Original Article

Design and Development of Transdermal Drug Delivery of Nonsteroidal Anti-inflammatory Drugs: Lornoxicam

Shivakumar H. N., Ruchira S. Kotian

Department of Pharmaceutics, KLE College of Pharmacy, Bengaluru, Karnataka, India

Abstract

Background: Conventional route, the most common route of administration, has drawbacks such as hepatic first-pass metabolism, poor bioavailability, and ability to alter drug concentrations in the blood. These problems can be overcome by a controlled-release drug delivery system, which can be accomplished with the development of transdermal drug delivery system. **Objective:** The objective of this study was to design and develop a lornoxicam-loaded matrix-type transdermal films with different permeation enhancers and determine their physicochemical characteristics. **Materials and Methods:** Lornoxicam-loaded transdermal films were prepared by the solvent evaporation technique. The Fourier transform infrared spectroscopic studies were performed to determine the drug–excipient interactions. Six formulations were prepared with different permeation enhancers such as propylene glycol, dimethylformamide, dimethyl sulfoxide (DMSO), sodium lauryl sulfate, Span 20, and TWEEN 80 by using 500 mg of sodium alginate as the polymer and 60% w/w glycerin as the plasticizer. The prepared formulations were evaluated for thickness, uniformity of weight, moisture loss, moisture uptake, drug content, and tensile strength. The effect of different permeation enhancers on diffusion was determined through a shed snakeskin by using Franz diffusion cells. **Results:** The preformulation studies conducted were fulfilled to design a matrix-type transdermal film. *In vitro* diffusion 24 h indicated that the steady state flux were in the order of F3 > F2 > F1 > F6 > F5 > F4. It was observed that the film prepared with DMSO showed higher diffusion than the formulations with other permeation enhancers. **Conclusion:** It was concluded that permeation enhancer to prepare lornoxicam-loaded matrix-type transdermal film to improve patient compliance.

Keywords: *Dimethyl sulfoxide, glycerin, lornoxicam, sodium alginate, transdermal drug delivery systems*

Introduction

Conventional route, the most frequently used route of administration, has shortcomings such as hepatic first-pass metabolism, poor bioavailability, and ability to alter drug concentration in the blood.[1] These complications can be overcome by the controlled-release drug delivery systems, which ease the drug release at a predetermined rate.[2,3] Controlled-drug delivery can be accomplished by transdermal drug delivery systems (TDDSs), which deliver drugs through the epidermis of the skin to attain the prolonged systemic circulation. The advantages of TDDS include increased patient compliance, maintained plasma drug concentration, enhanced bioavailability, no hepatic first-pass effect, sustained drug concentrations in the blood, and decreased side effects and gastrointestinal complications.[1,4]

Lornoxicam, also called chlortenoxicam, belongs to the oxicam group of nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs have highly potent analgesic and anti-inflammatory property.[5,6] Lornoxicam is a widely recommended NSAID for the treatment of patients with rheumatoid arthritis and osteoarthritis.[5] Moreover, lornoxicam is poorly soluble in water and has short plasma half-life. Owing to these advantages, lornoxicam is chosen as an ideal candidate for controlled-drug delivery.[6]

Lornoxicam, similar to other NSAIDSs, decreases the prostaglandin synthesis by inhibiting the cyclooxygenase (COX) branch of the arachidonic acid pathway. It inhibits both isoforms of COX, that is, COX-1 and COX-2 in the same proportions.[7] Inhibition of (PG) synthesis protects the gastrointestinal mucosal membrane by preventing the gastric acid secretion and strengthening the mucosal barrier for gastric acid. However, the inhibition of PG synthesis may cause gastric side

Address for correspondence:
Dr. Shivakumar H. N., Department of Pharmaceutics, KLE College of Pharmacy, Rajajinagar, Bengaluru 560010, Karnataka, India.
E-mail: shivakumarhn@gmail.com

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effects such as heartburn, mild dyspepsia, ulceration, and hemorrhage.[2]

Sodium alginate is a biopolymer that has been widely used as pharmaceutical agent in the formulation tablets as a binding and disintegrating agents.[8,9] Sodium alginate in the presence of calcium chloride forms gel and delays the dissolution of a drug from sustained release formulations.[10] Although there are several permeation enhancers, dimethyl sulfoxide(DMSO) is considered as the ancient, safe, and effective molecule, facilitating the transdermal delivery of both hydrophilic as well as lipophilic medications.[11] Hence, in our study, lornoxicam-loaded transdermal patches were developed with sodium alginate (as a polymer) and different permeation enhancers to regulate the release of lornoxicam concentrations up to 24 h.

Studies have formulated the transdermal patches of NSAIDs with different polymers and permeation enhancers.[12,13] However, to the best of our knowledge, studies with lornoxicam loaded-transdermal patches in the management of arthritis were scarce. Hence, this study focused to develop a newly modified lornoxicam-loaded transdermal drug delivery films with different permeation enhancers and determine their physicochemical characteristics.

Materials and Methods

Materials

Lornoxicam was procured from DM Pharma, Solan, Himachal Pradesh, India. The excipients such as sodium alginate, glycerin, methanol, potassium dihydrogen orthophosphate, sodium hydroxide pellets, calcium chloride, and DMSO were procured from S. D. Fine Chemicals, Mumbai, Maharashtra, India. Octanol was procured from Central Drug House, New Delhi, India.

Preformulation study

Preparation of stock and working standard solutions: An accurately weighed 50 mg of lornoxicam was dissolved in a slight amount of methanol and diluted with 50 mL phosphate buffer (pH 7.4) to attain the concentration of 1 mg/mL. A standard stock solution of 0.4 mL was drawn and diluted to 100 mL with phosphate buffer (pH 7.4) to prepare secondary standard solution of concentration 40 µg/mL. A series of working standard solutions was prepared by withdrawing 0.1, 0.2, 0.3, 0.4, and 0.5 mL of the secondary standard solution to attain the concentrations of 4, 8, 12, 16, and 20 µg/mL, respectively. The absorbance of the working standards was measured at 376 nm in a UV spectrophotometer with phosphate buffer (pH 7.4) as a blank. The obtained readings were plotted on the Figure, and the data were subjected to linear regression analysis in Microsoft Excel. The λmax obtained in this study was found to correspond well with that reported earlier.[14] The method developed was found to be sensitive, precise, and reliable.

Determination of melting point: A small amount of the drug (lornoxicam) was taken in a capillary tube closed at one end and placed in a melting point apparatus. The temperature at which the drug melted was recorded. This was repeated for at least three times and the average value was taken.

Determination of solubility: An excess amount of lornoxicam was taken and dissolved in a measured quantity of phosphate buffer (pH 7.4) in a glass vial to obtain a saturated solution. The solution was sonicated and kept at room temperature to attain equilibrium. After 24 h, the solution was filtered and the concentration of lornoxicam in the filtrate was determined spectrophotometrically.[15]

Determination of partition coefficient: An accurately weighed 10 mg of lornoxicam was taken and dissolved in 10 mL of 1-octanol (1 mg/mL). The 5 mL of octanol solution was taken and equilibrated into 5 mL of phosphate buffer (pH 7.4) in separating funnel and shaken intermittently and kept aside for 24 h at room temperature. After 24 h, the concentration of lornoxicam in the phosphate buffer was determined spectrophotometrically. The partition coefficient was determined by the following equation:[16]

$$\text{Partition coefficient} = \frac{\text{Concentration of drug in octanol}}{\text{Concentration of drug in phosphate buffer (pH 7.4)}}$$

Permeability studies

Preparation of shed snakeskin: The epidermis of the skin was taken after shedding and sealed in a polyethylene bag at room temperature. Before conducting the diffusion study, the shed snakeskin was hydrated in 0.002% w/v aqueous sodium azide for three days.[17,18]

Permeability studies using modified Franz diffusion cell: A standardized modified Franz-type diffusion cell consists of two compartments—donor compartment and receptor compartment. Different concentrations of drug in phosphate buffer were taken in donor compartment. The snake shed skin was mounted between the donor and receptor compartments. The phosphate buffer, as a medium, was taken in a receiver compartment to maintain the sink conditions. The medium was magnetically stirred at 600 rpm to maintain a temperature of 37°C. The amount of drug diffused was withdrawn periodically at 0, 1, 2, 3, 5, 8, 12, and 24 h and estimated spectrophotometrically at 376 nm.

Permeability coefficient: It is the velocity of drug passage through the skin or membrane (in µg/cm/h). The permeability coefficient[19] was determined from the slope of the Figure of percentage of drug versus time as follows:

$$\text{Permeability } (P) = \text{Slope} \times V_d / S$$

where, V_d = volume of donor solution and S = surface area of the tissue

Flux: Flux is defined as the amount of drug flowing through a unit cross-sectional barrier in unit time. It is calculated using the following equation:[20]

$$\text{Flux } (J) = P \times \text{CD}$$

where, CD = concentration of drug in the donor solution and P = permeability coefficient.

Preparation of transdermal films

Matrix films of sodium alginate containing lornoxicam were prepared by solvent-casting method. An accurately weighed 22 mg of lornoxicam was dissolved in a small amount of ethanol, and the solution was made up to 15 mL with distilled water adjusted to pH of 7.4 with phosphate buffer. Sodium alginate was added to the aqueous solution of the drug and casted in a petri plate measuring 4.5 cm in diameter. Glycerin was used as a plasticizer in a concentration of 60% w/w based on the dry weight polymer. After drying at room temperature for 48 h, circular films of 1 cm diameter, each containing 1 mg of the drug were taken cut out. Six different formulations containing different permeation enhancers were prepared as per Table 1. A 10% w/v solution of calcium chloride was prepared to harden the surfaces of the matrix films. The dried matrix films were wrapped in a butter paper and stored in a desiccator for further analysis.

Drug–excipient interaction study

Fourier transform infrared studies: Infrared (IR) spectrophotometry is an analytical technique utilized to check the chemical interactions between the drug and the excipients used in the formulations. Here, 10-mg sample was powdered and mixed with powdered potassium bromide. The powdered mixture was taken in a diffuse reflectance sampler, and the spectrum was recorded by scanning in the wavelength region of 4000–400 cm^{-1} in a Fourier transform infrared (FTIR) spectrophotometer. The IR spectrum obtained was compared with the IR spectrum of the pure drug to determine any possible drug–excipient interaction.[21]

Evaluation of transdermal films

All the prepared transdermal films were evaluated by the following parameters:[22,23]

Thickness determination

The thickness of the films was measured at four different points by using Baker digital caliper, Evansville, Wisconsin (WI), United states. The average of four readings was taken to determine the thickness.

Uniformity of weight

Three different films of the individual batches were taken randomly and weighed to calculate the average weight. The individual weight of the film should not deviate from the average weight of the three films.

Moisture loss

The films were accurately weighed and placed in a desiccator containing calcium chloride at 40°C and dried at least for 24 h. Then, the film was taken out and weighed repeatedly until it showed a constant weight. The percentage moisture loss was determined by the following formula:

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

Moisture uptake

The weighed film kept in the desiccator at 40°C was taken out and exposed to relative humidity (RH) at 75% (saturated solution of sodium chloride) and 93% (saturated solution of ammonium hydrogen phosphate) in a desiccator. The weights were measured periodically till a constant weight was obtained. The percentage moisture uptake or absorption was determined by the following formula:

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

Drug content

Transdermal films of the specified area (1.76 cm^2) were cut into pieces and taken in a 50-mL volumetric flask. Approximately 10 mL of ethanol was added and shaken on a mechanical shaker to obtain a homogeneous solution. Then, 0.5 mL of the solution was taken and diluted to 10 mL with saline phosphate solution (pH 7.4) and filtered. The absorbance of the filtrate was measured at 376 nm by UV spectrophotometer.

Tensile strength

It was measured by universal strength testing machine. In this, maximum stress was applied at any point on the film until the film gets broken. The tensile strength was calculated by the maximum tensile strength applied at the break divided by

Table 1: Composition of formulations

Formulation	Lornoxicam (mg/cm^2)	Sodium alginate (mg)	Glycerin (%)	Permeation enhancer
F1	1	500	60	Propylene glycol (1% v/v)
F2	1	500	60	Dimethylformamide (5% v/v)
F3	1	500	60	Dimethyl sulfoxide (5% v/v)
F4	1	500	60	Sodium lauryl sulfate (0.5% v/v)
F5	1	500	60	Sorbitan monolaurate (Span 20, 1% v/v)
F6	1	500	6	Polyoxyethylene sorbitan monooleate
		500		(TWEEN 80; 1% v/v)

the cross-sectional area of the film. The tensile strength was determined by the following formula:

$$\text{Tensile strength} = \frac{\text{Tensile load at break}}{\text{Cross-sectional area}}$$

In vitro diffusion study

In vitro diffusion study was also carried out in a Franz diffusion cell. The conditions were maintained same as the permeability studies, but in this, lornoxicam-loaded transdermal films were placed in the donor compartment.[24]

Results

Standard plot of lornoxicam

The absorbance values of the series of working standard solution are depicted in Figure 1. The curve was found to show a slope average of 0.053 with a regression coefficient of 0.9989. Beer–Lambert's range was 0–20 µg/mL.

Drug solubility pH

The solubility of the lornoxicam in buffer solutions of different pH levels is given in Table 2.

Melting point

The melting point of lornoxicam was found to be 225°C ± 0.028°C, represented as mean ± SD, n = 3 (SD = standard deviation).

Partition coefficient

The logarithmic P value (partition coefficient) of the lornoxicam was found to be 1.8 ± 1.21 in octanol and phosphate buffer (pH 7.4).

Permeability studies

The amount of lornoxicam diffused across the shed snakeskin using 2 and 5 mg/mL donor concentrations is presented in Figure 2. The permeability coefficient of lornoxicam was found to be 1.718 and 1.83 cm/h for 2 and 5 mg/mL concentrations, respectively. The steady state flux of lornoxicam was found to be 3.43 and 3.73 µg/cm^2/h at 2 and 5 mg/mL concentrations, respectively.

Drug–excipient interaction study

The prominent peaks in lornoxicam and sodium alginate were also reflected in the mixture of lornoxicam with sodium alginate as shown in Figures 3–5.

Evaluation of transdermal films of lornoxicam

Thickness determination: Figure 4 The thickness Figure 5 of the six films with six different permeation enhancers varied from 0.300 ± 0.003 to 0.358 ± 0.003 mm [Table 3].

Uniformity of weight: The variations of weights ranged between 0.021 ± 0.007 and 0.025 ± 0.001 g, which indicate that all the formulations were relatively similar [Table 3].

Moisture loss: The moisture loss ranged between 3.06% ± 0.102% and 4.04% ± 0.111% [Table 3].

Drug content: The drug content was found to be ranging between 0.902 ± 0.042 and 0.956 ± 0.063 mg [Table 3].

Tensile strength: The tensile strength of the films was found in the order of F1 > F2 > F4 > F5 > F6 > F3. The values varied between 1.41 ± 0.119 and 1.51 ± 0.120 g/cm^2 [Table 3].

Moisture uptake: The moisture absorption varied between 5.09%–7.12% and 8.95%–10.96% at RH 75% and 93%, respectively [Table 4].

In vitro diffusion study: The diffusion profile of the six formulations prepared with six different permeation enhancers

Table 2: Solubility of lornoxicam at different pH levels

pH	1.2	6.8	7.4
Solubility (µg/mL)	40 ± 0.018	84 ± 0.002	180 ± 0.005

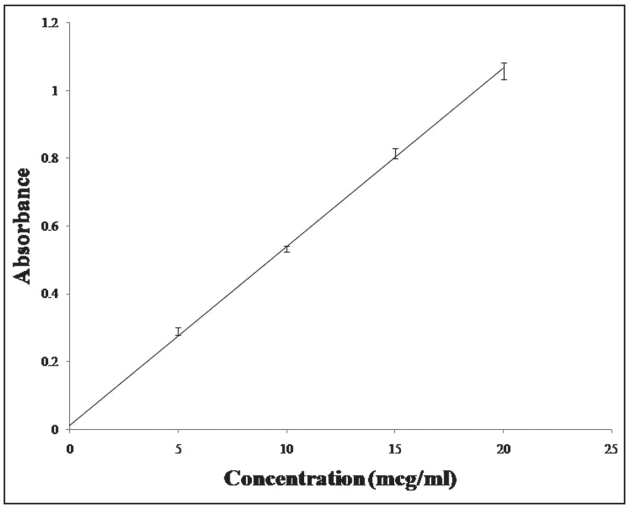

Figure 1: Standard curve of lornoxicam (n = 3) in phosphate buffer (pH 7.4)

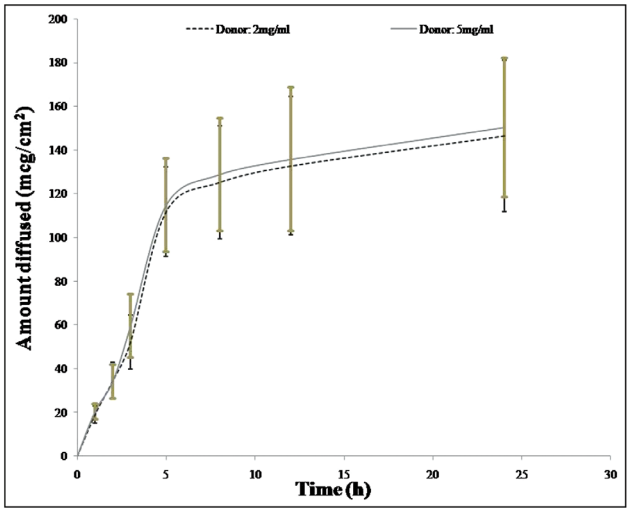

Figure 2: Permeation profile of lornoxicam (2 and 5 mg) across the shed snakeskin

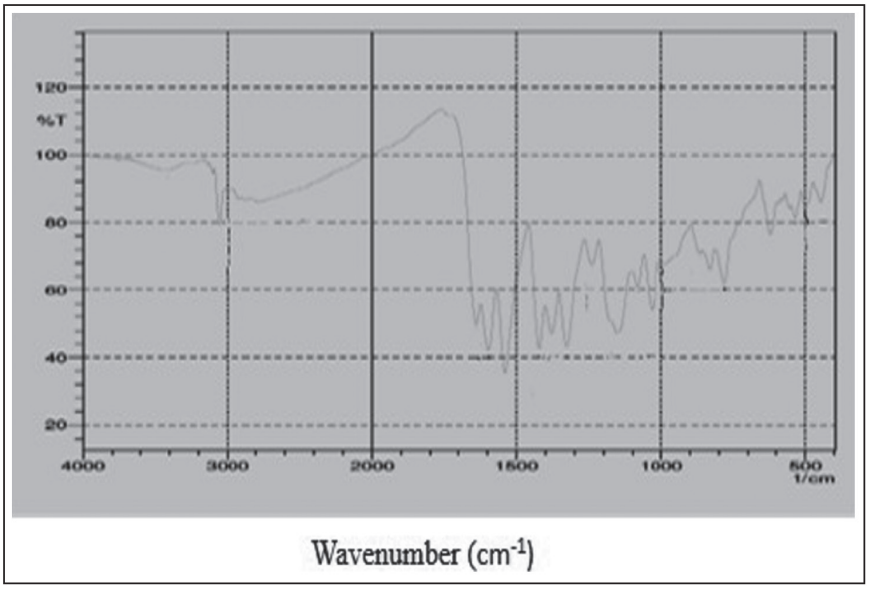

Figure 3: Fourier transform infrared spectroscopy spectrum of lornoxicam

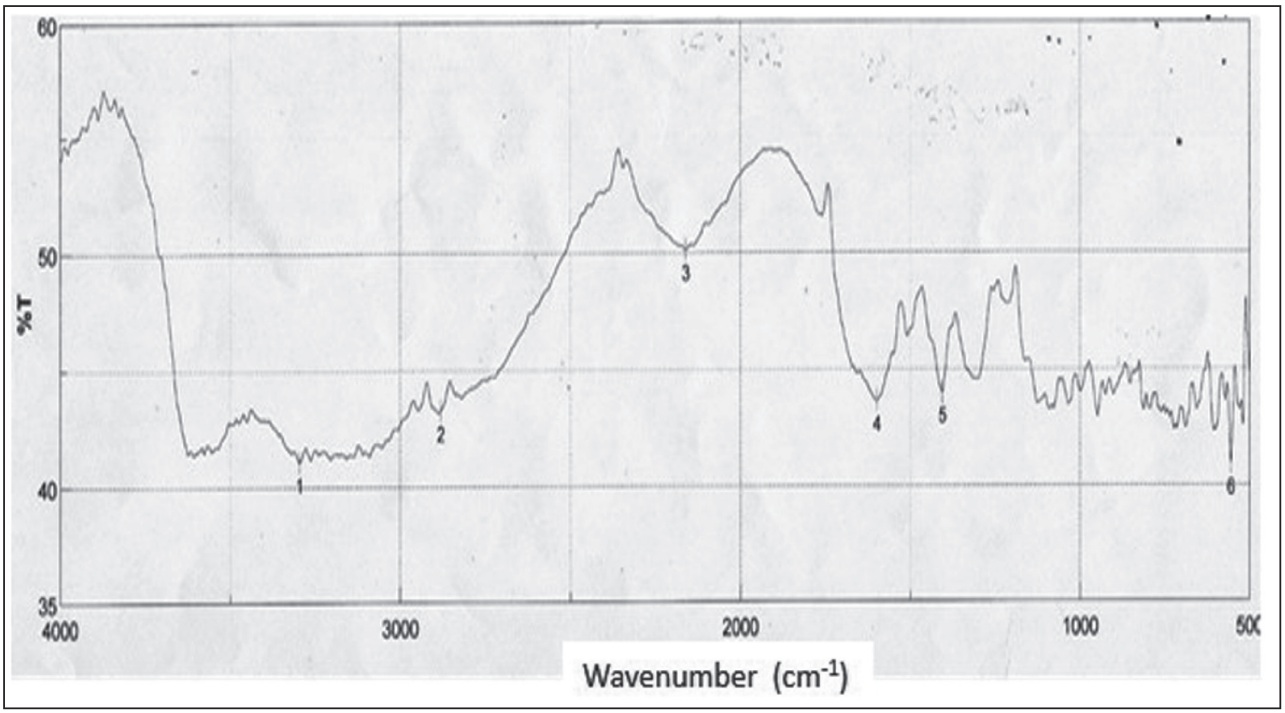

Figure 4: Fourier transform infrared spectroscopy spectrum of sodium alginate film

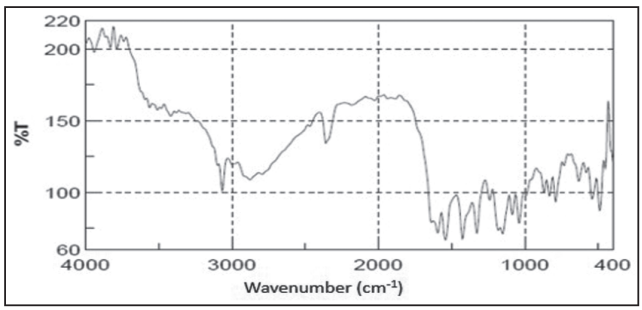

Figure 5: Fourier transform infrared spectroscopy spectrum of lornoxicam and sodium alginate

and the formulation without permeation enhancer is shown in Figures 6 and 7. The steady state flux Figure 7 of the formulations is shown in Table 5.

Discussion

The penetration of the drug into the lipid membrane depends on the partition coefficient. Partition coefficient determines the hydrophobicity of the chemical substance. Higher is the partition coefficient greater will be the penetration of drugs. The partition coefficient of lornoxicam of 1.8 ± 1.21 specifies that lornoxicam is an ideal candidate for TDDS.[25] However,

Table 3: Physical characterization of lornoxicam films prepared

Formulation code	Weight variation (g; $n = 3$)	Thickness (mm; $n = 3$)	Average moisture loss (%; $n = 3$)	Drug content (mg/cm^2; $n = 3$)	Tensile strength (g/cm^2; $n = 3$)
F1	0.025 ± 0.001	0.353 ± 0.007	3.15 ± 0.161	0.902 ± 0.042	1.51 ± 0.120
F2	0.023 ± 0.003	0.358 ± 0.003	3.06 ± 0.102	0.956 ± 0.063	1.48 ± 0.104
F3	0.024 ± 0.001	0.349 ± 0.001	3.24 ± 0.131	0.905 ± 0.042	1.41 ± 0.119
F4	0.022 ± 0.001	0.350 ± 0.001	4.04 ± 0.111	0.922 ± 0.014	1.46 ± 0.115
F5	0.022 ± 0.002	0.300 ± 0.003	3.67 ± 0.190	0.951 ± 0.077	1.44 ± 0.111
F6	0.021 ± 0.007	0.321 ± 0.003	3.82 ± 0.121	0.935 ± 0.016	1.43 ± 0.109

Table 4: Determination of moisture uptake (in weight %) of different formulations ($n = 3$)

Formulation code	Relative humidity, 75%	Relative humidity, 93%
F1	6.71 ± 1.22	8.95 ± 1.14
F2	5.77 ± 1.16	9.44 ± 1.42
F3	5.09 ± 1.26	9.50 ± 1.35
F4	7.12 ± 1.38	10.96 ± 1.24
F5	6.92 ± 1.14	10.50 ± 1.36
F6	5.83 ± 1.18	10.29 ± 1.42

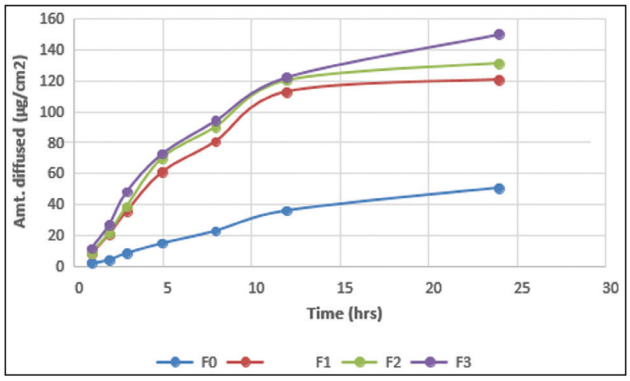

Figure 6: Comparison of amount of drug diffused from different formulations F0, F1, F2, and F3 through the shed snakeskin

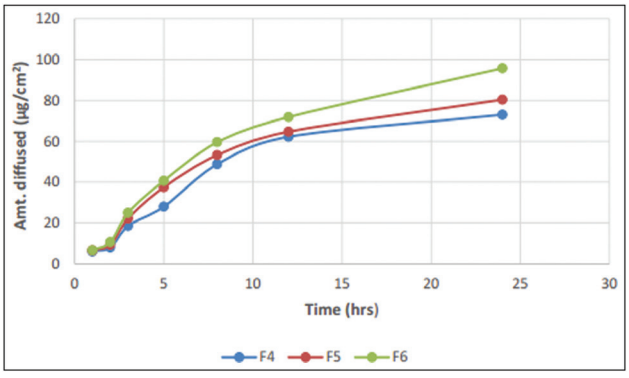

Figure 7: Comparison of amount of drug diffused from different formulations F4, F5, and F6 through the shed snakeskin

success of the drug mainly depends on the ability of its penetration through the skin in required quantities to accomplish therapeutic effect.[26] Hence, in our study, lornoxicam-loaded transdermal patches with different permeation enhancers was prepared and evaluated to optimize the ideal formulation for transdermal drug delivery.

FTIR spectral studies did not reveal any significant chemical reaction between lornoxicam and sodium alginate. Thus, they indicate that lornoxicam and sodium alginate were compatible for the formulation of transdermal film. A similar combination studied by Hadi *et al.*[27] was also found to have no interaction between the drug and the polymer.

Thickness marginally varied between the patches, which indicated that thickness of patches depended on the amount of polymer. Tensile strength slightly varied between the patches, which indicated that patches were found to be flexible, strong, and not brittle. The uniform drug content and weight of lornoxicam films indicated the process used to formulate the patches was ideal and able to fabricate patches with uniform weight and drug content. Overall, it was perceived that thickness, weight uniformity, moisture loss, moisture uptake, and tensile strength was apt for the maximum strength of prepared formulations. A study conducted by Baviskar *et al*.,[28] with different permeation enhancers, reported similar physiochemical data.

In our study, DMSO showed increased steady flux and gave higher drug release when compared with other enhancers such as propylene glycol, dimethylformamide, sodium lauryl sulfate, Span 20, and TWEEN 80. Various studies also reported that DMSO was the widely used permeation enhancer to increase the penetration of drugs into the biological membrane.[29-31] Moreover, the drug permeation from transdermal patches through snake shed skin confirmed that lornoxicam could perhaps permeate through the human skin.

Overall, current investigation stated that the film of lornoxicam with sodium alginate as a polymer, glycerin as a plasticizer, and DMSO as a permeation enhancer was suitable for the formulation of transdermal film.

Table 5: Steady state flux of transdermal formulation

Formulation	F0	F1	F2	F3	F4	F5	F6
Steady state flux (µg/cm^2/h)	3.2 ± 1.74	6.65 ± 1.84	6.8 ± 1.88	7.20 ± 1.94	3.68 ± 1.22	5.37 ± 1.64	6.43 ± 1.76

Conclusion

The *in vitro* diffusion studies were carried out in the Franz diffusion by using the shed snakeskin. The amount of lornoxicam diffused increased in the following order: F4 < F5 < F6 < F1 < F2 < F3. From the order, it was confirmed that the amount of lornoxicam diffused from the F3 formulation by 24h, that is, 149.4 μg/cm^2 was more when compared to other formulations.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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