

## Original Research Article

# Bioequivalence evaluation of new microparticulate capsule and marketed tablet dosage forms of lornoxicam in healthy volunteers

Pervaiz Akhtar Shah<sup>1</sup>, Sajid Bashir<sup>2</sup>, Muhammad Ahsan<sup>1\*</sup>, Nasir Abbas<sup>1</sup>, Muhammad Zubair Malik<sup>2</sup> and Hafiz Muhammad Irfan Nazar<sup>1</sup>

<sup>1</sup>University College of Pharmacy, University of the Punjab, Lahore, Pakistan 54000, <sup>2</sup>Faculty of Pharmacy, University of Sargodha, Sargodha, Pakistan

\*For correspondence: **Email:** ahsanshareef105@hotmail.com; **Tel:** +92 333 4060054

Received: 19 November 2015

Revised accepted: 20 March 2016

### Abstract

**Purpose:** To compare oral bioavailability and pharmacokinetic parameters of different lornoxicam formulations and to assess similarity in plasma level profiles by statistical techniques.

**Methods:** An open-label, two-period crossover trial was followed in 24 healthy Pakistani volunteers (22 males, 2 females). Each participant received a single dose of lornoxicam controlled release (CR) microparticles and two doses (morning and evening) of conventional lornoxicam immediate release (IR) tablet formulation. The microparticles were prepared by spray drying method. The formulations were administered again in an alternate manner after a washout period of one week. Pharmacokinetic parameters were determined by Kinetica 4.0 software using plasma concentration-time data. Moreover, data were statistically analyzed at 90 % confidence interval (CI) and Schuirmann's two one-sided t-test procedure.

**Results:** Peak plasma concentration ( $C_{max}$ ) was 20.2 % lower for CR formulation compared to IR formulation (270.90 ng/ml vs 339.44 ng/ml, respectively) while time taken to attain  $C_{max}$  ( $t_{max}$ ) was 5.25 and 2.08 h, respectively. Area under the plasma drug level versus time (AUC) curve was comparable for both CR and IR formulations. The 90 % confidence interval (CI) values computed for  $C_{max}$ ,  $AUC_{0-24}$ , and  $AUC_{0-\infty}$ , after log transformation, were 87.21, 108.51 and 102.74 %, respectively, and were within pre-defined bioequivalence range (80 - 125 %).

**Conclusion:** The findings suggest that CR formulation of lornoxicam did not change the overall pharmacokinetic properties of lornoxicam in terms of extent and rate of lornoxicam absorption.

**Keywords:** Analgesic, Microparticles, Controlled release, Lornoxicam, NSAIDs, Pharmacokinetics

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, International Pharmaceutical Abstract, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

## INTRODUCTION

Lornoxicam is a short-acting non-steroidal anti-inflammatory drug (NSAID) which belongs to the oxamicam group. It decreases prostaglandin production by reducing cyclo-oxygenase (COX) activity. It is successfully being used in clinical settings for alleviating the symptoms of

rheumatoid arthritis, osteoarthritis, acute sciatica and ankylosing spondylitis. Moreover, it has demonstrated comparable analgesic efficacy to morphine for relieving postoperative pain [3]. Due to short half-life of 3 to 5 h, the drug is highly feasible to be formulated as controlled release formulation [1,2].

Patient compliance to prescribed regimen of NSAIDs in chronic disorders (rheumatoid arthritis & ankylosing spondylitis) is generally poor [4]. The reasons for low compliance of NSAIDs include temporary relief of symptoms and gastric irritation associated with frequent intake of NSAIDs. Substantial variation in compliance has been observed in patients taking NSAIDs resulting in poor drug efficacy and safety [5].

Previous studies have revealed that switching from IR to CR formulations reduces the side effects as well as improves outcomes of therapy [6-8]. However, no report demonstrates in-vivo comparative pharmacokinetic analysis for any NSAID drug by formulating different release formulations. Therefore, an attempt was made to compare pharmacokinetic parameters ( $t_{max}$ ,  $C_{max}$ , AUC) of newly formulated CR lornoxicam microparticles with IR tablet counterpart.

## EXPERIMENTAL

### Preparation of lornoxicam-loaded microparticles

Lornoxicam microencapsulation was achieved by spray drying according to the polymer blend concentrations specified in table 1. We dissolved weighed quantities of polymers in acetone and ethanol mixture used in the ratio of 40:60. Hydroxy propyl methyl cellulose (HPMC) 15 cps was dissolved first in organic mixture followed by Eudragit L100 and clear solution was obtained. Then drug was added into polymer solution with continuous stirring for 45 - 60 min. Finally, drug polymer dispersion so prepared was spray-dried using Lab scale spray dryer with a nozzle of 2 mm diameter (YC 1500, Shangai, China). The dried particles enclosing core material were collected in the bottom of dryer [9]. The parameters set for spray drying were as follows: Inlet air temperature, 80 – 90 °C; inlet air volume, 200 - 300m<sup>3</sup>/h; spray rate, 8-10gm/min; product temperature, 40 - 50 °C; and atomizing air pressure; 1 bar.

### Characterization of microparticles

The formulated microcapsules were characterized for morphology, encapsulation efficiency, percent drug loading and *in-vitro* dissolution studies as described by Shah *et al* [9].

### Subjects' inclusion and exclusion criteria

Twenty four healthy subjects {age, 21.69 ± 2.32 years (range, 17.18 - 26 years); weight, 70.14 ± 7.98 kg (range, 60.12 - 89 kg); height, 180.25 ± 7.32 cm (range, 168.2 - 190.93 cm); and BMI, 21.59 ± 2.04 kg/m<sup>2</sup> (range, 18.73 - 24.82 kg/m<sup>2</sup>)} were selected for the study. All the subjects were examined to determine their health status based on medical history, physical examination, vital signs, and laboratory tests (hematology, biochemistry, hepatic function, and urinalysis). Subjects who had a history of gastric ulcers and those receiving oral corticosteroids were not included in the study. Written informed consent was taken from each participant before the commencement of study. They were free to withdraw from the study at any time. Physical examination took into account normal laboratory tests conducted before, during and after study.

### Study design

The present open label, randomized, two-way crossover, comparative bioavailability study was performed according to the principles of Helsinki Declaration (WMA) [10] and Good Clinical Practices (GCP) [11]. The study protocols were approved by the ethical committee of Human Research Review Board of University College of Pharmacy, University of the Punjab, Lahore, and the guidelines of Helsinki Declaration were followed. All the volunteers were fasted overnight at least 10 h prior to dosing with water as desired. Subjects received single dose of CR formulation and two doses of IR formulation followed by a washout period of 7 days and administration of alternate formulations.

**Table 1:** Formulation of microparticles by spray drying

Formulation code	Drug (mg)	Drug : polymer ratio	Eudragit L-100 (mg)	HPMC 15cps (mg)
AF-1	300	1:1	300	0
AF-2	300	1:1	0	300
AF-3	300	1:1	150	150
AF-4	300	1:1.5	225	225
AF-5	300	1:2	300	300
AF-6	300	1:2.5	375	375
AF-7	300	1:3	450	450

Lornoxicam IR formulation was administered twice after interval of 12 h in each period. None of the participants was on medication of any sort which may interfere with the release and detection of drugs under study. Standard meal was provided after 4 h of drug administration.

### Blood sampling and processing

At predetermined time interval, 5ml of blood was withdrawn at 0, 0.5, 1, 2, 3, 5, 8, 10, 12, 13, 14, 15, 18, 20 and 24 h by phlebotomists. Disposable 5 ml syringes were used to collect blood samples into heparin containing centrifuge tubes. The samples, immediate after collection, were centrifuged at 4000 rpm for 10 min to separate plasma which was carefully conveyed to eppendorf tubes using micropipette. The prepared plasma samples were kept at  $-20^{\circ}\text{C}$  until lornoxicam concentration was estimated by bio-analytical HPLC method.

### Determination of drug in blood samples

Lornoxicam levels in plasma samples were determined by specific and sensitive HPLC method. The mobile phase used was mixture of phosphate buffer (pH 4.5, adjusted with orthophosphoric acid) and acetonitrile (45:55, v/v). Freshly prepared mobile phase was degassed by vacuum filtration, sonicated and pumped with a flow rate of 1 ml/min. After adding 0.5 ml of methanol, 0.5 ml of trichloroacetic acid and 0.5 ml of internal standard solution (piroxicam, 20  $\mu\text{g/ml}$ ), plasma samples were vortex mixed for 3 min and then centrifuged at 2500 rpm for 5min. Then, samples were placed on extrelut-1 columns and dichloromethane (10 ml) was used to elute lornoxicam. The eluate was dehydrated under nitrogen stream ( $35^{\circ}\text{C}$ ) followed by reconstitution with 400  $\mu\text{l}$  of mobile phase. Finally, after centrifugation at 100 rpm, 50  $\mu\text{l}$  supernatant was injected into chromatographic system.

HPLC system consisted of hypersil ODS column (150  $\times$  4.5 i.d, 5 $\mu\text{m}$  particle size, Agilent) for carrying out separation. Class GC software was connected with variable wavelength UV detector for data processing and chromatographic integration. An isocratic pump (LC-10 ATVP, Shimadzu Corporation, Japan) was used for passing the mobile phase through the column.

### Tolerability assessment

Physical assessment and vital signs (pulse rate, blood pressure and body temperature) were monitored for each enrolled subject before administration of study drugs and during the

blood sampling. Subjects were continuously examined by the physicians throughout the study for incidence of adverse effects.

### Pharmacokinetic and statistical analyses

The parameters included  $C_{\text{max}}$ ,  $\text{AUC}_{0-24}$ ,  $\text{AUC}_{0-\infty}$ ,  $t_{\text{max}}$ , half-life ( $t_{1/2}$ ), mean residence time (MRT), and elimination rate constant ( $k_e$ ) were determined by Kinetica 4.0 (ThermoFisher Scientific, PK/PD software, USA) for each subject.  $T_{\text{max}}$  and  $C_{\text{max}}$  were also estimated directly from the constructed plot of plasma concentration- time profiles [12,13].

Significant difference in parameters was considered at  $p < 0.05$ . Analysis of variance (ANOVA) for a crossover ( $2 \times 2$ ) study design was calculated by SPSS software (IBM Statistics 21, USA). The formulations were considered comparable if 90 % CI for the geometric mean ratios (test: reference) of ln-transformed  $C_{\text{max}}$ ,  $\text{AUC}_{0-t}$ , and  $\text{AUC}_{0-\infty}$  rest between 0.80 and 1.25 - a stipulated criterion of US Food and Drug administration [14,15]. Average bioequivalence was further confirmed between test and reference formulations by applying Schuirmann two 1-sided tests [16].

## RESULTS

### Characteristics of microparticles

The microparticles were ellipsoidal in shape with surface morphology clearly showing presence of drug particles (Figure 1). The incorporation efficiency increased from 56.48 %  $\pm$  2.21 to 83.04 %  $\pm$  1.22 with the increase in the polymer contents. Percent loading was in the range of 42.88 %  $\pm$  1.4 to 68.35 %  $\pm$  1.13 and was independent of contents of polymer blend.

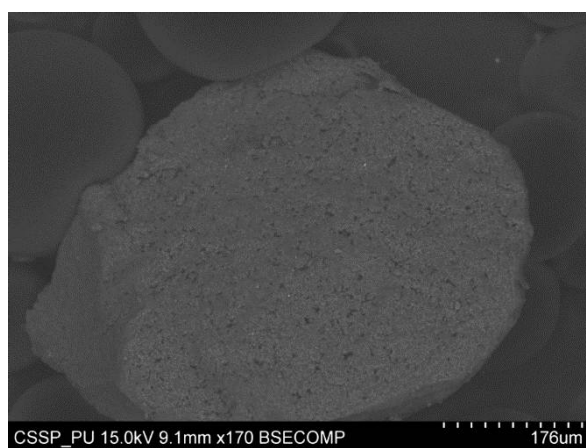
The release results showed that burst release was reduced in microparticles containing higher contents of polymers. This was due to decrease in surface associated drug. Microparticle formulations containing drug polymer blend in the ratio of 1:1 and 1:1.5 released 97.55  $\pm$  3.33 % and 92.6  $\pm$  3.92 % of drug, respectively at the end of 20 h without subsequent release. Similarly, formulation AF-6 liberated maximum drug amount of 96.16  $\pm$  3.88 % on the time point of 20 h. Only formulation AF-7 (1:3) sharply demonstrated drug release of 97.22  $\pm$  3.22 % after 24 h that was a typical sustained release pattern. Taken together, the release pattern clearly showed that rate of drug release but not the extent was decreased on increasing amounts of polymer matrices. Out of seven formulations,

microcapsules of one formulation (AF-7) were selected for *in-vivo* study based on promising results in terms of encapsulation efficiency and release studies. Moreover, the optimized formulation demonstrated near zero order kinetics.

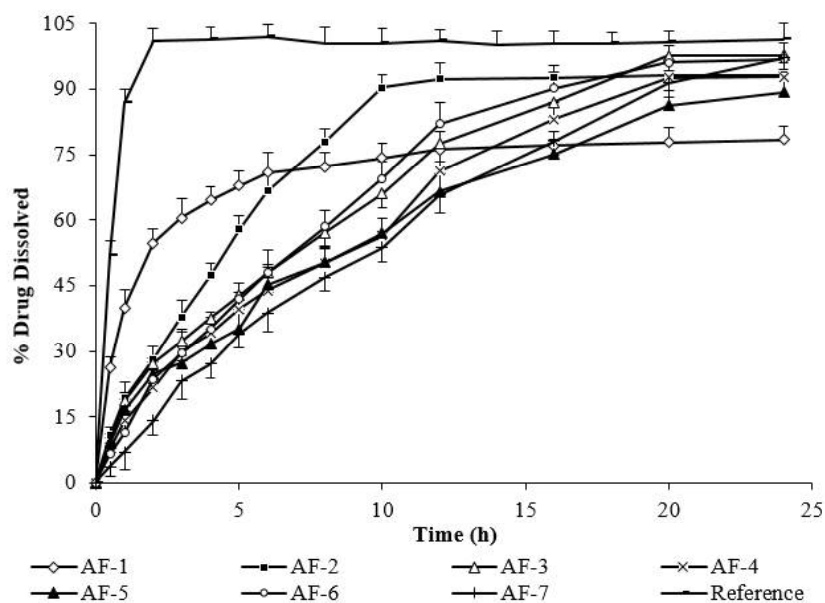
Finally, microparticles (AF-7) equivalent to 16 mg of lornoxicam were filled in 0 size capsules which acted as test formulation. Whilst, reference formulation was immediate release film coated tablets of lornoxicam (8 mg). The *in-vitro* release profiles of test and reference formulations are shown in Figure 2.

**Table 2:** Physical characteristics of formulated microparticles

Formulation	Incorporation efficiency (%)	Drug loading (%)	Recovery (%)
AF-1	56.48 ± 2.21	28.25 ± 0.2	62.29 ± 1.68
AF-2	65.52 ± 1.68	32.75 ± 0.2	53.27 ± 2.28
AF-3	61.04 ± 1.7	30.5 ± 0.1	55.89 ± 1.07
AF-4	68.1 ± 1.4	27.25 ± 0.3	64.16 ± 0.92
AF-5	67.59 ± 1.3	22.5 ± 0.4	42.88 ± 1.4
AF-6	74.27 ± 1.15	21.25 ± 0.1	59.34 ± 1.8
AF-7	83.04 ± 1.22	20.75 ± 0.2	68.35 ± 1.13



**Figure 1:** Scanning electron microscopy image of AF-7 microparticles



**Figure 2:** *In-vitro* release profiles of lornoxicam Reference (IR) and test (CR) formulations

### Validation parameters of developed HPLC method

Intra- and inter-day precision and recoveries (absolute and relative) of lornoxicam in human plasma are shown in Table 2.

### Pharmacokinetic properties

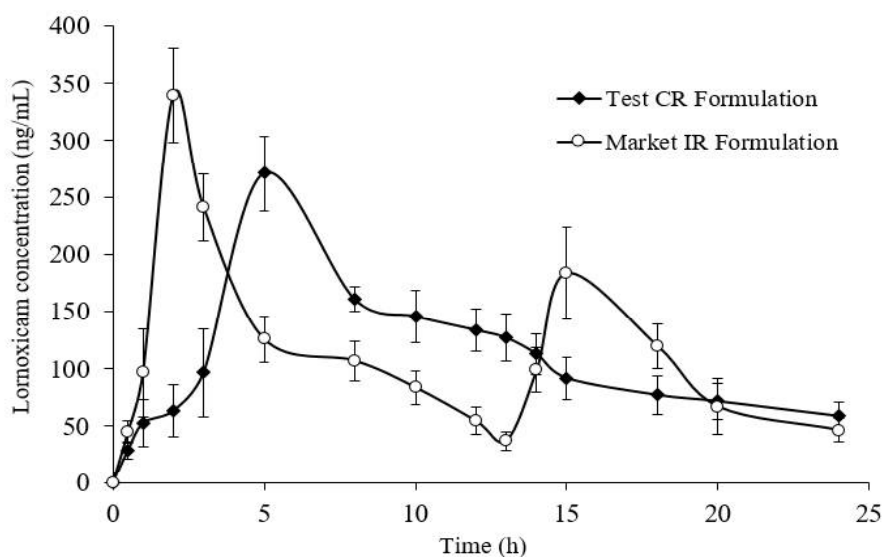
The plasma profiles (mean  $\pm$  SD) of test and reference formulations of lornoxicam were presented in Figure 3. The main pharmacokinetic parameters calculated were summarized in table 3. The mean ( $\pm$  SD)  $C_{max}$  values for test and reference formulations were 270.90  $\pm$  33 ng/mL and 339.44  $\pm$  41.39 ng/mL ( $p < 0.05$ ),

respectively. The mean  $AUC_{0-t}$  values in the test and reference formulations were 2643.03  $\pm$  35.03 and 2456.62  $\pm$  25.39 ng.h/mL, and the mean  $AUC_{0-\infty}$  were 2740.89  $\pm$  33.03 and 2640.98  $\pm$  27.91 ng.h/mL. The median (range)  $t_{max}$  was 5.3 (5.20 $\pm$ 8.30) and 1.93 (1.60–2.30) hours ( $p < 0.05$ ). The  $k_e$  was 0.115 (0.02) and 0.157 (0.02)  $h^{-1}$ , and the  $t_{1/2}$  was 6.13 (0.86) and 4.46 (0.45) hours ( $p < 0.05$ ). ANOVA shows no effect of sequence or period on the pharmacokinetic parameters. Surprisingly, the  $C_{max}$  for first dose of lornoxicam IR formulation was higher than that of second dose. This observation might relate to the influence of circadian rhythms on the kinetics of drugs leading to faster absorption in the morning compared with the evening [17].

**Table 2:** Validation results of lornoxicam method development (Values were mean  $\pm$  SD)

Conc. spiked ( $\mu$ g/ml)	Intra-day (n=9)*		Inter-day (n=9)*		Recovery	
	Amount quantitated ( $\mu$ g/ml)	RSD %	Amount quantitated ( $\mu$ g/ml)	RSD %	Absolute	Relative
0.2	0.19 $\pm$ 0.09	1.5	0.19 $\pm$ 0.06	4.9	89.7 $\pm$ 4.5	96.5 $\pm$ 5.37
3	2.99 $\pm$ 0.06	2.2	2.93 $\pm$ 0.03	2	98.4 $\pm$ 3.8	99.6 $\pm$ 2.14
4	4.00 $\pm$ 0.13	3.5	3.89 $\pm$ 0.08	0.7	100.4 $\pm$ 4.0	100 $\pm$ 3.1

RSD % = relative standard deviation; \*Mean of 3 concentrations and 3 replicates of each concentration, respectively



**Figure 3:** Plasma concentration-time profiles of test and reference formulations

**Table 3:** Pharmacokinetic parameters of test and reference formulations (mean  $\pm$  SD)

Parameter	Test (CR)	Reference (IR)	P-value
$C_{max}$ , ng/ml	270.90 $\pm$ 33	339.44 $\pm$ 41.39	0.05
$T_{max}$ , h	5.25 $\pm$ 0.87	2.08 $\pm$ 0.29	0.05
$AUC_{0-24}$ , ng.h/ml	2643.03 $\pm$ 35.03	2414.5 $\pm$ 16.37	NS
$AUC_{0-\infty}$ , ng.h/ml	2756.4 $\pm$ 29.3	2682.8 $\pm$ 21.8	NS
$t_{1/2}$ , h	6.13 $\pm$ 0.86	4.46 $\pm$ 0.45	0.05
$k_e$ , $h^{-1}$	0.115 $\pm$ 0.02	0.157 $\pm$ 0.03	NS
MRT, h	14.57 $\pm$ 1.42	12.51 $\pm$ 0.54	NS

'NS' means 'not significant'

**Table 4:** 90% CI and ratio for test and reference formulations of Lornoxicam

Parameter	Test : Reference ratio	90% CI
Ln C <sub>max</sub> , ng/ml	87.21	81.91 - 92.51
Ln AUC <sub>0-t</sub> , ng.h/ml	108.51	97.70 - 119.33
Ln AUC <sub>0-∞</sub> , ng.h/ml	102.74	89.50 - 115.98

Ln= natural logarithm

**Table 5:** Schuirmann two 1-sided t-tests for comparative analysis of CR and IR lornoxicam formulations\*

Parameter	TL	TU	t (0.05-22 df)*
C <sub>max</sub> , ng/ml	21.47	62.03	1.7171
AUC <sub>0-24</sub> , ng.h/ml	74.64	136.5	1.7171
AUC <sub>0-∞</sub> , ng.h/ml	4.88	142.32	1.7171

T- t statistic; TL-lower T; TU-upper T; df-degrees of freedom; \*Criteria: If TL ≥ T (0.05–22 df) and TU ≥ T (0.05–22 df), then bioequivalence can be deduced. If TL ≤ T (0.05–22 df) or TU ≤ T (0.05–22 df), then bioequivalence cannot be established between formulations

### Comparative pharmacokinetic profile

The analysis of 90 %CI of C<sub>max</sub>, AUC<sub>0-t</sub>, and AUC<sub>0-∞</sub> values for the test and reference formulations were 81.21 to 92.51 %, 97.70 to 119.33 %, and 89.50 to 115.98 %, respectively and were listed in Table 4. The values were well within acceptable bioequivalence criteria (80 - 125 %). The relative bioavailability of lornoxicam was 107.62 %. The findings of Schuirmann test also supported bioequivalence as shown in Table 5.

### Tolerability

Mild gastrointestinal problem (nausea) occurred in couple of volunteers receiving IR tablet during the second period of the study. Literature survey revealed that this mild side effect was associated with Lornoxicam salt (chlortenoxicam). The problem was immediately overcome by appropriate action of clinician and the subject successfully completed the study. CR formulation was found to lessen the side effects (nausea, diarrhea) of the salt as no active complaint was noticed from participants taking CR formulations. No other treatment related adverse event was recorded throughout the study.

### DISCUSSION

This study demonstrated the bioequivalence of two oral formulations of lornoxicam - a newly

developed CR microcapsule formulation and a marketed IR tablet - in healthy Pakistani volunteers. AUC<sub>0-t</sub> and AUC<sub>0-∞</sub> are indicators of total amount of absorption, C<sub>max</sub> reflects both extent and rate of absorption, and t<sub>max</sub> shows rate of absorption and elimination [18,19]. The C<sub>max</sub> and t<sub>max</sub> of the marketed lornoxicam tablet (reference) were comparable with previous reports [20,21]. The comparable C<sub>max</sub>, AUC<sub>0-24</sub> and AUC<sub>0-∞</sub> for lornoxicam CR and IR formulations showed that both formulations had similar apparent oral clearance. As expected, it was observed that transforming the dosage forms did not change total absorption of lornoxicam even with dose administered once. Moreover, a significant drop of 20.2 % in the mean value of C<sub>max</sub> was observed for lornoxicam CR formulation than for lornoxicam IR (270.90 ± 33 ng/mL and 339.44 ± 41 ng/mL, respectively). This pattern clearly indicates controlled release of lornoxicam from microparticles. Furthermore, these findings proposed that, at steady state, lornoxicam CR and IR formulations will demonstrate comparable bioavailability when administered at the same daily dose (16 mg/day). A considerable difference was seen in the values of t<sub>1/2</sub> and k<sub>e</sub> between the test and reference formulations, further corroborating the profound effect on parameters due to modification in the formulation.

The time to reach C<sub>max</sub> (t<sub>max</sub>) was 5.30 h for lornoxicam CR compared with 2.0 h for lornoxicam IR. In future, such delay in action can be avoided by incorporation of small IR fraction in microparticle dosage form. The longer elimination half-life of single CR dose compared with twice-dose of IR formulation (6.13 ± 0.86 h vs 4.46 ± 0.45 h, respectively) suggested that controlled release formulation is suitable for once daily dosing.

The geometric mean of lornoxicam CR/lornoxicam IR ratio for C<sub>max</sub>, AUC<sub>0-t</sub> and AUC<sub>0-∞</sub> were 87.21, 108.51 and 102.74 (90 % CIs 81.91 ± 92.51 %, 97.7 ± 119.3 % and 89.5 ± 115.98 % respectively), which were within bioequivalence pre-defined range (80 %–125 %) with respect to total amount of lornoxicam.

The study has some limitations as the pharmacokinetic data were obtained from healthy Pakistani volunteers so the findings of the study cannot be generalized to all patient populations. Furthermore, serum concentrations of 5-hydroxylornoxicam were not measured due to lack of clinical significance. Small sample size and open-label design were also study limitations.

## CONCLUSION

The findings of this non-replicated crossover study demonstrates that test lornoxicam microparticulate (CR capsules, OD) and reference (IR tablet, BD) formulations at the same molar dose of 16 mg possess comparable pharmacokinetic properties. The good controlled release properties of the microparticle formulation produced by spray drying recommend this approach for the design of once-daily administration of the drug to achieve prolonged analgesia in chronic painful disorders.

## ACKNOWLEDGEMENT

The authors are thankful to the Director, Bioequivalence Centre of University of Veterinary and Animal Sciences for financial and moral support, as well as to Ms. Wilshire Pharmaceuticals for providing facilities for HPLC analysis of plasma samples.

## REFERENCES

- Kidd B, Frenzel W. A multicenter, randomized, double blind study comparing lornoxicam with diclofenac in osteoarthritis. *J Rheumatol*. 1996; 23(9): 1605-1611.
- Ahmed MO, Al-Badr AA. Lornoxicam. *Profiles Drug Subst Excip Relat Methodol*. 2011; 36: 205-239.
- Rosenow DE, Albrechtsen M, Stolke D. A comparison of patient-controlled analgesia with lornoxicam versus morphine in patients undergoing lumbar disk surgery. *Anesth Analg*. 1998; 86(5): 1045-1050.
- de Klerk E, van der Heijde D, Landewé R, van der Tempel H, Urquhart J, van der Linden S. Patient compliance in rheumatoid arthritis, polymyalgia rheumatica, and gout. *J Rheumatol*. 2003; 30(1): 44-54.
- de Klerk E, Van der Linden SJ. Compliance monitoring of NSAID drug therapy in ankylosing spondylitis, experiences with an electronic monitoring device. *Br J Rheumatol*. 1996; 35(1): 60-65.
- Doughty J, Baker GA, Jacoby A, Lavaud V. Compliance and satisfaction with switching from an immediate-release to sustained-release formulation of valproate in people with epilepsy. *Epilepsy Behav*. 2003; 4(6): 710-716.
- Olver JS, Burrows GD, Norman TR. The treatment of depression with different formulations of venlafaxine: a comparative analysis. *Hum Psychopharmacol*. 2004; 19(1): 9-16.
- Figuroa C, Brecher M, Hamer-Maansson JE, Winter H. Pharmacokinetic profiles of extended release quetiapine fumarate compared with quetiapine immediate release. *Prog Neuropsychopharmacol Biol Psychiatry*. 2009; 33(2): 199-204.
- Shah PA, Bashir S, Tariq I, Hafiz MA. Fabrication of Lornoxicam Loaded Eudragit L-100 Microcapsules by Spray Drying. *Lat Am J Pharm*. 2014; 33(5): 828-34.
- World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. [cited 2014 March 9]. Available from: <http://www.wma.net/en/30publications/10policies/b3/ind ex.html.pdf>.
- European Medicines Agency. ICH Topic E 6 (R1): Guideline for Good Clinical Practice. Step 5. Note for guidance on good clinical practice (CPMP/ICH/135/95). [cited 2014 22 March]. Available from: <http://ethikkommission.meduniwien.ac.at/fileadmin/ethik/ media/dokumente/rechtsgrundlagen/GCP.pdf>.
- Williams RL, Chen M-L, Hauck WW. Equivalence approaches. *Clin Pharmacol Ther*. 2002; 72(3): 229-237.
- Rowland M, Tozer TN. *Clinical Pharmacokinetics: Concepts and Applications*. 3rd Edition ed: Lippincott Williams & Wilkins; 1995.
- U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for Industry. Statistical Approaches to Establishing Bioequivalence. [cited 2014 Feb 2014]. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070244.pdf>.
- Bukhari NI, Zafar A, Bashir MA, Mirza AA. Bioequivalence Assessment of Two Enteric-Coated Aspirin Brands, Nu-seals® and Loprin®, after a Single Oral Dose of 150mg in Healthy Male Adults. *Therapie*. 2005; 60(2): 167-73.
- Schuurmann DJ. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. *J Pharmacokinetic Biopharm*. 1987; 15(6): 657-680.
- Baraldo M. The influence of circadian rhythms on the kinetics of drugs in humans. *Expert Opin Drug Metab Toxicol*. 2008; 4(2): 175-192.
- Ahmad M, Pervaiz F. Comparative bioavailability and pharmacokinetics of investigational enteric- and film-coated formulations of flurbiprofen 100-mg tablets: A single-dose, randomized, open-label, two-period, two-way crossover study in healthy Pakistani male volunteers. *Clin Ther*. 2010; 32(3): 607-613.
- Wu H, Liu M, Wang S, Feng W, Yao W, Zhao H, Wei W. Pharmacokinetic properties and bioequivalence of two compound formulations of 1500 mg ampicillin (1167 mg)/probenecid (333 mg): A randomized-sequence, single-dose, open-label, two-period crossover study in healthy Chinese male volunteers. *Clin Ther*. 2010; 32(3): 597-606.
- Balfour JA, Fitton A, Barradell LB. Lornoxicam. A review of its pharmacology and therapeutic potential in the management of painful and inflammatory conditions. *Drugs*. 1996; 51(4): 639-657.
- Skjoldt NM, Davies NM. Clinical pharmacokinetics of lornoxicam. *Clin pharmacokinetic*. 1998; 34(6): 421-428