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Bioequivalence of Traline Tablet to Zoloft® Tablet (Sertraline HCI 50 mg)

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ABSTRACT − Sertraline HCl, (1S-cis)-4-(3, 4-dichloro-phenyl)-1, 2, 3, 4-tetrahydro-N-methyl-l-naphthalenamine hydrochloride, is a potent and selective serotonin reuptake inhibitor which is used in the treatment of depression and obsessive-compulsive disorders. The purpose of the present study was to evaluate the bioequivalence of two sertraline HCl tablets, Traline tablet (Myungin Pharm. Co. Ltd.) and Zoloft® tablet (Pfizer Inc.), according to the guidelines of the Korea Food and Drug Administration (KFDA). The *in vitro* release of sertraline from the two sertraline HCl formulations was tested using KP VIII Apparatus II method with various dissolution media. Twenty four healthy Korean male volunteers, 23.50± 1.74 years in age and 64.09±7.10 kg in body weight, were divided into two groups and a randomized 2 × 2 crossover study was employed. After a single tablet containing 50 mg as sertraline HCl was orally administered, blood samples were taken at predetermined time intervals and the concentrations of sertraline in serum were determined using an online column-switching HPLC method with UV/Vis detection. The dissolution profiles of two formulations were similar in all tested dissolution media. The pharmacokinetic parameters such as AUC_t, C_{max} and T_{max} were calculated, and computer programs (Equiv Test and K-BE Test) were utilized for the statistical analysis of the parameters using logarithmically transformed AUC_t, C_{max} and un-transformed T_{max}. The results showed that the differences between two formulations based on the reference drug, Zoloft® tablet, were 0.04, 3.26 and -1.29% for AUC_t, C_{max}, and T_{max}, respectively. There were no sequence effects between two formulations in these parameters. The 90% confidence intervals using logarithmically transformed data were within the acceptance range of log0.8 to log1.25. Thus, the criteria of the KFDA bioequivalence guideline were satisfied, indicating Traline tablet was bioequivalent to Zoloft® tablet.

Key words − Sertraline HCl, Traline tablet, Zoloft® tablet, Bioequivalence, Online column-switching HPLC

Sertraline HCl, (1S-cis)-4-(3, 4-dichloro-phenyl)-1, 2, 3, 4-tetrahydro-N-methyl-l-naphthalenamine hydrochloride, is a potent and selective serotonin reuptake inhibitor which is used in the treatment of depression and obsessive-compulsive disorders (Murdoch et al., 1992). It is well tolerated in man at clinically effective doses of 50~200 mg per day (Zhu et al., 1999). Following a single oral dose of 50 mg sertraline HCl to male volunteers, the maximum plasma concentration of drug was about 11 ng/mL. After oral administration, sertraline is slowly absorbed with peak plasma concentrations at 6~8 hr, and has a terminal elimination half-life of approximately 26 hr, indicating once-daily dosing is available (Larry et al., 1989; Zhu et al., 1999). In addition, it also exhibits higher plasma protein binding up to 97% and extensive first-pass metabolism (Zhu et al., 1999).

The present study was conducted to determine the pharmacokinetics and bioequivalence of two formulations of sertraline HCl 50 mg tablets, reference (Zoloft® tablet) and test (Traline tablet) formulation, for the purpose of generic substitution. The test included twenty four subjects of healthy Korean male volunteers was performed by latin square design. Volunteers were randomly assigned to receive a single dose of sertraline HCl 50 mg tablet. Sertraline in serum was measured using online column-switching high-performance liquid chromatography (Cho et al., 2006). The two formulations were compared in terms of standard pharmacokinetic parameters, such as area under the curve (AUC_t), the maximum plasma concentration (C_{max}), and the time to reach the maximum plasma concentration (T_{max}) according to the guidelines of Korea Food and Drug Administration (KFDA) (KFDA, 2002).

Materials and Methods

Materials and instruments

Each of the study formulations contained 50 mg of sertraline HCl. The test formulation (Traline tablet, Myungin Pharm. Co. Ltd., lot No. 339202) and reference formulation (Zoloft tablet, Pfizer Inc., lot No. 3280-2201) manufactured in accordance

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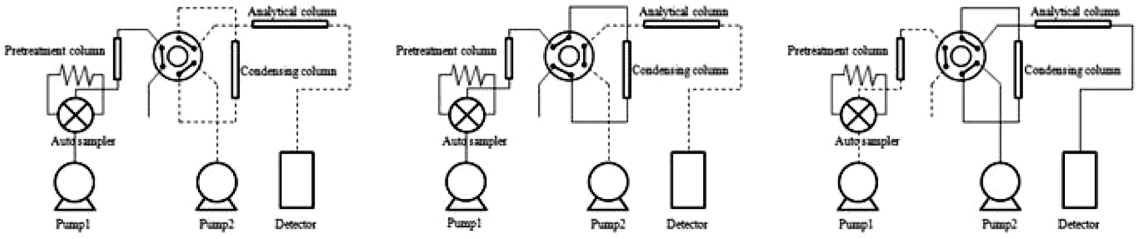

Figure 1. Flow diagram of the column-switching system; (A) position A (pretreatment); (B) position B (condensation); (C) position C (analysis).

with the Korean Good Clinical Practice (KGCP) guidelines (KFDA, 2000) were supplied as tablets.

Methanol and acetonitrile (HPLC grade) were purchased from Fisher Scientific (Fair Lawn, NJ, USA) and the other chemicals were of HPLC grade or higher. A Milli Q (Millipore Co., Milford, MA, USA) water purification system was used to obtain the purified water.

The HPLC system consisted of a Nanospace SI-2 system (Tokyo, Japan) equipped with pumps (model 3001) and an autosampler (model 3023), a degasser (model 3010), a column oven (model 3014) and a UV/Vis detector (model 3002). The instrument arrangement for the automated column-switching system and system flow diagram was shown in Figure 1. The pretreatment column used for online sample preparation was the Capcell Pak MF Ph-1 (10 mm × 4 mm i.d., Shiseido, Tokyo, Japan) and Capcell Pak C_{18} MG S5 (35 mm × 2 mm i.d., Shiseido, Tokyo, Japan) was used as the condensing column, using 20% acetonitrile-50 mM KH_2PO_4 containing 0.2% triethylamine. Capcell Pak C_{18} MG S5 (250 mm × 1.5 mm i.d., Shiseido, Tokyo, Japan) was used as the main analytical column. The analytical mobile phase used a 45% acetonitrile-50 mM KH_2PO_4 containing 0.2% triethylamine and 0.1% H_3PO_4. Detection was carried out at 210 nm with the UV/Vis detector.

In vitro dissolution test

In vitro dissolution testing was performed using Korean Pharmacopoeia (KP) VIII dissolution Apparatus II (paddle method) and 900 mL of dissolution solution (pH 1.2, 4.0, 6.8 and water) at 50 rpm at 37 ± 0.5°C. Samples were removed at 5, 10, 15, 30, 45, 60, 90, 120, 180, 240, 300 and 360 min, after which they were filtered and assayed by HPLC with UV/Vis detection at 210 nm.

Selection of volunteers

This study was conducted at Chonnam National University Hospital (Gwangju, Korea). The study population consists of twenty four healthy male Korean volunteers with an average age of 23.50 ± 1.74 years and an average weight of 64.09 ± 7.10 kg. Before enrollment, all subjects underwent clinical screening, including a physical examination and laboratory tests (blood analysis: hemoglobin, hematocrit, RBC, WBC, platelet, differential counting of WBC, total protein, albumin, sGOT, sGPT, alkaline phosphatase, total bilirubin, cholesterol, creatinine, blood urea nitrogen, and glucose fasting and urine analysis; specific gravity, color, pH, sugar, albumin, bilirubin, RBC, WBC, and cast).

Subjects were excluded if they had possible sensitivity to sertraline HCl; had a history of hepatic, renal, respiratory, endocrine, or cardiovascular illness; or had ingested alcohol or medications, including over the counter drugs, within 4 weeks before the study. This was done to ensure that existing degree of variation would not be due to an influence of illness or other medications. Written informed consent was obtained from all subjects after the nature and purpose of the study had been explained, in accordance with the KFDA guidelines for bioequivalence test (KFDA, 2002).

Blood sampling from volunteers

The study protocol was approved by the Institutional Review Board of the Institute of Bioequivalence and Bridging Study, Chonnam National University. The study was performed in accordance with the revised Declaration of Helsinki and the Good Clinical Practice guidelines (KFDA, 2000).

All of the volunteers avoided taking other drug for at least 4 weeks prior to the study and until its completion. They also refrained from consuming xanthine-containing foods, alcoholic beverage for 12 hr prior to each dosing and until the collection of the last blood sample. The study had a single-dose, randomized, two-treatment, two-period crossover design. Subjects were stayed at the hospital at 8:00 PM on the day before the study and fasted for 12 hr before and 4 hr after drug administration. At 8:00 AM, a heparin-locked catheter (JELCO™, 22G, Johnson & Johnson Medical, Pomezia, Italia) was inserted into the antecubital vein and the catheter was flushed

with 0.3 mL heparinized normal saline solution (150 units/mL) for injection to prevent clotting. Each subject was randomly assigned to receive a single dose of the reference or test formulation (50 mg of sertraline HCl) with 240 mL of spring water at 8:30 AM. Subjects received standardized meals at 4 hr after drug administration. After a washout of 7-days, subjects received the alternative formulation.

After 2 mL of blood was discarded, an aliquots of 5 mL of blood was drawn from the indwelling catheter into a 5 mL Vacutainer tube (Becton Dickinson and Company, Franklin Lakes, New Jersey) before administration (to serve as a control) and at 2, 4, 5, 6, 7, 8, 10, 12, 24, 48 and 72 hr after administration. After sampling, the catheter was flushed with 0.3 mL of heparinized normal saline solution for injection. The samples were centrifuged at 3000 rpm, 20 min and the serum was transferred to polyethylene tubes and stored at -70ºC until assayed.

Subjects were continuously monitored by hospital staff throughout the study period. Vital signs (temperature, blood pressure, and heart rate) were measured before and after drug administration. No drugs, alcohol, xanthine-containing foods or beverage were allowed during the study.

Determination of serum sertraline concentration

To prepare the sample for assay, an aliquot (500 μL) of a 100 mM KH_2PO_4 containing 0.1% triethylamine was added to 500 μL of a serum sample by vortex-mixing for 1 min and centrifuged at 12000 rpm for 6 min. Supernatant was filtered with a polyvinylidene-fluoride (PVDF) syringe filter (0.22 μm pore size, Millipore, Bedford, MA, USA) and transferred to autosampler vials. An aliquot of 200 μL of filtered sample was injected onto the pretreatment column by the autosampler according to the column-switching techniques (Cho et al., 2006; Falco et al., 1993). At the time of sample injection, the column-switching valve was placed in position A (Figure 1A). Protein and other interfering compounds were eluted with 20% acetonitrile-50 mM KH_2PO_4 containing 0.2% triethylamine at a flow rate of 0.5 mL/min. During this process, macromolecules such as proteins, which cannot enter the pore interior blocked by the water soluble polymer on the outer surface of pretreatment column, are easily eluted and not retained by the stationary phase. Other organic, low molecular weight compounds such as drugs, however, permeate into the pore interior and are retained by the stationary phase of the inner surface. The analytical column was filled with the analytical mobile phase, which was 45% acetonitrile-50 mM KH_2PO_4 containing 0.2% triethylamine and 0.1% H_3PO_4, at a flow rate of 0.1 mL/min. After the sample injection, the column-switching valve was shifted to position B (Figure 1B) to move samples containing the target compounds from the pretreatment column to the condensing column. The condensing mobile phase was 20% acetonitrile-50 mM KH_2PO_4 containing 0.2% triethylamine at a flow rate of 0.5 mL/min. After the sample condensation, the column-switching valve was shifted to position C (Figure 1C) to move samples from the condensing column to the analytical column. The analytical mobile phase was 45% acetonitrile-50 mM KH_2PO_4 containing 0.2% triethylamine and 0.1% H_3PO_4 at a flow rate of 0.1 mL/min. During the analysis, the pretreatment column was washed with washing solution.

The primary stock solution of sertraline HCl was prepared at 1000 μg/mL and stored at 4ºC. Sertraline HCl stock solution was serially diluted and added to the prepared sertraline drug-free serum to obtain final concentration of 1, 2, 5, 10, 20, 50 and 100 ng/mL for the preparation of calibration curve. The interference by endogenous compounds was assessed by analyzing standards of sertraline drug-free serum samples, serum spiked with sertraline, and serum samples obtained from subjects given sertraline HCl tablets. All peaks with the retention times of sertraline were confirmed using a UV/Vis detector. Sertraline was quantitated by weighted linear regression analysis of the peak area ratio versus concentrations of added sertraline using 1/concentration as the weighting factor. The calibration curves were linear from 1 to 100 ng/mL. The lower limit of quantitation (LLOQ) was defined as the lowest concentration at 10 times the signal-to-noise ratio that yielded a precision of <20% coefficients of variation (CV) and an accuracy between 80% and 120% of the theoretical value. The LLOQ was 1 ng/mL for sertraline in five replicate samples. In order to assess the intra- and inter-day precision and accuracy of the assay, low (2 ng/mL of serum), medium (10 ng/mL of serum), and high (50 ng/mL of serum) concentration standard samples were prepared. The intra-day precision of the assay was assessed by calculating the CV% for the analysis of samples in five replicates, and inter-day precision was determined through the analysis of samples on five consecutive days. The precision of the assay was evaluated based on the criterion that the relative standard deviation (S.D.) for each concentration level should not exceed ±15%, with the exception of the LLOQ, which should not exceed ±20%. Accuracy was determined by comparing the calculated concentrations to known concentrations with calibration curves. The criterion for accuracy was that the S.D. for the mean value should not exceed the nominal concentration by more than ±15%, except for the LLOQ, for which the limit was ±20%.

On the other hand, as suggested by Falco et al. for the column-switching techniques, we employed a simple sample

preparation and obtained sufficient reproducibilities and validated results in terms of specificity, linearity and accuracy without an internal standard.

Statistical analysis of pharmacokinetic parameters

Each volunteer received an oral dose of 50 mg of sertraline HCl in a standard 2 × 2 crossover method in a randomized order. Pharmacokinetic parameters such as AUC_t, C_{max} and T_{max} were calculated from total serum concentration-time curves of sertraline. C_{max} and T_{max} were recorded as actual measurement values and AUC_t was calculated by trapezoidal formular from 0 to 72 hr. Their test/reference ratios using log-transformed data, together with their means and 90% confidence intervals, were analyzed with the analysis of variance (ANOVA) that performed with the Equiv test (Statistical Solutions Ltd., 2002) and K-BE Test program® (Lee et al., 2000) at a significant level of 0.05. The bioequivalence of two sertraline HCl tablets was estimated by AUC_t and C_{max}. T_{max} used as a reference value.

Results and Discussion

Dissolution testing

Accordance of KP VIII dissolution Apparatus II method, dissolution testing was done to test and reference formation. Both formulations released >85% of sertraline HCl within 15 min in the water, within 45 min in the dissolution media of pH 1.2, within 30 min in the media of pH 4.0 and within 60 min in the media of pH 6.8 and had similar release profiles (Figure 2). So, two formulations have no difference in dissolution testing.

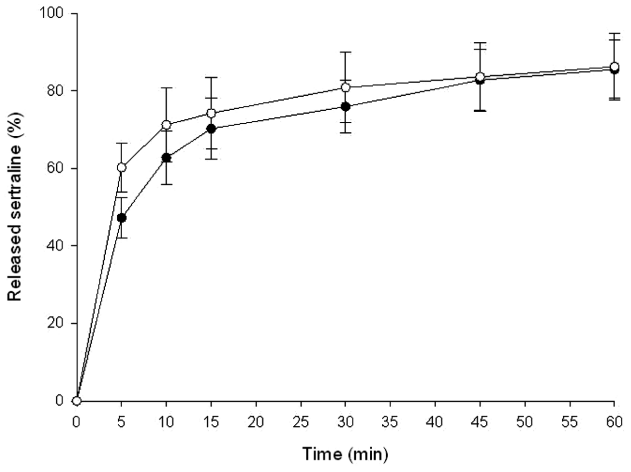

Figure 2. Dissolution profiles of sertraline in pH 6.8 solution from reference (●) and test (○) formulations. Vertical bars represent the standard deviations.

Analysis of sertraline in serum sample

Figure 3 shows chromatograms of blank, spiked sertraline and serum sample from a healthy subject obtained 7 hr after oral administration of sertraline HCl 50 mg. No interference from endogenous substances was observed in human serum with the online column-switching HPLC method. The retention time for sertraline was about 15 min. In this method, sertraline was well separated from the biological background under the described chromatographic condition. This peak was of good shape. The calibration curve, established by plotting the peak area ratio (y) versus concentration (x), was linear over the range from 1 to 100 ng/mL with the following regression equation: y = 4160.28x - 1826.93 (r = 0.9999). The LLOQ of sertraline in human serum was 1 ng/mL; at this concentration, the accuracy was 118%, and the CV for precision below 8.26%. During validation, the accuracy ranged from 101.00% to 118.00%, whereas intra- and inter-day CVs for precision remained below 10.95% and 11.90%, respectively. These results indicate that the present method has a satisfactory accuracy and precision (Table I).

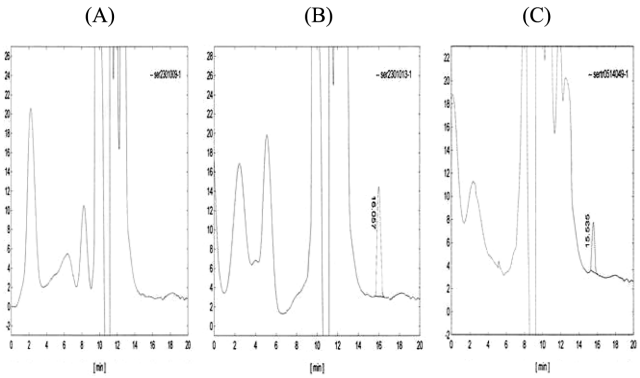

Figure 3. Chromatograms of (A) blank human serum; (B) blank human serum spiked with sertraline (10 ng/mL); and (C) a human serum sample from a healthy Korean male volunteer at 7 hr after administration of a single oral dose of sertraline HCl 50 mg.

Table I. *Precision and accuracy for the analysis of sertraline concentration in human serum*

Concentration (ng/mL)	Precision CV(%)		Accuracy (%, n=5)
	Intra-day CV(%) (n=5)	Inter-day CV(%) (n=5)	
1	8.26	6.93	118.00
2	10.16	4.91	109.50
10	10.95	8.58	101.00
50	8.69	11.90	113.24

CV (Coefficient of variation) = 100 × S.D./mean.

Pharmacokinetic analysis

Online column-switching HPLC method was successfully used for a bioequivalence test in which serum concentrations of sertraline in twenty four healthy male volunteers were determined up to 72 hr after the oral administration of 50 mg sertraline HCl. Figure 4 shows the mean serum concentration-time curves of sertraline following single oral administration of test and reference tablet, and descriptive statistics of the derived pharmacokinetic parameters such as AUC_t, C_{max}, and T_{max} for two formulations are summarized in Table II.

The mean (± S.D.) AUC_t was 257.96 ± 94.20 ng/mL/hr for the test formulation and 257.86 ± 111.02 ng/mL/hr for the reference formulation. Mean (± S.D.) C_{max} values were 8.86 ± 3.07 and 8.58 ± 3.45 ng/mL, with mean (± S.D.) T_{max} values of 6.38 ± 1.84 and 6.46 ± 2.08 hr, respectively. The differences of the means of the test to reference medication for AUC_t and C_{max} were 0.04% and 3.26%, respectively, which are generally

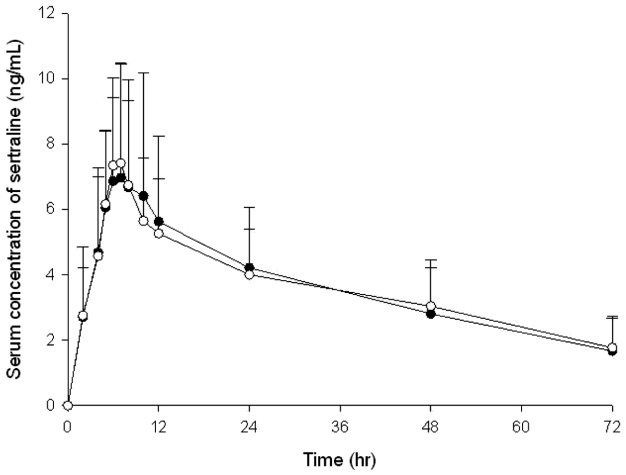

Figure 4. Mean serum concentration-time curves of sertraline after single oral administration of the reference (●) and test (○) sertraline tablets as sertraline HCl 50 mg. Vertical bars represent the standard deviations.

Table II. *Bioavailability parameters in normal and logarithmic scales for each volunteer obtained after oral administration of traline and zoloft® tablets at the sertraline HCl dose of 50 mg*

Subjects	Parameter									
	AUC_t (ng/mL/hr)				C_{max} (ng/mL)				T_{max} (hr)	
	Reference		Test		Reference		Test		Reference	Test
	Value	Log	Value	Log	Value	Log	Value	Log	Value	Value
X1	195.97	5.28	200.65	5.30	7.74	2.05	10.95	2.39	6.00	7.00
X2	542.54	6.30	295.30	5.69	14.65	2.68	9.12	2.21	10.00	5.00
X3	134.62	4.90	137.90	4.93	4.25	1.45	5.16	1.64	6.00	6.00
X4	273.07	5.61	245.80	5.50	8.52	2.14	5.47	1.70	5.00	12.00
X5	248.34	5.51	247.24	5.51	12.97	2.56	6.48	1.87	10.00	5.00
X6	150.74	5.02	265.23	5.58	5.64	1.73	8.81	2.18	6.00	6.00
X7	451.36	6.11	412.61	6.02	17.98	2.89	13.16	2.58	7.00	7.00
X8	371.58	5.92	539.28	6.29	10.85	2.38	12.72	2.54	4.00	8.00
X9	283.64	5.65	247.09	5.51	7.27	1.98	6.53	1.88	8.00	4.00
X10	206.66	5.33	113.54	4.73	6.15	1.82	3.39	1.22	6.00	6.00
X11	149.03	5.00	176.76	5.17	5.73	1.75	5.81	1.76	6.00	8.00
X12	217.62	5.38	224.12	5.41	6.78	1.91	11.28	2.42	6.00	6.00
Y1	490.54	6.20	370.71	5.92	12.07	2.49	11.57	2.45	7.00	6.00
Y2	341.22	5.83	301.81	5.71	8.73	2.17	12.00	2.48	7.00	7.00
Y3	185.43	5.22	171.18	5.14	4.34	1.47	7.83	2.06	6.00	5.00
Y4	290.25	5.67	346.35	5.85	10.71	2.37	13.51	2.60	5.00	8.00
Y5	195.69	5.28	306.50	5.73	7.14	1.97	10.18	2.32	4.00	7.00
Y6	247.23	5.51	290.67	5.67	7.07	1.96	11.15	2.41	7.00	6.00
Y7	248.41	5.52	293.86	5.68	7.57	2.02	10.17	2.32	12.00	5.00
Y8	121.88	4.80	205.07	5.32	5.42	1.69	4.68	1.54	2.00	2.00
Y9	198.46	5.29	198.36	5.29	8.22	2.11	6.06	1.80	6.00	6.00
Y10	157.42	5.06	229.14	5.43	5.87	1.77	6.73	1.91	7.00	8.00
Y11	260.00	5.56	167.84	5.12	7.46	2.01	7.02	1.95	5.00	7.00
Y12	227.05	5.43	204.14	5.32	12.77	2.55	12.84	2.55	7.00	6.00
Mean	257.86	5.47	257.96	5.49	8.58	2.08	8.86	2.12	6.46	6.38
S.D.	111.02	0.40	94.20	0.35	3.45	0.37	3.07	0.38	2.08	1.84

Table III. *Statistical results of bioequivalence evaluation between two sertraline HCL tablets*[#]

	Parameters		
	AUC_t	C_{max}	T_{max}
Difference	0.04%	3.26%	-1.29%
F_G[a)]	0.0012	0.1371	0.9612
Test/Reference point estimate	1.0195	1.0372	-0.0833
Confidence interval(δ)[b)]	log0.9128 ≤ δ ≤ log1.1388	log0.9170 ≤ δ ≤ log1.1731	-18.12% ≤ δ ≤ 15.54%

[#]The AUC_t and C_{max} values were calculated on the basis of In-transformed data, and the T_{max} values on the basis of un-transformed data.
[a)] $\alpha = 0.05$, F (1, 22) = 4.30, [b)]$\alpha = 0.05$.

accepted if the differences of mean values for AUC_t and C_{max} lie within ±20% (Table III).

No significant differences in AUC_t or C_{max} were found between the test and reference formulations, and pharmacokinetic values were comparable to those that have been reported previously (Larry et al., 1989; Zhu et al., 1999). For example, after oral administration of sertraline HCl 150 mg in Chinese subjects, the AUC_t was 1309.10 ± 6.25 ng/mL/hr and the C_{max} was 36.97 ± 7.89 ng/mL (Zhu et al., 1999).

Bioequivalence analysis

No significant sequence, subject, formulation or period effects were detected for any pharmacokinetic parameters. The point estimates for the mean ratio of the test to reference formulation for the AUC_t, C_{max} were 1.0195, 1.0372, respectively (Table III). The parametric 90% confidence intervals were in the range of log0.9128 to log1.1388 and log0.9170 to log1.1731, respectively (Table III), which were entirely within the regulatory acceptance limits for bioequivalence (80-125%). This proved that there was no significant difference between the bioavailability of reference and test formulations.

Conclusion

This validated online column-switching method was sensitive, reproducible and accurate for the determination of sertraline in human serum samples collected for bioequivalence studies. Using this method, the bioequivalence of two different sertraline HCl tablet formulations was examined at the dose of 50 mg in twenty four healthy male volunteers. No significant differences in AUC_t or C_{max} were found between the test and reference formulations and the calculated 90% confidence intervals for the ratios of mean AUC_t and C_{max} were within the regulatory acceptance range for bioequivalence (80-125%).

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