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Bioequivalence Study and Pharmacokinetic Evaluation of a Dihydropyridine Calcium Channel Blocker by LC-MS Method in Human Plasma

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ABSTRACT

Current investigation was aimed to study bioequivalence of two felodipine formulations and pharmacokinetic studies of human plasma were conducted. Pharmacokinetic parameters such as C_{max}, T_{max}, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, K_{eli} and $t_{½}$ were calculated and the blood plasma level data of the reference product and the test product were compared. Plasma onset of drug for both was 0.5 hr. The C_{max} for reference product was 10.72 1.15 ng/ml with T_{max} of 3.17 0.70 hr. The C_{max} and T_{max} of the Felodipine test product were 10.70 1.17 ng/ml and 3.75 0.44 hr. The $AUC_{(0-t)}$ for reference product was 216.24 33.66 ng.h / ml and 196.50 30.28 ng.h / ml for the test product. The K_{eli} for the reference product was 0.03 0.00 h^{-1} and 0.03 0.03 $h^{-1}$for the test product. The $t_{½}$ of reference product was 24.22 0.88 h and for test product it was found to be 25.01 0.99 h. The $AUC_{(0-\infty)}$ for the reference product was 240.87±34.56 ng.h/ml and for test product it was found to be 221.26±33.05 ng.h/ml. No subject developed any adverse experience during the study protocol. Based on the above observations after oral administration of tablets containing 10 mg of Felodipine it could conclude that the test product is bioequivalent of that of the reference product of felodipine and both are well tolerated. Further the results of the present investigation shown that there is scope for further studies on felodipine metabolism with respect to efficacy and pharmacokinetics.

Keywords: Felodipine, LC-MS, Pharmacokinetics, Bioequivalence studies.

INTRODUCTION

Felodipine is to treat hypertension, chronic stable angina pectoris and Prinzmetal's variant angina. It lowers blood pressure by reducing peripheral vascular resistance through a highly selective action on smooth muscle in arteriolar resistance vessels. Felodipine is having chemical name of (±)-Ethyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5 pyridinedicarboxylate with molecular formula of $C_{18}H_{19}Cl_2NO_4$, molecular weight 384.25

daltons, melting point: 142 to145^{o}C and used as antihypertensive and antianginal drug which is a slightly yellowish and crystalline powder that should be stored in light resistant container in a cool place. Felodipine is insoluble in water and freely soluble dichloromethane and ethanol with log P 3.8 [1-2].

The felodipine oral bioavailability is 15% with 99% Plasma protein binding and 1% Urinary excretion. The pharmacokinetic data also showed that the clearance is 0.8 L/min with 10 L/Kg volume of distribution and 11 h half-life. Felodipine prescribing dose is 2.5 to 10 mg daily. Mechanism of action: Felodipine inhibits the influx of extra cellular calcium across the myocardial and vascular smooth muscle cell membranes blocking the calcium channels. The decrease in intracellular calcium inhibits the contractile processes of the myocardial smooth muscle cells, causing dilation of the coronary and systemic arteries, increased oxygen delivery to the myocardial tissue, decreased total peripheral resistance and decreased systemic blood pressure [3-5].

LC-MS is the novel technique of liquid chromatography coupled with mass spectroscopy (LC-MS) is one of the most exciting developments of recent times in analytical methodology. LC-MS instrument consist of three major components. LC (to resolve a complex mixture of components), An interface (to transport the analyte in to the ion source) of a mass spectrometer and Mass spectrometer (to ionize and mass analyze the individually resolved components).

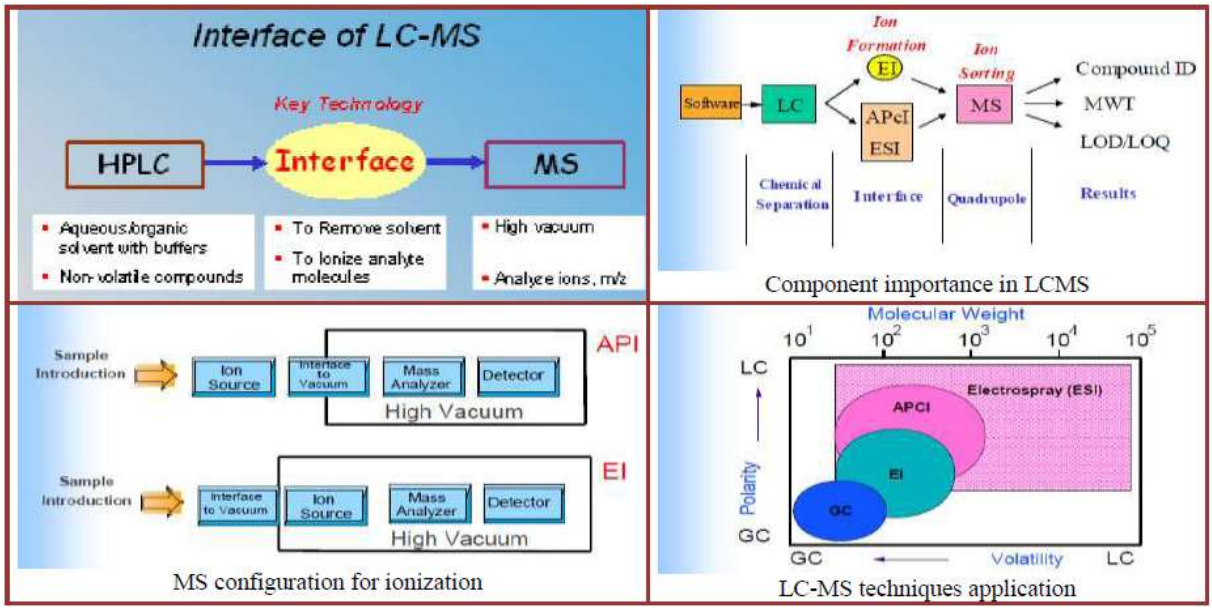

Figure 1: Schematic representation of LC-MS analytical technique

Liquid chromatography / Mass Spectroscopy (LC / MS) is a technique which combines high performance liquid chromatography HPLC, a powerful analytical separation technique with mass spectroscopy, a powerful analysis & detection technique. There are two common atmospheric pressure ionization (API) LC/MS process: Electrospray Ionization (ESI) and Atmospheric Pressure Chemical Ionization (APCI). Both are soft ionization technique. Both of these processes are compatible with most chromatographic separations. API processes are also compatible with most mobile phase solvents (volatile) & volatile buffers. The introduction of atmospheric pressure ionization (API) techniques greatly expanded the

number of compounds that can be successfully analyzed by LC/MS. In atmospheric pressure ionization, the analyte molecules are ionized first, at atmospheric pressure. The analyte ions are then mechanically and electrostatically separated from neutral molecules. Common atmospheric pressure ionization techniques are Electrospray ionization (ESI), Atmospheric pressure chemical ionization (APCI) and Atmospheric pressure photoionization (APPI) [6].

HPLC can be combined with Photo Diode Array detector (PDA) which has three dimensional projection over entire UV-VIS range. It is non-distructive detector so it can be put in series like HPLC-PDA Mass Spectrometer. . HPLC separations can be detected by PDA & Mass spectrometer as different detectors. Ion Trap MS/MS (MS n) function is done by Ion Injection and accumulation, Isolation (Ejection of masses above and below parent ion), Fragmentation (CID of precursor of all product ions) and Ejection of product ions to detector.

The quadrupole mass spectrometer is the most common mass analyzer. Its compact size, fast scan rate, high transmission efficiency and modest vacuum requirements are ideal for small inexpensive instruments. Most quadrupole instruments are limited to unit m/z resolution and have a mass range of m/z 1000.Many bench top instruments have mass range of m/z 500 but research instruments are available with mass range upto m/z 4000. In the mass spectrometer, an electric field accelerates ions out of the source region and into the quadrupole analyzer. The analyzer consists of four rods or electrodes arranged across from each other. As the ions travel through the quadrupole they are filtered according to their m/z value ion can strike the detector. The m/z value transmitted by the quadrupole is determined by the radio frequency (RF) and direct current (DC) voltages applied to the electrodes. These voltages produce an oscillating electric field that functions as a band pass filter to transmit the selected m/z value.

Previously Boo Edgar and co-workers have reported Pharmacokinetic and pharmacodynamic studies of felodipine in healthy subjects after various single, oral and intravenous doses to evaluate the pharmacokinetics and haemodynamic changes in healthy male subjects following the administration of three oral (5, 15, and 40 mg) and two intravenous (1 and 3 mg) doses of felodipine, a new calcium antagonist with a selective effect on the peripheral resistance vessels Felodipine was rapidly absorbed within 1 h when administered as an oral solution, but underwent extensive presystemic elimination. The systemic availability varied between 10 and 23 per cent [7]. Smith SR¸ and co-workers studied Pharmacokinetic interactions between felodipine and metoprolol. This double-blind, cross-over study in healthy male subjects evaluated the pharmacokinetics of felodipine and metoprolol given both separately and in combination. Both felodipine and metoprolol, given alone and in combination, were well tolerated. None of the felodipine pharmacokinetic variables (tmax, Cmax, Cmin, AUC (0-12) and t1/2) changed significantly when felodipine and metoprolol were given in combination. Cmax and AUC (0-12) for metoprolol increased significantly when metoprolol and felodipine were combined, although Tmax, Cmin and t1/2 for metoprolol remained unchanged. The changes in metoprolol pharmacokinetics induced by felodipine are small and unlikely to be clinically important [8]. Anca Pop and coworkers investigated Pharmacokinetic study of Felodipine after single oral dose of slow release formulations in healthy volunteers. The obtained plasmatic profiles of felodipine from the studied formulations were not similar regarding both shape and levels. The representative model for felodipine from Plendil product involves a zero order absorption kinetic, lag time of absorption, bicompartmental distribution and a 1st order elimination kinetics. Using the representative pharmacokinetic model for felodipine from each formulation, pharmacokinetic parameters were investigated [9].

Bioequivalence is defined as "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." BE documentation may be useful during the IND/NDA period to establish links between Early and late clinical trial formulations Formulations used in clinical trial and stability studies, if different Clinical trial formulations and to-be-marketed drug product and Other comparisons, as appropriate.

The present study, therefore, aims for the estimation of Felodipine in human plasma and evaluate the pharmacokinetic variables from the pre developed and validated LC-MS method [10]. It was also planned to investigate the bioequivalence of two formulations of Reference and Test formulations of Felodipine (10mg) after a single oral dose in 24 healthy male human volunteers in a randomised, two way, two period, complete crossover design.

MATERIALS AND METHODS

Active pharmaceutical ingredient and Reagents:
Working Standard of Felodipine was obtained from M/s Saimirra Innopharm Chennai, India and Pantaprazole internal standard was gifted by Dr Reddy's Laboratories, Hyderabad, India. Tablets were procured from the local market. Acetonitrile of HPLC grade by Merck, Ammonium Acetate AR grade obtained from Qualigens fine chemicals and Water HPLC grade from Milli-Q RO system were used. All other reagents used were of HPLC grade. Shimadzu LC2010A HT LCMS system with following configuration was used i.e. LC-10 AD-vp solvent delivery system (pump), SIL 10 AD-vp Auto injector, SPD M-10AVP photo diode array detector, CTO 10 vp column oven, GU 14AM degasser, LC –MS solution data station, Analytical columns of Symmetry (Waters) C18 (150 x 4.6 mm i.d.) Shimadzu 160A UV-VIS spectrophotometer. Sartorius single pan digital balance (R200D & 1702) Systronics - pH meter, pH system 361 and Ultra Sonicator were used for investigation.

Ethical approval
The detail of the study was approved by the Institutional Ethical Committee of J.S.S. College of Pharmacy, ootacamund. The volunteers were also instructed to refrain from consuming alcohol, smoking or other stimulant drinks during investigation period.

LC-MS analytical Conditions for estimation of felodipine in plasma:
A Shimadzu LC-MS system was used for the analysis with the following chromatographic conditions. **LC Conditions** Stationary phase: Princeton SPHER C18 (150 x 4.6 mm i.d. Mobile Phase: Acetonitrile: 2mM ammonium acetate Elution mode: Isocratic A: B= 80:20% v/v Flow rate: 0.8 ml/min Injection volume : 10 µl using Auto injector. **MS Conditions** Interface : ESI Operation mode : SIM Polarity : Negative Probe temperature : Ambient CDL Temperature : 250º C Block Temperature : 200º C Detector voltage : 1.3kv Nebulizer Gas flow : 1.5 l/min Drying gas : 10 l/min Detection : Felodipine – 382.05 Data station : LC-MS solution data station Internal Standard : Pantoprazole – 382.10 The mobile phase was filtered through a 0.22 µ membrane and degassed using ultrasonicator. The experiments were carried out at room temperature of about 20^0C.

Preparation of plasma samples:
At the time of analysis, the samples were removed from the deep freezer and kept in the room temperature and allowed to thaw. A volume of 0.5 ml of sample was pipetted into 2.0 ml

centrifuge tube with this 500 µl of internal standard solution (10.0 µg/ml) and 0.5 ml of precipitating agent (10% Perchloric acid) was added. The resulting solution was vortexed for 5 min and centrifuged at 4000 rpm for 10 min. Supernatants from the above solutions were separated and used for the analysis.

Pharmacokinetic Study Design and Data Handling:

Objective and Study Design:

The objective of the present study was to evaluate the pharmacokinetic variables and investigate the bioequivalence of Reference formulation of felodipine tablets containing 10 mg of Felodipine and Test formulation of Felodipine tablets containing 10mg of Felodipine after a single oral dose in 24 healthy male human volunteers in a randomized, two way, two period complete crossover design. In each dosing session, volunteers received either the Reference formulation of felodipine or Test formulation of Felodipine tablets as a single dose, only on the study day, as per the randomization code at a fixed time. **Products for evaluation: Test Product (T)** Felodipine Tablets (ER) containing 10 mg of Felodipine. **Reference Product (I)** Felodipine tablets containing 10 mg of Felodipine

Drug Assignment:

The subject was assigned a code number. Each subject was randomly assigned to one of the following dosing sequences. They were dosed in order of code number. **Period I Period II** 12 subjects, sequence I **R T** 12 subjects, sequence II **T R** The dosing sequences were randomized in blocks of two. Therefore, each group of two subjects should be the same gender, to the extent possible.

Table. 1: Human volunteer modes of treatment with felodipine during study Details:

Code	V_1	V_2	V_3	V_4	V_5	V_6	V_7	V_8	V_9	V_{10}	V_{11}	V_{12}
Period I	R	T	R	T	R	T	R	T	R	T	R	T
Period II	T	R	T	R	T	R	T	R	T	R	T	R
Code	V_{13}	V_{14}	V_{15}	V_{16}	V_{17}	V_{18}	V_{19}	V_{20}	V_{21}	V_{22}	V_{23}	V_{24}
Period I	R	T	R	T	R	T	R	T	R	T	R	T
Period II	T	R	T	R	T	R	T	R	T	R	T	R

Test Product (T) Felodipine tablets containing 10 mg of Felodipine.
Reference Product (R) Felodipine Tablets containing 10 mg of Felodipine.
Volunteers received either of the study formulations according to their code number along with 240 ml of water.

Subject Selection Criteria:

Subjects were adult (20 years of age or older), healthy volunteers capable of giving informed consent selected from the panel of volunteers recruited by Bioequivalence Centre, Centre for Advanced Drug Research and Testing, J.S.S. College of Pharmacy, Ootacamund. Volunteers were screened for inclusion in the study 7 days prior to the commencement of the study. Restrictions on admission into the study were based on safety considerations.

Subject Inclusion Criteria:

Males, Healthy, 20 - 40 years of age, not more than plus or minus 15% from ideal weight for subject's height and elbow breadth. General good health as determined by a medical history and physical examination within 30 days prior to the start of the study. Without a history of clinically significant organ-system disorders or ongoing infectious diseases. Without a history of benign prostatic hypertrophy, prostate infections, or urinary retention. Without a history of

asthma, without a history of peripheral neuropathy and without a history of alcohol abuse or drug addiction requiring treatment within the last 12 months. Blood chemistry (including alkaline phosphatase, glucose, AST, ALT, LDH, BUN GGT, Creatinine, bilirubin, electrolytes), hematology(including hemoglobin, hematocrit, red blood cell count, white blood cell count, differential, platelet count), and urinalysis values within clinically acceptable limits upon evaluation by the investigator. Serum Creatinine must be in the laboratories reference range. The above tests were performed within 30 days prior to the start of the study. No prescription drugs within 14 days, or OTC preparations, herbal remedies, or nutritional supplements (excluding vitamins, and occasional use of acetaminophen or ibuprofen) within 7 days prior to drug administration, each period. No ingestion of acetaminophen or ibuprofen within 24hours prior to drug administration. No grapefruit juice or grapefruit-containing products for at least 72hours prior to drug administration, each period. No alcohol consumption for at least 48 hours prior to drug administration, each period. No caffeine or Xanthine consumption for at least 12 hours prior to drug administration each period. No known allergy to nitrofurantoin, or other nitrofurans such as furazolidone or nitrofurozone. At screening, subjects must have blood pressure and pulse rate within 90-140mmHg 50-90mmHg 50-100bpm. Negative HIV 1, hepatitis B, surface antigen, and urine screen for drug abuse within 30 days prior to the start of the study.

Screening tests for Subjects:
Tests conducted were complete haemogram, Liver Function Tests, Renal Function Tests, Blood sugar, Lipid Profile, Routine Urine Examination, Chest X-Ray, ECG along with Virological Tests - HIV Antibody, HBS Antigen for inclusion in the study.

Subject Exclusion Criteria:
Clinically abnormal physical and / or clinical findings at the screening. Administration of any investigational drug in the period 0 to 1 month before entry to the study or a need for any medication within 14 days before entry to the study and during the study period. Presence or history of allergy, Loss of greater than 400 ml of blood, in the period 0 to 12 weeks before entry to the study or during the study. Inability to communicate or co-operate with the investigator due to language problem, poor mental development or impaired cerebral function. History of alcohol / drug abuse / smoking. Request of subject to withdraw from the study is permitted.

Subject Monitoring:
A physician was on site at dosing and for 4 hours after dosing and The blood pressure and pulse rate must be within the following ranges at 0 hour (Prior to dosing).

Systolic Blood Pressure Diastolic blood pressure Pulse:
The 90-140mmHg 50-90mmHg 50-100bpm Blood pressure and pulse were measured at 2,4,8,12, 24, 48, 72, 96 and 120 hours after the subject has been seated at least three minutes. Subjects with blood pressure and pulse measurements outside the ranges will have their vital signs measurements repeated according to Standard Operating Procedures. If 0-hour vital signs requirements are not met, the subject will not be dosed and must be withdrawn from the study.

Meals and Food Restrictions:
Subjects were fast for at least 10 hours prior to being served the standard breakfast. The drug was administered 3 hours before the subjects begin the standard breakfast. Subjects were

instructed to eat their entire breakfast in 30 minutes. Only the fluids given with breakfast and water (except within one hour prior to and until one hour after drug administration) were allowed. Standard meals, consisting of caffeine-free, xanthine-free, and grapefruit-free foods and beverages, were served at scheduled times during the in-house portion of the study. Only the foods served were allowed during the in-house confinement period. Food Breakfast -3 h. post administration Lunch - 6 h. post administration Refreshment - 9 h. post administration Dinner - 12 h. post administration

Observations:
The subjects showed normal B.P. during and after the study and are allowed for watching movies / listening to music / reading magazines after 3 hrs of administration during study. They showed normal psychological, health status with zero case withdrawal rate and no local Reactions. The subjects were withdrawed from the study with serious adverse effects, major violation of the protocol, withdrawal of consent, in case of any systemic illness occurred during requiring intake of other drugs in the study period. The volunteers were monitored for above abnormal symptoms / signs during the study period and for one week after the study period and if noticed, the details were entered in the case report sheets and tabulated at the end of the study.

Ethics Review Procedure:
The study protocol of the study was submitted to the Ethical Committee in advance of the study commencement and the approval was obtained. No concomitant medication (other than the study drug) was allowed during the study phase and two weeks prior to the study. The volunteers were also instructed to refrain from consuming alcohol, smoking or other stimulant drinks during this period.

Informed Consent:
Prior to the commencement of the study, each subject was provided with an information sheet giving details of the investigational drugs, procedure and potential risk involved. They were instructed that they are free to withdraw their consent and to discontinue their participation in the study at any time without prejudice. All subjects names were filed confidentially in the investigation files and all data were handled confidentially. The subjects were signed the consent form after discussion with the investigator.

Blood Collection:
Volunteers were given code numbers and were allocated to the treatment **R / T (Reference and Test products)** in accordance with the randomisation code. All the volunteers were assembled in Bioequivalence Centre, Centre for Advanced Drug Research and Testing, J.S.S. College of Pharmacy, Ootacamund at 7.00 a.m. on the study day of each phase, after overnight fasting of 12 hrs. Their pulse rate, BP was recorded and an indwelling intravenous catheter will be introduced with strict aseptic precautions for blood collection. They received either of the study formulations according to their code no with 240 ml of water. A total of 15 blood samples were collected at 0 hr (before drug administration) 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0, 18.0, 24.0, 48.0, 72.0, 96.0 and 120.0 h. Through I.V. Cannula, blood samples (5ml) were collected via disposable syringes in pre-citrated centrifugal tubes. The withdrawn samples were centrifuged at 4000 rpm for 10 minutes to separate plasma. They were transferred into airtight containers and stored at deep freeze condition.

Adverse Events:
The Physician was recorded the unusual sensations or adverse events at each visit. This was based on his own impression and observation and the subjects answer to the question "How do you feel?" Volunteers was questioned pre dose and at 3 and 12 hour post dose. Any adverse events reported were noted on the case record sheet.

Subject Safety:
Subjects were monitored throughout the study for adverse events to the study medication and/or procedures. In each period, a medical sub investigator was on site at least 30 minutes before dosing and for 6 hours after the administration of the study medication to the last subject. A medical sub investigator was also being on call for the remainder of the study. If necessary, a physician or in a nearby hospital will administer treatment for any adverse event. All adverse events were recorded for their seriousness, severity and relationship to the study medication. The evaluations of the results were done after tabulation of the data and respective graphical representation.

Quality Assurance:
The analysis was carried out in a GLP regulated environment and was conducted in compliance with the principles of Good Laboratory Practice. All the analytical instruments used for the study were calibrated & validated and the analytical methods adopted were validated as per the latest guidelines in force.

Evaluation of Pharmacokinetic Parameters:
Plasma concentrations and time points, Subject, period, sequence, treatment, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, and C_{max}, T_{max}, and $t_{½}$, Inter subject, intra subject, and/or total variability, In addition, the following statistical information shall be provided for $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, and C_{max}, Means and Ratio of means with Confidence intervals. Confidence interval (CI) values should not be rounded off; therefore, to pass a CI limit of 80-125, the value should be at least 80.00 and not more than 125.00.

RESULTS AND DISCUSSION

Bioequivalence Study of Felodipine Subjects:
The mean age of human volunteers participated in the study was 25.50 1.040 years. Their height 177.92 8.21 cm and 67.17 7.50 kgs weight were recorded respectively. **Study Design:** This was a single dose, randomized; complete two way, two period cross over study with a washout period of 12 days between the treatment sessions. In each dosing session, volunteers received either the reference or the test formulation of Felodipine tablets (10 mg) as a single dose, only on the study day, as per the randomization code at a fixed time as per the study protocol.

Pharmacokinetics Parameters Data:
Pharmacokinetic parameters such as Peak plasma concentration C_{max}, Time to peak Concentration T_{max}, Area under the plasma concentration - time curve $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ elimination rate constant K_{eli} and Elimination half-life $t_{½}$ were calculated separately and the blood level data of the reference product and the test product were compared. The observations are given in table 12 to 18 and fig 10 to 22. On oral administration of the reference product and the test product in the fasting state exhibited blood levels in all the volunteers from 0.5 hr onwards. The peak plasma concentration i.e. C_{max} after administration

of the reference product was 10.72 1.15 ng/ml at 3.17 0.70 hr (T_{max}). The C_{max} and T_{max} of the test product (Felodipine) were 10.70 1.17 ng/ml and 3.75 0.44 hr, respectively.

Table.2. Mean Plasma Concentrations of Felodipine Reference and Test Product (ng/ml) by LC analysis.

Time (h)	Test Product		Reference Product	
	Mean	S.D	Mean	S.D
0	0.00	0.00	0.00	0.00
0.5	1.26	0.55	1.33	0.48
1.0	2.38	1.14	2.67	0.86
2.0	4.26	1.67	4.41	1.44
3.0	7.30	2.84	8.02	2.76
4.0	10.17	1.10	9.99	1.18
6.0	7.69	0.75	7.91	0.86
8.0	5.88	0.99	6.44	0.88
12.0	4.24	0.76	4.86	0.97
18.0	3.07	0.76	3.56	0.79
24.0	2.03	0.70	2.46	0.63
48.0	1.10	0.35	1.30	0.47
72.0	0.85	0.10	0.85	0.10
96.0	0.72	0.05	0.70	0.05

Table.3. Felodipine Mean Pharmacokinetic parameters estimation data of human plasma (n=24)

S.No	Parameters	Test Product	Reference Product	% Ratio
1.	$AUC_{(0-t)}$ (ng .h/ml)	196.50± 30.28	216.24± 33.66	90.87
2.	$AUC_{(0-\infty)}$ (ng .h/ml)	221.26± 33.05	240.87± 34.56	91.85
3.	C_{max} (ng/ml)	10.70± 1.17	10.72± 1.15	99.81
4.	T_{max} (h)	3.75± 0.44	3.17± 0.70	118.29
5.	K_{eli} (h^{-1})	0.03± 0.00	0.03± 0.00	100
6.	$t_{½}$ (h)	25.01± 0.99	24.22± 0.88	103.26
Test Product (T) Felodipine tablets containing 10 mg of Felodipine. *Reference Product (R) Felodipine Tablets containing 10 mg of Felodipine.*				

The area under the plasma concentration-time curve i.e. $AUC_{(0-t)}$ for the reference product was 216.24 33.66 ng.h / ml. The $AUC_{(0-t)}$ of the test product (Felodipine) was found to be 196.50 30.28 ng.h / ml. The elimination rate constant (K_{eli}), for the reference product was 0.03 0.00 h^{-1}. The K_{eli} of the test product (Felodipine) was found to be 0.03 0.03 h^{-1}, respectively. The elimination half-life ($t_{½}$) for the reference product was 24.22 0.88 h. The $t_{½}$ of the test product (Felodipine) was found to be 25.01 0.99 hr. The area under the plasma concentration-time curve for infinitive time $AUC_{(0-\infty)}$ for the reference product was 240.87±34.56 ng.h/ml. The $AUC_{0-\infty}$ after administration of the test product (Felodipine) was found to be 221.26±33.05 ng.h/ml, respectively.

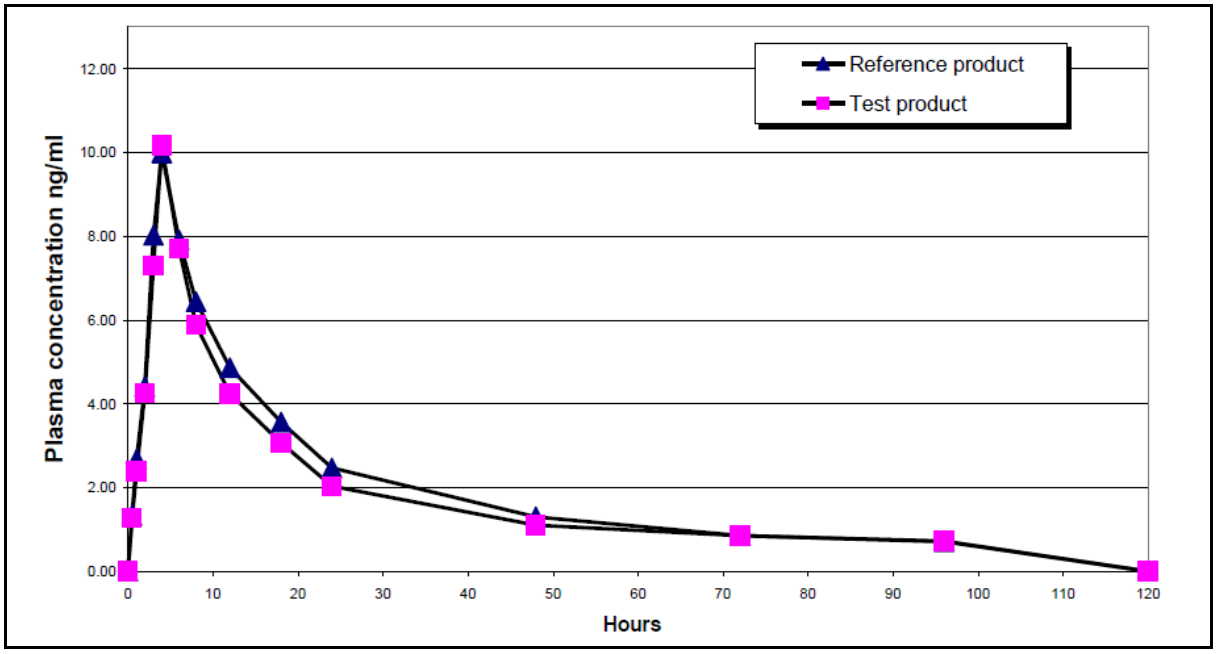

Fig.2. Mean plasma Concentration - Time Curve for 24 Volunteers during bioequivalence study of Felodipine Reference and Test Product

Based on the observations from the investigation after oral administration of tablets containing 10 mg of Felodipine it is could be concluded that the felodipine test product is bioequivalent to that of the felodipine reference product. The LC-MS analytical method can be used for estimation of felodipine in bulk and formulations and also it could be used for the pharmacokinetic and bioequivalence studies to estimate the plasma samples with ease and reproducibility.

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