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Formulation and Evaluation of Lornoxicam Topical Gel

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ABSTRACT

The aim of this work is to improve the anti-inflammatory activity of Lornoxicam through incorporating it in a topical gel using different polymers as Carbopol 934, Sodium carboxy methylcellulose or Sodium alginate. Various penetration enhancers (Glycerin, Polyethylene glycol or Sorbitol) were used with objective of enhancement in the percutaneous permeation of the drug. Formulations were evaluated for pH, drug content, rheological properties, spreadability, *in-vitro* drug release in phosphate buffer (pH 6.5) and permeation study through cellulose membrane. Anti-inflammatory activity of Lornoxicam gel was studied in rats by carrageenan induced paw edema method and compared with the commercial formulation (Feldene® gel). Considering physical properties, *in-vitro* release and *in-vitro* permeation studies, FS1 (Lornoxicam gel containing 1% Carbopol with 10% Sorbitol as penetration enhancer) was the best formula among the studied formulations, this formula also exhibited significantly higher anti-inflammatory activity in rats compared to Feldene® gel.

Keywords: Lornoxicam; Topical gel; Penetration enhancers; In-vitro drug diffusion study; Anti-inflammatory activity.

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INTRODUCTION

Topical preparations are used for the localized effects at the site of their application by virtue of drug penetration into the underlying layers of skin or mucous membranes.[1] Some of the advantages of topical drug delivery systems are the avoidance of first pass metabolism, convenient and easy to apply, avoidance of the risks and inconveniences of intravenous therapy and of the varied conditions of absorption, provide a relatively large area of application in comparison with nasal or buccal cavity, ability to deliver drug more selectively to a specific site, improve patient compliance and provide suitability for self-medication.[2]

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 don't penetrate the skin effectively, different strategies have been developed to increase drug skin penetration. Chemical penetration enhancers have been extensively used to increase drug percutaneous absorption.[3; 4]

Gels are semisolid systems consisting of dispersions of small or large molecules in an aqueous liquid vehicle rendering jelly-like by the addition of gelling agent. Gels often provide a faster release of drug substance, independent of the water solubility of the drug, as compared to ointments and creams.[5] Gels for dermatological use have several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removed, emollient, non-staining and compatible with several excipients.[6]

Lornoxicam belongs to an oxicam class of nonsteroidal anti-inflammatory drugs. It inhibits cyclooxygenase enzyme and thereby interferes with prostaglandins synthesis. This leads to desensitization of peripheral nociceptors which further reduces inflammation.[7] There is no topical dosage form of the drug available commercially. Oral administration requires repeated administration of Lornoxicam, also it has a very poor solubility in acidic pH of the stomach and hence remains in the stomach wall for a long period, aggravating its potential side effects like peptic ulcers and gastric irritation. Parenteral administration, on the other hand, is not applicable to chronic conditions. Topical delivery of Lornoxicam with high therapeutic efficacy will avoid its systemic side effects by targeting the drug to the skin.[8]

MATERIALS AND METHOD

Materials

Lornoxicam pure sample, Polyethylene glycol (PEG 400) and Sodium Carboxy methylcellulose (NaCMC) were kindly supplied by Global Napi Pharmaceuticals (GNP). Carbopol 934 was kindly

supplied by Novartis Pharma. Tween 80 and Triethanolamine were obtained from Delta Pharma. Sorbitol was supplied by EVA Pharma. Glycerin, sodium alginate were obtained from International Trade Association. Cellulose membrane, molecular weight cut off 10,000 (Arthur H. Thomas Co., Philadelphia, Pa, USA). Carrageenan was obtained from Sigma Chemical Company. Ethanol and saline were of analytical grade.

Methods

Determination of lornoxicam solubility and partition coefficient

The solubility of lornoxicam in water, phosphate buffer of pH 6.5, ethanol and mixture of ethanol & tween 80 (5%) were determined by equilibrating an excess amount of drug with the solvent in a thermostatically controlled water bath at 37^{o}C for 48 hours**.** The solution was then filtered through 0.45 µm filter, suitably diluted with an appropriate solvent and analyzed spectrophotometrically at λ_{max} 378 nm with reference to a corresponding calibration curve. The test was done in triplicate.[9]

To determine the partition coefficient, phosphate buffer pH 6.5 was used as water phase. The partition coefficient was determined using shake flask method by dissolving known concentration of lornoxicam in 20 ml of 50:50 octanol and phosphate buffer mixture in a conical flask. The flask was agitated for 2 hours at ambient temperature and then allowed to stand for 2 hours in order to separate into two layers completely. The aqueous phase was separating from the oil phase using separation funnel. The amount of lornoxicam in each layer was measured using UV-spectrophotometer at 378 nm and partition coefficient was calculated.[10]

Preparation of lornoxicam topical gels

The composition of lornoxicam topical gel formulae are shown in table 1. The calculated amount of lornoxicam (1% w/w) in each formula dispersed in the stated amount of tween 80 (5% w/w) and absolute ethanol (10% w/w) using magnetic stirring bar, then complete with phosphate buffer, pH 6.5 required to prepare 100 gm.[11] The specified amount of the gelling polymer, carbopol 934 (1%), NaCMC (4%) or sodium alginate (7%) was dispersed on drug mixture prepared using magnetic stirring bar. The other additives namely, glycerin or PEG 400 was added as plasticizer in a concentration 5% w/w while sorbitol was added in a concentration 10% w/w. The dispersion was left overnight to ensure complete swelling of the polymer. The carbopol gel was spontaneously formed by the addition of triethanolamine (TEA) dropwise till neutralization.[12]

Table 1: Composition of different lornoxicam formulations

Ingredients (%w/w)	F1	F2	F3	FG1	FP1	FS1	FG2	FP2	FS2	FG3	FP3	FS3
Lornoxicam	1	1	1	1	1	1	1	1	1	1	1	1
Carbopol 934	1	-	-	1	1	1	-	-	-	-	-	-
NaCMC	-	4	-	-	-	-	4	4	4	-	-	-

Sodium alginate	-	-	7	-	-	-	-	-	-	7	7	7
Ethanol	10	10	10	10	10	10	10	10	10	10	10	10
Tween 80	5	5	5	5	5	5	5	5	5	5	5	5
TEA	q.s.	-	-	q.s.	q.s.	q.s.	-	-	-	-	-	-
Glycerin	-	-	-	5	-	-	5	-	-	5	-	-
PEG 400	-	-	-	-	5	-	-	5	-	-	5	-
Sorbitol	-	-	-	-	-	10	-	-	10	-	-	10

Evaluation of lornoxicam gels

Colour, homogeneity and texture

Colour, homogeneity and texture of the prepared gels were tested by visual examination.

Determination of pH

pH of the prepared formulae was determined by digital pH meter using the following method: one gram of the gel was diluted with 9 grams of distilled water and shake well. The pH measurements were repeated three times for each formula and the reading was the average.[13]

Spreadability test

The spreadability of the formulated gels was measured by spreading of 0.5 gm of gel on a circle of 2 cm diameter pre marked on a glass plate and then a second glass plate was employed.[14] A 5 gm weight was permitted to rest on the upper glass plate for 5 minutes.[15] The diameter of the circle after spreading of the gels was determined.

Determination of drug content

Drug content was determined by dissolving 1 gm of gel in 100 ml of phosphate buffer solution pH, 6.5. Filter and then 1 ml of filtrate was transferred into 10 ml volumetric flask and final volume was made using phosphate buffer solution pH, 6.5. Finally absorbance of prepared solution was measured at 378 nm using UV visible spectrophotometer.[16]

Rheological properties measurement

The viscosity was determined using Rheometer (viscometer), Model Brookfield HVDV-III cp, USA (CTS Company). The measurement was started at 0.5 rpm; the speed was gradually increased till reached 250 rpm, the speed was then reduced gradually until reaching the starting rpm.[17; 18] 30 seconds interval between 2 successive speeds was adopted to generate a complete flow curve. A complete rheogram was obtained by plotting the shear rate as a function of shear stress.

***In-vitro* release studies**

The dissolution rate studies were performed on the prepared gels enclosed in tea bags[19] using USP dissolution tester, apparatus II (paddle method). The dissolution medium was 250 ml of phosphate buffer pH 6.5. The stirring speed was 50 rpm, and the temperature was maintained at 37^{o}C ±

0.5°C.[20] Samples of 5 ml were withdrawn and replaced with fresh medium at specified time intervals 5, 10, 15, 30, 45, 60, 90, 120, 150, 180, 210 and 240 minutes. The samples were filtered and analyzed spectrophotometrically.

Kinetic treatment of the *in-vitro* release data

Specific computer program was used to determine the kinetic parameter of the *in vitro* release of lornoxicam from prepared gels. Zero, first orders and diffusion model kinetics were tried to choose the most suitable kinetic order of lornoxicam release. Stating the proper mode of the release is based on the correlation coefficient (r) for parameters involved; where the highest correlation coefficient represents the actual mode of the release.

***In-vitro* diffusion study of lornoxicam gels, through cellulose membrane**

A sample of 0.5g (≡5 mg lornoxicam) of the preparation was spread on a cellulose membrane previously soaked overnight in the release medium. The loaded membrane was firmly stretched over the edge of a glass tube of 2 cm diameter; the membrane was tied up with a rubber to prevent leakage.[21; 22] Tubes were then immersed in the dissolution vessel and the same conditions of *in-vitro* release were applied at specified time intervals 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6 and 24 hours.[23; 24]

Anti-inflammatory evaluation of the selected formulae

All animal procedures were performed in accordance with protocols reviewed and approved by The Scientific Research Ethics Committee of Faculty of Pharmacy, Al-Azhar University, which complies with the Egyptian Law of Human Care and Use of Laboratory Animals.

Anti-inflammatory effect of topically applied lornoxicam was determined in adult male rats (180 ±20 gm) by the carrageenan induced rat paw edema method.[25]

Since no topical formulation of lornoxicam is available on the market, feldene® gel (0.5% w/w piroxicam) was used for comparison to study the anti-inflammatory activity.

The rats were housed in groups and allowed free access to food and water prior to the experiment. They were divided into four groups (n=6). Inflammation was induced by injecting 0.1 ml of the 1% w/v homogenous suspension of carrageenan in saline into the plantar surface of the left hind paw of the rats. The drug was given according to the following schedule: group 1 (control group): carrageenan (Injected) + no treatment, group 2 (Standard group): treated topically with feldene®, group 3 and 4: treated topically with FS1 and FS3 respectively.

The inflammatory response was determined by measuring the paw thickness (cm) using a micrometer caliper just before and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6 and 24 hours after carrageenan administration.[26]

The percentage inhibition of the edema was calculated for each group using the following formula:

% inhibition of odema = Co-Ct/Co × 100

Where, Co is the average increase in paw volume (average inflammation) of the control group at a given time; and Ct is the average inflammation of the drug treated group at the same time.[27]

Statistical analysis

The obtained data were compared statistically using one-way analysis of variance (ANOVA), using Tukey-Krammer Multiple Comparison Test. A P-value of 0.05 or less was considered to be significant.

RESULTS AND DISCUSSION

Lornoxicam solubility and partition coefficient

Solubility studies helped to rationalize the choice of vehicle for gel formulation. Lornoxicam is poorly soluble in water (0.007 ± 0.21 mg/ml). Among the different solubilizers screened, lornoxicam exhibited the highest solubility in the mixture of ethanol and tween 80 (5%) solution (2.14 ± 0.31 mg/ml) as shown in figure 1. Hence, the mixture of ethanol and tween 80 solution was selected as the vehicle of choice to formulate lornoxicam gels.

The partition coefficient was found to be 1.9. This value is less than 2.5 which means expected improvement in lornoxicam absorption.

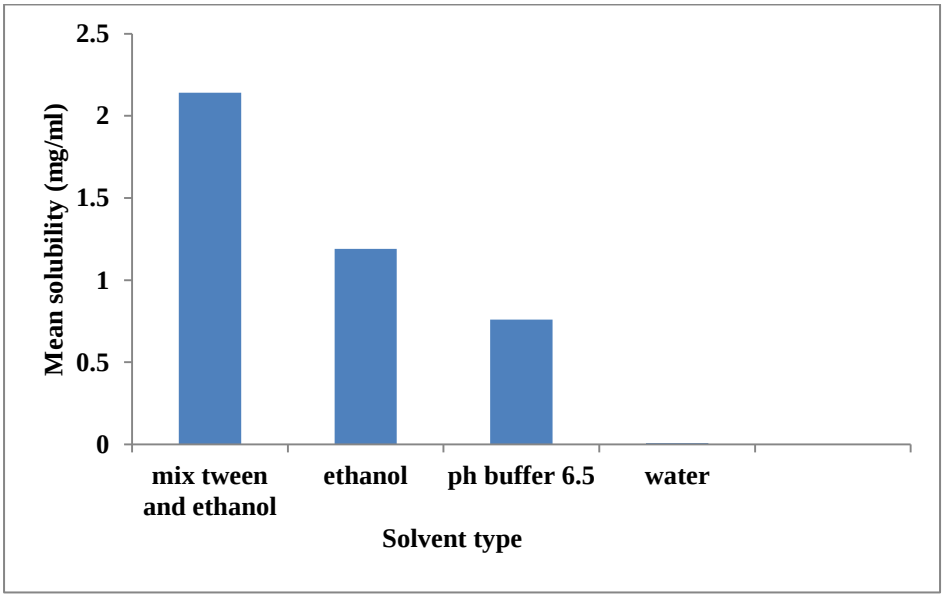


Figure 1: The mean solubility of lornoxicam in various types of solvents

Colour, homogeneity and texture

The visual observation of the selected bases shows yellow colour, smooth texture and homogeneity.

pH Determination

The pH values of all the prepared formulations ranged from 5.69±0.09 to 6.92±0.06, which probably would not produce skin irritation. Hence, the prepared lornoxicam gels are suitable for dermatological purpose.

Spreadability

Spreadability of the topically applied formulation is an important property considering patient compliance. Formulations with higher spreadability values allow ease of application and thereby increased surface area available for drug permeation.[28] The diameters following the spreadability test are found to be between 3.00±0.02 and 3.81±0.01 cm, which indicates good spreadability.

Drug content

The determined drug content values were ranged from 99.26±0.23 to 103.44±0.06%. All the gels show presence of high drug content and low standard deviations of results. It indicates that the drug is uniformly distributed in the gel formulation. Therefore, the method used in this study appears to be reproducible for the preparation of gels. Physical characters of gel bases are tabulated in table 2.

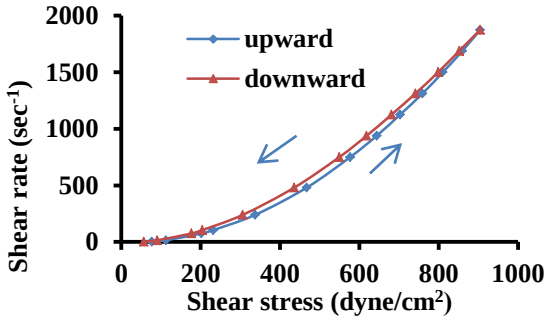
Table 2: Physical characters of the tested formulations containing lornoxicam

Formulations	Colour	Drug content (%)	pH	Spreadability diameter (cm)
F1	Opaque yellow	99.26 ±0.23	5.87±0.32	3.25 ±0.05
F2		103.04 ±0.29	6.52±0.13	3.63 ±0.01
F3		103.44 ±0.06	6.15±0.11	3.00 ±0.02
FG1		100.32 ±0.38	5.69±0.09	3.81 ±0.01
FP1		100.40 ±0.18	6.92±0.06	3.75 ±0.09
FS1		99.34 ±0.23	6.21±0.09	3.68 ±0.22
FG2		101.38±0.35	6.65±0.08	3.62 ±0.09
FP2		101.45±0.25	6.57±0.02	3.12 ±0.14
FS2		101.88 ±0.33	6.77±0.10	3.25 ±0.04
FG3		100.39 ±0.08	6.45±0.05	3.75 ±0.21
FP3		100.23 ±0.27	6.45±0.04	3.57 ±0.07
FS3		101.38 ±0.31	6.29±0.08	3.75 ±0.31

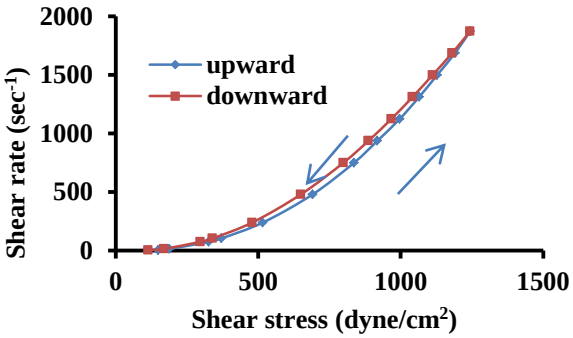
*All values are Mean ± SD, (n=3)

Rheological properties measurement

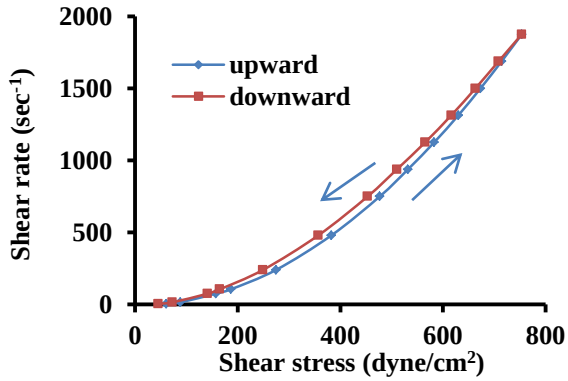
For topical analgesic formulations, the consistency of the samples is specially an important feature, due to the fact that it must be applied to the skin in thin layers.[29; 30] For this reason, it is preferable to formulate non-Newtonian flow system because of its low resistance to flow when applied under high shear conditions**.** In this study, lornoxicam gel formulations showed pseudo plastic non-Newtonian flow (shear thinning) as shown in figures (2-4).



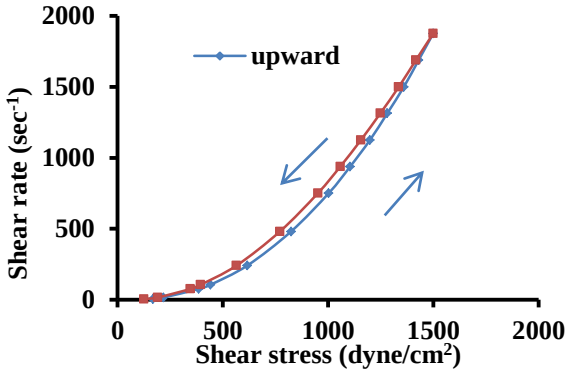
(F1)



(FG1)

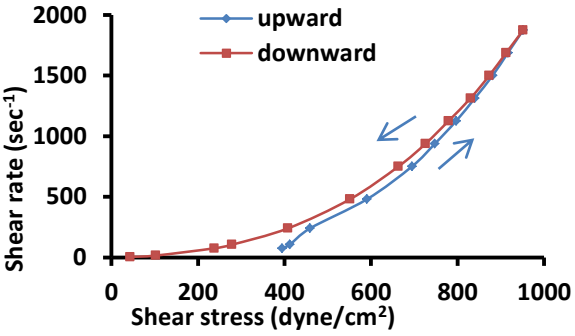


(FP1)

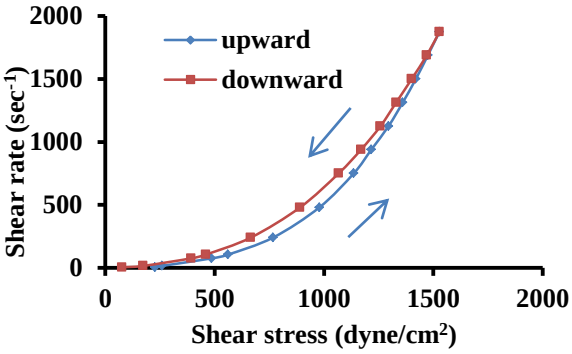


(FS1)

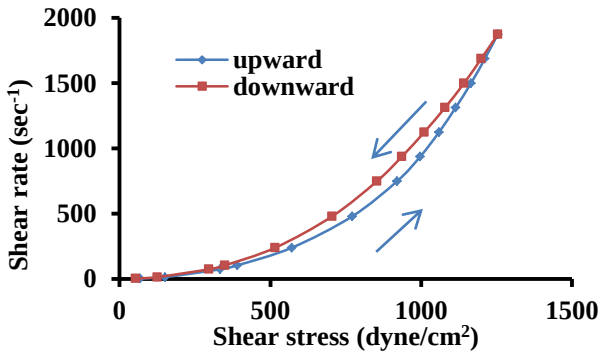
Figure 2: Rheograms of Carbopol 940 topical gels



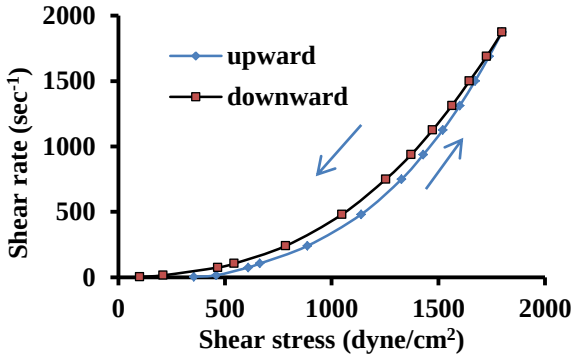
(F2)



(FG2)

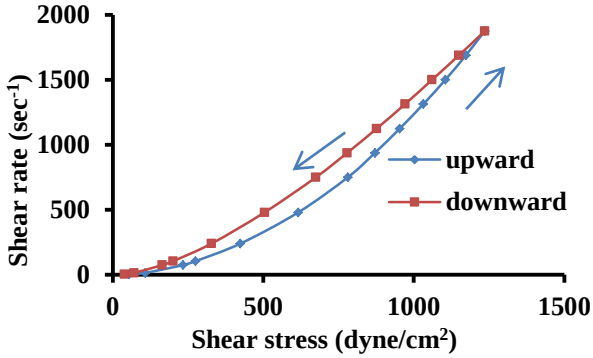


(FP2)

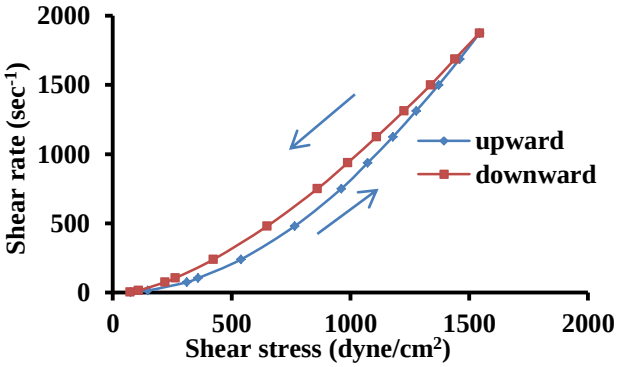


(FS2)

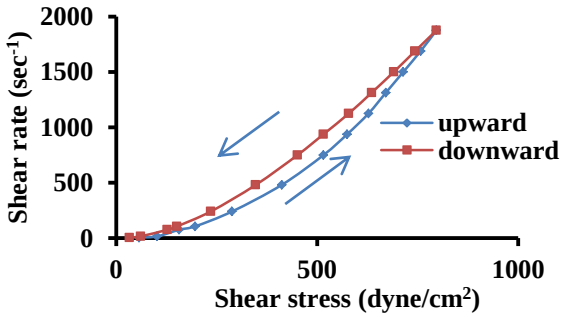
Figure 3: Rheograms of NaCMC topical gels



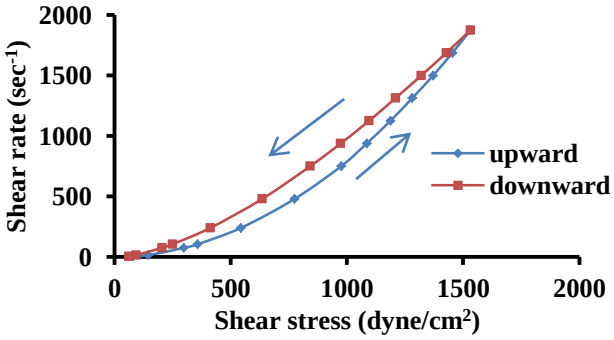
(F3)



(FG3)



(FP3)



(FS3)

Figure 4: Rheograms of Sodium alginate topical gels

***In-vitro* release of lornoxicam gels**

The release data of lornoxicam gels are graphically illustrated in figures (5-7). It was observed that the release of the drug from its different formulae can be arranged in the following descending order: FS1>FS3>FG3>FP3>FG1>F3>FP2>FP1>F1>FG2>FS2>F2; where the amounts of the drug released after 4 hours were 99.79%, 98.90%, 98.75%, 98.05%, 96.01%, 94.98%, 94.52%, 93.41%, 92.61%, 90.48%, 90.42% and 81.84% respectively. The *in-vitro* release of lornoxicam increased in

the presence of permeation enhancers, that may be attributed to the high concentration gradient (due to solubilized lornoxicam) and changing the gel consistency after addition of permeation enhancers.[31]

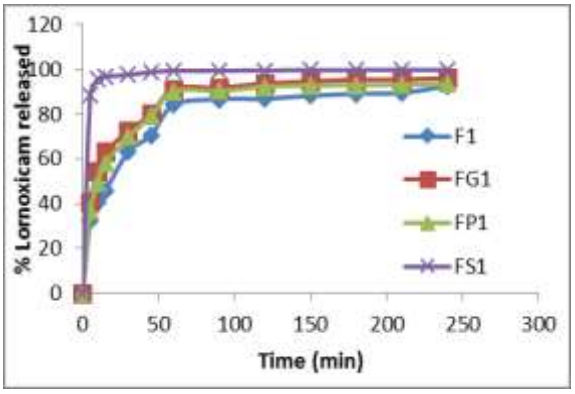


Figure 5: *In vitro* release of lornoxicam from Carbopol 934 gel bases

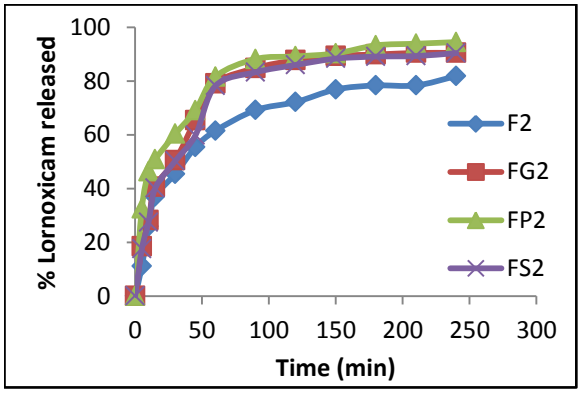


Figure 6: *In vitro* release of lornoxicam from NaCMC gel bases

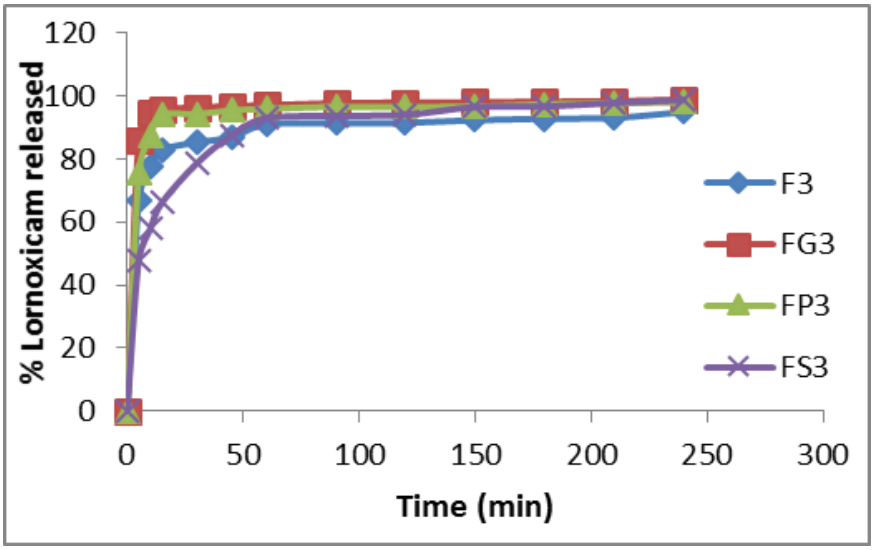


Figure 7: *In vitro* release of lornoxicam from Sodium alginate gel bases

Kinetic treatment of the *in-vitro* release data

The kinetic data showed that, the *in-vitro* release of lornoxicam follows different kinetic orders; first and diffusion as shown in table 3.

Table 3: Kinetic parameters of lornoxicam gel formulae

Formulations	Correlation coefficient (r)		
	Zero	First	Diffusion
F1	0.811855	0.90199	**0.906166**
F2	0.862104	0.94103	**0.941744**
F3	0.755873	**0.88166**	0.853454
FG1	0.785946	**0.90697**	0.887904
FP1	0.769859	0.86054	**0.876492**
FS1	0.777925	**0.95155**	0.881059

Formulations	Correlation coefficient (r)		
	Zero	First	Diffusion
FG2	0.823947	0.91019	**0.916278**
FP2	0.849196	**0.95009**	0.932721
FS2	0.835724	0.92054	**0.923754**
FG3	0.604985	**0.84864**	0.703856
FP3	0.60604	**0.81968**	0.714681
FS3	0.61363	**0.89114**	0.728358

***In-vitro* permeation of lornoxicam gels, through cellulose membrane**

The results of in vitro permeation studies of topical gel formulae across cellulose membrane are shown in figures (8-10).

It was found that all enhancers used showed significant enhancement in the release of lornoxicam in comparison with the enhancer-free base, but to a variable extent.

Formulation FS1 releases highest percentage of drug (75.47%) in 24 hours followed by FS3 (64.45%) then FG3 (64.37) while F2 released the lowest percentage (16.98%) in 24 hours. This clearly indicates that sorbitol (10%) showed higher permeation among all permeation enhancers. The addition of sorbitol has an important role in preventing the system from drying on the skin.[32] When the concentration is above 20% w/w a dehydrating process takes place on the skin and the skin becomes dry.[33] In this view the concentration of 10% was chosen.

Glycerin appears to augment percutaneous absorption by increasing the thermodynamic activity of the penetrant, thereby increasing the effective escaping tendency and concentration gradient of the diffusion species.[34]

The addition of PEG into different gel bases had resulted in enhancing drug release rate. This was related to the high water solubility of PEG where it readily absorb water and therefore speeds up the hydration rate and so the dissolution rate of the polymer into which these enhancer is incorporated.[35]

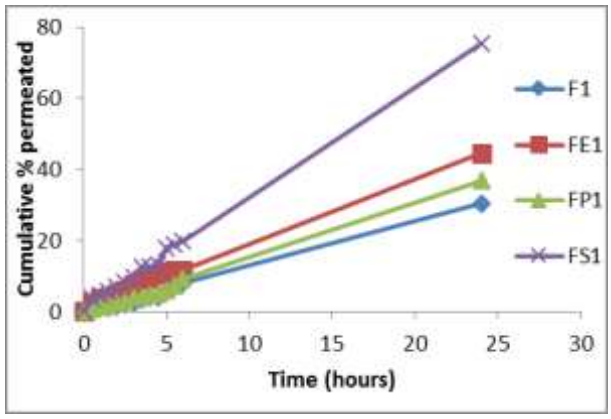


Figure 8: *In vitro* permeation profile of lornoxicam from carbopol 934 gel bases through cellulose membrane

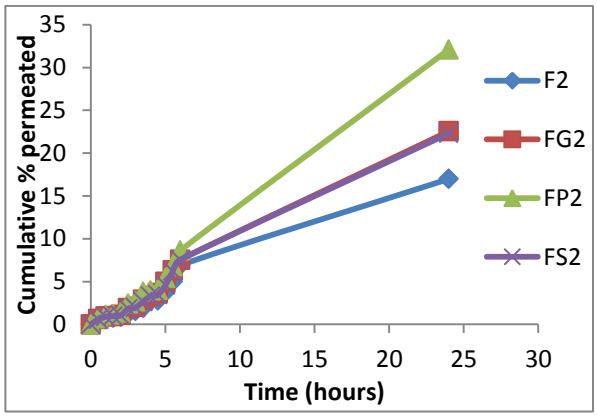


Figure 9: *In vitro* permeation profile of lornoxicam from NaCMC gel bases through cellulose membrane

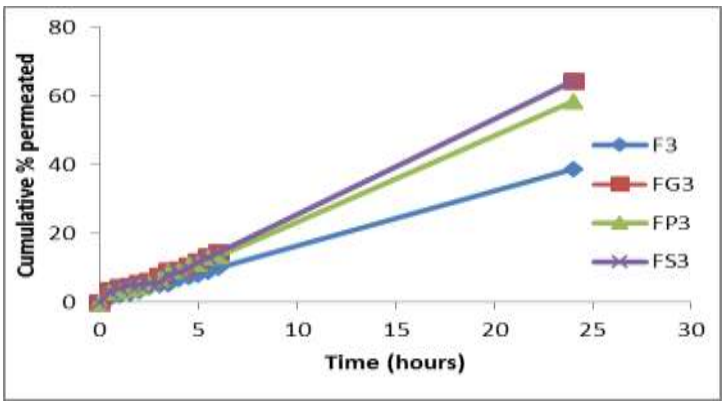


Figure 10: *In vitro* permeation profile of lornoxicam from sodium alginate gel bases through cellulose membrane

Anti-inflammatory study

In anti-inflammatory test using carrageenan as the phlogistic compound, (feldene® gel) and selected lornoxicam gels namely FS1 and FS3 exhibited anti-inflammatory activity up to 24 hours and the activity was observed between 0.5-24 hours for all formulations.

Table 4 and Figure. 11 showed the % inhibition of edema for the selected gels and commercial gel throughout 24 hours.

The anti-inflammatory activity after 6 hours for group 2 feldene® gel, groups 3 and 4 (lornoxicam gel formulae with penetration enhancer) can be arranged in descending order as follows: FS1 (94.58 %) > FS3 (88.86 %) > feldene® gel (83.02 %).

When the experimental data were statistically analyzed, after 6 hours, it was observed that all lornoxicam gels showing significance with each other and with feldene® gel. FS1 exhibited significantly higher anti-inflammatory activity compared to feldene® gel ($p < 0.05$).

The results confirm the fact that a significant amount of lornoxicam was delivered from the gel through skin to induce the anti-inflammatory effect.

Table 4: Anti-inflammatory activity of chosen formulae of lornoxicam and feldene® gels throughout 24 hours

Time (hours)	Control (mm)±SD	% edema inhibition of chosen formulae of lornoxicam and feldene® gels ±SD		
		Feldene® gel	FS1	FS3
0.5	0.55±0.22	19.37 ±0.07	62.65 ±0.45	62.85 ±0.30
1	0.95±0.76	29.31 ±0.95	66.19 ±0.36	67.33 ±0.34
1.5	0.96±0.40	56.70 ±0.85	70.36 ±0.29	68.59 ±0.10
2	1.29±0.67	56.76 ±0.86	72.62 ±0.38	74.02 ±0.22
2.5	1.35±0.65	59.56 ±0.35	74.46 ±0.18	75.94 ±0.39
3	1.36±0.53	61.68 ±0.38	77.63 ±0.58	77.73 ±0.39
3.5	1.72±0.47	63.34 ±0.37	79.64 ±0.35	78.79 ±0.28
4	1.99±0.47	64.65 ±0.28	80.44 ±0.40	80.42 ±0.07
4.5	2.56±0.27	72.28 ±0.58	84.18 ±0.15	83. 61 ±0.07
5	3.05±0.35	76.33 ±0.25	84.56 ±0.18	84.22 ±0.02
5.5	3.17±0.14	80.67 ±0.55	84.66 ±0.38	88.04 ±0.16
6	3.36±0.42	83.02 ±0.29	94.58 ±0.18	88.86 ±0.40
24	2.49±0.78	70.10 ±0.44	82.98 ±0.20	81.48 ±0.18

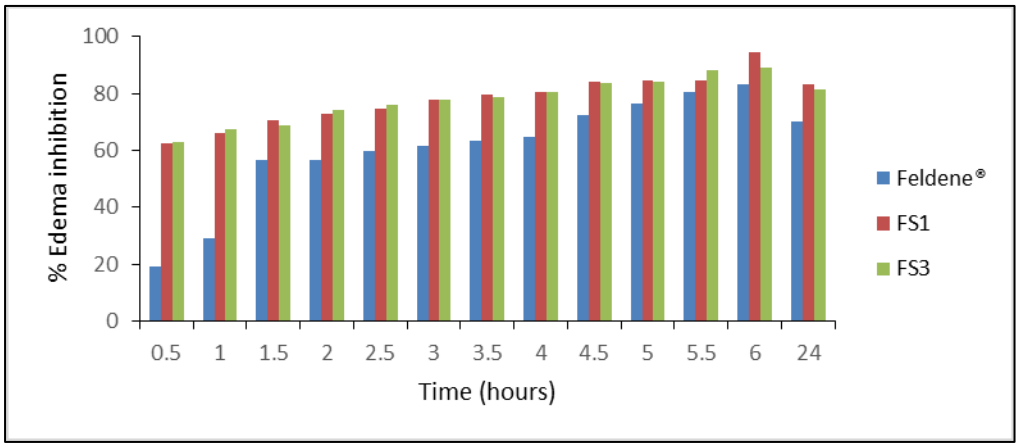


Figure 11: % edema inhibition of the chosen formulae (FS1 and FS3) and feldene® gel.

CONCLUSION

Formulations of lornoxicam as topical gel with addition of permeation enhancers could assist its dissolution enhancement and thus improve its skin permeability and anti-inflammatory activity. All the studied gels are of acceptable physical properties and drug content. They exhibited pseudo plastic non-Newtonian flow. Considering in vitro release, in-vitro permeation, rheological properties and anti-inflammatory study, FS1 (1% carbopol with 10% sorbitol) formula was the best among the studied formulations.

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