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Research Article

PHARMACOKINETIC AND BIOEQUIVALENCE COMPARISON BETWEEN TELMISARTAN TABLETS 80MG: AN OPEN LABEL, BALANCED, RANDOMIZED-SEQUENCE, SINGLE-DOSE, TWO-PERIOD CROSSOVER STUDY IN HEALTHY MALE VOLUNTEERS

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Abstract

Background: This present bioequivalence study was designed to determine the pharmacokinetic, bioavailability and bioequivalence of telmisartan 80mg tablets in comparison with MICARDIS™ telmisartan 80mg tablets after single dose administration under fed conditions in healthy adult male subjects. Therefore the design of an open label, balanced, randomized, two-sequence, single dose, two way crossover study with a wash-out period of at least 7 days was used.

Methods: An open-labeled, balanced, single-dose with food, two-treatment, two-period, two-sequence, randomized crossover study was conducted in 20 healthy male volunteers. Each volunteer received a 80mg tablet of the reference or test drug respectively. On the day of dosing, blood samples were collected before dosing and at various time points up to 72 hours after dosing. Analysis of telmisartan concentrations was performed using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method. The pharmacokinetic parameters including C_{max}, AUC_{0-t}, AUC_{0-inf}, T_{max}, $t_{1/2}$ and K_{el} were analyzed using the non-compartmental model. Drug safety and tolerability were assessed.

Results: The pharmacokinetic parameters including C_{max}, AUC_{0-t}, AUC_{0-inf}, T_{max}, $t_{1/2}$ and K_{el} were analyzed using the non-compartmental model. Drug safety and tolerability were assessed. The primary pharmacokinetic parameters (C_{max}, AUC_{0-t} and AUC_{0-inf}) 90%CI were within the 80 to 125% interval required for bioequivalence as stipulated in the current regulations of the USFDA acceptance criteria. The geometric mean ratios (Test/Reference) between the two products of 80mg tablets under fed condition were 92.34% (92.23%-117.37%) for C_{max} ratios, 91.84% (94.28%-110.31%) for AUC_{0-t} ratios and 99.42% (93.65%-106.97%) for AUC_{0-inf} ratios of Telmisartan. Twenty volunteers had completed both treatment periods. There was no significant difference of the T_{max} parameter between the two formulations ($p > 0.05$). No serious adverse events related to the study drugs were found.

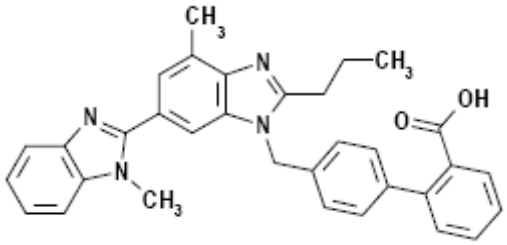
Conclusion: This single dose study found that the test formulation telmisartan 80mg tablets are bioequivalent to the reference formulation MICARDIS™ telmisartan 80mg tablets in terms of extent and rate of absorption, under fed condition in healthy adult male volunteers according to the USFDA regulatory guidance.

Keywords: Telmisartan, Bioavailability, Bioequivalence, Intrasubject Variability

Introduction

Telmisartan a nonpeptide molecule[1], is chemically described as 4'-[[1, 4'-dimethyl-2'-propyl [2, 6'-bi-1H-benzimidazol]-1'-yl] methyl]-[1, 1'-biphenyl] -2-carboxylic acid. Its empirical formula is $C_{33}H_{30}N_4O_2$, its molecular weight is 514.63 g/mol, and its struc-

tural formula is:



Telmisartan is a white to slightly yellowish solid. It is practically insoluble in water and in the pH range of 3 to 9, sparingly soluble in strong acid [except insoluble in hydrochloric acid], and soluble in strong base.

Telmisartan is an orally active, AT1 selective angiotensin II receptor antagonist [2-3]. Following oral administration, telmisartan is well absorbed with a mean absolute bioavailability of about 50% [4]. Mean peak plasma concentrations [C_{max}] of telmisartan are reached in 0.5-1.0 hour after dosing. The pharmacokinetic profile is characterized by greater than proportional increases in plasma concentrations [C_{max} and AUC] with increasing doses greater than 40 mg. Telmisartan shows bi-exponential decay kinetics with terminal elimination half life of approximately 24 hrs, and does not accumulate in plasma upon repeated once daily administration. Food slightly reduces the bioavailability of telmisartan. Telmisartan is extensively bound to plasma proteins [>99.5%] at concentrations achieved at the recommended dosage. The apparent volume of distribution is approximately 500 L, suggesting extensive tissue binding sites.

Telmisartan is metabolized by conjugation to form a pharmacologically inactive acylglucuronide; this is the only metabolite that has been detected in human plasma and urine [5]. Following both oral dosing and intravenous administration of radiolabelled telmisartan, the parent compound represented approximately 85%, and the glucuronide approximately 11% of total radioactivity in plasma. Total plasma clearance of telmisartan is >800 mL/min. Biliary excretion is the predominant route of elimination of telmisartan and its metabolite.

The rationale of this present bioequivalence study for two formulations of 80mg telmisartan tablets was examined between generic drug telmisartan 80mg tablets as the test product and MICARDIS™ (Boehringer Ingelheim) as the reference product. This bioequivalence study could give assurance when prescribing less expensive generic drugs as alternatives with similar efficacy and safety.

The study objectives of this present study are to assess the single dose bioequivalence of telmisartan 80mg tablets with MICARDIS™ (Boehringer Ingelheim) in healthy, adult, human study participants under fed conditions and to monitor the clinical status, adverse events, laboratory investigations and assess relative safety and tolerance of telmisartan formulations under fed conditions.

Materials and Methods

According to the USFDA regulatory individual product recommendations, two studies (fed and fasting) to be done with 80mg telmisartan tablets to obtain marketing authorization in USA.

USFDA waiver request of in-vivo testing [6]: 20 mg and 40 mg based on (i) acceptable bioequivalence studies on the 80 mg strength, (ii) acceptable in-vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths.

Study drugs

Telmisartan 80mg tablets and MICARDIS™ from Boehringer Ingelheim were used as the test and the reference products respectively. Both products were prepared as telmisartan tablets equivalent to telmisartan 80mg. Both the products were stored at controlled room temperature 25°c (77 °f).

Study population

The study was carried out at ClinSync clinical Research Private Limited, India. The study protocol was approved by the Ethics Committee. In addition, the protocol was performed in accordance with the Declaration of Helsinki Principles [7] as outlined in the ICH-E6 Guidelines for Good Clinical Practice (GCP) [8]. All subjects were given a detailed description of the study and written informed consent was obtained prior to the enrollment.

The sample size was estimated based on, Coefficient of variation (C.V.) of the drug, sufficient statistical power to detect 20% difference with the power of 0.8 in C_{max} and AUC between the test and reference product, Regulatory requirements.

Sample size was based on estimates obtained from reported literature and previous studies. Assuming a formulation ratio (T/R) ranging from 0.95-

1.05 a sample of 20 subjects including dropouts would be sufficient to show bioequivalence between the two formulations with a power of at least 80%. Hence sample size of 20 subjects was enrolled in the study.

Twenty healthy male volunteers between the ages of 18-45 years with a body mass index between 18.5 kg/m^2 and 24.9 kg/m^2, with body weight equal to or not less than 50 kg were assessed to be in good physical condition by a complete medical screening including a medical history, physical examination and laboratory screening test for hematologic and blood biochemistry parameters. Subjects with a history of hypersensitivity to any ingredients in the telmisartan products and/or related drugs or its constituents or who were taking any medication or alcohol for a 21-day period prior to the study were excluded. Subjects who had a history of cardiovascular, hepatic, renal, gastrointestinal or hematologic disease were excluded from the study.

Study design

The study was an open-labeled, single-dose, study taken with food, two-treatment, two-period, two-sequence randomized two way crossover with at least one week washout period. Subjects were randomly allocated to two groups by the sequence of product administered [Test-Reference (TR) and Reference-Test (RT) group]. In each period, 1X80mg tablet of telmisartan of the test or reference product was administered 30 minutes after starting a high fat, high calorie breakfast at the same time in the morning before dosing. Subjects were housed 12 hours prior to dosing in the clinical facility from a time adequate to ensure 10 hours supervised fasting before consuming high fat breakfast and were allowed to leave the facility after 24.00 hours post-dose sample in each period. The subjects received a standard meal at about 4.0, 9.0 and 13.0 hours after dosing in each period. During housing, all meal plans were identical for all the periods. Drinking water was not allowed from one hour before dosing till one hour post-dose (except for 240 ± 02 mL of drinking water given for dosing). Before and after that, drinking water was allowed at *ad libitum*. After a minimum of 1 week washout period, the subjects were crossed over to the next treatment following the same procedure as conducted in the 1st period.

Sample collection

During dosing day in each period, 21 blood samples (6 mL each) will be collected as per the following schedule:

Pre dose sample(0.00 hr) within 02 hrs prior to drug administration and the others at 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 3.00, 4.00, 5.00, 6.00, 7.00, 8.00, 9.00, 10.00, 12.00, 24.00, 36.00, 48.00 and 72.00 hours post dose. The total volume collected per study participant in this study will not exceed approximately 321 mL including up to 9 mL for screening, and 7-9 mL for post clinical assessment of lab parameters and 18 mL for discarded blood sample resulting from use of intravenous cannula for 12 hours and 2-9 mL was collected for repeat/additional lab tests, if required. For separating plasma, all blood samples were centrifuged at 3800 RPM for 10 minutes at 4°C ± 2°C.

Centrifugation of all samples was done as early as possible after each sample draw time point. After centrifugation, plasma samples were aliquoted into two sets in properly labeled polypropylene tubes and immediately stored at about -60°C or colder.

Telmisartan analysis by LC-MS/MS [11-28]

The published LC-MS/MS method [9] was validated according to USFDA regulations [10] for quantification of telmisartan from extracted subject plasma samples. The 50 µL of Ticlopidine dilution (about 100ng/mL) is added to 100 µL of plasma sample and vortexed to mix. Added 1 mL of Extraction solvent (Acetonitrile), vortexed for 2min. Centrifuged the polypropylene Centrifuge the centrifuge tubes at 14000 rpm and 5°C for 10 min, transferred approximately 0.8 mL of supernatant to pre-labeled HPLC vials and a 10-µL aliquot was injected into the chromatographic system[11-13].

HPLC was carried isocratically at room temperature using a Thermo BDS Hypersil C18 (4.6 x 50mm) column. The mobile phase consisted of 45:45:10 ACN: MeOH: 10 mM Ammonium acetate Buffer. The flow-rate was 0.8 ml/min. The duration of the analytical time was 2.5 min. The analytical column effluent is directed through the divert valve to a thermo electron TSQ quantum discovery mass spectrometer[14-16]. Source/gas parameters such as spray voltage is operated at 4500, sheath gas pressure, auxiliary gas and capillary temperature settings are maintained at 30 psi, 15 psi and 300 °C, respectively.

Chromatograms were acquired on a TSQ tandem mass spectrometry (Thermo Finnegan, Sanjose, CA, USA) equipped with Electrospray ionization (ESI) and connected to a PC runs with the standard software Xcalibur 2.0.7 and LC Quan 2.5.6 [18-20]. Mass spectroscopic detection was performed on a Triple quadrapole instrument (Thermo, TSQ Quantum Discovery Max). The calibration curve is constructed by weighted $1/x^2$ least-square linear regression analysis of the peak area ratio (drug/ISTD) vs. the concentration of drug[21].

Pharmacokinetic and statistical analysis [22-24]]

For the purpose of Average Bioequivalence analysis C_{max}, AUC_{0-t} and AUC_{0-inf} were considered as the primary variables and T_{max}, $t_{1/2}$ and K_{el} were considered as the secondary variables. General Linear Model for analysis of variance (ANOVA) for crossover design was performed for log-transformed data and used to assess the effect of formulations, periods, sequences and subjects nested in sequence on these parameters. The difference between two related parameters was considered statistically significant for a *p*-value equal to or less than 0.05. 90% confidence interval (CI) for the ratios of geometric mean Test/Reference (T/R) for C_{max}, AUC_{0-t} and AUC_{0-inf} was calculated based on least squares means from the ANOVA of log-transformed data. The 90% geometric CI of the ratio (T/R) of least squares means from the ANOVA of the log-transformed C_{max}, AUC_{0-t} and AUC_{0-inf} should be within 80.00% to 125.00%.

Tolerability assessment

Physical examination and measurement of vital signs (Blood Pressure, Pulse Rate and Oral Temperature) were examined at the time of Check-in, prior to administration of the each study drug (0.00 hr), 1.00, 3.00, 6.00, 12.00, 24.00, 36.00, 48.00 and 72.00 hours post dose and during the entire study period. Adverse events were monitored throughout the study and recorded by physicians.

Table 1: Demographic characteristics

Category		Treatment		TOTAL
		Test (T)	Reference (R)	
Age (years)	***Mean ± SD***	23.84 ± 4.10	23.84 ± 4.00	23.84 ± 4.05
	Range	18.0 – 36.0	19.0 – 36.0	18.0 – 36.0
	Median	23.0	23.0	23.0
	N	20	20	40
Age Groups	< 18	00	00	00
	18 – 40	20	20	20
	41 – 64	00	00	00
	65 – 75	00	00	00
	> 75	00	00	00
Gender	Female	00	00	00
	Male	20	20	40
Race	American	00	00	00
	Hispanic	00	00	00
	Caucasian	00	00	00
	Asian	20	20	40
Height (cm)	Mean ± SD	163.52 ± 5.69	164.24 ± 5.67	165.48 ± 5.67
	Range	157.0 – 174.0	159.0 – 177.0	157.0 – 177.0
	N	20	20	40
Weight (kg)	Mean ± SD	58.96 ± 6.24	61.56 ± 6.43	60.26 ± 6.41
	Range	52.0 – 70.0	52.0 – 77.0	52.0 – 77.0
	N	20	20	40
BMI (kg/m^2)	Mean ± SD	21.86 ± 1.46	22.10 ± 1.79	21.98 ± 1.62
	Range	20.1 – 24.8	20.0 – 24.9	20.0 – 24.9
	N	20	20	40

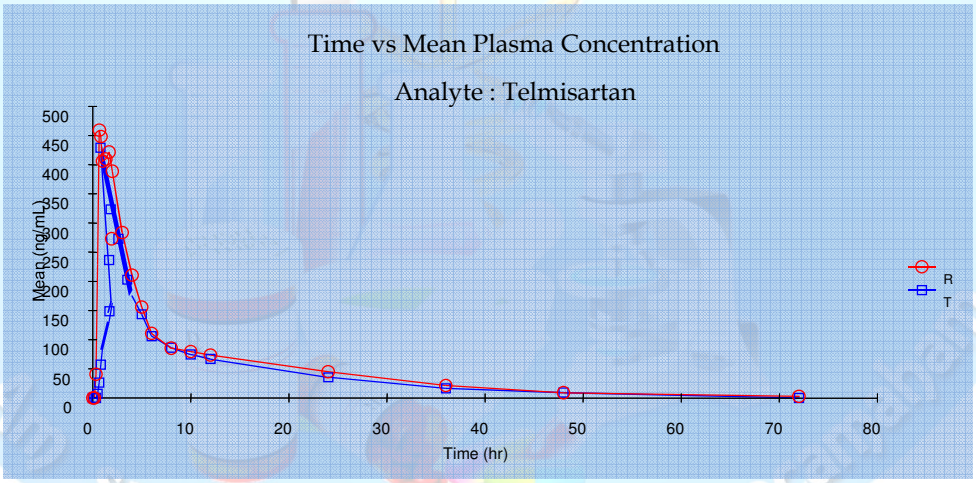
Table 2: Pharmacokinetic Parameters of Telmisartan for Both Formulations

PK Parameters	Formulation [Telmisartan]	
	Test	Reference
C_{max} [ng/mL]	423.743	458.899
AUC_{0-t} [ng.h/mL]	3114.93	3391.51
AUC_{0-inf} [ng.h/mL]	3698.54	3720.04
T_{max} [H]	3.4	1.234
K_{el} [H^{-1}]	0.056	0.053
$T_{1/2}$ [H]	13.269	14.619

Table 3: Bioequivalence Parameters for Telmisartan

Parameter	Telmisartan		
	C_{max}	AUC_t	AUC_{inf}
90% CI Lower Limit	92.23	94.28	93.65
90% CI Upper Limit	117.37	110.31	106.97
T/R Ratio (%)	92.34	91.84	99.42
Power	0.91	1	1
Intra Subject Variability	11.32	4.8	5.09
Inter Subject Variability	28.09	49	51.38
ANOVA (p-Value)			
Sequence	0.1329	0.18201	0.159
Period	0.818	0.307	0.324
Treatment	0.4754	0.411	0.695

Fig 2: Time vs. Mean Plasma Concentration Graph of Telmisartan



Results

Study population

Twenty healthy male adults eligible for the study enrollment were randomly divided into 2 groups [Test-Reference (TR) and Reference-Test (RT)] according to the sequence of drug administration. All the subjects had completed both the periods. Thus, this study was balanced in each sequence and the results from 20 volunteers were used for pharmacokinetic and statistical analysis. Table 1 demonstrates the demographic characteristics of the volunteers.

Tolerability

Almost all volunteers taking both telmisartan

formulations were noted for mild adverse events. Most common events were drowsiness, nausea and loss of appetite. However, no subject had any severe adverse event or withdrew from the study because of an adverse event.

DISCUSSION

An open-labeled, single-dose with food, two-treatment, two-period, two-sequence randomized two way crossover design in 20 healthy adult volunteers was considered appropriate and standard for bioequivalence evaluation of the generic and the reference products. The study simulates real life conditions including the influence of meals as well as circadian effects on the performance of the product. For a safety reason, co-administration of the drug with food can reduce nausea, a common side effect of telmisartan.

In general, the pharmacokinetic parameters for both formulations were similar to the pharmacokinetic parameters of telmisartan in previous published data. This study demonstrated that 90% CI of the logarithmic transformed of parameters C_{max}, AUC_{0-t} and AUC_{0-inf} were contained in 80.00-125.00%. In addition, no significant differences of the T_{max} values between the two formulations were observed ($p>0.05$). Therefore, the two formulations of telmisartan are considered bioequivalent in terms of the rate and extent of absorption. Moreover, both formulations were well tolerated. Hence, the test (telmisartan) and reference (MICARDIS) formulations of telmisartan 80mg are bioequivalent.

Conclusion

This single dose study found that the test formulation telmisartan tablets is bioequivalent to the reference formulation MICARDIS™ telmisartan tablets the extent and the rate of absorption, of 80mg under fed condition in healthy adult male volunteers according to the USFDA regulatory guidance.

References

[1] Pitt B, Konstam MA. Overview of angiotensin II. Am J Cardiol. 82, 1998; 47-49.

[2] Unger T., Significance of angiotensin type 1 receptor blockade: why are angiotensin II receptor blockers different. Am J Cardiol. 84, 1999; 9-15.

[3] Willenheimer R, Dahl B, Rydberg E, Erhardt L. Angiotensin II receptor antagonists. Eur Heart J. 20, 1999; 997-1008.

[4] Zhang P, Zhang Y, Chen X, Li R, Yin J, Zhong D. Pharmacokinetics of telmisartan in healthy Chinese subjects after oral administration of two dosage levels. Arzneimittelforschung. 56, 2006; 569-73.

[5] Ebner T, Heinzel G, Prox A, Beschke K, Wachsmuth H. Disposition and Chemical Stability of Telmisartan 1-O-Acylglucuronide. Drug Metab Dispos. 27, 1999; 1143-1149.

[6] Draft Guidance on Telmisartan, Recommended May 2008; Revised Oct 2010.

[7] World Medical Association Declaration Of Helsinki, Ethical Principles For Medical Research Involving Human Subjects, 59th WMA General Assembly, 2008

[8] International Conference On Harmonisation Of Technical Requirements For Registration Of Pharmaceuticals For Human Use, Guideline For Good Clinical Practice, E6, 1996.

[9] Raghunadha Reddy Seelam, Sarath Chandiran I, Koteswara Rao Divi, Jayaveera K. N., Development and Validation of High Performance Liquid Chromatography-Tandem Mass Spectrometric Method for Simultaneous Quantification of Telmisartan in Human Plasma, International journal of pharmaceutical sciences and Drug Research, 2010, Volume-2, Issue-3, Pages: 188-192 and ISSN No: 0975-248X.

[10] U.S. Department of Health and Human Services Food and Drug Administration, Bioanalytical Method Validation, 2001.

[11] Raghunadha Reddy S, Koteswara Rao.Divi, I. Sarath Chandiran, K.N. Jayaveera, Y.K. Naidu, M.P. Kalyan Reddy. Development and validation of high-throughput liquid chromatography–tandem mass spectrometric method for simultaneous quantification of Clopidogrel and its metabolite in human plasma, Journal of Chromatography B, Elsevier Publications, February- 2010, volume-878, Issue:3-4, pages:502–508, Impact factor-2.977, ISSN: 1570-0232.

[12] Y.K.N, Raghunadha Reddy Seelam, Koteswara Rao Divi, Penchala Kalyan Reddy Mule, Sarath Chandiran I and Jayaveera K N. Si-

multaneous Quantification of Alverine And Its Metabolite P-Hydroxy Alverine In Human Plasma With Robotic Liquid-Liquid Extraction By Using Fully Validated LC-MS/MS and Its Application To A Bioequivalence Study, Journal Of Pharmacy Research, 2010, Volume-3, Issue-6, Page-1407-1411, Impact Factor-1.5, ISSN: 0974-6943.

[13] Raghunadha Reddy.S, Koteswara Rao.Divi, I.Sarath chandiran and K.N. Jayaveera. Quantification of Artemether in human plasma with liquid- liquid extraction by using fully validated high performance liquid Chromatography–Tandem mass spectrometric method, Journal of Pharmacy Research, August-2010, Voumel-3, Issue-8, Impact Factor-1.5, ISSN: 0974-6943.

[14] I.Sarath Chandiran, K. N. Jayaveera and Raghunadha Reddy. S., High-Throughput Liquid Chromatography–Tandem Mass Spectrometric Method for Simultaneous Quantification of Carvedilol and Its Metabolite 4-Hydroxyphenyl Carvedilol in Human Plasma and Its Application to Bioequivalence Study, Journal of Chemical and Pharmaceutical Research, , 2011, 3[2]:341-353, ISSN No: 0975-7384, CODEN[USA]: JCPRC5.

[15] I.Sarath Chandiran, K. N. Jayaveera and Ragunadha Reddy. S. Development and Validation of High-Throughput Liquid Chromatography-Tandem Mass Spectrometric Method for Quantification of Itraconazole and its Metabolite in Human Plasma. Scholars Research Library, Der Pharmacia Lettre, 2011, 3[2]: 316-328.

[16] I.Sarath Chandiran K.N. Jayaveera and Raghunadha Reddy.S, Pharmacokinetic and Bioequivalence Comparison Between Extended Release Capsules of Venlafaxine Hydrochloride 150mg: An Open Label, Balanced, Randomized-Sequence, Single-Dose, Two-Period Crossover Study In Healthy Indian Male Volunteers, International Research Journal Of Pharmacy [IRJP], 2[3], 2011,262-269, ISSN 2230-8407.

[17] Raghunadha Reddy. S, I. Sarath Chandiran, K. N. Jayaveera and Koteswara Rao. Divi. Quantification of Ursodeoxy Cholic acid in human plasma by using High performance liquid chromatography–tandem mass spectrometric method and its applications in pharmacokinetics, Journal of Chemical and Pharmaceutical Research, 2010, volume-2, issue-3, Pages:59-69 and ISSN No: 0975-7384.

[18] Raghunadha Reddy.S, I.Sarath chandiran, K.N. Jayaveera and Koteswara Rao.Divi. Quantification of ibuprofen in human plasma by using high throughput liquid chromatography–tandem mass spectrometric method and its applications in pharmacokinetics, scholars research library, archives of applied research, 2010, volume-2, issue-3, pages-101-111, ISSN-0975-508x,coden[USA] AASRC9.

[19] Raghunadha Reddy.S, Koteswara Rao.Divi, Y.K.Naidu, I.Sarath Chandiran, k.N. Jayaveera and M.P.Kalyan Reddy. Development and validation of high-performance liquid chromatography tandem mass spectrometric method for quantification of Clonidine in human plasma, journal of chemical and pharmaceutical sciences, April - June'2010, volume-3, issue-2.

[20] Raghunadha Reddy.S, M.P. Kalyan Reddy, Y.K.Naidu, Koteswara Rao.Divi, I.Sarath Chandiran and K.N. Jayaveera. Development and Validation of High Performance Liquid Chromatography–Tandem Mass Spectrometric Method for Quantification of Lumefantrine in Human Plasma with Precipitation, International Journal of Pharma Research and Development [IJPRD], Apr -2010, Volume-2, Issue-2, Page-1-9 and ISSN: 0974 – 9446.

[21] Y.K.N, Raghunadha Reddy S., Koteswara Rao Divi, M.P. Kalyan Reddy, I. Sarath Chandiran and K.N. Jayaveera. Quantification of Levetiracetam in Human Plasma with Precipitation Extraction by Using Fully Validated LC-MS/MS and Its Application to a Bioequivalence Study, Research J. Pharm. and Tech., July-Sept 2010, Volume-3, Issue-3, and Page: 847-853 and ISSN: 0974-3618.

[22] S.Raghunadha Reddy, Pobba Rajani, Koteswararao. Divi, YK Naidu, Sarath Chandiran I and MP Kalyan Reddy. Anti- inflammatory and analgesic activity of Smilax chinensis, Research Journal of Pharmaceutical, Biological and Chemical Sciences, April – June 2010, Volume-1, Issue-2, Pages: 1-8, ISSN: 0975-8585.

[23] Kalyan Reddy MP, Jaya Chandra Reddy P, Raghunadha Reddy S, Jayaveera KN. Development and validation of bio-analytical method for Quantification of Pantoprazole in human plasma using LC-MS/MS, Journal of Pharmacy and Chemistry, July - September 2010,Volume-4, Issue-3, Pages:80-86 and ISSN No: 0973-9874.

[24] Raghunadha Reddy S, Naidu YK, Koteswara Rao Divi, Ravikiran V, Sandhya Rani Y, Kalyan Reddy MP. Development and Validation of High Performance Liquid Chromatography Tandem Mass Spectrometric Method for Quantification of Aceclofenac in Human Plasma, Journal of Pharmacy and Chemistry, July - September 2010, Volume-4, Issue-3, Pages:89-95 and ISSN No: 0973-9874.

[25] Mahitej Yadav Katteboina, Nageswara Rao Pilli, Ramesh Mullangi, Raghunadha Reddy Seelam and Shobha Rani Satla, LC-MS/MS assay for the determination of lurasidone and its active metabolite, ID-14283 in human plasma and its application to a clinical pharmacokinetic study, 10 November 2015, Biomed. Chromatogr.

[26] I. Sarath Chandiran, Raghunadha Reddy Seelam, Seelam Sai Satyanaraya Reddy, Ravindra Reddy S, Bioequivalence and Pharmacokinetic Comparison between Extended Release Capsules of Carvedilol Phosphate 40mg: An Open Label, Balanced, Randomized- Sequence, Single-Dose, Two-Period Crossover Study in Healthy Male Volunteers, International Journal of Medicine and Pharmaceutical Research, 2015, 3(4): 1105–1114.

[27] Raghunadha R Seelam, Sarath C Irisappan, Ravindra R Seelam, Sai SR Seelam, Bioequivalence comparison between two different Formulations of alverine citrate 120mg capsules: an open Label, balanced, randomized-sequence, single-dose, two period Crossover study in healthy male volunteers, Journal of Comprehensive Pharmacy, 2015, 2(3), 105-114.

[28] U.S. Department of Health and Human Services Food and Drug Administration, Statistical Approaches to Establishing Bioequivalence, 2001.