UNIT- II 10 Hours

Elimination: Drug metabolism and basic understanding metabolic pathways, renal excretion of drugs, factors affecting renal excretion of drugs, renal clearance, Non renal routes of drug excretion of drugs **Bioavailability and Bioequivalence:** Definition and Objectives of bioavailability, absolute and relative bioavailability, measurement of bioavailability, in-vitro drug dissolution models, in-vitro-in-vivo correlations, bioequivalence studies, methods to enhance the dissolution rates and bioavailability of poorly soluble drugs.

DRUG METABOLISM

Elimination is the major process for removal of a drug from the body and termination of its action. *It. is defined as the irreversible loss of drug .from the body.* Elimination occurs by two processes viz. Biotransformation and excretion.

Biotransformation *of drugs is defined as the conversion from one chemical form to another.* The term is used synonymously with metabolism. The chemical changes are usually affected enzymically in the body and chus, the definition excludes chemical instability of a drug within the · body; for e.g. conversion of penicillin to penicilloic acid by the bacterial ' penicillinase and mammalian enzymes is metabolism but its degradation by the stomach acid to penicillenic acid is chemical instability.

All chemical substances that are not nutrients for the body and enter the body through, ingestion, inhalation or absorption are called as xenobiotics (Greek: *xenos = foreign)* or exogenous compounds.

Drug Metabolizing Organs

Liver is the primary site for metabolism of almost all drugs (and other xenobiotics) because of its relative richness **in** possessing a large variety of enzymes **in** large amounts. Metabolism by organs other -than· liver (called as **extrahepatic metabolism)** is of minor importance_ since lower level of drug metabolizing enzymes are present in such tissues. The decreasing order of drug metabolizing ability of various organs is: *liver > lungs > kidneys > intestine > placenta > adrenals > skin.* Brain, testes, muscles, spleen, etc. also metabolize drugs to a small extent.

CHEMICAL f ATHW□YS OF DRUG BIOTRANSFORMATION

R. T Williams divided the pathways of drug metabolism reactions into two general categories: phase I and phase II reactions.

Phase I Reactions

These reactions generally precede phase II reactions and include oxidative, reductive and hydrolytic reactions. By way of these reactions, 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 also called as*** **functionalization reactions.**

The transformations are also called as **asynthetic reactions,** opposite to the synthetic phase II reactions. The resulting product of phase I reaction is susceptible to phase II reactions.

Phase II Reactions

These reactions generally involve covalent attachment of small polar endogenous molecules such as glucuronic acid, sulfate, glycine, etc. To either unchanged drugs or phase I products having suitable functional groups viz.' -OH, -COOH, -NH2 and -SH and for1n highly water-soluble_ ***conjugates*** which are readily excretable by the kidneys (or bile). Thus; these reactions are called as **conjugation reactions.** Since the outcome of such processes are generally products with increased molecular size (and altered physicochemical properties), they are also called as **synthetic reactions.** Quite often, a phase I reaction may not yield a metabolite that is sufficiently hydrophilic or phar111ac0Iogically inert but conjugation reactions generally result in products with total loss of pharmacologic activity and high polarity. Hence, ***phase II reactions are better known as*** **true detoxification reactions.** Since these reactions generally involve transfer of moieties to the substrate to be conjugated, the enzymes responsible are called as ***transferases.*** The biotransfor1nation of drug metabolites, particularly the glutathione conjugates which are excreted via bile in the gut, by the intestinal microflora, is considered by few researchers as **phase III reactions.** Quite commonly, the biotransfor1nation reactions proceed ***sequentially*** and the combination of several phase I and phase II reactions yield a range of metabolites (Fig).

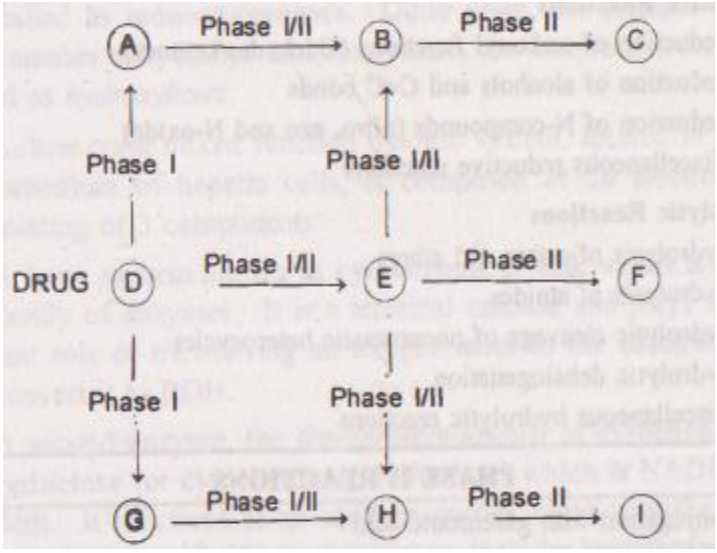


Fig. Sequence of phase I and phase II **reactions yielding a range of products**

The various phase I and phase II reactions are listed in Table

TABLE 5.2-Chemical Pathways of Drug Biotransformat:ion-(M) and (N)

Indicate Reactions Catalyzed by Microsomal and Nonmic rosomal Enzymes

PHASE I REACTIONS

A. Oxidative Reactions

1. Oxidation of aromatic carbon atoms

2. Oxidation of olefins (C=C bonds) .
3. Oxidation of benzylic, allylic carbon atoms and carbon atoms alpha to carbonyl and imines
4. Oxidation of aliphatic carbon atoms
5. Oxidation of alicyclic carbon atoms
6. Oxidation of carbon-heteroatom systems:
   - **(a)** Carbon-Nitrogen systems (aliphatic and aromatic amines)
     - **i.** N-Dealkylation _
     - **ii.** Oxidative. deamination
     - **iii.** N-Oxide formation
     - **iv.** N-Hydroxylation
   - **(b)** Carbon Sulfur systems:
     - **i.** S-Dealkylation
     - **ii.** Desulfuration
     - **iii.** S-oxidation
   - **(c)** Carbon-Oxygen systems (0-dealkylation)
7. Oxidation of alcohol, carbonyl and acid functions
8. Miscellaneous oxidative reactions

B. .Reductive --Reactions

1. Reduction of carbonyl functions. (aldehydes/ketones)
2. 2. Reduction of alcohols and C=C ·bonds ·
3. Reduction .of N-compounds (nitro, azo and N-oxide)
4. Miscellanecrlis reductive reactions -

C. Hydrolytic Reactions

1. l. Hydrolysis of esters and ethers
2. Hydrolysis of amides
3. Hydroiytic cleavage of nonaromatic heterocycles
4. Hydrolytic dehalogenation
5. Miscellaneous hydrolytic _reactions

PHASE II Reactions

1. Conjugation with glucuronic acid
2. Conjugation with sulfate moieties
3. C9njugation with alpha amino acids

4. Conjugation with glutathione and mercapturic acid fJnnation
5. Acetylation reactions
6. Methylation reactions
7. Miscellaneous conjugation reactions

Drug Excretion

•It is the loss of unchanged drug & its metabolites by secretary organs which eliminate polar compounds more efficiently than lipid soluble ones.

•Lipid soluble compound→ metabolized into more polar compound → eliminated.

Routes of drug excretion:

1. Renal excretion
2. Biliary & fecal excretion
3. Pulmonary elimination: for gases & vapor e.g. halothane & alcohol.
4. Excretion via other routes (breast milk, saliva, sweat, tears, hair & skin).

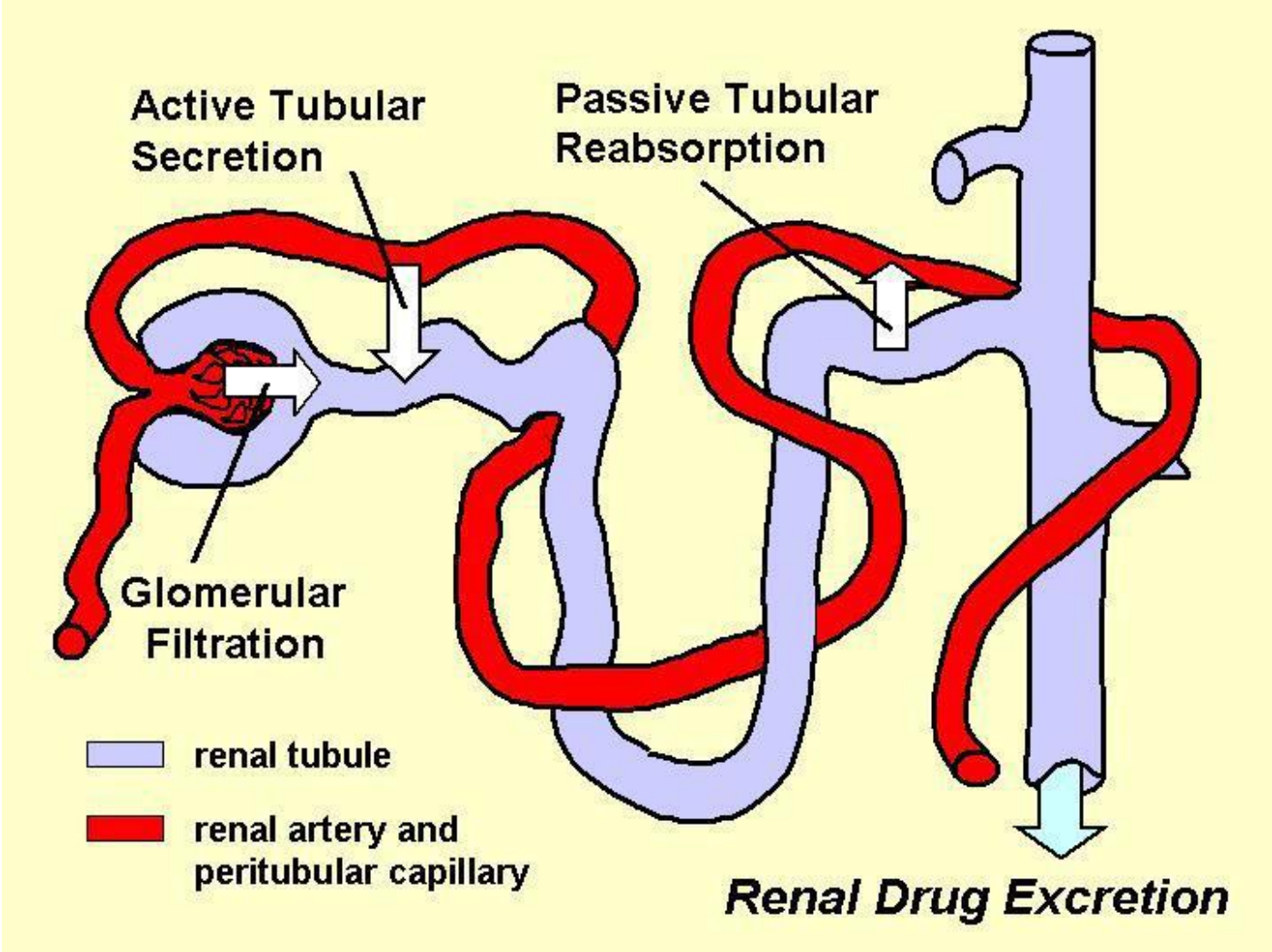
1.Renal drug excretion:

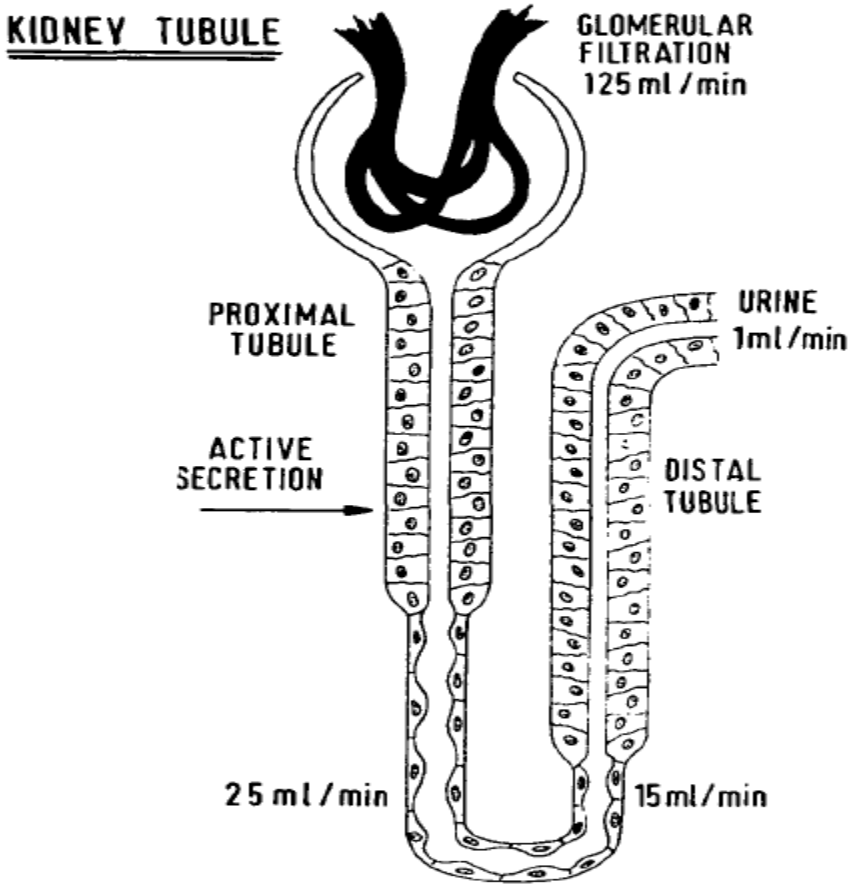
Kidney is the most important excretory organ for drugs & their metabolites.

A. Glomerular filtration

B. Active tubular secretion

C. Tubular reabsorption: Passive or active


Active Tubular Secretion
Passive Tubular Reabsorption
Glomerular Filtration
renal tubule
renal artery and peritubular capillary
Renal Drug Excretion



A.Glomerular filtration: It is a passive process.

•It depends on:

(a) Glomerular filtration rate (GFR):is the volume of fluid filtered from the renal capillaries into the Bowman's capsule per unit time

(b) Creatinine & inulin excretion rates are used to measure the GFR (completely removed by GF & are neither actively secreted nor reabsorbed) → as diagnostic indicators for kidney function.

(c) Protein binding of the drug: Protein binding limits GF but doesn't limit active tubular secretion.

(d) Molecular weight of the drug (M.W): ↓M.W drugs (below 20000)

B.Active tubular secretion (ATS):

80% of the drug deliver to the kidney is excreted by active tubular secretion.

(a) Acid carrier system: Transports acidic drugs & endogenous compounds (penicillins, probenecid, salicylic acid, phenobarbitone, frusemide, indomethacin & uric acid

(b) Base carrier system: Transports basic drugs & endogenous compounds (amphetamine, chloroquine, quinine, morphine, histamine, serotonin & dopamine).

•ATS may act as a site for drug-drug interactions:

•Probenicid inhibit active tubular secretion of penicillins.

•Probenicid also inhibits active secretion of methotrexate → toxicity.

•Aspirin (analgesic dose) inhibits uric acid excretion.

C.Tubular reabsorption:

a. Passive tubular reabsorption: lipid soluble drugs are rapidly and extensively reabsorbed.

•Polar compounds have low tubular permeability, mainly excreted in urine (digoxin and aminoglycosides).

•It is pH dependent (urinary acidification & alkalinization).

•Active tubular reabsorption: e.g. lithium, fluoride & uric acid

•Uricosuric drugs [probenicid, sulfinpyrazone and aspirin (high dose)] inhibit the active tubular reabsorption of uric acid.

•Some drugs concentrate in urine & precipitate in renal tubules (low urine solubility) → crystalluria e.g. sulfonamides.

Factors affecting renal excretion of drugs:

1. Alteration of urine pH & diuresis (alkaline diuresis for treating salicylates and phenobarbital intoxication).
2. Protein binding of the drug:
3. Limits GF but doesn't limit active tubular secretion
4. Age: ↓GFR & tubular functions in newborn.

GFR declines slowly with age

2.Biliary & fecal excretion:

A.Orally unabsorbed drugs

B.Metabolites excreted in the bile (active transport or P-glycoprotein) → GIT e.g. rifampicin.

•Molecular weight and polarity are the primary determinants of biliary excretion.

•conjugation enhances biliary excretion.

•Enterohepatic circulation of the drugs (E.H.C): The glucuronide conjugate of some drugs are excreted in bile → intestine (hydrolysis) →releasing the parent drug →reabsorbed to the blood.

•It prolongs the half-life of the drug & permits conservation of endogenous comp. such as bile acid, vit D & B12, folic acid & estrogens.

•e.g. Ivermectin, morphine & ethinyl estradiol.

•Interruption of the cycle→ traps drugs in GIT

Treatment of drug intoxication (cholestyramine with digoxin)

Treatment failure (tetracycline with oral contraceptive)

3. Excretion of drugs by other routes:

Quantitatively unimportant and mainly dependent on simple diffusion of unionized drug.

A. Excretion in breast milk: almost any drug present in the mother's blood may be detected in her milk, but since milk is more acidic than plasma (6.6), basic drugs may be trapped in breast milk.

•Drugs should be avoided as much as possible during lactation.

•If the drug is relatively safe, the nursing mother should take it 30-60 min. after nursing or 3-4 hrs before the next feeding.

•Drugs for which no data are available on safety during lactation should be avoided or breast feeding discontinued while they are being given.

•Examples of drugs that are contraindicated during lactation: Tetracyclines →permanent tooth staining in infant

INH →pyridoxine deficiency

Chloramphenicol → bone marrow suppression

Diazepam →sedation

Opiates ”morphine”→neonatal narcotic dependence. (if mother stop morphine or breast feeding)

B.Salivary excretion: The concentration of some drugs in saliva parallels that in plasma (bioavailability determination). e.g. phenytoin (gingival hyperplasia), acetaminophen, theophylline, lithium, tolbutamide & digoxin.

•Saliva is more acidic than plasma, so basic drugs are trapped in saliva e.g. . Lithium concentrations in saliva is 2-3 times higher than in plasma.

C. Excretion into hair and skin:

•Although excretion of drugs into hair and skin is quantitatively unimportant, sensitive methods for detection of toxic metals in these tissues have forensic significant .

Bioavailability and Bioequivalence:

INTRODUCTION

Define bioavailability as “The rate and extent to which the active drug ingredient or therapeutic moiety is absorbed from a drug product and become available at the site of drug action.”

Many studies illustrate that difference in manufacturing procedures, as well as the composition of the dosage form; can affect the bioavailability of a drug product. It is also influenced by the physiology of the patient and other factors such as the content of the gastrointestinal tract. A major factor in determing the bioavailability of an orally administered drug product is the dissolution rate of the drug. A drug must be in solution in order to be absorbed from the gastrointestinal tract.

Concept of Bioavailability: Bioavailability is used to describe the fraction of an administered dose of unchanged drug that reaches the systemic circulation. By definition, when a medication is administered intravenously, its bioavailability is 100%. But when a medicament is administered via other routes its bioavailability decreases. Bioavailability is a measurement of the extent of a therapeutically active drug that reaches the systemic circulation and is available at the site of action. It is expressed as the letter *F*.

Absolute bioavailability: Absolute bioavailability compares the bioavailability [estimated as

area under the curve (AUC)] of the active drug in systemic circulation following non-intravenous administration (i.e., after oral, rectal, transdermal administration) with the bioavailability of the same drug following intravenous administration. To determine absolute bioavailability of a drug, a pharmacokinetic study must be done to obtain a plasma drug concentration vs time plot for the drug after both intravenous (IV) and non-intravenous administration. The formula for calculating *F* for a drug administered by the oral route (p.o.) is given below.

$$F = \frac{[AUC]_{po} \times dose_{IV}}{[AUC]_{IV} \times dose_{po}}$$

Therefore, a drug given by the intravenous route will have an absolute bioavailability of 1 (F=1) while drugs given by other routes usually have an absolute bioavailability of less than one.

Relative bioavailability: This measures the bioavailability (estimated as area under the curve, or AUC) of a certain drug when compared with another formulation of the same drug, usually an established standard, or through administration via a different route.

$$relative\ \ bioavailability = \frac{[AUC]_A \times dose_B}{[AUC]_B \times dose_A}$$

MEASUREMENT OF BIOAVAILABILITY:

Pharmacokinetic method: These are widely used on the assumption that the pharmacokinetic profile reflects the therapeutic effectiveness of a drug. Thus, these are indirect methods. The two major pharmacokinetic methods are:

(i) Plasma level-Time studies: The three parameters considered for determination of bioavailability are: -

Cmax: - The peak plasma concentration gives an indication whether the drug is sufficiently absorbed systemically to provide a therapeutic response.

Tmax: - The peak times that gives an indication of the rate of absorption.

AUC: -The area under the plasma level-time curve that gives a measure of the extent of absorption or the amount of drug that reaches the systemic circulation. The extent of bioavailability can be determined by following equations.

$$F = \frac{[AUC]_{Oral}\, D_{i.v}}{[AUC]_{i.v} D_{oral}} \qquad Fr = \frac{[AUC]_{test}\, D_{std}}{[AUC]_{std}\, D_{test}}$$

Where D stands for dose administered and subscripts i.v and oral indicates the route of administration. Subscript test and std. indicate the test and the standard doses of the same drug to determine relative availability.

(ii) Urinary Excretion studies: The three major parameters examined in this study are:

(Dxu /dt) max:- The maximum urinary excretion rate, it is obtained from the peak of plot between rate of excretion versus midpoint time of urine collection period. It is analogous to the cmax derived from plasma level studies.

(tu) max :- The time for maximum excretion rate, it is analogous to the t_{max} of plasma level data.

Xu: -The cumulative amount of drug excreted in the urine, it is related to the AUC of plasma level data and increases as the extent of absorption increases.

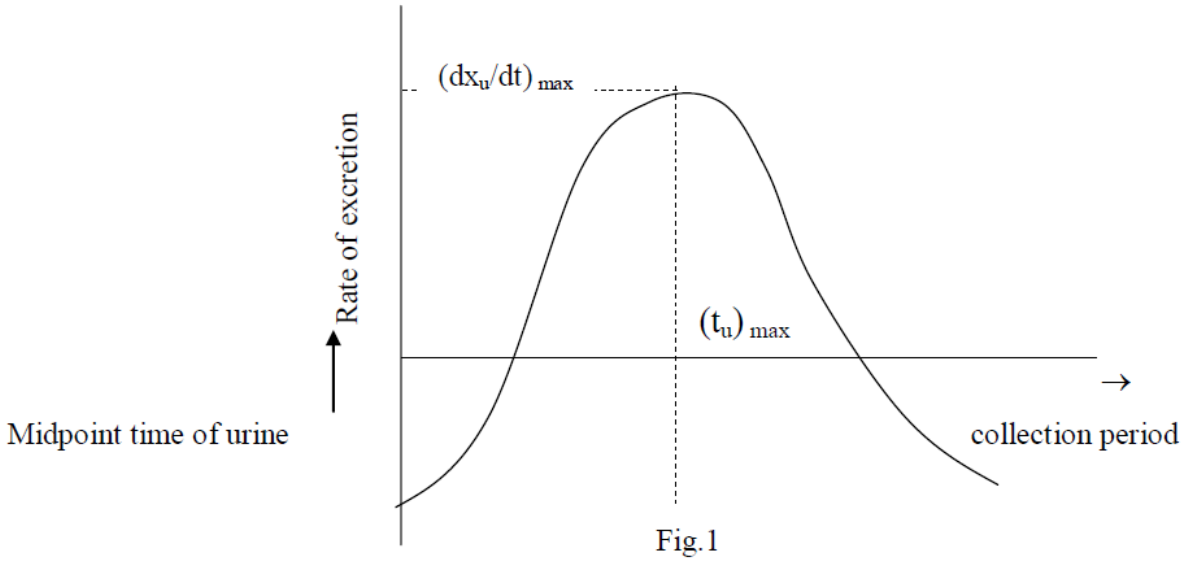


Fig.1

The extent of bioavailability is calculated from equation given below.

$$F = \frac{[X_U^{\infty}]_{Oral}\, D_{iv}}{[X_U^{\infty}]_{iv}\, D_{oral}} \qquad F_r = \frac{[X_U^{\infty}]_{test}\, D_{std}}{[X_U^{\infty}]_{std}\, D_{test}}$$

Pharmacodynamic Method: These methods are complementary to pharmacokinetic approaches and involve direct measurement of drug effect on a Physiologic process as a function of time. The two pharmacodynamic methods are;

(i) Acute pharmacologic response: When bioavailability measurement by pharmacokinetic methods is difficult, inaccurate or non-reproducible, an acute pharmacologic effect such as change in ECG or EEG reading, pupil diameter, etc is related to the time course of a given drug.

(ii) Therapeutic response: Theoretically this method is most definite. This method is based on observing the clinical response of a drug formulation given to patient suffering from disease for which it is intended to be used.

In-Vitro Drug dissolution Testing Models

For an *in* vitro test to be useful, it must predict the *in vivo* behaviour to such an extent that *in* vivo bioavailability test need not be performed.

Despite attempts to standardize the test perfonnance, the *in vitro* dissolution technique is still by no means a perfect approach. The efforts are mainly aimed at mimicking the environment offered by the biological system.

There are several factors that must be considered in the design of a dissolution test. They are:

1. *Factors relating to the dissolution apparatus* such as-the design, the size of the container (several mL to several liters), the shape of the container (round bottomed or flat), nature of: agitation (stirring, rotating or oscillating methods), speed of agitation, perfonnance precision of the apparatus, etc.

2. *Factors relating to the dissolution fluid* such as-composition (water, 0.1 N HCI, phosphate buffer, simulated gastric fluid, simulated intestinal fluid, etc.), viscosity, volume (generally larger than that **needed** to completely dissolve the drug u·nder test), temperature (generally 37°C) and maintenance of **sink** (drug concentration in solution maintained constant at a low level) or **nonsink** conditions (gradual increase in the drug concentration **in** the dissolution medium).

3. *Process parameters* such as method of introduction of dosage form, sampling techniques, changing the dissolution fluid, etc.

The dissolution apparatus has evolved gradually and considerably from a simple beaker type to a highly versatile and fully automated instrument.

The devices can be classified in a number of ways. Based on the absence of presence of sink conditions, there are two principal types of dissolution apparatus:

I. **Closed-compartment apparatus:** It is basically a limited volume apparatus operating under non sink conditions. The dissolution fluid is restrained to the size of the container, e.g. beaker type apparatus.

2. Open-compartment apparatus: It is the one in which the dosage form is contained in a column which is brought in continuous contact **with** fresh, flowing dissolution medium (perfect sink condition).

A third type called as dialysis **systems** are used for very poorly aqueous soluble drugs for which maintenance of sink conditions would otherwise require large volume of dissolution fluid. Only the official methods will be discussed here briefly.

1. **Rotating Basket Apparatus (Apparatus 1)**

It is basically a closed-compartment, beaker type apparatus comprising of a cylindrical glass vessel with hemispherical bottom of one liter capacity "'Partially immersed in a water bath to maintain the temperature at 37°C. A cylindrical basket made of 22 mesh to hold the dosage form 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 (Fig.**).** The basket should remain in motion during drawing of samples. All metal parts like basket and shaft are made of S.S. 316.

Rotating Paddle Apparatus (Apparatus 2)

The assembly is same as that for apparatus I except that the rotating basket is replaced with a paddle which acts as a stirrer (Fig.). The dosage form is allowed to sink to the bottom of the vessel. A small, loose, wire helix may be attached to the dosage for111 that would otherwise float.

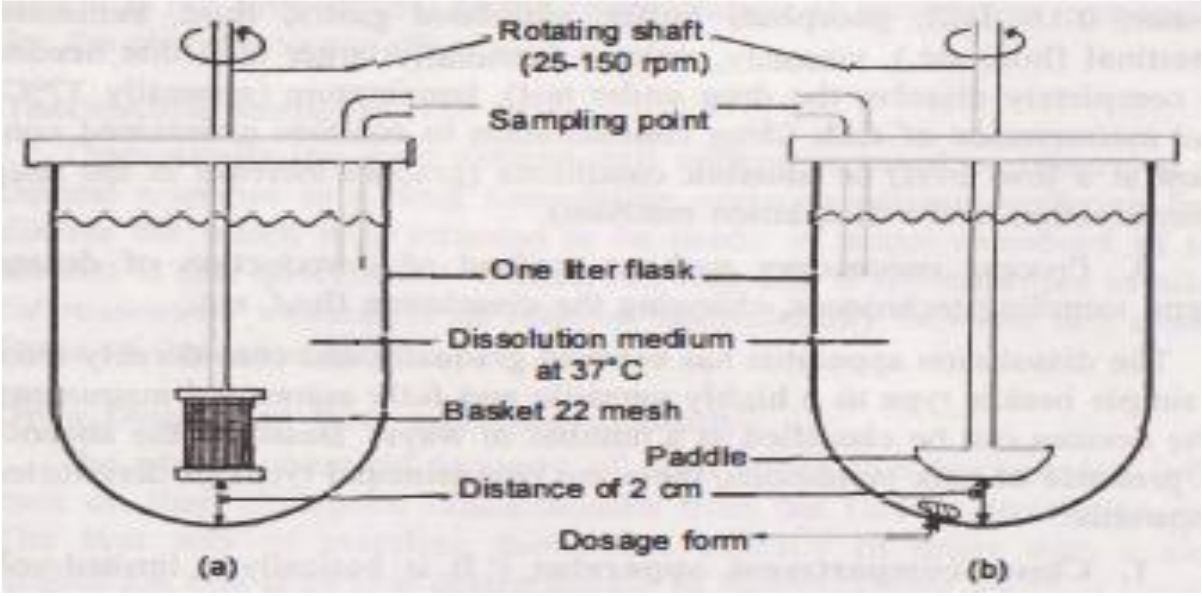


Fig. Schematic representation of official dissolution apparatus -forced convection non sink type (a) rotating basket apparatus, and (*b)* rotating paddle apparatus.

In-vitro & In-vivo Correlation:

Convincing correlation between in vitro dissolution behavior of drug and its in vivo bioavailability must be experimentally demonstrated to guarantee reproducibility of biologic response. There are two basic approaches by which a correlation between dissolution testing and bioavailability can be developed.

1. By establishing a relationship, usually linear, between the in-vitro dissolution and the in-vivo bioavailability parameters.

2. By using the data from previous bioavailability studies to modify the dissolution methodology in order to arrive at meaningful in vitro in vivo correlation**.**

Some of the often used quantitative linear in vitro-in vivo correlations are: -

Correlations based on the plasma level data: - Here linear relationship between dissolution parameters such as percent drug dissolved, rate of dissolution, rate constant for dissolution, etc. and parameters obtained from plasma level data such as percent drug absorbed, rate of absorption, Cmax, tmax, Ka etc.

Correlation based on the urinary excretion data: - Here dissolution parameters are correlated to the amount of drug excreted unchanged in the urine, cumulative amount of drug excreted as function of time, etc.

Correlation based on the pharmacologic response: - An acute pharmacologic effect such as LD50 in animals is related to any of the dissolution parameters.

CAUSES OF POOR AQUEOUS SOLUBILITY:

1. Effective surface area of drug:

Particle size: - The smaller the drug particles, the greater the surface area for a given amount of drug. So dissolution rate will increase as particle size decrease. The smaller granules of phenacetin dissolve more quickly than the larger granules and there is a graded response. The hydrophobic drug phenacetin has been manipulated by a pharmaceutical manufacturing process called granulation where by the hydrophilic diluent gelatin has been incorporated into the particle.

Disintegration and deaggregation: -Dosage form disintegrates into large particles, these large particles must deaggregate to yield fine particles this may be rate-limiting step in the dissolution process. Poor disintegration decrease rate of dissolution so availability of these drugs is less.

Effect of manufacturing processes: -Lubricating agents are often added to capsule or tablet dosage forms. Most lubricants are very hydrophobic lubricants e.g. magnesium stearate.

Increasing hydrophobicity decreases its dissolution rate and bioavailability**.**

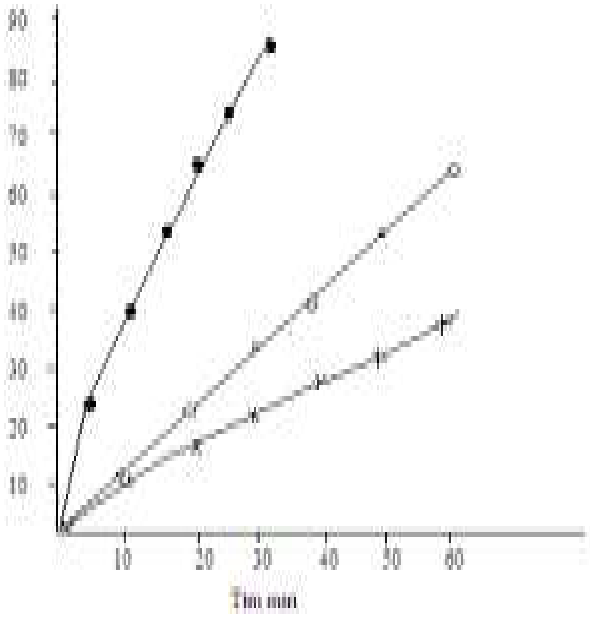


Fig 5 Effect of lubricant on dissolution rate of salicylic acid contained in compressed tablets. X, magnesium stearate □-- no lubricant □- sodium lauryl sulfate.

2. Saturation solubility of drug:

Salt form of drug: -Dissolution rate of poor aqueous soluble drug and non-ionized drug is less than salt form of the drug, because salt form is more soluble in aqueous medium. For e.g.

Paraaminosalicylic acid (PAS), all the state forms are more rapidly available than the non ionized PAS to a significant extent. Furthermore the extent of availability of the acid form is only about 77% of that of the salt forms because the acid form is less ionized than salt form in acid pH.

PH effect: - The effect of pH on the solubility of a drug from oral dosage form depends on: pH of the G.I. fluids, acid or base strength of the drug, physicochemical properties of the dosage form. The ionized form of a drug will be more soluble than the non-ionized form in the fluids of the G.I.T.

Polymorphism: - Polymorphism effects saturation solubility and hence the dissolution rate of drug stable thermodynamically. Thus making them poorly bioavailability e.g. chloramphenicol palmitate is available in two different forms A and B. B form is more soluble and less stable. So as the fraction of more stable polymorph increases in dosage form, the aqueous solubility of drug decreases**.**

Complexation: - A drug may complex with both absorbable and non absorbable excipient in a dosage form. This complexation may occur with in dosage form or in the solubilizing fluids and the resulting complex may be more or less soluble than the drug itself.

3. Concentration of the dissolved drug in bulk solution (Cg): The driving force for dissolution is the concentration gradient Cs-Cg. It is usually assumed that Cg is much under sink condition. If a drug is absorbed through G.I membrane very slowly, the drug concentration in the G.I.T fluid may build up. If a drug is more soluble in the bulk fluids than the boundary layer because of a difference in pH or by complexation other components. In this case, the gradient may decrease and dissolution may slow down or ever stop**.**

METHOD FOR ENHANCEMENT OF BIOAVAILABILITY:

Particle size reduction: Particle size reduction effectively increases the surface area to volume ratio, there by increasing the dissolution rate in the GIT and promoting absorption. Various technologies used for particle size reduction include micronization, nanoization and most recently, super critical fluid technology, which deposits nanometer sized drug particles on a pharmaceutically acceptable support matrix. E.g. The extent of absorption of an oral dose increased 2.5 times when the surface area was increased approximately six fold micronized griseofulvin permits a 50% decrease in dosage to obtain a satisfactory clinical response.

Use of surfactants: The surface-active agent enhance dissolution rate primarily by promoting wetting and penetration of dissolution fluid into the solid drug particles. They are generally used in concentration below their critical micelle concentration surfactants like polysorbets are widely used and concentration are formulated as clear aqueous solution by processes of micellar solubilization. For exampleCortisone acetate and fluorometholone are solubilized by polysorbate-8010.

Alteration of pH of the drug microenvironment: This can be achieved in two ways-insitu salt formulation, and addition of buffers to the formulation. The ionized form of a drug will be more soluble than the nonionized form in the aqueous fluid in G.I.T. The salt forms of the drug dissolve much faster than the nonionized forms in all media and that more of the salt forms of the drug are absorbed.The salt acts as its own buffer in the diffusion layer and goes into solution in this layer. Addition of the small amount of buffer

may not alter the pH of bulk fluids of G.I.T., but can alter the pH of diffusion layer to a pH which favours rapid dissolution of the active ingredient for e.g. buffered tablet of aspirin.

Use of metstable polymorphs: - The crystalline state of a drug may affect its saturation solubility and hence it's dissolution rate. A metstable polymorph is more soluble than the stable polymorph. Chloramphenicol palmitate is available in two different forms A and B. The B form is more soluble. In chloramphenicol palmitate suspension, as the fraction of the B form of chloramphenicol palmitate increases, it would appear that increase in rate and extent of bioavailability with an increasing percentage of the B form is due to the increasing rate of

dissolution.

Solute solvent complexation: - Solvates of drugs with organic solvents generally have higher aqueous solubility than their respective hydrates or original drugs. Much higher solubility can be attained by freeze drying such a solute in solution with an organic solvent with which it is known to form a solvate. Example, when griseofulvin in benzene solvent is freeze dried it forms powder of particles of submicron size such that 1:2 griseofulvin benzene solvate. However one should take care that the solvent is nontoxic.

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 by evaporation of solvent.

Selective absorption on insoluble carriers: - A highly active absorbent such as the inorganic clays like bentonite can enhance the dissolution rate of poorly water soluble drug such as griseofulvin, indomethacin and prednisone by maintaining the concentration gradient as its maximum. The reason for rapid release of drug from the surface of clays is due to the weak physical bonding between the absorbate and adsorbent and hydration and swelling of the clay in the aqueous media.

Solid solutions: - A solid solution is binary system comprising of a solid solute molecularly dispersed in a solid solvent. Since the two components crystallize together in a homogenous one phase system, solid solution are also called molecular dispersion or mixed crystals. Because of reduction in particle size to the molecular level, solid solutions show greater aqueous solubility and faster dissolution than eutectics and solid dispersion. They are generally prepared by fusion method where by physical mixture of solute and solvent are melted together followed by rapid solidification of such system e.g. griseofulvin-succinic acid. The griseofulvin from such solid solution dissolves 6 to 7 times faster than pure griseofulvin.

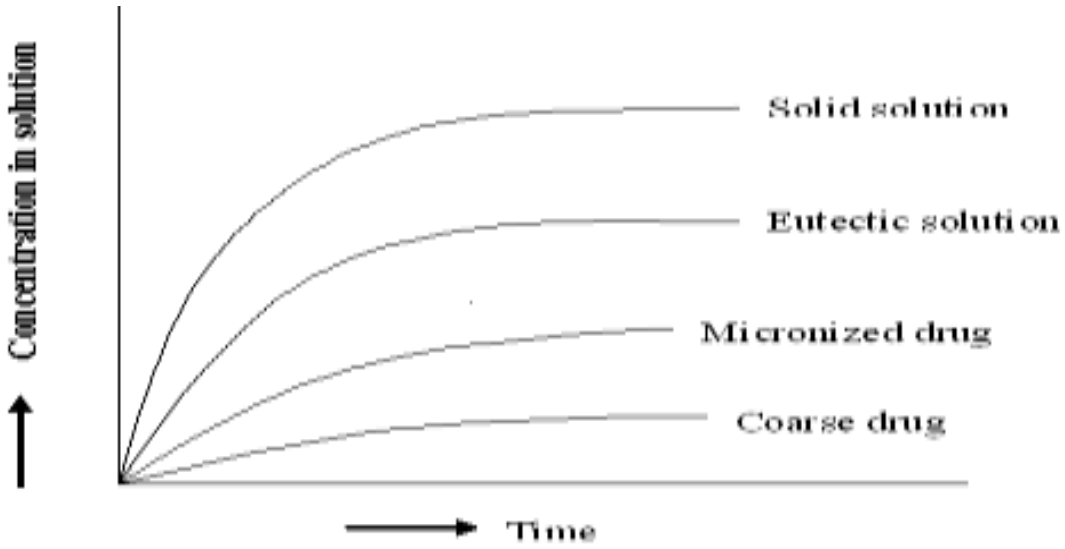


Fig. 10 Dissolution rates of griseofulvin as coarse particle, as micronized particle and as a eutectic and solid solution with succinic acid. The graph shows a comparison between the dissolution rates of different forms of griseofulvin.

Eutectic mixtures: - These systems are also prepared by fusion method. Eutectic melts differ from solid solutions in that the fused melt of solute solvent show complete miscibility of two crystalline components. When the eutectic mixture is exposed to water, the soluble carrier dissolves leaving the drug in a microcrystalline state which solubilizes rapidly**.**

Solid dispersions:- These are generally prepared by solvent or co-precipitation method where by both the guest solute and solid carrier solvent are dissolved in a common volatile liquid solvent such as alcohol. The liquid solvent is removed by evaporation under reduced pressure or by freeze drying which result in amorphous precipitation of guest in a crystalline carrier. The method is suitable for thermolabile substance but has a number of disadvantages like high cost of processing, use of large quantities of solvent, difficulty in complete removal of solvent etc. The carriers used are same as for eutectics or solid solution with glassy materials, the dispersion or glass suspensions**.**

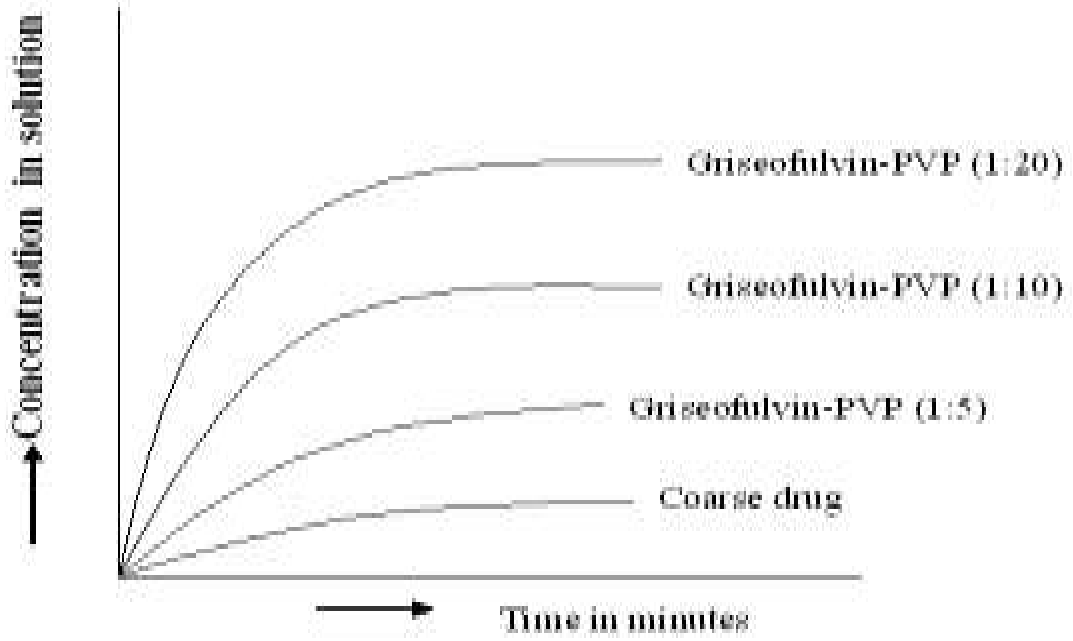


Fig.12 Dissolution rate enhancement of griseofulvin from PVP by solid dispersion technique

Molecular encapsulation with cyclodextrin: - The Beta-cyclodextrin is produced by the action of enzymes upon starch hydrolysate forming a cyclic structure comprised of 7-α-D-glucose units.

The outside of the molecule is hydrophilic and the central cavity hydrophobic. Subsequent propoxylation produces hydroxypropyl-β-cyclodextrin with modified characteristics. β- cyclodextrin is used for molecular encapsulation of a variety of molecular to enhance stability, solubility and reduce volatility Cyclodextrin are bucket-shaped oligosaccharides produced from starch. As a result of their molecular structure and shape, they possess a unique ability to act as molecular container by entrapping guest molecules in their internal cavity. Cyclodextrin are also used to reduce dermal, gastrointestinal or ocular irritation, mask unpleasant tastes or odour, prevent adverse drug ingredient interaction and convert oil/liquid into powders to improve handling. Drug delivery for prolong release, stability enhancement of sensitive compounds and taste masking of bitter drug.

BIOEQUIVALENCE STUDIES

It is commonly observed that there are several for1nulations of the same drug, in the same dose, in a similar dosage form and meant to be · given by the same route. Substitution of one product for another can be made provided they are equally effective therapeutically_ as the standard accepted. In order to ensure clinical perfo1mance of such drug products, bioequivalence studies should be performed. Some of the important terms relevant in this context will be defined.

Equivalence: It is a relative term that compares drug products with respect to a specific characteristic or function or to a defined set of standards. There are several types of equivalences.

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

Pharmaceutics Equivalence: This term implies that two -or more drug products are identical in strength, quality, purity, content uniformity and disintegration and dissolution characteristics; they may however differ in containing different excipients.

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.

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When statistically significant differences are observed in the bioavailability of two or more drug products, **bioinequivalence** is indicated.

Therapeutic Equivalence: This term indicates that two or more drug products that contain the same therapeutically active ingredients elicit identical pharmacologic effects and can control the disease to the same extent.

The *in vivo* bioequivalence study requires deter1nination of relative bioavailability after administration of a single dose of test and reference · formulations by the" Same route, in equal doses, but at different times.

The reference product· is generally a previously approved product, usually the innovator s product or some suitable reference standard. The study is performed in fasting, young, healthy, adult male volunteers to assure homogeneity in the population and to spare the patients, elderly or pregnant women from rigors of such a clinical investigation. Homogeneity in the study population per1nits focus on for1nulation factors. The volunteers are used in complete, open-label fashion such as the **Latin** cross-over **square cross-over design** in which--

-each formulation is administered just once to each subject and once in each study period, and

-Unlike parallel design, all the subjects do not - receive same type of formulation at the same, time; in a given study period, they are administered different formulation.

Such a randomised, balanced, cross-over .study has several *advantages*

1. It minimizes the intersubject variability in plasma drug levels.
2. Minimizes the carry-over effects which could occur when a given dosage form'.' influences the bioava1lability of a subsequently administered product (intra-subject variability).
3. Minimizes the variations due to time effect, and ·thus
4. Makes it possible to focus more on the for1nulation variables which is the key to success for any bioequivalence study.