Topical Delivery of Flurbiprofen from Pluronic Lecithin Organogel

M. S. PANDEY, V. S. BELGAMWAR* AND S. J. SURANA
Department of Pharmaceutics, R. C. Patel Institute of Pharmaceutical Education and Research, Shirpur-425 405, India

Belgamwar et al.: Pluronic Lecithin Organogel of Flurbiprofen

The purpose of this research is to formulate and evaluate the suitability of pluronic lecithin organogels containing flurbiprofen for topical application. Four formulations were developed using flurbiprofen, lecithin, Pluronic F127, isopropyl palmitate, water, sorbic acid and potassium sorbate were coded as FL1, FL2, FL3 and FL4. All the formulations carried 30% w/w of lecithin phase and 70% w/w of Pluronic phase. The formulated organogels were evaluated for appearance and feel psychorheologically, in vitro diffusion study, drug content, viscosity and pH. Release of flurbiprofen from all formulations was monitored via dialysis membrane-70 and Wistar rat skin as a semipermeable membrane into phosphate buffer saline (0.2 M, pH 7.4) using Keshary-Chien diffusion cell. The viscosities of different formulations were determined by using Brookfield Viscometer at 25°. An attempt has been made to explore the potential of pluronic lecithin organogels for topical delivery of flurbiprofen.

Key words: Pluronic lecithin organogel, flurbiprofen, topical delivery

Topical drug treatment aims at providing high concentration of the drug at the site of application so as to avoid systemic adverse effects associated with oral administration of drug. Organogel is a vehicle base for the delivery of drugs through the dermal and transdermal route. Organogels are formed by specific kind of small organic molecules, which in many solvents very effectively get self assembled into three dimensional networks there by turning a liquid into a gel[1]. Its micellar structure can contain both water and oil soluble ingredients; it shows excellent drug permeability by diffusion through the lipid intracellular matrix and by slight disorganization of skin. Pluronic and lecithin have become very popular in the topical delivery of drugs. A number of studies have shown that pluronic lecithin organogels (PLOs) have the unique capacity to deliver the drugs through the skin[1,2] and particular medications such as NSAIDs, hormones, antiemetics, opioids and local anesthetics[1] to a specific site when other routes of administration are not viable. Flurbiprofen, a
propionic acid derivative is effective antiinflammatory and analgesic recommended in the management of patients with osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. It has a logP/hydrophobicity 4.078, having half-life of 4.7-5.7 h and molecular weight of 244.261 g/mol. These properties make it a potential candidate for topical delivery.

Flurbiprofen and Soya Lecithin were received as gratis samples from FDC Ltd, Mumbai and Phosphoholipid GmbH, Nattermannallee, Germany, respectively. Pluronic F-127 was procured from Sigma Aldrich Chemie GmbH, Steinheim, Germany. Isopropyl palmitate, polyethylene glycol-600, sorbic acid and potassium sorbate were supplied by Loba Chemie, Mumbai, India. All other chemicals were of analytical grade and used as received.

The various formulations of PLO[4,5] (Table 1) were developed with different compositions. Oil phase was prepared by mixing soya lecithin and sorbic acid in appropriate quantity of isopropyl palmitate. The mixture was kept overnight at room temperature in order to dissolve its constituents. Aqueous phase was prepared by dispersing weighed amount of Pluronic F-127 and potassium sorbate in cold water. The dispersion was stored in refrigerator overnight for effective dissolution of Pluronic F-127. The next day, active ingredient flurbiprofen was dissolved in polyethylene glycol-600 and mixed with the lecithin-isopropyl palmitate solution; polyethylene glycol-600 was used for solubilization of flurbiprofen. Finally, aqueous phase (70%) was slowly added in oil phase (30%) with stirring at 400 rpm using mechanical stirrer.

The organogels prepared were evaluated for appearance and feel psychorheologically, drug content and content uniformity at 247 nm in ethanol, pH, viscosity using Brookfield Viscometer and in vitro diffusion/permeation using Keshary-Chien diffusion cell. The drug content of different formulations of organogel was determined by taking a standard curve of flurbiprofen in ethanol. For this, accurately weighed 50.0 mg of drug was transferred in a 50 ml volumetric flask, dissolved in ethanol and volume was made up with ethanol. Two millilitres of the solution was pipette out and diluted to 100 ml with ethanol. Then aliquots were further diluted with ethanol to get concentration of 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20 μg/ml. Absorbance were recorded spectrophotometrically and standard curve of flurbiprofen in ethanol was plotted at λ_{max} 247 nm. Further for determining drug content, each formulation (0.5 g) was taken in a 50 ml volumetric flask, diluted with ethanol and shaken to dissolve the drug in ethanol. The solution was filtered through Whatman filter paper No. 42, one ml of the above filtrate was pipette out and diluted to 10 ml with ethanol. The content of the drug was estimated spectrophotometrically by using standard curve plotted at λ_{max} 247 nm.

To test the pattern of release of drug from formulations, in vitro diffusion studies[4,6,7] were carried out. The developed formulations were subjected to in vitro diffusion through dialysis membrane-70, with molecular weight cut off 12000-14000 D and dehaired abdominal skin of Wistar albino rats was used as a semi permeable membrane using modified Keshary-Chien diffusion cell. The receptor compartment was filled with saline phosphate buffer (0.2 M, pH 7.4) and methanol (90:10). Methanol was added in medium to maintained sink condition. 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 247 nm for flurbiprofen content.

**TABLE 1: FORMULATION COMPOSITION OF PLO**

<table>
<thead>
<tr>
<th>Components</th>
<th>Content (%)</th>
<th>FL1</th>
<th>FL2</th>
<th>FL3</th>
<th>FL4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td></td>
<td>1.4</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Flurbiprofen</td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Polyethylene glycol-600</td>
<td></td>
<td>2</td>
<td>3</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Oil phase</td>
<td></td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Soya lecithin</td>
<td></td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Sorbic acid</td>
<td></td>
<td>2</td>
<td>3</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Isopropyl palmitate up to</td>
<td></td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Aqueous phase</td>
<td></td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Pluronic F-127</td>
<td></td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>
Viscosities of the formulated organogels were determined using Brookfield Viscometer with Spindle no.7 (Model: RV DV-E 230) at 25° with the spindle speed of 10 rpm. The pH of formulated organogels was determined using pH meter. The electrode was immersed in organogels and readings were recorded on pH meter. All the formulations showed drug content in the range of 96-99% indicating uniform distribution of drug throughout the base. The viscosity of all the formulations was found to be in the range 2910-3455 poise. The increase in viscosity with increase in lecithin concentration is might be due to formation of complex network. The results revealed that maximum in vitro cumulative percent drug release of flurbiprofen in 8 h was observed from FL2 formulation. Further increase in concentration of lecithin decreased cumulative percent drug release which might be due to extensive formation of network like structure with very high viscosity. Also from the in vitro diffusion studies it was found that the permeation of flurbiprofen through dialysis membrane-70 (fig. 1) was more as compared to rat skin (fig. 2). The pH of all the formulations was around the skin pH and found to be in the range of 5.9 to 6.5. All the formulations were smooth in feel and free from grittiness which increases the patient compliance. The data obtained is shown in Table 2. From above studies it may be concluded that formulation FL2, containing 3% lecithin is an effective formulation for topical delivery of flurbiprofen as it showed higher cumulative percent drug release and drug content.

ACKNOWLEDGEMENTS

The authors are thankful to the Phospholipid GmbH, Nattermannallee, Germany and FDC Ltd, Mumbai for providing gratis sample of soya lecithin and flurbiprofen respectively. Authors are also thankful to management, R. C. Patel Institute of Pharmaceutical Education and Research, Shirpur for providing all necessary facilities.

REFERENCES

1. Murdan S. A review of pluronic lecithin organogel as a topical and

Synthesis and Antimicrobial Activity of 5-Imidazolinone Derivatives

N. C. DESAI*, A. M. BHAVSAR AND B. B. BAlDANIyA
Medicinal Chemistry Division, University Department of Chemistry, Bhavnagar University, Bhavnagar-364 002, India

Desai et al.: Antimicrobial Activity of 5-Imidazolinones

Several 4-arylidene-2-phenyl-1-(2,4,5-trichlorophenyl)-1H-imidazol-5(4H)-ones (4a-q), N-(4-benzylidene-5-oxo-2-phenyl-4,5-dihydroimidazol-1-yl)-4-chlorobenzamides (5a-o) and N-(4-benzylidene-5-oxo-2-phenyl-4,5-dihydroimidazol-1-yl)-2,4-dichlorobenzamides (6a-m) were prepared. All newly synthesized compounds have been tested for their antibacterial activity against gram (+)ve and gram (–)ve bacteria and also on different strains of fungi. Introduction of OH, OCH3, NO2, Cl and Br groups to the heterocyclic framework enhanced antibacterial and antifungal activities.

Key words: 5-Imidazolinone, antibacterial activity, antifungal activity

*Address for correspondence
E-mail: dnisheeth@rediffmail.com

Imidazolinone ring system is of biological and chemical interest since long. The imidazolinones [1] are associated with a wide range of therapeutic activities [2-7] such as anticonvulsant, sedative and hypnotic, potent CNS depressant, antihistamine, antifilarial, bactericidal, fungicidal, antiinflammatory, MAO inhibitory, antiparkinsonian, antihypertensive and anthelmintic. Recently some new imidazolinone derivatives have been reported as antiinflammatory, herbicidal and hypertensive activities. Some workers have recognized 5-imidazolone as having anticancer activity[8] . The therapeutic importance of the compounds inspired us to synthesize some potential imidazolinones[9-13].

Desai et al. [14] have synthesized 4-benzylidene-2-phenyloxazole-5-one based on the methods described in the literature which is a special type of Perkin condensation in which reaction between aldehyde and benzoylglycine proceeds first followed by ring closure. It is observed that aldehyde condenses under the influence of a base with the reactive methylene group in the azalactone which is formed by the dehydration of benzoylglycine, when the latter reacts with Ac 2O in presence of sodium acetate. In view of these observations, we have synthesized imidazol-5-ones (Scheme I, Table 1).

Various 4-arylidene-2-phenyl-1-(2,4,5-trichlorophenyl)-1H-imidazol-5(4H)-ones (4a-q) were prepared by the reaction of 2,4,5-trichlorobenzenamine with 4-arylidene-2-phenyloxazol-5(4H)-ones (3a-q).