TN Dr.M.G.R Medical University, Chennai
The Directorate of Medical Education (DME), Chennai

Biopharmaceutics and Pharmacokinetics

UNIT-2

TOPICS:

- Elimination
- Bioavailability and Bioequivalence

ELIMINATION

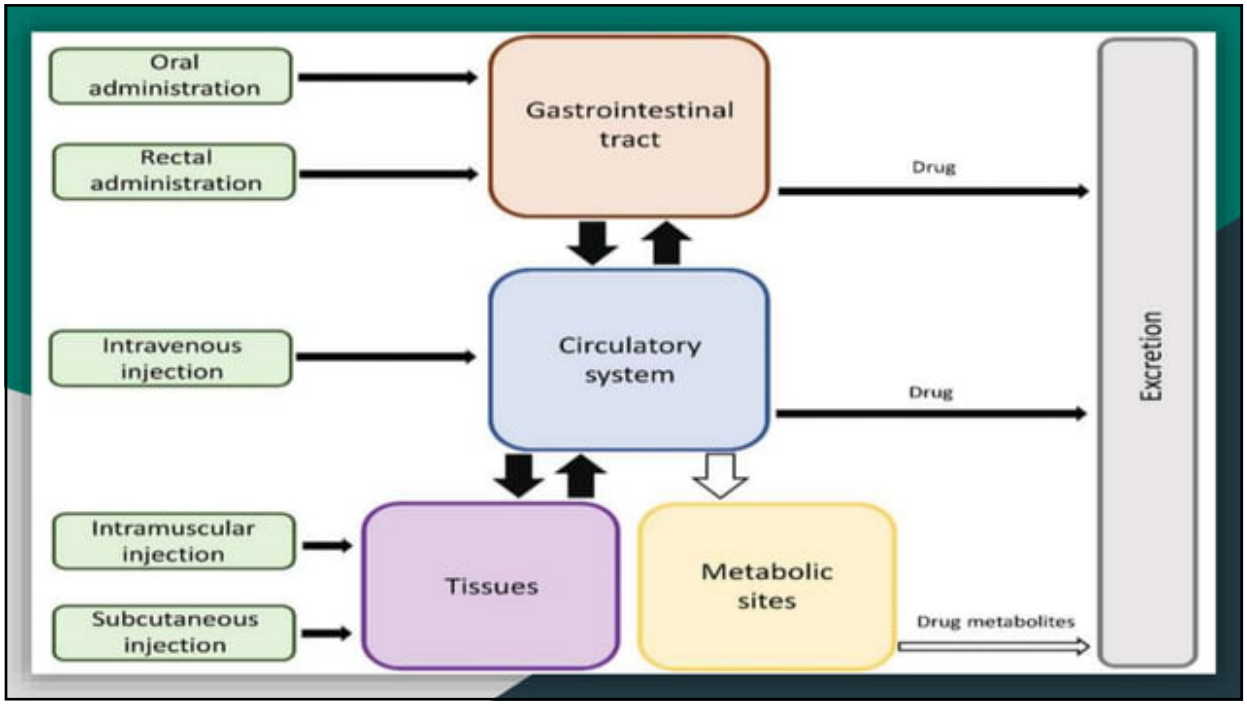
Of Drugs

DRUG ELIMINATION:

- Drugs are removed from the body by various elimination processes.
- It is defined as the irreversible loss of drug from the body.
- It occurs by two processes:

METABOLISM	EXCRETION

ELIMINATION = METABOLISM + EXCRETIONN



DRUG METABOLISM

METABOLISM OF DRUGS:

- It is also called as **BIOTRANSFORMATION**
- It is defined as the biochemical modification of a drug in the body.
- Once drug enters the body it undergoes ABSORPTION, DISTRIBUTION,METABOLISM, ELIMINATION.
- METABOLISM is an important process which reduces the toxicity of the Drug in the body.

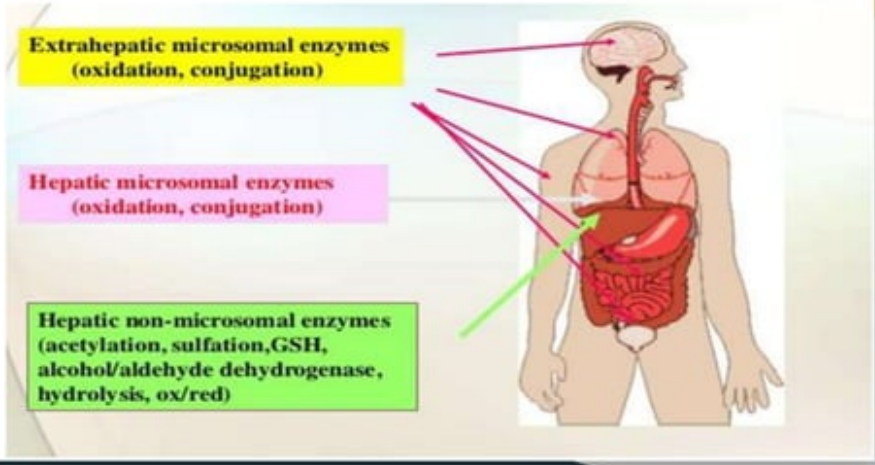
Protein soluble ------> water soluble

⇩

Excretion

SITES OF METABOLISM:

- LIVER (primary sites)
- GIT
- LUNGS
- KIDNEYS
- SKINS



ENZYMES INVOLVED IN METABOLISM:

PHASE I METABOLISM	PHASE II METABOLISM
★ Cytochrome P450. ★ Flavin containing mono oxygenase(FMO) ★ Esterase ★ Alcohol dehydrogenase(ADH) ★ Aldehyde dehydrogenase(ALDH) ★ Monoamine oxidase (MAO)	★ Uridine diphosphate glucuronosyltransferase (UDPGT) ★ Sulfotransferase (ST) ★ N- Acetyltransferase (NAT) ★ Glutathione S- Transferase (GST) ★ Methyl Transferase ★ Amino acid conjunction

METABOLIC PATHWAYS:

It is divided into two phases,

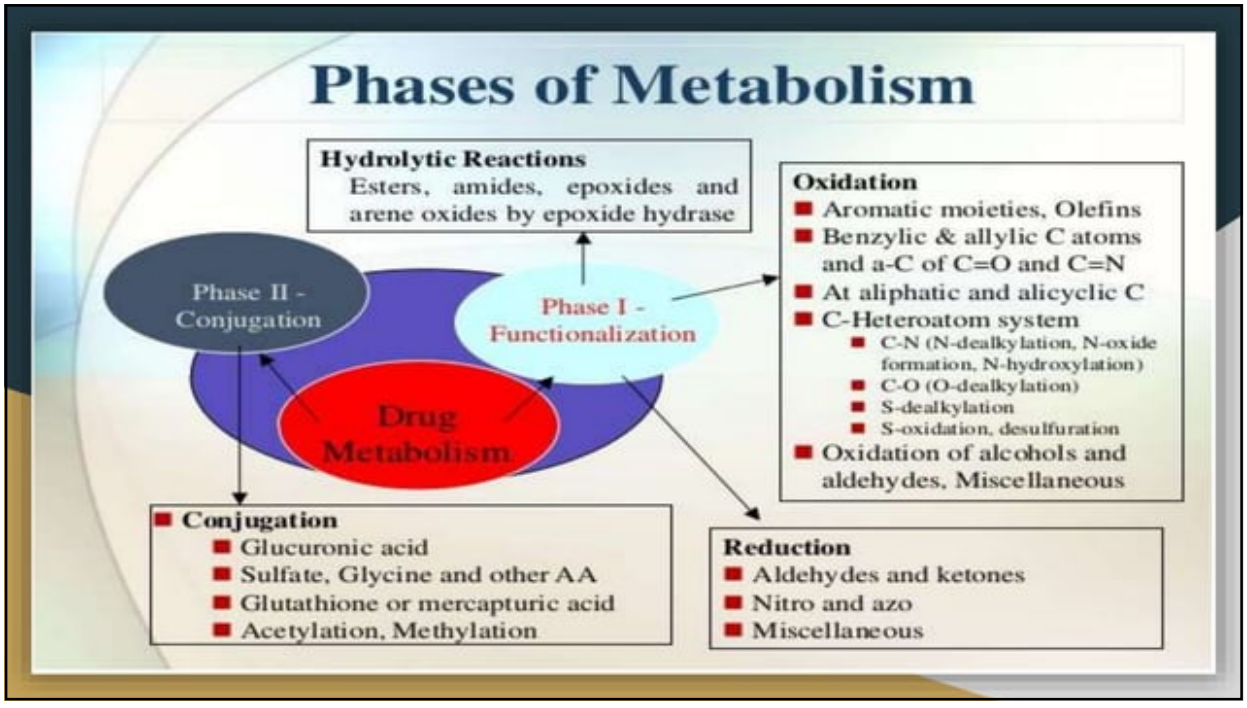
METABOLISM

PHASE I

- ★ OXIDATION
- ★ REDUCTION
- ★ HYDROLYSIS

PHASE II

- ★ SULPHONATION
- ★ ACETYLATION
- ★ METHYLATION
- ★ GLUTATHIONE CONJUGATION
- ★ GLUCURONIDATION



PHASE I METABOLISM:

- A molecule of drug initially enters into the PHASE I METABOLISM
- It undergoes sequence of reactions
- Attachment of functional groups to the drugs like -OH,-SH,-NH_2
- It helps in the CONJUGATION of drug in PHASE II easily.
- Converts itself into forms that shows reduced solubility in lipids as well as in water so that it's excretion is facilitated.

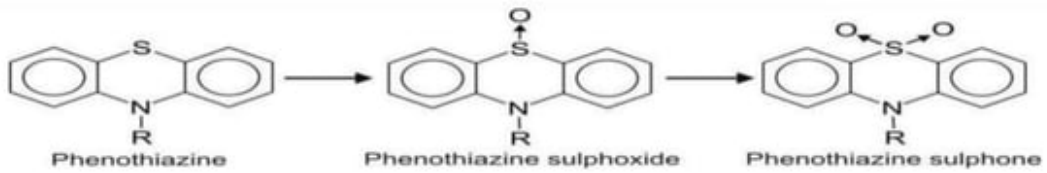
REACTIONS:

- ★ OXIDATION
- ★ REDUCTION
- ★ HYDROLYSIS

OXIDATION:

- Liver cells are the most common site for OXIDATION.
- Oxidation involves conversion of a C-H bond to a C-OH.
- This reaction sometimes converts a pharmacologically inactive compound (a prodrug) to a pharmacologically active one.
- By the same token, Phase I can turn a nontoxic molecule into a poisonous one (toxification).

$RH + O_2 + NADPH + H^+$ --------> $ROH + H_2O + NADP^+$



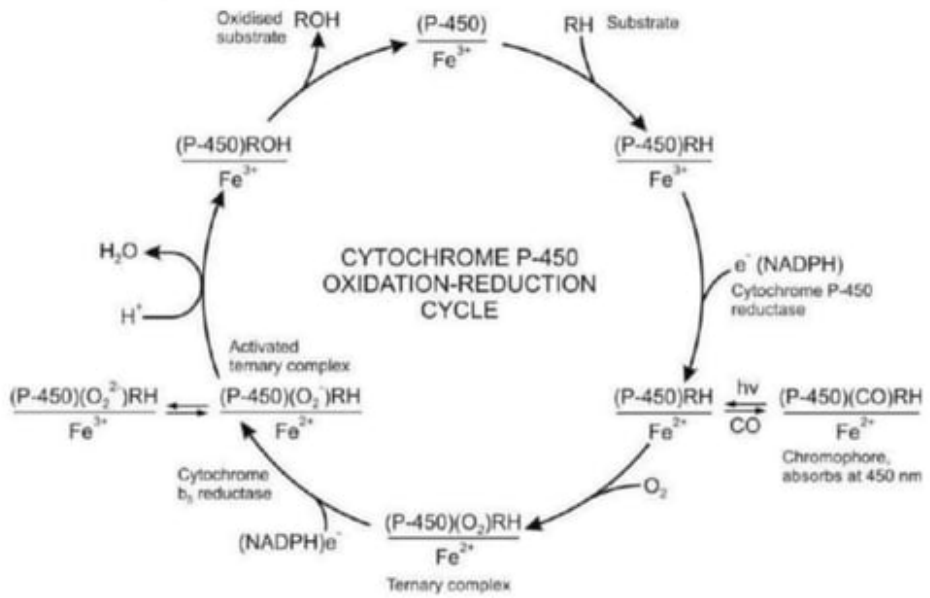
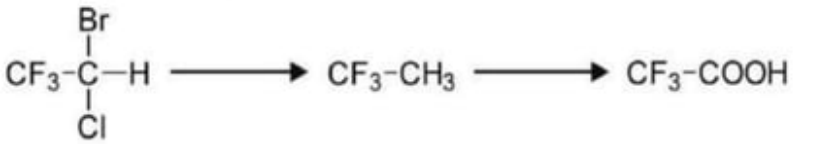


Fig. 5.3. Cytochrome P-450 oxidation-reduction cycle

REDUCTION:

- Drugs containing an aldehyde,ketone , disulphide,quinine,N- oxide ,alkene ,azo or Nitro group undergo In Vivo reduction.
- Alcohol dehydrogenation < ------ > carbonyl reduction
- N- Oxidation < ------- > Amine oxide reduction

Eg:



Halothane 1,1,1-Trifluoroethane Trifluoroacetic acid

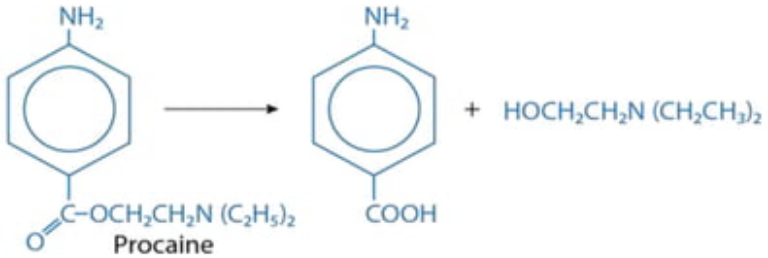
HYDROLYSIS:

- ❖ Cleavage of drug molecule by taking up a molecule of water.

SITES :

- ★ Liver
- ★ Intestines
- ★ Plasma
- ★ Other tissues

Eg.



Procaine

PHASE II METABOLISM:

- ❖ In PHASE II reactions,drugs are combined with hydrophilic endogenous compound to form complex which allows rapids excretion.
- ❖ It is also called as CONJUGATION REACTIONS.
- ❖ PHASE II reactions are much faster than PHASE I reactions.

- ★ SULPHONATION
- ★ ACETYLATION
- ★ METHYLATION
- ★ GLUTATHIONE CONJUGATION
- ★ GLUCURONIDATION

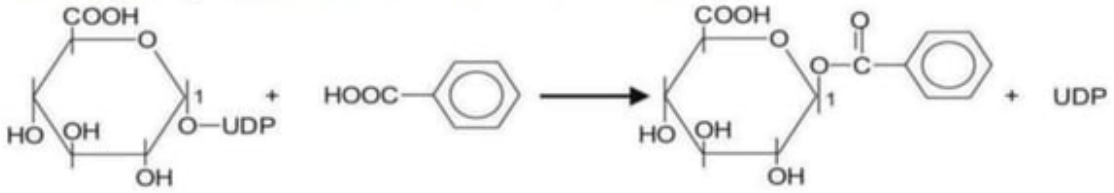
CONJUGATION REACTIONS & FUNCTIONAL GROUPS

Glucuronidation	-OH,-COOH,-NH_2, ,-SH,-CH,-NH
Sulphonation	Aromatic-OH,Aromatic -NH_2,alcohols
Acetylation	Hydrazine,-SO_2,-NH_2
Methylation	Aromatic -OH ,-NH_2 ,-NH,-SH
Glutathione conjunction	Epoxides and organic halides
Glycine conjunction	Aromatic-NH_2, and -COOH

GLUCURONIDATION:

- GLUCURONIDATION is quantitatively the most significant PHASE II reaction.
- Glucuronic acid conjunction occurs only when glucuronic acid gets activated.

An example of glucuronidation of benzoic acid is shown below.



UDPGA (α-linkage at C-1) | Benzoic acid | Glucuronide of benzoic acid (β-linkage at C-1)

A large number of functional groups are capable of forming oxygen, nitrogen and sulphur glucuronides. Carbon glucuronides have also been detected in a few cases.

FACTORS AFFECTING DRUG METABOLISM:

- Biological factor's
  - Age
  - Diet
  - Sex
  - Weight
  - Others
  - Body temperature
- Chemical factor's
  - Enzyme inhibitors
  - Enzyme stimulators
- Physico chemical properties of drug

DRUG EXCRETION

EXCRETION:

- EXCRETION remove the drugs or their metabolites from the body.
- KIDNEYS are the principal organs for excretion.
- The other organs include lungs,biliary system, intestines,salivary gland, sweat glands.
- All lipid soluble drugs are converted into water soluble compounds by the metabolic process which favours the excretion process.

CLEARANCE:

DEFINITION:

- It is defined as the complete removal of a drug in a specified time period from the hypothetical volume of body fluids containing the drug.

UNIT:. ml/min

It describes the relationship between plasma drug concentration and the rate of drug elimination.

$$\text{Clearance(cl)} = \frac{\text{Elimination rate}}{\text{Plasma drug concentration}}$$

RENAL CLEARANCE:

- The clearance takes place in kidney are called as RENAL CLEARANCE.
- Blood volume or plasma volume, completely cleared of the drug in its unchanged from , by the kidneys per unit time.
- Clearance is a measure of renal function.

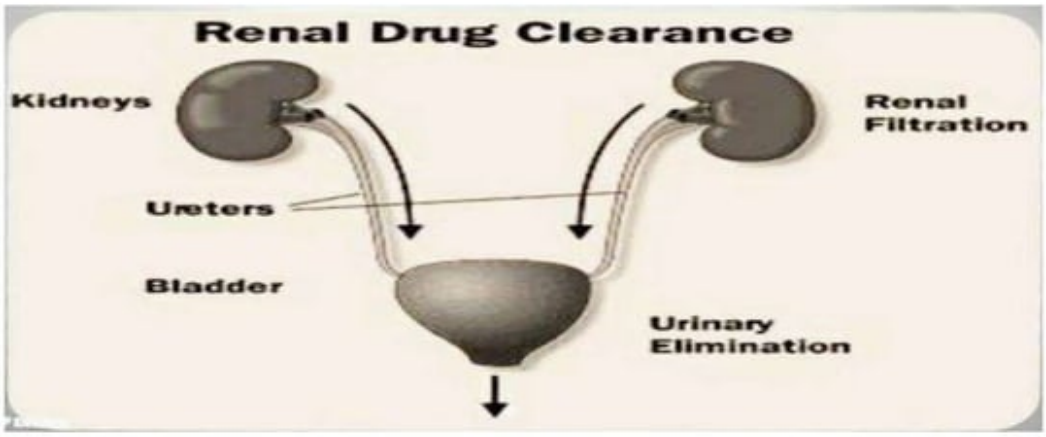
$$Cl_R = \frac{\text{Rate of urinary excretion}}{\text{Plasma drug concentration}}$$

$$Cl_R = \frac{\text{Rate of filtration+rate of secretion - rate of reabsorption}}{C}$$

EXCRETION OF DRUGS

Renal Excretion of Drugs	Non - Renal Excretion of Drug
★ The excretion of drugs by the KIDNEYS. ★ Eg: drugs like gentamicin ★ In this excretion, drugs are removed via Urine.	★ The excretion of drugs by all other routes except the Renal route(kidney). ★ It involves ○ Biliary excretion ○ Pulmonary excretion ○ Salivary excretion ○ Mammary excretion ○ Skin excretion ○ Gastrointestinal excretion

RENAL EXCRETION



RENAL EXCRETION:

- Kidneys are responsible for the excretion of nearly all drugs as well as their metabolites.
- Water soluble, non volatile, small molecule size (<500 Dalton's) are undergo excretion via Urine.
- NEPHRON is the basic functional unit of kidney. One million Nephrons are present in each kidney.

Rate of Excretion	=	Rate of Filtration	+	Rate of Secretion	-	Rate of Reabsorption

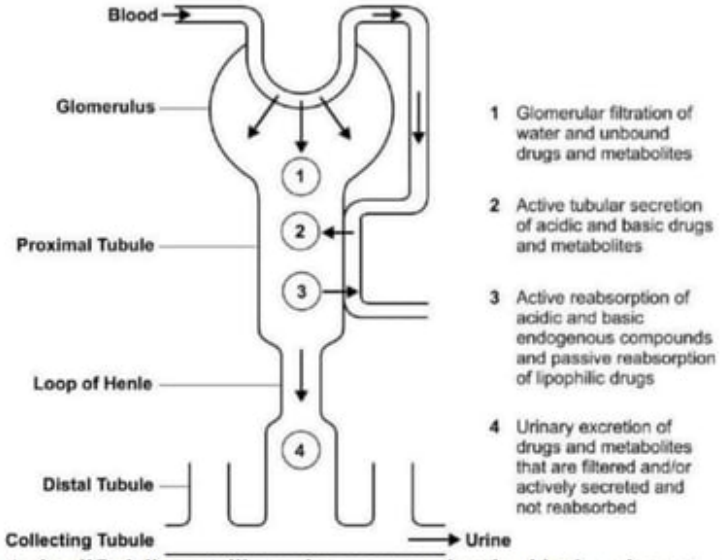


Fig. 6.1 A simplified diagram illustrating processes involved in the urinary excretion of drugs

PRINCIPLE OF RENAL MECHANISM INVOLVED:

- GLOMERULAR FILTRATION
- TUBULAR SECRETION
- TUBULAR REABSORPTION

GLOMERULAR FILTRATION:

- Most compounds are filtered except that are bound to plasma protein's
- Non - selective process
- Occurs in only one direction
- Glomerulus behaves as negatively charged
- Hydrostatic pressure of blood flowing in the capillaries acts as driving force for filtration.
- Only 10% of cardiac output is filtered through glomeruli.

- The rate of filtration is known as GLOMERULAR FILTRATION RATE (GFR)
- Compounds with 20Å to 42Å may undergo Glomerular filtration.
- Substance used for determination of GFR:
  - Creatinine
  - Inulin
  - Mannitol
  - Sodium thiosulphate

ACTIVE TUBULAR SECRETION:

- It is a carrier mediated process.
- Compounds are transported in a opposite direction to the concentration gradient by utilising energy.

TWO SECRETION MECHANISM

1.System for secretion of organic acids/ anions

Eg. penicillin, Salicylate, etc...

2.System for organic base / cations

Eg. Morphine, mecamylamine, hexamethonium .

TUBULAR REABSORPTION:

- Site - takes place all along Renal tubules.
- Results in increases in half life of a drugs.

TWO TYPES:

- Active tubular reabsorption:
  - High threshold endogenous substance or nutrients which the body needs to preserve.
  - Eg. Glucose , electrolytes,vitamins, amino acids,uric acids.
  - Drugs - oxopurinol

- Passive tubular reabsorption
  - For exogenous substance like drugs.
  - Concentration gradient takes place - driving force
  - Lipophilic substance are extensively reabsorbed and polar not reabsorbed.

REABSORPTION DEPENDS UPON:

- pH of Urine(4.5-7.5)
- Urine flow rate
- pKa of drug

FACTORS AFFECTING RENAL EXCRETION:

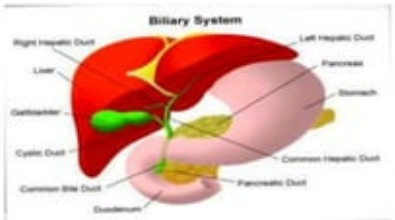
- Physico chemical properties
- Drug interactions
- Distribution and binding of drug
- Blood flow to kidney
- Urine pH
- Disease state
- Biological factor's
- Plasma concentrations

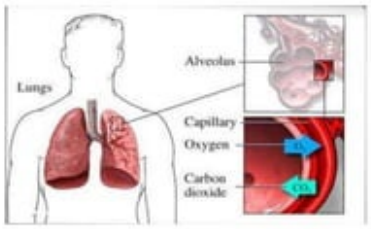
1. Physico chemical properties
    a. Molecular size
        i. Size <300 Dalton's
        ii. Excretion of drugs with larger molecular weight is difficult compared to that of drugs with smaller weights.
    b. Lipid solubility
        i. Inversely proportional to the urinary excretion
    c. Volume of distribution
        i. Inversely proportional to the clearance
        ii. Lage Vd - poor Excretion in Urine
        iii. Small Vd - high excretion in Urine

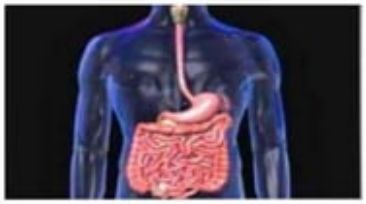
2. Plasma concentrations of drug
    - Glomerular filtration and reabsorption are directly affected by plasma concentrations

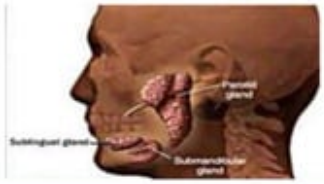
3.Biological factor's
    - Renal Excretion is 10% lower in females.
    - New born : 30-40% less
    - Old age : excretion decreased, increased t1/2.

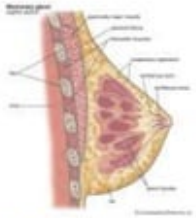
NON RENAL EXCRETION







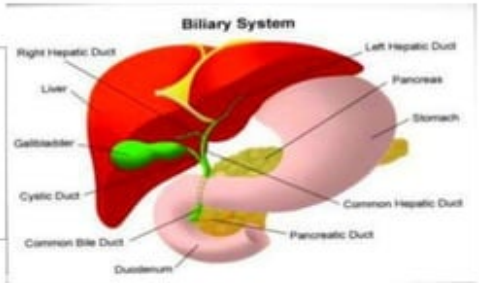




BILIARY EXCRETION OF DRUGS / ENTEROHEPATIC CYCLING

- Production and secretion of bile is active proces.
- Bile secreted in the liver , stored in gall bladder and released in the duodenum.
- Bile significantly helps in digestion and absorption of fats.
- Secretion of bile is a capacity limited process and gets saturated.

Drug concentration in bile (less)
Drug concentration in plasma (higher)
Biliary clearance is low.
Vice-versa.....

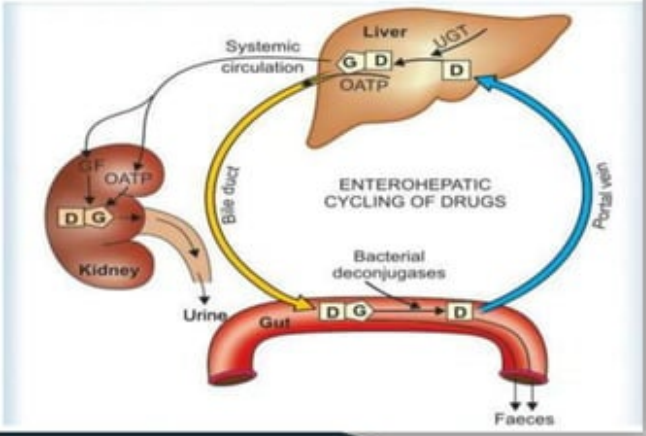


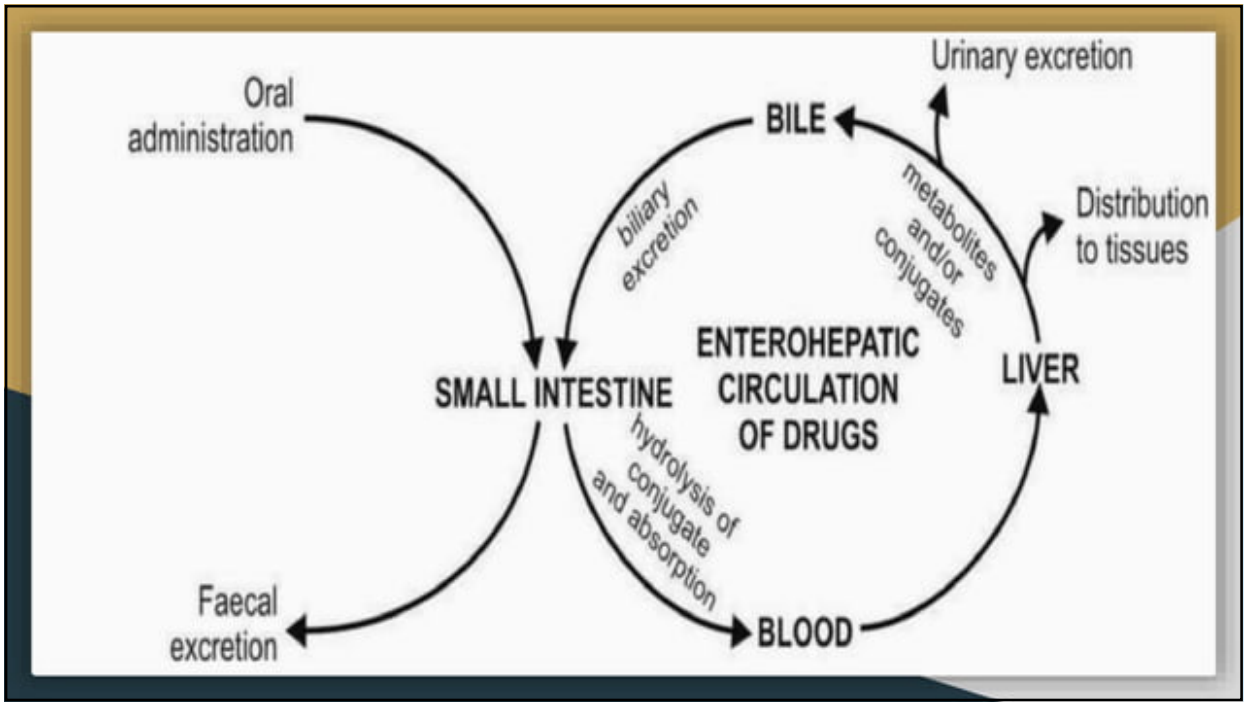
Based on their bile / plasma concentrations ratio's, the compounds excreted in bile can be grouped.

GROUPS	Bile / plasma concentrations	Example
GROUP A	About 1	Sodium,potassium,chloride,glucose
GROUP B	More than 1	Bile salts, creatinine, bilirubin Glucuronides.
GROUP C	Less than 1	Sucrose, inulin, phosphate, phospholipid.

ENTERO HEPATIC CIRCULATION OR CYCLING:

- The phenomenon of drug circulation between the intestines and the liver is called ENTEROHEPATIC CYCLING or CIRCULATION.
- Half life - t1/2 - INCREASED for drugs.
- Prolongation of drug action
- Eg. Cardiac glycosides , rifampicin, chlorpromazine, indomethacin.

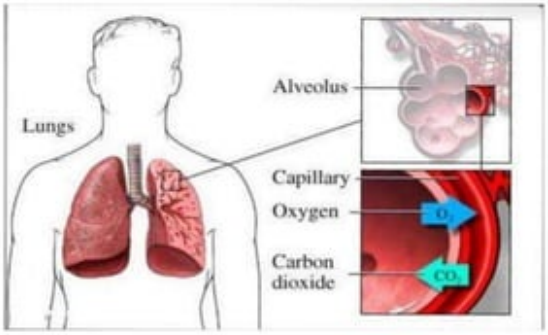




PULMONARY EXCRETION OF DRUGS:

- Gaseous and volatile substance such as general anaesthetics (Halothane) are absorbed through lungs by simple diffusion.
- Pulmonary blood flow ,rate of respirations and solubility of substance affect the pulmonary excretion.
- Alcohol which has high solubility in blood and tissues are excreted slowly by lungs.

Eg: General anaesthetics - Halothane, nitrous oxide
Alcohol - excreted slowly through lungs

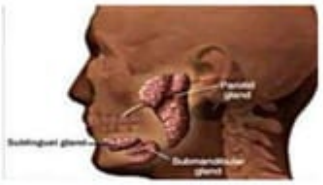


SALIVARY EXCRETION OF DRUGS

- It involves Excretion of drugs through saliva by the process of passive diffusion.
- The pH of Saliva varies from 5.8 to 8.4
- Unionised lipid soluble drug's are excreted passively
- The bitter taste is due to drug excreted

for weak acids,

$$R_a = \frac{S}{P} = \frac{1+10^{(pH_{saliva} - pK_a)}}{1+10^{(pH_{plasma} - pK_a)}} X \frac{f_{plasma}}{f_{saliva}}$$



for weak bases,

$$R_b = \frac{S}{P} = \frac{1+10^{(pK_a - pH_{saliva})}}{1+10^{(pK_a - pH_{plasma})}} X \frac{f_{plasma}}{f_{saliva}}$$

where, f_{plasma} and f_{saliva} are free drug fractions in plasma and in saliva respectively.

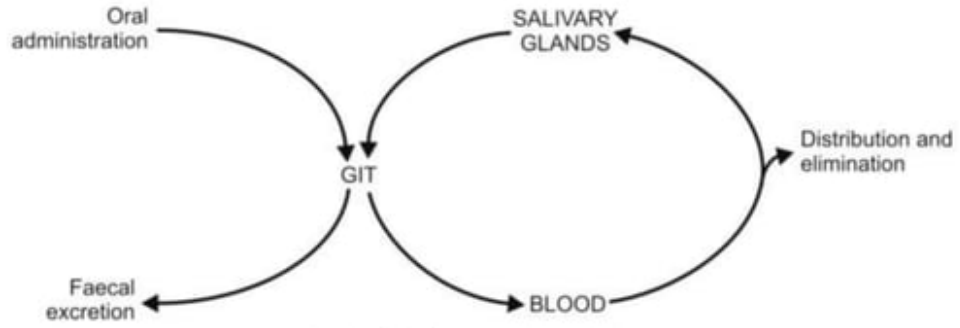


Fig. 6.6. Salivary cycling of drugs

- For weak acid ratio's found to be <1
- For weak base ratio's found to be >1
- Eg . Sulphonamides , antibiotics, clonidine ,etc...

MAMMARY EXCRETION OF DRUGS:

- A drug that is excreted in milk can enter in infants feeding.
- pH of milk ranges from 6.4-7.6 and a mean pH of 7.0
- Un ionised , lipid soluble drugs show Passive diffusion in the alveolar cells of the mammary gland.
- The excretion of drugs in milk is usually less than 1%.
- Milk bears an acidic nature as compared to plasma.
- Drugs are weak basic in nature show greater concentration in milk.

Eg. Chloramphenicol , diazepam , tetracyclines, etc...

DRUG EXCRETION IN MILK DEPENDS ON

- pH partition behaviour
- Molecular weight
- Lipid solubility
- Degree of ionisation

EFFECTS

- Some potent drugs may induce toxicity in infants.i.e barbiturates,morphine , ergotamine.
- Whenever possible, feeding mothers should avoid drugs .
- If medication is unavoidable, the infant should be bottle fed.

SKIN EXCRETION OF DRUGS

- It depends on pH partition hypothesis
- Passively excreted through skin
- Sweat : urea derivatives, amines , heavy metals.

Eg : benzoic acid, Salicylic acid, alcohol.

GASTROINTESTINAL EXCRETION OF DRUGS

- GI excretion takes place when drug administered through parenteral route.
- It undergoes passive diffusion
- GIT also shows the absorption and excretion of drugs that are administered orally.
- Stomach is the specific site that shows the excretion of water soluble and ionised forms of drugs that either weak acid or base.

Eg. Nicotine, quinine, magnesium sulphate, streptomycin neomycin, cholestyramine etc...

SUMMARY

Excretion Pathways, Transport Mechanisms and Drugs Excreted

Excretory Route	*Mechanism*	*Drugs Excreted*
Urine	Glomerular filtration, active secretion, active/passive reabsorption	Free, hydrophilic, unchanged drugs/metabolites/conjugates of MW < 500
Bile	Active secretion	Hydrophilic, unchanged drugs/metabolites/conjugates of MW ≥ 500
Lung	Passive diffusion	Gaseous and volatile, blood and tissue insoluble drugs
Saliva	Passive diffusion, active transport	Free, unionised, lipophilic drugs, some polar drugs
Milk	Passive diffusion	Free, unionised, lipophilic drugs (generally basic)
Sweat	Passive diffusion	Free, unionised, lipophilic drugs
Intestine	Passive diffusion	Water-soluble, ionised drugs

BIOAVAILABILITY
&
BIOEQUIVALENCE

Contents

- Bioavailability and Bioequivalence: Introduction
- Definition and Objectives of bioavailability,
- Bioavailability Study Designs
- Absolute and Relative Bioavailability
- Measurement of bioavailability,
- *In-vitro drug* Dissolution models,
- *In-vitro-in-vivo correlations,*
- *Bioequivalence studies.*

Bioavailability and Bioequivalence: Introduction

- The extent and the rate of drug absorption play an important role in pharmacokinetics, and this parameters are usually referred as the drug ***bioavailability***.
- For example, a fraction of the dose may be metabolized during the early passage through the gastrointestinal tract or through the liver after an oral dose, or part of the dose may not reach the blood due to drug malabsorption.
- The consequence is an incomplete absorption of the

Bioavailability and Bioequivalence: Introduction

DIFFERENCE BETWEEN BIOAVAILABILITY AND BIOEQUIVALENCE

- **Bioavailability**
  - 1. The rate and extent of drug absorption of unchanged drug from its dosage form into the systemic circulation.
  - 2. Measured by the demonstrated bioequivalence studies of reference protocol.
  - 3. Bioavailability is a comparison of the drug product to an IV formulation.
  - 4. This studies are expletory
  - 5. Evaluate geometric ratio but don't test a statistical hypothesis
  - 6. Not require a similar time to achieve peak blood concentrations.
  - 7. Provide indirect information regarding the pre-systemic and systemic metabolism of the drug
  - 8. Determined only which active ingredient or moiety become available in the site of action

Bioavailability and Bioequivalence: Introduction

- **Bioequivalence**
  - 1. Two or more similar dosage forms reach the systemic circulation at the same relative rate and extent.
  - 2. Bioequivalence has been established via bioavailability testing.
  - 3. Bioequivalence is a comparison with predetermined bioequivalence limits.
  - 4. This studies are confirmatory .
  - 5. Test a statistical hypothesis by evaluating geometric ratio.
  - 6. Require similar times to achieve peak blood concentrations.
  - 7. Provide a link between the pivotal and early clinical trial formulation.
  - 8. Determined the therapeutic equivalence between the pharmaceutical equivalence generic drug product and a corresponding reference listed drug.
  - 9. Provide information on product quality and performance when there are changes in components, composition and method of manufacture after approval of the drug product

Objectives 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.

Objectives of Bioavailability studies

- 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

- 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, antihypertensives, antidiabetics and antibiotics.
  - Drugs that are absorbed by an active transport, e.g.

Significance of Bioavailability

- 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

Bioavailability Study Designs

- Absolute Bioavailability (F) vs Relative Bioavailability:
  - "When the systemic availability of a drug administered orally is determined in comparison to its intravenous administration ,is called as absolute bioavailability".

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

Bioavailability Study Designs

- Relative Bioavailability (Fr)
  - "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

Bioavailability Study Designs

Single Dose vs Multiple Dose Studies

- Single dose study
  - Advantages
    - More common
    - Easy
    - less tedious
    - Less exposure to drug.

Bioavailability Study Designs

Multiple dose study

- Advantages
  - Accurate.
  - Easy to predict the peak & valley characteristics of drug.
  - Few blood samples required.
  - Ethical. And 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

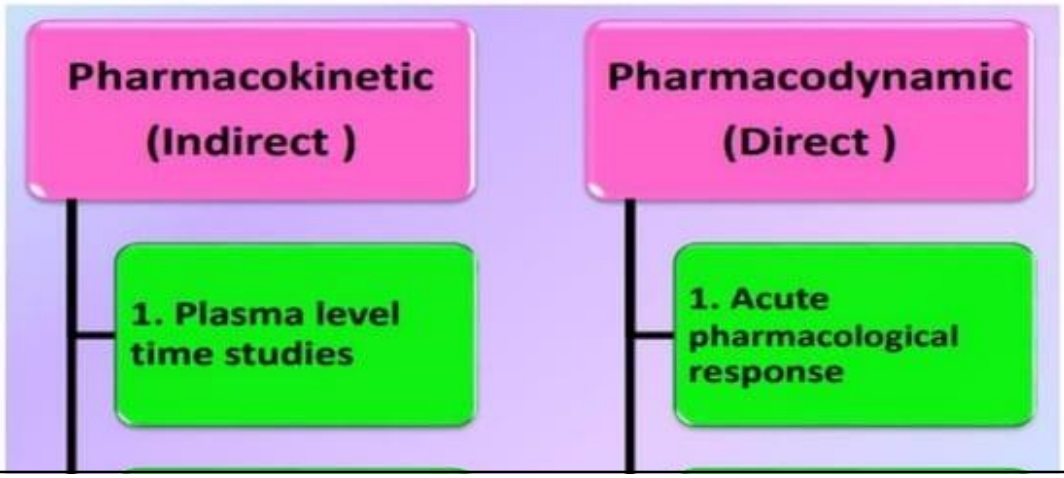
Bioavailability Study Designs

- Human Voluntiers: Healthy 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.

Bioavailability Study Designs

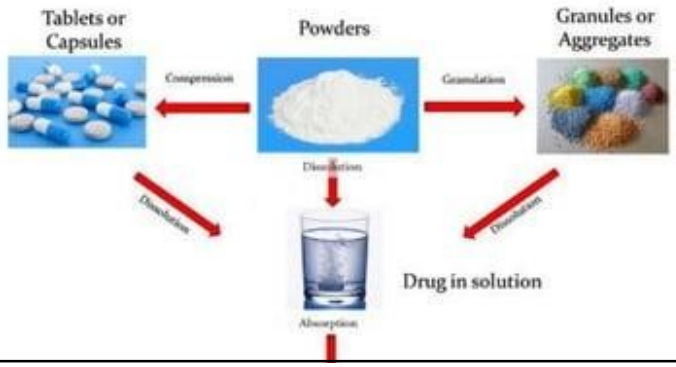
- Healthy human volunteers
  - i. Young
  - ii. Healthy
  - iii. Male (females : e.g. OC pills study)
  - iv. Body wt. within narrow range.
  - v. Restricted dietary & fixed activity conditions.

Measurement of bioavailability



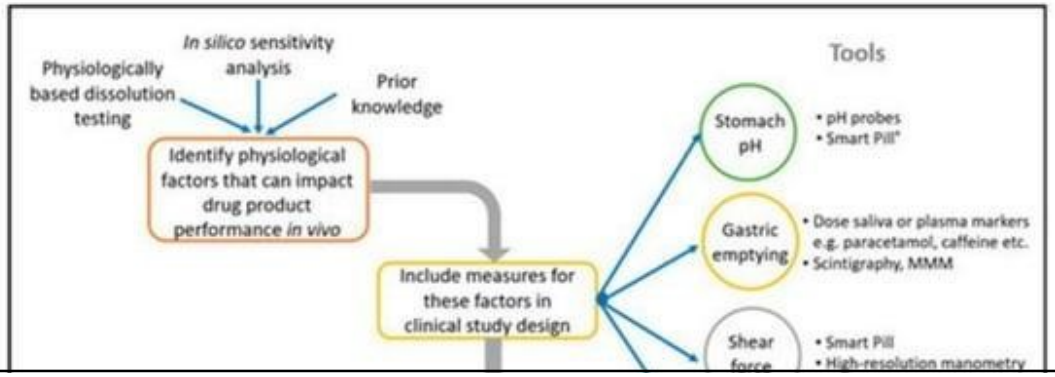
In-vitro drug Dissolution models

- Dissolution of drugs



In-vitro drug Dissolution models

- Dissolution testing plan



In-vitro drug Dissolution models

Types Of Dissolution Models

- 1 Diffusion layer model
- 2 Danckwert's model
- 3 Interfacial barrier model
- 4 Zero order model
- 5 First order model
- 6 Higuchi model
- 7 Korsmeyer- Peppas model
- 8 Hixson – Crowell model

In-vitro drug Dissolution models

1. Diffusion layer model

It is a simplest model where dissolution of crystal, immersed in liquid takes place without involving reactive or electrical forces. Consist of two consecutive steps:

1. Solution of the solid to form a thin film or layer at the solid / liquid interface called as stagnant film or diffusion layer which is saturated with the drug this step is usually rapid (instantaneous).

2. Diffusion of the soluble solute from the stagnant layer to the bulk of the solution this step is slower and is therefore the rate determining step in the drug dissolution.

In-vitro drug Dissolution models

- Using Fick's law, Noyes- Whitney equation for diffusion layer model is as follows:

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

Where,

dc/dt = dissolution rate of the drug

D = diffusion coefficient of the drug

A = surface area of the dissolving solid

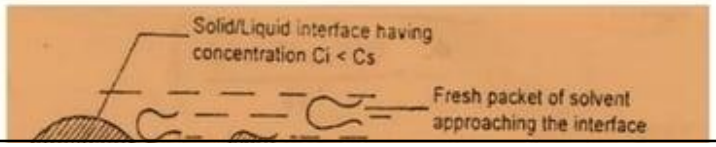
Kw/o = water/oil partition coefficient of the drug

V = volume of dissolution medium

In-vitro drug Dissolution models

2. Danckwert's model

- This theory assumes that solid-solution equilibrium is achieved at interface and mass transport is slow step in dissolution process.
- The model could be visualized as a very thin film having a conc. Ci which is less than saturation, as it is constantly being exposed to fresh surfaces of liquid having a conc. much less than Ci.



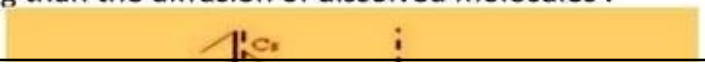
In-vitro drug Dissolution models

- Acc. to model, the agitated fluid consist of mass of eddies or packets that are continuously being exposed to new surfaces of solid and then carried back to bulk of liquid.
- Diffusion occurs into each of these packets during short time in which the packet is in contact with surface of solid. Since turbulence actually extends to surface, there is no laminar boundary layer and so no stagnant film exists. Instead, surface continually being replaced with fresh liquid.
- The Danckwert's model can be expressed by the following equation,

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

In-vitro drug Dissolution models

- 3. Interfacial Barrier model
  - Interfacial barrier model considers drug dissolution as crystal dissolution wherein solids get hydrated initially and is not instantaneous.
  - In this model it is assumed that the reaction at solid surface is not instantaneous i.e. the reaction at solid surface and its diffusion across the interface is slower than diffusion across liquid film.
  - Therefore the rate of solubility of solid in liquid film becomes the rate limiting than the diffusion of dissolved molecules .



In-vitro drug Dissolution models

- When considering the dissolution of crystal will have a different interfacial barrier given by the following equation,

$$dm/dt = Ki\ (Cs - C)$$

In-vitro drug Dissolution models

4. Zero order model
   - Dissolution of the drug from pharmaceutical dosage forms that do not disaggregate and release the drug slowly can be represented by the following equation:

$$Wo - Wt = Kt$$

   - Where, Wo = the initial amount of drug in the pharmaceutical dosage form Wt = the amount of

In-vitro drug Dissolution models

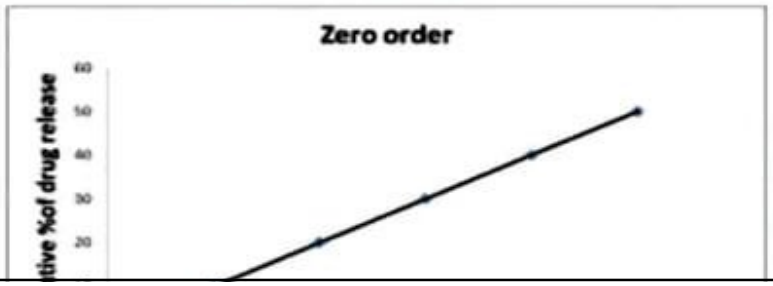
   - The pharmaceutical dosage forms following this profile release the same amount of drug by unit of time and it is the ideal method of drug release in order to achieve a pharmacological prolonged action. The following relation can, in a simple way, express this model:

$$Q_t = Q_0 + K_{0t}$$

Where, Qt = the amount of drug dissolved in time t, Q0 = the initial amount of drug in the solution and Ko = the zero order release

In-vitro drug Dissolution models

- Drug release rate - Independent of concentration
- Graphical representation - %CDR Vs Time and straight line is obtained



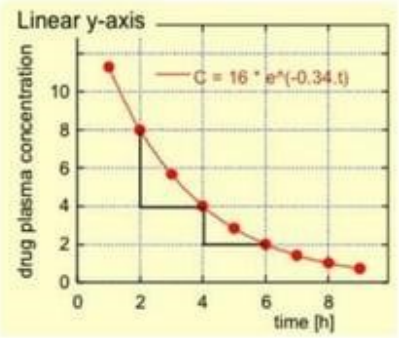
In-vitro drug Dissolution models

- 5. First order model
  - The application of this model to drug dissolution studies was first proposed by Gibaldi and Feldman (1967) and later by Wagner (1969).
  - This model has been also used to describe absorption and/or elimination of some drugs, although it is difficult to conceptualize this mechanism in a theoretical basis The dissolution phenomena of a solid particle in a liquid media imply a surface action, as can be seen by the Noyes–Whitney Equation:

$$dc/dt = K (Cs - C)$$

In-vitro drug Dissolution models

– The plot between time (hrs) Vs log cummulative % of drug remaining to be release gives a straight line



In-vitro drug Dissolution models

6. Higuchi Model

- This is the first mathematical model that describes drug release from a matrix system, proposed by Higuchi in 1961 .
- This model is based on different hypothesis that,
  - Initial drug concentration in the matrix is much higher than drug solubility,
  - Drug diffusion takes place only in one dimension (Edge effect should be avoided),
  - Drug particles are much smaller than thickness of system,
  - swelling of matrix and dissolution are less or negligible

In-vitro drug Dissolution models

- The study of dissolution from a planar system having a homogeneous matrix can be obtained by the equation:

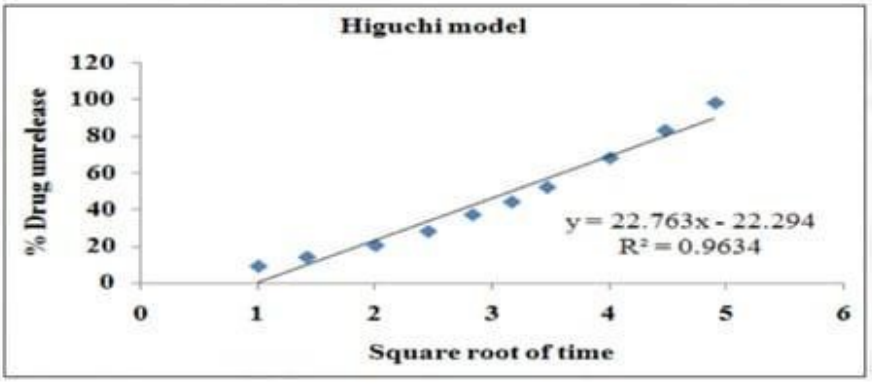
$$A=[D(2C-Cs)Cs \times t]1/2$$

Where, A = amount of drug released in time 't' per unit area

D = diffusivity of drug molecule in the matrix substance

In-vitro drug Dissolution models

- The following graph shows the drug release through Higuchi Model,



- Application : This relationship can be used to describe the drug

In-vitro drug Dissolution models

7. Hixson-Crowell Model

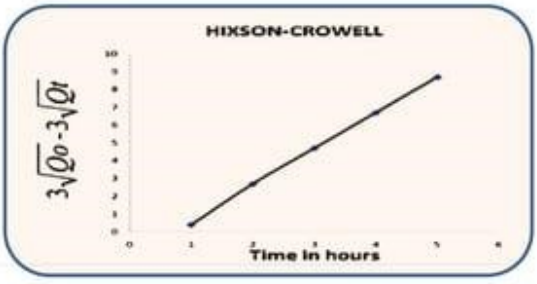
- Drug powder that having uniformed size particles, Hixson and Crowell derived the equation which expresses rate of dissolution based on cube root of weight of particles and the radius of particle is not assumed to be constant.
- This is expressed by the equation,

$$Mo^{1/3} - Mt^{1/3} = \kappa t$$

- Where, Mo = the initial amount of drug in the

In-vitro drug Dissolution models

- The plotted graph will be linear if the following conditions are fulfilled,
- The equilibrium condition are not reached and
- The geometrical shape of the pharmaceutical dosage form diminished proportionally over time.



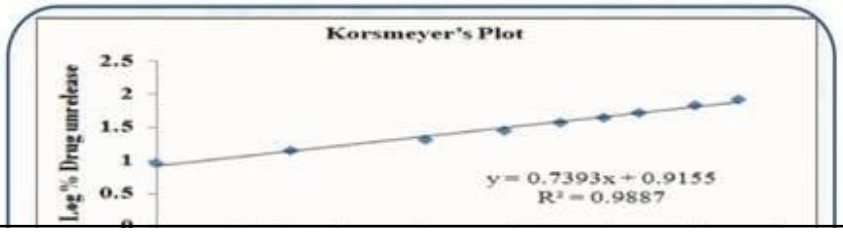
In-vitro drug Dissolution models

- 8. Korsemeyer- Peppas model
  - Korsemeyer (1983) derived a simple relationship which described drug release from a polymeric system equation.
  - To find out the mechanism of drug release, first 60% drug release data were fitted in Korsmeyer -Peppas model.
  - The Korsemeyer –Peppas empirical expression relates the function of time for diffusion controlled mechanism.
  - It is given by the equation,

$$Mt / M\infty = Ktn$$

In-vitro drug Dissolution models

- n = release component which is indicative of the drug release mechanism.
- where, n is diffusion exponent
  - if n = 1, the release is zero order
  - if n= 0.5 the release is best described by Fickian diffusion



In-vitro drug Dissolution models

- 9. Baker- Lonsdale model
  - This model was developed by Baker and Lonsdale (1974) from the Higuchi model and described the drug release from spherical matrices by using the equation:

$$f1= 3/2[1-(1-Ct/C\infty)2/3]\ Ct/C\infty = (3DmCms)/(ro2Co)X\ t$$

  - Where, At = drug released amount at time t A∞ = amount of drug released at an infinite time, Dm =

In-vitro drug Dissolution models

- To study the release kinetics, data obtained from in vitro drug release studies were plotted as [d (At / A∞)] / dt with respect to the root of time inverse. Application:
- This equation has been used to the linearization of release data from several formulations of microcapsules or

In-vitro drug Dissolution models

- 10. Wiebull Model
  - Wiebull model is generally applied to drug dissolution or release from pharmaceutical dosage forms ? These accumulated fraction of drug M in solution at time t is given by Wiebull equation,

$$M = Mo[1-e-(t-T/a)b]$$

  - Where, m = % dissolved in time 't' a= scale parameter

In-vitro drug Dissolution models

- This equation can be widely used for analysis and characterisation Of of Drug Dissolution process from different dosage form.
- The kinetic model that best fits the dissolution data is evaluated by comparing the correlation coefficient(r) values obtained in various models.

In-vitro drug Dissolution models

Applications of Dissolution models:

- 1. Product Development Important tool during development of dosage form.
- 2. Quality Assurance: D.T. performed on future production lots and is used to assess the lot-tolot performance characteristics of drug product and provide continued assurance of product integrity/similarity.
- 3. Product Stability: In-vitro dissolution also used

In-vitro drug Dissolution models

- 4. Comparability Assessment : Also useful for assessing the impact of pre- or postapproval changes to drug product such as changes to formulation or manufacturing process. Thus, in-vitro comparability assessment is critical to ensure continued performance equivalency and product similarity.
- 5. Waivers of in-vivo bioequivalence requirements: In-vitro dissolution testing or drug release testing may be used for seeking waiver of required product to conduct

In-vitro-in-vivo correlations

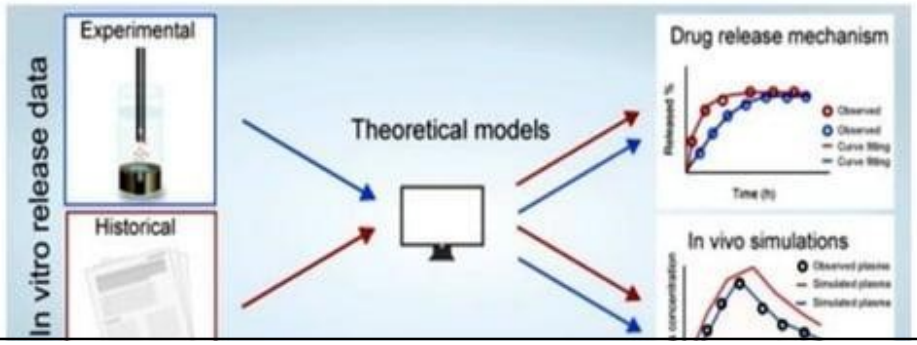
- An **in vitro** in **vivo correlation** (IVIVC) is a predictive mathematical model that describes the relationship between an **in vitro** property of a dosage form (primarily dissolution or drug release) and a relevant in **vivo** response (primarily a drug's plasma concentration or the amount of drug absorbed)

In-vitro-in-vivo correlations

- IVIVC could also be employed to establish dissolution specifications and to support and/or validate the use of :
  - Dissolution methods
  - Quality control procedures
  - Tablet or Capsule disintegration
  - Instrumental methods of analysis
  - Dissolution Rate Test
  - The rate of drug absorption
  - Dissolution Profile Parameters
  - In Vivo Performance
  - Proper In-Vitro Dissolution Rate
  - Correlate the data with the bioavailability

In-vitro-in-vivo correlations

- Presentation of *In-vitro-in-vivo correlations*



Bioequivalence studies

- It refers to the drug substance in two or more identical dosage forms, reaches systemic circulation at the same rate and to the same relative extent.
- i.e. their plasma concentration-time profiles will be identical without significant statistical differences.
- Advantages:
  - Minimizes the effect of inter subject variability.
  - It minimizes the carry over effect.
  - Requires less number of subjects to get meaningful results.
- Disadvantages:
  - Requires longer time to complete the studies.
  - Completion of studies depends on number of formulations evaluated

Bioequivalence studies

Requirements/Objectives:

- If a new product is intended to be a substitute for an approved medicinal product as a pharmaceutical equivalent or alternative,the equivalence with this product should be shown or justified.
- In order to ensure clinical performance of such drug products,bioequivalence studies should be performed. Bioequivalence studies are conducted if there is:
- A risk of bio - inequivalence and/or

Bioequivalence studies

- There are several types of equivalences.
  - A. Chemical Equivalence
  - B. Pharmaceutical Equivalence
  - C. Bioequivalence
  - D. Therapeutic Equivalence

- A. Chemical Equivalence :-
  - It indicates that two or more drug products contain the same labelled chemical substance as an active ingredient in the same amount.
- B. Pharmaceutical Equivalence :-

Bioequivalence studies

- C. Bioequivalence :-
  - It is a relative term which denotes that the drug substance in two or more identical dosage forms, reaches the systemic circulation at the same relative rate and to the same relative extent i.e. their plasma concentration-time profiles will be identical without significant statistical differences.
  - When statistically significant differences are observed in the bioavailability of two or more drug products, bioinequivalence is indicated.
- D. Therapeutic Equivalence :-

Bioequivalence studies

- Bioequivalence can be demonstrated either –
- In vivo, or In vitro

In-vivo

- The following sequence of criteria is useful in assessing the need for in vivo studies:
  - 1. Oral immediate-release products with systemic action-
    - Indicated for serious conditions requiring assured response.
    - Narrow therapeutic margin.
    - Pharmacokinetics complicated by absorption < 70 % or absorption window, nonlinear kinetics, presystemic elimination > 70 %.
    - Unfavorable physiochemical properties, e.g. low solubility, metastable

Bioequivalence studies

- 2. Non-oral immediate-release products.
- 3. Modified-release products with systemic action.

- In vivo bioequivalence studies are conducted in the usual manner as discussed for bioavailability studies, i.e. the pharmacokinetic and the pharmacodynamic methods.
- 1. Pharmacokinetic Methods
  - a) Plasma level-time studies
  - b) Urinary Excretion studies
- 2. Pharmacodynamic Methods

Methods to enhance the dissolution rates and bioavailability of poorly soluble drugs.

- 1)Particle Size Reduction
  - Conventional methods
  - Micronization
  - Nanosuspension
- 2)Hydrotropy
- 3)Cosolvency
- 4)Solubilization by Surfactants
- 5)Solid Dispersion
  - The fusion (melt) method
  - The solvent method
  - Dropping method

Methods to enhance the dissolution rates and bioavailability of poorly soluble drugs.

- 10) Complexation
  - Physical Mixture
  - Kneading method
  - Co-precipitate method
- 11) Spray Drying
- 12)Inclusion Complex Formation-Based Techniques
  - Kneading Method
  - Lyophilization/Freeze-Drying Technique
  - Microwave Irradiation Method
- 13) Liquisolid technique
- 14) Micro-emulsion
- 15) Self-Emulsifying Drug Delivery Systems
- 16) Neutralization 17)Cryogenic Method
  - Spray Freezing onto Cryogenic Fluids