

BIOPHARMACEUTICS – Multiple Dosage Regimen,.....

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1. INTRODUCTION

Biopharmaceutics is an important branch of the pharmaceutical sciences that examines the connection between a drug's physicochemical properties at the time of administration and the pharmacological, toxicological, or clinical reaction that follows. 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 drug's safety and efficacy are influenced by the dose schedule. The recommended dosage and administration periods for many drugs might vary significantly. In addition, different people may

require quite different dosages of a given medication. 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.

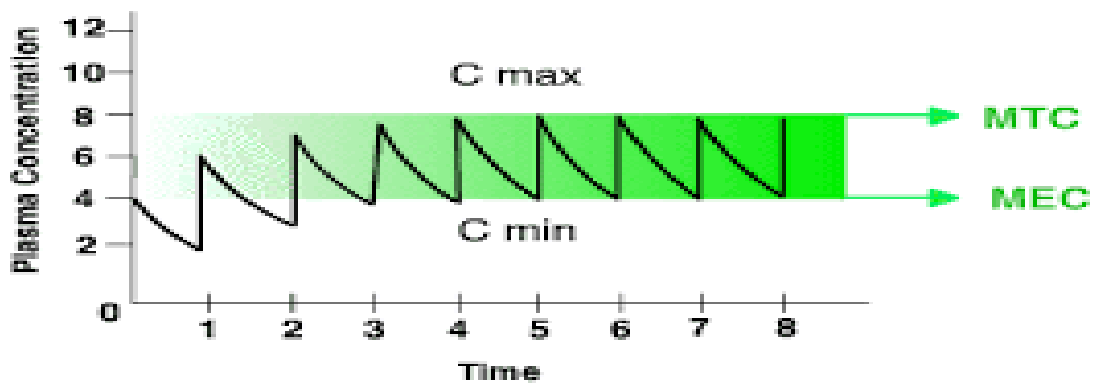
Even among academics and industry experts, the definition of the phrase "biopharmaceutics" sometimes raises questions. When used narrowly, "pharmaceutics" refers to a branch of science that deals with the manufacture, administration, or use of drugs. The idea of biopharmaceutics as it is described below is fundamental to the interplay between the biological characteristics of

living things and the physical-chemical rules that govern the synthesis and behavior of the medicinal agent or therapeutic product.

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 (D_0) and dosing interval (τ) 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 (D_m).

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. Every patient has a unique pathophysiological condition and differs in how well they absorb, distribute, and eliminate drugs. This will help to increase the therapeutic effectiveness of the treatment.
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

How simple or challenging it is to keep drug concentration inside the therapeutic window depends on the drug's therapeutic index.

1. The drug's half-life

2. Dosing convenience.

Maintaining such a level is extremely difficult for a medicine like heparin, which has a short half-life (less than 3 hours) and a narrow therapeutic index, as the dose frequency needs to be practically less than $t_{1/2}$. Penicillin is one example of a drug with a high therapeutic index that can be taken every 4 to 6 hours, but the maintenance dose needs to be greater to keep the plasma concentration above the minimal inhibitory threshold.

A medication with an intermediate half-life (3 to 8 hours) may be given at intervals of T_1 if the therapeutic index is low, whereas a medication with a high therapeutic index may be given 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. X_0 .

These early or first dosages intended to have therapeutic benefits are referred to as priming doses or loading doses. X_0 , L. An easy formula to determine loading dose is:

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

Because C_{max} is always lower after e.v. treatment than it is after i.v. administration, the loading dose is proportionately lower. For drugs with low therapeutic indices, the loading dose may be divided into smaller doses to be given before the first maintenance dose at different intervals. The following equation can be used to calculate the loading dose when V_d is unknown:

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

When $K_a > K_E$ 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:

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

loading dosage to maintenance dose ratio Dose ratio is defined as $X_{0,L}/X_0$. ..Generally speaking, the dose ratio needs to be lower than 2.0 when $t_{1/2}$ is greater than $t_{1/2}$ and higher when $t_{1/2}$. Figure 02 shows that when the loading dose is not optimal—that is, when it is too high or too low—the steady-state is attained in a way that is similar to what happens when there is no loading dose—after roughly five half-lives.

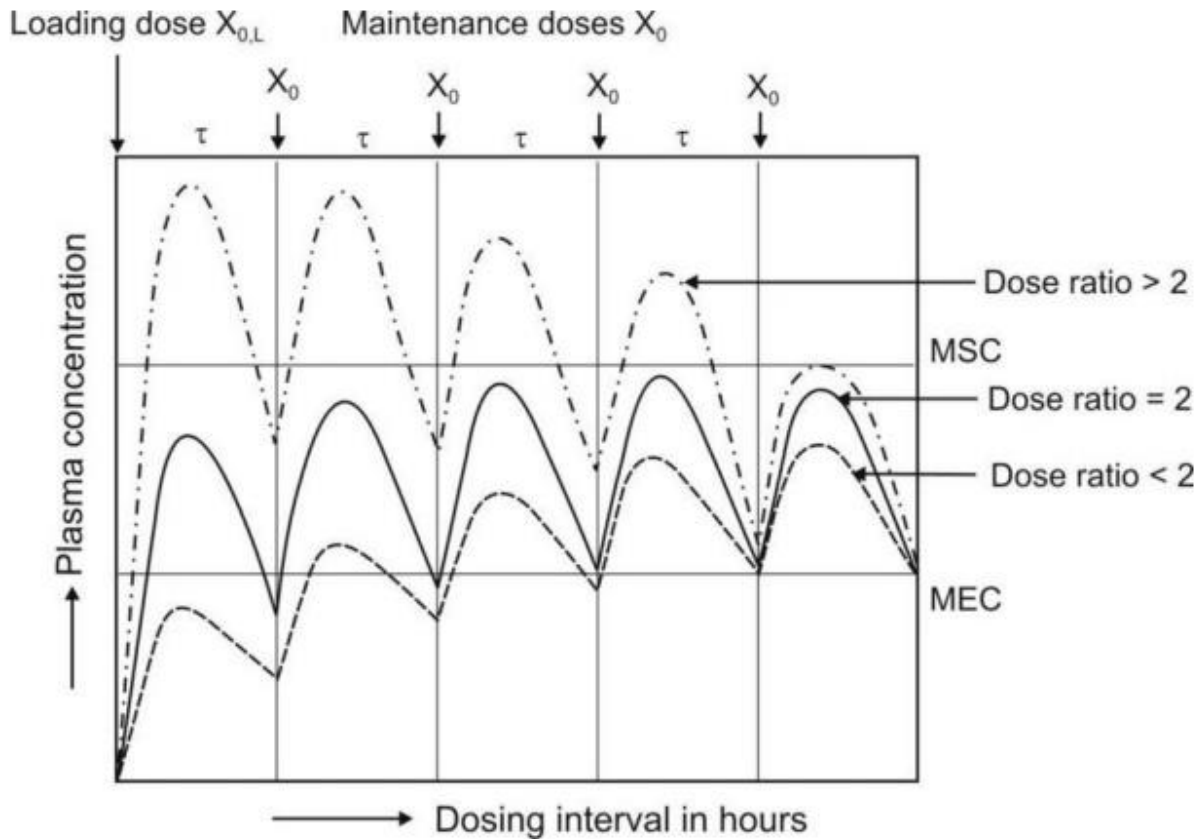


Figure No.:02 Schematic representation of plasma concentration-time profiles that result when dose ratio is greater than 2.0, equal to 2.0 and smaller than 2.0.

6. PRINCIPAL OF SUPERPOSITION

The pharmacokinetics of later dosages of a medicine are not affected by earlier ones, according to the concept of superposition. Therefore, the blood level obtained after the (n-1)th dose will overlap or superimpose the blood level obtained after the second, third, or nth doses.

Based on the plasma drug concentration-time curve obtained after a single dose, the principle of superposition can be used to project the plasma drug concentration-time curve of a drug.

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.

Based on the plasma drug concentrations observed following a single dose, it is possible to anticipate the plasma drug concentrations following subsequent doses. Following an initial dose, plasma drug concentrations are measured within the 0 to 24-hour timeframe.

Subsequently, the same drug dose is administered every 4 hours, and based on the data collected from the previous dose, the plasma drug concentrations are projected. This cumulative drug concentration, which includes the residual drug concentration from each previous dose, represents the anticipated plasma drug concentration in the patient.

Drug concentrations following several dosages of many different medications can be predicted using the superposition principle. The superposition principle can be applied as an overlay technique to predict medication concentrations after many doses given at varying or equal intervals. When a drug dose is given every eight hours, or three times a day before meals at eight in the morning, twelve at night, and six in the evening, for example, the plasma drug concentrations can 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

Examine the drug concentration in the body over time, which is obtained through repeated intravenous dosing with a dosing interval of one $t_{1/2}$. Initially, following the administration of the first dose X_0 at $t = 0$, the drug concentration in the body is $X = X_0$. As the next dosing interval approaches and $X = \frac{1}{2}X_0$, the amount of drug remaining in the body, when the next intravenous dose is administered, results in a total body content of $X = X_0 + \frac{1}{2}X_0$. This signifies the accumulation of the drug in the body, as previous doses of the medication have not been completely eliminated.

As the drug accumulates within the body, the rate of elimination also increases until a steady-state or plateau is reached, where the rate of drug entry into the body matches the rate of drug leaving it. During this plateau phase, the maximum and minimum values of X , denoted as $X_{ss,max}$ and $X_{ss,min}$, respectively, approach their respective asymptotic values. At the plateau,

$X_{ss,min}$ equals the amount of drug present in the body after the initial dose, which is $1X_0$, while $X_{ss,max}$ equals twice the initial dose, or $2X_0$. Additionally, $(X_{ss,max} - X_{ss,min})$ equals X_0 , and the ratio of $X_{ss,max}$ to $X_{ss,min}$ equals 2. It's important to note that these relationships hold true when $t = t_{1/2}$, and the drug is administered intravenously. When $t \neq t_{1/2}$, the degree of accumulation varies accordingly, with larger accumulation occurring when t is greater than $t_{1/2}$, 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. ASSESSMENT OF BIOAVAILABILITY IN MULTIPLE DOSE REGIMEN

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 adherence to the subject. challenging and time-consuming. exposure to drugs growing. more expensive and challenging.

In a multiple-dose experiment, the drug must be administered for five to six elimination half-lives in order to attain the steady-state before samples are collected.

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. Bioequivalence is a term that compares the relative performance of a drug ingredient, ensuring it reaches the systemic circulation at a consistent rate and to a similar extent

in two or more comparable dosage forms. This means their plasma concentration-time profiles should exhibit no significant statistical distinctions and remain virtually identical.

- b. In the in vivo bioequivalence study, it is necessary to determine the relative bioavailability of a single dose of both the test and reference formulations, administered via the same route, in equal quantities but at different time intervals. Typically, the reference product used is either an approved innovator's product or a designated reference standard.
- c. In order to maintain uniformity, the study involves the selection of fasting, young, and healthy adult male volunteers for the research.
- d. A Latin cross-over design is employed in which each formulation is administered only once to each subject within each study period. Additionally, all the subjects receive different formulations simultaneously during a specific study period.

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