Unit-2

Biopharmaceutics and Pharmacokinetics

B.Pharma 6th Sem Notes

Unit: 2

- **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 elimination:

Drug elimination is the process by which a drug is **removed from the body**, mainly through **metabolism (biotransformation)** and **excretion**.

Metabolism (Biotransformation):

It is the **chemical conversion** of a drug into more water-soluble compounds for easy excretion.

- **Main organ:** Liver
- **Other sites:** Kidneys, lungs, intestine, skin

Phases of Metabolism:

- **Phase I (Functionalization):** Oxidation, Reduction, Hydrolysis
- **Phase II (Conjugation):** Glucuronidation, Sulfation, Acetylation, Methylation

Purpose:
To convert **lipid-soluble drugs → water-soluble metabolites** (inactive or less active).

Excretion:

It is the **removal of drugs and metabolites** from the body.

Main routes:

- **Renal (urine)** – major route
- **Biliary (feces)**
- **Sweat, saliva, milk, lungs** – minor routes

Renal Excretion Steps:

1. **Glomerular Filtration** – free (unbound) drug passes into urine
2. **Tubular Secretion** – active transport of drug into renal tubule
3. **Tubular Reabsorption** – lipid-soluble drugs may return to blood

Factors Affecting Drug Elimination:

- Blood flow to organs
- Urine pH
- Plasma protein binding
- Age and disease state (kidney/liver)
- Drug interactions

Drug Metabolising Organs:

- Liver is the primary site for metabolism of almost all drugs 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 metabolising enzymes are present in such tissues.
- The decreasing order of drug metabolising ability of various organs is:

Liver > Lungs > Kidneys > Intestine > Placenta > Adrenals > Skin

Drug Metabolising Enzymes:

- The enzymes that biotransform xenobiotics differ from those that metabolise food materials. They are versatile and non-specific in metabolising a large number of drugs.

The enzymes are broadly divided into 2 categories:

- Microsomal enzymes
- Non-microsomal enzymes.

Microsomal enzymes:

- The microsomal enzymes catalyse a majority of drug biotransformation reactions.
- The microsomes are basically artefacts which resulted when attempts were first made to isolate endoplasmic reticulum of the liver homogenate.
- The large variety of microsomal enzymes catalyse a number of oxidative, reductive and hydrolytic and glucuronidation reactions.

Non-microsomal enzymes:

- The non-microsomal enzymes_include those that are present in soluble form in the cytoplasm and those attached to the mitochondria but not to endoplasmic reticulum.
- These are also non-specific enzymes that catalyse few oxidative reactions, a number of reductive and hydrolytic reactions and conjugation reactions other than glucuronidation.

Chemical pathways of drug biotransformation:

The leading pioneer in drug biotransformation research, divided the pathways of drug metabolism reactions into two general categories.

- Phase I reactions,
- 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, - NH_2 and -SH. Thus, phase I reactions are also called as functionalization 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, sulphate, glycine, etc. to either unchanged drugs or phase I products having suitable functional groups viz. -OH, -COOH, -NH2 and -SH and form highly water soluble conjugates which are readily excretable by the kidneys (or bile). Thus, these reactions are called as conjugation reactions.

Renal Excretion of Drugs:

Almost all drugs and their metabolites are excreted by the kidneys to some extent or the other. Some drugs such as gentamicin are exclusively eliminated by renal route only. Agents that are excreted in urine are –

1. Water-soluble.
2. Non-volatile.
3. Small in molecular size (less than 500 Daltons).
4. The ones that are metabolised slowly.

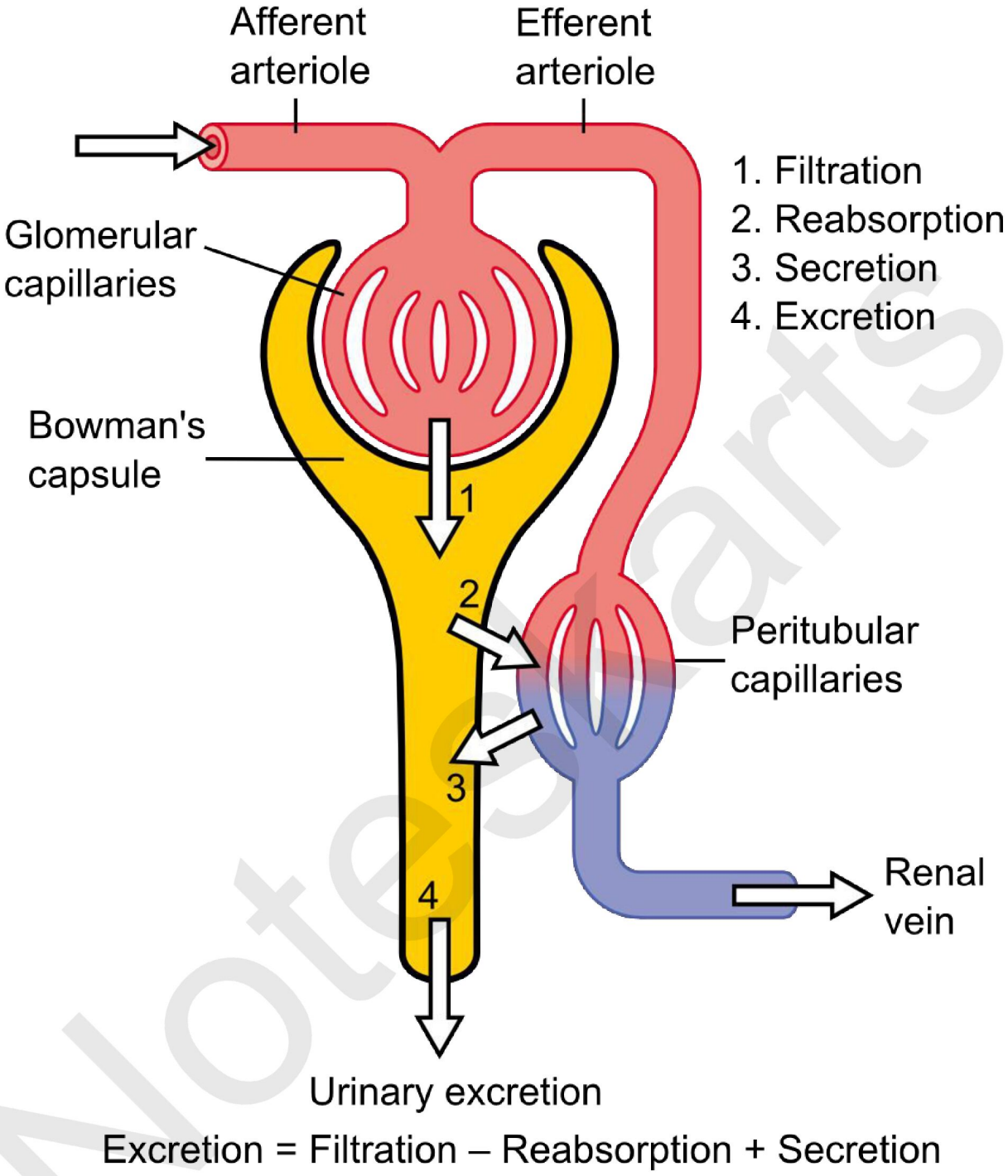
The principal processes that determine the urinary excretion of a drug are

1. Glomerular filtration.
2. Active tubular secretion.
3. Active or passive tubular reabsorption.

1. Glomerular filtration.

Glomerular filtration and active tubular secretion tend to increase the concentration of drugs in lumen and hence facilitate excretion whereas tubular reabsorption decreases it and prevents the movement of drug out of the body. Thus, the rate of excretion can be given by equation:

Rate of Excretion = Rate of Filtration + Rate of Secretion Rate of Reabsoprtion



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

- 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.
- Since a majority of drugs are weak electrolytes (weak acids or weak bases), diffusion of such agents through the lipoidal tubular membrane depend upon the degree of ionisation which in turn depends on three factors:
  1. pH of the urine.
  2. pKa of the drug.
  3. Urine flow rate.

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.

Equation of Henderson-Hasselbalch

The Henderson-Hasselbalch equation can be written as:

$$\mathbf{pH = pK_a + \log_{10}([A^-]/[HA])}$$

Where $[A^-]$ denotes the molar concentration of the conjugate base (of the acid) and [HA] denotes the molar concentration of the weak acid. Therefore, the Henderson-Hasselbalch equation can also be written as:

$$pH = pKa + \log \frac{[\text{ conjugate base }]}{[\text{ acid}]}$$

An equation that could calculate the pH value of a given buffer solution was first derived by the American chemist Lawrence Joseph Henderson.

This equation was then re-expressed in logarithmic terms by the Danish chemist Karl Albert Hassel Balch. The resulting equation was named the Henderson-Hasselbalch Equation.

Factors Affecting Renal Excretion:

Apart from the three physiologic processes that govern the urinary excretion, other factors influencing renal clearance of drugs and metabolites are:

- Physicochemical properties of the drug
- Plasma concentration of the drug
- Distribution and binding characteristics of the drug
- Urine pH
- Blood flow to the kidneys
- Biological factors
- Drug interactions
- Disease states

Physicochemical Properties of the Drug:

- Important physicochemical factors affecting renal excretion of a drug are - Molecular size, pKa and lipid solubility.
- The molecular weight of a drug is very critical in its urinary elimination. An agent of small molecular size can be easily filtered through the glomerulus. Compounds of weights below 300 Daltons, if water-soluble, are readily excreted by the kidneys.
- The influence of drug pKa Urinary excretion of an unchanged drug is inversely related to its lipophilicity.
- This is because, a lipophilic drug is passively reabsorbed to a large extent. Stereochemical nature of the drug may also influence renal clearance.
- If a drug exhibits stereoselective protein binding then the drug enantiomers would exhibit differential filtration rates.

Plasma concentration of the drug:

- Glomerular filtration and reabsorption are directly affected by plasma drug concentration since both are passive processes.
- A drug that is not bound to plasma proteins and excreted by filtration only, shows a linear relationship between rate of excretion and plasma drug concentration.
- In case of drugs which are secreted or reabsorbed actively, the rate process increases with an increase in plasma concentration to a point when saturation of carrier occurs.
- In case of actively reabsorbed drugs, excretion is negligible at low plasma concentrations. Such agents are excreted in urine only when their concentration in the glomerular filtrate exceeds the active reabsorption capacity, e.g. glucose.
- With drugs that are actively secreted, the rate of excretion increases with increase in plasma concentration up to a saturation level.

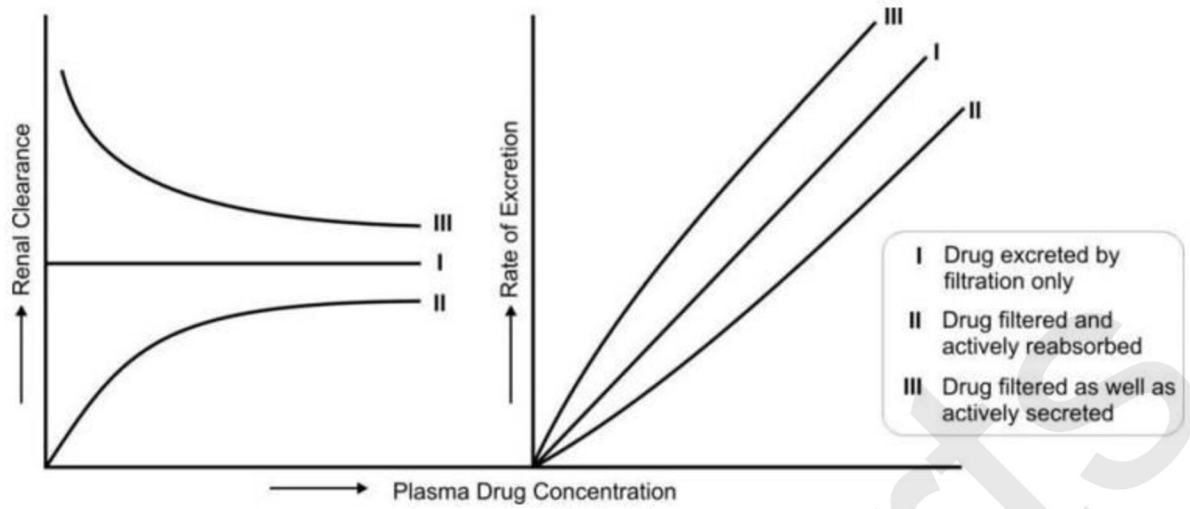


Fig. 6.3. Renal clearance and rate of excretion of a drug in relation to its plasma concentration as affected by the physiologic processes — filtration, active reabsorption and active secretion

Distribution and Binding Characteristics of the Drug:

- Clearance is inversely related to apparent volume of distribution of drugs.
- A drug with large Vd is poorly excreted in urine.
- Drugs restricted to blood compartment have higher excretion rates.
- Drugs that are bound to plasma proteins behave as macromolecules and thus cannot be filtered through the glomerulus.
- Only unbound or free drug appear in the glomerular filtrate.

Blood Flow to the Kidneys:

- The renal blood flow is important in case of drugs excreted by glomerular filtration only and those that are actively secreted.
- In the latter case, increased perfusion increases the contact of drug with the secretory sites and enhances their elimination. Renal clearance in such instances is said to be perfusion rate-limited.

Biological Factors:

- Age, sex, species and strain differences, differences in the genetic make-up, circadian rhythm, etc. alter drug excretion.
- Renal excretion is approximately 10% lower in females than in males.
- The renal function of newborns is 30 to 40% less in comparison to adults and attains maturity between 2.5 to 5 months of age. In old age, the GFR is reduced and tubular function is altered, the excretion of drugs is thus slowed down and half-life is prolonged.

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 States—Renal Impairment

- **Renal dysfunction** greatly impairs the elimination of drugs especially those that are primarily excreted by the kidneys. Some of the causes of renal failure are hypertension, diabetes mellitus, hypovolemia (decreased blood supply to the kidneys), pyelonephritis (inflammation of kidney due to infections, etc.), nephroallergens (e.g. nephrotoxic serum) and nephrotoxic agents such as aminoglycosides, phenacetin and heavy metals such as lead and mercury.
- **Uraemia**, characterized by impaired glomerular filtration and accumulation of fluids and protein metabolites, also impairs renal clearance of drugs. In both these conditions, the half-lives of drugs are increased. As a consequence, drug accumulation and toxicity may result. Determination of renal function is therefore important in such conditions in order to monitor the dosage regimen.

Non renal routes of drug excretion of drugs.

- Drugs and their metabolites may also be excreted by routes other than the renal route, called as the extrarenal or nonrenal routes of drug excretion. The various such excretion processes are:

Biliary Excretion (via bile):

- Drugs or their metabolites are secreted by the **liver** into the **bile**, which passes into the **intestine** and is eliminated in feces.
- Some drugs undergo **enterohepatic circulation**, where they are reabsorbed from the intestine back into the bloodstream.
- Examples: Chloramphenicol, Rifampicin, Morphine.

Pulmonary Excretion (via lungs):

- Volatile drugs and gaseous anesthetics are excreted through the **lungs** by exhalation.
- Examples: Alcohol, Ether, Chloroform, Nitrous oxide.

Salivary Excretion (via saliva):

- Some drugs are excreted into **saliva** and may give a metallic or bitter taste.
- Examples: Iodides, Lithium, Theophylline.

Sweat and Sebaceous Gland Excretion:

- Small amounts of certain drugs are excreted through **sweat** or **sebaceous glands**.
- This route is usually minor but can cause **skin irritation or rashes**.
- Examples: Heavy metals, Sulfonamides.

Milk Excretion (via breast milk):

- Drugs can be excreted into **breast milk**, which may affect the **nursing infant**.
- Examples: Barbiturates, Morphine, Tetracyclines, Alcohol.

Intestinal Excretion:

- Some drugs are directly excreted into the **intestinal lumen** from the blood and then removed in feces.
- Examples: Tetracyclines, Indomethacin.

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.

Bioavailability and Bioequivalence

Introduction

- The effectiveness of a drug depends not only on its pharmacological activity but also on **how much of it reaches systemic circulation** in an active form.
- **Bioavailability** and **bioequivalence** studies are crucial in drug development, formulation optimization, and regulatory approval.

Definitions

1. **Bioavailability (BA):**
    - The **rate and extent** to which the active drug ingredient is absorbed from a drug product and becomes available at the site of action.
    - Essentially, it measures **how much and how fast** a drug reaches systemic circulation.
2. **Bioequivalence (BE):**
    - Two drug products are **bioequivalent** if they show **no significant difference** in the rate and extent of absorption when administered at the same molar dose under similar conditions.
    - Usually applied for **generic vs. innovator formulations**.

Objectives of Bioavailability Studies

- To determine the **rate and extent of drug absorption**.
- To **compare different formulations** (e.g., generic vs. brand).
- To help in **optimizing drug formulations**.
- To **predict therapeutic equivalence**.
- To establish **dose adjustments** in special populations (renal, hepatic impairment).

The Route we take a drug can affect how much of it gets into our body.

Parenteral > Oral > Rectal > Topical

Absolute and relative bioavailability

Absolute Bioavailability (F_{abs})

- Measures how much of a drug enters the bloodstream after **non-IV administration** (e.g., oral, subcutaneous, transdermal) compared to **IV administration**.
- **IV drugs have 100**
- **Formula:**

$$F_{\text{abs}} = \frac{AUC_{\text{extravascular}} \times \text{Dose}_{IV}}{AUC_{IV} \times \text{Dose}_{\text{extravascular}}}$$

- **Where:**
  - AUC (Area Under the Curve) = Total drug exposure in blood over time.

Relative Bioavailability (F_{rel})

- Compares the bioavailability of a drug from two different non-IV formulations (e.g., tablet vs. capsule).
- Helps determine if a new formulation is as effective as an existing one.
- **Formula:**

$$AF_{\text{rel}} = \frac{AUC_{\text{Formulation A}} \times \text{Dose}_{\text{Formulation B}}}{AUC_{\text{Formulation B}} \times \text{Dose}_{\text{Formulation A}}}$$

- Used in drug formulation studies to compare new and existing drug versions

Factors Affecting Bioavailability

1. **Drug-Related Factors**
   - **Solubility** – Poor solubility reduces absorption.
   - **Molecular Size** – Larger molecules have lower absorption.
   - **Chemical Stability** – Degradation in GI tract reduces bioavailability.
   - **Ionization State** – Ionized drugs at physiological pH have lower absorption.
2. **Patient-Related Factors**
   - **Age** – Alters drug metabolism and absorption.
   - **Genetics** – Variations in enzymes affect bioavailability.
   - **Disease State** – Conditions impact drug absorption & metabolism.
   - **Drug Interactions** – Can enhance or inhibit drug absorption.
   - **Food Interactions** – Food can alter GI pH and drug solubility.

3. **Formulation-Related Factors**

- **Dosage Form** – Tablets, capsules, liquids affect absorption.
- **Drug Release Rate** – Affects dissolution and absorption.
- **Excipients** – Ingredients impact drug dissolution & uptake.
- **Particle Size** – Smaller particles dissolve faster, improving bioavailability.
- **Polymorphism** – Different crystal forms affect solubility.

Measurement of Bioavailability:

The methods useful in quantitative evaluation of bioavailability can be broadly divided into two categories - pharmacokinetic methods and pharmacodynamic methods.

Pharmacokinetic Methods:

- These are very widely used and based 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:
    a. Plasma level-time studies.
    b. Urinary excretion studies.

Pharmacodynamic Methods:

- These methods are complementary to pharmacokinetic approaches and involve direct measurement of drug effect on a (patho) physiological process as a function of time.
- The two pharmacodynamic methods involve determination of bioavailability from:
    a. Acute pharmacological response.
    b. Therapeutic response.

Bioavailability is measured using **pharmacokinetic parameters**, such as:

1. **Cmax (Maximum plasma concentration):**
   Indicates the rate of absorption.
2. **Tmax (Time to reach Cmax):**
   Time required to achieve the maximum plasma concentration.
3. **AUC (Area Under the Curve):**
   Represents the extent of absorption.
4. **Urinary excretion data:**
   The amount of unchanged drug excreted in urine can also be used to estimate absorption.

In Vitro Drug Dissolution Models:

- In Vitro tests predict drug behavior without the need for in vivo bioavailability tests.
- Aim to mimic biological conditions.

Characteristics of an Ideal dissolution Apparatus:

- Simple easy operation
- Precise dimensions, reproducible
- Easy dosage form introduction and holding.
- Controlled non-abrasive liquid agitation.
- Maintain ideal Conditions.
- Prevent evaporation, maintain temperature.
- Allow Uninterrupted sample collection.
- Ensure agreement b/w labs.
- Detect changes in process/ formulation.

Types of dissolution Apparatuses:

There are two main types of dissolution apparatus, depending on whether or not sink conditions exist:

a) **Closed-compartment apparatus:** This is essentially a limited-volume apparatus that operates outside of a sink. For example, the rotating basket and rotating paddle apparatus.
b) **Open-compartment (continuous flow-through) apparatus:** It is the one in which the dosage form is brought in continuous contact with fresh, flowing dissolution medium (perfect sink condition).

Available official or compendia dissolution models:

a) The Rotating Basket Apparatus (Apparatus 1) - is a closedcompartment, beaker-style apparatus with a cylindrical basket made of 22 mesh in the centre to hold the dosage form. Application: Conventional Tablets
b) Rotating Paddle Apparatus (Apparatus 2) - The rotating basket is replaced with a paddle that acts as a stirrer, just like in apparatus 1. Sinkers are recommended to keep capsules and other floatable forms from floating. Application: Tablets, capsules, controlled release products.
c) Reciprocating Cylinder Apparatus (Apparatus 3) - consists of a set of cylindrical glass vessels with flat bottoms and reciprocating cylinders. Application: controlled release bead-type (pellet) formulations.
d) Flow-Through Cell Apparatus (Apparatus 4) - consists of a dissolution medium reservoir and a pump that forces dissolution medium through the test sample cell.

Fresh dissolution media is pumped on a regular basis (between 240 and 960 mL/h), ensuring sink conditions. Application: Formulations containing poorly soluble drugs.

e) Paddle Over Disc Apparatus (Apparatus 5) - consists of a productholding sample holder or disc located at the bottom of the apparatus. 2. Application: evaluation of transdermal products.
f) Cylinder Apparatus (Apparatus 6) - A stainless steel cylinder is used to hold the sample instead of a basket, as in apparatus 1. Application: transdermal product evaluation.
g) Reciprocating Disc Apparatus (Apparatus 7) - The samples are placed on vertically reciprocating disc-shaped holders. Application: for testing transdermal products and non-dissolving controlledrelease oral preparations.

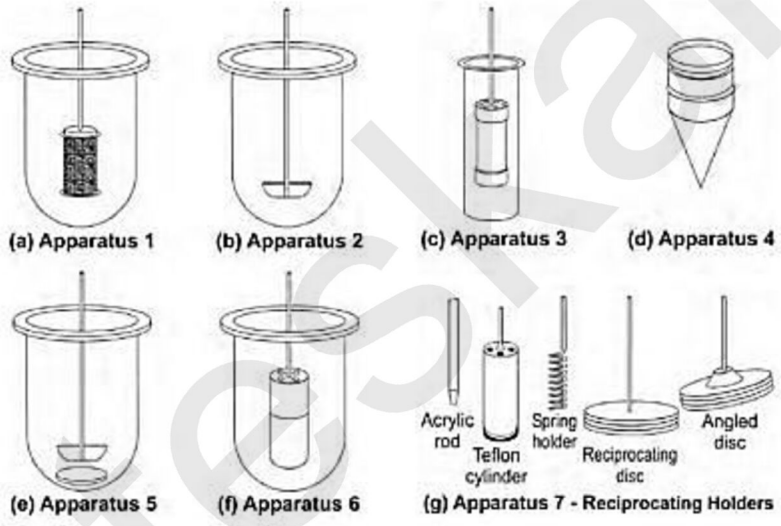


Diagram showing various compendia dissolution model.

IN VITRO—IN VIVO CORRELATION (IVIVC):

The predictive mathematical model that describes the relationship between an in-vitro property (such as the rate and extent of dissolution) of a dosage form and an in-vivo response is known as in vitro-in vivo correlation (such as the plasma drug concentration or amount of drug absorbed).

Goal:

The main goal of developing and evaluating an IVIVC is to make the dissolution test a surrogate (alternative) for human in vivo bioavailability studies.

The applications of developing such an IVIVC are:

1. To ensure batch-to-batch consistency in the physiological performance of a dosage form.
2. To serve as a tool in the development of a new dosage form.
3. To assist in validating or setting dissolution specifications.

There are two basic approaches by which a correlation between dissolution testing and bioavailability can be developed:

1. By establishing a relationship between in vitro dissolution and in vivo bioavailability parameters, which is usually linear.
2. By modifying the dissolution methodology based on data from previous bioavailability studies, we were able to achieve a meaningful in vitro-in vivo correlation.

The following are some of the most commonly used quantitative linear in vitro-in vivo correlations:

1. Correlations based on plasma level data: This section develops linear relationships between dissolution parameters and plasma level data parameters. Plots of percent drug dissolved versus percent drug absorbed, for example.
2. Urine Excretion Data Correlation: Dissolution parameters are correlated with the amount of drug excreted unchanged in the urine, the cumulative amount of drug excreted as a function of time, and so on.
3. Pharmacological Response Correlation: Any of the dissolution parameters is related to an acute pharmacological effect such as LD50 in animals.

IN VITRO-IN VIVO CORRELATION LEVELS:

Three IVIVC levels have been defined and categorized in descending order of usefulness.

Level A: It represents a point-to-point relationship between in-vitro dissolution and in-vivo rate of absorption, or a superimposable in-vitro and in-vivo profile, in the highest category of correlation.

The following are some of the benefits of level a correlation:

1. No additional human studies are required to justify any change in manufacturing procedure or formula modification.
2. In-vivo dissolution is used as a quality control procedure for predicting the performance of dosage forms.

Level B: The mean in vitro dissolution time is compared to either the mean in vivo dissolution time or the mean residence time. However, because there is no point-to-point correlation, level B correlation cannot be used to justify manufacturing or formula changes.

Level C: It is a single point correlation. It relates one dissolution time point (e.g. t50%, etc.) to one pharmacokinetic parameter such as AUC, t_{max} or C_{max}. This level is generally useful only as a guide in formulation development.

Bioequivalence Studies:

bioequivalence studies evaluate whether two formulations of a drug produce similar effects in the body.

They compare the absorption, distribution, and elimination of the drug from the body to ensue that a generic or modified version of a drug works the same as the original or reference version.

Objectives:

- New products that want to replace or be alternatives to approved medicines must show they work the same way.
- Bioequivalence studies ensure similar clinical performance of drug products.
- Conducted when there is a risk of differences in biological effects or concerns about therapeutic or safety.
- Key terms will be defined to clarify their significance.

Advantages:

- Minimizes Variability b/w different individuals.
- Reduces carry over effects.
- Requires fewer subjects to achieve meaningful results.

Disadvantages:

- Take longer time to complete studies.
- Study completion depends on the number of formulations evaluated.
- Longer study periods may lead to more subject dropouts.
- Medical ethics restrict too many trials on subjects continuously over a long time.

Equivalence:

It compares drug products based on specific characteristics or standards.

Types of Equivalence:

1. **Chemical Equivalence:** Indicates that multiple drug products contain the same active ingredient in the same amount.
2. **Pharmaceutical Equivalence:** Shows that multiple drug products are identical in strength, quality and other characteristics, but may have different excipients.
3. **Bioequivalence:** indicates that drug substances in identical dosage forms reach the bloodstream at the same rate and extent.
4. **Therapeutic Equivalence:** Signifies that multiple drug products with the same active ingredient produce identical pharmacological effects and disease control.

Types of Bioequivalence studies:

There are two types if bioequivalence studies:

1. InVivo
2. In Vitro

1. In Vivo bioequivalence studies:

Criteria for Assessment:

- Immediate release oral products used for serious conditions with a narrow therapeutic margin.
- Complicated pharmacokinetics due to factors like low absorption (<70%), non linear kinetics or high pre-systemic elimination (>70%).
- Unfavorable physicochemical properties of the drug.
- Documented evidence of bioavailability issues.
- Lack of relevant data, unless justified by the applicant.

Conduct of Studies:

1. Pharmacokinetic methods:

- Plasma level time studies
- Urinary excretion studies

2. Pharmacodynamics Method:

- Acute pharmacological response
- Therapeutic response

2. In Vitro bioequivalence studies:

- Comparative dissolution studies may be sufficient if In-Vivo studies are not required.
- In vitro studies can serve as biowairers under certain conditions:
- If minor reformulations or manufacturing modifications are made by the original manufacture.
- For products in solution or solubilized form with specific concertation and excipient criteria.
- When acceptable in vitro and in vivo correlation and dissolution rates equivalent to approved products are demonstrated.

Certain types of products, like topical administrations or those not intended for adsorption, may also qualify for bio waivers.

These criteria show when it's clear that the drugs bioavailability and equivalence are proven so additional studies might not be needed.

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