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REVIEW ON BIOEQUIVALENCE STUDIES

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ABSTARCT

From this study, we can get a clear idea about how bioequivalence studies are being carried out. Different methods are being adopted for conducting bioequivalence studies, which helps the researchers gain good exposure to performing bioequivalence studies. In-vitro and in-vivo bioequivalence studies play a vital role in comparing the pharmacokinetic and pharmacodynamic activity of multi-brand generic molecules and in providing enough therapeutic activity of the dosage form. In this review article we have compiled the information on in-vitro bioequivalence studies and in vivo bioequivalence studies along with its importance and the various methods involved in these studies, which are suitable for both institutional and industrial practice as per the pharmacopoeial limits and requirements.

KEYWORDS: Bioavailability, Bioequivalence, i*n-vitro &* in-vivo studies, Pharmacokinetic parameters.

1. INTRODUCTION

Bioequivalence is a term in pharmacokinetics used to evaluate the predictable *in vivo* biological equivalence of two proprietary preparations of a drug. If two drug products are said to be bioequivalent it means that they would be predictable to be, for all objectives and purposes, the same.[1]

- Both bioavailability and bioequivalence focus on measuring the absorption of the drug into systemic circulation.
- Bioavailability is a comparison of the drug product to an IV formulation, a solution or a suspension, whereas bioequivalence is a comparison with predetermined bioequivalence limits.
- The bioequivalence is said to exist when the bioavailability of a drug with different formulation is same.[2]

Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent and their bioavailabilities after administration in the same dose are similar to such a degree that their effects, with respect to both efficacy and safety, can be expected to be for all intents and purposes the same. Pharmaceutical equivalence infers the same amount of active substances, in the same dosage form, for the same route of administration and meeting the same or comparable standards.

The two drugs; test drug and reference are supposed to be bioequivalent if.

- The rate and extent of absorption (frequency of absorption) of the test drug do not show an important difference from the rate and extent of absorption of the reference drug when administered at the same molar dose of the therapeutic ingredient under similar experimental circumstances in either a single dose or multiple doses,
- The extent of absorption of the test drug does not show a major difference from the extent of absorption of the reference drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses.

In a few cases, a drug product that differs from the reference listed drug in its frequency of absorption, but not in its extent of absorption, may be measured bioequivalent if the difference in the rate of absorption is calculated and the rate of absorption is not disadvantageous to the safety and effectiveness of the drug product. Bioequivalent drug products may contain different inactive ingredients, provided that manufacturer identifies the differences and provides information that the differences do not affect the safety or efficacy of the product.

Bioequivalence studies should be showed the comparison of two medicinal products holding the same active substances. Two products sold by different names, containing same active ingredients, must be presented to be therapeutically equivalent to one another in order to be measured interchangeable. Several test methods are existed to measure equivalence, including.

- Comparative bioequivalence studies, in which the active drug substance is measured in an accessible biological fluid such as plasma, blood.
- Comparative clinical trials.
- Comparative pharmacodynamic studies in human.

It should be remembered that generic drug applications are termed "abbreviated" because they are generally not required to include preclinical and clinical data to establish safety and effectiveness. Many guidelines and regulations covering the licensing of generic products have been announced to ensure that the medicinal products reaching the market have well established efficacy and safety profile.[3]

What is Bioequivalence?

A generic drug is considered to be bioequivalent to the brand name drug if.

- The rate and extent of absorption do not show a significant difference from listed drug, or
- The extent of absorption does not show a significant difference and any difference in rate is intentional or not medically significant
- However, bioequivalence is not straight forward for all the drugs. Many drugs showbioinequivalence.
- In 1973 ad hoc committee (**a group of people assembled to address a specific issue)** on drug product selection of American Pharmaceutical Association published a list of drug that shows bioinequivalence.

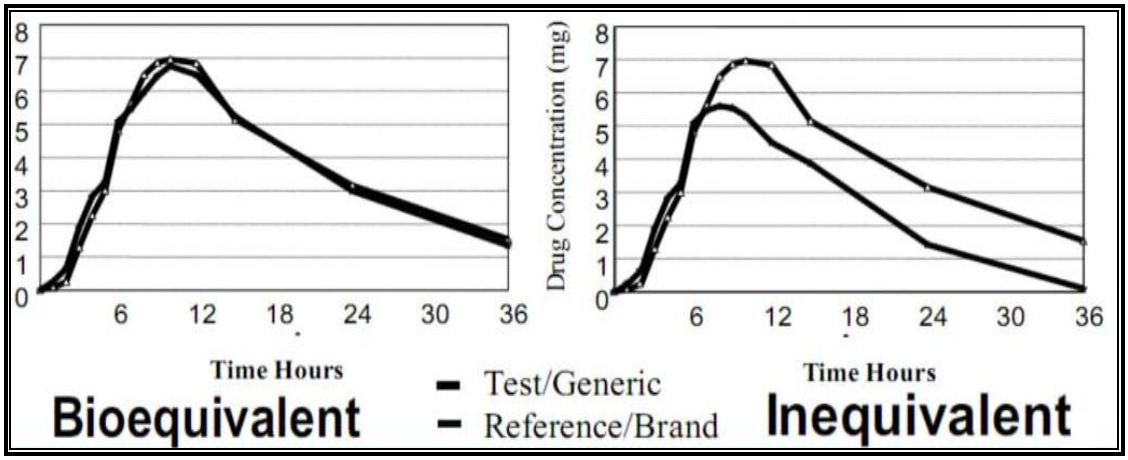

Fig No. 1: Graph Shows Bioequivalent & Inequivalent.

- Based on this list drug has been divided into 3 categories[4]
  - High risk potential
  - Moderate risk potential
  - Low risk potential

Table No. 1: Risk Categories Of Drugs.

HIGH RISK POTENTIAL	MODERATE RISK POTENTIAL	LOW RISK POTENTIAL
Aminophylline	Amphetamine	Acetaminophen
Bishydroxycoumarine	Ampicillin	Codeine
Digoxin	Chloramphenicol	Hydrochlorothiazide
Phenytoin	Digitoxin	Ephedrine
Prednisolone	Erythromycin	Isoniazide
Prednisone	Griseofulvin	Meprobamate
Quinidine	Penicillin G	Penicillin V
Warfarin	Pentobarbital	Sulfixazole

DEFINITION

EQUIVALENCE

Equivalence is more relative term that compares one drug product with another or with a set of established standards.[2]

BIOEQUIVALENCE

"It is a relative term which denotes that the drug substance in two or more identical dosage forms, reaches the circulation at the same relative rate &to same relative extent i.e. their plasma concentration time profiles will be identical without significant statistical differences."

PHARMACEUTICAL EQUIVALENCE
"Drug products are considered to be pharmaceutical equivalents if they contain the same active ingredients and are identical in strength or concentration, dosage form, and route of administration."

THERAPEUTIC EQUIVALENCE
"It indicates that two or more drug products that contain the same therapeutically active ingredientto evoke pharmacological effects & can control the disease to the same extent"

CLINICAL EQUIVALENCE:
"when the same drug from two or more dosage forms gives identical in vivo effects as measured by a pharmacological response or by control of a symptom or a disease."[4]

NEED FOR BIOEQUIVALENCE
- Bioequivalence studies provide a link between the pivotal and early clinical trial formulation.
- Bioequivalence studies are for determination of the therapeutic equivalence between the pharmaceutical equivalencegeneric drug product and a corresponding reference listed drug.
- Bioequivalence studies provide information on product quality and performance when there are changes in components, compositionand method of manufacture after approval of the drug product.[2]
- Clinical Service Form to Final Market Form
- Change of formulations (capsules to tablet)
- Generic Formulations
- Change of Process or manufacturing site
- Regulatory requirement.
- Establishment of pharmacokinetic parameters.
- Study of formulations & process variables.[4]

POSSIBLE PROBLEMS IN BIOEQUIVALENCE
Absence of bioequivalence may be supposed when the proof from the well-controlled clinical trials in patients of different marketed drug products do not give comparable therapeutic effects. These drug products want to be designed either *in vitro* (e.g., drug dissolution) or *in vivo* (e.g., bioequivalence study) to determine if the drug product has bioavailability problem. Moreover, during the progress of a drug substance, certain biopharmaceutical properties of the active drug substance or the design of the drug product may show that the drug may have variable bioavailability or bioequivalence problem.

Some of these problems include.
- The active drug material has fewer than 5 mg/ml solubility in aqueous medium.
- The dissolution rate is slow (i.e., less than 50% in half an hour).
- The particle size or external area of the active drug ingredient is critical in determining the bioavailability.
- Certain structural forms of the active drug ingredient (e.g., polymorphic forms) dissolve poorly, thus disturbingabsorption.
- The active drug ingredient or beneficial moiety is absorbed in large portion in a particular part of the GI tract or is absorbed a specific place only.
- Preparation may have a high proportion of excipients to active ingredients (i.e., greater than 5:1).Specific ingredients such as hydrophilic & hydrophobic excipient & lubricant may interfere with absorption
- The amount of permeability of the active drug constituent is less than 50% when compared to an intravenous dose.
- The active drug substance is quickly metabolized or excreted.[3]
- The active drug constituent is unstable in different surroundings of gastrointestinal tract.
- Rapid metabolism in intestinal wall or in liver during absorption process.[4]

METHODS USED TO ASSESS BIOEQUIVALENCE[5]
- Pharmacokinetics Studies
- Pharmacodynamic Studies
- Comparative Clinical Studies
- Dissolution Studies

ELEMENTS OF BIOEQUIVALENCE STUDY PROTOCOL
The bioavailability studies are done by measuring the concentration of the administered drug in the plasma or blood. This is done by following the systemic protocol of studies and is documented over time.

The protocol is helpful for clinical trials in the early drug development, and the data obtained is used in subsequent bioequivalence studies.

They are carried out to distinguish between two pharmaceutical products containing the same active substance.

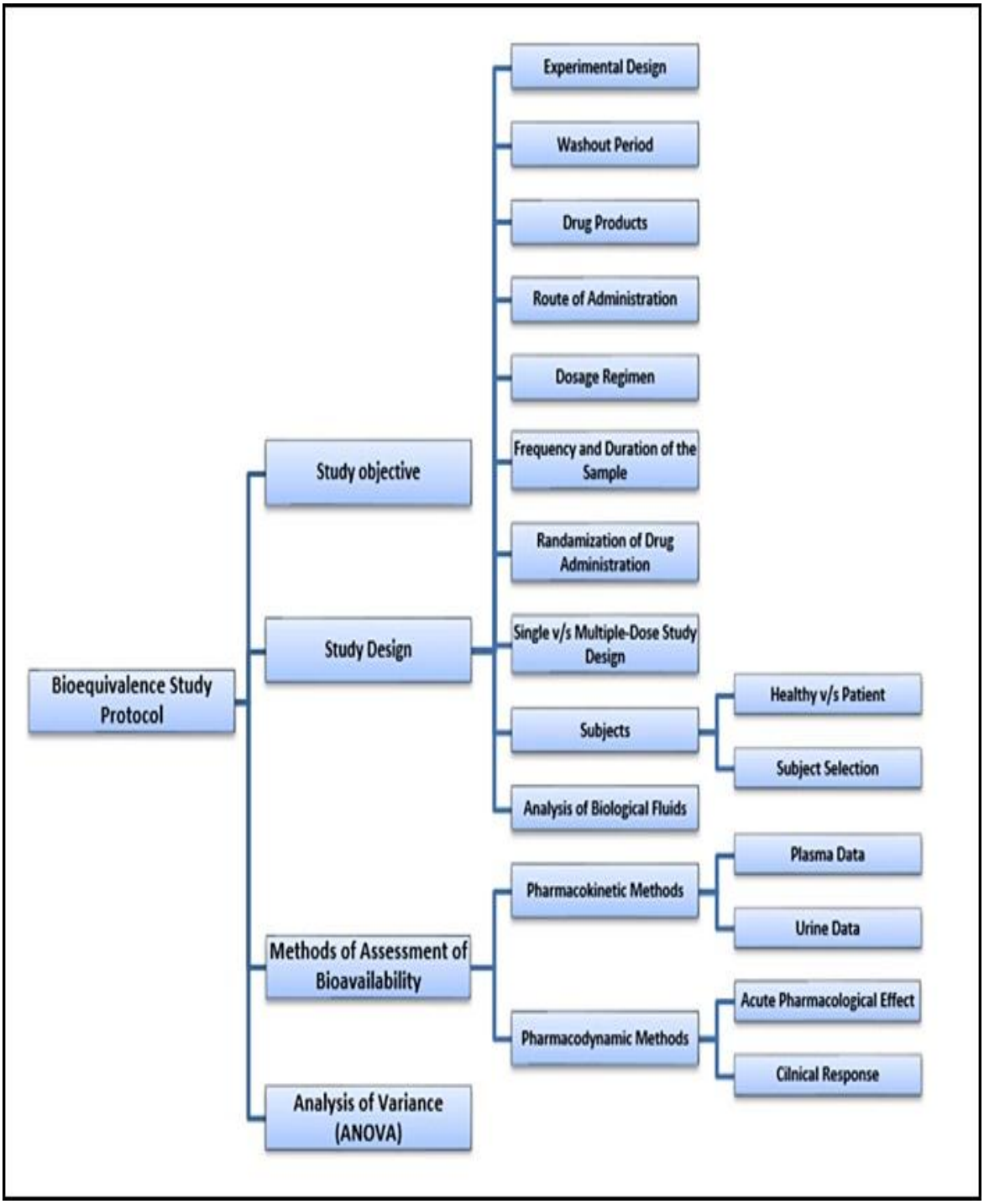

Fig No. 2: Bioequivalence Study Protocol.

Study Objective

If a new product is intended as a substitute for an approved medicinal product as a pharmaceutical equivalent or alternative, the equivalence with this product should be shown or justified. To ensure the clinical performance of such drug products, the bioequivalence studies should be performed.

Bioequivalence studies are conducted if there is.

- A risk of bio-in equivalence and/or
- A risk of pharmacotherapeutic failure or diminished clinical safety.

Study Design

For many drugs the FDA, division of bio equivalence provides guide lines for the performance of in-vivo and in-vitro bioequivalence studies.

1. Experimental Design
2. Washout Period
3. Drug Products
4. Route of Administration
5. Dosage Regimen
6. Frequency and Duration of Sample
7. Randomization of Drug Administration
8. Single versus Multiple Dose Study Design

9. Subjects
10. Analysis of Biological Fluids

1. Experimental Design

The experimental designs are of two types:

a) Parallel design, and
b) Cross over design.

a) Parallel Design

In this design, two formulations are administered to two groups of volunteers. To avoid bias, they are administered randomly.

Disadvantages

Inter-subject variability is not corrected.But parallel design is considered in the following conditions:

- Inter-subject variability is relatively small compared with intra-subject variability.
- If the drug is potentially toxic and has a long elimination half-life.
- The population of interest consists of ill patients.
- The cost of the increasing number of subjects is less than adding additional treatment periods.

b) Cross over design

The cross over design is of following types:

i. Latin Cross Over Design
ii. Balanced Incomplete Block Design (BIBD)
iii. Replicated Crossover Design

i. Latin Cross over Design

The main features are

- Each subject receives just once each formulation.
- Each formulation is administered only once in each study period.

Advantages

- It minimizes the effect of inter-subject variability.

Disadvantages

- It requires a long time to complete the study since the washout period exists between two study periods and to complete the study as the number of formulations increase.
- An increase in the number of study periods leads to dropouts.
- Medical ethics do not allow too many trials continuously on a subject for a longer time.

Table No.2: two-Way Crossover Design.

Group No.	Subjects in groups	Study Period	
		I	II
1	(1 – 6)	A	B
2	(7 – 12)	B	C

Table No. 3: Three-Way Crossover Design.

Group No.	Subjects in Groups	StudyPeriod		
		I	II	III
1	(1-6)	A	B	C
2	(7-12)	B	C	A
3	(13-18)	C	A	B

ii. Balanced Incomplete Block Design (BIBD)

It eliminates the difficulties encountered with Latin square crossover design.

Salient Features

- Each subject receives not more than two formulations.
- Each formulation is administered equally.
- Each pair of formulations occurs together in the same number of subjects.

Table No 4: balanced Incomplete Block Design (Bibd).

Subject	Treatment Period	
	I	II
1	A	B
2	B	A
3	A	C
4	C	A
5	A	D
6	D	A
7	B	C
8	C	B
9	B	D
10	D	B
11	C	D
12	D	C

***Drugs**: A B C D.
Subjects: 12.
Combinations: 6 (AB, AC, AD, BC, BD, CD).

iii. Replicated Crossover Design

It is useful to estimate the intra-subject variants in an individual by bioequivalence approach for both test and standard processes.

Following is the four study periods, two formulations, two sequences recommended to replicate the bioequivalence study.

TABLE NO: 5REPLICATED CROSSOVER DESIGN

Period	I	II	III	IV
Group 1	T	S	T	S
Group 2	S	T	S	T

2) Washout Period

It is the time interval between two periods. The number of washout periods mainly depends upon the type of crossover design and number of formulations to be evaluated.

For Digitoxin (elimination half-life=6-9days), if four formulations are to be administered by Latin square crossover design, the study period may exceed up to one year.

3) Drug Products

a. Test Product

- It may be a new drug formulation developed by a pharmaceutical technologist or a new dosage form of an existing drug.
- It may be compared with the reference product recognized by USFDA.

It is evaluated for the following reasons:

- To select the best dosage form of a new drug.
- To compare the biological performance of the test product with that of a recognized standard.

b. Reference Product (Recognized Standard Product)

It is the standard dosage form to which a new drug is compared to verify its in-vivo performance. The USFDA accepts any innovator drug product as a reference standard.The innovator is the one who originally receives approval from the FDA to market the product in the country.

4) Route of Administration

Oral administered drugs or dosage forms are subjected to bioavailability studies.Dosage forms administered by other routes such as transdermal, buccal are also evaluated for their biological performance.

5) Dosage Regimen

It is the frequency at which a drug is administered.

6) Frequency and Duration of Sample

Before the commencement of bioavailability studies, one has to decide which biological fluid has to be selected for the determination of drug concentration.If it is the blood sample, one has to estimate the plasma concentration-time profile (C_{oax}, T_{max}, and AUC).

The sampling should be done frequently to define the absorption phase, peak and elimination phase during drug in the body.

Urinary excretion studies are suggested when it is not possible to measure the given drug concentration in blood and when ethical consideration do not allow the collection of samples for a longer time.

7) Randomization of Drug Administration

Generally, after the administration of the drug at a fixed time interval, the drug samples are withdrawn.If treatment is administered to a subject sequentially, during sampling, a time gap of 5 to 10mins occurs between the first and last subject, which leads to the increase in plasmadrug concentration, which is due to the difference between the time of administration and sampling. To avoid this, drug products are randomly administered

8) Single versus Multiple Dose Study Design

For bioequivalence purposes, a single-dose study is sufficient for dosage forms (tablets or capsules). Dosage form meant for single-dose administration for a therapeutic benefit such as analgesic needs only a single-dose study.

A multiple-dose study is done for time-release products, enteric-coated preparations and IM injections.

9) Subjects

Ideally, the bioavailability study should be carried out in patients for whom the drug is intended to be used because of.

- The patient will be benefited from the study.
- Reflects better on the therapeutic efficacy of a drug.
- Drug absorption patterns in the disease states can be evaluated.
- Avoids the ethical quandary of administering drugs to healthy subjects.
- Patients are generally preferred in multiple-dose bioavailability studies.
- Drawbacks include disease, other drugs, physiological changes, etc., which may modify the drug absorption pattern.
- Healthy male volunteers under restricted dietary and fixed activity conditions are preferred.
- Female volunteers are used only when drugs such as oral contraceptives are to be tested.
- The number of subjects to be selected depends upon the extent of inter-subject variability but should be kept to a minimum required to obtain reliable data.
- Before starting the study, the consent of volunteers must be taken and they must be informed about the importance of the study, conditions to be followed during the study and possible hazards.
- Medical examination should be performed to exclude subjects with any kind of abnormality or disease.
- The drug washout period for a minimum of ten biological half-lives must be allowed between any two studies in the same subject.

10) Analysis of Biological Fluids

The volume and type of biological fluids must be specified and analyzed for the studies.

Methods of Assessment of Bioavailability

The methods useful in the quantitative evaluation of Bioavailability can be broadly divided into two categories.

a) Pharmacokinetic methods
b) Pharmacodynamic methods

a) Pharmacokinetic Methods

These are 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:

i. Plasma level- time studies
ii. Urinary excretion studies.

i. Plasma Level - Time Studies

It is the most reliable and method of choice in comparison to urine data. The method is based on the assumption that two dosage forms exhibit superimposable plasma level - time profiles in a group of subjects result in an identical therapeutic activity.

In the case of a single-dose study, the samples must be collected for a period of 2-3 biological half-lives after drug administration to obtain a plasma concentration-time profile.

For IV dose administration, the sample must be collected within 5mins after administration and subsequent samples are withdrawn at an interval of 15mins.

If drug administration follows a one-compartment open model, then at least 3 sample points must be considered to describe the disposition phase.

If drug administration follows a two-compartment open model, then 5-6 sample points are to be considered to describe the disposition phase.

For oral administration, at least 3 sample points should be taken on the ascending part of the curve and for accurate determination of K_a and remaining sample points in the disposition phase are similar to IV bolus dose.

In the case of the multiple-dose study, the method involves drug administration for at least five biological half-lives, with a dosing interval equal to or greater than half-life to reach a steady state.The blood samples should be taken at the end of the previous dosing interval and 8-10 samples are collected after administration of the next subsequent doses.

The extent of bioavailability is given as.

$$F_r = \frac{AUC_{(test)}}{Dose_{(test)}} \times \frac{Dose_{(std)}}{AUC_{(std)}} \times \frac{\tau_{(test)}}{\tau_{(std)}}$$

Fr = Relative Bioavailability.

Bioavailability can also be determined from the peak plasma concentration at steady-state as:

$$F_r = \frac{(Css,max)_{(test)}}{Dose_{(test)}} \times \frac{Dose_{(std)}}{(Css,max)_{(std)}} \times \frac{\tau_{(test)}}{\tau_{(std)}}$$

C_{ss} = Concentration at steady state.

ii. Urine Excretion Studies

This method of assessing Bioavailability is based on the principle that urinary excretion of unchanged drugs is proportional to the plasma concentration of the drugs.

Urinary data collection method is considered for the following drugs.

- A 20% unchanged drug should be excreted in the urine.
- Drugs were extensively excreted unchanged in the urine.
  E.g., Thiazides and Sulphonamides
- Drugs having urine as the site of action.

E.g., Antiseptics, Nitrofurantoin.

The method involves

- Collection of the urine samples at regular intervals for some time equal to seven biological half-lives.
- Analysis of unchanged drug in collected samples by using accurate methods.
- Determination of the amount of the drug excreted in each time interval and the cumulative amount excreted.
- Total emptying of the bladder must be done during sample collection to avoid errors.

The major parameters examined in urinary excretion data are.

1. $(dX_u / dt)_{max}$.

It is the maximum urinary excretion rate, which is obtained from a peak of a plot between the rate of excretion versus midpoint time of urine collection period.It is analogous to C_{max} since the rate of appearance of the drug in urine is proportional to its concentration in the systemic circulation. It increases as the rate and extent of absorption increases.

2. $(t_u)_{max}$

It is the time for maximum excretion rate, which is analogous to t_{max} of plasma level data.

3. X_u^{∞}

It is the cumulative amount of drug excreted in the urine, which is related to the AUC of plasma level data.

The extent of Bioavailability is calculated from the following equation:

$$F_a = \frac{(X_u^{\infty})_{Oral}}{D_{Oral}} \times \frac{D_{IV}}{(X_u^{\infty})_{IV}}$$

$$F_r = \frac{(X_u^{\infty})_{Oral}}{D_{test}} \times \frac{D_{std}}{(X_u^{\infty})_{std}}$$

With multiple-dose study at steady-state concentration, the equation for Bioavailability is:

$$F_a = \frac{(X_{u,ss})_{test}}{D_{tset}} \times \frac{D_{std}}{(X_{u,ss})_{std}} \times \frac{\tau_{(test)}}{\tau_{(std)}}$$

b) Pharmacodynamic Methods

These methods are complementary to pharmacokinetic approaches and involve direct measurement of drug effect on a physiological process as a function of time.

This is generally useful when there is a lack of a sensitive analytical method for the measurement of the drug in plasma.

The two pharmacodynamic methods involved in the determination of Bioavailability are/

i. Acute Pharmacological response, and
ii. Therapeutic response.

i. Acute Pharmacological Response

In this method, acute Pharmacological effects such as changes in ECG, EEG, BP, pupil diameter are related to the time course of a drug.

It can be determined by the construction of the pharmacological effect versus time graph.

This response is calculated for at least three biological half-lives to get a good estimate of AUC.

Disadvantage

It is difficult to obtain an accurate linear relationship between the drug level and pharmacological effect.

ii. Therapeutic Response

It is the most definitive method which is based on observing the clinical response of a patient to a drug formulation, but practically, it is not possible because of the difference in clinical response, observed among individuals, not only due to formulations but also due to difference in both pharmacokinetic and pharmacodynamic behavior.

Various factors such as age, drug tolerance, drug interactions may also influence the pharmacodynamic behavior of the drug.

Analysis of Variance (ANOVA)

This indicates the deviation of the test product in comparison to the standard product. The type of deviation and also the cause of deviation can be estimated.It is important in bioavailability and bioequivalence studies.ANOVA compares the Bioavailability of the test and standard formulations. In some cases, the metabolites of drugs are also concentrated in the sample that interferes with the estimation of the unchanged drug in the sample. Urinary samples should be collected for ten biological half-lives of the drug.[6]

TEST CONDUCTED TO STUDY *IN – VITRO*BIOEQUIVALENCE:

Content Uniformity

In order to conduct bioequivalence study it is important to know if there are variations in % content of active ingredients. To check whether a tablet contains a proper amount of drug, % content of drug should be routinely measured. Analysis of drug potency in tablets indicates the presence of drug in dosage form and their stability. The content uniformity test has been included in the monographs for all dosage forms and the samples of tablets are selected and assayed individually. Maximum tablets must have assay content within ±15% of the declared potency and should not exceed +25%. Uniformity of weight ensures consistency of dosage units during compression.

Weight Variation

Factors that affect tablet weight includes tooling of the compression machine, head pressure, machine speed and flow properties of the powder. Weight variation is calculated by taking twenty tablets from each brand. An analytical weighing balance is usually used for weighing the tablets. From the mean value average weights for each brand and percentage deviation were calculated. According to pharmacopoeia, not more than two of the individual weights should deviate from the average weight.

Hardness

Hardness test is important as it determines the resistance of the tablet to chipping, abrasion or breakage during storage, transportation and handling before usage. Space between the upper and lower punches at the time of compression, weight of the material used and pressure applied during compression affect the hardness of the tablet.

Different types of apparatus used for measuring hardness are as follows.

- Monsanto or Stokes hardness tester
- Pfizer hardness tester
- Strong cob hardness tester
- Heberlein or Schleuniger hardness tester.

Friability

Friability is a phenomenon where surface of tablet is damaged or shows a site of damage due to mechanical shock. This test is performed to make sure that the edges of tablet do not break away. Apparatus used is Roche friabilator. Initial weight (W1) of randomly chosen 20 tablets is calculated. After subjecting the tablets to the friabilator for 4 min at 25 rpm, the final weight (W2) is calculated. % loss is determined using the formula.

$$\textbf{\% Friability} = \left[\frac{(W_1 - W_2)}{W_1}\right] \times 100$$

Disintegration

Disintegration study is important for the evaluation of drug release. To find time taken for the tablets or capsules to completely disintegrate, disintegration test is performed. Earlier in order to find the uniformity of compression characteristics, disintegration test is employed. Nowadays for the optimization of compression characteristics we prefer this test. If disintegration time is too high, the tablet is highly compressed or capsule shell gelatin is not of required quality. If disintegration time is not uniform it results in

lack of batch uniformity and batch inconsistency. There are different types of disintegration apparatus for different drugs but principle and construction remains the same. The apparatus consists of basket with six tubes of equal diameter. A wire mesh is fixed to each of these tubes. Reciprocating motor is used for the movement of the basket. The entire assembly is kept immersed in a vessel containing the medium in which the test is carried out.

Dissolution Test

The dosage effectiveness depends on the amount of drug dissolving in the body fluids and its absorption into the systemic circulation. Thus it is important to calculate the dissolution rate of a dosage form. In a dissolution apparatus biological conditions are maintained by providing appropriate dissolution media and temperature with the help of thermostat. Samples are withdrawn at regular intervals. In order to maintain sink conditions an equal amount of media is added. Assays are carried out accordingly. For a successful dissolution test, selection of dissolution media, apparatus and agitation rate plays an important role.

Dissolution test is conducted for

- Optimization of therapeutic effectiveness during product development and stability assessment.
- Routine assessment of production quality to ensure uniformity between production lots.
- Assessment of 'bioequivalence'.
- Prediction of in-vivo availability, i.e. bioavailability (Where applicable).

Different types of apparatus are employed for this purpose as per the Pharmacopeia for different dosage forms. They are given below:

Table No. 6: Dissolution Apparatus Details As Per Usp.

APPARATUS	NAME	DRUG PRODUCT
Apparatus 1	Rotating basket	Tablets
Apparatus 2	Paddle	Tablets, capsules modified drug products
Apparatus3	Reciprocating cylinder	Extended-release drug products
Apparatus 4	Flow cell	Drug products containing low water-soluble drug
Apparatus 5	Paddle over disk	Transdermal drug products
Apparatus 6	Cylinder	Transdermal drug products
Apparatus 7	Reciprocating disk	Extended-release drug products

Analytical Parameters

According to the Pharmacopoeial limits, the amount of drug dissolution should be more than 80% of the labelled amount during the first 30 min. When the drug dissolution is more than 85% within 15 min, further mathematical evaluations are not necessary. For those that did not meet the criteria mathematical evaluations were used to demonstrate bioequivalence. The mathematical evaluation involves the calculation of fit factor (similarity and dissimilarity factors), dissolution efficiency, correlation coefficient, ANOVA test and Dunnett's test.[7]

IN *VIVO* BIOEQUVALENCE TESTING

The process of in vivo bioequivalence testing starts with Fundamental Bioequivalence Assumption followed by conducting a bioequivalence study under a valid study design, appropriate statistical methods for assessment of average bioequivalence and regulatory submission, review and approval.[8]

CONCLUSION

From the above study it is clear that how bioequivalence studies are being carried out. Different methods are being adopted for conducting bioequivalence studies, which helps the researchers gain good exposure to performing bioequivalence studies. In-vitro and in-vivo bioequivalence studies play a vital role in comparing the pharmacokinetic and pharmacodynamic activity of multi-brand generic molecules and in providing enough therapeutic activity of the dosage form. In this review article we have compiled the information on in-vitro bioequivalence studies and in vivo bioequivalence studies along with its importance and the various methods involved in these studies, which are suitable for both institutional and industrial practice as per the pharmacopoeial limits and requirements.

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