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Bioequivalence of Hana Loxoprofen Sodium Tablet to Dongwha Loxonin® Tablet (Loxoprofen Sodium 60 mg)

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ABSTRACT − Loxoprofen sodium, a 2-phenylpropionate non-steroidal anti-inflammatory drug (NSAID), has marked analgesic and antipyretic activities and relatively weak gastrointestinal ulcerogenicity. The purpose of the present study was to evaluate the bioequivalence of two loxoprofen sodium tablets, Hana loxoprofen sodium tablet (Hana Pharm. Co., Ltd.) and Dongwha Loxonin® tablet (Dongwha Pharm. Co., Ltd.), according to the guidelines of the Korea Food and Drug Administration (KFDA). The *in vitro* release of loxoprofen from the two loxoprofen sodium formulations was tested using KP IX Apparatus II method with various dissolution media. Twenty four healthy Korean male volunteers, 22.83±1.86 years in age and 69.92±9.14 kg in body weight, were divided into two groups and a randomized 2×2 crossover study was employed. After a single tablet containing 60 mg as loxoprofen sodium was orally administered, blood samples were taken at predetermined time intervals and the concentrations of loxoprofen in serum were determined using a 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 2002) 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, Dongwha Loxonin® tablet, were 2.03, 2.99 and -9.49% 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 (e.g., log0.9831~log1.0535 and log0.9455~log1.1386 for AUC_t and C_{max}, respectively). Thus, the criteria of the KFDA bioequivalence guideline were satisfied, indicating Hana loxoprofen sodium tablet was bioequivalent to Dongwha Loxonin® tablet.

Key words − Loxoprofen sodium, Hana loxoprofen sodium tablet, Dongwha Loxonin® tablet, Bioequivalence, Online column-switching HPLC

Loxoprofen sodium, sodium (±)2-[4-(2-oxocyclopentylmethyl) phenyl]propionate dihydrate (Figure 1), a 2-phenylpropionate non-steroidal anti-inflammatory drug (NSAID), has marked analgesic and antipyretic activities and relatively weak gastrointestinal ulcerogenicity (Terada et al., 1984). The mechanism of action of loxoprofen sodium is inhibition of prostaglandin biosynthesis by its action on cyclooxygenase. However, loxoprofen sodium itself is not the major *in vivo* inhibitor. After oral administration, loxoprofen sodium is absorbed as the free acid rather than the sodium salt from the gastrointestinal tract, which causes only weak irritation of the gastric mucosa, and is then converted to an active metabolite by reduction of the ketone carbonyl to the *trans*-OH form. The active isomer has the 2S, 1'R, 2'S configuration (Figure 1), which potently inhibits prostaglandin biosynthesis (Riendeau et al., 2004; Sugimoto et al., 1991; Matsuda et al., 1984). The time to reach the maximum plasma concentration (T_{max}) of loxoprofen sodium has been reported to 27.7±4.39 min after oral administration, and the half life ($t_{1/2}$) of the plasma of loxoprofen sodium has been reported to be 64.46±9.68 min (Cho et al., 2006).

The present study was conducted to determine the pharmacokinetics and bioequivalence of two formulations of loxoprofen sodium 60 mg tablets, reference (Dongwha Loxonin® tablet) and test (Hana loxoprofen sodium 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 loxoprofen sodium tablet 60 mg. Loxoprofen sodium in serum was measured using online column-switching high-performance liquid chromatography (Cho et al., 2006). The two formulations were compared

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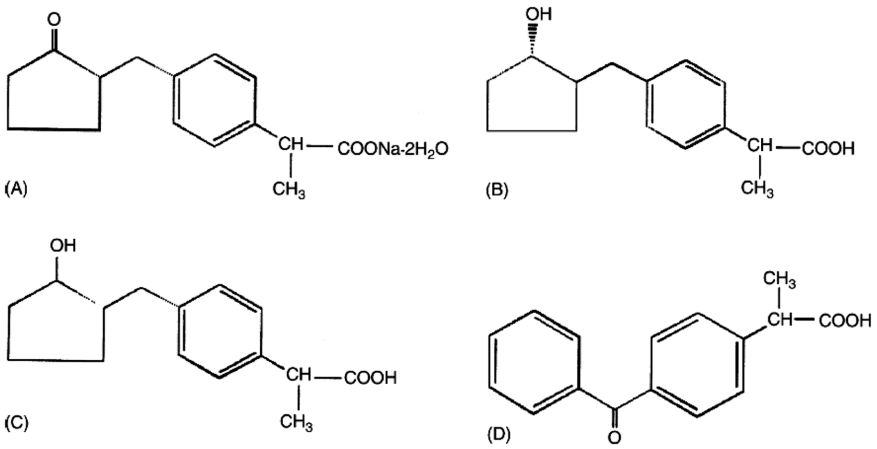

Figure 1. Chemical structures of (A) loxoprofen sodium dihydrate, its (B) *trans*- and (C) *cis*-alcohol metabolites, and (D) ketoprofen (internal standard).

in terms of standard pharmacokinetic parameters, area under the curve (AUC_t), the maximum plasma concentration (C_{max}), as well as T_{max} according to the guidelines of Korea Food and Drug Administration (KFDA) (KFDA, 2010).

Materials and Methods

Materials and instruments

Each of the study formulations contained 60 mg of loxoprofen sodium. The test formulation (Hana loxoprofen sodium tablet, Hana Pharm. Co., Ltd., lot no. 4001; expiration date, October 2007) and reference formulation (Dongwha Loxonin® tablet, Dongwha Pharm. Co., Ltd., lot no. 3029; expiration date, October 2007) manufactured in accordance with the Korean Good Clinical Practice (KGCP) guidelines (KFDA, 2009) were supplied as tablet.

Methanol and acetonitrile (HPLC grade) were purchased from Fisher Scientific (Fair Lawn, NJ, USA) and the other chemical 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 Shimadzu LC-VP system (Kyoto, Japan) equipped with pumps (model LC-10AD*vp*) and an autosampler (model SIL-HTC), a degasser (model DGU-14A), a column oven (model CTO-10AC*vp*), a UV/Vis detector (model SPD-10A*vp*), and Shimadzu CLASS-VP software. The instrument arrangement for the automated column-switching system and system flow diagram was shown in Figure 2. The pretreatment column used for online sample preparation was the Shim-pack MAYI-ODS (50 μm particle size, 10 mm× 4.6 mm i.d., Shimadzu, Kyoto, Japan), using 20 mM phosphate buffer (pH 6.9)/acetonitrile (95/5, v/v). A Shim-pack VP-ODS column (5 μm particle size, 150 mm×4.6 mm i.d.,

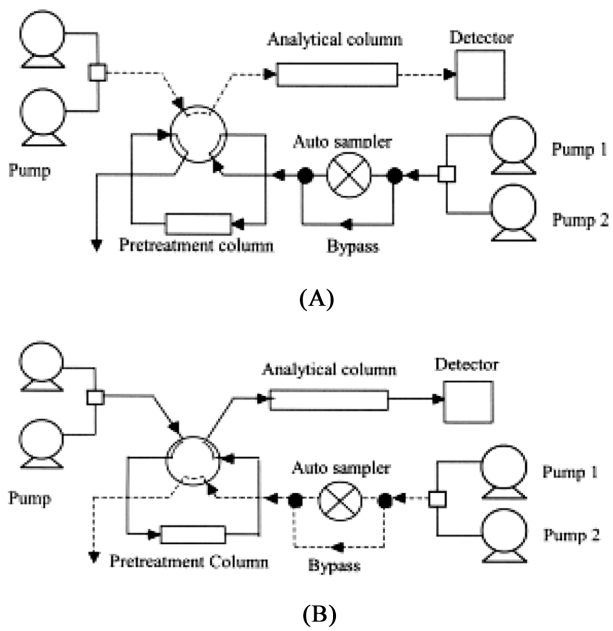

Figure 2. Flow diagram of the column-switching system; (A) position A (pretreatment); (B) position B (analysis).

Shimadzu, Kyoto, Japan) was used as the main analytical column. The analytical mobile phase used acetonitrile/water (45/55, v/v) containing 0.1% formic acid. Detection was carried out at 225 nm with the UV/Vis detector. The column temperature was maintained at 30°C.

In vitro dissolution test

In vitro dissolution testing was performed using Korean Pharmacopoeia (KP) IX 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 (Korean Pharmacopoeia IX, 2007). Samples were removed at 5, 10, 15, 30, 45, 60, 90, 120 and 180 minutes, after which they were filtered and assayed by

HPLC with UV/Vis detection at 220 nm. The dissolved loxoprofen content was expressed as a percentage of the labelled loxoprofen content.

Selection of volunteers

This study was conducted at Gwangju Christian Hospital (Gwangju, Korea). The study population consist of twenty four healthy male Korean volunteers with an average age of 22.83±1.86 years and an average weight of 69.92±9.14 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 loxoprofen sodium; 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, 2010).

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, 2009).

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 hours 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 hours before and 4 hours after drug administration. At 8:00 AM, a cannula (JELCO™, 22G, Johnson & Johnson Medical, Pomezia, Italia) was inserted into the median cubital vein and the cannula was flushed with 0.3 mL heparinized normal saline solution for injection (150 units/mL) to prevent clotting. Each subject was randomly assigned to receive a single dose of the reference or test formulation (60 mg of loxoprofen sodium) with 240 mL of spring water at 8:30 AM. Subjects received standardized meals at 4 hours 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 cannula into a 5 mL Vacutainer tube (Becton Dickinson and Company, Franklin Lakes, New Jersey) before administration (to serve as a control) and at 10, 20, 30, 45, 60, 90, 120, 150, 180, 240 and 360 minutes after administration. After sampling, the cannula was flushed with 0.3 mL of heparinized normal saline solution for injection. The samples were centrifuged at 3000 rpm, 20 minutes and the serum was transferred to polyethylene tubes and stored at -80°C 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 6 hours after drug administration. No drugs, alcohol, xanthine-containing foods or beverage were allowed during the study.

Determination of serum loxoprofen concentration

To prepare the sample for assay, an aliquots of 100 μL of ketoprofen solution (internal standard, 100 μg/mL in methanol) was added to a 1 mL of serum sample by vortex-mixing for 30 s. 1.1 mL of serum samples were filtered with a polyvinylidene-fluoride (PVDF) syringe filter (13 mm, 0.45 μm pore size, Millipore, Bedford, MA, USA) and transferred to autosampler vials. An aliquots of 50 μL of filtered sample was injected onto the pretreatment column by the autosampler. At the time of sample injection, the column-switching valve was placed in position A (Figure 2A). Protein and other interfering compounds were eluted with 20 mM phosphate buffer (pH 6.9)/acetonitrile (95/5, v/v) and 0.1% formic acid at a flow rate of 0.3 and 2 mL/min, respectively. 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 acetonitrile/water (45/50, v/v) containing 0.1% formic acid, at a flow rate of 1 mL/min. After the sample injection, the column-switching valve was shifted to position B (Figure 2B) to move samples containing the target compounds from the pretreatment column to the analytical column. The analytical column was washed with a linear gradient of acetonitrile/water (45/55, v/v) containing 0.1% formic acid

from 100 to 20%, and acetonitrile/water (80/20, v/v) from 0 to 80%. The total flow rate was 1.0 mL/min. During sample analysis, the pretreatment column was washed with acetonitrile/50 mM ammonium acetate (60/40, v/v) at a flowrate of 1.0 mL/min by switching the valve in pump 2 (Figure 2).

The primary stock solution of loxoprofen sodium was prepared at 1000 μg/mL in methanol and stored at 4°C. Loxoprofen sodium stock solution was serially diluted with methanol and added to the prepared loxoprofen drug-free serum to obtain final concentration of 0.1, 0.5, 1, 5, 10 and 20 μg/mL for the preparation of calibration curve. The interference by endogenous compounds was assessed by analyzing standards of loxoprofen drug-free serum samples, serum spiked with loxoprofen, and serum samples obtained from subjects given loxoprofen sodium tablets. All peaks with the retention times of loxoprofen were confirmed using a UV/Vis detector. Loxoprofen was quantitated by weighted linear regression analysis of the peak area ratio versus concentrations of added loxoprofen using 1/concentration as the weighting factor. The calibration curves were linear from 0.1 to 20 μg/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 0.1 μg/mL for loxoprofen in five replicate samples. In order to assess the intra- and inter-day precision and accuracy of the assay, low (0.5 μg/mL of serum), medium (5 μg/mL of serum), and high (10 μg/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%.

Statistical analysis of pharmacokinetic parameters

Each volunteer following the oral dose of 60 mg of loxoprofen sodium 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 loxoprofen. C_{max} and T_{max} were recorded as actual measurement values and AUC_t was calculated by trapezoidal formular from 0 to 6 hours. 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., 2001) and K-BE Test program® (Lee et al., 2000) at a significant level of 0.05. The bioequivalence of two loxoprofen sodium tablets was estimated by AUC_t, C_{max} and T_{max} used as reference values.

Result and Discussion

Dissolution testing

Accordance of KP IX dissolution Apparatus II method, dissolution testing was done to test and reference formation. Both formulations released >85% of loxoprofen sodium within 30 minutes in all test dissolution media (pH 1.2, 4.0, 6.8, and water) and had similar release profiles. So, two formulations had no difference in dissolution testing.

Analysis of loxoprofen in serum samples

Figure 3 shows chromatograms of blank, spiked loxoprofen and serum sample from a healthy subject obtained 30 minutes after oral administration of loxoprofen sodium 60 mg. No interference from endogenous substances was observed in human serum with the online column-switching HPLC method. The retention times for loxoprofen and IS (ketoprofen) were ~8.5 and ~10.7 minutes, respectively. In this method, loxoprofen and ketoprofen were well separated from the biological background under the described chromatographic condition, respectively. These peaks were of good shape, completely resolved one. The calibration curve, established by plotting the peak area ratio (y) versus concentration (x), was linear over the range from 0.1 to 20 μg/mL with the following regression equation: $y = 0.10735x + 0.00062$ ($r = 0.9999$). The LLOQ of loxoprofen in human serum was 0.1 μg/mL; at this concentration, the CV for accuracy was 107.89%, and the CV for precision below 15.37%. During validation, the CV for accuracy ranged from 95.32 to 107.89%, whereas intra- and inter-day CVs for precision remained below 11.70 and 15.37%, respectively. These results indicate that the present method has a satisfactory accuracy and precision (Table I).

Pharmacokinetic analysis

Online column-switching HPLC method was successfully used for a bioequivalence test in which serum concentrations of loxoprofen in twenty four healthy male volunteers were

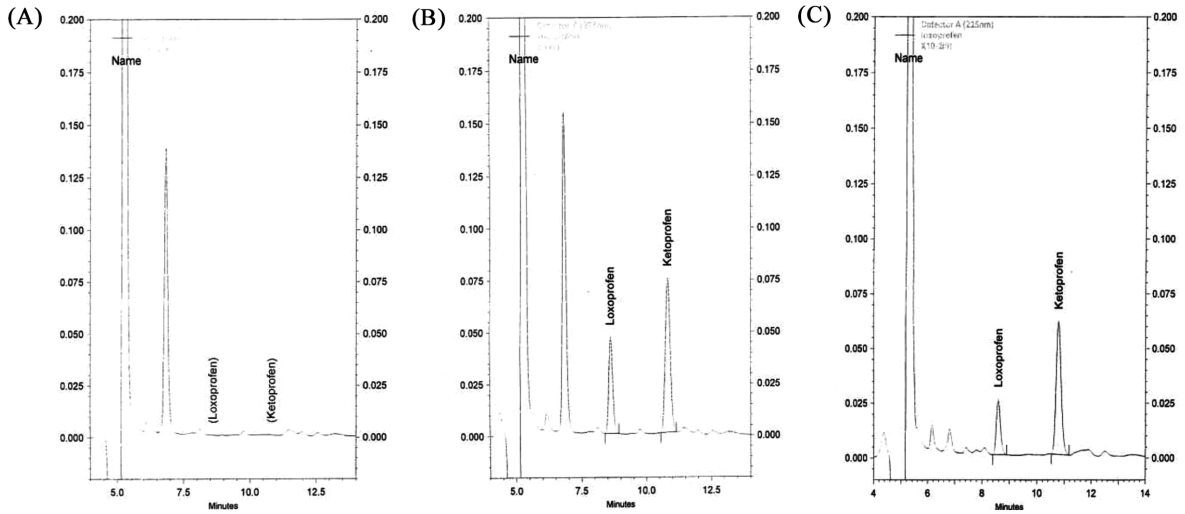

Figure 3. Chromatograms of (A) blank human serum; (B) blank human serum spiked with loxoprofen (5 μg/mL) containing ketoprofen (internal standard) 10 μg/mL; and (C) a human serum sample from a healthy Korean male volunteer at 30 minutes after administration of a single oral dose of loxoprofen sodium 60 mg.

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

Concentration (μg/mL)	Precision CV(%)		Accuracy (%, n=5)
	Intra-day CV(%) (n=5)	Inter-day CV(%) (n=5)	
0.1	11.70	15.37	107.89
0.5	8.58	7.23	97.71
5	2.16	7.10	96.33
10	3.33	6.33	95.32

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

determined up to 6 hours after the oral administration of 60 mg loxoprofen sodium. Figure 4 shows the mean serum concentration-time curves of loxoprofen following single oral administration of test and reference tablets, 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 393.38±75.43 μg/mL/min for the test formulation and 385.55±68.28 μg/mL/min for the reference formulation. Mean (± S.D.) C_{max} values were 4.13±0.90 and 4.01±0.99 μg/mL, with mean (± S.D.) T_{max} values of 29.79±15.91 and 32.92±10.52 min, respectively. The differences of the means of the test to reference medication for AUC_t and C_{max} were 2.03 and 2.99%, respectively, which are generally 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 (Kim et al., 1997; Fan et al., 2003). For example, after oral administration of loxoprofen sodium 60 mg in Chinese subjects, the AUC_t was 426±78 μg/mL/min and the C_{max} was 3.9±1.1 μg/mL (Fan et al., 2003).

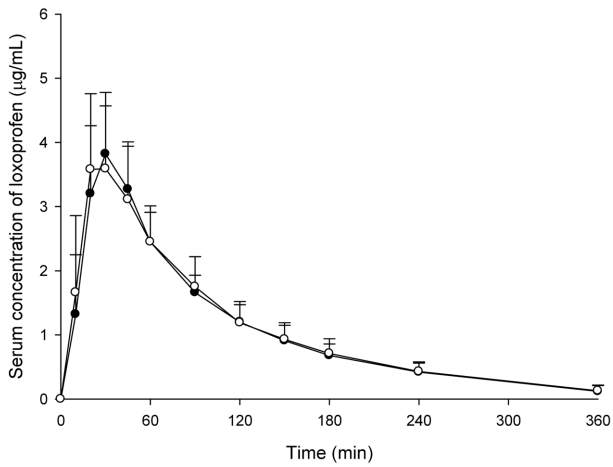

Figure 4. Mean surum concentration-time curves of loxoprofen after single oral administration of the reference (●) and test (○) loxoprofen tablets as loxoprofen sodium 60 mg. Vertical bars represent the standard deviations.

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 1.0177, 1.0376, respectively (Table III). The parametric 90% confidence intervals were in the range of log0.9831 to log1.0535 and log0.9455 to

Table II. *Bioavailability parameters in normal and logarithmic scales for each volunteer obtained after oral administration of Hana loxoprofen sodium and Dongwha Loxonin® tablets at the loxoprofen sodium dose of 60 mg.*

Subjects	Parameter									
	AUC_t (μg/mL/min)				C_{max} (μg/mL)				T_{max} (min)	
	Reference		Test		Reference		Test		Reference	Test
	Value	Log	Value	Log	Value	Log	Value	Log	Value	Value
X1	253.70	5.54	265.15	5.58	4.22	1.44	3.91	1.36	30.00	20.00
X2	350.10	5.86	408.48	6.01	3.95	1.37	4.13	1.42	45.00	30.00
X3	335.93	5.82	344.75	5.84	3.79	1.33	3.74	1.32	30.00	20.00
X4	452.33	6.11	498.48	6.21	4.07	1.40	3.42	1.23	45.00	90.00
X5	408.65	6.01	396.10	5.98	5.12	1.63	4.99	1.61	30.00	20.00
X6	536.38	6.28	577.73	6.36	4.97	1.60	5.55	1.71	45.00	20.00
X7	336.68	5.82	362.63	5.89	2.45	0.90	3.79	1.33	30.00	20.00
X8	438.08	6.08	459.88	6.13	5.63	1.73	4.70	1.55	30.00	30.00
X9	354.05	5.87	362.38	5.89	3.98	1.38	4.21	1.44	30.00	20.00
X10	376.98	5.93	382.75	5.95	4.53	1.51	3.04	1.11	30.00	20.00
X11	352.40	5.86	340.55	5.83	3.41	1.23	3.25	1.18	20.00	20.00
X12	420.33	6.04	427.08	6.06	4.76	1.56	3.64	1.29	30.00	30.00
Y1	308.35	5.73	293.23	5.68	4.04	1.40	3.93	1.37	20.00	30.00
Y2	304.85	5.72	321.45	5.77	1.83	0.60	4.46	1.50	60.00	20.00
Y3	380.80	5.94	376.80	5.93	3.51	1.26	4.12	1.42	45.00	30.00
Y4	349.30	5.86	458.43	6.13	4.20	1.44	5.65	1.73	20.00	20.00
Y5	372.95	5.92	316.27	5.76	4.84	1.58	4.20	1.44	30.00	30.00
Y6	414.13	6.03	385.38	5.95	3.78	1.33	3.40	1.22	30.00	30.00
Y7	370.78	5.92	430.18	6.06	3.07	1.12	3.68	1.30	45.00	30.00
Y8	363.25	5.90	335.93	5.82	3.16	1.15	3.26	1.18	45.00	30.00
Y9	567.55	6.34	542.65	6.30	5.82	1.76	5.42	1.69	20.00	30.00
Y10	391.48	5.97	370.88	5.92	3.20	1.16	4.77	1.56	30.00	20.00
Y11	395.23	5.98	432.38	6.07	5.15	1.64	5.67	1.74	20.00	45.00
Y12	418.90	6.04	351.58	5.86	2.77	1.02	2.08	0.73	30.00	60.00
Mean	385.55	5.94	393.38	5.96	4.01	1.36	4.13	1.39	32.92	29.79
S.D.	68.28	0.17	75.43	0.19	0.99	0.27	0.90	0.23	10.52	15.91

Table III. *Statistical results of bioequivalence evaluation between two loxoprofen sodium tablets*[#]

	Parameters		
	AUC_t	C_{max}	T_{max}
Difference	2.03%	2.99%	-9.49%
F_G[a)]	0.0504	0.3870	0.1201
Test/Reference point estimate	1.0177	1.0376	-3.1250
Confidence interval(δ)[b)]	$\log 0.9831 \le \delta \le \log 1.0535$	$\log 0.9455 \le \delta \le \log 1.1386$	$-28.88\% \le \delta \le 9.89\%$

[#]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)]$\alpha = 0.05$.

log1.1386, 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 lox-

oprofen in human serum samples collected for bioequivalence studies. Using this method, the bioequivalence of two different loxoprofen sodium tablet formulations was examined at the dose of 60 mg in twenty four healthy normal 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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