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Formulation and Evaluation of Topical Gel of Lornoxicam Using a Range of Penetration Enhancers

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ABSTRACT

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Topical gel of lornoxicam and enhancement in its percutaneous permeation from carbopol 974p gel by using various penetration enhancers and comparison with marketed formulation was investigated. Skin delivery of non steroidal anti inflammatory agents offers several advantages over the oral route which is associated with potential side effects. Topical gel of lornoxicam was formulated using triethanolamine (5%) as a solvent, carbopol 974p as a gelling polymer and various penetration enhancers. Lornoxicam gel was evaluated with respect to different physicochemical parameters such as pH, viscosity, spreadability. Permeation study was carried out using freshly excised rat skin. Anti-inflammatory activity of lornoxicam gel was studied in albino Wistar rats and compared with the marketed formulation of piroxicam (Pirox® gel, 0.5 %w/w). The optimized formulation (G2) containing 2 % of transcutol P as permeation enhancer gave higher drug release than other penetration enhancers. After 6 h, cumulative permeation of lornoxicam through excised rat skin was 212.46 ± 2.1 µg cm^{-2} with corresponding flux value of 35.41 ± 1.1µg cm^{-2} h^{-1}. Lornoxicam gel exhibited approximately same anti-inflammatory activity in rats compared to Pirox® gel using the rat paw edema method. Physicochemically stable and non-irritant LRN gel was formulated which could deliver significant amounts of active substance across the skin *in vitro* and *in vivo* to elicit the anti-inflammatory activity.

Keywords: Lornoxicam, Penetration enhancers, NSAID, Skin permeation, Transcutol P

INTRODUCTION

The transdermal route has numerous advantages for the administration of drugs for local and systemic therapy[1]. The outermost layer of skin, the stratum corneum (SC) having multilayered wall-like structure, forms a strong barrier to most of the substances including drugs[2]. One of the approach to deliver drug through skin is to reversibly reduce the barrier function of skin with the aid of penetration enhancers or accelerants.[3] The therapeutic efficacy of a drug, following its application to the skin, mainly depends on its capability to penetrate the skin. Since the majority of drugs show inappropriate physicochemical properties to penetrate the skin effectively, different strategies have been developed to increase drug skin permeation[4]. Chemical penetration enhancers have been extensively used to increase drug percutaneous absorption inspite of their disadvantages.[5] The treatment of skin diseases as well as of musculoskeletal disorders might be advantageous from topical administration, obtaining a considerable reduction of the oral side effects with improved patient compliance[1].

Lornoxicam (LRN) is a potent nonsteroidal anti-inflammatory drug (NSAID) used for a variety of inflammatory conditions. The mechanism of action of lornoxicam, like that of other NSAIDs, is primarily due to the inhibition of prostaglandin biosynthesis through the inhibition of the cyclooxygenase (COX) enzymes COX-l and COX-2. Like other NSAIDs, the most common side effect of oral dosage of lornoxicam is gastrointestinal irritation. Thus, the possibility of delivering lornoxicam through the skin for local inflammation at low doses is desirable. Literature survey also reveals that no topical preparation of lornoxicam has been reported till date. In order to increase therapeutic efficacy of topically applied drugs, it is necessary to employ penetration enhancers and /or appropriate vehicle. An attempt has been made, to enhance the transdermal permeation of lornoxicam by using different penetration enhancers in gels made using carbopol[6].

Synthetic penetration enhancers used were transcutol-p, labrasol and triton X-100 to study the topical delivery of lornoxicam across rat skin.

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MATERIALS AND METHODS

Materials:

Materials used were carbopol 974p (Noveon Inc., Cleveland), lornoxicam (FDC, Mumbai), labrasol, transcutol P (Gattefosse, France) and triton X-100 (Loba Chemie, Mumbai). All the solvents used were AR grade.

Animals:

Approximately 170-220 g of male Wistar rats were used. All the experimental procedures and protocols used in this study were reviewed and approved (SCOP/IAEC/Approval/2011-12/17) by the Institutional Animal Ethics Committee (IAEC) of Sinhgad College of Pharmacy, Pune, constituted under

Committee for Purpose of Control and Supervision of Experiments on Animals (CPCSEA). Ethical guidelines were strictly followed during all the experiments

Solubility studies:

Solubility of LRN was determined in distilled water, phosphate buffer solution (pH 7.4), chloroform and 5% triethanolamine solution in water by the shake flask method. Briefly, an excess amount of LRN was added to each vial containing 10 mL of the selected solubilizer. The mixtures were subjected to mechanical agitation for 72 h in an isothermal shaker (Remi, India) at 25 ± 1°C, followed by filtration through Wattmann's filter paper (0.45µm) prior to UV analysis.

Compositions of gels:

0.2% Lornoxicam containing gel formulations were prepared. Carbopol 974p as a base was slowly dispersed into distilled water and allowed to swell for 12 h; lornoxicam (20mg) solution was prepared by dissolving it in triethanolamine (5%) and volume of gel was made up with distilled water. Finally penetration enhancer was added to the base with gentle stirring. The enhancers used in the gel were 1% and 2% of transcutol P, labrasol and triton X-100 (Table 1).

Evaluation of LRN gel:

Drug content was determined by dissolving 0.2g of gel in 100 ml of phosphate buffer solution pH7.4. 1 ml of this solution was transferred into 10 ml volumetric flask and final volume was made by using phosphate buffer solution pH 7.4. Finally absorbance of prepared solution was measured at 378nm using UV visible spectrophotometer.

Brookfield viscometer, model CAP 2000 + L was used for determining viscosity of LRN gel at 50 rpm. pH of each formulation was determined by using pH meter (Equiptronics, Model EQ-610). The pH meter was first calibrated using solutions of pH 4.5 and pH 7.

Table 1: Composition of LRN gel formulations

Ingredients	Composition (%)						
	G0	G1	G2	G3	G4	G5	G6
LRN	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Carbopol 974p	1	1	1	1	1	1	1
5% TES	2	2	2	2	2	2	2
Methyl parabem	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Propyl paraben	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Ethanol	1	1	1	1	1	1	1
Transcutol P	-	1	2	-	-	-	-
Triton X-100	-	-	-	1	2	-	-
Labrasol	-	-	-	-	-	1	2
Distilled water to	100	100	100	100	100	100	100

To determine the spreadability of LRN gel, 2.5 g was placed over one of the slides, over which a second glass plate was placed. A weight of 1000 g was allowed to rest on the upper glass plate for 5 min. The distance travelled by upper slide after removing of weight was calculated and spreadability was calculated using formula.

$$S = ML / T$$

Where,

S, is the spreadability of gel formulations

M, is the weight (g) tied on the upper plate,

L, is the length (cm) of the glass plates, and

T, is the time taken for plates to slide the entire length.

In vitro permeability studies:

Skin preparation:

Abdominal skin of male Wistar rats was used for permeation studies. The rat was sacrificed with ether and the hair of abdomen was carefully removed. Full-thickness skin samples were cut and washed with normal saline. Adhering fats and connective tissues were carefully removed.[7]

In vitro skin permeation studies:

Full-thickness skin was mounted on Franz diffusion cells (vertical; with diffusion area, 1.76 cm^2, volume of receiver cell, 8 mL) with a water jacket (32 ± 1ºC) to assess skin permeability. Phosphate buffer pH7.4 was filled in receiver cells with constant stirring by magnetic beads to ensure adequate mixing and maintenance of sink conditions. Samples were withdrawn at time intervals of 0.5, 1, 2, 3, 4, 5, 6 hr and an adequate volume of blank solution was added immediately.

Anti-inflammatory activity:

Anti-inflammatory effect of topically applied LRN gel was determined in male Wistar rats (180 ± 10 g, 6–8 weeks) by the carrageenan induced rat paw edema method.[8-9] For this purpose, rats were divided into three groups (n = 6): group 1 – LRN gel without penetration enhancer (G0), group 2 – optimized LRN gel (G2), group 3 – Pirox® gel. They were housed individually in the animal house with free access to food and water. Briefly, 30 min after formulation application (0.5 g), rats of both treated groups were challenged by a subcutaneous injection of a 1 % (w/v) solution of carrageenan in saline (0.1 mL) into the plantar site of the right hind paw. The paw volume was measured using digital plethysmometer (Orchid Nasik) just before and 1, 2, 3, 4 and 6 h after carrageenan administration. The percent inhibition of edema at any time was calculated for each rat and the difference between LRN gel and Pirox® gel was evaluated statistically. Animal care and handling throughout all three experimental

procedures described above were performed in accordance with the CPCSEA guidelines. The experimental protocols were approved by the Animal Ethics Committee of the Sinhgad College of Pharmacy, Pune, India.

RESULTS AND DISCUSSION

Solubility:

Solubility studies helped to rationalize the choice of vehicle for gel formulation. LRN is poorly soluble in water (0.0385 ±0.01 mg mL^{-1}). Among the different solubilizers screened, LRN exhibited the highest solubility in 5% triethanolamine solution (42.5 ± 0.36 mg mL^{-1}). Solubility of LRN in chloroform and in PBS pH7.4 was 0.26 ± 0.03 and 0.15 ± 0.05 mg mL^{-1} respectively. Hence 5% triethanolamine solution was selected as the vehicle of choice to formulate LRN gel, based on its solubilization capacity.

Formulation and evaluation of LRN gel:

1%w/w of carbopol 974p was used for preparing gel on the basis of the optimum viscosity and spreadability because at 0.5% w/w it produced a gel with fluid consistency as well as 1.5% w/w produces a gel with high viscosity and lower spreadability.

LRN content of optimized gel was found to be 100.01 ± 0.2% (n = 3). Viscosity of LRN gel was found to be 10170 ± 50cps. The pH of LRN gel was 6.75 ± 0.13 (n = 3), which is a physiologically acceptable pH for topical preparations.

Topical formulation with higher spreadability allows ease of application and thereby increased surface area available for drug permeation. The spreadability of LRN gel was found to be 6.5 ± 0.38 g.cm/sec (n =3), which is indicative of good spreadability.

In vitro permeability studies:

The amount of LRN released after 6 was 212.46 ± 2.1 for G2. The corresponding LRN flux was 35.41± 0.15 for G2 (Table 2). About 60 % of the applied amount of LRN permeated across the skin from G2. This clearly indicates that the TP (2%) showed higher permeation amongst all penetration enhancers (Fig. 1). Thus there was 2 fold increase in the flux for G2 formulation as against the one which had no penetration enhancer.

Table 2: Effect of penetration enhancers on topical permeation of lornoxicam across rat skin

Parameter	Formulation						
	G0	G1	G2	G3	G4	G5	G6
Flux (µg/cm^2)	109.92	170.69	244.68	114.58	128.59	121.58	140.67
Flux (µg/cm^2/hr)	18.32	28.45	40.78	19.09	21.43	20.26	23.45
% drug permeated in 6h	27.48	44.72	59.52	28.38	32.78	30.59	35.29

Anti-inflammatory activity:

In anti-inflammatory activity test using carrageenan as the phlogistic compound, Pirox® and optimized LRN gel exhibited anti-inflammatory activity up to 6 h (Fig. 2) and peak activity was observed between 2–6 h for all formulations. Gel (G2) exhibited approximately similar anti-inflammatory activity compared to Pirox® gel. % edema inhibition produced by the application of Pirox® gel was 18 and 50 % after 1and 6 h respectively and for gel G2 % edema inhibition was 14 and 42 % after 1and 6 h respectively. The observed increase in activity of G2 and Pirox® was around 3.23 fold and 3.84 fold respectively as compared to gel without penetration enhancer (G0). Since no topical formulation of LRN is available on the market, Pirox® gel (0.5 %, w/w piroxicam) was used for comparison to study the anti-inflammatory activity. The results confirm the fact that a significant amount of LRN was delivered from the gel through skin to induce the anti-inflammatory effect (Fig. 2). Transcutol P enhances topical penetration of drug by increasing partitioning and solubility within the stratum corneum so this may be the probable mechanism for permeation of LRN across skin.

Fig. 1: % cumulative release of all formulations through rat skin

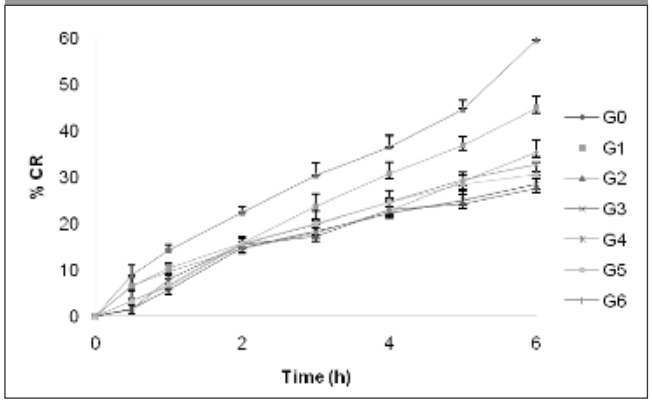
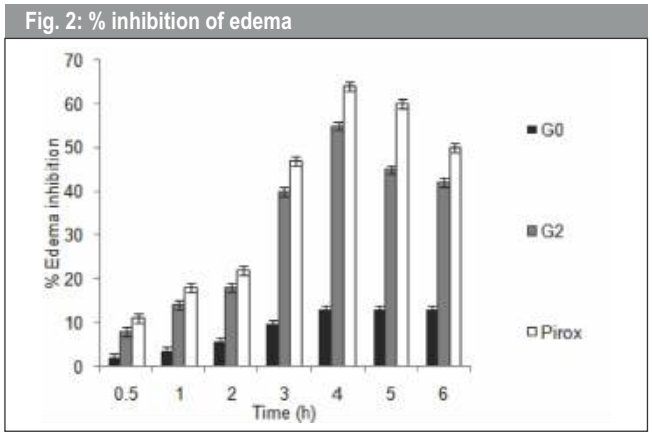


Fig. 2: % inhibition of edema



CONCLUSION

Above investigation presents physiologically stable topical gel of lornoxicam which would minimize oral side effects of lornoxicam and deliver significant amount of lornoxicam across skin. Transcutol P in 2% concentration showed maximum flux rate for lornoxicam across skin among all penetration enhancers. The present formulation provides anti inflammatory effect similar to marketed formulation (Pirox®).

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