

## Formulation and Evaluation of Lecithin Organogel for Treatment of Arthritis

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### Abstract

Arthritis is a disease of the joint that involves inflammation of one or more joints. The common symptoms of arthritis disorders include varied levels of pain, swelling, joint stiffness, and sometimes a constant ache around the joints. More than 20 million individuals with arthritis have severe limitations in function on a daily basis. The objective of this study was to resolve conventional dosage forms of NSAIDs, which are at increased risk for serious gastrointestinal complications, when administered through oral route. Topical administration of NSAIDs could deliver lornoxicam to the site of action in rheumatic diseases which would reduce the gastrointestinal complications and side effects of the drug. The prepared organogel of lornoxicam were evaluated for its appearance, organoleptic characteristic, viscosity, gelation temperature, drug content and *in vitro* release study. *In vivo* evaluation for analgesic activity of formulation was carried out in terms of skin irritation study, hot plate method, writhing test and edema paw induce method.

**Keywords:** Lornoxicam, lecithin, organogel, Arthritis, Topical delivery

### 1. Introduction

Arthritis is frequently accompanied by joint pain, which is referred to as arthralgia. The disease is symmetrical and can lead to severe deformity in a few years if not treated. Lornoxicam (chlortenoxicam) is a strong analgesic and anti-inflammatory NSAID of the oxicam class with better tolerability profile when compared to other NSAIDs. It has been shown to be effective in the treatment of postoperative pain and rheumatoid arthritis. Lornoxicam has short half life of 3-4 hrs, log P value 1.8 and molecular weight of 371.82 g/mol, which makes it potential candidate for transdermal drug delivery [1]. Skin is a natural barrier against the penetration of most drugs[2], and the ability of drug to penetrate the skin epidermis, dermis, and subcutaneous fat layers depend on the properties of the drug and the carrier base [3]. The topical administration of drugs, in order to achieve optimal cutaneous and percutaneous drug delivery has recently gained an importance because of various advantages such as ease of administration noninvasive, better tolerated and compliance, local enhanced transdermal

delivery, avoidance of local gastrointestinal toxicity, avoidance of first pass metabolism of drugs. In search of a delivery vehicle to deliver the medicament into the skin layers (cutaneous delivery) or through the skin and into the systemic circulation varied kinds of formulation systems and strategies have been evolved. The topical delivery has been attempted and made successful using several lipid-based systems viz e., liposomal formulations [4-6], nanostructured lipid carrier [7-8], lipid microemulsions [9], solid lipid microparticles [10], elastic liposomes or transfersomes [11], ethosomes [12,13] and lipid cubic phases [14,15] etc. In recent development, phospholipids in conjunction with some other additives have been shown to provide a very promising topical drug delivery vehicle known as lecithin organogels (LOs).[16,17]. The organogels are gels based on non-aqueous liquids, which have been mentioned in various pharmacopoeias as useful topical deliveries for lipophilic drugs [18]. They not only exert a local effect but also are capable of achieving a systemic effect via

transdermal absorption, when their lipophilic nature and occlusive effect are potentiated by the presence of a penetration enhancer.

Lecithin organogels are thermodynamically stable, clear, viscoelastic, biocompatible, and isotropic gels composed of phospholipid, appropriate organic solvent, and a polar solvent [17]. Lecithin organogels, consist of a 3-dimensional network of entangled reverse cylindrical (polymer-like) micelles, which immobilizes the continuous or macroscopic external organic phase, thus turning a liquid into a gel. The formulation of a 3-dimensional network in the organogel is the result of transition at the micellar level in a low viscous Newtonian liquid consisting of lecithin micelles in non polar organic liquid. This spherical reverse micellar state of lipid aggregates turns on to form elongated tubular micelles with the addition of water and subsequently entangles to form a temporal 3-dimensional network in the solution bulk, the latter serves to immobilize the external organic phase, thus producing a gel form or the jelly-like state of the initial non viscous solution. However, The transparency and optical isotropy of the organogel remains as before. These systems can also be called as polymer-like micelles or wormlike or threadlike micelles [19].

The traditional topical drug delivery systems like emulsion and suspension have various limitations such as instability and minimal systemic absorption of drug. On other hand the conventional dosage form of NSAIDs are at increased risk for serious gastrointestinal complications, when administered through oral route. However topical administration of NSAIDs offers the advantage of local enhance drug delivery to affected tissues with reduced bioavailability as well as incidence of systemic adverse effects, such as peptic ulcer disease and gastrointestinal hemorrhage. Therefore in the present work, topical organogel of lornoxicam is selected as alternative route to oral delivery in order to improve its penetration ability and overcome the problems related with oral route.

In present work an attempt was made to prepare lornoxicam entrapped lecithin organogel of phospholipids (lecithin) propylene glycol and isopropyl myristate to transport the drugs in to and across the skin. The developed topical preparation could effectively deliver lornoxicam to the site of action in rheumatic diseases which will effectively reduce the gastrointestinal side effects of the drug.

## 2. Material and Methods

Lornoxicam was received as a gift sample from Aristo Pharmaceuticals, Baddi, India. The lecithin was procured from Ruchi Soya Pvt. Ltd.

Indore, India. Isopropyl myristate, propylene glycol and sorbic acid were purchased from CDH Pvt. Ltd., Delhi, India. All other chemicals were of analytical grade.

The experiment protocol was approved by the institutional ethics committee of Truba Institute of Pharmacy, Bhopal and as per CPCSEA guidelines (approval no. 1196/a/08/CPCSEA).

### 2.1 Experimental work

#### 2.1.1 Method of preparation of Lecithin organogel

In present work lornoxicam containing lecithin organogel was prepared by method established by Scartazzini and Luisi in 1988.[20]; with slight modification. In this method the oily phase was prepared by dispersing the specific amount (ratio; 40:60) of purified lecithin at room temperature in isopropyl myristate as dispersing and emulsifying agent. The mixture was kept overnight for complete dissolution of lecithin then the sorbic acid was added as preservative in this solution and finally lornoxicam was dissolved in oily phase. The aqueous phase of polypropylene was prepared by dispersing a weighed amount of polypropylene and glycerol in water. The dispersion was stored in a refrigerator at 2-4 °C overnight for the effective dissolution. The aqueous phase was slowly added in oily phase with stirring at 400 rpm using a mechanical stirrer. The various formulations of lecithin organogel developed with different compositions are shown in table-1.

#### 2.1.2 Characterization of Organogel

The lecithin organogels prepared were characterized for following parameters.

##### 2.1.2.1 Physical evaluation of organogels

**Organoleptic characteristics:** Each formulation was tested for color, odor, texture and phase separation as well as feels upon application (stiffness, grittiness, greasiness and tackiness). The results are given in the table-1.

**Homogeneity test:** - A small quantity of each gel was pressed between the thumb and the index finger in order to notice the consistency of cream that any coarse particles being attached or detached on the finger. The results are given in the table-1.

**Occlusiveness:** - Prepared gel was taken in vial and visually observed whether it is occlusive or not. The observations are given in the table-1.

**pH determination:-** The pH of organogels was determined using pH meter (Systronic pH system 361) which was calibrated before each use with buffered solutions at pH 4 and 7. A solution containing 1 gm of organogel in 30 ml of neutralized distilled water was prepared and subjected to pH measurement [21]. The results are given in table-1.

**Rheological studies [22]:-** Rheological studies were performed with a thermostatically Fungilab

Viscometer by using concentric cylinder spindle 61(L4) at 100 rpm and temperature 25°C. The results are given in table-1.

**Drug content:** - The content of lornoxicam in the formulations was determined as per method described by Willmann and Luisi (1991)[23]. Accurately weighed gel (1g) was diluted with 100 ml of 0.1 N NaOH and analyzed spectrophotometrically at 376.5 nm for lornoxicam content and are shown in table-1.

**Gel Transition Temperature:** - Gelation temperature, defined as the temperature at which the liquid phase makes a transition to gel. The phase behavior of organogels varies on changing the temperature conditions. The phase transition temperature (PTT) (i.e., sol-to-gel,  $T_{SG}$ , or gel-to-sol,  $T_{GS}$ ) gives insight into the nature of microstructures that form the gelling cross-linked network. The phase transition temperature also helps in optimizing the organogel composition [24]. The gel transition temperature was determined in a test tube enclosing 0.25 g of gel and observed over the temperature range 2-30°C. The change from sol to gel was said to have occurred when the meniscus would not move immediately upon tilting the test tube to 90°. The temperature was raised slowly with the help of water bath and the temperature at which the physical state of the formulation was changed was regarded as the gelation temperature. The observations are given in table-1.

**Swelling Index Study of Organogel:** - Swelling of the polymer depends on the concentration of the polymer, ionic strength and the presence of water. To determine the swelling index of prepared topical gel, 1 gm of gel was taken on porous aluminum foil and then placed separately in a 50 ml beaker containing 10 ml 0.1 N NaOH. Then samples were removed from beakers at different time intervals and kept it on dry place for some time after that it was reweighed. Swelling index was calculated as follows. [25,26]. The results are given in table-1.

**Swelling Index (SW) %** =  $[(W_t - W_o) / W_o] \times 100$ .

Where, (SW) % = Equilibrium percent swelling,

$W_t$  = Weight of swollen gel after time  $t$ ,

$W_o$  = Original weight of gel at zero time.

### 2.1.3 In vitro Drug Release Studies

The different formulations were subjected to *in vitro* drug release studies. The release of lornoxicam from lecithin organogel was determined as a function of time in phosphate buffer saline (pH 7.4) using dialysis membrane-150 (Himedia) the release profile of lornoxicam from different formulations are given in table no 01 .

### 2.1.4 In vivo studies

#### Analgesic activity of lornoxicam organogel

The analgesic activity of lornoxicam entrapped formulation was determined on albino rats

of 4 months, of both sexes, weighing between 150 to 170 gm. The animals were acclimatized to the standard laboratory conditions in cross ventilated animal house at temperature  $25 \pm 2^\circ\text{C}$  with relative humidity 44 –56% and light and dark cycles of 12:12 hours. All rats were fed with standard pellet diet and water *ad libitum* during experiment. The experiment protocol was approved by the institutional ethics. The experiment for analgesic activity was performed in terms of Skin irritation study, Hot Plate method; Acetic acid induced writhing test and Carrageenan-induced paw edema method.

**Skin irritation study:** - The purpose of this test was to determine the skin irritation potential of lornoxicam incorporated into organogel to the intact skin of albino rats.

**Hot Plate method:** - Eddy's Hot Plate Analgesimeter was used for screening of analgesic drug properties and to evaluate alterations of animal pain sensitivity [27,28].

**Acetic acid induced writhing test:** - A noxious substance is injected in the abdominal cavity (intraperitoneally) of the animal causing severe abdominal pain and contraction of abdominal musculature (writhing).

**Carrageenan-induced paw edema:** - the evaluation of Antiedematogenic activity was carried out by rat-paw edema test. Albino rats ( $n=4$ ) were randomized and assigned to different experimental groups. Edema inhibition rate (I) after different treatments was calculated using following equation:

$$E = V_t - V_o / V_o \dots\dots\dots(1)$$

$$I\% = E_c - E_t / E_c \times 100, \dots\dots\dots(2)$$

Where  $V_o$  is the mean paw volume before 1% carrageenan (w/v) injection,  $V_t$  is the mean paw volume after 1% carrageenan (w/v) injection,  $E_c$  is the edema rate of the control group, and  $E_t$  is the edema rate of the treated group. (29).

### 2.2 Statistical analysis

All the values are expressed as mean  $\pm$  standard error of mean (S.E.M.) and analyzed for ANOVA and posthoc Dunnet's *t*-test by employing statistical software, GraphPad InStat 3. Differences between groups were considered significant at  $P < 0.05$ .

## 3. Results and Discussion

The aim of present work is to develop pharmaceutically acceptable lecithin organogel for topical delivery of lornoxicam with improved therapeutic performance by their penetration enhancing property. In order to achieve this objective, the formulations were prepared with lecithin (95%), isopropyl myristate and propylene glycol as a cosurfactant. The developed formulations were

characterized for their organoleptic properties, pH, swelling index, viscosity, gel transition temperature, *in vitro* drug release studies and analgesic activity of formulation.

The physiological observation shows that organogel formulations were washable, yellowish in color with no phase separation, smooth in feel, and showed no clogging which indicate good texture of system. Freedom from grittiness reflects the degree of acceptability of lornoxicam formulation by the patients.

The *in vivo* studies shown the better reducing inflammatory activities of organogel compare the standard formulation. The activities performed by the writhing test, hot plate method, skin irritation study and carrageenan-induced paw edema method.

### 3.1 Effect of pH

There was no significant difference in pH between the batches. The pH of all the formulations was around the skin pH reflecting no risk of skin irritation. It was determined by using pH meter (Systronic pH system 361) (Table.1).

### 3.2 Rheological measurements

It was observed that on increasing the concentration of lecithin, viscosity increases from **5261 to 5581 poise**. The increase in viscosity with increase in concentration of lecithin (table-1) was might be due to formation of complex network as in gel, consistency depends on percentage of solid in relation to liquid.

### 3.3 Drug content

The drug content of organogel formulations was found in the range of **92.43±2.10-97.93±0.31%** indicating uniform distribution of drug through the base and no interaction of drug with component of base. The drug content of all formulations are depicted in table- 1.

### 3.4 Effect on swelling index

All the formulations showed swelling index in the range of **71-96% depicted** in table- 1. It was observed that increase in percentage of organogelator decrease the swelling index.

### 3.5 Effect on Gel transition temperature

On increasing the viscosity of the system; gel transition temperature decreases and stronger is the work of adhesion. The transition temperatures of formulations are given in table-1.

### 3.6 *In vitro* Drug Release Studies

The effects of lecithin concentration on the release rate of lornoxicam from organogels formulation were evaluated in phosphate buffer (pH-7.4).The lornoxicam release was found to be decrease with an increase in lecithin content, an inverse correlation existed between the release rate and the gel viscosity values. But a significant decrease in

lornoxicam release was obtained as the lecithin concentration was further increased from 5-10% in the formulations **LOF6, LOF7, LOF8, LOF9 to LOF10**

This effect may be due to a decreased in thermodynamic activity of concentrations, there is more extensive entanglement of long cylindrical micelles with each other, forming a network-like structure with a very high viscosity. The entrapment of the drug within this network lowers the amount of free drug available for release, causing a decrease in release rate of lornoxicam across the membrane.

Further increase in concentration of organogelator decrease cumulative percentage drug release which might be due to extensive entanglement of long cylindrical micelles with each other, forming network like structure with very high viscosity. Its shown in figure 1.

### 3.7 Analgesic activity of lornoxicam organogel

The purpose of this study was to examine the efficacy of prepared organogel formulation as a topical drug delivery system, which enhances drug diffusion inside the deeper layer of skin and could reduce systemic side effects of drug. In present work the effect of optimized lornoxicam organogel formulation on basal reaction time (hot plate method), rat-paw edema test, and skin irritation study and on acetic acid induced abdominal writhing in albino rats was evaluated.

The animals were divided in three groups, each consisting of four animals. The hairs of animals were shaved in 2 cm<sup>2</sup> areas with the help of hair removing cream in interscapular region. For study of the lornoxicam organogel was applied topically. The treated areas of animals were protected by using nylon mesh, which was supported by plastic squares having small pores. Treated animals were kept in separate cages and housed in standard laboratory conditions. Group (I) was kept as a control (without treatment); group (II) was kept as standard; treated with marketed formulation of diclofenac sodium gel (4 mg/kg) which was topically applied on shaved surface; group (III) was considered as test group which was treated with organogel formulation of lornoxicam (4mg/kg). The formulation was topically applied on shaved surface, respectively.

### 3.8 Skin irritation study

The purpose of this test was to determine the skin irritation potential of lornoxicam incorporated into organogel to the intact skin of albino rats. The hairs were removed from the back of rats using hair remover cream and area of 2 cm<sup>2</sup> diameter was marked on both sides. One side served as control while other as test and animals were used after 24 hrs. The gel was applied (100mg/rat) once a day for 7 days and sight was covered with cotton bandage. The rats

were observed for sensitivity and the reaction if any. No sensitivity and no reaction of any type were observed and are given in table 2 and graded as.

#### Hot Plate method:-

The hot plate consists of an electrically heated surface. The temperature was controlled for 50° to 55 °C. The rats were placed individually on the hot plate and the time until either licking or jumping occurs was recorded by a stop-watch. The results in table 3; revealed that applied lornoxaicom organogel formulation produced significant analgesic action in terms of increasing the time of paw licking and jump response. The results of organogel formulation was compared with standard marketed formulation (Volini gel, Ranbaxy) as are shown table 3.

#### Acetic acid induced writhing test:-

Acetic acid in a concentration of 1% v/v, 1 ml/kg was injected intraperitoneal to animals of each group. The animals were placed individually into glass beakers and are allowed for 5 min to elapse. The animals were observed for a period of ten min and the number of writhes was recorded for each animal. Writhes were indicated by stretching of the abdomen with simultaneous stretching of at least one hind limb. The percent inhibition of writhes was calculated and compared with test formulation of lornoxicam organogel and the control formulation of marketed diclofenac sodium gel its shown in table-4. The lornoxaicom organogel formulation produced decreasing writhes and shows similar effect as marketed standard formulation.

#### Carrageenan-induced paw edema:-

Carrageenan-induced paw edema is the standard experimental model for acute inflammation. Carrageenan is the phlogistic agent of choice for testing anti inflammatory drugs as it is not known to be antigenic and is devoid of apparent systemic effects. Moreover the experimental model exhibits high degree of reproducibility. The development of edema has been described as biphasic.[30] The first phase (1h) is mediated through the release of serotonin and histamine and the second phase (over 1 h) is mediated by prostaglandins, cyclooxygenase products. Continuity between the two phases is provided by kinins [31].

Acute inflammation was caused by injecting 0.1 ml of 1 % (w/v) carrageenan in saline into the sub-plantar region of the right hind paw of each rats. The paw volume was measured plethysmometrically at 1h, 2h, 3h, 4h, 5h and 6h after the carrageenan injection. Edema was expressed as mean paw volume. The lornoxaicom organogel formulation produced Anti-inflammatory action and decreased paw volume of rats as compared marketed standard formulation (Volini gel, Ranbaxy) as are shown in table-5.

In present experimental studies reveals that lornoxicam organogel formulation (at dose 4mg/kg topically) produced significant analgesic action by increasing the time of paw licking and jump response in the model of Hot plate and decreasing writhes in acetic acid induced pain. Anti-inflammatory action produced by lornoxicam organogel formulation was found significant decreasing the paw volume in the model of carrageenan-induced paw edema.

**Table 1:- Characterization of lecithin organogel system**

Formulation code	Oil: water phase	pH	Drug content %	Swelling index % after 1 hrs	Viscosity at 10 rpm (poise)	Gelation temp	Physiological observation						
							Wash ability	Occlusiveness	Homogeneity	Organoleptic Characteristics			
										Color	Odour	Phase separation	Feel upon application
LOF1	30:70	7.02±0.2	97.93±0.31	87	5483.1	30.3	No	Yes	Yes	Yellow	No	No	Smooth
LOF2	40:60	6.88±0.4	97.87±1.03	96	5567.2	30.1	Yes	Yes	Yes	Yellow	No	No	Smooth
LOF3	50:50	7.21±0.1	96.87±0.54	84	5028.6	24.9	No	Yes	Yes	Yellow	No	No	Smooth
LOF4	60:40	7.15±0.2	95.05±1.54	82	5492.4	27.8	Yes	Yes	Yes	Yellow	No	No	Gritty
LOF5	70:30	6.88±0.3	96.62±0.25	86	5362.6	26.4	No	Yes	Yes	Yellow	No	Yes	Smooth
	<b>Lecithin : IPM</b>												
LOF6	30:70	6.13±0.2	96.37±0.12	88	5261.7	25.3	Yes	Yes	Yes	Yellow	No	No	Smooth
LOF7	40:60	7.01±0.4	95.18±2.00	91	5481.8	27.8	Yes	Yes	Yes	Yellow	No	No	Smooth
LOF8	45:55	7.00±0.1	93.37±1.54	87	5475.2	27.0	Yes	Yes	Yes	Yellow	No	No	Smooth
LOF9	50:50	6.87±0.1	94.81±1.78	80	5568.2	27.0	Yes	Yes	Yes	Yellow	No	No	Stiffness
LOF10	60:40	6.98±0.2	94.18±1.01	89	5477.7	23.8	No	Yes	Yes	Yellow	No	Yes	Gritty
	<b>Propylene Glycol (ml)</b>												
LOF11	2	7.13±0.1	93.25±1.64	82	5367.2	28.4	No	Yes	Yes	Yellow	No	No	Smooth
LOF12	4	5.98±0.3	93.00±1.51	71	5423.7	30.2	Yes	Yes	Yes	Yellow	No	No	Stiffness
LOF13	6	7.02±0.2	95.00±0.21	85	5532.6	30.3	Yes	Yes	Yes	Yellow	No	No	Smooth
LOF14	8	6.88±0.4	92.43±2.10	81	5532.8	30.1	Yes	Yes	Yes	Yellow	No	No	Gritty
LOF15	10	7.21±0.1	93.68±1.56	86	5581.6	32.5	Yes	Yes	Yes	Yellow	No	Yes	Smooth

**Table:-2 Effect of lornoxicam organogel formulation on reaction time of rats in skin irritation study.**

Time (hrs)	Activity
0	No reaction
0.5	No reaction
1	No reaction
2	No reaction
3	No reaction
4	No reaction

**Table 3:-Effect of lornoxicam organogel formulation on reaction time of rats in hot plate method.**

Group	Treatment	Reaction time in sec.							
		Paw licking				Jump response			
		15min	30min	45min	60min	15min	30min	45min	60min
I	Control	38.5±0.4	32.2±0.4	35.4±1.3	38.3±1.4	75.3±1.7	79.0±1.1	72.6±0.9	75.6±0.6
II	Standard	46.6±0.6	49.4±1.2**	62.6±2.3**	68.3±0.5**	89.7±1.5	95.6±0.7**	106.5±2.3**	112.7±1.8**
III	Test	45.4±0.7	47.1±2.5**	50.8±1.5**	55.8±0.4**	81.0±0.7	85.6±0.4**	97.8±0.4**	109.4±0.9**

(Values are mean ± SEM from a group of four animals. \*p<0.05, \*\*p<0.01 when all treatment groups compared to group-I (control). (\* = 95%, \*\* = 99% purity)

**Table 3:-Effect of lornoxicam organogel formulation on 1% acetic acid induced wriths in rats.**

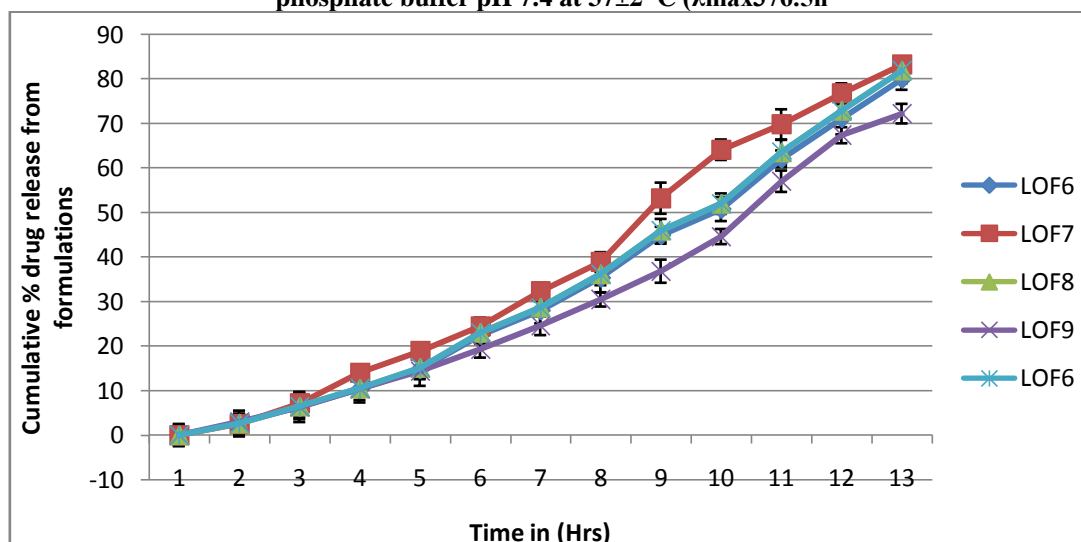
Group	Treatment	Wriths (Mean±SEM)	%Inhibition of Wriths
I	Control	8.0±0.32	-
II	Standard	4.5±0.23**	43.75
III	Test	5.0±0.12**	37.5

(Values are mean ± SEM from a group of four animals. \*p<0.05, \*\*p<0.01 when all treatment groups compared to group-I (control).)

**Table 4:-Effect of lornoxicam organogel formulation on carrageenan induced paw edema.**

Group	Treatment	Paw volume (ml)						% Inhibition
		0h	1h	2h	3h	4h	5h	
I	Control	0.5±0.02	0.8±0.04	1.0±0.03	1.2±0.07	1.5±0.06	1.6±0.08	-
II	Standard	0.5±0.03	0.6±0.05	0.7±0.04	0.8±0.05	0.7±0.03	0.6±0.09	62.5
III	Test	0.5±0.05	0.7±0.02	0.8±0.01	0.8±0.03	0.8±0.05	0.7±0.03	56.25

**Figure 1: Cumulative Effect of Oil: water concentration ratio on in-vitro release profile of lornoxicam in phosphate buffer pH 7.4 at 37±2°C (λmax376.5n**



#### 4. Conclusion

The transdermal organogel formulation of lornoxicam could provide significant anti-inflammatory and antirheumatic activity when applied topically and was observed to be functional for topical

delivery of lornoxicam. The system will not only exert a local effect but also would be capable of achieving a systemic effect via transdermal absorption and their effects are potentiated by the presence of a penetration enhancer. Prepared lornoxicam organogels containing lecithin, isopropyl myristate and polypropylene glycol

were observed to be safe, stable, and cost-effective drug delivery system.

This delivery system particularly helpful for patients with gastrointestinal symptoms (*e.g.*, nausea and vomiting) dizziness, increased drowsiness, headache, increased sweating, taste disorders, dry mouth, agitation, dyspepsia, diarrhoea, palpitation by targeted delivery of lornoxicam to the site of action. it has Thermo reversibility, Reduce pain effectively in arthritis, Easy to apply, Safe for long-term application, Enhance topical performance and biocompatibility, Thermodynamically stable, the structural integrity maintained for longer time periods, Avoidance of the variation in the absorption and metabolism associated with oral administration, Avoidance of the risk and inconveniences of injection.

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