BIOPHARMACEUTICS – Multiple Dosage Regimen

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1. INTRODUCTION

A key area of the pharmaceutical sciences known as biopharmaceutics studies the relationship between the physicochemical characteristics of a medication when it is administered and the pharmacology, toxicological, or clinical response that results. It is the more sophisticated area of pharmacy. It entails the investigation of behaviors and associated mechanisms of action in living things. The outputs of cutting-edge biotechnology research are frequently discussed in the biopharmaceutics course. It focuses on maximizing the therapeutic and pharmacological effects of medications in living things and identifies the variables affecting their bioavailability. The dosing regimen affects both the safety and effectiveness of a drug. For many medications, there can be significant variations in the ideal dosage and dosing intervals. Additionally,

the ideal dosage for a particular medicine might vary greatly between patients.

Knowing what the medicine does to the body is important, but it is also important to understand what the body does to the drug. Knowing a drug's pharmacodynamic and pharmacokinetic characteristics in people and animals is essential for changing drug dosage and comprehending the drug's various impacts on different species.

The fundamental idea of pharmacokinetics is the drug's plasma concentration. The amount of free drug present in the circulation has a significant impact on dose estimations based on the drug's protein binding. There is an equilibrium between some body tissues and the medication concentration in the plasma.

A cutting-edge approach to creating new medicinal compounds is currently being adopted by biopharmaceuticals. In addition to polypeptides, oligonucleotides (DNA, siRNA, and microRNA), antibodies (monoclonal and conjugated antibodies), and PNA (peptide nucleic acid) structures, the field of biologic medicine is now including novel molecular variety. Biopharmaceutics is the study of the intricate interactions between the administration of medications, the body's response to those interactions, and related scientific studies.

Researchers and innovators are always in demand in the pharmaceutical sector. The foundational knowledge required to comprehend the intricate mechanics of pharmaceuticals in living things is provided by biopharmaceutics courses. Professionals in the field of biopharmaceutics have excellent job prospects. Every day, new doors to fascinating challenges are being opened by research in the domains of virology, cancer treatment, and other branches of medicine.

Definition

Biopharmaceutics is defined as the study of the connections between a drug's physical and chemical characteristics, dosage, and route of administration, and its physiological effects on a living organism.

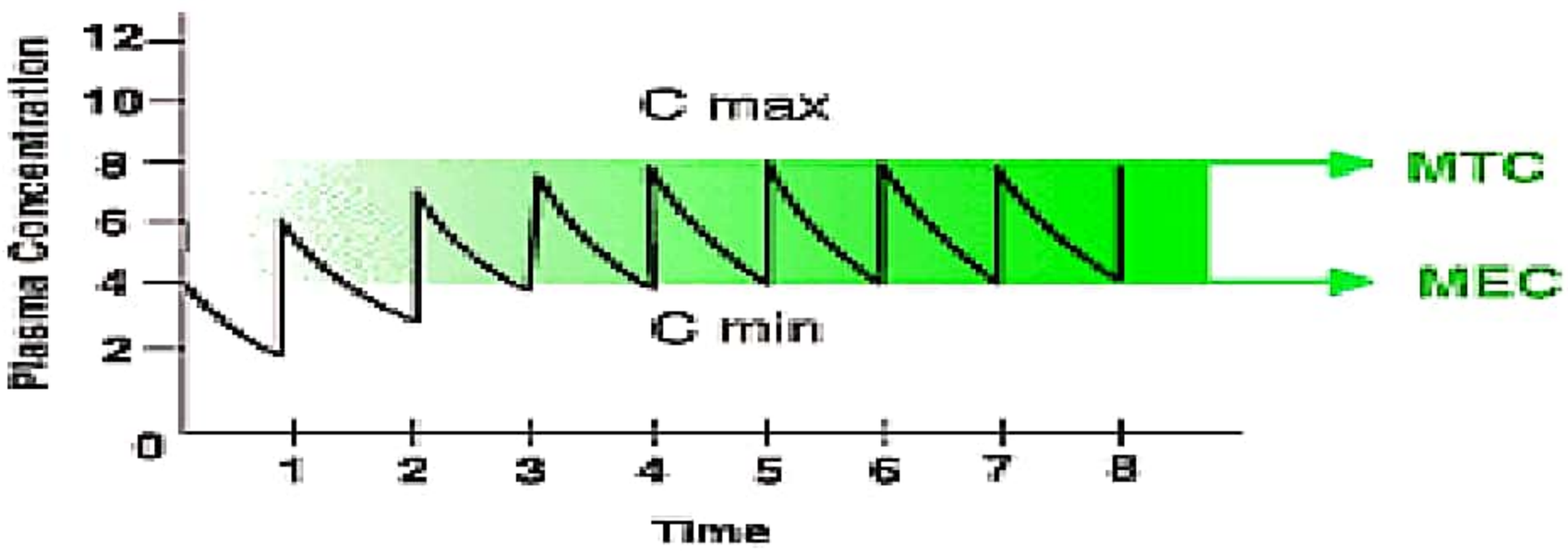
Even among academics and industry experts, the definition of the phrase "biopharmaceutics" sometimes raises questions. When used narrowly, "pharmaceutics"

refers to a branch of science that deals with the manufacture, administration, or use of drugs. The interaction between biological features of living organisms and the physical-chemical laws that regulate the creation and behavior of the medicinal agent or drug product is inherent in the notion of biopharmaceutics as it is presented below.

2. DOSAGE REGIMEN / MULTIPLE DOSAGE REGIMEN

The therapeutic impact decreases after a single dose of medication is administered due to the plasma drug level rising above and then dropping below the minimal effective concentration (MEC). Many medications are administered in a multiple-dosage regimen in order to maintain sustained therapeutic action. To achieve maximum clinical efficacy, the plasma levels of medications administered in successive doses must be kept within the strict confines of the therapeutic window (e.g., plasma drug concentrations over the MEC but below the minimal toxic concentration, or MTC). Antibacterials, cardiotonics, anticonvulsants, and hormones are a few of these medications. To achieve the proper plasma level without excessive fluctuation and drug accumulation outside the therapeutic window, a dosing regimen should ideally be designed for each medicine.

The drug administration method selected to achieve the therapeutic goal is the dose regimen. This is dependent on the medication being used, the illness being treated, and the characteristics of the patient.



Plot of plasma concentration versus time showing accumulation after multiple administration of drugs

Figure No.:01 Plot the Graph between plasma concentration versus time showing

accumulation after multiple administration of drugs.

- **Definition of Dose, Dosage, Dosage Form, Dosage Regimen**

- Please define the following terms:

- • Dose: The word "dose" is derived from the Greek word "dosis," which means "a portion prescribed or gifted," from the verb didonai, or "to give," in Middle French.

- • Dosage: The specified quantity and rate at which a medicine is administered to a patient is known as the dosage. Dosage is defined as the prescribed administration of a drug in a predetermined amount, number, and frequency over a predetermined length of time by the AMA (American Medical Association) Manual of Style. Lesinurad 200 mg once daily, as an example.

- Dosage Form: A dosage form is a physical substance that comprises active pharmaceutical ingredients (API) together with a few more substances (excipients) and is designed to be administered by one of several routes to the body's sites of action. The dosage form is often referred to as drug products and unit dosages. Solid dosage forms, such as tablets, capsules, pellets, pills, and lozenges, for instance.
- Liquid Dosage Forms: Linctus, Solution, Suspension, Elixir, and Gargle, among others.
- Semisolid Dosage Forms: Paste, Cream, and Ointments, among others.
- Gaseous Dosage Forms: Insufflations, Aerosols, etc.
- The optimal dose (D0) and dosing interval (, tau) for a particular drug, or the systematized dosage plan for a drug therapy.
- substance accumulation (R): The accumulating effects of a substance after receiving several doses in the body.
- Drug superposition: The pharmacokinetics of drug dosages administered early do not alter those administered later. The blood levels achieved following the

second, third, or nth dose will overlap or superimpose the blood levels attained following the first dose.

- Steady state is when, for a certain dosage regimen, the mass (amount) of drug injected (for intravenous) or absorbed (for extravascular route) is equal to the mass (amount) of drug removed throughout a dosing interval.
- **Loading dose (DL):** A single dose given to quickly bring about steady-state conditions. The dose given at each dosing interval to maintain the steady-state condition is known as the maintenance dose (Dm).

To put it another way, a dosage form is a physical form in which an exact combination of active pharmaceutical ingredients (APIs) and excipients is delivered to aid in simple administration, delivery to sites of action, quick commencement of action, and other objectives. The choices that go into defining a dosing regimen concern:

1. Route of administration
2. Galenic formulation
3. Unit dose
4. Frequency
5. Loading dose
6. Length of treatment

3. THERAPEUTIC DRUG MONITORING

1. The choice of drug and the design of the drug product's dosage regimen have a significant impact on the outcome of drug therapy.
2. While the patient's features and the drug's pharmacokinetics are taken into account when selecting a drug and drug product.
3. For the improvement of the therapeutic effectiveness of the treatment, each patient has distinct drug absorption, distribution, and elimination as well as different pathophysiological conditions.
4. It specializes in determining the blood levels of medications. It primarily focuses on medications with a limited therapeutic window, i.e., medications that are readily under- or overdosed.

5. Therapeutic drug monitoring is crucial because Undertreatment or drug resistance will result from insufficient drug levels in the plasma, while toxicity and overdose can result from insufficient drug levels.
6. There is a limited treatment window, which is one of the TDM indicators. Potential issues with patient compliance exist. Clinical observation alone cannot be used to optimize the medicine dose. Understanding the medication level affects management. Analyzing samples and drugs Drug assays often involve the use of plasma or serum. Drug test techniques should be unique to the drug (or metabolite) being analyzed, have suitable sensitivity, and be accurate and precise.
7. It is possible to utilize gas liquid chromatography (GLC), high performance liquid chromatography (HPLC), and automated immunoassay techniques (e.g., amiodarone, perhexiline).

4. MAINTENANCE OF DRUG WITH IN THE THERAPEUTIC RANGE

The drug's therapeutic index determines how easy or difficult it is to maintain drug concentration within the therapeutic window.

1.The drug's half-life

2. Dosing convenience.

For a medication with a short half-life (less than 3 hours) and narrow therapeutic index, such as heparin, it is very challenging to maintain such a level because the dose frequency must be essentially less than t12. Drugs having a high therapeutic index, like penicillin (t1/2 = 0.9 hours), can be administered less often (every 4 to 6 hours), but the maintenance dose must be higher to ensure that the plasma concentration stays above the minimal inhibitory level.

If the therapeutic index is low, a drug with an intermediate half-life (3 to 8 hours) may be administered at intervals of T1, but a drug with a high therapeutic index may be administered at intervals of 1 to 3 half-lives. It is easier to dose medications whose half-lives are longer than eight hours. These medications are typically taken once every half-life. In these circumstances, a loading dose can be used to quickly achieve steady-state.

A once daily dose is highly practical for medications with relatively long half-lives (over 24 hours), such as amlodipine.

5. CONCEPT OF LOADING DOSE, MAINTENANCE DOSE.

Until a medicine reaches the desired steady-state, it does not begin to exhibit therapeutic activity. It takes around 5 half-lives to reach it, thus if the drug has a lengthy half-life, the time required will be excessive. Before the start of maintenance dosages, a dose that produces the required steady-state instantly can be administered to quickly attain plateau. Xo.

Priming doses or loading doses are terms used to describe such an initial or first dose meant to have therapeutic effects. Xo, L. An easy formula to determine loading dose is:

$$X_{0,L} = \frac{C_{ss,av} V_d}{F}$$

Because Cmax is always lower after e.v. treatment than it is after i.v. administration, the loading dose is proportionately lower. The loading dose for medications with low therapeutic indices may be split into smaller doses to be administered at various intervals prior to the initial maintenance dose. The following equation can be used to calculate the loading dose when Vd is unknown:

$$\frac{X_{0,L}}{X_0} = \frac{1}{\left(-e^{-K_a \tau}\right)\left(-e^{-K_E \tau}\right)}$$

When Ka > KE and the medication is dispersed quickly, the aforementioned equation is applicable. The absorption phase is ignored when the medication is administered intravenously or when absorption is exceedingly quick, and the resulting equation becomes accumulation index:

$$\frac{X_{0,L}}{X_0} = \frac{1}{(1 - e^{-K_E \tau})} = R_{ac}$$

loading dosage to maintenance dose ratio Dose ratio is defined as Xo,L/Xo. As a general rule, the dose ratio should be equal to 2.0 when = t12, but it must be lower than 2.0 when > t12 and higher when t12. According to Fig. 02, if the loading dose is not optimal either too low or too high the steady-state is reached in a manner comparable to when no loading dose is provided after about 5 half-lives.

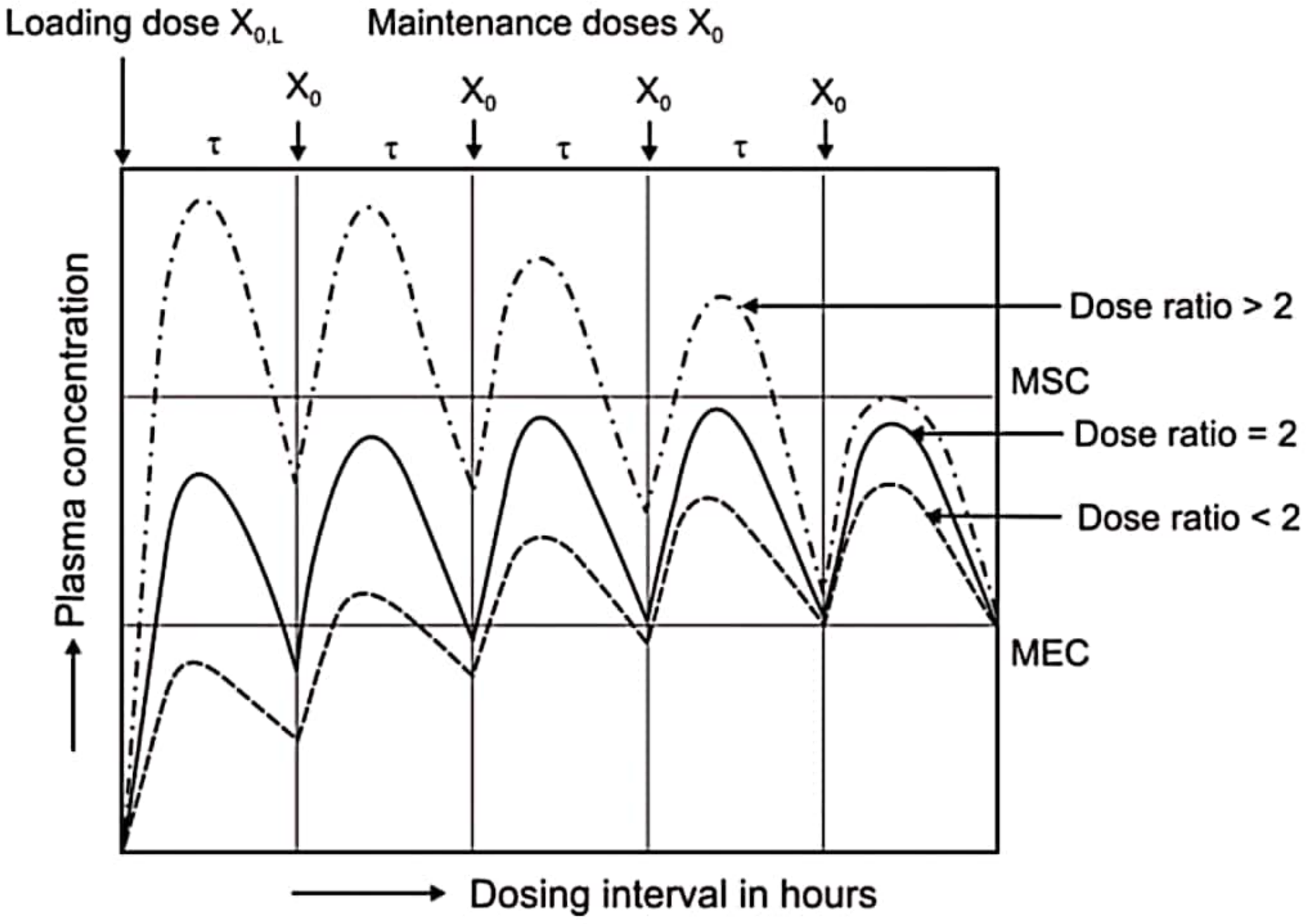


Figure No.:02 Schematic representation of plasma concentration-time profiles that result when dose ratio is greater than 2.0, equal to 2.0 and smaller than 2.0.

6. PRINCIPAL OF SUPERPOSITION

The pharmacokinetics of later dosages of a medicine are not affected by earlier ones, according to the concept of superposition. The blood levels achieved following the

second, third, or nth doses will therefore overlap or superimpose the blood level attained following the (n-1)th dose.

The plasma drug concentration-time curve of a drug can be projected using the principle of superposition based on the plasma drug concentration-time curve acquired after a single dose.

- **Basic assumptions are;**

First-order kinetics governs the drug's elimination, and secondly, the drug's pharmacokinetics following a single dose (first dose) are unaffected by taking additional doses.

From the plasma drug concentrations found after a single dose, the plasma drug concentrations after subsequent doses can be predicted. After a single dose, the plasma drug concentrations from 0 to 24 hours are measured. Every 4 hours, the same dose of the drug is administered, and using the information from the previous administration, the plasma drug concentrations are created. As a result, the total drug concentration produced by adding the residual drug concentration obtained after each prior dose is the projected plasma drug concentration in the patient.

Drug concentrations following several dosages of many different medications can be predicted using the superposition principle. As an overlay method, the superposition principle can be used to forecast drug concentrations following numerous doses given at either equal or different dosage intervals. For instance, the plasma drug concentrations when a drug dose is administered every 8 hours, or three times a day before meals at 8 AM, 12 PM, and 6 PM, may be predicted.

Principal of superposition does not apply;

a) When the drug's pharmacokinetics vary after several doses for a variety of reasons, such as

b) the patient's pathophysiology changing,

c) the drug carrier system becoming saturated,

d) enzyme induction and inhibition.

e) Medicines with nonlinear pharmacokinetics

7. DRUG ACCUMULATION

Take into account the medicine dosage in the body-time profile obtained following sequential IV dosing with a one-t12 dosage interval. Following the administration of the first dose, Xo at = 0, the body will contain X = 1Xo of the medicine. The administration of the following intravenous dose increases the body content to X = Xo + 12Xo, showing drug accumulation in the body, when the next dosing interval occurs and X = 12Xo, the amount of medication left in the body, is measured. As a result, since the drug from earlier dosages has not been completely cleared, accumulation happens.

The rate of elimination rises progressively along with the amount of drug in the body as a result of accumulation until a steady-state or plateau is reached where the rate of drug entry into the body is equal to the rate of outflow. The highest and lowest values of X—Xss,max and Xss,min—approach their respective asymptotes at plateau. At plateau, the equations Xss,min = 1Xo and Xss,max = 2Xo show that Xss,min represents the amount of drug in the body following the initial dose and Xss,max represents twice that amount. Additionally, Xss,max/Xss,min = 2 and (Xss,max - Xss,min) = Xo. All of this is accurate only if t12 = 1 and medication is given intravenously. The accumulation degree is greater with t12, and vice versa.

Thus, the *extent to which a drug accumulates* in the body during multiple dosing is independent of dose size, and *is a function* of –

- Dosing interval, and
- Elimination half-life.

The extent to which a drug will accumulate with any dosing interval in a patient can be derived from information obtained with a single dose and is given by **accumulation index R_{ac}** as:

$$R_{ac} = \frac{1}{1 - e^{-K_E \tau}}$$

8. ASSESSMENTOFBIOAVAILABILITYINMULTIPLEDOSAGEREGIMEN

The term bioavailability refers to the rate and extent (quantity) of unmodified medication absorption from its dose form.

The study of several doses

Preliminary clinical trials define the dose to be administered for a bioavailability study. Multiple dose studies have both advantages and cons.

Advantages

- Accurate.
- It is simple to estimate the drug's peak and valley features.
- A small number of blood samples must be collected.
- Ethically carried out.
- Small intersubject variation.
- Improved assessment of controlled release formulations.
- Nonlinearity in pharmacokinetics can be detected.
- Increasing blood levels (d/t cumulative effect).
- Removes the requirement for a lengthy washout interval between dosages

Disadvantages

Poor subject compliance. Difficulty and time consuming. Increased drug exposure. More difficult and costly.

In a multiple-dose trial, the steady-state must be reached by providing the drug 5-6 elimination half-lives prior to sample collection.

Bioavailability Evaluation

1. Indirect pharmacokinetic approaches

These assume that a drug's pharmacokinetic profile reflects its therapeutic effectiveness.

a) Plasma concentration time studies

b) Urinary excretion studies

2. Pharmacodynamic (Direct) techniques

These entail the direct measurement of a drug's effect on a (patho)physiological process throughout time.

(a) Acute pharmacological response

(b)Therapeutic response

9. **ASSESSMENT OF BIOEQUIVALENCE IN MULTIPLE DOSAGE REGIMEN**

a. The term "bioequivalence" refers to the therapeutic ingredient entering the systemic circulation at the same rate and to the same relative extent in two or more similar dose forms; in other words, their plasma concentration-time profiles will be the same without any appreciable statistical differences.

b. For the in vivo biequivalence study, it is necessary to compare the relative bioavailability of a single dosage of the test and reference formulations delivered by the same route in equal amounts but at various intervals. A previously authorized innovator's product or some form of reference standard is typically used as the reference product.

c. To preserve homogeneity, fasting, young, healthy adult male volunteers are chosen for the investigation.

d. Alatincross-over design has been released, in which each formulation is only given to each subject and each research period once. Additionally, throughout

the course of the study, various formulations are given to each person at the same time.

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