DESIGN AND EVALUATION OF PECTIN BASED MATRIX FOR TRANSDERMAL PATCHES OF MELOXICAM

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ABSTRACT

Transdermal drug delivery system was developed using meloxicam as a model drug. Meloxicam is a non steroidal anti-inflammatory (NSAID) drug. The suitability of drug with respect to solubility, lower molecular weight and short half life makes this drug as a suitable candidate for administration by transdermal route. The polymer selected for the study is pectin. The polymer is non-toxic and biodegradable in nature. In the present investigation various concentration ratios of polymer were used for the fabrication of the matrix diffusion controlled transdermal drug delivery system by solvent evaporation technique. These transdermal drug delivery systems were characterized for their thickness, weight variation, folding endurance, swelling index, content uniformity, compatibility, in-vitro release and skin irritation studies of the drug from the polymeric matrix. Meloxicam was found to be compatible with pectin as revealed by Fourier Transform Infrared Spectroscopy (FTIR) studies and showed satisfactory physiochemical characteristics. In-vitro release studies were carried out with modified Franz diffusion cell using pH 7.4 phosphate buffer as receptor medium and it showed controlled release of drug. Thus the prepared transdermal films can be used to achieve controlled release and improved bioavailability of meloxicam.

KEY WORDS: Transdermal Drug Delivery, Pectin, Meloxicam

INTRODUCTION

The systemic treatment of disease via transdermal route is not a recent innovation. But, in the last two decades, transdermal drug delivery has gained increasing interest. The delivery of drugs using skin as the port of entry is known as transdermal administration and the drug delivery systems are known as transdermal therapeutic systems or transdermal drug delivery systems or popularly known as transdermal patches. The success of this approach is evidenced by the fact that there are currently more than 85 approved transdermal drug delivery products for the treatment of a wide variety of conditions including: hypertension, angina, motion sicknesses, and recently contraception and urinary incontinence. There are also several products in late-stage development that will further expand transdermal drug delivery usage into new therapeutic areas, including Parkinson’s disease. Transdermal controlled drug delivery systems have been investigated & developed in order either to avoid hepatic first-pass effect improving drugs bioavailability or to decrease the dosing frequency required for oral treatment.

Meloxicam is a non-steroidal anti-inflammatory drug preferably used for management of pain, inflammation, tenderness, swelling and stiffness of the joints in patients of osteoarthritis, rheumatoid arthritis, and juvenile rheumatoid arthritis. It has also been used to treat signs and symptoms of ankylosing spondylitis, acute low back pain, and acute sciatica. The mean elimination half-life (1%) ranges from 15 hours to 20 hours. The usual oral dosage regimen is 7.5 mg – 15 mg once daily. Patient compliance in the form reduced administration frequency can best be achieved by development of matrix type transdermal patches of meloxicam.

MATERIALS AND METHODS

Meloxicam was obtained from Unichem Labs, India as a gift sample. Pectin & other chemicals including Dimethylformamide, Polyethylene Glycol 400, Menthol & Glycerin were procured from Central Drug House, Delhi, India. All other chemicals & solvents used were of analytical grade.

INVESTIGATION OF PHYSIOCHEMICAL COMPATIBILITY OF DRUG & POLYMER

In order to evaluate the integrity and compatibility of the drug with the carrier polymer in the polymer-drug matrix formulations, IR spectra of the drug and its formulations were obtained using a potassium bromide pellet method. For determining drug-polymer compatibility (100 mg) of the hydrogel powder was mixed with potassium bromide (400 mg) and was compressed in a hydraulic press to form a pellet at 15 tons pressure. The pellets were scanned in the wavelength region between 4000 to 400 cm⁻¹ by FTIR spectrophotometer (Perkin Elmer-1000, Japan)
PREPARATION OF MELOXICAM-POLYMER FILMS

The transdermal films were prepared by solvent casting technique. The polymeric matrix was prepared by dissolving 6% w/v pectin in distilled water to which (0.1% v/v PEG) was added as plasticizer. The drug solution was prepared by dissolving (50 mg) drug in 2 mL dimethylformamide and shaken on a mechanical shaker for 30 min. to ensure complete solubilisation of the drug. Then the drug solution was added to polymeric solution and mixed thoroughly by continuous stirring to ensure uniform distribution forming a homogenous mixture. To the prepared mixture (0.25% w/v and 0.5% w/v menthol) and (1% w/w and 1.5% w/w glycerin) were added as penetration enhancers. A measured volume of each of the polymeric solutions (10 mL) was poured into petri dish and dried at room temperature. To prevent fast evaporation from the patches an inverted funnel was placed on the mould. After ensuring the complete evaporation of the solvent, patches of 2 cm diameter were cut and stored for further study.

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Quantity</th>
<th>Formulation code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meloxicam</td>
<td>50 mg</td>
<td>F1</td>
</tr>
<tr>
<td>Pectin</td>
<td>6% w/v</td>
<td>F2</td>
</tr>
<tr>
<td>PEG 400</td>
<td>0.1% v/v</td>
<td>F3</td>
</tr>
<tr>
<td>Menthol</td>
<td>0.25% w/v</td>
<td>F4</td>
</tr>
<tr>
<td>Glycerin</td>
<td>1% w/w</td>
<td>F5</td>
</tr>
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</tbody>
</table>

FORMULATION VARIABLES

Selection of Polymer Concentration
Pectin at different concentrations was used (1% w/v to 10% w/v) among which 6% w/v was found to give better results. Film properties (surface properties, thickness and folding endurance) at 6% w/v showed better results as compared to other concentrations.

Selection of Plasticizer
For pectin PEG 400 at different concentrations (0.1% v/v to 0.5% v/v) was used as plasticizer. It was observed that PEG 400 at (0.1% v/v and 0.2% v/v) showed better film properties with good plasticity.

Selection of Penetration Enhancers
Various penetration enhancers were used to modify the release profile of the drug. Menthol at different concentrations (0.1% w/v to 0.5% w/v) was added to the films, it was observed that menthol at (0.25% w/v and 0.5% w/v) modified the release pattern of the drug. Other penetration enhancer glycerin was used at (1% w/w to 3% w/w), it was found that glycerin at (1% w/w and 1.5% w/w) concentration showed better results and modified the release pattern of the drug.

EVALUATION OF FILMS

Thickness**
The thickness of each film was measured using digital micrometer screw gauge at three different positions of the film and the mean value was calculated.

Weight Variation**
For determining weight of films, three films of each formulation were taken and weighed individually using digital balance. The average weight was calculated.

Folding Endurance**
The folding endurance of the films was determined by repeatedly folding one film at same place till it broke. The number of times the film could be folded at the same place without breaking / cracking gave the value of folding endurance.

Swelling Studies†
A drug loaded film of 2 cm² was weighed on a pre weighed cover slip. It was kept into a petri dish and 50 mL of phosphate buffer (pH 7.4) was added. The films were observed for increase in weight for 10 min. The difference in the final and initial weight
gives the weight increase due to absorption of water and swelling of films.

**Surface pH**

For the determination of surface pH the patches were left to swell for 2 hours on the surface of agar plate, prepared by dissolving 2% (w/v) agar in warmed phosphate buffer (pH 7.4) under stirring and then pouring the solution into the petri dish till gelling at room temperature. The surface pH was measured by means of pH paper placed on the surface of swollen patches. The mean of three readings was recorded.

**Drug content**

For determining content uniformity each film of size 2 cm² was cut and placed in volumetric flask and 10 mL of dimethylformamide was added. It was placed on a mechanical shaker and shaken for 3-4 hours. Then 1 mL of the solution was transferred to a 10 mL volumetric flask and diluted with dimethylformamide up to the mark. The absorbance of the solutions was measured against corresponding blank solution using UV-Visible spectrophotometer at 375 nm.

**In-Vitro Release Study**

A modified Franz diffusion cell was used to study drug release from the transdermal films. Phosphate buffer pH 7.4 was used as the receptor fluid (200 mL). Dialysis membrane hydrated over a period of 24 hours was used as the barrier.

**Skin Irritation Studies**

The skin irritation studies were done on Guinea pigs. The animals were observed for any sign of erythema or edema for a period of 7 days and scores as reported by Draize et al.

**RESULTS AND DISCUSSION**

The results obtained from different experiments of this work were summarized in different tables and graphs. All the films were soft, smooth translucent in texture and showed easy removal from the substrate. Thicknesses of all the formulations were in the range of (0.243 ± 0.009 mm to 0.322 ± 0.036 mm). Formulation F4 and F5 showed increased thickness due to presence of glycerin. Weight of all the formulations was found to be uniform and varied from (111.6 ± 0.458 mg to 117.9 ± 0.776 mg). Folding endurance was in the range of (73.6 ± 1.52 to 197.6 ± 0.57) indicating that the films possessed good ability to withstand breakage or rupture. Formulation F1 represented least value of folding endurance, without any plasticizer. Percentages swelling of various formulations were in the range (57% to 65%). The least percentage swelling was found in formulation F4 and F5 in comparison to F2 and F3 which can be attributed to presence of glycerin. The surface pH of all the films was found to be 7 which indicate that the pH was close to the pH of skin. Hence no skin irritation was expected. Good uniformity of drug content among the formulations was observed and ranged from (90% to 97%). The drug content analysis of the prepared formulations has shown that the process employed to prepare formulation in this study was capable of giving films with uniform drug content. Release of the drug from transdermal formulation is controlled by the chemical properties of the drug and delivery form, as well as physiological and physiochemical properties of the biological membrane. Drug permeation profile from different formulations showed that cumulative percentage release of drug from the formulations F4 and F5 was found to be high (94% and 95%) as compared to other formulations F2 and F3 (90% and 92%) and F1 (86%) respectively. The drug release pattern was modified by incorporation of penetration enhancers showing higher release value.
as compared to F1 due to absence of penetration enhancer.

Table 2 Characterization of transdermal films

<table>
<thead>
<tr>
<th>Parameter</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
</tr>
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<tbody>
<tr>
<td>Avg. Thickness * (mm)</td>
<td>0.243 ± 0.009</td>
<td>0.263 ± 0.009</td>
<td>0.257 ± 0.007</td>
<td>0.311 ± 0.015</td>
<td>0.322 ± 0.0367</td>
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<tr>
<td>Avg. Weight * (mg)</td>
<td>111.6 ± 0.458</td>
<td>113.2 ± 0.655</td>
<td>113.0 ± 0.650</td>
<td>116.1 ± 0.757</td>
<td>117.9 ± 0.776</td>
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<tr>
<td>Folding Endurance *</td>
<td>73.6 ± 1.52</td>
<td>197.6 ± 0.57</td>
<td>182.3 ± 1.52</td>
<td>150.6 ± 2.08</td>
<td>141.3 ± 2.51</td>
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<tr>
<td>Swelling index* Increase in weight in (mg)</td>
<td>300.0 ± 1.563</td>
<td>315.8 ± 1.550</td>
<td>330.7 ± 2.577</td>
<td>289.1 ± 0.953</td>
<td>274.8 ± 2.170</td>
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<tr>
<td>Drug Content* (mg)</td>
<td>5.463 ± 0.041</td>
<td>5.223 ± 0.040</td>
<td>5.363 ± 0.041</td>
<td>5.996 ± 0.060</td>
<td>6.063 ± 0.041</td>
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</table>

* Average of three determinations ± S.D

Table 3 Cumulative % drug release

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
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<td>5</td>
<td>3.55</td>
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<td>13.51</td>
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<tr>
<td>10</td>
<td>9.37</td>
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<td>15</td>
<td>17.5</td>
<td>20.07</td>
<td>22.05</td>
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<td>30</td>
<td>22.93</td>
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<tr>
<td>45</td>
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<td>60</td>
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<tr>
<td>90</td>
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<td>480</td>
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<td>90.1</td>
<td>92.64</td>
<td>94.1</td>
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</table>

* Cumulative % drug released

Figure 2 Cumulative % drug released
CONCLUSION
Pectin based matrix for transdermal patches of meloxicam can be developed for effective & controlled management of arthritis. From the present study it may be concluded that transdermal patches of meloxicam provides the convenience of self application and ease of removal whenever required and allow the luxury of more accurate dosing than primary dosage forms.

REFERENCES:

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