RESEARCH ARTICLE

Formulation, characterization, and evaluation of matrix-type transdermal patches of a model antihypertensive drug

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The present investigation was aimed to evaluating the possibility of using different polymeric grades of hydroxy propyl methyl cellulose (6cps, 15cps, and K4M) for the development of transdermal drug delivery systems of nicorandil, an antianginal drug. Prepared matrix-type patches were evaluated for their physicochemical characterization followed by *in vitro* evaluation. Selected formulations were subjected for their *ex vivo* studies on porcine ear skin.

Key words: *HPMC, in vitro release study, nicorandil, porcine ear skin and permeation study, transdermal patch*

INTRODUCTION

The benefits of using transdermal drug delivery include improved systemic bioavailability resulting from bypassing the first hepatic metabolism. Variables due to oral administration, such as pH, the presence of food or enzymes, and transit times can all be eliminated. The aim in the development of new transdermal drug delivery devices is to obtain a controlled, predictable, and reproducible release of the drug into the blood stream of the patient. The transdermal device acts as a drug reservoir and controls the rate of drug transfer. When the transdermal drug flux is controlled by the device instead of by the skin, delivery of the drug is more reproducible, leading to smaller inter- and intrasubject variations because the drug release from the device can be controlled accurately than the permeability of the skin.[1,2]

The relief of chest discomfort remains one of the primary objectives in the management of patients with angina pectoris. Beta blockers, calcium antagonists, and nitrates are indicated and are widely used for this purpose, but all these agents have limitations and are therefore not a complete answer to the problem. Nicorandil belongs to the class of compounds known as potassium channel activators, which are characterized by their arteriodilating and venodilating properties, and represents a novel type of compound for use in the treatment of angina pectoris.[3] Nicorandil has a short half life and the usual oral dosage regimen is 5–40 mg taken two to four times a day. To reduce the frequency of administration and to improve patient compliance, a once-daily matrix-type transdermal drug delivery system (TDDS) of nicorandil is desirable.[4]

The aim of the present study is to formulate, characterize, and evaluate nicorandil transdermal patches.

MATERIALS AND METHODS

Nicorandil, as a gift sample, was obtained from Torrent Research Center, Ahmedabad, India and hydroxy propyl methyl cellulose (HPMC K4M, 6cps, and 15cps) was from Microlabs Pvt. Ltd., Bangalore, India. All other chemicals used were of analytical grade.

Preparation of the nicorandil transdermal patch

The solvent-casting technique[5] was used to formulate the HPMC patches containing different grades of HPMC polymer, poly ethylene glycol (PEG 400) as plasticizer, and nicorandil. The drug polymer (5 mg/ml) solution was transferred into a glass Petridish containing mercury. The Petridish was then kept in an air circulation drier and maintained at a temperature of 45–50°C for 6 hours. Poly vinyl acetate (PVA) membrane was used as the backing membrane. One surface of the drug reservoir matrix was slightly moistened with water and placed against the PVA membrane and allowed to dry at 45–50°C for 2 hours. The patches did not bear a rate controlling membrane. This served as a matrix-type transdermal

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Table 1: Formulation of nicorandil transdermal patches

Formulation	Polymer (2% w/v)	Solvent system (water:ethanol)	Plasticizer (PEG 400 %w/v)	Permeation enhancer (DMSO w/v %w/v)	Drug (mg/ml)
NicHPMC-1	HPMC 6cps	8:2	30	-	5
NicHPMC-2	HPMC 15cps	8:2	30	-	5
NicHPMC-3	HPMC K4M	8:2	30	-	5
NicHPMC-4	HPMC 6cps	8:2	30	6	5
NicHPMC-5	HPMC 15cps	8:2	30	6	5
NicHPMC-6	HPMC K4M	8:2	30	6	5

delivery system [Table 1].

Solubility measurement

The solubility of nicorandil was determined according to the method adopted by Krishnaiah.[6] An excess amount of drug was taken and dissolved in a measured volume of distilled water in a glass vial to get a saturated solution. The solution was kept at room temperature for the attainment of equilibrium. The concentration of nicorandil in the filtrate was determined spectrophotometrically by measuring at 260 nm after 24 hours.

Partition coefficient (Kp)

The partition coefficient of the drug was determined by shaking equal volumes of oil and the aqueous phase in a separating funnel.[7] A drug solution of 1 mg/ml was prepared in distilled water and 50 ml of this solution was taken in a separating funnel and shaken with an equal volume of octanol for 10 minutes and allowed to stand for 24 hours with intermittent shaking. Then, the aqueous phase was assayed before and after partitioning using a UV spectrophotometer to get the partition coefficient values.

Permeability coefficient (P)

Permeability coefficient[8] is the velocity of drug passage through the membrane/skin in mcg/cm^2/hour. The permeability coefficient was calculated from the slope of the graph of percentage of drug transported vs time as:

$$P = \text{slope} \times Vd/S \quad (1)$$

where Vd = volume of donor solution,
S = surface area of tissue.

Flux (J)

Flux is defined as the amount of material flowing through a unit cross-sectional barrier in unit time.[8] It is calculated by:

$$\text{Flux (J)} = P \times CD \quad (2)$$

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

Spectrophotometric UV/VIS analysis

Nicorandil was determined using a Shimadzu UV spectrophotometer at 260 nm. A correlation coefficient of 0.9877 was obtained with a slope value of 0.0546.

Drug-excipient interaction studies

In order to find out the possible interactions between nicorandil and the polymer, Fourier transform infra red spectroscopy (FT-IR) and differential scanning calorimetry (DSC) analysis were carried out on the pure substance, their physical mixtures, and the final TDDS.[9-11]

IR spectral analysis was carried out using FT-IR (Thermo Nicolet, Japan) by the KBr disc method. The sample and KBr were triturated and compressed to get discs. The prepared patches of desired size and the discs were kept in the holder and scanned between 400 and 4000 per cm. Thermograms of drug and optimized transdermal patches were recorded. All the samples were hermitically sealed in flat-bottomed aluminum pans and heated over a temperature range of 40–240°C at a rate of 10°C/min using alumina as a reference standard. IR spectra and thermograms are shown in Figures 1 and 2, respectively.

Characterization of the transdermal patches

Physical appearance

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

Folding endurance

A strip of film (4 × 3 cm) was cut evenly 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 gave the value of the folding endurance.[12,13]

Thickness of the films

The thicknesses of the drug-loaded polymeric films were measured at five different points using a digital micrometer (Mitutoyo, Japan).[13,14] The average and standard deviation of five readings were calculated for each batch of the drug-loaded films.

Weight uniformity

The films of different batches were dried at 60°C for 4 hours before testing. Five patches from each batch were accurately weighed in a digital balance.[13] The average weight and the standard deviation values were calculated from the individual weights.

Percentage moisture uptake

The weighed films were kept in a desiccator at room temperature for 24 hours and then exposed to 84% relative humidity using a saturated solution of potassium

chloride.[15] Finally, the films were weighed and the percent moisture uptake was calculated using the formula:

Percentage moisture uptake = [Final weight - Initial weight/ Initial weight] × 100 (3)

Percentage moisture content

The prepared films were weighed individually and kept in a desiccator containing fused calcium chloride at room temperature for 24 hours.[15] The films were again weighed and the percentage moisture content was calculated using the formula:

Percentage moisture content = [Initial weight - Final weight/ Final weight] × 100 (4)

Water vapor transmission

The film was fixed over the glass vial with an adhesive containing 3 g of fused calcium chloride as a desiccant.[13] Then, the vial was placed in a desiccator containing saturated solution of potassium chloride (relative humidity 84%). The vial was taken out periodically and weighed.

Stability studies

Stability studies were conducted according to the International Conference on Harmonization (ICH) guidelines by storing the TDDS in a stability chamber (Thermo Lab., Mumbai, India).[2] The samples were withdrawn at 0, 30, 60, and 90 days and the drug content was analyzed by a UV spectrophotometer method.

Evaluation of transdermal patches

Skin irritation test

Skin irritation test was performed on seven healthy albino rabbits weighing between 2.0 and 3.5 kg.[2,13,16] Aqueous solution of formalin 0.8% was used as the standard irritant. Drug-free polymeric patches of 4.874 cm^2 were used as test patches. Standard irritant was applied on the left dorsal surface of each rabbit and drug-free patches were applied on the right dorsal surface of the rabbit. The patches were removed after a period of 24 hours with the help of an alcohol swab. The skin was examined for erythema/edema.

Drug content

Transdermal system of specified area (3.066 cm^2) was cut into small pieces and taken into a 50 ml volumetric flask and 25 ml of phosphate buffer pH 7.4 was added,[17] gently heated to 45°C for 15 minutes, and kept for 24 hours with occasional shaking. Then, the volume was made up to 50 ml with phosphate buffer of pH 7.4. Similarly, a blank was carried out using a drug-free patch. The solutions were filtered and the absorbance was measured at 260 nm.

In vitro drug release studies

A Paddle over disc assembly (USP 23, Apparatus 2) was used for the assessment of release of drug.[2] The TDDS patch was mounted on the disc and placed at the bottom of the dissolution vessel. The dissolution medium was 900 ml phosphate buffer of pH 7.4. The apparatus was equilibrated to 37 ± 0.5°C and operated at 50 rpm. The samples (5 ml aliquots) were withdrawn at appropriate time intervals up to 8 hours and analyzed on a UV spectrophotometer at 260 nm.

In vitro skin permeation studies

Preparation of the skin barrier: Fresh full-thickness (75–80 mcm) porcine ear skin was used for the study. The skin was immersed in water at 60°C for a period of 5 minutes. The epidermis was peeled from the dermis. The isolated epidermis (25 ± 5 mcm thick) was rapidly rinsed with hexane to remove surface lipids and then rinsed with water and used immediately.

The *in vitro* skin permeation[18-20] from the prepared polymeric patches across the porcine ear skin barrier was studied using a Keshary Chien diffusion cell. Fifty-four milliliters of phosphate buffer of pH 7.4 was used as an elution medium. The patches to be studied were placed in between the donor and the receptor compartment in such a way that the drug releasing surface faced toward the receptor compartment. The elution medium was magnetically stirred for uniform drug distribution at a speed of 60 rpm. The temperature of the whole assembly was maintained at 37 ± 1°C by thermostatic arrangements. An aliquot of 1 ml was withdrawn at a suitable interval and an equivalent volume of fresh buffer was replaced. The amount of drug permeated across the skin was determined on a UV spectrophotometer at 260 nm. The flux (mcg/cm^2) was calculated from the slope of the plot of the cumulative amount of drug permeated per cm^2 of skin at steady state against time using linear regression analysis. The values are tabulated in Table 5. The data were tabulated and fitted into various classical equations to characterize the kinetics and mechanism of diffusion.

RESULTS AND DISCUSSION

Matrix-type transdermal patches of nicorandil were prepared using three different grades of HPMC (6 cps, 15 cps, and K4M) to get the desired drug release profile. The prepared patches were subjected to folding endurance, thickness of the film, weight uniformity, drug content, percentage moisture uptake, percentage moisture content, water vapor transmission, stability studies at different temperature, and skin irritation test and their values are shown in Table 2.

Partition coefficient of nicorandil in the octanol/water system was found to be 0.07226. Solubility and permeability of nicorandil were evaluated at various values of pH with phosphate buffer. It was seen that solubility increased with increase in the pH.

The permeability studies of nicorandil through the porcine ear skin showed that the flux of nicorandil and permeability coefficient (P) was found to be 26.235 mcg/cm^2/hour and 0.0000526, respectively.

Table 2: Characterization of transdermal patches

Parameter	NicHPMC-1	NicHPMC-2	NicHPMC-3	NicHPMC-4	NicHPMC-5	NicHPMC-6
Folding endurance	21 ± 0.81	150 ± 2.56	150 ± 2.56	22 ± 0.34	149 ± 2.23	149 ± 2.16
Thickness of the films (mm)	0.037 ± 0.001	0.042 ± 0.001	0.074 ± 0.002	0.036 ± 0.006	0.041 ± 0.005	0.073 ± 0.06
Weight uniformity (g)	0.430 ± 0.023	0.441 ± 0.019	0.432 ± 0.02	0.445 ± 0.015	0.474 ± 0.03	0.478 ± 0.06
Percentage moisture uptake	2.27 ± 0.013	3.77 ± 0.015	5.80 ± 0.021	2.29 ± 0.017	3.89 ± 0.021	5.93 ± 0.011
Percentage moisture content	1.04 ± 0.025	1.41 ± 0.016	0.69 ± 0.012	1.16 ± 0.041	1.52 ± 0.019	0.73 ± 0.015
Water vapor transmission (gm/cm^2/24 hours)	0.047 ± 0.046	0.054 ± 0.051	0.089 ± 0.05	0.046 ± 0.041	0.053 ± 0.053	0.087 ± 0.04
Tensile strength in Newton (N)	1.36 ± 0.025	2.23 ± 0.031	3.32 ± 0.038	1.41 ± 0.032	2.38 ± 0.021	3.41 ± 0.044
Drug content (mg)	3.577 ± 0.002	3.498 ± 0.002	3.665 ± 0.002	3.512 ± 0.003	3.495 ± 0.005	3.659 ± 0.008
Dissolution profile after 8 hours	92.59 ± 1.64	92.91 ± 1.71	93.0 ± 1.89	92.47 ± 1.33	92.84 ± 1.63	93.25 ± 1.78
Steady flux mcg/cm^2/hour	12.87 ± 0.039	7.11 ± 0.025	5.97 ± 0.012	12.87 ± 0.039	7.11 ± 0.025	5.97 ± 0.012
Percentage elongation (mm)	6.95 ± 0.058	11.85 ± 0.072	23.96 ± 0.098	7.23 ± 0.042	12.56 ± 0.055	25.12 ± 0.067

The permeability of the drug through the skin was less than the required flux. Thus, flux studies were performed again by the addition of permeation enhancer, dimethyl sulfoxide (DMSO), at different concentrations. 6% w/v DMSO showed a maximum flux of 93.972 mcg/cm^2/hour.

The FT-IR spectral analysis showed that there were no physical and chemical interactions between the drug and the polymer [Figure 1].

The DSC thermograms of nicorandil and loaded HPMC (6 cps, 15 cps, and K4M) films are represented in Figure 2. The DSC thermogram of nicorandil displayed the characteristic peak at 92°C corresponding to its melting point. The drug peak appeared in the thermogram for all the drug-loaded films, confirming the chemical integrity of the drug. A slight shift in the nicorandil peak in the thermograms of the drug-loaded films could be due to the presence of moisture in the film samples.

All the polymers used for the fabrication of the transdermal system showed good film forming properties. HPMC films were thin, flexible, smooth, and transparent. The method adopted for casting the film on a mercury surface was found to be satisfactory. All the patches showed good folding endurance properties.

Thickness of each film was determined and decrease in thickness of various TDDS were found to be of the order of NicHPMC-3 > NicHPMC-2 > NicHPMC-1.

The drug content analyses of the prepared formulations have shown that the process employed to prepare the patches was capable of giving a uniform drug content, with minimum batch variability.

Moisture absorption studies showed strong water absorbing capacity, an inherent property of HPMC. The results of moisture content have indicated that all transdermal systems have a specific amount of moisture content in them. All the formulations were permeable to water vapor.

All the formulations were selected for stability studies and observed for changes in color, appearance, flexibility, and drug content. Temperature and humidity values selected were as per the ICH guidelines and the tests were carried out in a stability chamber. Patches were analyzed at an interval of 30 days for a period of 3 months. No physical changes were observed but decrease in drug content was observed at higher temperatures (45 ± 5°C).

Skin irritation test performed on rabbits did not show any erythema/edema for test patches without DMSO. However, patches containing DMSO 6% w/v as penetration enhancer showed slight erythema (NicHPMC-2 and NicHPMC-3) [Table 3].

All the formulations were evaluated for their tensile strength and the values ranged from 1.36 to 3.32 N, indicating a good tensile strength. Drug distribution was found to be uniform in all the formulations and the content varied from 69.96 to 73.3% per cm^2.

The mean (n = 3) cumulative amounts of drug released (*in vitro* dissolution) and permeated (*in vitro* skin permeation)

Table 3: Skin irritation test

Parameter	NicHPMC-1	NicHPMC-2	NicHPMC-3
Control	+ +	+ +	+ + +
Test	----	----	----
Test (DMSO 6% + 50 mg drug)	----	+	+

----, no erythema; +, slight erythema; + +, well-defined erythema; + + +, moderate to severe erythema.

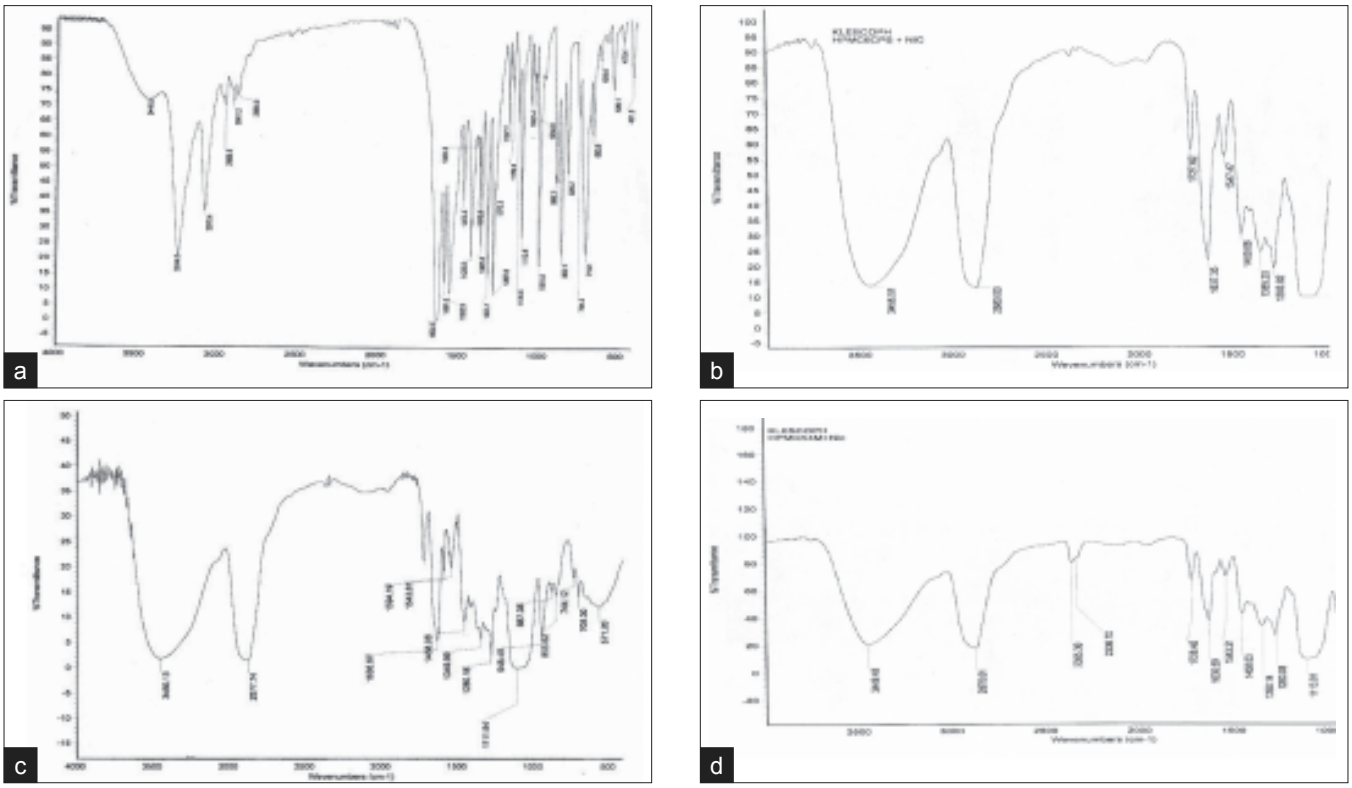

Figure 1: (a) Infrared (IR) spectra of nicorandil, (b) IR spectra of hydroxy propyl methyl cellulose (HPMC) 6 cps + nicorandil, (c) IR spectra of HPMC 15 cps + nicorandil, and (d) IR spectra of HPMC K4M + nicorandil

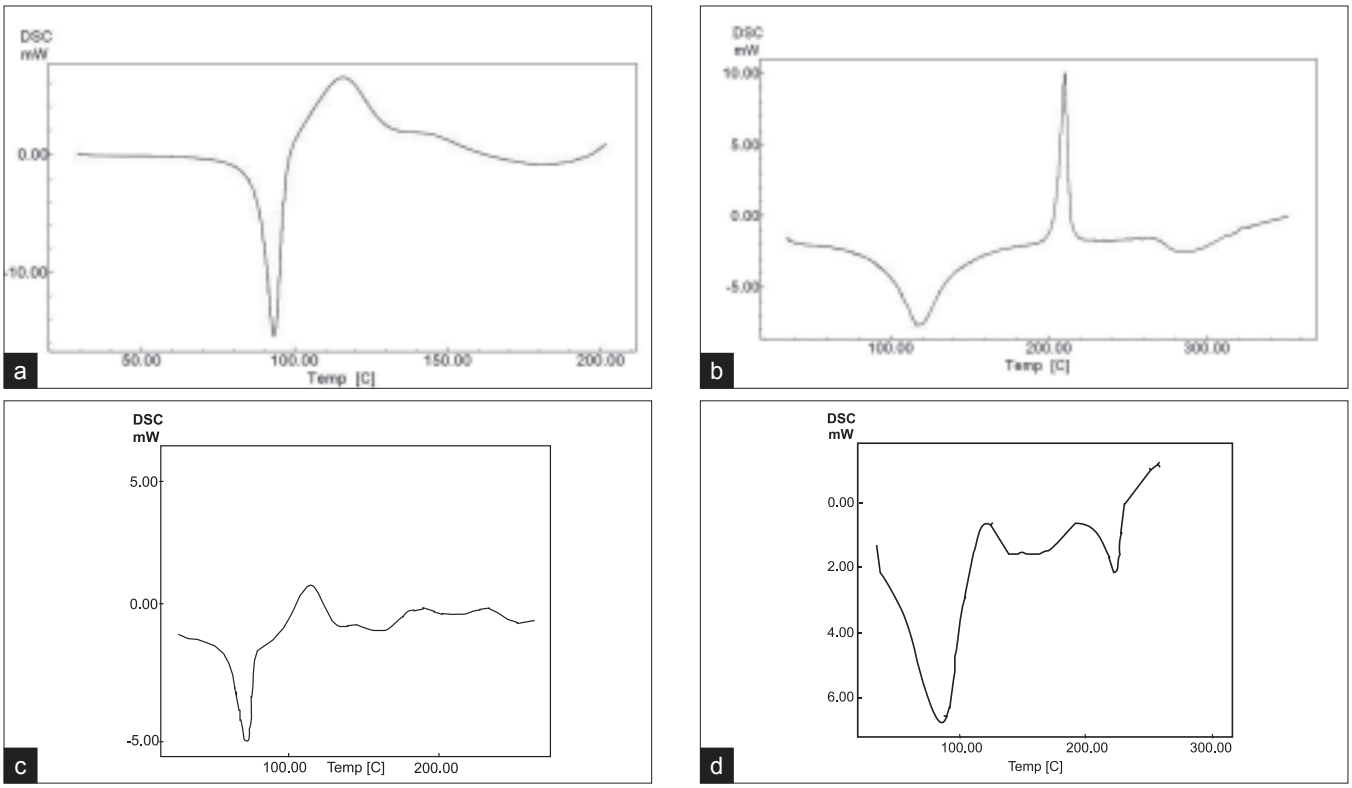

Figure 2: (a) Differential scanning calorimetry (DSC) spectra of nicorandil, (b) DSC spectra of hydroxy propyl methyl cellulose (HPMC) 6 cps + nicorandil, (c) DSC spectra of HPMC 15 cps + nicorandil, (d) DSC spectra of HPMC K4M + nicorandil

Table 4: *In vitro* **release studies**

Parameter	NicHPMC-1	NicHPMC-2	NicHPMC-3
Cumulative amount of drug released in 8 hours	58.3%	43.2%	38.5%
	NicHPMC-4	**NicHPMC-5**	**NicHPMC-6**
Cumulative amount of drug released in 8 hours (6% DMSO)	92.59%	84.91%	79.20%

Table 5: *In vitro* **skin permeation**

Parameter	NicHPMC-1	NicHPMC-2	NicHPMC-3
Cumulative amount of drug permeability in 8 hours	14.5%	7.5%	7.1%
	NicHPMC-4	**NicHPMC-5**	**NicHPMC-6**
Cumulative amount of drug permeability in 8 hours (6% DMSO)	44.7%	23.8%	20.0%

Table 6: Flux values of transdermal patches

Parameter	NicHPMC-4	NicHPMC-5	NicHPMC-6
Flux (µg)	37.93	18.92	17.85

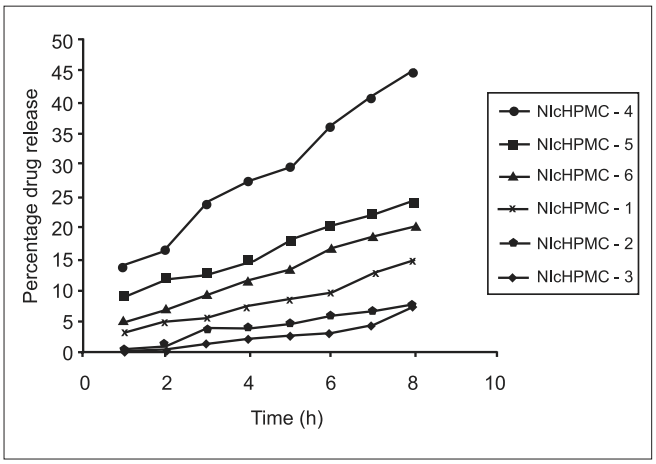

Figure 3: *In vitro* drug release studies

from different grades of HPMC after 8 hours were analyzed and their values are shown in Tables 4 and 5 and Figures 3 and 4, respectively.

HPMC 6 cps with 6% DMSO showed a maximum release of 44.7%. This patch offered very low resistance to the movement of drug due to its hydrophilic nature and its high permeability to water. To know the mechanism of release, the data were plotted according to the Higuchi equation and the plots were found to be linear, with a regression coefficient of 0.9890. Further, the mechanism was precisely confirmed by plotting as per the Korsemeyer and Peppas equation. The flux values are calculated and are tabulated in Table 6.

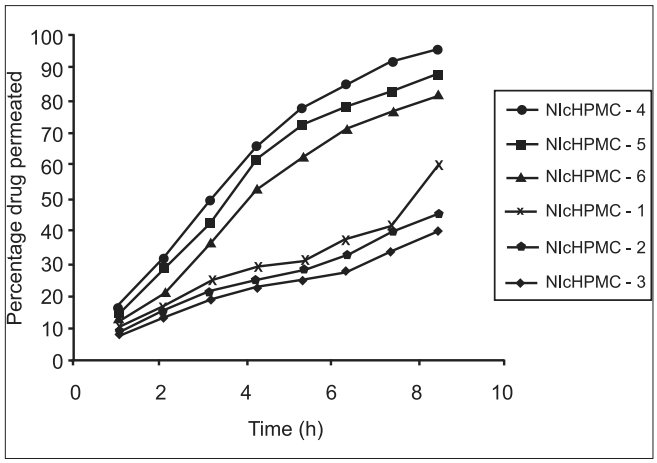

Figure 4: *In vitro* skin permeation studies

CONCLUSION

TDDS are ideally suited for drugs that undergo hepatic first pass metabolism along with a short elimination half life of less than 4 hours. Among the six different HPMC formulations, transdermal patch with 6 cps and 6% w/v DMSO as permeation enhancer showed maximum release and offered least resistance to the movement of the drug molecule due to its high hydrophilic nature and high water permeability value to water.

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