Formulation and evaluation of lornoxicam emulgel

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Abstract

Transdermal route of administration of drug is effective route of administration for different kind of indications. The purpose of present investigation was to develop Lornoxicam emulgel for systemic effect and to avoid side effects and minimize frequency of administration. Lornoxicam (NSAIDS) is a cox-1 and cox-2 inhibitor used in the treatment of pain, inflammations rheumatoid arthritis. Emulgel of lornoxicam was formulated using triethanolamine (5%) as solvent, carbopol 934 and carbopol 940 as gelling agents and various preservatives formulated gel was evaluated with respect to different physiochemical parameters such as ph, viscosity, Spreadability % drug content. All the prepared emulgel showed acceptable physical properties like homogeneity, colour, consistency, ph value, Grittiness, Spreadability, Extrudability % drug content. The results of *in vitro* drug release showed that carbopol 940 (0.4 gm) based emulgel gave better release. Also it was found that the gelling agent concentration had the most pronounced effect on the drug release from the emulgel.

Keywords: Lornoxicam, Carbopol, Hydroxyl Propyl methyl cellulose, Anti-inflammatory activity

Introduction

The delivery of drugs across the skin is widely acceptance among patients and termed as Topical drug delivery. It is a viable administration route for low molecular weight, potent therapeutic agents susceptible to first pass metabolism.(1) Topical drug delivery is referred to as a localized drug delivery system anywhere in the body through rectal, ophthalmic, vaginal and skin as topical routes. Skin is one of the most readily accessible organs of human body for topical administration and is main route of topical drug delivery system.(1-3) In developing a transdermal delivery system, two criteria are considered: one is minimizing the lag time and other is achieving adequate flux across the skin in skin permeation.(1,4)

To minimize these limitations an emulsion based approach is used, so that a hydro-phobic moiety can be incorporated and used through gels. When emulsion and gels are used in combined form the dosage forms are called as emulgels.(5,6) Emulgels for dermatological use have several properties such as easily spreadable, greaseless, emollient, easily removable, non-staining and transparent.(7)

Lornoxicam is a highly potent non-steroidal anti-inflammatory drug, used for the variety of inflammatory conditions. The mechanism of action of Lornoxicam is an inhibition of prostaglandin synthesis through the inhibition of cyclooxygenase (COX) enzymes. Like other Non Steroidal Anti-inflammatory (NSAIDs) drugs, common side effect of Lornoxicam is GI irritation. So delivery of the Lornoxicam through the skin for inflammation is desireable7. To increase therapeutic efficacy of topically applied drug, it is required to employ physical and chemical enhancers8. An attempt has been made, to enhance the permeation of Lornoxicam by using physical enhancers and chemical enhancers in gels made using Carbopol 934 to study the topical delivery of Lornoxicam through the skin.

Materials and Method

Lornoxicam was provided by Naprod Life Science P. LTD (India), Carbopol 934, Carbopol 940, HPMC, Triethanolamine, (S.D fine chemicals Pvt. Ltd, Mumbai). All other chemicals and reagents used were of analytical grade. Deionized distilled water was used throughout the study.

Solubility study: The solubility of Lornoxicam drug was determined in phosphate buffer, distilled water, triethanolamine (5%) and chloroform solution in water by shake flask method. Briefly, an excess amount of lornoxicam is added to each vial containing 10 ml of selected solubilizers. The mixtures were subjected to the mechanical agitation for 72 hours in isothermal shaker at 25ºC followed by the filtration through whatmann's filter paper prior to UV.(8)

Emulgel Preparation

Step 1: Formulation of emulsion either O/W or W/O
Step 2: Formulation of gel base
Step 3: Incorporation of emulsion into gel base with continuous stirring.

The Gel was prepared by dispersing Carbopol 940, Carbopol 934 and HPMC separately in purified water with constant stirring and then the pH was adjusted to 6 to 7 using Triethanolamine.

The oil phase of the emulsion was prepared by dissolving cetosterol alcohol, propyl paraben in light liquid paraffin and Glycerine monostearate while the aqueous phase was prepared by dissolving methyl paraben and Glycerine in purified water. Both the aqueous and oily phases were separately heated at 70°

to 75°C; then the oily phase was added to the aqueous phase with continuous stirring until cooled to room temperature.

Then Lornoxicam dissolved in PEG-400 and add into an emulsion. Then emulsion is added to gel base with continuous starring at 600 RPM.[7]

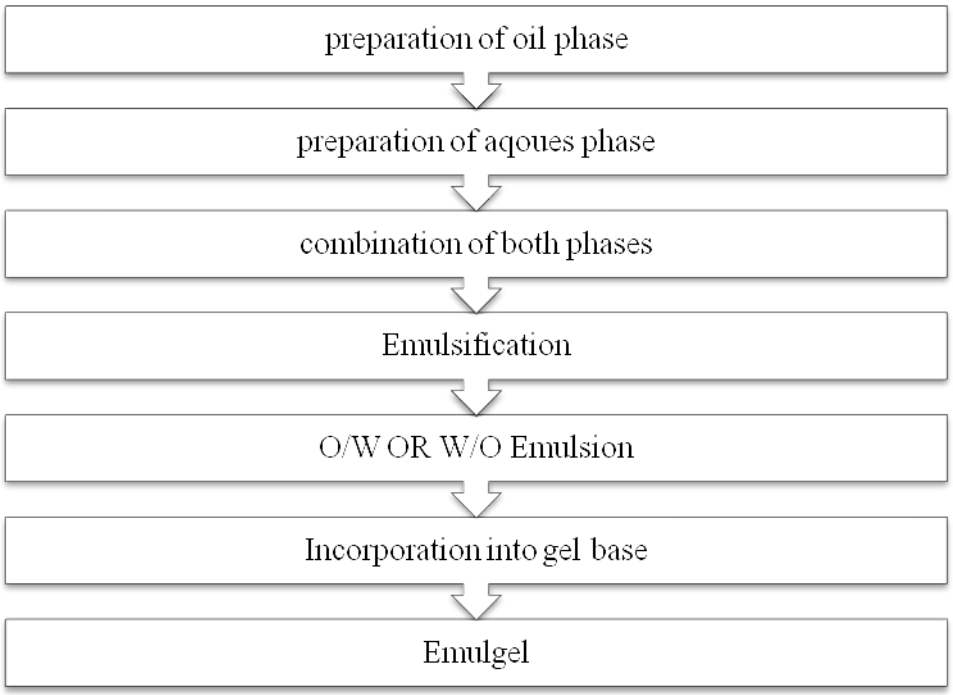

Fig. 1: Preparation method of Emulgel

Table 1: Different gel formulations

Sr. No	Ingredients	Formulation Code								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Lornoxicam(mg)	20	20	20	20	20	20	20	20	20
2	Cetosterol alcohol (gm)	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7
3	Liquid paraffin(ml)	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
4	Propyl paraben(gm)	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
5	Glycerine monostearate (ml)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
6	Methyl paraben(gm)	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
7	Glycerine(ml)	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
8	Carbopol 934	0.3	0.4	0.5	-	-	-	-	-	-
9	Carbopol 940(gm)	-	-	-	0.3	0.4	0.5	-	-	-
1O	HPMC(gm)	-	-	-	-	-	-	4	6	8
11	Ethanolamine(ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
12	PEG-400(ml)	2	2	2	2	2	2	2	2	2
13	Purified water(ml)	50	50	50	50	50	50	50	50	50

Characterization of emulgel

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

Grittiness: All the formulations were microscopically evaluated for the particles if any no particulate matter was seen under light microscope. Hence obviously the gel preparation fulfils the requirement of free from particular matter and from grittiness as desired for any topical preparation.

Extrudability: The gels after formulating were filled into collapsible tubes. Then Extrudability of the formulation has been checked.

PH: The pH of Lornoxicam gels were determined by using a calibrated pH meter. The readings were taken for average of three samples. The pH meter was calibrated before each use with standard 4, 7 and 9 pH buffer solutions.[4]

Drug content: Drug content analysis was determined by dissolving 1 g of gel in 100 ml of phosphate buffer pH 6.8 and methanol (50:50). Then 1ml of this solution was transfer to the 100 ml volumetric flask and final volume was made by same solutions. Finally absorbance of prepared solution was measured at 380 nm using UV visible spectrophotometer. The percentage drug content was calculated.(5)

Viscosity: A Brookfield digital viscometer with a suitable sample adaptor was used to measure the viscosities of the Carbopol gel in cps. All the measurements were conducted using spindle no.6 using about 100 ml sample volume at 50 RPM. Direct multiplication of the dial readings with factors given in the Brookfield Viscometer catalogue gave the viscosity in centipoises.

Spreadability: Spreadability was determined by excess of sample was applied within the two glass slides then compressed to uniform thickness by placing 1kg weight for 5 min. Weight (50 gm) was added to the pan. The time required separating the two slides, i.e. the time in which the upper glass slide moves over the lower plate was taken as measure of Spreadability (S).

Spreadability (g.cm/s) (S) =M×L/T
Where M = weight tide to upper slide,
L = length moved on the glass slide,
T= time taken (5)

***In- vitro* diffusion study:** The experiments were conducted in Franz diffusion cells with a receiver and donor compartment. A suitable size of pre-treated cellophane membrane was mounted in between donor and receptor cells of the Franz diffusion cells (locally fabricated). The receiver compartment contains 15 ml phosphate buffer solution (PBS); PBS pH 6.8 was constantly stirred by magnetic stirrer at 100 rpm and was maintained at a temperature of 37°C throughout the experiments. A formulation containing equivalent to 20 mg Lornoxicam drug was applied homogenously into the donor compartments; 1ml samples were withdrawn from receiver compartment at pre-determined time intervals over 5 hours and immediately replaced with an equal volume of fresh PBS. Samples were assayed for drug content spectrophotometrically. Sink condition was maintained throughout the experiments.(5)

Stability study: The prepared emulgels was packed in aluminum collapsible tubes (5 g) and subjected to stability studies at studies were carried out at 40° to 45^0C and 75% relative humidity. Samples was withdrawn at 30 days time intervals and evaluated for physical appearance, drug content, spreadability pH, and % CDR.

Results and Discussions

Solubility: Lornoxicam is poorly soluble in water (0.0385 mg/ml). Among the different solubilizers screened Lornoxicam exhibited the highest solubility in 5% triethanolamine (42.5mg/ml). Solubility in chloroform and PBS pH 6.8 was 0.25and 0.15 mg/ml respectively. Hence 5% triethanolamine is selected for the formulation of Lornoxicam gel.

Evaluation of Lornoxicam gel

PH: The pH of Lornoxicam gels were determined by using a calibrated pH meter and pH of the gel were found to be 6.8 to 7.32 and tabulated in Table 2.

Drug content: The drug content of Lornoxicam gel were found to be 90.21 % to 99.75% and tabulated in Table 3.

Viscosity: The viscosity of prepared emulgel was determined at 35°C using a Brookfield viscometer with spindle no 6 at 50 rpm by Brookfield viscometer. Viscosity of the Emulgel from F1 to F9 was shown in Table 2.

Spreadability: The Spreadability of the Lornoxicam gels was found to be 21.56 to 31.56 g.cm/sec, which is indicative of good Spreadability and tabulated in Table 3.

***In- vitro* diffusion studies:** From the *iv-vitro* studies it's found that the percentage of Lornoxicam release after 6 hours was 42% to 74% from all formulations. Formulation F2 and F5 releases highest percentage of drug (74%) in 6 hours and F8 released lowest percentage (42%) in 6 hours. This clearly indicates that Carbopol 940(gm**)** showed higher permeation among all permeation enhancers due to the stratum corneum modification.

Stability study: The promising formulation F5 was subjected at 40 °C temperature and 75 RH for 1 month to check the stability. The results of physical appearance, drug content, folding endurance and other parameters after 1 month storage of prepared Emulgel are shown in Table 5 and 6.

Table 2: Evaluation data of Lornoxicam gels

Formulation code	Homogeneity	Grittiness	Extrudability	PH	Viscosity
F1	**	--	**	6.61	6759
F2	***	--	***	7.10	7623
F3	**	--	**	6.75	8523
F4	**	--	**	6.60	6895
F5	***	--	***	7.14	7653
F6	**	--	**	6.89	8536
F7	**	--	**	7.45	4236
F8	**	--	**	7.22	5363
F9	**	--	**	7.32	5956

Excellent ***, good **, satisfactory *, No grittiness:-

Table 3: Physical characters of the tested formulations containing Lornoxicam

Formulations	Colour	Drug content (%)	Spreadability g.cm/s
F1	Yellow	97.45	28.56
F2	Yellow	99.75	30.46
F3	Yellow	97.21	26.25
F4	Yellow	96.33	27.26
F5	Yellow	99.45	31.56
F6	Yellow	97.95	27.36
F7	Yellow	90.21	23.54
F8	Yellow	92.23	22.66
F9	Yellow	93.56	21.56

Table 4: In vitro drug release data

Time(min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
15	16.25	21.86	18.11	17.23	22.02	17.69	14.26	12.36	13.66
30	39.21	40.69	38.26	38.75	41.20	38.26	32.56	30.44	31.22
60	41.22	48.23	43.35	40.80	48.29	44.56	37.23	34.36	36.45
120	56.89	60.35	59.45	55.60	62.69	59.63	47.23	46.32	45.45
180	69.24	73.27	71.35	68.45	73.64	71.36	56.33	55.36	55.36
240	76.19	85.36	82.36	75.96	86.34	82.30	64.86	62.86	63.69

Table 5: Stability study of promising batch F2 and F5

Parameter	Before 30 days	After 30 days
PH	7.05	7.04
Viscosity (cps)	7623	7610
Spreadability	30.28	30.12
%drug content	99.70	99.65

Table 6: %Cumulative drug release study of F2 and F5 at 0 day and after 30 days

Cumulative % drug release		
Time	**Before 30 days**	**After 30 days**
0	0	0
15	23.31	21.26
30	42.35	40.23
60	49.32	47.36
120	63.24	61.56
180	74.62	72.36
240	88.23	86.36

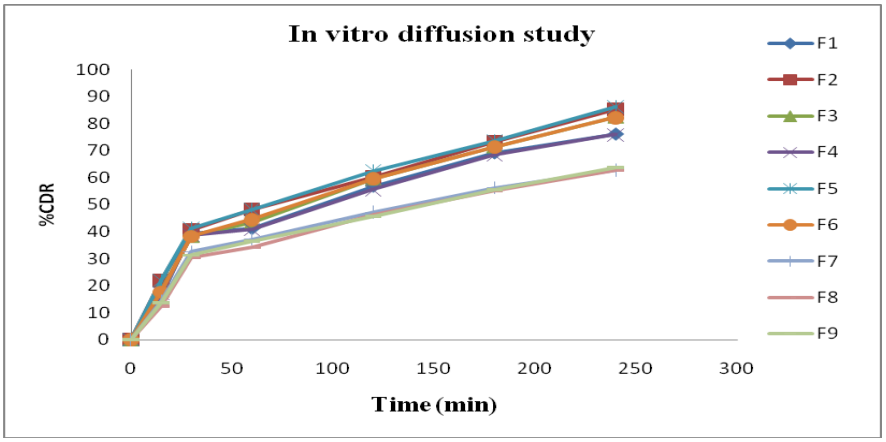

Fig. 2: In vitro Drug release of F1 to F9 batches

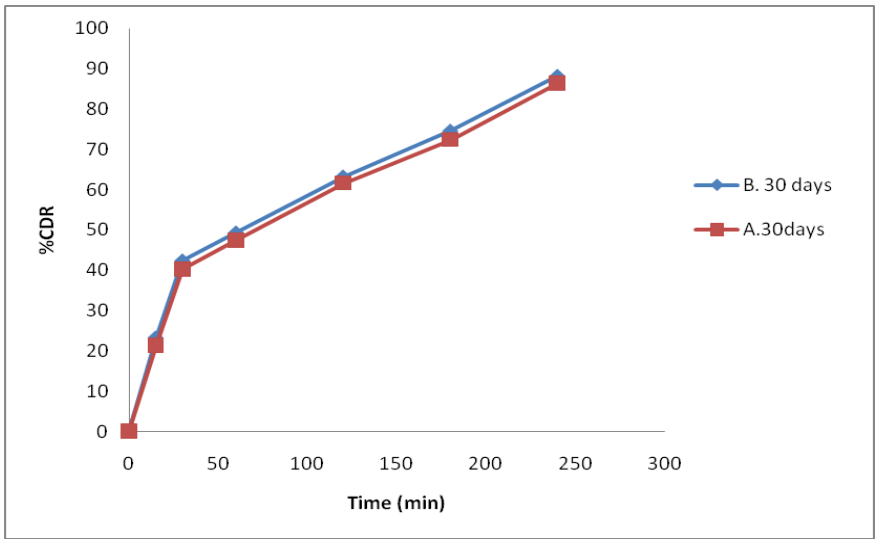

Fig. 3: In vitro Drug release of F1 to F9 batches before and after 30 days

Conclusion

From the experimental work finding it can be concluded that Lornoxicam is a non-steroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic activities and used for the treatment of rheumatoid arthritis. Lornoxicam by oral administration can produces stomach indigestion, so it is not suitable for the treatment of rheumatoid arthritis patient with gastric ulcer, so, to avoid gastric irritation to G.I.T, minimizing systemic toxicity. To overcome the side effects associated with oral Lornoxicam therapy and to have the benefits associated with topical therapy; Lornoxicam topical gels are prepared in this study. Studies showed that drug release was decrease with increase in gelling agent concentration because polymer concentration increases; viscosity increases.

On the basis of physical parameters F2, F5 selected as best formulations.

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