Research paper www.ijcps.com

International Journal of
Chemical and Pharmaceutical Sciences
2011, June., Vol.2 (2)

ISSN: 0976-9390
IJCPS

Transdermal Delivery of Lornoxicam from Pluronic Lecithin Organogel

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ABSTRACT

The objective of this study is to formulate Pluronic lecithin organogel of lornoxicam and evaluate its suitability for topical application. This is an attempt to explore the suitability of lornoxicam for transdermal drug delivery and potential of Pluronic lecithin organogels for topical delivery of lornoxicam. Ten formulations were developed (code of formulation F-1 to F- 10) using lornoxicam, Pluronic F-127, lecithin, isopropyl myristate, water, sorbic acid and potassium sorbate. All the formulation, were prepared by altering the quantity of Pluronic F-127 and lecithin. The formulated organogels were evaluated for appearance, texture, in vitro diffusion study, drug content, viscosity, spreadability and pH. The in vitro drug realease study was monitored via egg membrane in phosphate buffer (pH 7.4) using modified Keshary-Chein diffusion cell. The viscosities and pH of different formulation were determined by brookfield viscometer and digital pH meter respectively. From the evaluation study it may be concluded that formulation F-2, containing 3% lecithin and 20% pluronic is an effective formulation for transdermal delivery of lornoxicam as it showed satisfactory pH, viscosity, spreadability, drug content and high % cummulative percent drug release (which is 90.13 %). Lornoxicam is a potential candidate for Transdermal delivery and Pluronic lecithin organogel showed satisfactory Transdermal permeation.

Key words: Pluronic Lecithin Organogel, Transdermal Delivery System, Lornoxicam.

1. INTRODUCTION

The fundamentals of successful formulation are to deliver the active substance at target organ with minimal discomfort and side effects. In this respect, transdermal route excels because of avoidance of hepatic first pass metabolism, typical peak trough plasma profile, ease of administration etc[1].

The topical delivery has been attempted and made successful using several lipid-based systems viz vesicular systems, lipid microspheres, lipid nanoparticles, lipid-microemulsions, and polymeric gels. In a 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). LOs are thermodynamically stable, clear, viscoelastic, biocompatible, and isotropic gels composed of phospholipids (lecithin), appropriate organic solvent, and a polar solvent. LOs, the jelly-like phases, 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[2]. These systems are currently of interest to the pharmaceutical scientist because of their structural and functional benefits. Several therapeutic agents like NSAIDs, hormones, anti-emetics, opiods and local anesthetics, have been formulated as LOs for their facilitated transport through topical route (for dermal or transdermal effect), with some very encouraging results. The improved topical drug delivery has mainly been attributed to the biphasic drug solubility, the desired drug partitioning, and the modification of skin barrier function by the organogel components[3]. Being thermodynamically stable, LOs are prepared by spontaneous emulsification and therefore possess prolonged shelf life. The utility of this novel matrix as a topical vehicle has further increased owing to its very low skin irritancy potential[1,4].

Pluronic-lecithin-organogel (PLO) is a transdermal carrier used by pharmacists to deliver drugs through the skin when other routes of administration are not viable. PLO gel is non-irritating to the skin and is absorbed quickly. It is best used with drugs with molecular weights, preferably less than about 400. PLO gel includes isopropyl palmitate, soy lecithin, water, and pluronic F127. Isopropyl palmitate is a non-oleaginous emollient with a high capacity for spreading. Lecithin is a naturally occurring mixture of diglycerides of fatty acids linked to the

choline ester of phosphoric acid. It is used as a penetration enhancer in compounding the PLO gel. It is a liquid at room temperature and may become solid upon cooling. Water acts as a stabilizing and structure-forming agent in the process of PLO formation. It is also used for solubilizing the Pluronic F-127 and polar drugs[1,4,5].

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 (RA). It has short half life of 3-4 hrs, log P value 1.8 and molecular weight of 371.82 g/mol, which makes it potentential candidate for Transdermal drug delivery[6].

2. MATERIAL AND METHODS

Lornoxicam and lecithin were received as a gift sample from Unichem Laboratories, Mumbai, India and Ruchi Soya Pvt. Ltd. Indore, India respectively. Pluronic F-127 was procured from Sigma Aldrich, Delhi. Isopropyl myristate, polyethylene glycol-400, sorbic acid and potassium sorbate were supplied by CDH Pvt. Ltd., Delhi, India. All other chemicals were of analytical grade.

2.1. Experimental Work

2.1.1. Method of preparation of Pluronic Lecithin organogel

The various formulation of PLO were developed with different compositions. Pluronic Lecithin Organogel is a microemulsion based gel. It is made up of 2 phases an oil phase and a aqueous phase. Oil Phase was prepared by mixing soya lecithin and sorbic acid in appropriate quantity of isopropyl myristate. The mixture was kept overnight at room temperature in order to dissolve its constituents completely. Aqueous phase was prepared by dispersing weighed amount of pluronic F-127 and potassium sorbate in cold water. The dispersion was stored in refrigerator (at 4°c) for effective dissolution of Pluronic F-127. The next day, active ingredient lornoxicam was dissolved in Polyethylene glycol-400 and mixed with the lecithin-isopropyl solution. Polyethylene glycol-400 was used for solubilization of Lornoxicam. Finally, aqueous phase (70%) was slowly added in oil phase (30%) with constant stirring using mechanical stirrer[1].

2.1.2. Evaluation Parameters

The organogel prepared were evaluated for appearance and feel psychorheologically, drug content in 0.05 N NaOH at 376nm, pH by digital pH meter, spreadability, viscosity by Brookfield viscometer and in-vitro diffusion using Keshary-Chien diffusion cell.

2.1.3. Drug Content

The drug content of different formulations were determined by taking a standard curve of Lornoxicam in 0.05 N NaOH. For this, accurately weighed 100mg of drug was transferred in 100ml volumetric flask, dissolved in 0.05 N NaOH and volume was made up with 0.05 N NaOH. From this stock solution further aliquots were made to get concentration of 5, 10, 15, 20, 25, 30 and 35 µg/ml. Absorbance were noted spectrophotometrically and standard curve of Lornoxicam in 0.05 N NaOH was plotted at 376nm. For further determining the drug content, each formulations (1g) was taken in 100 ml volumetric flask, diluted appropriately with 0.05 N NaOH and shaken to dissolve the drug in 0.05 N NaOH. The solution was filtered through the whatman filterpaper , one ml of the above filtrate was pipette out and diluted to 100 ml with 0.05 N NaOH. The content of the drug was estimated spectrophotometrically by using standard curve plotted at λ_{max} 376 nm[7].

2.1.4. In vitro Diffusion study

To test the pattern of release of drug from formulations, *in vitro* diffusion studies were carried out. The developed formulations were subjected to *in vitro* diffusion through egg membrane was used as a semi permeable membrane using modified Keshary-Chien diffusion cell. The receptor compartment was filled with saline phosphate buffer (pH 7.4). The whole assembly was maintained at 37±1° and receptor solution was stirred with a magnetic stirrer at 100 rpm throughout the experiment. Aliquots (1 ml) were withdrawn at regular interval of 1 h for a period of 8 h and replaced with equal volume of fresh medium equilibrated at 37±1°. All the samples were suitably diluted with medium and analyzed spectrophotometrically at 376 nm for lornoxicam content[7].

2.1.5. Viscosity

Viscosities of the formulated organogels were determined using Brookfield digital viscometer (model DV-I+, Brookfield Engineering Laboratory, INC., USA) was used to measure the viscosity (in cps) of the prepared gel formulations. The spindle (T-D) was rotated at 5 rpm[1,8,9].

2.1.6. Spreadability

Concentric circles of different radii were drawn on a graph paper and a glass plate of 100 ± 5 g was fixed onto it. Weighed amount of Gel (1 g) was transferred to the centre of this plate and allowed to spread over an area of 2 cm diameter

on the glass plate. The other glass plate of 100 ± 5 g was placed gently on the spreaded gel. Again the gel was allowed to spread and the spread diameter was recorded after 1 minute. Then subsequent glass plates were added one by one and the spread diameter of the gel was recorded after 1 minute of each addition. Glass plates were added till the spread diameter became constant. Results were presented as the spreading area being a function of the applied mass[10].

2.1.7. pH

The pH of formulated organogels was determined using digital pH meter. The electrode was immersed in organogels and readings were recorded on pH meter[1,8].

2.1.8. Stability Studies

On the basis of above mentioned evaluation parameters two optimized formulations (F-2 & F-4) were selected from all the ten formulations and subjected to the stability testing for 90 days. Formulation were kept at 40^0C, 25^0C & room temperature for 90 days & evaluated for following parameters:

2.1.8.1. Physical stability

The gel formulations were evaluated in terms of physical character like phase separation & rheological parameters. Physical stability testing was done by visual inspection of the formulation at 15 days interval for 3 months.

2.1.8.2. Chemical stability

The gel formulations were evaluated for % drug content. The % drug content of the formulations were determined, by method given chapter 6, section 6.1.2.3, at 15 days interval for 3 months [11,12].

3. RESULT AND DISCUSSION

The results of evaluation studies are given in Table 2. All the formulations showed drug content in the range of 93-99% . The viscosity of all the formulations was found to be in the range 2910-3234 poise. The pH of all the formulations was in the range of 5.9 to 6.5. All the formulations were smooth in feel and free from grittiness . The results shown in Fig. 1 revealed that maximum *in vitro* cumulative percent drug release of Lornoxicam in 8 hr. was observed from F2 formulation.

The transdermal drug delivery is one of the promising route of drug delivery system, since it by passes the first pass metabolism, avoids inactivation of drugs by pH effects and enzymes present in GI tract, provides a continuous mode of administration at rates approaching zero order similar to that provided by an intravenous infusion, increase the half life of the drug, the delivery is non-invasive, no hospitalization is required, and improves patient compliance.

Any drug for its permeation through skin should be potent, must be lipophilic as well as hydrophilic in nature, optimum partition coefficient etc, this prompted us to carryout the present study on Lornoxicam.

The transdermal anti-inflammatory gels containing Lornoxicam & different polymers, were prepared and evaluated for different parameters. The formulations were also evaluated for pH, drug content, spreadability & viscosity and results found were all satisfactory. All the formulations showed drug content in the range of 93-99% indicating uniform distribution of drug throughout the base. The viscosity of all the formulations was found to be in the range 2910-3234 poise. The increase in viscosity with increase in lecithin concentration is might be due to formation of complex network. The pH of all the formulations was around the skin pH and found to be in the range of 5.9 to 6.5. The spreadability of all the formulations was found in the range of 2.9 to 3.55 cm (in diameter). The results show that spreadability of all the formulation was found to be good. These formulations were taken for further studies.

All ten formulations were evaluated for In-vitro release study. Study was carried for 8 hrs for all formulation and results reported in Fig. 1 shows that, the Formulation F2, F3, F4 and F10 showed good cumulative % Release profile of Lornoxicam in 8 hr. But the linear curve (shown in fig. 1) was obtained from F2 formulation. Further increase in concentration of lecithin & pluronic, decreases cumulative percent drug release shown in Fig. 3 & 4 which might be due to extensive formation of network like structure with very high viscosity.

Stability study indicated that all the selected formulations (F2 and F4) were stable enough at different temperature conditions (40^0C, 25^0C, room temperature) for 90 days as there was no change in drug content, phase separation, rheological properties and pH. Thus it may concluded that formulation were physically and chemically stable.

Table .1. Formulation composition of PLO

CONTENT		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
DRUG	Lornoxicam (gm)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
	PEG 400 (ml)	15	15	15	15	15	15	15	15	15	15
OIL PHASE (%)	Soya Lecithin (gm)	1	3	5	7	9	3	3	3	3	3
	Sorbic acid (gm)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	02
	Isopropyl Myristate q.s. (ml)	100	100	100	100	100	100	100	100	100	100
AQUEOUS PHASE	Pluronic F-127 (gm)	20	20	20	20	20	5	10	15	30	25
(%)	Potassium Sorbate (gm)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
	Distilled water q.s. (ml)	100	100	100	100	100	100	100	100	100	100

Table2. Drug content, viscosity and pH of different formulations

Formulations	pH	Viscosity (cps)	Spreadability (cm)	% Drug content
F1	5.9 ± 0.1	2912 ± 1.67	2.9	93.96 ± 0.17
F2	6.4 ± 0.17	3145 ± 40	3.26	93.77 ± 0.63
F3	6.03 ± 0.17	3179 ± 21.34	3.4	96.25 ± 0.52
F4	6.27 ± 0.17	3174 ± 9.34	3.4	99.51 ± 0.27
F5	5.93±0.16	3234 ± 24.33	3.27	99.49 ± 0.13
F6	6.06 ± 0.06	3028 ± 25.67	3.55	96.86 ± 0.36
F7	6.03 ± 0.16	3149 ± 18	3.18	95.85 ± 0.71
F8	5.86 ± 0.06	3150 ± 19.33	2.84	98.46 ± 0.32
F9	6.16 ± 0.16	3113 ± 14.33	2.87	98.32 ± 0.38
F10	5.96 ± 0.16	3162 ± 15.67	3.36	97.15 ± 0.15

Table .3. Spreadability of different formulations

No. of plates placed on gel	Spread diameter of different gel formulations (cm)									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	2.1	2.6	2.3	2.6	2.5	2.12	2.3	2.3	2.5	2.0
2	2.5	2.76	2.6	2.8	2.7	2.16	2.4	2.38	2.7	2.4
3	2.62	2.84	2.7	3.0	2.8	2.28	2.7	2.45	2.72	2.7
4	2.7	2.93	2.8	3.2	3.1	2.36	2.8	2.56	2.79	2.8
5	2.78	3.0	3.0	3.3	3.2	2.44	2.86	2.66	2.8	2.9
6	2.8	3.08	3.1	3.36	3.25	2.48	3.0	2.75	2.83	3.0
7	2.88	3.16	3.2	3.38	3.26	2.52	3.16	2.8	2.85	3.2
8	2.9	3.24	3.3	3.40	3.27	3.55	3.18	2.84	2.86	3.34
9	2.9	3.26	3.4	3.41	3.27	3.55	3.18	2.84	2.87	3.36

Table .4. In-vitro Release study in PBS 7.4 pH

% Drug release from gel formulations										
Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0	0	0	0	0	0	0	0	0	0	0
1	6.63	9.28	5.92	7.871	3.80	4.9	5.22	5.48	6.28	8.05
2	14.37	19.19	16.67	16.18	10.97	10.97	8.76	9.99	15.7	17.78
3	23.52	32.59	27.46	26.62	20.12	20.96	10.87	18.13	26.23	30.91
4	39.09	40.73	38.69	39.71	31.49	30.86	18.49	28.13	34.89	40.99
5	51.83	56.56	43.43	51.57	39.98	39.09	28.13	37.50	42.98	55.01
6	59.62	66.87	53.51	62.27	51.11	43.65	38.7	2.81	51.57	64.30
7	68.19	81.02	65.1	71.82	61.16	54.26	49.0	50.06	60.23	75.98
8	78.18	90.13	83.94	80.53	70.28	60.50	60.94	66.25	71.51	85.62

Fig. 1. In vitro Cummulative Release profile of Lornoxicam in 8 hrs of F1, F2, F3, F4 & F5

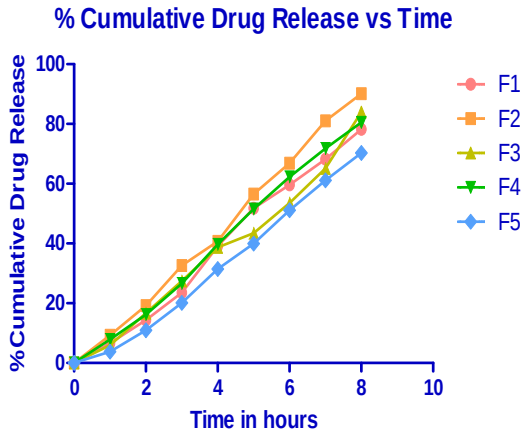
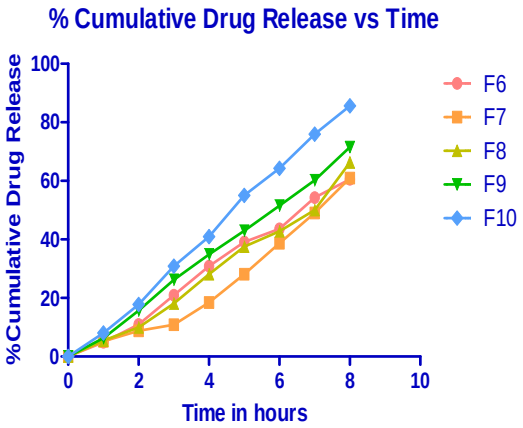


Fig. 2. In vitro Cummulative Release profile of Lornoxicam **in 8 hrs of F6, F7, F8, F9 & F10**



4. CONCLUSION

From above studies it may be concluded that formulation FL2, containing 3% lecithin is an effective formulation for topical delivery of Lornoxicam as it showed higher cumulative percent drug release and drug content.

5. ACKNOWLEDGEMENT

The authors are thankful to the Ruchi soya Pvt. Ltd. Indore, India and Unichem laboratories Mumbai, India for providing gratis sample of soya lecithin and Lornoxicam respectively. Authors are also thankful to management, Swami Vivekanand College of pharmacy, Indore (M. P.), India for providing all necessary facilities.

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