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Formulation and Evaluation of Transdermal Patches of Piroxicam

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ABSTRACT

The current research work was an attempt to develop and evaluate a matrix-type transdermal therapeutic system containing Piroxicam with different ratios of hydrophilic and hydrophobic polymeric combinations by the solvent evaporation technique. The physicochemical compatibility of the drug and the polymers was studied by infrared spectroscopy. The results suggested no physicochemical incompatibility between the drug and the polymers. Three transdermal patch formulations (F1, F2, and F7) consists of Hydroxypropyl methylcellulose E5 and Ethylcellulose in the ratios of 5:0, 0:5 and 1:1, respectively were prepared. All formulations carried 4% w/v of Tween-80 as a penetration enhancer for Piroxicam and 10% w/v of Polyethylene glycol as a plasticizer in dichloromethane and methanol (4:1) as solvent system. The prepared transdermal patches were evaluated for *in-vitro* release, moisture absorption, moisture loss, and mechanical properties. The diffusion studies were performed by using modified Franz diffusion cells. The formulation, F1 (Hydroxypropyl methylcellulose E5 alone) showed a maximum release of 95.76 ± 1.38 % in 8 h, whereas F2 (Ethylcellulose alone) showed maximum release of 58.64 ± 1.14 % in 24 h. The formulation, F3 with a combination of polymers (1:1) showed maximum release of 76.76 ± 2.1 % in 24 h, emerging to be ideal formulations for Piroxicam and the mechanism of release was diffusion mediated. The developed transdermal patches increase the efficacy of Piroxicam for the therapy of arthritis and other painful muscular conditions.

1. INTRODUCTION

Conventional systems of medication that require multi-dose therapy have numerous problems and complications. The design of a conventional dosage form, whether a tablet, an injection or a patch, to deliver the right amount of medicine at the right target site becomes complicated if each medication were to be delivered in an optimal and preferred manner to the individual patient. The impetus for the development of novel drug delivery systems apart from therapeutic efficacy is cost. Redesigning the modules and means to transport medicine into the body is the less demanding and more lucrative task. To address these problems, controlled release drug delivery system, a novel drug delivery approach evolves, which facilitates the drug release into systemic circulation at a pre-determined rate Controlled drug release can be achieved by transdermal drug delivery systems (TDDS) which can deliver medicines via the skin portal to systemic circulation at a predetermined rate over a prolonged period gained a lot of interest during the last decade as it offers many advantages over the conventional dosage forms and oral controlled release delivery systems notably avoidance of hepatic first-pass effect, less frequency of administration, reduction in gastrointestinal side effects and improves patient compliance 6. For transdermal products, the goal of dosage design is to maximize the flux through the skin into the systemic circulation and simultaneously minimize the retention and metabolism of the drug in the skin 7.

Piroxicam is a newer NSAID of oxicam class. It is a strong analgesic and anti-inflammatory agent. Its analgesic activity is comparable to that of opioids (more effective than 10 mg morphine when used at doses > or = 8 mg to control pain after oral surgery). Clinical investigations have established it as a potent analgesic with excellent anti-inflammatory properties in a range of painful and/or inflammatory conditions, including Rheumatoid arthritis and postoperative pain 8, 9, 10.

Like all NSAIDs, Piroxicam acts by inhibiting the metabolites of the COX branch of the arachidonic acid pathway. It inhibits both isoforms in the same proportion, a perfectly balanced inhibition of COX-1 and COX-2 is achieved. Prostaglandins play an important role in gastrointestinal mucosal protection by strengthening the mucosal barrier for acid and in inhibiting gastric acid secretion. Thus inhibition of prostaglandin synthesis leads to adverse effects. The gastric side effects range from mild dyspepsia and heartburn to ulceration and hemorrhage 11, 12.

Piroxicam is absorbed rapidly and almost completely from the gastrointestinal tract. Peak plasma concentration is attained within 2.5 hrs. Food reduces the absorption of the drug. The absolute bioavailability of Piroxicam is 90-100%. It has a relatively short plasma half-life (3 to 5 hours). It is eliminated following biotransformation to 5'-hydroxy-Piroxicam, which does not undergo enterohepatic recirculation 13.

Thus in current research work, an attempt was made to develop transdermal patches of Piroxicam to supply local medication to the affected tissues (painful joints), avoid its gastrointestinal side effects and to improve patient compliance by supplying sustained release patch.

2. MATERIALS AND METHODS

2.1. MATERIALS

Piroxicam was received as a gift sample from Micro Labs, Hosur, India. Hydroxypropyl methylcellulose (HPMC) E5 and ethyl cellulose (EC) were procured from Shreeji chemicals and Rolex chemical industries Mumbai, India, respectively. Tween-80 and Polyethylene glycol (PEG-400) were procured from S.D Fine chemical Ltd. (Mumbai, India). All other laboratory chemicals used in the study were of analytical reagents grade. Double distilled water was used throughout the study. 2.2. Investigation of physicochemical compatibility of drug and polymer.

2.2 Physicochemical compatibility:

The physicochemical compatibility between Piroxicam and polymers used in the films was studied by using Fourier transform-infrared (FT-IR- 8300, Shimadzu Co., Kyoto, Japan) spectroscopy. The pelletization was done by the KBr pellet method 6, 14, 15. The FT-IR spectra were recorded in the wavelength region between 4000 and 400 cm-1. The spectra obtained for Piroxicam and physical mixtures of Piroxicam with polymers were compared.

2.3. Preparation of transdermal patch:

In the present study, drug-loaded matrix type transdermal films of Piroxicam were prepared by solvent evaporation method 3, 6, 16. Teflon plates having a diameter of 6 cm and a total area of 28 cm2 were used. The bottom of the plates was wrapped with aluminum foil, 300 mg of the polymer(s) was accurately weighed and dissolved in 7 ml of Dichloromethane:

methanol (4:1) and kept aside to form a clear solution. Polyethylene glycol (PEG-400) was used as a plasticizer and Tween-80 is used as a permeation enhancer. 8 mg of Piroxicam was dissolved in the above solution and mixed for 10 min. The resulted uniform solution was cast on the aluminum foil.

and dried at 40oC in the hot air oven for 24 h. An inverted funnel was placed over the mold to prevent the fast evaporation of the solvent. After 24 h the dried films were taken out and stored in a desiccator for further studies. Compositions of different formulations are represented in Table 1.

Table 1
Composition of different formulations containing Piroxicam

Formulations	F1	F2	F3
Piroxicam (mg)	100	100	100
HPMC E-5 (mg)	200	-	100
EC (mg)	-	200	100
PEG-400 (ml)	0.6	0.6	0.6
Tween-80 (ml)	0.25	0.25	0.25
Dichloromethane: Methanol (4:1)	7	7	7

2.4. Evaluation of transdermal patches

1. Physical appearance:

All the prepared patches were visually inspected for color, clarity, flexibility and smoothness 5.

2. Thickness uniformity:

The thickness of the formulated film was measured at 3 different points using a digital caliper and an average thickness of three readings was calculated.

3. Weight uniformity:

For each formulation, three randomly selected patches were used. For weight variation test, 3 films from each batch were weighed individually and the average weight was calculated 18.

4. Folding endurance:

The folding endurance was measured manually for the prepared films 17, 19, 20. A strip of film (3 x 3 cm) was cut and repeatedly folded at the 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.

5. Percentage of moisture absorption:

The films were weighed accurately and placed in the desiccators containing 100 ml of a saturated solution of potassium chloride, which maintains 80-90% RH 20, 21. After 3 days, the films were taken out and weighed. The study was performed at room temperature. The percentage of moisture absorption was calculated using the formula:

$$\% \text{ moisture absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

6. Percentage moisture loss: The films were weighed accurately and kept in a desiccator containing anhydrous calcium chloride. After 3 days, the films were taken out and weighed. The moisture loss was calculated using the formula:

$$\% \text{ moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

7. Water vapor transmission rate:

Glass vials of 5 ml capacity were washed thoroughly and dried to a constant weight in an oven. About 1 g of fused calcium chloride was taken in the vials and the polymer films of 2.25 cm2 were fixed over the brim with the help of an adhesive tape. Then the vials were weighed and stored in a humidity chamber of 80-90 % RH condition for a period of 24 h 7, 23. The vials were removed and weighed at 24 h time intervals to note down the weight gain.

$$\text{Transmission rate} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Time} \times \text{Area}} \times 100$$

8. Tensile strength:

The tensile strength of the film was determined with a Universal strength testing machine (Hounsfield, Slinfold, Horsham, U.K.). The sensitivity of the machine was 1 g. It consisted of two load cell grips. The lower one was fixed and the upper one was movable.

The test film of size (4 Ã— 1 cm^2) was fixed between these cell grips and force was gradually applied to the film broke 17,24.

The tensile strength of the film was taken directly from the dial reading in kg.

Tensile strength is expressed as follows:

9. Drug content uniformity of films:

The patches (1 cm^2) were cut and added to a beaker containing 100 ml of phosphate-buffered saline of pH 7.4 5, 25. The medium was stirred with a magnetic bead. The contents were filtered using Whatman filter paper and the filtrate was examined for the drug content against the reference solution consisting of placebo films (contains no drug) at 376 nm spectrophotometrically. The experiment was repeated to validate the result.

10. *In-vitro* drug release studies:

In-vitro skin permeation studies were performed by using a modified Franz diffusion cell with a receptor compartment capacity of 20 ml 7, 22. The synthetic cellophane membrane was mounted between the donor and receptor compartment of the diffusion cell. The formulated patches were cut into the size of 1cm2 and placed over the drug release membrane and the receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. The whole assembly was fixed on a magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads at 50 rpm; the temperature was maintained at 37 ± 0.5^0C. The samples of 1 ml were withdrawn at a time interval of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, and 24 h, analyzed for drug content spectrophotometrically at 376 nm against a blank. The receptor phase was replenished with an equal volume of phosphate buffer at each time of sample withdrawal. The cumulative amounts of drug permeated per square centimeter of patches were plotted against time.

RESULTS AND DISCUSSION

3.1. *Physicochemical compatibility of drug and polymer*

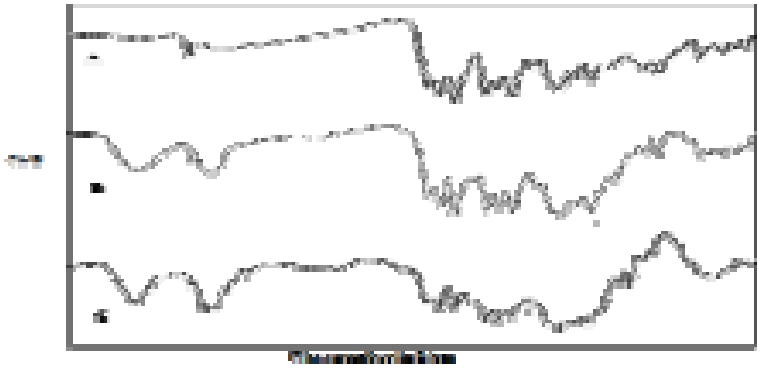

Fig. 1

FTIR Spectra of, A= pure drug Piroxicam,
B= Physical mixture of drug and HPMC E5,
C= Physical mixture of Piroxicam and EC.

Table 2

Formulation code	Thickness (mm)	Weight (g)	Folding endurance
F1	0.200 ± 0.020	0.860± 0.017	111.0 ± 4.582
F2	0.203 ± 0.011	0.832 ± 0.017	55.33 ± 6.806
F3	0.190 ± 0.026	0.865 ± 0.017	95.66 ± 7.371

* Indicates all the values from tables are in the form of (mean ± SD) for n = 3.

Table 3

Formulation code	%Moisture absorption	% Moisture loss	Drug content in mg
F1	6.973 ± 2.324	12.5 ± 2.50	0.279 ± 0.008
F2	1.753 ± 1.518	9.64 ± 1.51	0.249 ± 0.016
F3	6.348 ± 1.374	9.29 ± 2.32	0.271 ± 0.025

Table 4

Formulation code	Water vapour transmission rate	Tensile strength (kg/mm^2)
F1	0.0045 ± 0.0001	3.84 ± 0.125
F2	0.0026 ± 0.0005	2.96 ± 0.110
F3	0.0042 ± 0.0004	3.41 ± 0.079

Table 6

Formulation code	R Square values			
	Zero Order	First Order	Higuchi	Peppas
F1	0.9901	0.7563	0.9009	0.9865
F2	0.9113	0.9877	0.8958	0.9994
F3	0.9325	0.9816	0.8931	0.9979

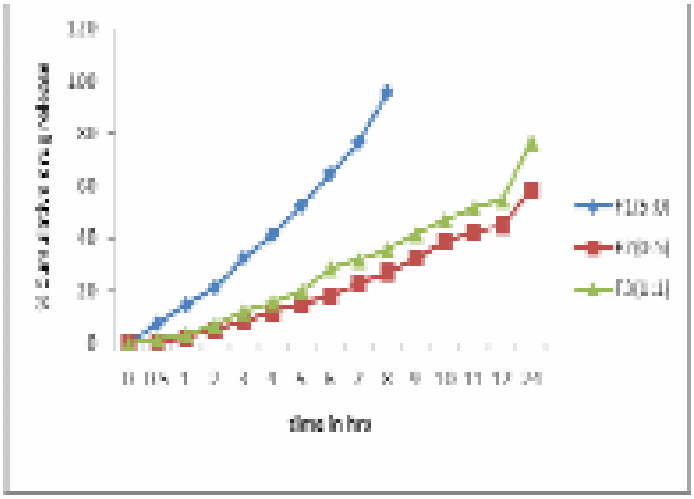

Figure 2

1) Physical appearance:

The transdermal patches were transparent, smooth, uniform and flexible.

2) Thickness Uniformity:

The thickness of the patches was varied from 0.190 ± 0.026 mm to 0.203 ± 0.011 mm (Table 2). Low standard deviation values ensured uniformity of the patches.

3) Weight Uniformity:

The weights ranged between 0.832 ± 0.017 mg and 0.860 ± 0.017 mg (Table 2), which indicates that different batches of patch weights, were relatively similar.

4) Folding endurance:

Folding endurance was found to be >111 which is sufficient (Table 2).

5) The % moisture loss:

The % moisture loss was found to be between 9.29 ± 2.32 to 12.5 ± 2.50 (Table 3). The moisture loss was found to increase with increasing concentration of hydrophilic polymers.

6) The % moisture absorption:

% moisture absorption was found to be 1.753± 1.518 to 6.973 ± 2.324 (Table 3), and it increases with increasing concentration of hydrophilic polymers.

7) Water vapor transmission rate:

The water vapor transmission rate for prepared transdermal patches was found to be 0.0026± 0.0005 to 0.0045 ± 0.0001 (Table 4).

8) Tensile strength:

The Tensile strength of patches is found in order F1>F3>F1. As the concentration of hydrophilic polymer was increased there is an increase in tensile strength. The mean value was found to vary between 2.96 4 0.110 to 3.84 ± 0.125 kg/mm2 (Table 4).

9) Drug content uniformity of films:

Drug content was found to be 0.249 ± 0.016 mg to 0. 279 ± 0.08 mg (Table 3).

3. *In-vitro* drug release studies:

The result indicated that the release of drug from patches increases with increasing concentration of HPMC E5. The cumulative percentage of drug release in 8 h was found to be the highest (95.76 ± 1.38 %) from formulation.

F1 (Table 5, Fig. 2) and minimum (58.64 Â± 1.14 %) from formulation F2. The drug release was found to increase as the concentration of hydrophilic polymer increases. Formulation F3 containing HPMC E5: EC (1:1) showed a cumulative % drug release of 76.76 Â± 2.1 % in 24 h, emerging as the best formulation by fulfilling the requirement of better and sustained release which was not possible with HPMC E5 and EC alone.

4. DISCUSSION

Piroxicam in combination with HPMC E5, EC and with the incorporation of PEG (10%) and Tween-80 (4%) produced smooth, flexible and transparent films. FT-IR spectral studies indicated there was no interaction between Piroxicam and polymers used. Piroxicam patches were prepared with a combination of these polymers and evaluated. From the results, it was observed that thickness, weight variation, low moisture loss, low moisture absorption, tensile strength were suitable for maximum stability of the prepared formulations. The drug content of TDDS patches ranged from 0.249-0.279 mg.

The drug release rate increased when the concentration of the hydrophilic polymer was increased. The cumulative percentage drug release for F1 was found to be 95.76 Â± 1.38 % at 8 h and for F2 it was found 58.64 Â± 1.14 % at 24 h. The formulation, F3 [HPMC E5: EC (1:1)] is considered as the best formulation since it shows a maximum *in-vitro* drug release as 76.76 Â± 2.1 % at 24 h. The drug release kinetics studies showed that except formulation F1 all other formulations follow first-order while formulation F1 follows zero-order (Table 5).

5. CONCLUSION

In conclusion, controlled release TDDS patches of Piroxicam can be prepared using the polymer combinations, HPMC E5: EC (1:1) with PEG-400 and Tween-80 as plasticizer and enhancer, respectively. The release rate of drug through patches increased when the concentration of hydrophilic polymer was increased. The drug release kinetics of all fabricated patches follows first-order kinetics except F1 showing zero-order release kinetics (Table 5). Further, *in-vivo* studies have to be performed to correlate with *in-vitro* release data for the development of suitable controlled-release patches for Piroxicam.

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