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Comparative Study on the Bioequivalence of Two Formulations of Pioglitazone Tablet in Healthy Thai Male Volunteers

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The bioequivalence study of two 30 mg pioglitazone formulations was determined in healthy Thai male volunteers after a single dose administration in a randomized cross-over study with a 1-week washout period. Due to the high variability of the rate and extent of absorption of pioglitazone, an add-on subject study was required to assess bioequivalence. Reference product (Actos®, Takeda Chemical Industries, Ltd., Osaka, Japan) and test product (Glubosil®, Silom Medical Co. Ltd., Bangkok, Thailand) were given to 35 volunteers after overnight fasting. Blood samples were collected at specified time intervals. Plasma was analyzed for pioglitazone concentration using a validated HPLC method. Pharmacokinetic parameters were compared between test and reference products from plasma concentration-time profile by using non-compartment analysis. The statistical comparison of C_{max} and AUC_{0-t}, $AUC_{t-\infty}$ clearly indicated that no significant difference in two products of pioglitazone tablets in add-on subject study. The 90% confidence intervals for the mean ratio (test/reference) of C_{max} and AUC_{0-t}, $AUC_{t-\infty}$ were within the Thailand Food and Drug Administration acceptance range. Based on the pharmacokinetic and statistical results of this study, we can conclude that Glubosil® is bioequivalent to Actos®, and that two products can be considered interchangeable in medical practice.

Keywords bioequivalence; pharmacokinetics; pioglitazone; add-on subject study

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INTRODUCTION

Pioglitazone hydrochloride is an oral anti-diabetic agent that acts primarily by decreasing insulin resistance. Pharmacological studies indicate that pioglitazone improves sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis. Pioglitazone is used in the management of non-insulin-dependent type 2 diabetic mellitus. (Chilcott, Tappenden, Lloyd, & Wight, 2001; Takeda Pharmaceutical Co. Ltd., 2004; Waugh, Keating, Plosker, Easthope, & Robinson, 2006). Previous clinical trials in healthy subjects have shown that pioglitazone is well absorbed after oral administration without regard to meals. Peak concentration of pioglitazone (T_{max}) is achieved approximately 1.5 hr and elimination half-life ($T_{1/2}$) of drug is closely 9 hr. It is highly bound to plasma proteins and extensively metabolized by the hepatic cytochrome P450 enzyme system. With single oral doses between 2 and 60 mg, the maximal drug concentration (C_{max}) and the area under concentration time curve (AUC) increased linearly with dose (Eckland & Danhof, 2001).

Bioequivalence has gained increasing attention since many generic products have launched to the markets, which may exhibit difference therapeutic responses form the proprietary products. Bioequivalence of two formulations of the same drug comprises equivalence with respect to the rate and extent of their absorption. AUCs generally serve as the characteristic of absorption and C_{max} has been widely used for the rate of absorption. Although several researches have been published regarding pioglitazone pharmacokinetics, very few of them have pointed on the proof of bioequivalence. The objective of this study was to determine the pharmacokinetic parameters and to evaluate the bioequivalence of two different 30 mg

pioglitazone tablet formulations in healthy Thai male volunteers. Three main pharmacokinetic endpoints (C_{max} and AUC_{0-t}, $AUC_{t-\infty}$) of pioglitazone satisfy the statistical criteria for bioequivalence were presented. The add-on subject study has further been applied in this study.

MATERIALS AND METHODS

Product Information

Samples of tablets containing 30 mg of pioglitazone. Glubosil® (Lot No. A50609-A, expiration date 6/2008, Silom Medical Co. Ltd., Bangkok, Thailand) was used as test product while Actos® (Lot No. O054, expiration date 8/2006, Takeda Chemical Industries, Ltd., Osaka, Japan) was used as reference product. The dissolution profiles of both products were carried out and compared, according to the guideline (Thailand FDA, 2001) prior this study.

Study Design and Subjects

The clinical protocol was approved by the Naresuan University Ethical Committee and all the volunteers gave written informed consent after they had receive detailed instructions about the aims, restrictions, and possible adverse effect which could be experienced as a result of taking of drug. Twenty-four volunteers were enrolled in the initial study. The add-on design was carried out strictly according to the same protocol using 14 volunteers. Volunteers were selected after passing a clinical screening procedure including a physical examination and laboratory tests (hematology; RBC, WBC, hemoglobin, hematocrit, platelets, clinical chemistry; blood urea nitrogen, creatinine, albumin, total protein, AST (SGOT), ALT (SGPT), bilirubin, alkaline phosphatase and glucose, virology; HBs antigen and Anti-HCV; and urine analysis). The subjects were instructed to abstain from alcoholic beverages, smoking, and medication for 2 weeks prior to and during the study period.

The study was based on a single-dose, randomized, two-treatment two-sequence, two-period cross-over design with a one week wash out interval and conducted at Naresuan University Hospital (Phitsanulok, Thailand). During the first period, volunteers from group A received a single 30 mg dose of Actos®, while volunteers group B received a single dose 30 mg of Glubosil®. During the second period, the procedure was repeated on the groups in reverse. Vital signs of the subjects were determined before dosing and after each blood sampling times. The ALT level of subjects was monitored after each period. After the bioequivalence study was completed, all subjects were re-examined by physician.

Drug Administration and Sample Collection

The subjects took a single 30 mg pioglitazone dose of each product at 7 a.m. with about 240 mL of water under overnight-fasting condition. They were then in the seated position for at least 30 min. For each period, the subjects were provided with standard meals no less than 4 hr after drug administration and allowed water as desired except for 1 hr before and after drug administration. Approximately 8 mL of blood samples were obtained by catheterized venipuncture immediately prior to and at the following times after administration of each product: 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 48, and 72 hr. Blood samples were withdraw into a lithium heparin-coated plastic tube (Becton Dickinson and Company, Franklin Lakes, NJ). Plasma samples were obtained by centrifugation at 4°C for 15 min at 5,000 rpm (Beckman J2-MC, Beckman Coulter, Inc., Fullerton, CA) and stored frozen, at –80°C, in the cryogenic tube (Nalge Nunc International, Rochester, NY) pending analysis.

Sample Analysis

The reference standards were purchased from Crosschem Intercontinental Company, Derb & Co. (Lugano, Switzerland). The solid-phase extraction tube (SPE, Strata C18-T, Phenomenex, Torrance, CA) was pre-activated with acetonitrile (1 mL) and then 0.1 M KH_2PO_4 (1 mL). Aliquots of 1 mL of plasma were dispensed into test tube, and 70 µL of 50 µg/mL of rosiglitazone internal standard solution and 500 µL of 0.1 MKH_2PO_4, were added. The mixture was then vortexed for 30 sec and was then was applied to the activated SPE tube. The tube was washed with 2 mL of methanol-0.1 M KH_2PO_4 (30:70) followed by 1 mL of 0.1 M KH_2PO_4 buffer solution and was then dried for 5 min. Finally, the analytes were eluted with 500 µL of acetonitrile-H_2O (40:60) followed by 500 µL of acetonitrile-H_2O (50:50). The eluate was filtered through 0.45 µm nylon disposable filter (Alltech) and a 100 µL aliquot was injected onto the HPLC system for analysis. An HPLC set was equipped with a pump (LC-10ATVP, Shimadzu, Kyoto, Japan), a system controller (SCL-10AVP, Shimadzu), a variable wavelength UV detector (SPD-10AVP, Shimadzu) and a Rheodyne (7725) sample injector (Rohnert Park, CA) fitted with a 100 µL sample loop. Separations were performed on Apollo C18 column (250 mm × 4.6 mm i.d., 5 µm, 250Å, Alltech, Deerfield, IL) at room temperature. The mobile phase consisted of methanol, acetonitrile, and 10 mM mixed phosphate buffer pH 2.6 (40:12:48), was previously filtrated and degassed. The flow rate was 1.2 mL/min and the UV detector wavelength was set at 269 nm. The HPLC assay for determination of plasma pioglitazone concentration was validated by following the international guideline (US FDA, 2000).

Pharmacokinetic and Statistical Analysis

All pharmacokinetic parameters were determined by noncompartmental models and performed by use of WinNonlin Professional version 4.0.1 (Pharsight Corporation, Mountain View, CA). The maximum plasma concentration (C_{max}) and the time to reach C_{max} (T_{max}) were taken directly from the

observed concentration-time profile. The slope of the terminal log-linear portion of the pharmacokinetic profile was determined by least-squares regression analysis and used as the terminal rate constant (λ_z). The terminal half-life ($T_{1/2}$) was calculated as $0.693/\lambda_z$. The area under the concentration-time curve of pioglitazone in plasma from the time of dosing to the last measurement concentration (AUC_{0-t}) was calculated by the log-linear trapezoidal rule and the area under the curve extrapolated from the last quantifiable point (C_t) to infinity ($AUC_{t-\infty}$) was determined as C_t/λ_z. Total area under the curve ($AUC_{0-\infty}$) was the sum of AUC_{0-t} and $AUC_{t-\infty}$. The total body clearance (Cl) and the volume of distribution (V_d) were calculated as dose/$AUC_{0-\infty}$ and Cl/λ_z, respectively.

An analysis of variance (ANOVA) was performed by SPSS for Windows Standard version 12.0 (SPSS, Inc., Chicago, IL), on three pharmacokinetic parameters, C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ (log-transformed), using general linear models procedures, in which sources of variation were sequence, subject nested within sequence, period and formulation. For evaluation of bioequivalence, the point of estimates for the mean of test/reference product of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ and their 90% confidence intervals were within the 0.80 – 1.25 range.

RESULTS

Subject Population

Three volunteers were excluded from the add-on study as they did not follow the bioequivalence protocol. Subjects (n = 35) were aged between 18 and 24 years ($M \pm SD$, 21.2 ± 1.15 years), weighed 59.3 ± 8.34 kg, averaged 169.1 ± 5.58 cm in height and 20.7 ± 2.35 kg/m^2 of body mass index. The ALT levels for all volunteers were not elevated during this study. The tolerability of both pioglitazone formulations was good and no adverse effects were reported by the subjects or revealed by clinical or laboratory tests.

Chromatographic Analysis

Validation was accomplished through determination of recovery, linearity, quantification limit, precision, accuracy, specificity, and stability (Sripalakit, Neamhom, & Saraphanchotiwitthaya, 2006). As shown in Figure 1, no significant interference in the blank plasma traces were seen from endogenous substances in drug-free human plasma at the retention time of the analytes. The quantification limit of pioglitazone in plasma was 50 ng/mL based on a signal-to-noise ratio of 5.0. The calibration curve was ranged from 50 to 2000 mg/mL. The retention time of rosiglitazone and pioglitazone were around 4.1 and 8.2 min, respectively and the total run time for each sample was 10 min.

Pharmacokinetic Studies

The mean of plasma concentration of Glubosil® and Actos® of healthy Thai male volunteers at various time points are summarized in Table 1. The average concentration-time curves of both products of pioglitazone tablets were presented in Figure 2. Pharmacokinetic parameters (T_{max}, C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $T_{1/2}$, λ_z, Cl, and V_d) were calculated individually on the basis of concentration-time data. From individual pharmacokinetic parameters, their mean values for both test and reference products in the initial study and the add-on subject study are compared in Table 2. According to the mean plasma levels of the 35 subjects completing the study, the relative bioavailability values of test/reference product were found to be 1.07 ± 0.47, 0.91 ± 0.33, and 0.90 ± 0.31 on the basis of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, respectively.

Bioequivalence Evaluation

The results of the analysis of variance for pharmacokinetic parameters, C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, are shown in Table 3. For the initial study and the add-on subject study, the point estimates and 90% confidence intervals for test/reference ratios of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, using logarithmic transformed data, are compared in Table 4. High intersubject variability for C_{max} (41.2 and 30.2%), AUC_{0-t} (42.5 and 27.4%), and $AUC_{0-\infty}$ (40.9 and 27.2%) was found in both test and reference products, respectively (Figure 3).

DISCUSSION

The total average T_{max} was 1.6 ± 0.8 hr. This result was consistent with the reported literature values (Eckland & Danhof, 2001; Hanefeld, 2001). $T_{1/2}$ for both test and reference products were 5.1 ± 1.2 and 5.3 ± 1.4 hr, respectively (total mean $T_{1/2}$ was 5.2 ± 1.3 hr), which were lower than the previous report (Eckland & Danhof, 2001; Hanefeld, 2001). C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ in both formulations were found to be higher than the reference product of other report, which were 1.05 μg/mL, 10.98 μg hr/mL and 10.62 μg hr/mL, respectively (Wong, Ozalp, Lainesse, & Alpan, 2004).

The sample size for using in the initial study was suggested by Thailand FDA (2000), which was the maximum number (n = 24). In this initial study, the 90% confidence intervals for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were not corresponding to the bioequivalence criteria. Intrasubject coefficient of variation from ln-ANOVA of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ values were respectively, 42.0, 34.2, and 31.5%. These results confirm that pioglitazone, with respect to all three pharmacokinetic parameters, behaves as a highly variable drug. In case of the add-on subject study according to the same protocol, the subjects were enrolled using not less than half the number of subjects ($n \geq 12$) in the initial study (WHO, 2005). However, the total subject remained only 35 for this study since three subjects were excluded. According to the sample size determination (Diletti, Hauschke, & Steinijans, 1991), 32 subjects, calculated from ln-AUC_{0-t} of 35 subjects (intrasubject coefficient of variation = 30.3%; μ_T/μ_R = 0.99), is adequate to attain a power of 80% at a significance

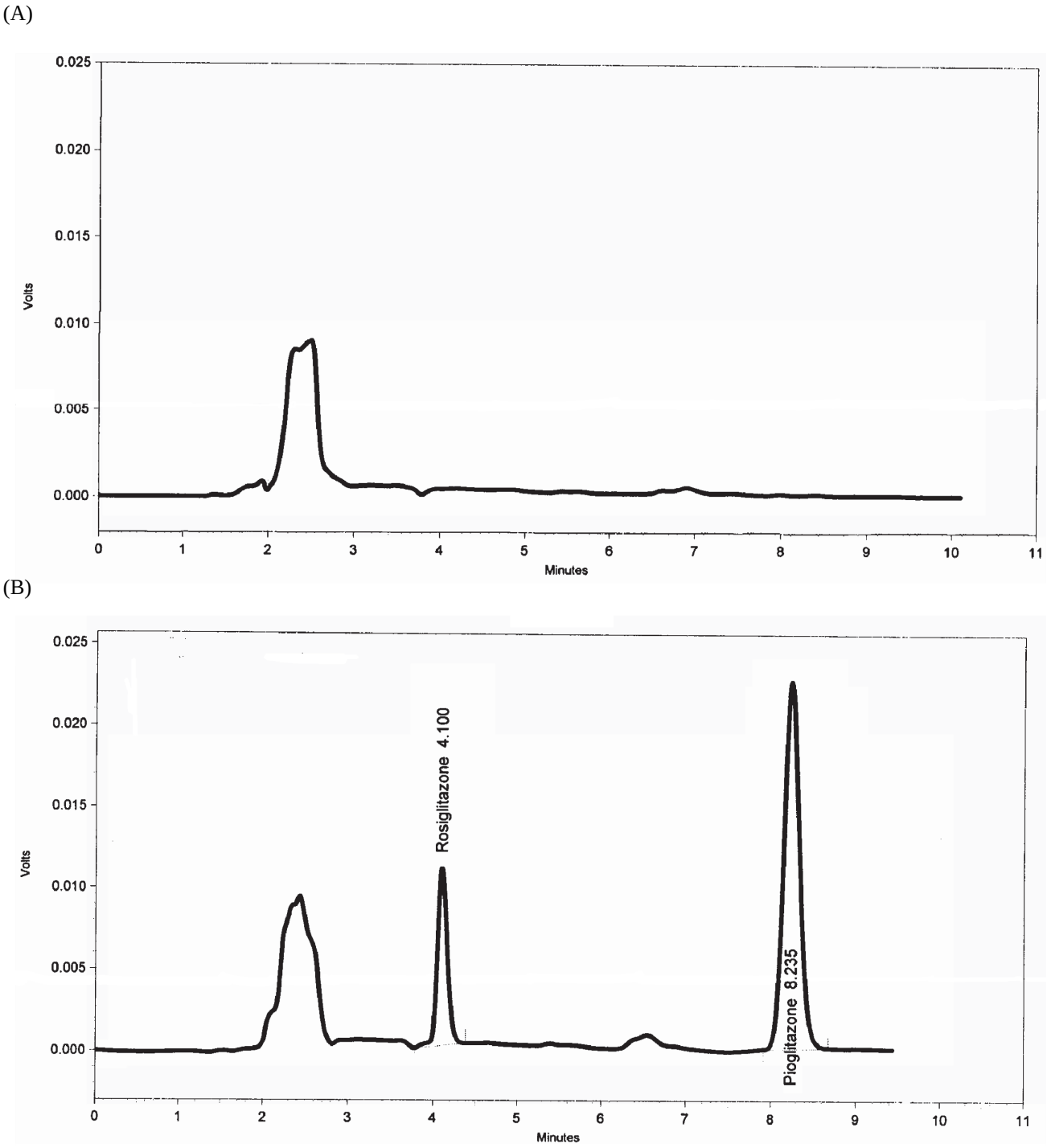

FIGURE 1. Chromatograms for the analysis of pioglitazone in drug-free human plasma. (A) blank plasma (B) human plasma spiked with 50 µg/mL rosiglitazone and 2,000 ng/mL pioglitazone.

level of 0.05. Thus, the data from the initial and add-on subject studies can be pooled and statistically analyzed.

The analysis of variance on logarithmic transformed data revealed the absence of both period and formulation effects in C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$. No significant sequence effect was found for all of pharmacokinetic parameters indicating the crossover design was properly performed. Significant F values were found between the subjects and subjects nested within sequence for both AUC_{0-t}, and $AUC_{0-\infty}$ in both studies, indicating a substantial intersubject variation from the two formulations. In

TABLE 1
Mean Plasma Concentrations of Pioglitazone After Administration of Glubosil® (Test) and Actos® (Reference) to Healthy Thai Male Volunteers (n = 35)

	Plasma Concentrations (ng/mL)					
	Test Product			Reference Product		
Time (hr)	*M*	*SD*	C.V. (%)	*M*	*SD*	C.V. (%)
0	0.00	0.00	–	0.00	0.00	–
0.5	964.40	722.29	74.90	808.03	490.46	60.70
1	1393.47	666.80	47.85	1291.96	443.91	34.36
1.5	1515.18	670.83	44.27	1434.61	450.06	31.37
2	1462.84	633.68	43.32	1432.94	438.19	30.58
2.5	1403.97	608.41	43.33	1364.52	362.20	26.54
3	1312.81	576.70	43.93	1306.35	372.50	28.51
4	1174.27	491.54	41.86	1184.45	308.91	26.08
6	825.94	318.25	38.53	821.15	226.69	27.61
8	631.89	285.83	45.23	628.64	170.36	27.10
12	348.00	149.88	43.07	368.22	129.04	35.04
18	190.12	86.19	45.33	210.08	80.58	38.36
24	85.00	48.69	57.28	107.23	63.88	59.57
48	0.00	0.00	–	12.20	33.14	271.70
72	0.00	0.00	–	0.00	0.00	–

ND: not detectable

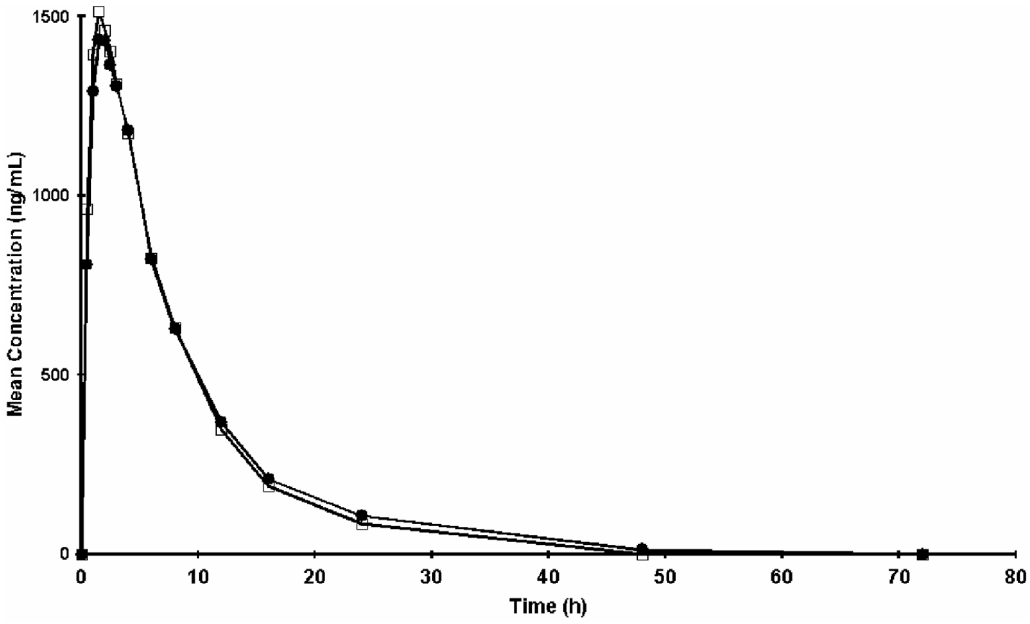

FIGURE 2. Mean plasma concentration-time curve of pioglitazone after administration of 30-mg single dose of glubosil® (test, □) and Actos® (reference, ●) in healthy Thai male volunteers (n = 35).

the add-on subject study, the point estimates for the mean of test/reference ratios and their 90% confidence intervals for pioglitazone were C_{max}, 1.02 (0.88 – 1.19); AUC_{0-t}, 0.90 (0.80 – 1.02); and $AUC_{0-\infty}$, 0.90 (0.80 – 1.00), which were within the commonly accepted bioequivalence range of 0.80 – 1.25 (Thailand FDA, 2001). The results show that Glubosil® and Actos®, after single administration of a 30 mg oral dose, are bioequivalent with respect to both their extent and rate of absorption.

TABLE 2
Comparison of Pharmacokinetic Parameters of Glubosil® (Test) and Actos® (Reference) in Healthy Thai Male Volunteers

Pharmacokinetic Parameters		Initial study (n = 24)		Add-on subject study (n = 35)	
		Glubosil®	Actos®	Glubosil®	Actos®
C_{max} (ng/mL)	*M*	1598.98	1558.16	1707.87	1555.28
	SD	659.04	470.07	638.85	438.76
	C.V. (%)	41.2	30.2	37.4	28.2
T_{max}(hr)	*M*	1.5	2.0	1.4	1.9
	SD	0.8	0.8	0.7	0.8
	C.V. (%)	52.0	37.6	52.6	42.2
AUC_{0-t} (ng·hr/mL)	*M*	11860.77	12973.19	12501.74	12913.64
	SD	5042.16	3547.94	4818.03	3345.22
	C.V. (%)	42.5	27.4	38.5	25.9
$AUC_{0-\infty}$ (ng·hr/mL)	*M*	12547.60	13898.15	13220.34	13850.38
	SD	5127.19	3785.77	4988.68	3722.61
	C.V. (%)	40.9	27.2	37.7	26.9
$T_{1/2}$ (hr)	*M*	5.2	5.3	5.1	5.3
	SD	1.3	1.3	1.2	1.4
	C.V. (%)	24.9	25.6	23.3	26.6
λ_z (1/hr)	*M*	0.1378	0.1394	0.1398	0.1386
	SD	0.0231	0.0315	0.0237	0.0306
	C.V. (%)	16.8	22.6	17.0	22.1
Cl (mL/min/kg)	*M*	0.90	0.65	0.82	0.65
	SD	0.71	0.14	0.61	0.15
	C.V. (%)	79.4	22.1	74.4	22.5
V_d (L/kg)	*M*	0.42	0.29	0.37	0.29
	SD	0.40	0.08	0.34	0.07
	C.V. (%)	95.9	28.3	91.3	25.6

TABLE 3
Analysis of Variance of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ (Logarithmic Transformed) for the Assessment of Sequence, Subject Nested Within Sequence, Period and Formulation Effects, After Administration of Glubosil® (Test) and Actos® (Reference) to Healthy Thai Male Volunteers (α = 0.05)

	ANOVA (*P* value)			
	Source of variation			
Pharmacokinetic parameters	Sequence	Subject (seq)[a]	Period	Formulation
Initial study (n = 24)				
C_{max}	0.689	0.126	0.910	0.594
AUC_{0-t}	0.635	0.018	0.930	0.080
$AUC_{0-\infty}$	0.640	0.013	0.866	0.060
Add-on subject study (n = 35)				
C_{max}	0.761	0.073	0.930	0.806
AUC_{0-t}	0.833	0.003	0.851	0.155
$AUC_{0-\infty}$	0.867	0.001	0.773	0.114

[a]Subject nested within sequence

TABLE 4
Point Estimate and 90% Confidence Intervals (90% C.I.) of the Test/Reference Ratios for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ (Logarithmic Transformed) After Administration of Glubosil® (Test) and Actos® (Reference) to Healthy Thai Male Volunteers

	Glubosil®/ Actos®		
Pharmacokinetic parameters	Point estimate	90% C.I.	Acceptance range
Initial study (n = 24)			
C_{max}	0.94	0.76–1.15	0.80–1.25
AUC_{0-t}	0.83	0.70–0.99	0.80–1.25
$AUC_{0-\infty}$	0.84	0.71–0.98	0.80–1.25
Add-on subject study (n = 35)			
C_{max}	1.02	0.88–1.19	0.80–1.25
AUC_{0-t}	0.90	0.80–1.02	0.80–1.25
$AUC_{0-\infty}$	0.90	0.80–1.00	0.80–1.25

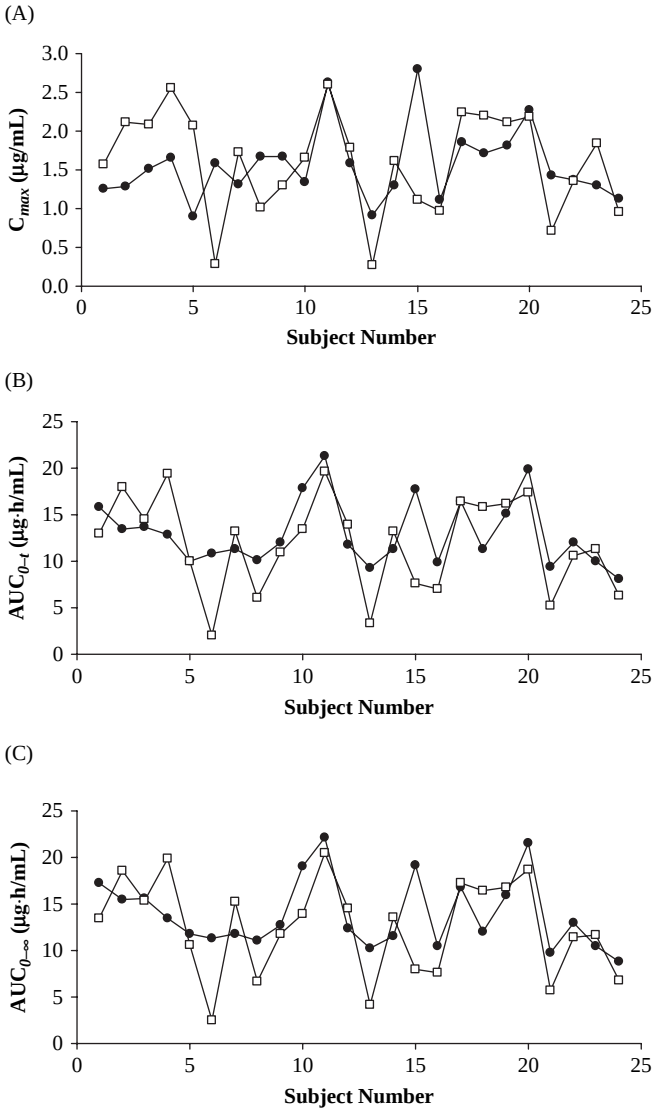

FIGURE 3. Intrasubject and intersubject variability in the estimation of C_{max} (A), AUC_{0-} (B), and $AUC_{0-\infty}$ (C) after administration of 30-mg single dose of Glubosil® (Test, □) and Actos® (Ref, •) in healthy Thai male volunteers.

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