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Fabrication of Organogel Based Transdermal Delivery System of Loxoprofen Sodium †

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Abstract: Joint pain with high prevalence and yet without any specific treatment option is posing a challenge to healthcare professionals day by day. Amongst several treatment options currently utilized for arthritic joint pain are merely giving symptomatic relief rather than curative treatment. Non-steroidal Anti-inflammatory Drugs (NSAIDs) are the most widely accessed treatment option amongst all. But their adverse effects profile is a major hurdle for their use, especially in elderly patients. Present study was focused to develop a transdermal patch of a novel NSAID Loxoprofen sodium with enhanced penetration and improved patient compliance. Pluronic lecithin organogel (PLO) was selected as transdermal drug delivery platform to enhance its penetration through skin. Moreover transdermal route will bypass first pass metabolism, GI side effects and necessity to administer drug through oral route. All of these credentials ultimately improved patient compliance. Several experimental batches (PL1 to PL8) were formulated to prepare PLO of loxoprofen sodium. All the batches were evaluated for physical appearance, pH, viscosity, spreadability, drug content and in vitro drug diffusion profiles. An optimized batch was selected on the basis of obtained results. It showed sustained drug release upto 12 hrs. The study evidenced that similar transdermal formulations of other NSAIDs can significantly enhance current treatment scenario for joint pain. Moreover, conversion of such formulations in transdermal patch or other forms ensure sustained and reproducible transdermal flux which can be further fabricated as bioequivalent to the oral formulations. Further studies can be designed to evaluate the clinical applicability of the formulation.

Keywords: NSAID.; Loxoprofen sodium; Organogel; Lecithin; Pluronic

1. Introduction

Elderly people have most common complaint of the joint pain. Treatment through oral NSAIDs is widely utilized for the same. Though effective, it suffers from several side effects, especially GI side effects [1]. Thus successful administration of NSAIDs through other than oral rout is the need of hour to avoid GI side effects [2]. Loxoprofen sodium (LOX), a non selective COX inhibitor, having prominent GI side effects and contrary to that a good cardiovascular safety profile, makes it a potential candidate for transdermal delivery [3,4]. Moreover its sustained release formulation help reduce dosing frequency and hence improving patient compliance. Thus it was considered as a potential candidate to fit the perviews of present study. Transdermal permeation of the drug was enhanced through incorporating it into organogel formulation.

2. Experiments

2.1. Materials

Loxoprofen was a kind gift from Yatai Pharmaceutical Research Institute Co., Ltd. Wuhan, China. Pure soya lecithin was purchased from AmitexAgro Product, India. Pluronic F127 was purchased from Sigma-Aldrich, St. Louis, MO, USA. All other chemicals were received as gift samples from Cadila Pharmaceuticals Ltd., Ahmedabad, India.

2.2. Methods

Preformulation studies were performed to check reporoduciblity of reported analytical methods for LOX in various buffers and solvents [5]. Drug excipients compatibility study was carried out to check compatibility between the excipients.

Formulation batched PL1 to PL8 were prepared as shown in Table 1. For oil phase, soya lecithin was dissolved in Isoproply Palmitate (IPP) and kept overnight. Sorbic acid was dissolved in it the next day. For aqueous phase, Pluronic F127, PVP-K30 and Potassium sorbate (Pot. Sorbate) were dissolved into cold water (2–8 °C) and was kept in refrigerator overnight. At the time of preparing organogel, accurately weighed Lox was dissolved in oil phase and aqueous phase was added slowly to this oil phase with constant stirring. Thus obtained organogel was evaluated for various parameters for physical appearance, pH, viscosity, spreadability, drug content and in vitro drug diffusion profiles utilizing literature reported methods [6–9]. Amongst the experimental batches, selected optimized batch organogel containing 120 mg LOX was spreaded over an area of 7 cm × 7 cm of non permeable backing layer cut into the dimensions of 8 cm × 8 cm. To prevent loss of formulation from the patch, the organogel facing layer was covered with non permeable protective layer. It was further evaluated for relevant parameters. A schematic diagram of prepared transdermal patch is shown in Figure 1.

Table 1. Experimental batches of Loxoprofen Sodium organogel.

Ingredient	PL1	PL2	PL3	PL4	PL5	PL6	PL7	PL8
LOX (mg)	120							
Oil Phase								
Soya Lecithin (mg)	100	100	100	100	150	150	150	150
Sorbic acid (mg)	10							
IPP upto (mL)	1.2							
Aqueous Phase								
Pluronic F127 (mg)	200	250	300	350	200	250	300	350
PVP-K30 (mg)	100							
Pot. Sorbate (mg)	50							
Propylene glycol (mL)	1							
Water upto (mL)	2.8							
Ratio (Aq.phase:Oil phase) = 70:30								

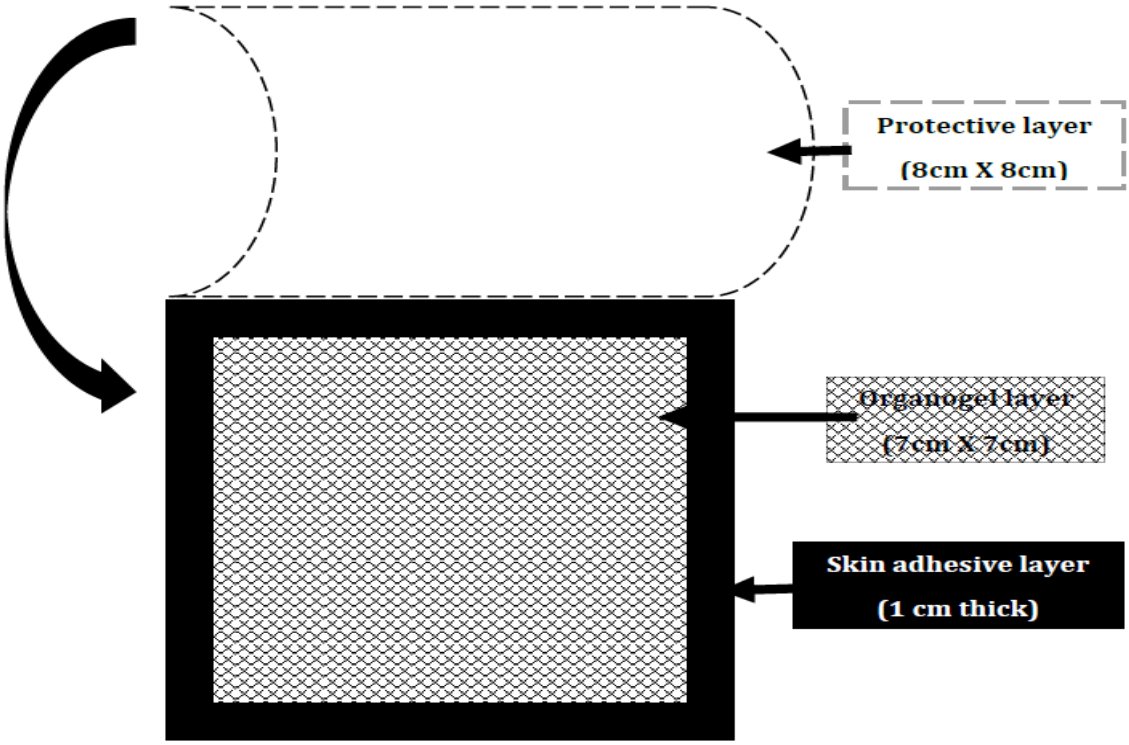

Figure 1. Schematic diagram of transdermal patch of Loxoprofen sodium.

3. Results

Preformulation studies revealed suitability of the reported analytical method for the present study. Drug excipients compatibility study also depicted no drug-excipients interaction.

Evaluation results for the experimental batches are shown in Table 2.

Table 2. Evaluation of Experimental batches of Loxoprofen Sodium organogel.

Evaluation Parameter	Obtained Results							
	PL1	**PL2**	**PL3**	**PL4**	**PL5**	**PL6**	**PL7**	**PL8**
Physical appearance	Hazy thick liquid	Hazy thick liquid	Hazy Gel like	Hazy Gel	White thick liquid	White Gel like	White Gel	White thick Gel
pH	5.9 ± 0.2	6.1 ± 0.2	6.2 ± 0.1	6.2 ± 0.1	5.4 ± 0.2	5.5 ± 0.2	5.7 ± 0.2	5.6 ± 0.1
Viscosity(cPs)	1203 ± 57.4	1742 ± 71.2	2223 ± 65.6	2477 ± 83.1	1818 ± 71.3	2164 ± 85.9	2904 ± 102.1	3311 ± 98.6
Spreadability (gm cm/s)	132.7 ± 4.1	112.1 ± 3.9	105.6 ± 3.3	92.5 ± 2.8	125.7 ± 5.5	102.1 ± 3.9	88.8 ± 5.3	72.3 ± 7.1
Drug content (%)	99.4 ± 2.3	101.5 ± 1.9	99.9 ± 3.1	98.3 ± 2.7	102.4 ± 2.0	99.4 ± 3.0	100.2 ± 2.5	100.8 ± 1.1
In vitro drug diffusion (%)								
1 h	57.4 ± 1.7	49.7 ± 1.1	42.9 ± 2.2	36.2 ± 0.9	51.3 ± 2.3	45.5 ± 1.4	41.0 ± 2.3	38.7 ± 2.0
2 h	73.9 ± 1.5	62.1 ± 1.5	51.0 ± 1.8	45.7 ± 3.1	65.4 ± 3.2	58.7 ± 3.1	51.1 ± 2.4	47.3 ± 3.0
4 h	84.4 ± 2.5	73.5 ± 3.0	63.1 ± 3.6	57.2 ± 2.8	78.9 ± 2.7	66.0 ± 2.8	58.7 ± 3.5	55.3 ± 3.9
8 h	99.7 ± 3.3	97.9 ± 5.2	85.2 ± 3.6	77.8 ± 1.9	96.3 ± 4.2	90.3 ± 3.9	72.5 ± 2.8	67.7 ± 2.4
12 h	99.9 ± 2.1	100 ± 4.7	96.6 ± 4.0	92.2 ± 3.3	100 ± 2.7	100 ± 3.8	90.3 ± 3.2	83.4 ± 4.6
N = 3 for all observations								

As it was clearly evidated from the obtained results that Batch PL4 was optimal formulation (Figures A1 and A2). It was further used for preparing sustained release transdermal patchs of LOX. A 12 h drug release profile was found suitable for 12 h on off cycle for the transdermal patch. In other words, patch can be removed after 12 h of application and again a new patch can be applied after 12 h.

4. Discussion

The study evidenced that similar transdermal formulations of other NSAIDs can significantly enhance current treatment scenario for joint pain. This preliminary study can be further carried out with systematic formulation development approach with emphasis on animal or human studies. Additionally, a formulation with 48 h or longer drug release profiles can also be designed by appropriate modifications.

5. Conclusions

Conversion of oral route to transdermal route of administration for NSAIDs not only avoids GI side effects but also improves patient compliance and hence oerall safety profile. Ensuring reproducibility of transdermal flux of drug may result in bioequivalence to the oral formulations. Further studies can be designed to evaluate the clinical applicability of the formulation.

Author Contributions: D.M. and M.K. conceived and designed the experiments; M.K. performed the experiments and analyzed the data; D.M. provided all the supportive guidance and wrote the paper. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

The following abbreviations are used in this manuscript:

NSAIDs	Non-steroidal Anti-inflammatory Drugs
LOX	Loxoprofen Sodium
PLO	Pluronic lecithin organogel
IPP	Isopropyl Palmitate
Pot. Sorbate	Potassium sorbate
GI	Gastro Intestinal

Appendix A

Figure A1. Optimized organogel formulation (Batch PL4).

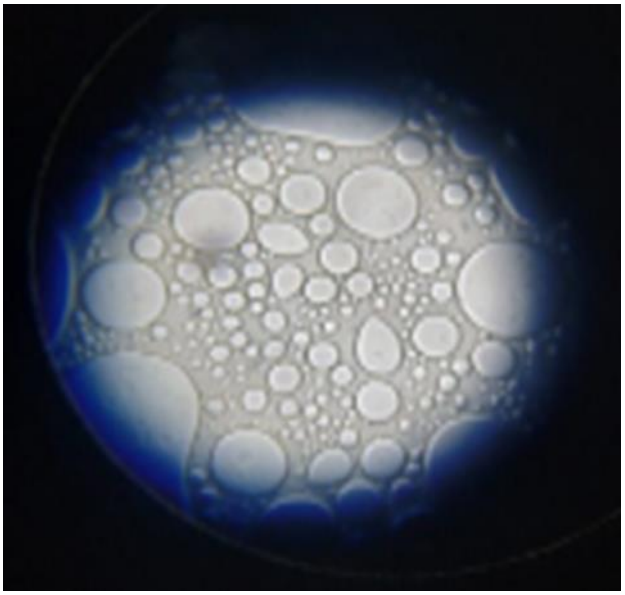

Figure A2. Microscopic analysis of optimized organogel formulation (Batch PL4).

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