Fabrication of an Organogel-Based Transdermal Delivery System of Loxoprofen Sodium †

Mahesh Katariya and Dharmik Mehta *

School of Pharmacy, RK University, Rajkot 360007, India; katariyamahesh62@gmail.com
* Correspondence: dharmik.mehta@rku.ac.in; Tel.: +91-937481-9895
† Presented at the 1st International Electronic Conference on Pharmaceutics, 1–15 December 2020; Available online: https://iecp2020.sciforum.net/.

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. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most widely accessed treatment option amongst all of the options. However, their adverse effects profile is a major hurdle for their use, especially in elderly patients. The present study was focused on developing 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, the transdermal route bypasses first-pass metabolism, gastrointestinal (GI) side effects, and the necessity to administer drug orally. All of these credentials ultimately improved patient compliance. Several experimental batches (PL1 to PL8) were formulated to prepare the 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 the obtained results. It showed sustained drug release up to 12 h. 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 patches 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 are the group that most commonly complain of joint pain. Treatment through oral nonsteroidal anti-inflammatory drugs (NSAIDs) is widely utilized for this purpose. Though effective, it suffers from several side effects, especially gastrointestinal (GI) side effects [1]. Thus, successful administration of NSAIDs through methods other than the oral route is currently needed to avoid GI side effects [2]. Loxoprofen sodium (LOX), a nonselective COX inhibitor, has prominent GI side effects and, contrary to that, a good cardiovascular safety profile, which makes it a potential candidate for transdermal delivery [3,4]. Moreover its sustained release formulation helps to reduce dosing frequency, hence improving patient compliance. Thus, it was considered as a potential candidate to fit the purviews of the present study. Transdermal permeation of the drug was enhanced by incorporating it into an 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 the reproducibility 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.

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

A schematic diagram of prepared transdermal patch is shown in Figure 1.
Proceedings 2021, 78, 20

3. Results

Preformulation studies revealed the suitability of the reported analytical method for the present study. The 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          | 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        | 2 h        | 4 h        | 8 h        | 12 h       |
|                             | 57.4 ± 1.7 | 73.9 ± 1.5 | 84.4 ± 2.5 | 99.7 ± 3.3 | 99.9 ± 2.1 |
|                             | 49.7 ± 1.1 | 62.1 ± 1.5 | 73.5 ± 3.0 | 97.9 ± 5.2 | 100 ± 4.7 |
|                             | 42.9 ± 2.2 | 51.0 ± 1.8 | 63.1 ± 3.6 | 85.2 ± 3.6 | 96.6 ± 4.0 |
|                             | 36.2 ± 0.9 | 45.7 ± 3.1 | 57.2 ± 2.8 | 77.8 ± 1.9 | 92.2 ± 3.3 |
|                             | 51.3 ± 2.3 | 65.4 ± 3.2 | 78.9 ± 2.7 | 96.3 ± 4.2 | 100 ± 2.7 |
|                             | 45.5 ± 1.4 | 58.7 ± 3.2 | 66.0 ± 2.8 | 90.3 ± 3.9 | 100 ± 3.8 |
|                             | 41.0 ± 2.3 | 51.1 ± 2.4 | 66.0 ± 2.8 | 72.5 ± 2.8 | 90.3 ± 3.2 |
|                             | 38.7 ± 2.0 | 47.3 ± 3.0 | 55.3 ± 3.9 | 67.7 ± 2.4 | 83.4 ± 4.6 |

N = 3 for all observations

As was clearly evidenced from the obtained results, Batch PL4 was the optimal formulation (Figures 2 and 3). It was further used for preparing sustained release transdermal patches of LOX. A 12 h drug release profile was found suitable for a 12 h on–off cycle
for the transdermal patch. In other words, the patch can be removed after 12 h of application and again a new patch can be applied after 12 h.

Figure 2. Optimized organogel formulation (Batch PL4).

Figure 3. Microscopic analysis of optimized organogel formulation (Batch PL4).

4. Discussion

The study evidenced that similar transdermal formulations of other NSAIDs can significantly enhance the current treatment scenario for joint pain. This preliminary study can be further carried out with a 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 from the oral route to the transdermal route of administration for NSAIDs not only avoids GI side effects but also improves patient compliance, and hence the overall safety profile. Ensuring the reproducibility of the transdermal flux of drugs 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.

Acknowledgments: Authors are thankful to the sources from which materials required for the study were gifted. Also, we are thankful to School of Pharmacy, RK University, Rajkot for providing facilities to carry out the work.

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

Abbreviations

The following abbreviations are used in this manuscript:

- NSAIDs: Nonsteroidal anti-inflammatory drugs
- LOX: Loxoprofen sodium
- PLO: Pluronic lecithin organogel
- IPP: Isopropyl palmitate
- Pot. Sorbate: Potassium sorbate
- GI: Gastrointestinal

References

1. Abdulla, A.; Adams, N.; Bone, M.; Elliott, A.M.; Gaffin, J.; Jones, D.; Knaggs, R.; Martin, D.; Sampson, L.; Schofield, P. Guidance on the management of pain in older people. Age Ageing 2013, 42 (Suppl. 1), i1-57, doi:10.1093/ageing/afs200.
2. Baranowski, D.C.; Buchanan, B.; Dwyer, H.C.; Gabriele, J.P.; Kelly, S.; Araujo, J.A. Penetration and efficacy of transdermal NSAIDs in a model of acute joint inflammation. J. Pain Res. 2018, 13, 2809–2819, doi:10.2147/JPR.S177967.
3. Fan, M.; Cao, S.; Tu, L.; Wei, Q.; Yuan, R.; Li, X.; Gu, J. Efficacy and safety of loxoprofen hydrogel patch versus loxoprofen tablet in patients with ankylosing spondylitis: A 4-week randomized, open-label study. Biomed. Rep. 2019, 10, 331–336, doi:10.3892/br.2019.1209.
4. Hamaguchi, M.; Seno, T.; Yamamoto, A.; Kohno, M.; Kadoya, M.; Ishino, H.; Ashihara, E.; Kimura, S.; Tsubakimoto, Y.; Takata, H.; et al. Loxoprofen sodium, a non-selective NSAID, reduces atherosclerosis in mice by reducing inflammation. J. Clin. Biochem. Nutr. 2010, 47, 138–147, doi:10.3164/jcbn.10-33.
5. Palanivel, V.; Janardhanan, V.; Muralidharan, C.; Valliappan, K. Improved HPLC method with the aid of chemometric strategy: Determination of loxoprofen in pharmaceutical formulation. Acta Chim. Slov. 2012, 59, 242–248.
6. Ibrahim, M.M.; Hafez, S.A.; Mahdy, M.M. Organogels, hydrogels and bigels as transdermal delivery systems for diltiazem hydrochloride. Asian J. Pharm. Sci. 2013, 8, 48–57, doi:10.1016/j.ajps.2013.07.006.
7. Kriplani, P.; Sharma, A.; Aman, P.P.; Chopra, B.; Dhangra, A.; Deswal, G. Formulation and evaluation of transdermal patch of Diclofenac Sodium. Glob. J. Pharm. Pharm. Sci. 2018, 4, 1–3.
8. Pawar, S.A.; Patil, M.P.; Sadgir, P.S.; Wankhede, N.B. Review on organogel as topical delivery system. World J. Pharm. Pharm. Sci. 2014, 3, 393–409.
9. Gupta, S.; Samanta, M.K.; Raichur, A.M. Dual-drug delivery system based on in situ gel-forming nanosuspension of forskolin to enhance antiglaucoma efficacy. AAPS PharmScitech 2010, 11, 322–335.