



Pharmacokinetics and Bioavailability Comparison of two oral Tablet Formulations of Escitalopram 20 mg: A Single-Dose, Open-Label, Two-Period Crossover Study in Healthy Indian Adult Subjects

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Abstract

This study was undertaken to assess bioequivalence between test and reference formulations of escitalopram oxalate 20 mg in healthy Indian male subjects. This single-dose, randomized, open-label, 2-period crossover study was carried out in 12 Healthy Indian Male volunteers aged 18 to 55 years under fasting conditions with a wash out of 14 days. The subjects were randomly assigned to receive the test formulation followed by the reference formulation, and then vice versa. Blood samples were collected for up to 156 h postdose. Quantification was carried out using a validated LC-MS/MS method. Maximum plasma concentrations C_{max} of 26.386 ± 5.54 ng/mL (test) and 24.430 ± 3.52 ng/mL (reference) were achieved. Areas under the plasma concentration-time curve AUC_{0-inf} of 854.241 ± 91.22 ng. hr/mL (test) and 825.135 ± 1.37 ng. hr/mL (reference), AUC_{0-t} of 848.766 ± 93.26 ng. hr/mL (test), 819.504 ± 1.91 ng. hr/mL (reference) were calculated. The median T_{max} was 4.00 hr for test and reference formulation, respectively. Plasma elimination half-lives $T_{1/2}$ of 19.26 ± 5.95 hr (test), 20.94 ± 2.88 hr (reference) were determined. Both formulations were well tolerated. The 90% confidence intervals obtained by analysis of variance were 94.49-120.68% for C_{max} and 98.22-108.18% for AUC_{0-t} which were within the predefined regulatory acceptance limit of 80.00-125.00%.

Key words: Bioavailability, Bioequivalence, Escitalopram, Human volunteers, Pharmacokinetics, Psychiatric disorders.

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1. Introduction

Escitalopram is s-enantiomer of racemic citalopram. Escitalopram oxalate is a drug which belongs to the group of specific serotonin reuptake inhibitors. The pharmacological effect of citalopram resides in the S-Enantiomer. The antidepressant action of escitalopram is presumably linked to the potentiation of serotonergic activity in the central nervous system (CNS) resulting from its inhibitory

effect on the reuptake of 5-HT from the synaptic cleft. Escitalopram has no or low affinity for a number of receptors including 5-HT_{1A}, 5-HT₂, DA D₁ and D₂ receptors, α ₁, α ₂, β ₁-adrenoceptors, histamine H₁, muscarine cholinergic, benzodiazepine, and opioid receptors [1]. Escitalopram is twice as potent as racemic citalopram and more than 100 fold more potent than R-enantiomer with respect to inhibition of 5-HT reuptake and inhibition of 5-HT neuronal firing rate [2, 3]. It is used alone or in combination with other antidepressive and antipsychotic drugs to help treat a variety of psychiatric disorders. Escitalopram has shown efficacy in placebo-controlled clinical studies and has been marketed in several countries for the treatment of major depression.

The pharmacokinetics of escitalopram [4] is linear over the clinical dosage range. Absorption is expected to be almost complete and independent of food intake (mean T_{max} is 4 hours after multiple dosing). While the absolute bioavailability of escitalopram is about 80%, it is unlikely to differ significantly from that of racemic citalopram. The apparent volume of distribution (V_d, β /F) after oral administration is about 12 to 26 L/kg. The binding of escitalopram to human plasma proteins is independent of drug plasma levels and averages 55%. Escitalopram is metabolised in the liver to the demethylated and didemethylated metabolites. Biotransformation of escitalopram to the demethylated metabolite is mediated by a combination of CYP2C19, CYP3A4 and CYP2D6

Escitalopram and major metabolites are, like

racemic citalopram, assumed to be eliminated both by the hepatic (metabolic) and the renal routes with the major part of the dose excreted as metabolites in urine. The elimination half-life (T_{1/2 β}) after multiple dosing is about 30 hours and the oral plasma clearance CL_{oral} is about 0.6 L/min.

Although the pharmacokinetic characteristics and clinical pharmacology of escitalopram have been studied previously, insufficient data are available in an Indian population. The aim of the present study was to compare the relative bioavailability and tolerability of newly developed test formulation Stalopam 20; Lupin Pharma Ltd; India and branded reference formulation: CipraleX, H. Lundbeck A/S, Copenhagen, Denmark) escitalopram 20 mg tablets and to determine bioequivalence.

2. Materials and Methods

2.1. Subjects and Methods

The clinical study was carried out at Clingyn Clinical Research Center, Hyderabad, India. Prior to study initiation, the study protocol and other study-related documents were reviewed and approved by the Independent Ethics Committee (IEC) (Hyderabad, India). Informed consent presentation was carried out in local language on the day of check-in for period-I, and all the subjects voluntarily provided written consent to participate in the study. This study was carried out in accordance with the basic principles of ICH-GCP E6 (International Conference on Harmonization-Guideline for Good Clinical Practices), as per

Schedule Y (version, 2005) of CDSCO (Central Drugs Standard Control Organization) (Ministry of health and family welfare, Government of India), [Ethical guidelines for biomedical research on human participants, ICMR (Indian Council of Medical Research (2006)], Good Clinical Laboratory Practices (GCLP), and Declaration of Helsinki (Seoul 2008).

2.2. Subject Selection

For our study, a different set of eligible male healthy Indian adult subjects aged 18 to 55 years were recruited. Volunteers were selected randomly and underwent a standardized screening procedure 14 days before admission in to study. Screening included an evaluation of medical history; demographic data; substance use history; physical examination; 12-lead ECG; chest radiography; and laboratory analysis of hematologic profile, hepatic and renal function, and disease markers for syphilis, HIV, and hepatitis B and C viruses. The volunteers were assessed again just before admission. Only medically healthy subjects with clinically normal laboratory profiles were enrolled in the study. Volunteers were instructed not to use any medication other than vitamin preparations before admission and not to consume any alcohol, tobacco or xanthine-containing products within 48 hours before admission and during their stay in the RCPU. Male volunteers of normal weight as per the Life Insurance Corporation of India height/weight chart for nonmedical cases who met the limits of the above evaluation were eligible for participation in

the study after voluntarily providing written informed consent.

Exclusion criteria was allergy to any study medication, signs or symptoms of organ dysfunction, sitting systolic blood pressure (BP) <100 mm Hg and diastolic BP <60 mm Hg, positive urinary drug screen (for cannabinoids and opioids), use of enzyme-modifying drugs within 30 days of admission, or any evaluation parameter significantly outside the reference ranges.

2.3. Study Design

This single-dose, randomized, open-label, balanced, 2-period crossover study compared 2 formulations (Newly developed Escitalopram tablet formulation as Test [Stalopam 20; Lupin Pharma Ltd; India, lot no. E7027003; expiration April 2012] and a branded innovator formulation (Cipralex H. Lundbeck A/S, Copenhagen, Denmark (lot no. F0016; expiration March 2012) of escitalopram 20-mg tablets in healthy Indian male subjects.

2.4. Study Drug Administration

Subjects were assigned to receive, in randomized order per a computer-generated balanced randomization schedule (SAS Institute Inc., Cary, North Carolina), a single oral dose of the test formulation or the reference formulation of escitalopram 20 mg. Study periods were separated by a 14-day washout period. Study drugs were administered after an overnight fast of ≥ 10 hours, with 240 mL of water, under the supervision of a trained health care professional

2.5. Admission and Stay

Subjects were admitted to the Clingyn labs 24 hours before the administration of the first dose of study drug (period 1). During period 2 all of the subjects reported to the RCPU ≥ 12 hours before administration on day 1. After blood sampling for 24 hours after administration on day 1, subjects were discharged on the morning of day 2. Subjects were asked to refrain from food intake for 4 hours after administration. Water was disallowed from 1 hour before dosing until 2 hours after administration. Subjects received standardized meals at 4, 9, and 13 hours after administration (lunch, snacks, and dinner, respectively) in all 3 study periods. Compliance was assessed using a thorough examination of the oral cavity by trained study personnel after administration and using measurements of plasma escitalopram concentrations during the analytic phase.

2.6. Sample Collection and Processing

A total of 312 blood samples of 4 mL each were collected from each volunteer into tubes containing EDTA (Vacutainer, Becton, Dickinson and Company, Franklin Lakes, New Jersey) through an indwelling venous catheter placed in a forearm vein. Samples were collected for pharmacokinetic assessment 0 (predose), 2, 4, 8, 12, 24, 36, 48, 72, 96, 120, 144 and 156 hours after administration in each period. The baseline blood sample in each period was collected in a single aliquot, within a period of ~1.5 hours before administration; postdose samples were collected within 2 minutes of the

scheduled times. After collection, blood samples were centrifuged at 4000 rpm for 15 minutes at 4°C to separate plasma. All plasma samples were divided into 2 aliquots and transferred to suitable labeled tubes and rechecked to ensure transfer of plasma to the correct tube. The plasma samples were stored at $\leq -15^{\circ}\text{C}$ until they were packed with dry ice and transferred to the analytical facility for assay.

2.7. Determination of plasma escitalopram concentrations

Plasma escitalopram concentrations were analysed using a high-performance liquid chromatography (HPLC) coupled to tandem mass spectrometry method (LC-MS/MS) [5]. The total running time per sample was 3 min. This method was validated for selectivity, matrix effect, precision, accuracy, linearity, sensitivity, recovery and stability according to US Food and Drug Administration (FDA) guidelines for the validation of bioanalytical methods.

After spiking 50.0 μL of the solution of internal standard to 1000.0 μL of plasma samples, liquid-liquid extraction was performed. To it 3.0 ml of the a mixture of diethyl ether and dichloromethane (70:30, v/v) was added and vortexed for about 3.0 min. After allowing to settle for 5.0 min., about 2.0 ml of the supernatant organic layer was transferred to the evaporation tube. The supernatant was evaporated to dryness in the thermostatically controlled water-bath maintained at 40 °C under the stream of nitrogen for about 15.0 min. After drying,

the residue was reconstituted in 300.0 μ L of acetonitrile–water mixture (50:50, v/v).

Chromatography was performed on LC–MS system from Agilent 6430 triple quad LC-MS/MS. The data acquisition was carried out on Mass hunter B.03.01 version. Chromatographic separation was achieved on Symmetry C18 50.0mm \times 4.6mm 3.5 μ analytical column (Waters, Milford, MA, USA) maintained at 35 $^{\circ}$ C. The mobile phase consisting of 5.0mM ammonium acetate and acetonitrile (20:80, v/v with 0.1% v/v of formic acid) was delivered at a flow rate of 0.6 mL/min. About 3 μ L of sample was injected into LC–MS. Vaporizer temperature and Gas temperatures were set at 250 $^{\circ}$ C. and 325 $^{\circ}$ C respectively. The drying gas flow was maintained at 6 L/min and nebulizer gas was at 60 psi from nitrogen gas generator (Peak scientific instruments, USA). Single ion monitoring (SIM) of the ions was carried in positive mode and the ion signals; m/z 325.0 and 330.0, were measured for escitalopram and internal standard (Paroxetine), respectively. Quantitation of the analytes in human plasma was based on the ratio of the detector response of escitalopram versus internal standard. The linearity of the assay method range from 0.303–120.071 ng/mL was used to determine concentrations of escitalopram. The range of precision and accuracy of the back-calculated concentrations of the calibration curve standard points during the study were 1.8–4.2% and 96.7– 106.3%, respectively.

2.8. Tolerability Assessment

For tolerability assessment, vital signs such as oral temperature, BP, and radial pulse were measured during admission and before and at 3, 8, 12, and 24 hours after study drug administration in each period. Brief clinical examinations were conducted by a qualified medical designate before study drug administration and at discharge. Subjects were also specifically asked about any adverse events every 4 hours for 12 hours after administration and at discharge.

2.9. Pharmacokinetic and Statistical Analyses

The pharmacokinetic parameters were calculated from the plasma concentration–time profile by non-compartmental analysis using Phoenix[®] WinNonlin software version 6.2.1 (Pharsight[®] Corporation, Mountain View, California, USA) for escitalopram. The PK parameters included maximum measured plasma concentration (C_{max}), time to reach maximum concentration (T_{max}), Area under the plasma concentration time curve from time zero to the last quantifiable concentration (AUC_{0-t}), area under the plasma concentration time curve from zero to time infinity (AUC_{0-Inf}), terminal phase rate constant (K) and elimination half-life ($T_{1/2}$). The value of C_{max} was determined as the peak concentration for each subject for each treatment, and T_{max} was the time corresponding to C_{max} . AUC_{0-t} and AUC_{0-Inf} were estimated by numerical integration using the linear trapezoidal method. The terminal elimination phase rate constant K was estimated via linear regression of time versus log

concentration, this was calculated by linear least squares regression analysis using at least last three or more non-zero plasma concentration values. The adjusted r^2 value of 0.80 was considered as the cut-off point for the estimation of K. $T_{1/2}$ was calculated using the formula $0.693/K$. All concentration values below the lower limit of quantification were presented as “BLQ” and disregarded for the pharmacokinetic and statistical calculations.

Statistical analysis was performed using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina, USA). Comparison of the PK parameters C_{max} , AUC_{0-t} and AUC_{0-Inf} of Escitalopram for both un-transformed and ln-transformed data, with respect to the test and reference, was done using ANOVA with the General Linear Model (PROC GLM) procedure [6]. The ANOVA model included sequence, subject nested within sequence, treatment, and period as fixed effects. An F-test was performed to determine the statistical significance of the effects involved in the model at a significance level of 5% ($\alpha = 0.05$). Statistical inferences were based on log-transformed values for C_{max} , AUC_{0-t} and AUC_{0-Inf} parameters. Each analysis of variance includes calculation of least square mean (LSM). Two one-sided test procedures at a 5% level of significance were used to compare the average values of pharmacokinetic parameters determined after administration of test and reference products. The 90% confidence intervals (CI) for the ratio of the test and reference product averages (geometric least square means) were calculated for escitalopram by first calculating the 90% CI for the

differences in the averages (least square means, LSM) of the log transformed data and then taking the anti-logs of the obtained confidence limits. BE was concluded if the 90% CI fell within the acceptance range of 80.00–125.00% for log-transformed PK parameters C_{max} and AUC_{0-t}

3. Results and Discussion

3.1. Demographic Data

A total of 12 healthy, adult, male subjects were dosed in the study. Demographic profile (Mean \pm standard deviation) of all the study subjects is summarized in Table 1. Safety was assessed throughout the study. There were no deaths or serious adverse events reported.

Table 1. Demographic profile of study subjects.*

Parameter	Mean \pm SD
Age (years)	29.50 \pm 5.83
Body Weight (Kg)	67.23 \pm 8.94
Height (cm)	176.21 \pm 7.87
BMI (kg/m ²)	21.90 \pm 1.78

*Values are given mean \pm SD.

SD, Standard deviation; BMI, Body mass index.

3.2. Pharmacokinetics

The mean plasma concentration–time curves after single-dose oral administration of escitalopram 20-mg test and reference formulations are shown in the Figure-1. Comparisons of the pharmacokinetic parameters between the 2 formulations are shown in Table 2. Maximum plasma concentrations C_{max} of 26.386 ± 5.54 ng/mL (test) and 24.430 ± 3.52

Table 2. Pharmacokinetic parameters (Mean \pm SD) of Test and Reference formulations of Escitalopram Tablets 20 mg.

Parameter (unit)	Escitalopram	
	Test ^a	Reference ^b
C_{max} (ng/mL)	26.386 \pm 5.538	24.430 \pm 3.516
AUC_{0-t} (ng.hr/mL)	848.766 \pm 93.257	819.504 \pm 1.905
AUC_{0-inf} (ng.hr/mL)	854.241 \pm 91.224	825.135 \pm 1.371
T_{max} (hr) ^c	4.00	4.00
$T_{1/2}$ (hr)	19.262 \pm 5.948	20.942 \pm 2.888

^aTest = Stalopam 20; Lupin Pharma Ltd; Pune; India (lot no. E7027003; expiration April 2012) .

^bReference = CipraleX; H. Lundbeck A/S; Copenhagen; Denmark (lot no. F0016; expiration March 2012)

^cTmax is reported as median.

C_{max} , maximum plasma concentration; AUC_{0-t} , area under the plasma concentration-time curve from time zero to last measurable concentration; AUC_{0-inf} , AUC from time zero to infinity; T_{max} , time to reach C_{max} ; K_{el} , elimination rate constant; $T_{1/2}$, elimination half-life; SD, standard deviation.

ng/mL (reference) were achieved. Areas under the plasma concentration-time curve AUC_{0-inf} of 854.241 \pm 91.22 ng.hr/mL (test) and 825.135 \pm 1.37 ng.hr/mL (reference), AUC_{0-t} of 848.766 \pm 93.26 ng.hr/mL (test), 819.504 \pm 1.91 ng.hr/mL (reference) were calculated. The median T_{max} was 4.00 hr for test and reference formulation, respectively. Plasma elimination half-lives $T_{1/2}$ of 19.26 \pm 5.95 hr (test), 20.94 \pm 2.88 hr (reference) were determined.

3.3. Bioequivalence

The 90% CI and LSM ratio for the primary PK parameters of escitalopram (C_{max} and AUC_{0-t}) were calculated and are summarized in Table 3. The 90% CI for escitalopram obtained by analysis of

variance were 94.49-120.68% for C_{max} and 98.22-108.18% for AUC_{last} and basing on the results it is observed that the 90% CI and LSM ratio met the regulatory [7-9] BE criteria of 80.00–125.00%. ANOVA applied on log-transformed values for C_{max} and AUC_{0-t} parameters for the difference between all the factors, sequence, subject nested within sequence, treatment, and period were found to be statistically insignificant ($p < 0.05$), indicative of an absence of significant differences between the test and reference formulations.

3.4. Tolerability

No adverse events were found or reported by any of the subjects throughout the study.

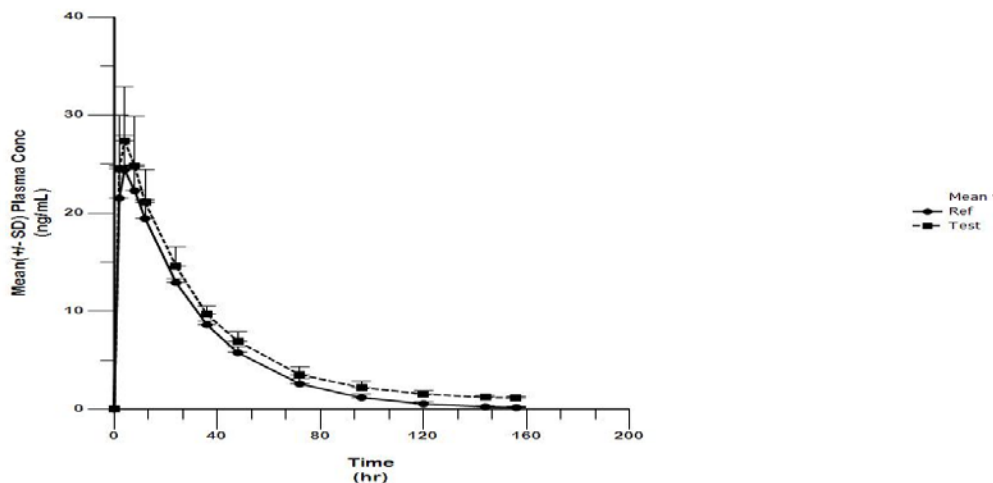


Figure 1. Mean (\pm SD) Plasma Escitalopram concentrations versus time profile following single oral dose administration of Escitalopram 20 mg Test and Reference formulations in healthy Indian Male volunteers (n = 12).

3.5. Discussion

The results of our study suggest that the reference and test tablet formulations of escitalopram were not statistically different in terms of their PK parameters (C_{max} and AUC).

Considering that all 90% CIs of the ratios of the PK parameters (C_{max} and AUC) were found to be within the predetermined range (80% -125%).

No adverse events were found or reported by any of the subjects throughout the study.

Table 3. Summary statistics of the Pharmacokinetic (PK) properties of Test and Reference formulation of Single-dose oral Escitalopram 20 mg in Healthy Indian Male Volunteers (n = 12).

Geometric Least Square Means					
Parameter	Test ^a	Reference ^b	(T/R) Ratio (%)	90% CI	Power (%)
Ln(C_{max})	24.22	25.87	106.79	94.50 -120.69	91.46
Ln(AUC _{last})	819.50	844.78	103.08	98.22 – 108.18	99.99

^aTest = Stalopam 20; Lupin Pharma Ltd; Pune; India (lot no. E7027003; expiration April 2012).

^bReference = Ciprallex; H. Lundbeck A/S; Copenhagen; Denmark (lot no. F0016; expiration March 2012)

Three bioequivalence studies (all of the 3 studies were, tablets vs tablets comparison) of escitalopram are reported in the literature [10-12]. In one study, escitalopram 10-mg test and reference tablet formulations were compared after single-dose administration in healthy volunteers of both gender. Both formulations were considered bioequivalent because the 90% CIs of the mean treatment ratios of log-transformed C_{max} and AUC values were within the range of 0.80 to 1.25. In the second study, both test and reference tablet formulations of escitalopram 10-mg tablets were assumed to be bioequivalent based on the 90% CIs of the mean treatment ratios of log-transformed C_{max} , T_{max} , and AUC values in 20 chinese male healthy volunteers. In the third study, a test and a reference formulation of escitalopram 10-mg tablets were found to be bioequivalent. The present study compared the bioavailability of test and reference formulations of escitalopram 20-mg tablets in Indian volunteers and the findings from this study suggest that test formulation and the reference formulation were bioequivalent.

Escitalopram is slowly absorbed, based on the median T_{max} values in the present study 4.00 hours after the administration of test formulation and the reference formulation, respectively. $AUC_{0-t}/AUC_{0-\infty}$ values for all 2 products were >80%, suggesting that the duration of sample collection was appropriate, covering >80% of the complete drug profile. Overall, escitalopram was well tolerated in all of the subjects, with no adverse events reported during the study.

4. Conclusion

Based on the results shown above, that the 90% confidence interval of the test/reference AUC-ratios were within the acceptance range for bioequivalence, it was concluded that the newly developed escitalopram oxalate tablet formulation, Stalopam 20; Lupin Pharma Ltd; India was bioequivalent to 20 mg escitalopram tablet (Ciprallex[®]) produced by the innovator Lundbeck. Both the formulations were well tolerated.

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References

- [1] Sa´nchez, C., P. B. F. Bergqvist, L. T. Brennum, S. Gupta, S. Hogg, A. Larsen & O. Wiborg: Escitalopram, the S-(+)-enantiomer of citalopram, is a selective serotonin reuptake inhibitor with potent effects in animal models predictive of antidepressant and anxiolytic activities. *Psychopharmacology* (2003a) 167: 353–362.
- [2] Auquier, P., S. Robitail, P. M. Llorca & B. Rive. Comparison of escitalopram and citalopram efficacy: a meta-analysis. *Int. J. Psych. Clin. Pract.* (2003) 7: 259–268.
- [3] Cremers, T. I. F. H. & B. H. C. Westerink. Pharmacological difference between escitalopram and citalopram. *Int. J. Psychiatry Clin. Pract* (2003) 7: 306.
- [4] Niranjana Rao. The clinical pharmacokinetics of escitalopram, *Clin Pharmacokinet* (2007) 46(4) 281-90.
- [5] Sonu Sundd Singh, Hiten Shah, Sapna Gupta, Manish Jain, Kuldeep Sharma, Purav Thakkar, Ruchy Shah, Liquid chromatography–electrospray ionisation mass spectrometry method for the determination of escitalopram in human

plasma and its application in bioequivalence study. *Journal of Chromatography B* (2004) 811: 209–215.

[6] Chow SC, Liu JP. Statistical methods for average bioavailability. Chow SC, Liu JP (2nd ed) In: *Design and Analysis of Bioavailability and Bioequivalence Studies*. Marcel Dekker New York, NY (2007) 79-124.

[7] US Dept of Health and Human Services (HHS), Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER). Guidance for Industry. Bioavailability and bioequivalence studies for orally administered drug products—general considerations. [http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/How Drugs are Developed and Approved/Approval Applications/ Abbreviated New Drug Application ANDA Generics/ UCM154838.pdf](http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/How%20Drugs%20are%20Developed%20and%20Approved/Approval%20Applications/Abbreviated%20New%20Drug%20Application%20ANDAs/UCM154838.pdf). (Accessed on Jan 12, 2014)

[8] Central Drugs Standard Control Organization, Directorate General of Health Services, Ministry of Health & Family Welfare. Guidelines for bioavailability & bioequivalence studies.

<http://www.cdsc.nic.in/html/BE%20Guidelines%20Draft%20Ver10%20March%2016,%2005.pdf>. (Accessed on Jan 12, 2014)

[9] Nakai K, Fujita M, Ogata H. International harmonisation of bioequivalence studies and issues shared in common. *Yakugaku Zasshi* (2000) (120):1193–1200.

[10] G.D. Mendes, T. Babadopulos et al, Comparative bioavailability of two escitalopram formulations in healthy human volunteers, *Int. Journal of Clinical Pharmacology and Therapeutics* (2010) 48(8): 554-62.

[11] Jing Li , Yuan Tian , Zun-jian Zhang et al, Pharmacokinetics and Bioequivalence Study of Escitalopram Oxalate Formulations after Single-dose Administration in Healthy Chinese Male Volunteers, *Arzneimittelforschung* (2009) 59(5): 228-232.

[12] S.Almeida, P.Pedroso, A.Flipe et al, Bioequivalence of Two Formulations of Escitalopram , *Arzneimittelforschung* (2012) 62(7): 307-312.