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Review Article

BIOEQUIVALENCE AND BIOAVAILABILITY STUDY OF ANTIHYPERTENSIVE DRUG: A REVIEW

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INTRODUCTION

Drug administered orally or parenterally must reach the general circulation in their pharmacological active form to be distributed throughout the body and to exert therapeutic effect. The intensity of therapeutic actions of many drugs correlate well with the concentration of the drug in the biological fluid. The rate of absorption is therapeutically important in case of narrow therapeutic index drugs, where relatively small changes in the concentration can lead to marked changes in action of drug.

Bioavailability and bioequivalence terms related to extend of drug. That determine the pharmacokinetic, pharmacodynamic, pharmacological action of drug.[1, 2]

1.1 BIOAVAILABILITY

Bioavailability is defined in the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action.

This definition focuses on the processes by which the active ingredients or moieties are released from an oral dosage form and move to the site of action.

From a pharmacokinetic perspective, BA data for a given formulation provide an estimate of the relative fraction of the orally administered dose that is absorbed into the systemic circulation

In addition, BA studies provide other useful pharmacokinetic information

related to distribution, elimination, the effects of nutrients on absorption of the drug, BA that can also provide information indirectly about the properties of a drug substance before entry into the systemic circulation, such as permeability and the influence of

presystemic enzymes . BA for orally administered drug products can be documented by developing a systemic exposure profile. A profile can be obtained by measuring the concentration of active ingredients and/or active moieties and, when appropriate, its active metabolites over time in samples collected from the systemic circulation. Systemic exposure patterns reflect both release of the drug substance from the drug product and a series of possible presystemic/systemic actions on the drug substance after its release from the drug product. We recommend that additional comparative studies be performed to understand the relative contribution of these processes to the systemic exposure patternhrough normal digestion.

The bioavailability fraction f is the fraction of the administration dose that enters systemic circulation.[3,4]

f = bioavailability dose / administered dose

1.2 BIOEQUIALENCE

Bioequivalence is defined in the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study. As noted in the statutory definitions, both BE and product quality BA focus on the release of a drug substance from a drug product and subsequent absorption into the systemic circulation.

Three situation have been defined in which bioequivalence study are required

1. When the proposed marketed dosage form is different form that used in Pivotal clinical trial

2. When significant changes are made in the manufacture of the marketed formulation.
3. When a new generic formulation is tested against the innovator's marketed product.

Bioequivalence studies compare both the rate and extent of absorption of various multisource formulation with the innovator (reference) product, on the basis that if two formulation exhibit similar drug concentration-time profile in the blood/plasma, they should exhibit similar therapeutics effects.

We recommend that similar approaches to measuring BA in an NDA generally be followed in demonstrating (dected) BE for an NDA or an ANDA. Establishing product quality BA is a benchmarking effort with comparisons to an oral solution, oral suspension, or an intravenous formulation. In contrast, demonstrating BE is usually a more formal comparative test that uses specified criteria for comparisons and predetermined BE limits for such criteria.

BE documentation can be useful during the NDA period to establish links between

(1) early and late clinical trial formulations;

(2) formulations used in clinical trial and stability studies, if different;

(3) clinical trial formulations and to-be-marketed drug product; and

(4) other comparisons, as appropriate. In each comparison, the new

formulation or new method of manufacture is the test product and the prior formulation

or method of manufacture is the reference product.[3,4].

2. Bioequivalence and Bioavailability studies

Bioequivalence and Bioavailability consist following studies-

In vitro methods can be used to measure product quality BA and to establish BE. these include pharmacokinetic, pharmacodynamic, and clinical studies.

2.1 Pharmacokinetic Studies

The definitions of BA and BE, expressed in terms of rate and extent of absorption of the active ingredient or moiety to the site of action, emphasize the use of pharmacokinetic measures in an accessible biological matrix such as blood, plasma, and/or serum to indicate release of the drug substance from the drug product into the systemic circulation.

This approach rests on an understanding that measuring the active moiety or ingredient at the site of action is generally not possible and, further more, that some relationship exists between the efficacy/safety and concentration of active moiety And its important metabolite or metabolites in the systemic circulation. To measure product quality BA and establish BE, reliance on pharmacokinetic measurements may by viewed as a bioassay that assesses release of the drug substance from the drug product into the systemic circulation.

In this type of we studied, clearance, volume of distribution, and absorption, as determined byphysiological variables. (e.g. gastric emptying, motility, pH)

2.2 Pharmacodynamic Studies

Pharmacodynamic studies are not recommended for orally administered drug products when the drug is absorbed into the systemic circulation and a pharmacokinetic approach can be used to assess systemic exposure and establish BE. However, in those instances where a pharmacokinetic approach is not possible, suitably validated pharmacodynamic methods can be used to demonstrate BE.

2.3 Comparative Clinical Studies

Where there are no other means, well-controlled clinical trials in humans can be useful to provide supportive evidence of BA or BE. However, we recommend that the use of comparative clinical trials as an approach to demonstrate BE generally be considered insensitive and be avoided where possible.[5]

3. HYPERTENSION

The term hypertention is used to describe blood pressure that is sustained at a higher than the generally accepted normal maximum level for a particular age group.

Category(Hg)	Systolic (mm hg)	Diastolic (mm)
Optimal BP	< 120	< 80
Normal BP	< 130	< 85
High-normal BP	130 – 139	85 - 89
Stage 1 (mild)	140 – 159	90 - 99
Stage 2 (moderate)	160 – 179	100 - 109
Stage 3 (severe)	≥ 180	≥ 110

Hypertension is described as essential (primary, idiopathic) or secondary to other disease. Irrespective of the cause, hypertation commonly affect the kidneys[6].

3.1 Classification of Hypertension

1) Essential hypertation

This means hypertation of unknown cause. It account for 85 to 90% of all causes and is subdivided according to the rate at which the disease progresses.

A) Bening (chronin) hypertation.
B) Malingnant (accelerated) hypertation.

2) Secondary hypertation

Hypertation From other diseases accounts for 10 to All cases.

A) Kidney diseases
B) Adrenal cortex
C) Adrenal medulla.[6]

4. ANTIHYPERTENSIVE DRUGS

Antihypertensives are a class of drugs that are used to treat hypertension (high blood pressure). Antihypertensive therapy seeks to prevent the complications of high blood pressure, such as stroke and myocardial infarction. Evidence suggests that reduction of the blood pressure by 5 mmHg can decrease the risk of stroke by 34%, of ischaemic heart disease by 21%, and reduce the likelihood of dementia, heart failure, and mortality from cardiovascular disease.[7]

4.1 Classification of Antihypertensive drug

	Category	Class	Examples
1)	Diuretic	Loop diuretic	Furosemide, Bumetanide
		K+-sparing diuretics	**A**miloride, Triamterene
2)	Sympatholytic drugs	**A**drenergic antagonists	Prazosin, Terazosin
		Mixed adrenergic antagonists	Labetalol, Carvedilol
		Adrenergic neuron blocking agent	Guanadreal, Reserpine
3)	Ca2+ channel blockers		Verapamil, Diltiazem
4)	Angiotensin convertin enzyme inhibitors		Captoprial, Enalaprial
5)	Angiotensin II receptor antagonists	Arterial Vasodilator	Losartan , Candesartan
6)	Vasodilator		Hydralazine, Minoxidil

4.2 Basic Pharmacology of Antihypertensive Drug

All antihypertensive agents act at one or more of the four anatomic control sites and produce their effects by interfering with normal mechanism of blood pressure regulation A useful classification of these agents categorizes them according to the principal regulatory site or mechanism on which they.

The categories include

1. **Diuretics,** Which lower blood pressure by depleting the body of sodium and reducing blood volume and perhaps by other mechanism.
2. **Sympathoplegic agent**, Which lower blood pressure by reducing peripheral vascular, inhibiting cardiac function, and increasing venous pooling in capacitance vessels.
3. **Direct vasodilators,** Which reduce pressure by relaxing vascular smooth muscle ,thus dilating resistance vessels and to varying degrees increasing capacitance as well.
4. **Agents that block production or action of angiotensin,** and thereby reduce peripheral vascular resistance and (potentially) blood volume.[8]

4.3 DIURETICS

4.3.1 Introduction of drug: Diuretics it is First-line drug for hypertension. Relatively safe and effective. Suitable for older adults. Given orally, alone or together with other antihypertensive agents.

4.3.2 Use of diuretics

This medication is a "water pill" (diuretic) that decreases the amount of water in the body by increasing urination. It is used to decrease body fluid and swelling of the hands or feet (edema), and for high blood pressure.

This drug increases urination, it is best taken early in the day. This drug may be taken by mouth with food or milk to reduce stomach upset.

4.3.3 Side effects

This drug may cause dizziness and lightheadedness especially during the first few days as your body adjusts to it. , loss of appetite, itching, stomach upset, headache and weakness may also occur during initial therapy as your body adjusts to the medication. Symptoms of an allergic reaction include: rash, itching, swelling, dizziness, trouble breathing.

4.3.4 Precaution

Tell your doctor your medical history, especially about: gout, diabetes, liver problems, urinary problems, any allergies (especially to sulfa medications). Thiazide diuretics may increase sensitivity to sunlight. Avoid prolonged sun exposure. If you become sun sensitive, use a sunscreen and wear protective clothing when outdoors. This medication should be used during pregnancy only if clearly needed.

4.3.5 Drug interaction

This drug is not recommended for use with: dofetilide, especially if you take: lithium, digoxin, oral drugs used for diabetes, aspirin, NSAIDs (e.g., ibuprofen, naproxen), fluconazole. If you take colestipol or cholestyramine for high cholesterol, take the diuretic 1 hour before or 4 hours after because of decreased absorption into the bloodstream. Avoid any drugs that increase your heart rate or make you excited like decongestants because it may counter-act your blood pressure medicine.

4.3.6 Storage

Store at room temperature away from moisture and sunlight. Do not store in the bathroom

Exampale- Thiazoid diuretics- Hydrochlorothiazoide.

Loop diuretic- Furosemide, Bumetanide.

K+-sparing diuretics- Amiloride, Triamterence.[9]

4.4 Thiazide diuretics

Diuretics lower BP by depleting body sodium stores. Effects take 2 stages:

(1) reduction of total blood volume and therefore cardiac output; initially causes increase of peripheral vascular resistance;

(2) when CO returns to normal level (6-8 wks), PVR declines.

It act on distal convoluted tubule and inhibit Na+-Cl- symport. They can counteract the Na+ and H2O retention effect of hydralazine (direct vasodilator), and therefore are suitable for combined use. Thiazides areparticularly useful for elderly patients, but not effective when kidney function is inadequate.

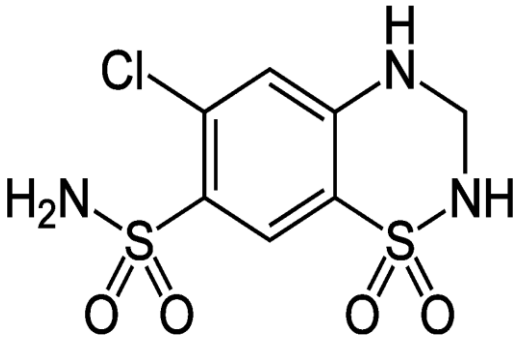
Thiazides reduce blood K+ and Mg2+ levels, and induce hypokalemia and hyperuricemia. Thiazides retain Ca2+ and decrease urine Ca2+ content. Use carefully and monitor serum K+level in patients with cardiac arrhythmias and when *digitalis* is in use.[9]

4.5 HYDROCLOROTHIAZIDE

Hydrochlorothiazide is a thiazide diuretic (water pill) that helps prevent your body from absorbing too much salt, which can cause fluid retention. Hydrochlorothiazide, abbreviated

HCTZ, HCT, or HZT, is a diuretic drug of the thiazide class that acts by inhibiting the kidneys' ability to retain water. This reduces the volume of the blood, decreasing blood return to the heart and thus cardiac output and, by other mechanisms, is believed to lower peripheral vascular resistance.

Hydrochlorothiazide appears to be a potent diuretic as well as antihypertensive agent. Its main action is to produce sodium and chloride diuresis. Ten patients with essential hypertension and one with congestive heart failure were given 50 mg. of hydrochlorothiazide three times a day. The 10 experienced a fall in blood pressure, and the patient with edema had diuresis. The drug was well tolerated by all, and no major toxic effects were noted. Patients were discharged after one week of therapy in the hospital and examined weekly thereafter in the outpatient department. Perhaps the best way to regulate blood pressure in essential hypertension is to admit the patient to the hospital, place him on a no-sodium diet for several days, and then give a general diet along with a sodium diuretic agent.[10]



IUPAC name-
6-chloro-1,1-dioxo-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide

4.5.1 Mechanism of action

Hydrochlorothiazide belongs to thiazide class of diuretics. It reduces blood volume by acting on the kidneys to reduce sodium (Na) reabsorption in the distal convoluted tubule. The major site of action in the nephron appears on an electroneutral Na+-Cl− co-transporter by competing for the chloride site on the transporter. By impairing Na transport in the distal convoluted tubule, hydrochlorothiazide induces a natriuresis and concomitant water loss. Thiazides increase the reabsorption of calcium in this segment in a manner unrelated to sodium transport. Additionally, by other mechanisms, HCTZ is believed to lower peripheral vascular resistance.[11]

4.5.1 Brand names

Hydrochlorothiazide is sold both as a generic drug and under a large number of brand names, including BP Zide 12.5 & 25 (Stadmed), Apo-Hydro, Aquazide H,Dichlotride, Hydrodiuril, HydroSaluric, Hydrochlorot, Microzide, Esidrex, and Oretic.

Hydrochlorothiazide is also used in combination with many popular drugs used to treat hypertension such as Diovan HCT, Zestoretic, Ziac, Benicar HCT, Olmy-H, Atacand HCT, and Lotensin HCT, Temax-H and others.

4.5.1 Pharmacokinetics

Basic pharmacokinetic parameters

Both the therapeutics and toxic effects,depends upon the concentration of drug at the site of action which is difficults to measure. However, it correspond to a specific concentration of drug in plasma, Which can be measured with accuracy. The drug fails to elicit a therapeutics response when the concentration is below the effective level and precipitate adverse reaction when above toxic level. This limit is called therapeutics window or therapeutic concentration range. And the ratio of maximum safe concentration to the minimum effective concentration is termed as therapeutic index'.Thus in order to achive therapeutics success of a particular product it is necessary that drug should remain in to therapeutic index.[12]

Peak Plasma Concentration(Cmax) or peak Exposure

The point of maximum concentration in plasma is called as the peak and the concentration of drug at peak is known as peak plasma concentration.

Time of Peak Concentration(Tmax)

It is a time for drug to reach the peak concentration in plasma after extra-vascular administration, is called as the time of peak concentration. This parameter is particularly important to know that at what time there will be highest concentration of a drug in the plasma this will be helpful to understand that when will be the maximum response of a drug in the body

Area Under Curve(AUC) or Total Exposure

AUC represent the total amount of drug present in blood. Thisgives an idea that after absorption of a drug how much has become available in the blood.

Half life t1/2

Time taken by plasma concentration to reduce to 50% during the elimination phase. t1/2=Kel.

Half life of hydrochlorothiazoid was found to be 5.6-14.8.

Bioavailability
Variably absorbed from GI tract. Bioavailability ~ 70%.

Metabolism
Does not undergo significant metabolism (>95% excreted unchanged in urine)[1]

Excretion
Primarily excreted unchanged in urine.

Dose for Hypertension
Initial dose: 25 mg orally once a day.

Maintenance dose
May increase to 50 mg orally as a single or 2 divided doses.

Side effect of Hydrochlorothiazide
Get emergency medical help if you have any of these signs of an allergic reaction to hydrochlorothiazide: hives; difficulty breathing; swelling of your face, lips, tongue, or throat. Stop using hydrochlorothiazide if you have a serious side effect such as:

1. eye pain, vision problems
2. dry mouth, thirst, nausea, vomiting
3. feeling weak, drowsy, restless, or light-headed
4. fast or uneven heartbeat
5. muscle pain or weakness
6. numbness or tingly feeling
7. a red, blistering, peeling skin rash.[13]

4.6 Basic Requirement for BA/BE Studes: (3,13)

CDSCO (India)	USFDA (USA)	EMEA (Europe)	HPFB (Canada)
1.Age			
Minimum 18	18 yrs and older	18-55	18-55
2.Total No.of Subjects			
Minimum12 subjects	Minimum 12 subjects	Minimum 12 subjects	Minimum 12 subjects
3.Total No. of blood sample per subject			
At least 11	12-18		12-18
4.Dosing Restriction			
Drug should be administered with 240 ml of water ,Restriction:no No food for atleast 4 hr post dose	Drug should be administration with 240 ml(8fld.once) Water, Restriction: one hr before and after drug admn.		Dose: with 150 ml of water.water Restriction: 2hr predose and post dose.
5.For immediate release dosage forms			
Both single dose and steady state dose of modified releaseformulation should bcompared with the dosage of the immediate releaseformulation which it is intended toreplace	Total 2 studies 1.single dose crossover study fed.(If food mentioned in the monograph)	Total 1-2 studies 1.single dose crossover study fasted.or fed condition according to recommendations Related with food interaction effects.	Total 1 study 1 single dose crossover study fasted.

A three-treatment, single-dose, crossover bioequivalence study was conducted in healthy volunteers to compare urinary drug recovery following administration of hydrochlorothiazide tablets, the currently marketed capsule formulation of triamterene and hydrochlorothiazide (Dyazide), and a new tablet preparation of these active ingredients (Maxzide). No significant differences were observed in the urinary recovery of hydrochlorothiazide after the administration of hydrochlorothiazide tablets and Maxzide tablets. However, only about one-half as much hydrochlorothiazide was recovered following the administration of Dyazide capsules. Similarly, the urinary recovery of triamterene and the sulfate ester of hydroxy-triamterene after administration of Dyazide capsules was approximately one-half the levels observed after giving the new tablet formulation.

The study was conducted as an open label, balanced, randomised, two-treatment, two-period, two- sequence, single-dose, crossover bioavailability study comparing hydrochlorothiazide 50 mg tablet, containing 50 mg of hydrochlorothiazide of Ohm Laboratories (A subsidiary of Ranbaxy pharmaceuticals USA) with hydrochlorothiazide 50 mg tablet, containing 50 mg of hydrochlorothiazide of IVAX Pharmaceuticals, in healthy, adult, human, male subjects under fasting condition.

During the course of the study safety parameters assessed were vital signs, clinical examination, medical history and clinical laboratory safety tests (hematology, biochemical, serology parameters and urine analysis) at base line. Laboratory parameters of hematology and biochemistry were repeated at the end of the study. In addition serum electrolytes Sodium, Potassium and Chloride were measured on admission and at the discharge of each period.

A total of 36 subjects were randomized to receive single oral dose of hydrochlorothiazide 50 mg tablet and 31 subjects completed both the periods of the study.

5. CLINICAL CONDUCTIONCE (TRIALS)

Clinical trial it is a systematicstudy of pharmaceutical product on human subject (whether patient or non-patient volunteers) in order to discover or verify the clinical, pharmacological(includeing pharmacokinetic, pharmacodynamic),and adverse effects ,with the object of determining their safety and efficacy. Any study conducted on humen being is classified as clinical research. There are many other way to classify research, but it divided into further two group,

1)Therapeutics.
2)Non-therapeutics research.

1**)The main object of therapeutics research is** to evaluate the safty and efficacy of diagnostic, or therapeutics agent. This research has immediate impact on the health of patients since it culminates in the introduction of a new drug or device.

2)**Non-therapeutics research has** objectives different than those of therapeutics research. In this type of research, mechanism processes and risks of disease are studied. This research leads to a wider understanding of disease but does not concern itself with testing of new diagnostic, therapeutics agent or device.

They are an essential means for growing our clinical professions. Clinical trials are gateways through which new diagnostic tests and new treatments pass in becoming the professional tools of clinicians. clinical trials place prominently in the process of evidence-based practice.

clinical trial might assess a new screening protocol, a new technology, a new diagnostic protocol, a new treatment protocol, or a new dimension of outcome (e.g., quality of life). In which a bioequivalence study has four important dominans, which are critical for providing bioequivalence with innovator's product. These domains are clinical, Bioanalytical, Statistical and Data management. Study always starts with clinical phase and ends with data manegment and report preparation[13].

5.1 Trial phases

The first in human to a new drug is scary. For the simple reason that we do not know the outcome. Experience shows that the risk in first in humans. Is so small as to be negligible.The first in human study is safe because, by this time the drug has been studied in animals for toxicity and has been found to be safe. The application for initiating clinical studies on a drug candidate. Known as investigational New Drug Application (IND)

1) PHASE I

Phase I trials which typically involve initial safty and human pharmacology studies. In trials start with the initial administration of an investigational new drug to it human. In studies typically involve the estimation of initial safty and tolerability, after both single and multipal dose administerd.These trials typicaliy involve 20 to 80 objectives of phase I studies. In the trial would being at a dose of about 0.1 mg/kg. the dose may be slowely increased to 1 mg/kg.

2) PHASE II

phase II studies are generally carried out following the phase I studies. For these studies too. The written approval of the DCGI and the Institutional Review Board is required. The DCGI has to be approached for permission after the information as for phase I, along with the data obtained in phase I studies. The fee payable to the DCGI for permission to conduct phase II studies is Rs 25.000/. Phase II clinical trials typically involve 100 to 200 subjects.

3) PHASE III

Phase III studies are generally are larger studies (with 1000+ subject) conducted on in house or out patient. The number of patieny to be studied depend upon the statisticians advice and on the opinion of the regulators, Phase III studies are usually multicentric and may involve tens of investigatiors and sites. Application for permission to conduct a phaseIII study has to be made to the DCGI, and the fee for the same is Rs. 25000/.

4) PHASE IV

In this trials the post marketing phase many type of studies are conducted. They be post marketing surveillance or/ and continued pharmacovigilance. Each of these studies tries to capture new adverse event that may occun in response to the drug.During clinical trials, the investigators chosen are acknowledge experts in their fields and the patient are selected with care.

FOR HYDROCHLOROTHIAZIDE

Hydrochlorothiazide appears to be a potent diuretic as well as antihypertensive agent. Its main action is to produce sodium and chloride diuresis. Ten patients with essential hypertension and one with congestive heart failure were given 50 mg. of hydrochlorothiazide three times a day. The 10 experienced a fall in blood pressure, and the patient with edema had diuresis. The drug was well tolerated by all, and no major toxic effects were noted. Patients were discharged after one week of therapy in the hospital and examined weekly thereafter in the outpatient department. Perhaps the best way to regulate blood pressure in essential hypertension is to admit the patient to the hospital, place him on a no-sodium diet for several days, and then give a general diet along with a sodium diuretic agent

5.2 Protocols

'Protocol is defined as a document singned and dated by the investigator and the sponsor that fully describes thr objectives (s), design, methodology, statistical consideration and organization of a study'.

The study was performed according to protocol.The protocol was prepared as per schedule Y. The protocol was prepared by the senior CRA of the Facility and reviewed by various department like analytical, statistical. The inputs from all the departments are incorporated in the final protocol.

Study related protocol of drug Hydrochlorothiazide:-

- ✓ General information,
- ✓ Background information,
- ✓ Study objective,
- ✓ Study design,
- ✓ Methodology,
- ✓ Investigational product details,
- ✓ Subject enfollment criteria including inclusion, exclision,
- ✓ Assasement of safety,
- ✓ Bioanalytical analysis,
- ✓ Statistical analysis,
- ✓ Ethical consideration,
- ✓ Quality assurance,
- ✓ Data handling and reporting.

After the approval of the protocol, it was discussed among the investigators of the study and clinical staff. The summary of the protocol includes:

- ✓ The name of the investigational product, reference drug
- ✓ Dose to be administered
- ✓ Type of study whether it is a single center study, a fast or fed study, analyst study etc,
- ✓ Number of subjects to be enrolled in the study.(15)

6.1 Inclusion criteria

- ✓ Willingness to provide information consent to participate in the study
- ✓ Healthy males between 18.0 and 45.0 years of age(inclusion) and body weight not less than 50 kg.
- ✓ Having a body mass index between 18.0 and 25.0 (inclusive), calculate as (weight in kg)/(weight in m)2 Were neither overweight nor underweight for his height as per the Life Insurance Corporation of India height/weight chart for non-medical cases.
- ✓ Had voluntarily given written informed consent to participate in this study.
- ✓ Having no significant disease or clinical significant abnormal laboratory values on laboratory evaluation , medical history or physical examination during screening.
- ✓ Normal 12 lead ECG
- ✓ Normal X-ray chest

- ✓ Having Negative Breath Alcohol Test
- ✓ Having Negative Urine Screen for Drugs[5]

6.2 Exclusion criteria

- ✓ Volunteer incapable of understanding informed consent.
- ✓ Personal / family history of allergy or hypertensive to test drug or its congeners or history if any hypersensitivity or intolerance.
- ✓ Had history of allergy or hypersensitivity to hydrochlorothiazide or any other sulphonamide
- ✓ Had history of diarrhoea, vomiting or headache within past two weeks
- ✓ Had history of hypotension (systolic BP<100 mmHg)
- ✓ Had history of allergy or bronchial asthma
- ✓ Had history of muscle cramps or muscle weakness
- ✓ Had history of any anaphylactic reactions, necrotizing angiitis (vasculitis and cutaneous vasculitis), respiratory distress including pneumonitis and pulmonary edema, photosensitivity, fever, urticaria, rash, purpura, Systemic Lupus Erythematoses(SLE)
- ✓ Had clinically abnormal chemical and microscopic examination of urine defined as presence of RBC, WBC (>4/HPF), epithelial cells (>4/HPF), glucose (positive) or protein (positive).
- ✓ Had clinically abnormal ECG or Chest X-ray.
- ✓ Had history of serious gastrointestinal, hepatic, renal, cardiovascular, pulmonary, neurological or haematological disease, diabetes or glaucoma.
- ✓ Evidence of impairment of renal ,hepatic ,cardiac, lings or gastrointestinal function
- ✓ Volunteers with clinically significant abnormal values of laboratory parameters.
- ✓ History of any psychiatric disorder.
- ✓ Consumption of alcohol within 48 hours prior to dosing or difficulty in abstaining alcohol for the duration of the study .any indication of the regular use of more than one unit of alcohot per day.
- ✓ Smoker, who smoke more than 10 cigarettis / day or inability to abstain from smoking during the study.
- ✓ Participation in any clinical trial within past three months.
- ✓ Donation of blood within 90 days prior to receiving the first dose of study medication
- ✓ Receipt of any prescription drug therapy or over the counter (OTC) drugs two weeks prior to receiving the first dose of study medication or repeated use of drugs within the last two weeks.
- ✓ Dufficulty in swallowing solids like capsules or tablets.
- ✓ Inaccessibility of veins in left or right arm
- ✓ Having significant disease by referring medical history or physical examination during screening.[5]

7. SUMMARY

The Bioavailability and Bioequivalence studies have been made for the safe use of Antihypertensive drug on human volunteers which are in order giving the physicochemical parameters of the drug.

In which the given Diuretic that is Hydrochlorothiazide are studied that the rate and extend of active ingredient of hydrochlorthiazide to the administration site.

Dose – 50mg for 3 time a day.

For safe use of hydrochlothiazide as an antihypertensive agent, the Inclusion and Exclusion criteria of drug on subject are essentialy studied.

8. CONCLUSIONS

Based on , Pharmacokinetic and statistical data obtain from studying human subject under clinical trials. It conclude that Diuretics in which hydrochlothiazide are given 50 mg of mentainance dose given oraly for antihypertensive treatment to the humen volunteers.

Hydrochlorothiazide belongs to thiazide class of diuretics. It reduces blood volume by acting on the kidneys to reduce sodium (Na) reabsorption in the distal convoluted tubule.

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