RESEARCH ARTICLES

Bioequivalence Study of the Generic Meloxicam (Melox®) Compared with the Innovator Mobic®.

Panawan Thummati, Boonyium Kumsorn and Noppamas Rojanasthien

Division of Clinical Pharmacology, Department of Pharmacology, Faculty of Medicine, Chiang Mai University.

Abstract

The bioequivalence of two brands of 7.5 mg meloxicam were demonstrated in healthy volunteers after a single oral dose in a randomized 2-period crossover study. The reference and the test formulation were administered to fasted male volunteers, thereafter, the blood samples were collected at specific time interval from 0-96 h. The washout period was 2 weeks. The plasma meloxicam concentrations were determined by HPLC. The pharmacokinetic parameters obtained after non-compartmental analysis were statistically evaluated for bioequivalence using ANOVA. RESULT; The median T_{max} (h) of the two products were similar (4.5 VS 4.0), however, the range of T_{max} (h) for the reference product (2.0-10.0) was more variable than that of the test (4.0-10.0). Bioequivalence analysis showed that the C_{max} and the AUC $_{0-\infty}$ did not differ significantly. The point estimator (90%CI) for the ratio $\frac{\text{Test}}{\text{Reference}}$ of log transformed data of the AUC $_{0-\infty}$ and C_{max} were 0.97 (0.90-1.06) and 0.95 (0.84-1.08), respectively. These values were within the bioequivalence range of 0.80-1.25, thus our study demonstrated the bioequivalence of the test and the reference preparations.

Key words : bioeqivalence, meloxicam

Address correspondence and reprint request to: Noppamas Rojanasthien, Department of Pharmacology, Faculty of Medicine, Chiang Mai University, 50200 Thailand.

การทดสอบชีวสมมูลของยาสามัญมีล็อกซิแคมในอาสาสมัครชายไทยสุขภาพดี

พนาวรรณ ธรรมธิ, บุญเยี่ยม คำสอน, นพมาศ โรจนเสถียร

ภาควิชาเภสัชวิทยา คณะแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่

บทคัดย่อ

การศึกษาชีวสมมูลของยาเมล็อกซิแคมขนาด 7.5 มิลลิกรัมในอาสาสมัครชายไทยสุขภาพดี โดยอาสาสมัคร 12 คน จะได้รับการสุ่มไขว้เพื่อรับประทานยาทั้งยาทดสอบและยาต้นแบบ อย่างละหนึ่งครั้งหลังจากงดน้ำและอาหาร ระยะเวลาการศึกษาห่างกัน 2 สัปดาห์ ตัวอย่างเลือดจะเก็บตามเวลาที่กำหนดในเวลา 0-96 ชั่วโมง หลังจากรับประทานยา และนำไปตรวจวัดหาความเข้มข้นของยาเมล็อกซิแคมโดยวิธีโครมาโตกราฟฟีชนิดของเหลวสมรรถนะสูง ประเมินค่าทางเภสัชจลนศาสตร์โดยวิเคราะห์แบบ non-compartment และวิเคราะห์ชีวสมมูลโดยใช้อะโนวา ผลการศึกษา พบว่าเวลาที่ระดับยาในเลือดสูงสุดของยาต้นแบบ (ค่ามีเดียน 4.5 ชม., ช่วง 2.0-10.0 ชม.) มีค่าแปรปรวนมากกว่าค่าของยาทดสอบ (ค่ามีเดียน 4.0 ชม., ช่วง 4.0-10.0 ชม.) การวิเคราะห์ชีวสมมูล พบว่าค่าเฉลี่ย (ช่วงความเชื่อมั่นร้อยละ 90) ของพื้นที่ใต้กราฟที่เวลา 0 ถึงอสงไขยและค่าความเข้มข้นสูงสุดของยาในเลือด มีค่าเท่ากับ 0.97 (0.90 - 1.06) และ 0.95 (0.84 - 1.08) ตามลำดับ ซึ่งอยู่ในช่วงของชีวสมมูลที่ยอมรับคือ 0.80-1.25 การศึกษานี้จึงสรุปว่ายาทั้งสองมีชีวสมมูลเท่าเทียมกัน

คำสำคัญ bioeqivalence, meloxicam

Introduction

Meloxicam is a nonsteroidal anti-inflammatory drug (NSAID) useful for patients with rheumatoid arthritis and osteoarthritis [1,2]. It is a partially selective cyclo-oxygenase-2 (COX-2) inhibitors, therefore, it is less likely to adversely affect the cytoprotective function of arachidonic acid metabolites formed by COX-1 in the gastric mucosa, or prostaglandin E_2 (PGE_2) in the kidney [3-5]. Moreover, it has displayed a favourable gastrointestinal profile when compared to other NSAIDs e.g. piroxicam, naproxen and diclofenac[6]. Following oral administration, meloxicam is completely absorbed and its steady state level was achieved within 3–5 days[7]. It is eliminated predominantly by metabolism with balanced excretion in the form of inactive metabolites occurring in urine and feces. An elimination half-life of about 20 h makes meloxicam a suitable agent for once-daily dosing[7] For the treatment of osteoarthritis the recommended starting and maintenance dose is 7.5 mg once daily, although some patients may receive additional benefit by increasing the dose to 15 mg once daily [8].

The aim of this study was to investigate the bioequivalence of the generic meloxicam in order to assess any possible difference between the test and the reference due to manufacturing process.

Materials and Methods

Drug formulations

Reference product : Mobic® 7.5 mg tablet [OLIC (Thailand) Limited Ayudhaya, Thailand for Boehringer Ingelheim International GmbH Ingelheim am Rhein, Germany]. Lot No. B. 1015, MFD 6/11/2001, EXP 6/11/2003.

Test product : Melox® 7.5 mg tablet [The Siam Bheasach company, Bangkok, Thailand] LOT D22ME14, MFD 04/2002.

Volunteers

Twelve healthy nonsmoking male volunteers, aged between 20-28 years old were enrolled in this study. All were deemed healthy based on medical history and physical examination. Routine blood test including CBC with differential, BUN, creatinine (Cr) and LFT were screened to exclude volunteer with abnormal hematology, liver or kidney functions. Volunteer with known contraindication or hypersensitivity to meloxicam was excluded as well as those with known history of peptic ulcer disease, dyspepsia, gastrointestinal disease, recent cigarette smoking, alcoholism or drug abuse. No other drug was allowed 1 month before and during the study period to avoid the effects of inducing or inhibiting hepatic metabolizing enzyme and the risk of drug interactions. After given written informed consent, volunteers were enrolled to the study.

Design, dosage and drug administration

The study was conducted as an open-label, randomized, single dose, two-period crossover design with a two-week washout period. Equal numbers of volunteers were randomly assigned to one of the two sequence groups and each volunteer received a single 7.5 mg dose of each of the two preparations under fasting condition with 240 ml water. Volunteers remained upright and fasted for 2 h after drug administration. Water and lunch were served at 2 h and 4 h, respectively. An intravenous catheter connected to an injection plug was used for serial blood sample collections. Venous blood samples (10 ml) were collected into heparin tubes before and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10,15, 24, 36, 48, 72, 84, and 96 h after dose administration. The blood samples were centrifuged for 10 minutes at 3,000 rpm to separate the plasma. Thereafter, the plasma samples were immediately kept at -20°C until assay.

Determination of the plasma meloxicam concentrations

Plasma concentrations of meloxicam were measured by using a high-performance liquid chromatography (HPLC) after solid phase extraction; (Strata® 50 µm C18-E 100 mg/ml, Phenomenex, USA). The HPLC system consisted of an isocratical pump (LC-10AS), degasser (DUG-3A), UV detector (SPD-10A), integrator communication bus module (CMB-10A), column oven (CTO-10A) and auto injector (SIL-10Ai). Separation was performed at 50°C on an analytical column (Inersil ODS-2, 5 µm 4.6x150 mm, GL Sciences, Japan) coupled with a guard column (Inersil ODS-2, 5 µm 4.6x10 mm, GL Sciences, Japan). The mobile phase was a mixture of 10 mM potassium dihydrogen phosphate (pH 4.4)/methanol/acetonitrile (5/4/1, v/v/v). This method was modified from Velpandian *et al* [9] using piroxicam as an internal standard (IS). The retention time for meloxicam and internal standard were approximately 8.8 and 6.5 min, respectively. The linear regression analysis between meloxicam concentration with the peak height ratios of meloxicam and IS over the determination range between 10-2,000 ng/ml gave the correlation coefficients of 0.999 or better. Samples containing drug concentrations in excess of 2,000 ng/ml were analyzed after dilution with drug free plasma. Within-run accuracy and precision was determined using 5 aliquots of each 3 levels control sample and single calibration curve-run concurrently. The data of 5 different days in the same manner study were calculated for between-run assay validation. The precision (CV,%) of within-run and between-run were 3.81 and 3.94, respectively. The mean recovery of meloxicam and IS were 97.83% and 103.30%, respectively.

Pharmacokinetic analysis

Maximal plasma concentration (C_{max}, ng/ml) and time to reach the peak concentration (T_{max}, h) were obtained directly by visual inspection of each volunteer's plasma concentration-time profile. The area under the plasma concentration-time curve (AUC) from time 0-infinity ($AUC_{0-\infty}$, ng×h/ml) and half-life ($t_{1/2}$, h) were determined by non-compartmental analysis. The slope of the terminal log-linear portion of the concentration-time profile were determined by least-squares regression analysis and used as the elimination rate constant (K_e). The elimination half-life were calculated as 0.693/ K_e. The AUC_{0-t} from time zero to the last quantifiable point (Ct) were calculated using the trapezoidal rule. Extrapolated AUC from Ct to infinity ($AUC_{t-\infty}$) were determined as Ct/*Ke*. Total $AUC_{0-\infty}$ was the sum of AUC_{0-t} + $AUC_{t-\infty}$.

Statistical analysis

An analysis of variance (ANOVA) was used to determine the statistical differences of pharmacokinetic parameters (T_{max}, C_{max} and AUC) which represented the rate and extent of drug absorption. The variability between subjects, treatment groups, study periods, and formulations were determined and the two one-sided test procedure was performed. This procedure is referred to as the confidence interval (CI) approach [10,11]. The AUC and C_{max} were transformed to logarithmic values (ln) before calculation by using ANOVA appropriated for the design. The 90% CI of the Test/Reference for AUC and C_{max} ratios were analysed by the following formula [11,12].

$$90\%\ CI\ (\mu_T - \mu_R) = (\overline{X}_T - \overline{X}_R) \pm t^{v}_{0.1}\sqrt{\frac{2S^2}{n}}$$

Where $\overline{X}_T$, $\overline{X}_R$ are the observed means of the ln transformed parameters (either C_{max} or AUC) for the test product (T) and the reference (R), S^2 is the error variance obtained from the ANOVA, n is the number of subjects, $t^{v}_{0.1}$ is the tabulated two-tail *t* value for 90% CI and v is the number of degrees of freedom of the error mean square from the ANOVA. The antilogarithm of the CI (μ_T - μ_R) will express the bioequivalence as a ratio of the

test product and the reference product. The bioequivalence intervals of 0.80 – 1.25 for $\frac{\text{Test}}{\text{Reference}}$ ratios of the $AUC_{0-\infty}$ and the C_{max} are accepted by the Thai FDA [12]. An analysis of T_{max} difference [T_{max} Test - T_{max} Reference] was expressed as untransformed data. The bioequivalence range of the difference is ± 20 % of the median T_{max} of the reference formulation.

Result and Discussion

Single dose administration of 7.5 mg meloxicam in healthy male volunteers under fasting condition was well tolerated and all volunteers completed the study without any adverse effects. Table 1 and 2 showed meloxicam plasma concentrations versus time as well as their mean ± S.D., while table 3 and 4 showed their calculated pharmacokinetic parameters for the test and the reference, respectively. The pharmacokinetic parameters were compared and showed in table 5. The mean plasma concentration-time profiles after oral administration of the test and the reference was depicted in figure 1. After oral administration, the rates of meloxicam absorption from the two products were relatively variable (%CV = 43% and 48% for the test and the reference, respectively). The range of time to reach the maximal concentration (T_{max}) for the test (median 4.5 h, range 2.0-10.0 h) was more variable than the reference (median 4.0 h, range 4.0-10.0 h) (table 2). Although the point estimate of the T_{max} difference (0.67 h) was within the acceptable range of ± 1.03 h (less than ± 20% of the mean T_{max} of the reference), the upper and the lower confidence limit of the T_{max} difference [(-1.09) – 2.42 h)] were outside the acceptable range (Table 6). However, this statistical difference was not considered to affect the efficacy and safety of the two products, since meloxicam is recommended for used as chronic therapy and T_{max} at steady-state (T_{max-ss}) is clinically a more relevant value. The mean plasma concentration-time curves of the test and the reference products were relatively comparable although the C_{max} and $AUC_{0-\infty}$ of the reference (846.24 ng/ml and 34,106.26 ng.h/ml) was slightly higher than those of the test (798.6 ng/ml and 32,771.02 ng.h/ml). Despite of this, there were no statistically significant difference of these parameters between the two formulations and the relative bioavailability (F_{rel}) calculated from C_{max} and $AUC_{0-\infty}$ of the Test / Reference was 97.64% and 98.57%, respectively. Furthermore, the bioequivalence analysis after ln transformed data of the $AUC_{0-\infty}$ and C_{max} showed that the mean (90% CI) of ratios for Test/ Reference were 0.97 (0.90-1.06) and 0.95 (0.84-1.08), respectively. These values fell within the bioequivalence criteria of 0.80-1.25 as shown in table 6. From the ANOVA, the inter-volunteers variability in the $AUC_{0-\infty}$ and C_{max} were significantly high (p=0.0007 and p=0.0154, respectively). These findings were expected since meloxicam is a drug with high first-pass metabolism and some volunteers may exhibit either extremely high or extremely low $AUC_{0-\infty}$ and C_{max} concentrations. The intra-volunteer coefficient of variation (%CV) estimated from S^2 obtained from the ANOVA after logarithmic transformed, for the $AUC_{0-\infty}$, and C_{max} were 11% and 17%, respectively. The higher CV value of C_{max} attributed to the fact that C_{max} is a single concentration value and is dependent on the discrete sampling scheme therefore tends to show higher variability than $AUC_{0-\infty}$ which is an integrated parameter. According to the nomograms and tables of Diletti [13] the power of tests obtained from this study for $AUC_{0-\infty}$ and C_{max} were 90% and 70%, respectively. To attain the test power of greater than 80% for the C_{max}, the sample size should be 16 volunteers. Concerning the duration of sampling time, it should be sufficient to ensure that the area extrapolated beyond the last sample time was less than 20%. Since the guidelines recommend that sampling should be continued for at least 3 times the terminal half-life of drug ($t_{1/2}$ approximately 20 h), the sampling time in this study was continue until 96 h. The AUC analysis in

this study showed that the sampling time was adequate and the calculated AUC-extrapolation was less than 20%, except in one volunteer (Volunteer No 3) whose elimination $t_{1/2}$ was significantly longer than other volunteers ($t_{1/2}$ = 39.3 h and 42.8 h) and the AUC-extrapolation was 19.61% and 20.84% for the test and the reference, respectively.

Conclusion

We have conducted the bioequivalence study of 7.5 mg oral preparations of meloxicam manufactured by the Siam Bheasach Company, Bangkok, Thailand in comparison with the innovator in 12 healthy Thai male volunteers. The result demonstrated that the mean (90% CI) of the AUC $_{0-\infty}$ and C_{max} ratios for [Test/Reference] were 0.97 (0.90-1.06) and 0.95 (0.84-1.08), respectively. Since the mean Test/ Reference ratio of the two parameters was close to 1 and its 90% CI were fell within the bioequivalence range of 0.80 – 1.25, the result concluded the bioequivalence of the two products.

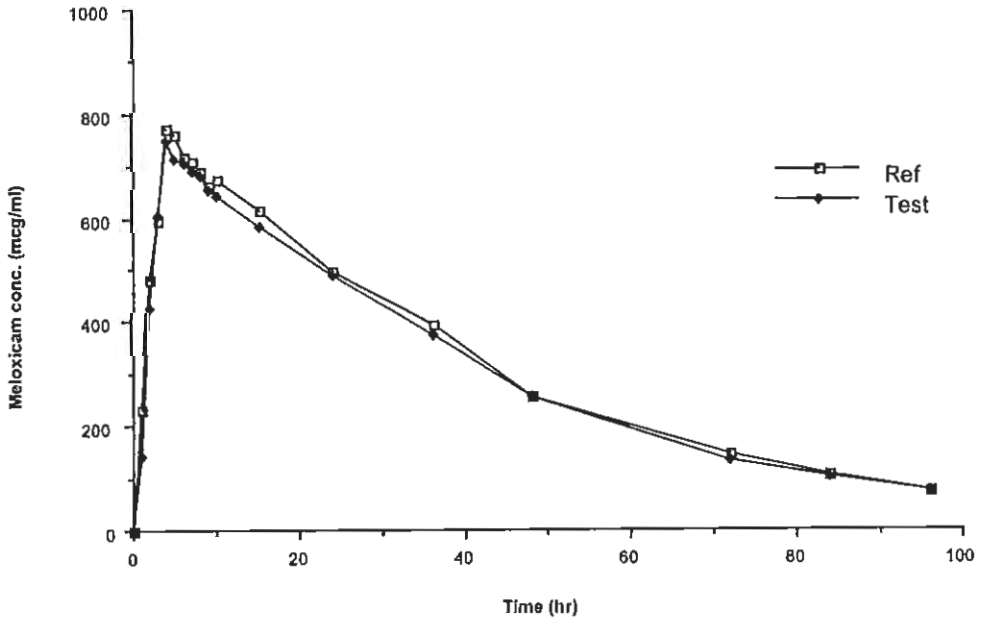

Figure 1 Mean plasma concentration-time profiles after single oral administration of 7.5 mg Meloxicam [Ref (-□-) and Test (-♦-)].

Table 1 Plasma meloxicam concentrations (ng/ml) after oral administrations of 7.5 mg of the test .

Subject No	Plasma meloxicam concentration (ng/ml)																	
Time→	0.0	1.0	2.0	3.0	4.0	5.0	6.0	7.0	8.0	9.0	10.0	15.0	24.0	36.0	48.0	72.0	84.0	96.0
1	0.00	268.08	762.39	824.53	866.34	837.30	710.71	758.60	772.42	736.42	624.52	653.95	472.76	405.54	305.00	184.33	143.78	62.73
2	0.00	137.94	343.25	351.49	376.77	389.44	357.41	381.98	383.66	394.72	389.76	371.16	384.39	295.92	189.12	109.75	74.83	51.62
3	0.00	255.84	559.61	831.49	881.68	885.83	906.85	842.16	834.96	827.78	756.61	771.39	741.14	630.05	467.37	288.73	280.87	206.78
4	0.00	255.84	425.77	594.71	880.94	708.83	671.69	663.34	645.78	549.82	594.75	530.92	392.53	282.57	212.24	85.55	56.18	35.50
5	0.00	56.90	440.44	545.25	572.50	521.64	634.69	593.66	593.68	580.27	644.22	560.54	501.47	427.33	303.22	169.78	114.21	103.46
6	0.00	64.60	300.70	492.76	610.44	599.25	552.30	534.60	508.38	496.71	510.61	472.65	366.79	204.46	128.47	57.26	45.38	29.77
7	0.00	40.76	66.30	102.50	313.79	552.54	635.89	649.24	667.19	653.33	673.40	545.50	453.65	367.92	257.39	116.42	90.90	52.89
8	0.00	99.02	433.82	822.60	1071.75	872.27	847.10	788.90	758.11	710.95	753.05	653.10	546.88	381.43	262.02	113.17	78.28	52.28
9	0.00	187.98	249.03	321.67	603.69	679.30	670.90	743.82	732.08	714.22	627.39	486.37	399.31	294.08	222.11	107.50	82.19	72.73
10	0.00	53.13	375.18	706.80	901.78	799.83	782.90	721.70	715.55	712.01	721.61	705.95	518.72	360.22	223.13	107.69	78.91	53.65
11	0.00	106.57	643.33	872.09	906.59	846.58	827.76	833.61	804.34	822.37	746.02	682.53	601.29	444.06	284.76	142.59	93.30	82.18
12	0.00	186.80	505.97	740.46	982.30	871.33	874.03	746.77	764.65	650.44	637.43	572.74	465.75	417.67	224.89	122.10	94.27	76.48
Mean	0.00	142.79	425.48	600.53	747.38	713.68	706.02	688.20	681.73	654.09	639.95	583.90	487.06	375.94	256.64	133.74	102.76	73.34
S.D.	0.00	85.51	183.58	244.94	244.01	165.77	155.74	133.49	131.87	129.28	107.55	113.45	106.94	107.04	83.13	59.49	61.55	46.68

Table 2 Plasma meloxicam concentrations (ng/ml) after oral administrations of 7.5 mg of the reference.

Subject No	Plasma meloxicam concentration (ng/ml)																	
Time→	0.0	1.0	2.0	3.0	4.0	5.0	6.0	7.0	8.0	9.0	10.0	15.0	24.0	36.0	48.0	72.0	84.0	96.0
1	0.00	210.06	468.67	484.07	607.77	638.95	661.62	640.45	602.95	569.32	616.61	543.78	430.97	367.34	241.43	114.50	90.09	58.80
2	0.00	33.62	204.82	490.62	506.86	511.53	504.41	467.50	464.83	455.23	432.50	436.70	439.86	396.71	247.64	128.87	102.15	80.87
3	0.00	551.96	781.77	801.45	1143.91	1027.84	989.72	956.68	930.17	843.69	823.08	876.51	902.83	722.56	576.62	451.17	362.75	252.43
4	0.00	116.30	145.58	156.36	344.19	597.32	562.92	644.09	660.26	631.19	672.82	473.26	444.33	413.36	222.63	134.52	81.83	52.61
5	0.00	44.65	72.98	172.08	479.63	575.69	594.33	604.47	618.43	643.35	691.06	606.57	514.67	404.15	271.41	119.30	89.92	69.37
6	0.00	57.46	272.28	526.96	637.09	641.31	590.12	567.33	573.08	487.06	505.15	487.84	365.15	233.69	151.07	70.27	44.00	27.36
7	0.00	569.05	1219.97	1084.64	1075.87	898.06	839.00	786.73	691.51	668.13	701.03	626.68	521.03	401.60	210.79	127.63	97.14	62.26
8	0.00	211.17	292.38	512.19	1101.01	1056.27	926.33	946.51	935.07	855.84	863.17	828.78	535.07	342.49	236.94	133.76	86.18	66.07
9	0.00	197.74	250.52	333.69	590.60	739.93	667.69	640.45	605.57	622.47	668.36	507.01	396.74	314.91	234.98	106.97	91.11	73.00
10	0.00	317.79	605.08	708.46	761.72	650.24	578.36	597.03	582.33	597.43	637.87	583.58	402.63	267.79	160.42	87.44	74.59	48.38
11	0.00	146.32	686.82	1013.03	1156.41	1053.86	1044.87	971.62	924.54	875.43	805.31	760.89	580.10	464.45	318.58	170.62	120.36	82.64
12	0.00	326.03	745.67	853.53	842.02	734.46	643.19	681.00	691.48	707.29	671.53	661.34	413.51	379.54	213.26	102.17	55.00	45.78
Mean	0.00	231.85	478.88	594.76	770.59	760.45	716.88	708.66	690.02	663.04	674.04	616.08	495.57	392.38	257.15	145.60	107.93	76.63
S.D.	0.00	180.89	337.36	303.18	287.39	197.47	183.61	167.61	156.51	137.24	123.49	142.54	143.85	122.43	110.02	99.53	82.75	57.54

Table 3 Pharmacokinetic parameters of meloxicam after a single oral dose of 7.5 mg of the test.

Subject No.	T_{max} (h)	C_{max} (ng/ml)	AUC (ng×h/ml.)	$T_{1/2}$ (h)
1	4.0	866.34	36,195.32	27.3
2	9.0	394.72	22,920.08	25.0
3	6.0	906.85	59,781.46	39.3
4	4.0	880.94	25,725.64	20.9
5	10.0	644.22	35,931.62	31.1
6	4.0	610.44	20,238.32	20.2
7	10.0	673.40	28,692.28	24.3
8	4.0	1,071.75	33,225.55	22.1
9	7.0	743.82	28,190.03	27.9
10	4.0	901.78	31,556.15	21.8
11	4.0	906.59	37,448.91	23.8
12	4.0	982.30	33,346.92	30.5
Mean	5.83	798.60	32,771.02	26.18
S.D.	2.52	189.45	10,074.92	5.47
% C.V.	43.14	23.72	30.74	20.90
Median	4.00	873.64	32,390.85	24.65
Maximum	10.00	1,071.75	59,781.46	39.30
Minimum	4.00	394.72	20,238.32	20.20
Max - Min	6.00	677.03	39,543.14	19.10

Table 4 Pharmacokinetic parameters of meloxicam after a single oral dose of 7.5mg of the reference .

Subject No.	T_{max} (h)	C_{max} (ng/ml)	AUC (ng×h/ml)	$T_{1/2}$ (h)
1	6.0	661.62	29,471.07	25.4
2	5.0	511.53	28,945.17	26.4
3	4.0	1,143.91	74,722.28	42.8
4	10.0	672.82	28,168.64	21.4
5	10.0	691.06	31,395.00	24.9
6	5.0	641.31	21,374.57	19.7
7	2.0	1,219.97	34,424.25	24.3
8	4.0	1,101.01	35,244.64	22.9
9	5.0	739.93	28,684.29	27.1
10	4.0	761.72	26,113.33	23.3
11	4.0	1,156.41	41,074.69	25.6
12	3.0	853.53	29,657.20	19.4
Mean	5.17	846.24	34,106.26	25.27
S.D.	2.48	243.12	13,703.09	6.05
% C.V.	48.00	28.73	40.18	23.96
Median	4.50	750.82	29,564.14	24.60
Maximum	10.00	1,219.97	74,722.28	42.80
Minimum	2.00	511.53	21,374.57	19.40
Max - Min	8.00	708.44	53,347.71	23.40

Table 5 Comparison of meloxicam pharmacokinetic parameters following oral administration of the Reference and the Test.

Parameters	Test	Reference
C_{max} (ng/ml)	798.60 ± 189.45	846.24 ± 243.12
T_{max} (median,h)	4.00	4.50
$AUC_{0-\infty}$ (ng×h/ml)	32,771.02 ± 10,074.92	34,106.26 ± 13,703.09
$t_{1/2}$ (h)	26.18 ± 5.47	25.27 ± 6.05
Frel. C_{max} (T/R, %)	97.64 ± 23.19	
Frel. AUC (T/R, %)	98.57 ± 15.44	

Table 6 The means and 90% CI of ratios Test/Reference of $AUC_{0-\infty}$ and C_{max} and the 90% CI of the difference in T_{max}.

Pharmacokinetic parameters	Mean	90% CI	Acceptable range
$AUC_{0-\infty}$ (Test®/Reference®)	0.97	0.90-1.06	0.80-1.25
C_{max} (Test®/Reference®)	0.95	0.84-1.08	0.80-1.25
T_{max} (Test®- Reference®)	0.67	-1.09 -2.42	± 1.03

References

1. Goei T HS, Lund B, Distel MR, Bluhmki E. A double-blind, randomized trial to compare meloxicam 15 mg with diclofenac 100 mg in the treatment of osteoarthritis of the knee. *Osteoarthritis Cartilage* 1997;5(4):283-288.
2. Yocum D, Fleischmann R, Dalgin P, Caldwell J, Hall D, Roszko P. Safety and efficacy of meloxicam in the treatment of osteoarthritis: a-12 week, double-blind, multiple-dose, placebo-controlled trial. The Meloxicam Osteoarthritis Investigators. *Arch Intern Med* 2000;160 (19):2947-2954.
3. Noble S, Balfour JA. Meloxicam. *Drugs* 1996;51(3):424-430.
4. Mitchell JA, Akarasereenont P, Thiemermann C, Flower RJ, Vane JR. Selectivity of nonsteroidal anti-inflammatory drugs as inhibitors of constitutive and inducible cyclooxygenase. *Proc Natl Acad Sci USA* 1993;90 (24):1166-1169.
5. Engelhardt G, Bogel R, Schnitzler C, Utzmann R. Meloxicam: influence on arachidonic acid metabolism. Part II. In vivo findings. *Biochem Pharmacol* 1996;51(1):29-38.
6. Distel M, Mueller C, Bluhmki E, Fries J. Safety of meloxicam: a global analysis of clinical trials. *Br J Rheumatol* 1996;35 Suppl 1:68-77.

7. Turck D, Roth W, Busch U. A review of the clinical pharmacokinetics of meloxicam. *Br J Rheumatol* 1996;35 Suppl 1:13-16.
8. Davies NM, Skjodt NM. Clinical pharmacokinetics of meloxicam. A cyclo-oxygenase-2 preferential nonsteroidal anti-inflammatory drug. *Clin Pharmacokinet* 1999;36(2):115-126.
9. Velpandian T, Jaiswal J, Bhardwaj RK, Gupta SK. Development and validation of a new high-performance liquid chromatographic estimation method of meloxicam in biological samples. *J Chromatogr B Biomed Sci Appl* 2000; 738 (2):431-436
10. Sauter R, Steinijans VW, Diletti E, Bohm A, Schulz HU. Presentation of results from bioequivalence studies. *Int J Clin Pharmacol Ther Toxicol* 1992;30(7):233-256.
11. Schuirmann DJ. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. *J Pharmacokinet Biopharm* 1987;15(6):657-680.
12. Thai FDA.: Criteria and Guideline for the Bioequivalence Study of Generic Drugs. 2000.
13. Diletti E, Hauschke D, Steinijans VW. Sample size determination for bioequivalence assessment by means of confidence intervals. *Int J Clin Pharmacol Ther Toxicol* 1991;29(1):1-8.