Topical Delivery of Lornoxicam: Design, Evaluation and Effect of Penetration Enhancers

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ABSTRACT

The present work reports formulation development and evaluation of a topical gel of Lornoxicam (0.5% w/w) a non-steroidal anti-inflammatory drug is a potent inhibitor of cyclooxygenase-2 using different gelling agents and different penetration enhancers. The gels were formulated using gelling agents like Carbopol 974 and Poloxamer 407. Various penetration enhancers/solubilizers like Cremophore RH 40, DMSO and Transcutol P and variation in their concentration was studied for their effect on the drug release profiles, permeation enhancement and flux values of the gels. The gels were evaluated for pH, clarity, viscosity, drug content, in vitro and ex vivo diffusion studies. The finalized formulations were evaluated for caregennan induced rat paw edema to demonstrate anti-inflammatory effect. The final gel prepared with Poloxamer 407 and Transcutol P showed excellent aesthetic appeal. Viscosity and pH were well within the acceptable range. In vitro and ex vivo diffusion study of formulations prepared using Transcutol P and Poloxamer 407 showed drug release of 68.45% and 76.69% respectively at the end of 5 hours. Rat Paw edema corroborated with the in vitro and ex vivo diffusion. A significant difference (p<0.5), was seen in the finalized Poloxamer based formulation as compared to placebo gel for a duration of 4 hours.

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INTRODUCTION:
The terms “arthritis” and “rheumatic disease” refer to more than 100 diseases that cause inflammation, pain, and limited joint mobility throughout the body. In the U.S (United States), almost 21 million adults deal with osteoarthritis while more than 400,000 people are affected with Rheumatoid Arthritis in the UK [1]. The cost of treatment of Arthritis and other rheumatic diseases is around $86.2 billion, including an estimated $51.1 in direct medical costs (payments) and $35.1 in indirect costs (lost productivity) [2]

Non-steroidal anti-inflammatory drugs are used to relieve the symptoms of RA. Both the benefits and potential risks of NSAID exerts their effect on the formation of prostaglandins from arachidonic acid, through inhibition of the enzyme COX [3]. Oral NSAIDs/COX-2 inhibitors should be used at the lowest effective dose for the shortest possible period of time. All oral NSAIDs/COX-2 inhibitors have analgesic effects of a similar magnitude but vary in their potential gastrointestinal, liver and cardio-renal toxicity[4].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are mainstays of the treatment of osteoarthritis (OA) but have dose- and age-related risks of gastrointestinal, cardiovascular, and renal adverse events (AEs). As a result, US and international guidelines recommend caution when prescribing oral NSAIDs, particularly in older patients and those with significant comorbidities. For OA of the hands and knees, topical NSAIDs provide efficacy similar to oral NSAIDs, with far less systemic distribution. At present, only 2 topical NSAIDs are approved in the United States for the treatment of OA: diclofenac sodium 1% gel for hand or knee OA and diclofenac sodium 1.5% in 45.5% dimethylsulfoxide solution for knee OA [5,6].

Lornoxicam, NSAID, of the oxicam class is a potent inhibitor of cyclooxygenase-2 with the advantage of less gastric irritation. It is a BCS class II drug. Like most of the NSAIDs, lornoxicam is very sparingly soluble in water. This insolubility causes serious hindrance in the formulation of such compounds for topical, oral, parenteral or ophthalmic administration, in particular for intravenous use. Lornoxicam being is a weak acid (pKa of 4.7), its aqueous solubility is pH dependent. Decreasing the pH leads to an increase in the ratio of non-ionized to ionized drug, and in solubility-pH profiles, the solubility of lornoxicam increases exponentially with the increase of pH from 3.0 to 9.0 [7,8,9,10,11].

Singla, et al have investigated a topical Emulsion of Lornoxicam using carbopol 934, carbopol 940 and HPMC K4M[12]. Stationwala et. al formulated a Pluronic F127 and lecithin organogel of Lornoxicam [13]. It is evident that research on topical application of lornoxicam is underway but currently there are no topical marketed preparations available. It is imperative to avoid the gastric and other associated side effects of oral NSAIDs. this can be achieved by topical application of NSAIDS directly to the affected area which will reduce the adverse effects and optimal relief from pain will be achieved in a shorter span of time with equal probable efficacy. Hence formulation development and evaluation of a topical gel of Lornoxicam (0.5% w/w) using different gelling agents and different penetration enhancers is presented here.

**MATERIALS:**

Lornoxicam was obtained as a gift sample from Alkem Labs India Pvt Ltd. Transcutol P was gifted by Gatefosse Ltd, Carbopol 974 from Lubrizol, Lutrol F 127 from BASF India Ltd. All solvents used were of AR grade and were obtained from SD Fine and Qualigens

**METHODS:**

**Drug Characterization:** Lornoxicam was characterized for its physical and chemical properties. The appearance and particle size of the drug was determined using photographic microscope (Motik, BI-Advanced series). FTIR spectra (Spectrum-RXI) was recorded and the spectral peaks were compared to that of Lornoxicam. The absorbance maximum of the drug was determined by Ultra Violet spectroscopy (Perkin-Elmer, Lambda 25) and an accurate method for analysis was developed.

**Drug Excipient Compatibility Study:** Although considered pharmaceutically inert, excipients can initiate, propagate or participate in chemical or physical interaction with drug compounds, which may compromise the
effectiveness of a medication. hence to predict possible drug and excipient interactions drug excipient compatibility study was carried out. The ratios of drug and excipients were selected, considering the required ratio of each excipient to the drug in final formulations. They were kept at a temperature of 50°C in order to facilitate chemical reactions if any. Compatibility was checked using FTIR. At the end of 15 days an FTIR spectra was recorded. The integrity of loroxamic was checked by presence or absence of prominent peaks [14].

**Development of Topical Gels:** Carbopol 974 and Poloxamer 407 (Lutrol F127) were investigated for their gelling properties. Since Loroxamic is insoluble in most aqueous and organic solvents, it posed difficulties in development of a homogenous, transparent gel. The drug being soluble in only basic pH, 0.1 N sodium hydroxide, was used to solubilize the drug. Different solubilizers are required to reduce quantity of 0.1 N NaOH and to maintain pH between 6 -7. Cremophore RH 40, Transcutol P and DMSO play the dual roles of permeation enhancers as well as solubilizers. To provide soothing and cooling effect menthol was added. Menthol being a terpene is also beneficial as a permeation enhancer. Methyl Paraben was used to preserve the aqueous based gel. Few drops of Triethanolamine were added to neutralize formulations while utilizing carbopol as the gelling agent.

**Formulation of gels containing carbopol 974 as the gelling agent:**
A 1% gel of carbopol was initially prepared to which an ethanolic solution of methyl paraben and menthol was added. The drug was dissolved by sonication in required amount of 0.1 N sodium hydroxide along with solubilizers like transcutol, DMSO and Cremophore and this solution/dispersion was then added to the gel under constant stirring. The pH of the gel was adjusted to neutral with Triethanolamine. The formulations were coded from CF1 to CF8 and are given in table 1.

**Formulation of gels containing Poloxamer 407 as the gelling agent:**
A 20% gel of Poloxamer 407 was prepared by dissolving poloxamer in water. Initially bubbles formation was observed when water was used at room temperature so to overcome this, cold method was used where the poloxamer was dispersed in the water at 4 - 8°C and was maintained at this temperature for 6 – 8 hours till a clear solution was visible. Drug was dissolved into 0.1 N NaOH along with a solubilizer using sonication. Ethanolic solution of methyl paraben and menthol were added to the gelling solution. The formulations were coded from PF1 to PF6.

**EVALUATION OF GELS:**

**Physicochemical Evaluation:**
Gels were evaluated for their visual and aesthetic appeal, homogeneity and clarity of the gels were observed. The gels which showed promising attributes were further evaluated for viscosity using a Brookfield’s viscometer (DV pro II) and their pH was measured using a calibrated pH meter. Drug content using UV spectrophotometer was determined for all batches of Poloxamer 407 and Carbopol. Only the batches showing desired properties were evaluated for in vitro, ex vivo diffusion studies and in vivo activity on rats.

**Drug release:**

- **In Vitro:** Drug release from selected gels was studied through a 0.45 µm dialysis membrane. The membrane was mounted on Franz diffusion cells having a surface area of 3.14 cm² and receptor compartment with a capacity of 20 ml. The Receptor compartment was filled with Phosphate buffer solution (PBS) pH 7.4 as diffusion medium at 37±0.5°C. Reservoir solution was stirred continuously. 500 mg of gel was applied on membrane. Aliquots were withdrawn and were suitably diluted with isotonic PBS pH 7.4 and analyzed against a blank by UV spectrophotometer at 376 nm. The flux of the gels was calculated.
**Ex Vivo Diffusion studies:** Fresh skin was excised from the porcine ear region and adhering fat and other cartilage tissues were removed, the skin was used immediately after excising. It was sandwiched between the recipient and donor compartments of the Franz diffusion cells. Diffusion coefficient and Flux were determined.

**Table No 1: Key Formulation trials of Lornoxicam gels**

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>CF1</th>
<th>CF2</th>
<th>CF3</th>
<th>CF4</th>
<th>CF5</th>
<th>CF6</th>
<th>CF7</th>
<th>CF8</th>
<th>PF6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lornoxicam</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
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<td>Carbopol 974</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Poloxamer 407</td>
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<td>...</td>
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<td>DMSO</td>
<td>...</td>
<td>5</td>
<td>10</td>
<td>...</td>
<td>...</td>
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<td>...</td>
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<td></td>
</tr>
<tr>
<td>Cremophore RH 40</td>
<td>...</td>
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<td>...</td>
<td>1</td>
<td>...</td>
<td>...</td>
<td>...</td>
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<td></td>
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<tr>
<td>Transcutol*P</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>10</td>
<td>15</td>
<td>20</td>
<td>25</td>
<td>10</td>
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<tr>
<td>0.1 N NaOH</td>
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<td></td>
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<td></td>
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<tr>
<td>Methyl Paraben</td>
<td>1</td>
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<tr>
<td>Menthol</td>
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<td>Ethanol</td>
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<td></td>
<td></td>
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<tr>
<td>Water</td>
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<td></td>
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</tbody>
</table>

*Quantity sufficient to solublize the drug
Quantity sufficient to dissolve menthol and methyl paraben
To Adjust pH to Neutral
Q.S to100%

**In Vivo anti-inflammatory activity:**

The experimental protocol (CPCSEA/IAEC/SPTM/P-16-2012) was designed and approval of Institutional Animal Ethics Committee. The animals were housed in institutional animal house under standard conditions with free access to food and water. Carrageenan induced Rat Paw Edema was conducted on formulation code PF 6 and CF5 along with Placebo and control groups. The rats were divided into 4 groups, group I was control where carrageenan was not injected, group II was placebo where carrageenan was injected but gel was not applied. Group III was treated with gel coded CF5, group IV was treated with gel coded PF6. Each group comprised of 6 rats. Subplanar injection of 0.1 ml of a 1% (w/v) solution of carrageenan was given in the hind paw of the rats and a preweighed amount of gel was applied to it. Reduction in edema was measured using vernier callipers on an hourly basis in three different directions. An average of three readings was taken every hour for 5 hours. Student’s t test was applied to the results and the reduction in inflammation was statistically evaluated for significance (p).

**RESULTS:**

The FTIR spectrum of lornoxicam showed a characteristic peak at 3433.73 cm\(^{-1}\) corresponding to –NH stretches vibration. Intense absorption peak was found at 1647.31 cm\(^{-1}\) due to the stretching vibration of the C=O group in the primary amide. Other peaks in the range between 1600 to 1400 cm\(^{-1}\) were observed and were assigned to bending vibrations of the N–H group in the secondary amide.
**Fig1: FTIR spectra of lornoxicam**

**Appearance, viscosity, pH and drug content:** The results obtained for appearance, color, odour, viscosity and pH are listed in table no 2. pH was found between the range of 6 and 7 and viscosities of the gels were satisfactory. Drug content was also found satisfactory in the range of 95 – 105%.

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Appearance</th>
<th>Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Colour</td>
</tr>
<tr>
<td>CF1</td>
<td>Homogeneous/without any air bubbles</td>
<td>Yellow</td>
</tr>
<tr>
<td>CF2</td>
<td></td>
<td>Yellow</td>
</tr>
<tr>
<td>CF3</td>
<td></td>
<td>Yellow</td>
</tr>
<tr>
<td>CF4</td>
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<td>Yellow</td>
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<tr>
<td>CF5</td>
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<td>Yellow</td>
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<tr>
<td>CF6</td>
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<td>Yellow</td>
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<tr>
<td>CF7</td>
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<td>Yellow</td>
</tr>
<tr>
<td>CF8</td>
<td></td>
<td>Yellow</td>
</tr>
<tr>
<td>PF1</td>
<td>Air Bubbles</td>
<td>Yellow</td>
</tr>
<tr>
<td>PF2</td>
<td></td>
<td>Yellow</td>
</tr>
<tr>
<td>PF3</td>
<td></td>
<td>Yellow</td>
</tr>
<tr>
<td>PF4</td>
<td></td>
<td>Yellow</td>
</tr>
<tr>
<td>PF5</td>
<td>Clear gel, Less Air Bubbles</td>
<td>Yellow</td>
</tr>
<tr>
<td>PF6</td>
<td>Clear gel, No Air Bubbles</td>
<td>Yellow</td>
</tr>
</tbody>
</table>
In vitro and Ex Vivo drug diffusion results indicate that the drug release is higher in case of Formulation PF6 than CF5 (Fig 2).

![Invitro Drug diffusion from Gels](image1)

**Figure 2:** In-vitro drug diffusion of Lornoxicam from gels

Ex vivo diffusion was studied for the formulation trials CF5 and PF6 using porcine ear skin to demonstrate the drug release (Fig 3).

![Ex Vivo drug Diffusion from gels](image2)

**Figure 3:** Ex-Vivo drug diffusion of Lornoxicam from gels CF5 and PF6

The% drug release at the end of 5 hours was found 68.53% and 77.89% for CF5 and PF6 respectively. The results indicate that drug release is higher in case of PF6 than CF5. Rat Paw edema corroborated with the in vitro and ex vivo diffusion.

![Flux values of gels](image3)

**Figure No 4:** Flux values of Lornoxicam from the gels
DISCUSSION:
Drug excipient compatibility results did not show significant difference in the FTIR spectra. All the prominent peaks of Lornoxicam were present in the drug excipient mixtures which clearly indicate that the drug has retained its identity without losing its characteristics.

The complication of bubble generation was not observed while formulating the carbopol formulations. Poloxamer 407 formulations had problems such as air bubbles which were overcome using the cold method of formulating a gel instead of the hot method. The formulations obtained by carbopol were not transparent while those obtained using poloxamer were transparent and aesthetic in appearance.

Increasing the concentration of DMSO from 5% to 10% did not show any significant increase in the enhancement of flux of the gels and neither did use of Cremophore affect the invitro permeation of the drug. The drug release was hence not considered as satisfactory using cremophore and DMSO. Transcutol P showed a significant increase in the penetration of Lornoxicam, but it was observed that increasing its concentration from 10 % to 15% and 20 % did not further enhance the penetration.

Poloxamer based formulation PF6 enhanced activity as compared to the placebo. Poloxamer based formulation shows a significant difference (p<0.5), from placebo for a duration of 4 hours while carbopol based formulation shows a significant difference from the placebo for a period of 2 hours. Statistical difference was also observed when the anti-inflammatory effect of PF6 was compared to that of CF5, where PF6 was found significantly better than CF5 Thus, use of Poloxamer 407 as a gelling agent and & Transcutol as a penetration enhancer gives better results.

CONCLUSION:
An aesthetic, homogenous gel of Lornoxicam was developed. Based on flux and invitro drug diffusion studies, it was observed that transcutol shows better enhancement of penetration as compared to Cermophore RH 40 and DMSO as penetration enhancers. Use of Poloxamer 407 showed more control of inflammation as compared to Carbopol 974 as a gelling agent. Alleviation of pain can thus be achieved by use of a topical gel of Lornoxicam. Looking forward there is scope to develop microemulsions and emulgels as topical delivery systems of Lornoxicam in order to aid permeation through the lipophillic skin barrier.

ACKNOWLEDGEMENTS
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CONFLICT OF INTREST
The authors declare no conflict of interest.
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