



Received on 23 March 2014; received in revised form, 13 June 2014; accepted, 02 August 2014; published 01 October 2014

DEVELOPMENT OF ECONOMIC TRANSDERMAL PATCHES CONTAINING LORNOXICAM FOR TREATMENT OF ACUTE AND CHRONIC INFLAMMATORY MODELS IN ALBINO RATS (A PRECLINICAL STUDY)

Nagla Ahmed El Nabarawy ^{*1}, Rehab A. Abd Elmonem ² and Hadel A. Abo Enin ^{3,4}

National Egyptian Center of Environmental and Toxicological Research (NECTER) ¹, Cairo University, Cairo, Egypt.

Department of Pharmaceutics and Industrial Pharmacy ², College of Pharmacy, MUST University, 6 October City, Giza, Egypt.

Department of Pharmaceutics ³, National Organization of Drug Control and Research (NODCAR), Giza, Egypt.

Department of Pharmaceutics ⁴, Taif University, Taif, Saudi Arabia.

Keywords:

Lornoxicam, Transdermal patch, Anti-inflammatory activity, Rat paw edema, Granuloma pouch

Correspondence to Author:

Nagla Ahmed El Nabarawy

National Egyptian Center of Environmental and Toxicological Research (NECTER), Cairo University, Cairo, Egypt.

E-mail: drrahoba@yahoo.com

ABSTRACT: Objective: To formulate economic transdermal patch of lornoxicam (LX) and to study its anti-inflammatory activity on acute and chronic inflammatory in rat models. **Method:** Three LX transdermal patches (F1, F2, and F3) consist of Eudragit RL-100, and RS-100 in three different ratios (1:2, 1:1 and 2:1) were prepared respectively by the solvent evaporation technique. All formulations contain diethyl phthalate as a plasticizer. The physicochemical compatibility of the drug and the polymers was studied by differential scanning calorimetry. The prepared LX transdermal patches were evaluated for their drug content, patch thickness, folding endurance, surface pH, and in vitro drug permeation. The anti-inflammatory activity of LX transdermal patch was determined using two experimental animal designs, one for acute inflammation (rat paw edema) and the other for chronic inflammation (granuloma pouch) on eighty adult albino rats. The results obtained were statistically analyzed. **Results:** The data showed physicochemical compatibility between the drug and the polymers used. The LX patches (F1, F2, and F3) prepared were uniform thickness, drug content, and the pH of the LX patch was found to be 6.5. Increasing the ratio of the Eudragit[®] RL-100 polymer to eudragit RS 100 (F3) showed a corresponding increase in the folding endurance of patches. Diethyl phthalate led to increasing elasticity for the patches. F3 showed higher drug permeation than F2 and F1. Edema (anti-inflammatory effect) was significantly decreased in group V followed by group IV then by group III in case of the two animal experimental designs. Group V received LX transdermal patch (F3). **Conclusion:** The present study showed that the prepared economic lornoxicam transdermal patch has good properties with high efficiency as an anti-inflammatory drug on acute and chronic inflammatory models.

INTRODUCTION: Inflammation is a reaction of tissue to injury, expressed by five cardinal points: pain, swelling, redness, heat, and loss of function.

Inflammation and pain-relieving drugs are the most commonly used drugs worldwide either through prescription or as over the counter medication.

None steroidal anti-inflammatory drugs (NSAIDs) have analgesic, antipyretic, and anti-inflammatory effects. Lornoxicam (LX) is a new NSAID belonging to the oxicam class. As with other NSAIDs, the principle mechanism of action of LX relates to the inhibition of cyclooxygenase (COX), the key enzyme of the arachidonic acid pathway,

<p>QUICK RESPONSE CODE</p> 	<p>DOI: 10.13040/IJPSR.0975-8232.5(10).4195-02</p> <hr/> <p>This article can be accessed online on www.ijpsr.com</p> <hr/> <p>DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.5(10).4195-02</p>
---	---

resulting in the inhibition of prostaglandin (PG) synthesis¹⁻³. It differs from other oxicam compounds in its potent inhibition of (PGs) biosynthesis a property that explains the pronounced efficacy of the drug. (PGs) are involved in all phases of inflammatory events including fever, pain reaction, and physiological functions like intestinal motility, vascular tone, and gastric acid secretion⁴. LX is distinguished from established oxicams by its short plasma half-life (3-5h) and good gastrointestinal tolerability^{5,6}.

Thus, in rat polymorphonuclear leukocytes, LX potently inhibited the formation of PGD₂ *in-vitro*¹. *In-vivo* LX exhibited anti-inflammatory activities in acute (carrageenan-induced paw edema) as well as in chronic inflammation (adjuvant-induced arthritis) that were more potently than the ones of other oxicams⁵. Clinical investigations have established LX as a potent analgesic with excellent anti-inflammatory properties in a range of painful or inflammatory conditions, including postoperative pain and rheumatoid arthritis (RA)^{7,8}. LX had protective effects on myocardial infarction in rats under ischemia and ischemia-reperfusion⁹.

An experimental study in mice has demonstrated its protective effects against herpetic stromal keratitis (HSK) through down-regulation of nuclear factor Kappa B (NF-Kappa B) activation¹⁰. It is effectively relieved the symptoms of osteoarthritis, and ankylosing spondylitis^{11, 12, 13}. LX had shown strong analgesic effects after dental surgery, hysterectomy, Lumbar disk surgery and in controlling lower back pain^{14, 15, 16}. In a series of studies LX was administered intraperitoneally, intravenously, intramuscularly and this play a role in the mechanism of systemic absorption and incidence of adverse effects¹⁷. Studies the effect of the drug by the topical application are not enough studies. Thus, the purpose of this study is to develop economic LX transdermal patch and to investigate LX effects as an anti-inflammatory for the treatment of inflammation in the rat model in acute and chronic models.

MATERIALS AND METHODS:

Materials: Lornoxicam (LX) was kindly donated by Delta Pharmaceuticals company, Cairo, Egypt; Eudragit[®] RS-100 and RL-100 were a gift from

Evonic, Darmstadt, Germany; Diethyl phthalate (Lobochemie Pvt. Ltd, India), methyl alcohol, ethyl alcohol, calcium chloride, sodium chloride, sodium hydrogen phosphate and potassium dihydrogen phosphate of analytical grade were purchased from Adwic pharmaceutical company, Egypt. Carrageenan was purchased from Sigma-Aldrich Chemicals Co., ST Louis USA.

Methods:

Preparation of Lornoxicam (LX) transdermal patches: LX transdermal patches contained 16mg lornoxicam were prepared using Eudragit[®] RL-100 and RS-100 in three different ratios: 1:2 (F1), 1:1 (F2) and 2:1 (F3) respectively. Diethyl phthalate was used as a plasticizer in the concentration of 20% w/w. The transdermal patches were prepared by solvent evaporation casting technique as follows: Eudragit polymers, drug, and plasticizer were dissolved in methanol. The alcoholic solution was mixed in a beaker and stirred with a magnetic stirrer to accomplish a homogeneous mixture, and the resulting solution was poured in a plastic container of diameter 2 cm. The solvent was allowed to evaporate at ambient conditions, and the obtained transdermal patches were stored in a desiccator over calcium chloride (CaCl₂) and evaluated within one week¹⁸.

Evaluation of Lornoxicam Transdermal Patches:

- 1. Drug Content of the Patch:** A 2cm² patch was cut into small pieces, put into a 100 ml phosphate buffered saline PBS (pH 7.4), and shaken in a mechanical shaker at 37 °C and 100 rpm for 24 h. Then the whole solution was ultrasonicated for 15 min. After filtration, the drug was estimated spectrophotometrically (UV-VS-Spectrophotometer, multicell changer, 6705-Jenway, Bibby scientific. Ltd, UK) at a wavelength of 376 nm and the concentration was deduced in accordance to a pre-constructed calibration curve in PBS (pH 7.4). The experiment was repeated three times, and the mean drug content for each formulation was determined¹⁸.
- 2. LX Patch Thickness:** The thickness of the patches was determined by measuring the thickness at the 4 edges and the center of the formulated films using a micrometer screw

gauge¹⁹ (Mitutoyo Corp, Japan) and the results were expressed as average thickness \pm SD.

3. Differential Scanning Calorimetry (DSC):

Samples of the drug, pure patch components and the physical mixture of the drug and the polymers were analyzed by DSC using a Shimadzu DSC-60 (Shimadzu, Kyoto, Japan).

4. Folding Endurance of LX Patches:

The mechanical properties of the transdermal patches were determined. Three patches of each formulation of size 2×2 cm were cut by using a sharp blade. Folding endurance of the buccal films was determined by repeatedly folding patch at the same place till it broke. The mean value was calculated^{19,20}.

5. Determination of LX Patch Surface pH:

Drug patch was left to swell for 30 min on the surface of 2% w/v agar plate. The surface pH was measured using pH paper (Whatman, USA) placed on the surface of the swollen patch²¹.

6. In-vitro Drug Permeation from the Patch:

The drug permeated from different transdermal patches through synthetic cellulose acetate membrane was studied. USP dissolution tester (BLHMO15K-10, Oriental Motor, Japan) of basket type with slight modification was utilized. Glass cylinders of 10 cm length and 2.5 cm diameter were used instead of the regular baskets. Cellulose acetate membrane with a 12,000-14,000 molecular weight cut off was soaked in saline PBS (pH 7.4) overnight before the study.

Drug patch was placed under the presoaked cellulose membrane, were wrapped on one end of the glass cylinders and were fitted on the basket shaft from the other end. The glass cylinders were placed in the vessels of the dissolution tester so that the membrane and film were only touching the surface of 100 ml of saline PBS (pH 7.4) at 37 °C and stirred at a constant speed of 50 rpm¹⁹. At predetermined time intervals 0.5, 1, 1.5, 2, 4, 8, 10 and 24 h, 5 ml aliquots of the release medium were withdrawn for analysis and replaced with an equal volume of fresh buffered solution to maintain a

constant volume. The absorbencies of the collected and filtered samples were measured spectrophotometrically at 376 nm. Each patch was evaluated three times, and the results were expressed as the mean value of three experiments \pm SD.

Animals and Experimental Design: This study was conducted on eighty adult albino rats weighing 180-200gm. They bred in the animal house of Kasr El Aini, Faculty of Medicine, Cairo University. They were caged in a fully ventilated room, exposed to natural daily light/dark cycle. They were allowed food and water *ad libitum*. The animals were handled according to the guidelines of Helsinki declaration rights (1975) of using laboratory animals.

1. For Acute Experimental (Rat Paw Edema):

Animals were divided into 5 groups each of 8 animals. Carrageenan-induced rat paw edema in all groups for the present study according to the method described by Winter²² and El Nabarawi *et al.*²³.

Suspension of 1% carrageenan is prepared freshly in normal saline and injected into the subplantar region of the right hind paw in a dose of 0.1 ml. The intensity of edema was assessed by measuring the paw volume (ml) by plethysmometer (7410 Ugo Basile, Italy) after 1 h and 5 h. The edema and inhibition rate percentage of each group was calculated as follows:

Equation 1: Determination of edema rate %

$$\text{Edema rate (E \%)} = \frac{V_t - V_0}{V_0} \times 100$$

Equation 2: Determination of Inhibition rate %

$$\text{Inhibition rate} = \frac{E_c - E_t}{E_t} \times 100$$

Where V_0 is the mean paw volume before carrageenan injection (ml), V_t is the mean paw volume after carrageenan injection (ml), E_c is the edema rate of the control group, and E_t is the edema rate of the treated group²⁴.

Group I received no treatment, Group II rats received LX 5mg/kg parenterally SC (behind the neck) one hour before induction of inflammation. Group III, Group IV, and Group V were subjected to the application of LX patch (F1), (F2), (F3) respectively.

2. For Chronic Experimental (Granuloma Pouch 25):-Forty white albino rats were divided into five groups, each containing 8 rats. The hair of each rat was removed with electric hair clipper from the skin of the dorsal region 48 h before use. The shaved area was investigated that's no wounds, or any blood comes out. Sterile air (10 ml) was injected into the loose SC connective tissue of each rat back. Carrageenan gel solution (2%), 5 ml was then injected into this air mold. The rats were then left for one day later; the air bleb was deflated to accelerate the formation of the exudate.

The animals (40 rats) were divided according to the scheme described below: All groups received Carrageenan gel solution in the dorsal back of each rat. Group I received no treatment Group II, III, IV, V received treatment as previously described in the acute experiment model.

Before application of LX patches to the dorsal of rats, a piece of cotton wetted with ethanol was used to clean the skin from any debris three times respectively. LX patches were applied to the dorsal shaved area and covered with a piece of adhesive tape.

Each rat in each group was put in a separate cage and left for 7 days. The rats were under observation all over 7 days after application. At the end of 7 days, the rats were slaughtered, and the volume of exudate present in the air cavity was determined for each rat in each group using a small pipette. The volume of exudate and percent inhibition in volume for all groups was measured.

Statistical Analysis Methods: Data were collected, checked, revised, and entered the computer. Data were analyzed by SPSS statistical package version 17. Excel computer program was used to tabulate the results and represent it graphically. Qualitative variables were expressed as percentages. Quantitative variables from normal distribution were expressed as mean and S.D. One Way ANOVA used to declare the significant difference between groups at $p < 0.05$. Duncan multiple comparison test at $p < 0.05$ was used to declare the significant between each group and the control group²⁶.

RESULTS AND DISCUSSION: A transdermal patches of lornoxicam were prepared with Eudragit RL 100: Eudragit RS 100 in three different ratios with diethyl phthalate as plasticizer using the solvent evaporation technique. Results showed that the drug content of the patches was ranged from 96.45 to 103.33%. The patches thickness was ranged from 0.36 to 0.46 mm. Results obtained showed that films prepared were a uniform thickness. The difference in thickness was due to the concentration of polymer in each device. The pH of the LX patch was found to be 6.5.

Fig. 1 showed the thermograms of pure drug and the physical mixture of the drug and the polymers (Eudragit[®] RL-100, Eudragit[®] RS-100) in ratio 1:1. The superimposition of the thermograms of the physical mixture, prepared by simple blending of drug and polymer, to those of the patch components indicated the absence of interactions between the drug and the polymers.

The obtained data revealed that when increasing the ratio of the Eudragit[®] RL-100 polymer (F3), there was a corresponding increase in the folding endurance of patches. Diethyl phthalate 20% in the Eudragit[®] patches led to increasing elasticity for the patches. The order of increasing folding endurance of patches was in order: F3 > F2 > F1. These results were in a good agreement of Entwistle C and Rowe R²⁷.

They found that DEP in the Eudragit[®] film increase in elongation and correspond in a decrease in tensile strength. This was because plasticizers acted by inserting themselves between the polymer strands, breaking the polymer-polymer bond, which led to an increase in the molecular mobility of the polymer strand²⁷.

Thus, it was expected that as the concentration of the plasticizer increased, the degree of the film stiffness decreased, whereas the film ductility increased. Upon addition of plasticizer, flexibilities of polymer macromolecules or macromolecular segments increase as a result of the loosening of tightness of intermolecular forces²⁸. It was also found that weakening of interaction of the polymer chains led to a decrease in the tensile strength and an increase in the percent elongation of the films²⁹.

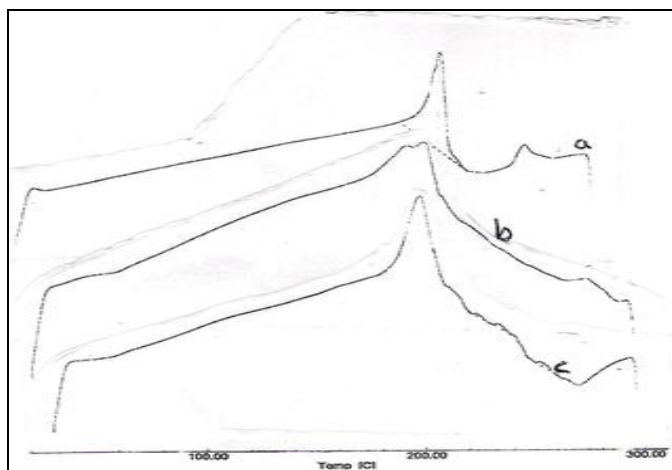


FIG. 1: DSC THERMOGRAMS OF (A) LORNOXICAM; (B) LORNOXICAM: EUDRAGIT RS PHYSICAL MIXTURE AND (C) LORNOXICAM: EUDRAGIT RL PHYSICAL MIXTURE

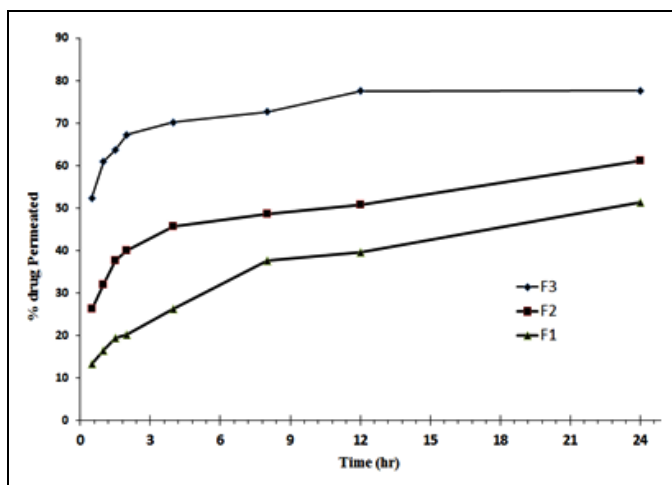


FIG. 2: PERMEATION OF LORNOXICAM FROM DIFFERENT PATCHES THROUGH CELLULOSE ACETATE MEMBRANE

Fig. 2 showed the permeation profile of lornoxicam patches (F1, F2, and F3) composed of different ratios of Eudragit[®] RL-100: RS-100 in PBS (pH 7.4). The permeation of drug from F3 showed higher drug release than F2 and F1 this could be explained on the fact that, F3, which was composed of a higher ratio of Eudragit[®] RL-100. These results could be attributed to the lower content of

quaternary ammonium groups present in Eudragit[®] RL-100 than in RS-100, resulting in less swelling in the aqueous medium³⁰.

Also, the inclusion of Eudragit[®] RS-100 polymer in the films led to a slight reduction in the permeation profile of the drug F2 and F1. In case of the patches prepared using a higher percent of Eudragit[®] RS-100 (F1 and F2), it was found that the drug permeation decreased significantly.

Table 1 and Fig. 3 showed the effect of LX in different formulae tested for *in-vitro* permeation in rat paw edema after 1 and 5 h. The swelling is markedly increased in group I then after injection by LX the marked inhibition showed in group II after 1 h. The degree of swelling was significantly decreased by F3 followed by F2 followed by F1 after one and five hours.

The degree of inhibition was significantly increased by F3, followed by F2 followed by F1 after five hours. These results were in a good agreement with *in vitro* drug permeation from different patches through cellulose acetate membrane.

Table 2 showed the maximum edema was shown group I. Edema was significantly decreased in group V followed by group IV followed by group III and then group II. These results demonstrated that the maximum inhibition of edema was by patch F3 and not by injection as in the acute study.

Our results are by^{31, 32} which stated that LX is approved for intravenous, intramuscular, and oral use, no toxicological data are available regarding its intra-articular administration. The peripheral effects of NSAIDs are peripheral, and therefore, local application to the site of injury should produce analgesia while minimizing systemic side effects.

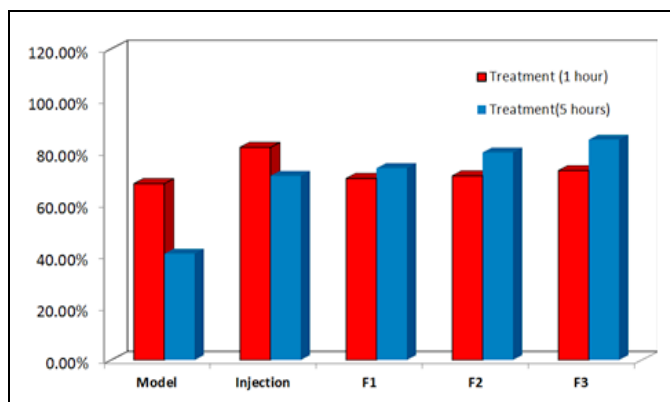
TABLE 1: EFFECT OF LX PATCHES TESTED ON RAT PAW EDEMA AFTER ONE AND 5 h

		% Swelling				% Inhibition			
		1 h	5 h	Z- value	p-value	1 h	5 h	Z- value	p-value
Group I	Control	32	59	3.98	0.000*	68	41	3.98	0.000*
Group II	Injection	18	29	1.85	0.069	82	71	1.85	0.064
Group III	F1	30	26	0.63	0.528	70	74	0.63	0.528
Group IV	F2	29	20	1.49	0.137	71	80	1.49	0.137
Group V	F3	27	15	2.11	0.035*	73	85	2.11	0.035*

* = There is a significant difference between the two proportions by using Fisher's exact test at p<0.05

TABLE 2: EFFECT OF MEDICATED F1, F2, F3 AND S.C LORNOXICAM IN REDUCING VOLUME OF INFLAMMATORY EXUDATES AFTER 7 DAYS

	Time 7 days		
	Formulation	Mean \pm SD	% \pm SD
Group I	Carrageenan gel solution	2.76 \pm 0.06 e	
Group II	Commercial injection	2.55 \pm 0.03 d	7.64 \pm 0.01 a
Group III	F1	1.94 \pm 0.06 b	29.82 \pm 0.04 c
Group IV	F2	2.22 \pm 0.07 c	19.63 \pm 0.01 b
Group V	F3	1.35 \pm 0.05 a	51.26 \pm 0.05 d
	F-value	300.662	1062469.6
	P-value	0.000*	0.000*

**FIG. 3: HISTOGRAM SHOWING PERCENTAGE INHIBITION EFFECT OF LX PATCHES TESTED ON RAT PAW EDEMA AFTER ONE AND FIVE HOURS**

Smith *et al.*,³³ showed that the principal mechanism of action of NSAIDs relies on inhibition of COX, which is the rate-limiting enzyme in the arachidonic acid pathway. COX exists in two isoforms COX 1 and COX 2.

While COX 1 is thought to account for homeostatic amounts of eicosanoids, COX2 is induced during inflammation leading to the formation of pathologic amounts of prostaglandins (PGS). The inhibition of (PGS) synthesis by NSAIDs has been demonstrated to reduce inflammatory symptoms such as edema and pain^{34, 35, 36}.

Other mediators of inflammation such as reactive oxygen products and cytokines which contribute to inflammation and pain^{37, 38} leading to transcriptional induction of COX-2 gene, the expression of the gene encoding inducible nitric oxide synthase (iNos) is induced, leading to increase level of nitric oxide in inflammation tissue which leads to edema formation and pain^{38, 39}.

LX was found to be the most potent balanced inhibitor of human COX 1, 2. The *in-vitro* activities

described supporting the marked anti-inflammatory and analgesic activities of LX found in animal models as well as in clinical studies³⁷.

LX is at least 10 times more potent as an anti-inflammatory agent than piroxicam and was also tenfold more active than tenoxicam in inhibiting carrageenan-induced edema in the rat paw swelling in the adjuvant-induced polyarthritic rat^{8, 11}.

The volume of exudates obtained was significantly decreased by F3 followed by F2 followed by F1 after 7 days of treatment. These results were in a good agreement with *in-vitro* drug permeation from different patches through cellulose acetate membrane. The order of decreasing volume of exudates was as follows: F3 > F2 > F1 > injection.

The potent nonselective COX inhibition by LX was observed *in vitro* is in good agreement with animal experiments where inhibition of COX 1 mediated PGS synthesis is thought to be involved in compound efficacy such as acetylcholine-induced writhing or where COX 2 inhibition such as carrageenan-induced paw edema has been suggested to be causal for anti-inflammatory effects³⁶. Furthermore, LX was potentially effective as anti-inflammatory and analgesic activity¹⁴⁻¹⁶. Moreover, several studies have examined the role of nonselective COX inhibitors both in animal models and in patients^{40, 41, 42} demonstrated beneficial effects of NSAIDs on the TNF- α level which can be ameliorated⁴³.

LX has also shown marked inhibitory activity on endotoxin-induced IL6 formation in THP1 monocytes with less activity on TNF- α and IL-1. LX treatment suppressed both NF-Kappa B activation and TNF- α expression in biological analysis^{44, 45}.

In addition, Pruss *et al.*⁵ stated that the powerful inhibition of cyclo-oxygenase had manifested itself as a highly potent analgesic and anti-inflammatory effects in animal studies. Studies have demonstrated that LX inhibits polymorphonuclear (PMN) leukocyte migration, inhibits the release of superoxide from human PMN-leukocytes, inhibits the release of platelet-derived growth factor (PDGF) from human platelets and stimulate the synthesis of proteoglycans in cartilage in tissue culture^{8, 37}.

CONCLUSION: The present study showed that lornoxicam transdermal patches proved to be economic in the manufacture, non-irritant, and had anti-inflammatory effects on acute and chronic models of inflammation using albino rats. Also, topical application of LX transdermal patch reduces side effects of the drug which induced by other routes. Furthermore, F3 patch possesses superior to injection route in the treatment of edema in chronic models.

ACKNOWLEDGEMENT: Nil

CONFLICT OF INTEREST: Nil

REFERENCES:

1. Smith WL, Meade EA and Dewitt DL: Interactions of PGH synthase isozymes-1 and -2 with NSAIDs. *Ann NY Acad Sci* 1994; 744: 50-7.
2. Vane JR and Botting RM: New insights into the mode of action of anti-inflammatory drugs. *Inflamm Res* 1995; 44: 1-10.
3. Wallace JL and Cirino G: The development of gastrointestinal - sparing non-steroidal anti-inflammatory drugs. *TIPS* 1994; 15: 405-6.
4. Breg J, Christoph T, Widerna M and Bodenteich A: Isoenzyme specific cyclooxygenase inhibitors: A whole cell assay system using the human erythroleukemic cell line HEL and human monocytic cell line Monomac 6. *J Pharmacol Toxicol Meth* 1997; 37: 179-86.
5. Pruss TP, Stroissnig H, Radhofer-Welte S, Wendtland W, Mehdi N and Takacs F: Overview of the pharmacological properties pharmacokinetics and animal safety assessment of lornoxicam. *Postgrad Med J* 1990; 66 (Suppl 4): S18-21.
6. Aabakken L, Osnes M and Frenzel W: Gastrointestinal tolerability of lornoxicam compared to that of naproxen in healthy male volunteers. *Aliment Pharmacol Ther* 1996; 10: 151-6.
7. Julia A, Balfour AF and Barradell LB: Lornoxicam: A Review of its pharmacology and therapeutic potential in the management of painful and inflammatory conditions. *Drug* 1996; 51(4): 639-57.
8. Welte SR and Rabbeseda X: Lornoxicam, a new potent NSAID with improved tolerability profile. *Drugs of Today* 2000; 36(1): 55-76.
9. Gavrilova SA, Lipina TV, Zagidullin TR, Fominykh ES and Semenov PA: Protective effect of lornoxicam on development of myocardial infarction in rats under conditions of ischemia and ischemia-reperfusion. *Kardiologiia* 2008; 48(12): 42-8.
10. Prasad DS, Medhi B, Spatyar and Swadhwa: A Review of Lornoxicam a newer NSAID *IJPMR* 2009; 20(1): 27-31.
11. Balfour JA, Fitton A and Barradell LB: Lornoxicam: A review of its pharmacology and therapeutic potential in the management of painful and inflammatory conditions. *Drugs* 1996; 51: 639-57.
12. Berry H, Bird HA, Black C, Blake DR, Freeman AM and Golding DN: A double-blind, multicenter, placebo-controlled trial of lornoxicam in patients with osteoarthritis of the hip and knee. *Ann Rheum Dis* 1992; 51: 238-42.

13. Kidd B and Frenzel WA: A multicenter, randomized, double-blind study is comparing lornoxicam with diclofenac in osteoarthritis. *J Rheumat* 1996; 23: 1439-50.
14. Norholt SE, Sindet-Pederson S, Bugge C, Branebjerg PE, Ersboll BK and Bastian HL: A randomized, double-blind, placebo-controlled, dose-response study of the analgesic effect of lornoxicam after surgical removal of mandibular third molars. *J Clin Pharmacol* 1995; 35: 606-14.
15. Norholt SE, Sindet-Pederson S, Larsen U, Bang U, Ingerslev J and Nielsen O: Pain control after dental surgery: a double-blind, randomized trial of lornoxicam versus morphine. *Pain* 1996; 67: 335-43.
16. Ilias W and Jansen M: Pain control after hysterectomy: an observer-blind, randomized trial of lornoxicam versus tramadol. *Br J Clin Pract* 1996; 50: 197-02.
17. LigY, Yang BX and Liu H: Analgesic actions after local peripheral administration of lornoxicam in a model of formalin test in the rat. *J of Sich Univ* 2005; 36(5): 703-5.
18. El-Nabarawi MA, Shaker DS, Attia DA and Hamed SA: In vitro skin permeation and biological evaluation of lornoxicam monolithic transdermal patches. *Int J of Pharmacy and Pharm Sci* 2013; 5(2): 242-48.
19. El-Nabarawi MA, El Meshad AN and Moutasim MY: Assessment of bioavailability of sumatriptan transdermal delivery systems in rabbits. *Int J of Pharmacy and Pharm Sci* 2013; 5(S2): 225-40.
20. El-Nabarawi MA, Makky AA, El-Setouhly DA, ElMonem RA and Jasti BA: Development and Characterization of Ketorolac Tromethamine (KT) orobuccal Films. *Int J of Pharmacy and Pharm Sci* 2012, 4(4): 186-93.
21. Shidhaye SS, Saindane NS, Sutav S and Kadam V: Mucoadhesive bilayered patches for Administration of Sumatriptan Succinate. *AAPS Pharm Sci Tech* 2008, 9(3): 909-16.
22. Winter CA: Carrageenan-induced edema in hind paws of the rats –an assay for anti-inflammatory drugs. *Proceedings of the Society for Experimental Biology and Medicine* 1962; 111: 544-47
23. El-Nabarawi MA, El-Miligi MF, Khalil IA and El-Nabarawy NA: Applying QBD approach to developing ODTs containing aceclofenac solid dispersion with ranitidine HCl using direct compression technique, then pharmaceutically evaluating and pharmacologically confirming the therapeutic actions. *International Journal of Pharmacy and Pharmaceutical Sciences* 2013; 5(4): 577-93
24. Mei Z, Li X, Wu Q, Hu S and Yang X: The research on the anti-inflammatory activity and hepatotoxicity of triptolide-loaded solid lipid nanoparticle. *Pharmacological Research* 2005; 51(4): 345-51.
25. Sugio K and Tsurufuji S: Mechanism of anti-inflammatory action of glucocorticoids re-evaluation of vascular constriction hypothesis. *Br J Pharmacol* 1981; 73: 605.
26. Armitage P, Berry G and Matthews JNS: *Statistical Methods in Medical Research*, Copyright © 2002 Blackwell Science Ltd, London. Published Online: 11 Feb 2008.
27. Entwistle C and Rowe R: Plasticization of cellulose ethers used in the film coating of tablets. *J Pharm Pharmacol* 1979; 31(1): 269-72.
28. Hofer R and Hinrichs K: *Additives for the Manufacture and Processing of Polymers: Polymers-Opportunities Risks* 2010: 97-145.
29. Felton LA: *Film coating of oral solid dosage forms* 2006.
30. Rowe RC, Sheskey PJ, Owen SC, Association AP and Library R: *Handbook of Pharmaceutical excipients: vol. 4: Pharmaceutical press London* 2003.

31. Bianchi M and anera A: Effect of Lornoxicam, Piroxicam and meloxicam in a model of thermal hind paw hyperalgesia induced by formalin injected in rat tail. *Pharmacol Res* 2002; 45: 100-5.
32. Buritova J and Besson JM: Dose related anti-inflammatory/analgesic effects of lornoxicam: A spinal C-fos protein study in rat inflamm *Res* 1998; 47: 18-25.
33. Smith WL and Marnett LJ: Prostaglandin endoperoxide synthase: structure and catalysis *Biochim Biophys Acta* 1990; 1083: 1-17.
34. Vane JR, Bakhle YS and Botting RM: Cyclooxygenase 1 and 2 *Annu Rev. Pharmacol toxicol* 1998; 38: 97-120.
35. Ferreira SH: Prostaglandins, aspirin like drugs and hyperalgesia *Nature* 1972; 240: 200-3.
36. Portanova JP, Zhang Y, Anderson GD, Hauser SD, Masferrer JL and Seibert K: Selective neutralization of prostaglandin E2 blocks inflammation, hyperalgesia, and interleukin 6 production *in-vivo*. *J Exp Med* 1996; 184: 883-91.
37. Watkins LR, Maier SF and Goehler LE: Immune activation: the role of pro-inflammatory cytokines in inflammation, illness response and pathological pain states. *Pain* 1995; 63: 289-02.
38. Anbar M and Gratt BM: Role of nitric oxide in the physiopathology of pain. *J pain Symptom Manage* 1997; 14: 225-54.
39. Vane JR, Mitchell JA, Appleton I, Tomlinson A, Bishop-Balley D and Croxatall J: inducible isoforms of cyclooxygenase and nitric oxide synthase in inflammation *proc Natl Acad Sci USA* 1994; 91: 2046-50.
40. Beamer KC, Daly T and Vargish T: Hemodynamic evaluation of Ibuprofen in canine hypovolemic shock. *Circ Shock* 1987; 23: 51-57.
41. Wanecek M, Rudehill A, Hemsén A, Lundberg JM and Weitzberg E: The endothelin receptor antagonist, bosentan, in combination with the cyclooxygenase inhibitor, diclofenac, counteracts pulmonary hypertension in porcine endotoxin shock. *Cr Car Med* 1997; 25: 848-57.
42. Strong VE, Mackrell PJ, Concannon EM, Naama HA, Schaefer PA, Shaftan GW, Stapleton PP and Daly JM: Blocking prostaglandin E2 after trauma attenuates pro-inflammatory cytokines and improves survival. *Shock*, 2000, 14: 374-79.
43. Fletcher JR, Collins JN, Graves III ED, Luterma A, Williams MD, Izenberg SD and Rodning CB: Tumor necrosis factor-induced mortality is reversed with cyclooxygenase inhibition. *Ann Surg* 1993, 217: 668-74.
44. Towart R, Graup J and Stimmeder D: Lornoxicam potentiates morphine antinociception during visceral nociception in the rat. *Naunyn-Schmied Arch Pharmacol* 1998; 358(1): 172.
45. Yin J, Huang Z, Xia Y, Ma F, Zhang LJ, Ma HH and Wang L: Lornoxicam suppresses recurrent herpetic stromal keratitis through down-regulation of nuclear factor-kappa B. an experimental study in mice. *Mol Vis* 2009; 15: 1252-9.

How to cite this article:

El-Nabarawy NA, Elmonem RAA and Enin HAA: Development of economic transdermal patches containing lornoxicam for treatment of acute and chronic inflammatory models in albino rats (a preclinical study). *Int J Pharm Sci & Res* 2014; 5(10): 4195-02. doi: 10.13040/IJPSR.0975-8232.5(10).4195-02.

All © 2013 are reserved by International Journal of Pharmaceutical Sciences and Research. This Journal licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 3.0 Unported License.

This article can be downloaded to **ANDROID OS** based mobile. Scan QR Code using Code/Bar Scanner from your mobile. (Scanners are available on Google Playstore)