임상약학회지 제8권 제2호
Kor. J. Clin. Pharm., Vol 8, No. 2. 1998

정상 성인 한국인에서 Piroxicam-β-cyclodextrin 정과 Piroxicam 확산정의 1회 투여시의 흡수속도 비교

전성실[a,b] · 차혜리[b] · 박연주[b] · 이병철[b] · 김남득[a]
[a]부산대학교 약학대학, [b]왈레스기념침례병원

Comparison of Absorption Rate Between Piroxicam-β-Cyclodextrin and Piroxicam in Korean Healthy Subjects After A Single Dose Administration

Seong Sill Jeon[a,b], Hye Ri Cha[b], Yun Ju Park[b], Byung Chul Lee[b], and Nam Deuk Kim[a]
[a]Dept. of Pharmacy, College of Pharmacy, Pusan National University, Pusan 609-735, Korea
[b]Wallace Memorial Baptist Hospital, P.O. Box 76, Pusan, Korea

Piroxicam-β-cyclodextrin은 piroxicam을 β-cyclodextrin으로 포접시킨 비스테로이드성 항염증약물이다. 이러한 포접형 약물은 위장관에서의 흡수속도가 증가하는 것으로 외국자료에서 보고되고 있으며 이는 이 약물의 위장관 내성에 보다 나은 영향을 끼칠 수 있음을 시사하고 있다. 본 연구는 정상성인 한국인을 대상으로 randomized, crossover design에 의해 piroxicam-β-cyclodextrin (Brexin®)정과 piroxicam 확산정(Feldene®)의 흡수속도를 비교하고자 하였다. 건강한 성인 8명의 피험자를 2군으로 나누어 시험약 또는 대조약을 각각 20 mg씩 20일의 휴약 기간을 두고 이중 맹검으로 교차 투여하였다. 시험약 또는 대조약의 투여 후 24시간 동안 일정 간격으로 채혈하여 HPLC 방법으로 혈장 내 piroxicam 농도를 측정하였다. $AUC_{0\text{-}24}$ (μg·h/mL)는 piroxicam-β-cyclodextrin군에서 56.1±4.9, piroxicam군에서 57.3±5.6으로 통계적인 유의성이 없었으나, 투여 후 0.5시간에서의 혈중농도는 piroxicam-β-cyclodextrin군 2.9±0.4 μg/mL, piroxicam군 1.6±0.3 μg/mL으로 통계적인 유의성을 보였다($p<0.05$). 또한 최고혈중농도는 piroxicam-β-cyclodextrin(4.3±0.5 μg/mL), piroxicam(3.5±0.3 μg/mL)으로 유의성이 있었으며($p<0.05$), 흡수 속도상수는 piroxicam-β-cyclodextrin(3.00±0.49 h^{-1}), piroxicam(1.80±0.21 h^{-1})이었다($p<0.1$). 이상의 결과에서, piroxicam-β-cyclodextrin 정은 piroxicam 확산정과 비교하여 흡수되는 정도는 서로 비슷하지만 흡수 초기의 혈장농도 및 흡수속도상수에서 보다 빠른 약동학적 특성을 나타내었다. (Kor. J. Clin. Pharm. 1998; 8(2): 95-100)

Keywords – Piroxicam-β-cyclodextrin, Absorption rate, Pharmacokinetic parameters

Piroxicam is an oxicam derivative of nonsteroidal anti-inflammatory drugs (NSAIDs) which shows anti-inflammatory and analgesic properties.[1,2] Piroxicam also causes gastroduodenal mucosal injury like other NSAIDs and it shows a low surface wettability as a lipophilic drug with long half-life in pharmacokinetic.[1,3]

교신저자 : 전 성 실
Wallace Memorial Baprist Hospital, Pharmacy dept.
P.O. Box 76, Pusan, 600-600 Korea
TEL. 051-461-3195, FAX. 051-461-3195

β-Cyclodextrin is a water soluble oligosaccharide composed of seven glucopyranose units.[4] The cyclodextrin molecule can form an inclusion complex with molecules of other substances and cyclodextrin complexation might modify the pharmacokinetic and possibly pharmacodynamic characteristics of a drug.[4,5]

Piroxicam-β-cyclodextrin is a 1:2.5 molecular complex of piroxicam and β-cyclodextrin, an inert cyclic macromolecule, and it is equivalent to piroxicam in

pharmacological effects.[4,6-8] Complexing piroxicam with β-cyclodextrin increases its rate of dissolution and solubility.[2,9] It improves the rate of absorption of piroxicam, and possibly also reduces staying period in gastrointestinal tract.[5,10] These findings might have better gastrointestinal tolerance, however, there is no long term clinical trial to evaluate it.[11-14]

Several pharmacokinetic studies were reported that the absorption rate of piroxicam was increased markedly through complexing with β-cyclodextrin.[9,15-18] There was only one study on the pharmacokinetic profile between piroxicam-β-cyclodextrin and piroxicam in Korea,[19] however, the profile was different from the results by the foreign studies. And the study was done to evaluate mainly the clinical efficacy in patients with osteoarthritis and the numbers of patients included for pharmacokinetic study were only two patients for each piroxicam formulation. Although they reported that piroxicam-β-cyclodextrin tablet was absorbed more rapidly and effectively than the piroxicam dispersible tablet, the time to peak plasma concentration after taking piroxicam-β-cyclodextrin was much longer (1.4 hrs vs. 5 hrs) and showed low peak plasma concentration compared to the results of the foreign studies.[9,16]

The objective of this study was to investigate the absorption profile and other pharmacokinetic variables of two new oral formulations of piroxicam-β-cyclodextrin tablets and piroxicam dispersible tablets in healthy young Korean.

Methods

Study population

Eight healthy volunteers including three women and five men completed the study. Their ages ranged from 20 to 35 years (median: 25 years) and they had a normal body weight from 45 to 90 kg (median: 59 kg) relative to their height. (155-178 cm; median: 165.5 cm). The numbers of regular smokers in the study was two and the rest were nonsmokers. All volunteers were Korean.

All subjects had a screening evaluation within two weeks of the study that included a medical evaluation consisting of a medical history, medical and physical examination, with recording of vital signs. The checked medical examination were as followings; i) Routine CBC: WBC, RBC, Hgb, Hct, and platelet, ii) Blood chemistry: albumin, total protein, total bilirubin, SGOT, SGPT, γ-GTP, Fasting glucose, BUN, creatinine, Na^+, K^+, and Cl^-, iii) Urine analysis: protein and glucose.

Exclusion criteria in the subjects were: a) a history of liver or kidney disease, gastrointestinal tract disease, and clinically significant abnormalities, b) allergy of any origin, c) a history of drug or alcohol abuse, d) pregnancy, nursing or non-use of contraception, e) participation in another clinical trial, f) donation blood within the preceding one month, g) weight over 10% of the ideal body weight, and h) taking any prohibited drug during the study period.

Study design

The study was approved by the Institutional Review Board of the Wallace Memorial Baptist Hospital. Before the study entry, each subject signed an informed consent form in the presence of a witness.

The study was designed as a single-dose trial with

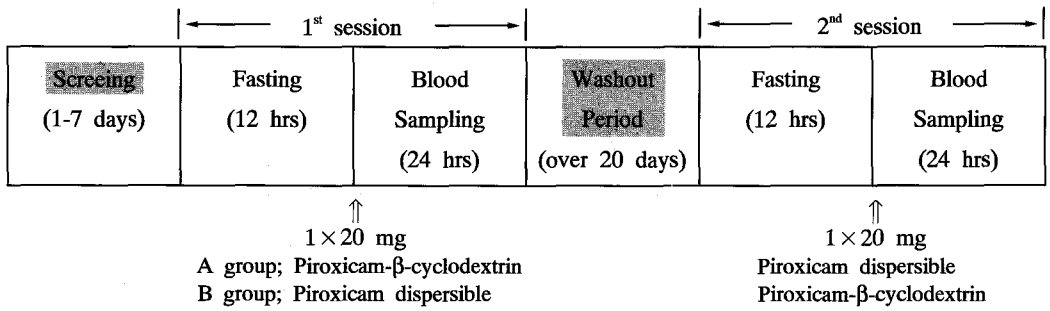

Fig. 1. Schematic representation of the design of this study.

randomized, crossover study in 8 healthy volunteers (Fig. 1). Subjects who fulfilled the admission criteria were randomized into two groups. Each subject received one of the two treatments, consisting of either 20 mg piroxicam-β-cyclodextrin tablet or 20 mg piroxicam dispersible tablet taken with 200 ml water. In the 2nd period, they were crossed over to receive the other treatment and the two treatment periods were separated by a wash-out period of 20 days (1 subject: 34 days). On each day of study, the subjects fasted over 12 hrs and received study medication at 08:00. They were remained in the clinical center during 12 hrs after taking study drug. During the fasting, smoking was also forbidden. Meals were supplied from lunch and controlled by the investigator. The studied drug formulations were as following; A) Piroxicam-β-cyclodextrin tablet: piroxicam-β-cyclodextrin 95.6 mg (Piroxicam 10 mg)/tab (Brexin® tablet), B) Piroxicam dispersible tablet: piroxicam 10 mg/tab (Feldene® dispersible tablet).

Blood samples were collected into evacuated tubes containing edetic acid by puncture of a forearm vein. An indwelling catheter with heparin (100 Unit /ml) was cannulated on a forearm vein which was used during the first few hours. Serial venous blood samples (5 ml) were collected immediately before the dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 12, and 24 hrs after the dose. The blood samples were immediately centrifuged at 4℃ with 3500 rpm for 10 min. The separated plasma was stored at -20℃ until assayed.

Clinical monitoring

During each hospitalization period after taking the drug, the subjects remained under constant surveillance by investigators and they had to stay within the clinical center. During the two study sessions, the subjects maintained daily contact with the clinical investigator and reported any adverse events, whether seemingly related or not to the ongoing drug treatment. Concomitant medications which might cause any effect on the absorption, distribution, metabolism, and excretion of piroxicam were forbidden over the period starting from two weeks before the trial (2 months for enzyme-inducing drugs) and ending two days after it. For women, oral contraception was allowed during this period.

Assay of plasma piroxicam

The assay of piroxicam in plasma was done using HPLC (High Performance Liquid Chromatography) with UV detection as adapted from other reports.[16,20] The 1.0 ml plasma were taken from the tube, and after mixing with 2.0 ml 0.1 N-HCl and 10 ml chloroform, chloroform layer was gathered into glass tube. Chloroform layer was evaporized at room temperature. And after melting it completely with adding 1.0 ml solvent, the extracted was used for further test. The standard solution was prepared by dissolving 30 mg piroxicam in 0.1 N HCl (in MeOH) and its concentration was 3 mcg/ml. The mobile phase was water/acetonitrile/sodium heptansulfonate (545/450/2 g, v/v/w), adjusted to pH 3.5 with diluted phosphoric acid and the flow rate was 1.0 ml/min. And 100 μl was injected into HPLC pump equipped with a μ-BondaPak C18 column and an UV spectrophotometric detector operating at 356 nm.

Data Analyses

The maximum plasma concentration (C_{max}) and the time to maximum plasma concentration (T_{max}) were read directly from the observed data. The area under the plasma concentration time-curve ($AUC_{0\text{-}24h}$) were calculated by use of the linear trapezoidal rule.[21] Percent cumulative absorption at any time was calculated using the Wagner-Nelson Method[16,21] and it was arbitrarily set at 100% whenever it exceeded that value. The mean plasma concentration from the oral dosing was fitted to one-compartment and two-compartment models with first-order input with and without lag time using WINNONLIN software to obtain estimates of absorption rate constant (K_a). And the apparent terminal elimination rate constant (K_{el}), absorption half-life, elimination half-life was also obtained from NONLIN. Differences in piroxicam absorption rate were also illustrated graphically by use of Wagner-Nelson cumulative absorption plots.

These data analyses were estimated for the statistical significance using ANOVA, paired *t*-test, Wilkoxon

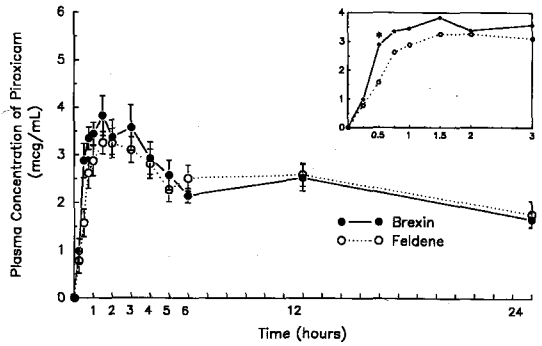

Fig. 2. Plasma concentrations of piroxicam (Mean ±SEM, n=8) after a 20 mg dose of piroxicam-β-cyclodextrin (Brexin®) tablet and piroxicam dispersible (Feldene®) tablet. Inset: enlargement of the 0-3 hrs time period for piroxicam. Arithmetic means. Statistical significance *p<0.05.

signed rank test, and % cumulative absorption data was analysed by arcsin transformation.[22,23]

Results

The data of this study were calculated based on the plasma concentration of piroxicam obtained from the study. The mean plasma concentration-time profiles of piroxicam-β-cyclodextrin tablet and piroxicam dispersible tablet are shown in Fig. 2. Plasma concentrations from each piroxicam formulation were generally quite variable between subjects.

Pharmacokinetic parameters for administered each piroxicam formulations are shown in Table 1. The results of fitting the concentration data showed that the one-compartment model with first order input with no lag time fitted the data well. Although piroxicam pharmacokinetic is better described by two-compartment models, the one-compartment approximation is used in this study.[16] Neither AUC_{0-6}, AUC_{0-24}, K_{el}, elimination half-life nor absorption half-life calculated were statistically significantly different between complex tablets and dispersible tablets (α=0.05). But, for the first 0-2 hrs, mean plasma concentration-time curves showed that piroxicam-β-cyclodextrin tablet was absorbed more rapidly than the absorption of piroxicam dispersible tablet (Inset of Fig. 2). The plasma concentration of piroxicam-β-cyclodextrin showed about twice those of piroxicam dispersible tablet at 0.5 hrs after taking study drug and peak plasma concentration was also significantly higher in the piroxicam-β-cyclodextrin group. The mean time to peak plasma concentration did not show any statistical significance. However, it showed rapid tendency slightly in piroxicam-β-cyclodextrin tablet group. Also, Wagner-Nelson cumulative absorption plots showed that piroxicam-β-cyclodextrin tablet was absorbed at more rapid ratio than the piroxicam dispersible tablet group (Fig. 3). Absorption rate constant was calculated to analyse more clearly the difference of absorption ratio and the calculated K_a for piroxicam-β-cyclodextrin tablet was not statistically significant at α=0.05. However, it was significant at α=

Table 1. Pharmacokinetic parameters of plasma piroxicam after a single dose of 20 mg piroxicam in 8 healthy subjects (mean±SEM)

Parameter	β-cyclodextrin piroxicam tablet	Piroxicam dispersible tablet	Statistical Significance
C_p 0.5 hrs (μg/mL)	2.9±0.4	1.6±0.3	P<0.05
C_{max} (μg/mL)	4.3±0.5	3.5±0.3	P<0.05
T_{max}, median (h)	1.25	1.75	NS
AUC_{0-2} (μg · h/mL)	5.9±0.5	4.8±0.5	P<0.05
AUC_{0-6} (μg · h/mL)	17.7±1.6	15.8±1.3	NS
AUC_{0-24} (μg · h/mL)	56.1±4.9	57.3±5.6	NS
K_a (h^{-1})	3.00±0.49	1.80±0.21	P<0.1
K_{el} (h^{-1})	0.04±0.01	0.03±0.01	NS
Absorption half-life (h)	0.3±0.1	0.4±0.1	NS
Elimination half-life (h)	16.8±1.6	28.9±5.7	NS

Abbreviations: C_p: plasma concentration. AUC_t: area under the plasma concentration-time curve to last measurement point. C_{max}: maximum plasma concentration. T_{max}: time to maximum concentration. K_a: absorption rate constant. K_{el}: apparent terminal elimination rate constant.

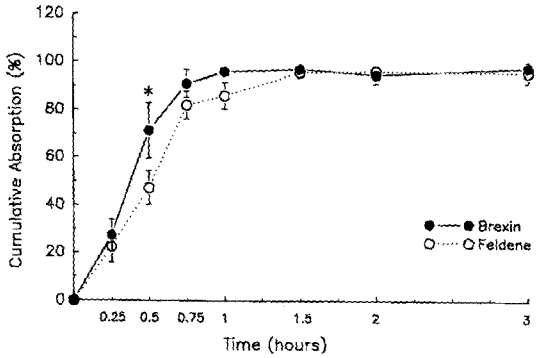

Fig. 3. In vivo cumulative absorption (Mean±SEM, n=8) up to 3 hrs after 20 mg dose of piroxicam-β-cyclodextrin (Brexin®) tablet and piroxicam dispersible (Feldene®) tablet. Statistical significance *p<0.05.

0.1 compared to the piroxicam dispersible tablet.

In clinical tolerance, no manifestations of intolerance or any adverse reaction were observed by the clinical investigator nor were any mentioned by any of the subjects during each session in the study.

Discussion

Comparison of the first 6 hrs of the plasma concentration-time curves showed that piroxicam was absorbed more rapidly after administration of piroxicam-β-cyclodextrin complex tablet than the piroxicam dispersible tablet (Fig. 2). The mean plasma concentrations at 0.5 hrs after administration of the complex formulation were statistically significantly higher than those after administration of the dispersible tablet but did not differ at 0.25 hrs as the other study.[9,16] Peak plasma concentrations of piroxicam were higher in 7 out of 8 subjects for the complex tablet and in the other one subject, there was no difference between two tested formulations. Absorption of piroxicam was complete within 0.5 hrs in 3 out of 8 subjects receiving the complex tablet compared with no subjects receiving the dispersible tablet and the number of subjects who completed absorption was smaller than the others, comparatively (33% vs 75%).[4,16]

Although the median time to peak plasma concentration was reported as 5 hrs after standard piroxicam formulation compared with 1 hr after complex tablet in other study,[16] there were not big difference between two formulations evaluated in this study (complex tablet/dispersible tablet=1.25/1.75 hrs). The reason might be that fasting was continued over 4 hrs after taking the studied drugs and/or reference formulation was dispersible tablet in this study. Based on this result, the interaction of food with the complex tablet might influence on the absorption of the piroxicam smaller than the dispersible tablet. Therefore, it is necessary for studying further on the effect of the food with each piroxicam formulations. And the preparation process might be considered to affect the absorption parameters of the complex.

The elimination half-life of about 17-29 hrs apparently does not represent the true elimination half-life, since we did not have any data after the 24 hrs plasma sample and these are shorter than those of the foreign studies. The difference was appeared as marked tendency in complex tablet than the dispersible tablet and it needs to study the elimination profile of two formulations further.

The obtained C_{max} after taking piroxicam-β-cyclodextrin from this study was higher than the results of other study in Korea and T_{max} was small.[19] Compared to the results of the foreign studies, these results are similar in the T_{max} but the obtained C_{max} and plasma concentration at 0.5 hrs after taking piroxicam-β-cyclodextrin was slightly higher in this study. These results showed that piroxicam-β-cyclodextrin tablet was more rapidly absorbed than the piroxicam dispersible tablet, and the difference was not appeared markedly as the reported by Woodcock et al.[9] and Acerbi,[16] but it is almost similar to the result of Deroubaix et al.[17]

The clinical meaning of these results needs to be carefully interpreted. Because the C_{max} obtained in this study was higher than the reported minimal effective concentration for analgesic and anti-inflammatory, however, it was less than the trough plasma concentration at steady-state after multiple dose administration. Therefore, the significant increase in C_{max} and Cp 0.5 hrs from this single dose study is unlikely to be clinically significant during long term therapy.

Conclusion

This study indicates that piroxicam-β-cyclodextrin tablet has tendency of the more rapid absorption during the early phase than the piroxicam dispersible tablet in healthy Korean volunteers. And the amount of oral absorption of piroxicam-β-cyclodextrin tablet is similar to the piroxicam dispersible tablet and it suggests that the higher plasma concentration during the early absorption phase after taking piroxicam-β-cyclodextrin tablet is not a result from increased bioavailability. From these results, we conclude that piroxicam-β-cyclodextrin is likely to have clinical relevance only in the initial treatment for acute pain relief.

References

1. Gerald KM. Piroxicam. AHFS Drug Information 1996; 1448-52.
2. Brodgen RN, Heel RC, Speight TM, et al. Piroxicam: a reappraisal of its pharmacology and therapeutic efficacy. Drugs 1984; 28: 292-323.
3. Woodcock BG, Acerbi D, Merz PG, Rietbrock S, Rietrock N. Supermolecular inclusion of piroxicam with β-cyclodextrin: Pharmacokinetic properties in man. Eur J Rheumatol Inflamm 1993; 12: 3-19.
4. Szejtli J. Cyclodextrins: properties and applications. Drug Invest 1990; 2 S 4: 11-21.
5. Rainsford KD. NSAID gastropathy : novel physicochemical approaches for reducing gastric mucosal injury by drug complexation with cyclodextrins. Drug Invest 1990; 2 S 4: 3-10.
6. Lister RE, Acerbi D, Cadel S. Supermolecular inclusion of piroxicam with β-cyclodextrin: a review of its pharmacological properties in laboratory animals. Eur J Rheumatol Inflamm 1993; 12 (4): 6-11.
7. Ambanelli U, Nervetti A, Colombo B, et al. Piroxicam-β-cyclodextrin in the treatment of rheumatic diseases: a prospective study. Curr Ther Res 1990; 48: 58-68.
8. Reginster JY, Franchimont P. Piroxicam-β-cyclodextrin in the treatment of acute pain of rheumatic disease. Eur J Rheumatol Inflamm 1990; 12 (4): 38-46.
9. Woodcock BG, Acerbi D, Merz PG, Rietbrock S, Rietbrock N. Supermolecular inclusion of piroxicam with β-cyclodextrin: pharmacokinetic properties in man. Eur J Rheumatol Inflamm 1993; 12: 12-28.
10. Santucci L, Fiorucci S, Patoia L, Farroni F, Sicilia A, Chiucchiu S, Bufalino L, Morelli A. Gastric tolerance of piroxicam-β-cyclodextrin compared with placebo and with other NSAIDs: an endoscopic and fuctional study for evaluation of transmucosal potential difference. Drug Invest 1990; 2 (S 4): 56-60.
11. Bonardelli P, Oliani C, Preti PAM, Pellican P, Quattrocchi G. Efficacy and gastrointestinal tolerability of β-cyclodextrin-piroxicam and tenoxicam in the treatment of chronic osteoarthritis. Clin Ther 1990; 12: 547-55.
12. Warrington S. Effects of piroxicam-beta-cyclodextrin on the gastrointestinal tracts. Eur J Rheumatol Inflamm 1993; 12 (4): 29-37.
13. Santucci L, Fiorucci S, Chiucchiu S, Sicilia A, Bufalino L, Morelli A. Placebo-controlled comparison of piroxicam-β-cyclodextrin, piroxicam, and indomethacin on gastric potential difference and mucosal injury in humans. Dig Dis Sci 1992; 37: 1825-32.
14. Rhoda Lee C, Balfour J. Piroxicam-β-cyclodextrin. Drugs 1994; 48 (6): 907-929
15. Acerbi D, Bonati C, Boscarino G, Bufalino L, Cesari F, D'Ambrosio E, Mansanti P, Scali G. Pharmacokinetic study on piroxicam at the steady-state in elderly subjects and younger adults after administration of piroxicam beta-cyclodextrin. Int J Clin Pharmacol Res 1988; 8: 175-80.
16. Acerbi D, Lebacq Jr E, Rondelli I, Stockis A, Ventura P. Rapid oral absorption profile of piroxicam from its β-cyclodextrin complex. Drug Invest 1990; 2: 50-5.
17. Acerbi D, Pharmacokinetic profile of piroxicam-β-cyclodextrin. Drug Invest 1990; 2: 42-9.
18. Deroubaix X, Stockis A, Allemon AM, Lebacq E, Acerbi D, Ventura P. Oral bioavailability of CHF 1194, an inclusion complex of piroxicam and β-cyclodextrin, in healthy subjects under single dose and steady-state conditions. Eur J Clin Pharmacol 1995; 47: 531-536.
19. Sang-heon Lee, Do-jun Min, Sung-hwan Park, Chul-soo Cho, Dong-jun Park, Ho-youn Kim. The pharmacokinetic study of β-cyclodextrin-piroxicam and its efficacy in the treatment of osteoarthritis. Korean J Rheumatol 1994; 1: 3-11.
20. Richardson CJ, Ross SG, Verbeeck RG (1986) HPLC analysis of piroxicam and its major metabolite 5'-hydroxypyroxicam in human plasma and urine. J Chromatogr 382: 382-388.
21. Gibaldi M, Perrier D (1982) Pharmacokinetics, 2nd ed. Dekker, New York.
22. Steinijans VW, Hauschke D. Update on the statistical analysis of bioequivalence studies. Int J Clin Pharmacol Ther Toxicol 1990; 28: 105-110.
23. Hauschke D, Steinijans VW, Diletti E. A distribution -free procedure for statistical analysis of bioequivalence studies. Int J Clin Pharmacol Ther Toxicol 1990; 28: 72-78.