

## DESIGN AND EVALUATION OF MONOLITHIC DRUG-IN-ADHESIVE TRANSDERMAL PATCHES OF MELOXICAM

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*The objective of this study was to develop a transdermal therapeutic system for meloxicam (MX) using various polymers like hydroxy propyl methyl cellulose (HPMC), ethyl cellulose (EC) and polyvinyl pyrrolidone (PVP) and plasticisers by solvent casting technique. The prepared patches were evaluated for physicochemical properties, in vitro release, in vitro skin permeation and in vivo release. The physicochemical interactions between MX and polymers were investigated by Fourier Transform Infrared (FTIR) spectroscopy. The in vitro release studies revealed that the release was sustained up to 24 hours and it followed zero order kinetics ( $r^2=0.998$ ). Finally, the patch formulation containing MX (MX-2) selected through our in vitro study was characterised for in vitro skin permeation using various biological membranes like snake shed skin and porcine ear skin. The patch exhibited no skin irritation and better pharmacodynamic activity when compared with a commercially available diclofenac patch with all the tested in vivo parameters. As a patient friendly and once a day dosing therapeutic system, the transdermal patches incorporating MX could be promising in the pasture of controlled drug delivery.*

**Keywords:** Meloxicam, Transdermal patches, Solvent casting technique, In vitro skin permeation studies

### INTRODUCTION

Meloxicam [4-hydroxy-2-methyl-N-(5-methyl-2-thiazoyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide, MX], is a non-steroidal antiinflammatory drug (NSAID) with preferential inhibition of cyclo-oxygenase-2 (COX-2) over cyclo-oxygenase-1 (COX-1). MX does not have known cardiovascular toxicity at doses of less or equal to 15 mg/day, which are recommended for the treatment of osteoarthritis and rheumatoid arthritis (Davies and Skjodt 1999). The common oral dosage of MX in clinical treatment was 7.5–30.0 mg/day (Turck *et al.* 1997). MX shows similar efficacy for reducing pain and inflammatory symptoms but lesser toxicity than other NSAIDs (Lipscomb *et al.* 1998; Degner, Sigmund and Zeidler 2000). Even though MX is relatively safer than other NSAIDs, adverse effects relating to the gastro-intestinal tract are still a limitation of MX (Gambero *et al.* 2005). To

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overcome these adverse effects in the gastrointestinal (GI) tract while sustaining the therapeutic efficiency of MX, an alternative drug delivery method might be useful. Transdermal drug delivery (TDD) is a promising method to administer the drug to overcome the adverse effects from oral administration.

The transdermal route of administration is recognised as one of the potential route for the local and systemic delivery of drugs (Ranade 1991) as it provides controlled release of the drug, and produces a steady blood-level profile, leading to reduced systemic side effects and, sometimes, improved efficacy over other dosage forms and improves patient compliance (Modamio, Lastra and Marin 2000; Dais and Mc Deasy 1996; Ramesh Gannu *et al.* 2007). Transdermal delivery of NSAIDs is an effective approach for evading NSAIDs' adverse effects in the GI tract and for increasing patient compliance (Galer *et al.* 2000; Heyneman, Lawless-Liday and Wall 2000). MX can be applied to the skin and mucosa because it has lower tissue toxicity than piroxicam, indomethacin, ketoprofen, ibuprofen and diclofenac (Stein *et al.* 1996).

Previous studies stated that MX has been used as a drug candidate in TDD formulations such as gels (Gupta *et al.* 2002; Jantharaprapap and Stagni 2007) and microemulsions (Yuan *et al.* 2006), which has been unsuccessful in controlling the delivery amount and time regulation.

In the present work, we have tried to enhance the *in vivo* effectiveness of MX, a suitable candidate for transdermal delivery, by formulating the transdermal systems of MX using ethyl cellulose (EC) [hydrophobic], hydroxyl propyl methyl cellulose (HPMC) [hydrophilic] and polyvinyl pyrrolidone (PVP) [hydrophilic], combinations, which were evaluated with respect to various *in vitro* and preclinical *in vivo* parameters.

## METHODS

MX was a gift sample obtained from Sun Pharmaceuticals Ltd. (India). The polymers such as HPMC (15 cps), EC (20 cps) and PVP (15 cps) were purchased from S.d. Fine Chemicals (Mumbai). All other chemicals were of analytical grade.

### Determination of Partition Coefficient

The partition coefficient of MX was carried out in n-octanol/phosphate buffer (PB) pH 7.4 (Dais and McDeasy 1996). The two phases were shaken in a separating funnel together initially to ensure mutual saturation. 10 mg of MX was dissolved in 10 mL of n-octanol phase and shaken manually against 10 mL aqueous phase in a sealed container and kept aside for 24h to separate the n-octanol phase. The separated n-octanol phase was assayed by UV spectroscopy to determine its residual concentration and hence the amount partitioned into the aqueous phase. The partition coefficient was expressed as the concentration of drug in the n-octanol phase (% w/v) divided by the concentration in the aqueous phase (Marin and Modamio 1998).

### Drug-polymer Interaction Study

The interaction studies were conducted on MX and polymeric materials of the patches using infrared (IR) spectroscopy (Perkin Elmer FT-IR, Perkin Elmer Inst., USA) by KBr

pellet method and differential scanning calorimeter (DSC; Shimadzu DSC-60, Shimadzu, Tokyo).

### Fabrication of Patches

Transdermal patches were fabricated using different polymers containing MX by solvent casting technique (Aqil and Ali 2002; Multilink and Udupa 2006). Adhesive patches containing MX were prepared by dissolving polymers individually or in combinations in suitable solvents namely dichloromethane and ethanol. Propylene glycol (30% v/v) of polymer composition was used as a permeation enhancer. The solution was poured into a glass ring, which was covered with funnel. The solvent was allowed to evaporate at ambient conditions [temperature, 32°C and relative humidity (RH), 45%] for 24 h. Aluminium foil was used as backing film and the prepared patches were stored in a desiccator for further studies. Table 1 enlists the composition of different formulations prepared using varying amounts of the polymers.

**Table 1:** Composition of transdermal patches using MX.

Formulation code	Drug (mg)	HPMC (%)	EC (%)	PVP (%)
MX-1	7.5	1	-	-
MX-2	7.5	2	-	-
MX-3	7.5	-	1	-
MX-4	7.5	-	2	-
MX-5	7.5	-	-	1
MX-6	7.5	-	-	2

Notes: Volume of solution used for all formulation is 10 mL; permeation enhancer used is propylene glycol (30% v/v)

### Physicochemical Evaluation of the Prepared Patches

#### Thickness and drug content

The thickness of the patch at three different points was determined using digital vernier callipers and the mean value was calculated (Mundada and Avari 2009). To determine the drug content, the patch was placed in a 100 mL volumetric flask containing PB (pH 7.4) and sonicated for 8 h and the sample was filtered and analysed by UV spectrophotometer at 365 nm in triplicate (Mazzo *et al.* 1994).

#### Folding endurance test

Folding endurance test was carried out by folding the patch at the same point a number of times till it broke (Ubaidulla *et al.* 2007). The test was carried out to check the efficiency of the plasticiser and the strength of the film prepared using varying ratios of the polymers. The test was carried out in triplicate.

#### *Moisture uptake*

The formulations (n=3) were kept in a desiccator at room temperature (37°C) and then exposed to 79.5% RH using saturated solution of aluminium chloride and weighed after 3 days (Mukherjee *et al.* 2005). The percentage of moisture uptake was calculated as the difference between final and initial weight.

#### *Moisture loss*

The formulations (n=3) were kept in a desiccator at room temperature (37°C) and then exposed to an atmosphere of 98% RH using anhydrous calcium chloride and weighed after 3 days (Kusum Devi *et al.* 2003). The percentage of moisture loss was calculated as the difference between initial and final weight.

#### *Tensile strength and percentage elongation at break*

Mechanical properties of the film were evaluated using an Instron Tensile Strength tester (Series IX Automated Material Testing System, Instron, Canada). A film strip (15 x 7.5 cm) free from air bubbles (or physical imperfections) was prepared and cut in a dumbbell shape, before fed into the equipment. This test was carried out with 50% humidity at 20°C (Ghosal and Panigrahi 2002). The crosshead speed employed were 100 mm/min, with the full-scale load range of 500 Kgf. The force and percentage elongation were measured when the films broke. Measurements were run in three replicates for each formulation.

#### *Water vapour transmission (WVT) rate*

Transmission cell of equal diameter were used for water vapour transmission (WVT) studies (Raghavendra *et al.* 2000). These cells were thoroughly washed and dried in an oven. About 1 gm of anhydrous calcium chloride was placed in the cell and the patch was fixed over the rim with the aid of the solvent. They were accurately weighed and placed in a desiccator containing potassium chloride saturated solution to maintain 84% RH. The cells placed in the desiccator were removed and weighed after the 1, 2, 3, 4, 5, 6 and 7<sup>th</sup> day. WTV can be determined using the following equation:

$$WVT = WL/S$$

where, W is transmitted water vapour in mg, L is patch thickness in mm and S is exposed surface area in cm<sup>2</sup>.

#### **In vitro Drug Release Studies**

A Franz diffusion cell was used for the drug release study of the formulations (Thacharodi and Panduranga Rao 1995; Andronis, Mesiha and Plakogiannis 1995). Phosphate buffered saline (PBS; 20 mL, pH 7.4) was used as the receptor fluid. The receptor fluid was agitated at 600 rpm by a teflon-coated magnetic stirrer. The semi permeable membrane was mounted between the donor and receptor compartment. The MX drug matrix was placed on one side of the dialysis membrane. The receptor compartment was surrounded by a water jacket to maintain temperature at 37±0.5°C during the drug release study. Samples

were collected from the sampling port at 6h intervals and were replaced with equal volume of fresh receptor fluid. The collected samples was subjected HPLC to determine the content of the MX. The test was carried out in triplicate.

### **In vitro Skin Permeation Studies**

Ethical clearance for the handling of experimental animals was obtained from the Institutional Animal Ethical Committee (IAEC) formed for this purpose. The approval number was 661/05/c/CPCSEA AWD dt 07.06.2005/KMCP/IIECA/018/08 dt 19.01.2008.

Snake skin (Hatanaka *et al.* 2006) offers considerable advantages over human material, as it is relatively abundant. In shed snake skin, the permeability co-efficient of lipophilic drugs was in the same range as those of the human skin. Shed skin of *Naja naja* was collected and soaked in pH 7.4 PB for half an hour and then used. The shed skin was mounted in such a way that the ventral surface side of the skin was kept in intimate contact with the formulation whereas the dorsal region of skin is kept in contact with the release surface of the donor compartment.

Albino porcine ear (Singh and Zha 1999) was obtained from a local slaughterhouse. The epidermis was prepared by a heat separation technique. The whole skin was soaked in water at 60°C for 45 seconds, followed by careful removal of the epidermis. The epidermis was then washed with pH 7.4 PB and used.

The in vitro skin permeation studies were also carried out using Franz diffusion cell. The temperature of receptor phase was maintained at 37±1°C throughout the experiment. The compartment was in contact with the ambient environment. The amount of drug permeated through the above mentioned various animal skins were determined by withdrawing 1 mL samples at predetermined time intervals. The same volume of freshly degassed buffer was supplemented to the receptor after each sampling. The samples were filtered through a 0.2 µ filter membrane, and an aliquot of 20 µL filtrate containing MX was assayed by HPLC method.

### **In vivo Studies**

#### *Primary skin irritation test*

The dorsal part of the rabbit was shaved carefully, and the patch was applied on that skin for 7 days. Conditions of the skin were observed after the patch was removed and are evaluated most often by modification described by Draize, Woodard and Calvery (1944), which is based on a scoring method. Scores as assigned from 0 to 4 based on the severity of erythema or oedema formation. The safety of the patch decreases with increase in scoring.

#### *In vivo drug release*

Protocols for all animal experiments were approved by JAEC or Biosafety Committee, ANCP. Fours male rabbits of (*Corytolagus cuniculus*) 10-12 weeks old weighing 2-3 kg were selected (Saisivam *et al.* 1999). They were kept with husk bedding and fed with standard rodent pellet diet and water. Light and dark cycle with 12 h light and 12 h dark was maintained. The temperature, RH conditions were 28±2°C and 60±15% respectively. The dorsal surface of the selected rabbits was cleaned and hair were carefully shaven

using a hair clipper and an electric razor. The dose of MX for oral medication was 1 mg/kg. The animal dose of MX (0.528 mg) was calculated according to the body weight. The area of each patch sample was 2 × 2 cm. Patch samples were applied on the shaved site in the dorsal surface. At specific time intervals, the films were removed carefully and analysed for the remaining drug content, by HPLC method. The drug content at any interval was obtained by subtracting final drug content (after removing the film) from the initial content (before placing film). The value obtained denotes the amount of drug released in the rabbits (Jayaprakash *et al.* 2010).

### Pharmacodynamic Study

#### *Carrageenan induced edema model*

The antiinflammatory activities were found out against carrageenan induced paw edema in rats. Male albino rats weighing approximately 200–250 g were divided into 3 groups and each group consists of 6 animals (Swingle, Grant and Jaques 1969). One day before the experiment, the left hind thigh of each animal was shaved without damaging the skin. The patch samples were applied to the shaved area in the left hind thigh. The first group (control) received 0.5 mL of normal saline solution orally. The second (standard) group received diclofenac sodium patches. The third groups received prepared MX transdermal formulation respectively. The dose was calculated as 0.133 mg. 60 minute before patch application, 0.1 mL of 1% carrageenan in isotonic saline was injected subplantarily into the left hind paw. The volume of the left hind paw was measured using a plethysmometer.

### Stability Evaluation

Stability studies were performed for 3 months using MX prepared patches (Martin Swarbrick and Cammarata 1991; Panchagula *et al.* 2005). Prepared patches (formulation MX-2) were kept in a refrigerator, stability chamber and incubator for maintaining the temperature of 4°C, 40°C and 60°C respectively. Patch sample was taken from formulation and analysed for drug content by HPLC.

### Statistical Analysis

All values were expressed as mean±SD. Oneway ANOVA (Graph Pad Prism version 5) followed by Dunnet's test were used for significance analysis.  $p < 0.05$  was set as significant for all studies.

## RESULTS

Monolithic drug-in-adhesive transdermal drug delivery system containing MX was prepared by using different polymeric ratios of HPMC, PVP and hydrophobic polymer of EC in combination or individually.

The observed partition coefficient of MX using n-octanol/PB pH 7.4 was found to give log K value of 2.54. The IR spectral analysis of MX alone showed that the principal peaks were observed at wave numbers of 3905.79, 3856.30, 3676.80, 3652.64, 1457.19 and 1267.05. In the IR spectra of the physical mixture of MX, HPMC, EC and PVP, peaks at

3904.89, 3856.04, 3678.25, 3651.29, 1459.48 and 1267.95  $\text{cm}^{-1}$  were observed. However, some additional peaks were observed with physical mixtures, which could be due to the presence of polymers. The thermograms of pure drug and physical mixture of drug with excipient are presented in Figures 1 and 2. The IR spectra of MX, HPMC, EC, PVP and physical mixture of MX patch formulations are presented in Figures 3 to 5. The thermogram of the MX has one endothermic melting point peak (190.30°C), which shows a broad asymmetric melting peak, crystallisation and cross linking.

The results of various physico-chemical parameters are listed in Tables 2 and 3. The thickness of the patches varied from  $0.29 \pm 0.01$  to  $0.35 \pm 0.04$ . Folding endurance values of matrix films were found within 255–282 number of folds, indicating good strength and elasticity. The moisture uptake in the formulations ranged from  $1.614 \pm 0.032$  to  $6.613 \pm 0.01$ . The moisture loss in the formulations ranged from  $1.858 \pm 0.01$  to  $6.143 \pm 0.01$ . The formulation MX-2 (2% HPMC) has shown the highest value for tensile strength at 354.25 and lowest percentage elongation at 0.210. The formulation MX-2 has shown maximum water vapor transmission of  $9.297 \times 10^{-6}$  among all the patches.

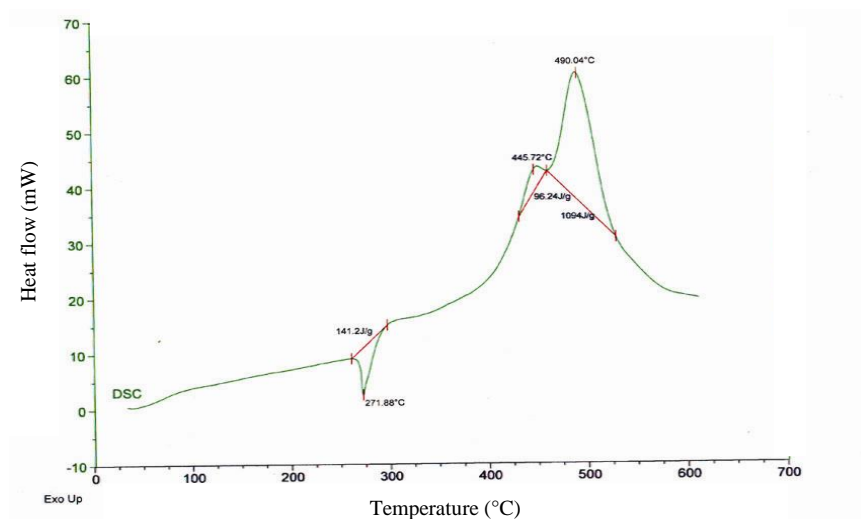


Fig. 1: DSC curves of pure MX sample.

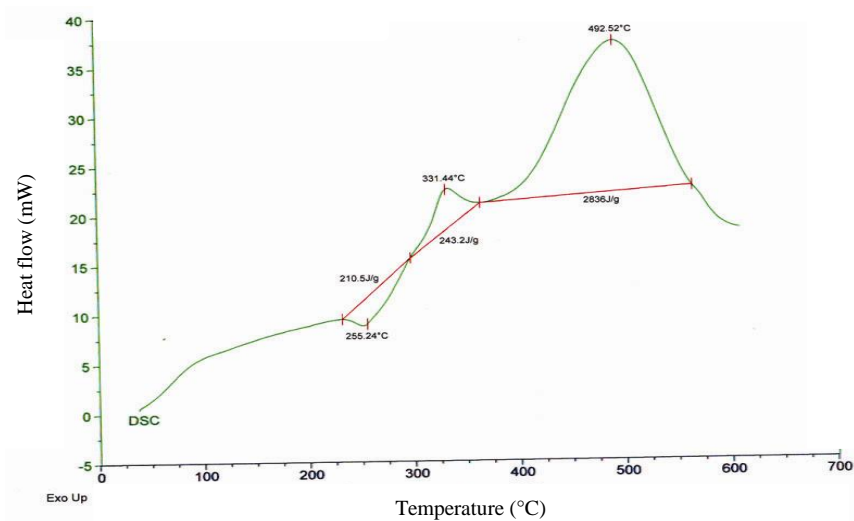


Fig. 2: DSC curve of MX with polymer.

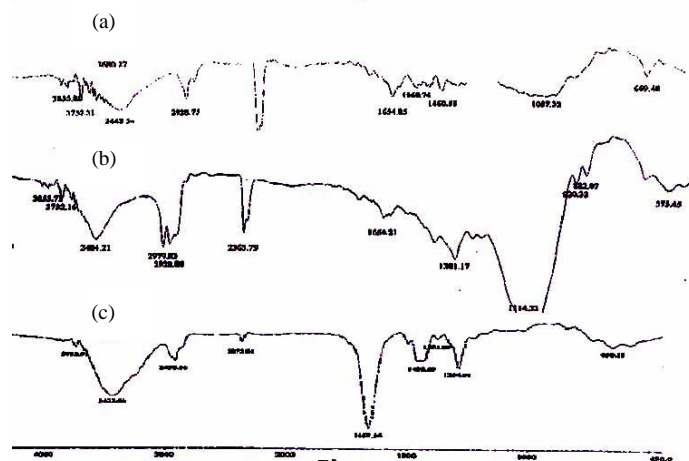


Fig. 3: IR spectral data of pure (a) HPMC, (b) EC and (c) PVP.



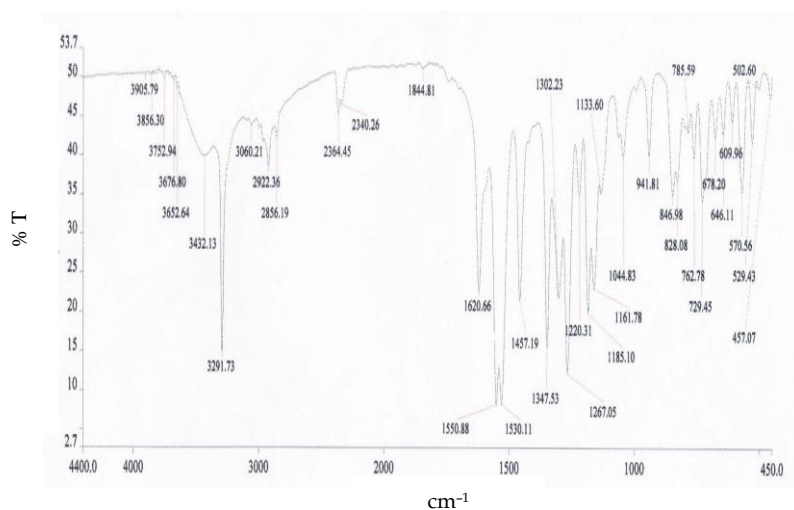


Fig. 4: IR spectral data of pure MX drug sample.

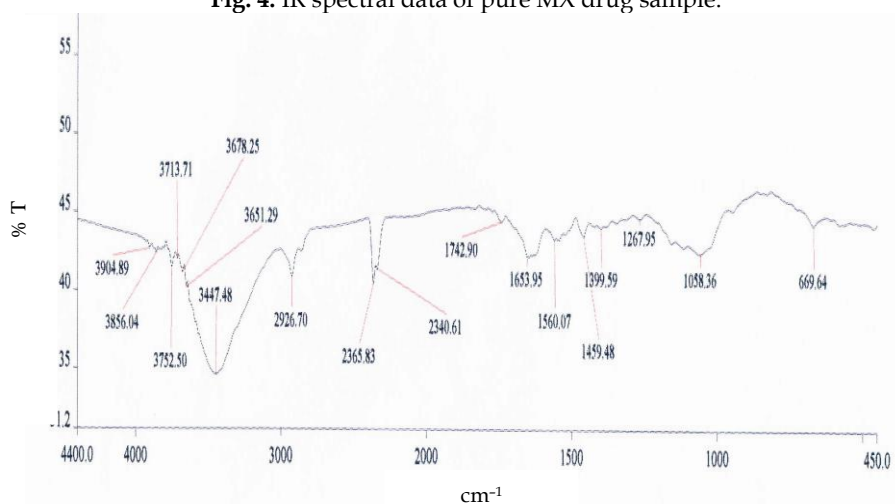


Fig. 5: IR spectral data of MX with polymers.

Table 4 lists the cumulative drug release percentage of various formulations. The cumulative percentage of drug released in 24 h was found to be the highest (99.29%) from formulation MX-2. Figure 6 exhibits the dissolution profile obtained for formulation MX-2. The Higuchi's plot has shown the regression value ( $r^2$ ) of 0.995, which indicated that diffusion mechanism is influencing the drug release. In order to confirm this fact, Peppas's plot was drawn which has shown a slope value of 0.690, which confirms that the diffusion mechanism is involved in the drug release was of non-fickian diffusion type. Hence formulation MX-2 was selected as the optimised formulation by virtue of its drug release kinetics.

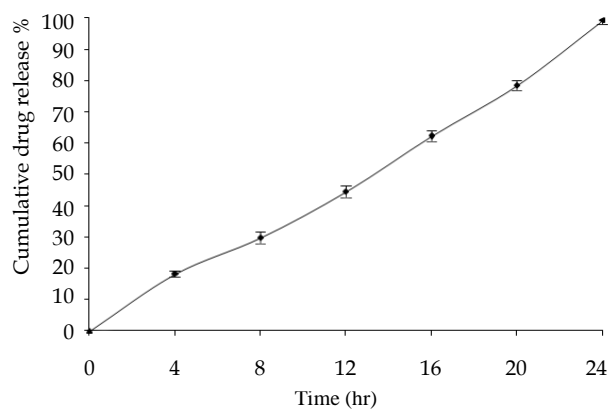
**Table 2:** Physicochemical evaluation of the prepared patches.

Formulation code	Thickness (mm) $\pm$ SD*	Drug content (mg) $\pm$ SD*	Folding endurance $\pm$ SD*	Moisture uptake $\pm$ SD*
MX-1	0.31 $\pm$ 0.01	7.24 $\pm$ 0.02	282 $\pm$ 1.0	4.40 $\pm$ 0.015
MX-2	0.35 $\pm$ 0.04	7.45 $\pm$ 0.05	260 $\pm$ 1.5	6.613 $\pm$ 0.01
MX-3	0.28 $\pm$ 0.02	7.32 $\pm$ 0.04	272 $\pm$ 2.0	1.614 $\pm$ 0.03
MX-4	0.34 $\pm$ 0.05	7.32 $\pm$ 0.02	255 $\pm$ 2.5	2.662 $\pm$ 0.02
MX-5	0.29 $\pm$ 0.01	7.43 $\pm$ 0.01	276 $\pm$ 2.00	1.965 $\pm$ 0.02
MX-6	0.29 $\pm$ 0.02	7.36 $\pm$ 0.05	270 $\pm$ 1.52	2.187 $\pm$ 0.15

Note: \*Average of three determinants for each parameter.

**Table 3:** Physico chemical evaluation of the prepared patches.

Formulation code	Moisture loss $\pm$ SD*	Tensile strength Kgf/cm <sup>2</sup> $\pm$ SD*	Percentage elongation (mm <sup>-2</sup> ) $\pm$ SD*	Water vapour transmission rate (mg/cm <sup>2</sup> /24 hr)
MX-1	3.907 $\pm$ 0.05	281.61 $\pm$ 0.02	0.322 $\pm$ 0.02	8.050X10 <sup>-6</sup>
MX-2	6.143 $\pm$ 0.01	354.25 $\pm$ 0.03	0.210 $\pm$ 0.04	9.297X10 <sup>-6</sup>
MX-3	1.858 $\pm$ 0.01	225.02 $\pm$ 0.04	0.286 $\pm$ 0.02	5.619X10 <sup>-5</sup>
MX-4	2.00 $\pm$ 0.014	205.32 $\pm$ 0.02	0.325 $\pm$ 0.05	3.588X10 <sup>-6</sup>
MX-5	2.599 $\pm$ 0.31	282.20 $\pm$ 0.02	0.326 $\pm$ 0.04	8.428X10 <sup>-6</sup>
MX-6	2.540 $\pm$ 0.10	332.21 $\pm$ 0.01	0.235 $\pm$ 0.03	4.169X10 <sup>-6</sup>

**Fig. 6:** In vitro drug release study of MX-2.

**Table 4:** Drug release parameters of various formulations.

S. no.	Drug release studies	Percentage drug release at the end of 24 hr
1	In vitro drug release study	
	MX-1	96.28±1.3
	MX-2	99.29±1.1
	MX-3	89.45±1.5
	MX-4	85.89±1.1
	MX-5	92.21±1.9
	MX-6	93.19±1.2
2	In vitro skin permeation study for MX-2	
	Shed snake skin	95.52±0.9
	Porcine ear skin	88.20±1.1
3	In vivo drug release for MX-2	98.69±1.5

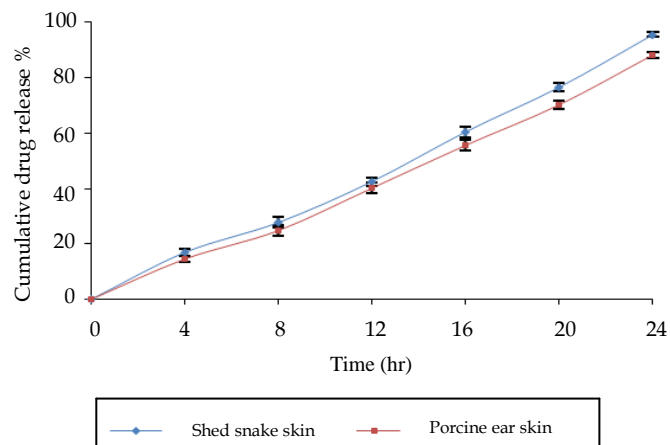
Note: All values expressed as mean±SD, (n=3)

The in vitro skin permeation of MX-2 was performed using various biological membranes such as shed snake skin and porcine ear skin showed drug diffusion of 24 h up to the extent of 95.52% and 88.20% respectively. The formulation MX-2 with HPMC (2%) exhibited the greatest cumulative amounts of drug permeation, which were significantly ( $p<0.05$ ) (Fig. 7) different compared to the lowest values observed with the other formulations at the end of 24 h. Table 4 lists the in vitro skin permeation of various biological membranes. Further it also showed no significant difference among the different barriers used. Between barriers used the shed snake skin was found to be more permeable. Figure 8 exhibits the comparison of drug permeation across shed snake skin, porcine ear skin and in vivo drug release.

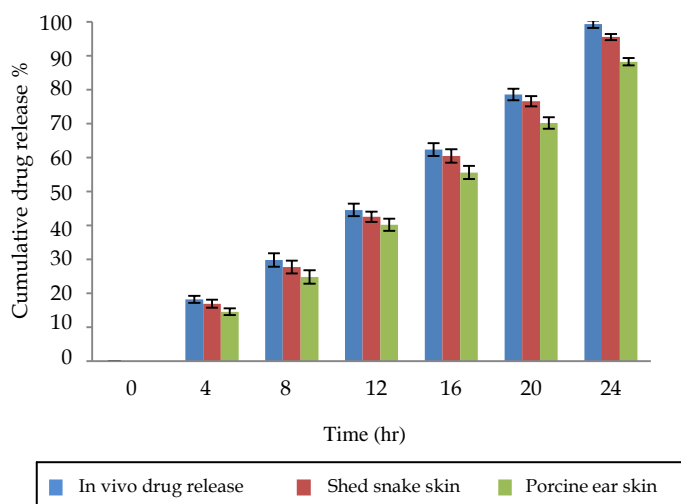
The safety of MX-patch was evaluated with primary skin irritation study. The results indicated that neither the adhesive nor the drug MX caused any noticeable irritation on the rabbit skin throughout the study. Table 4 lists the in vivo drug release of formulation MX-2. At the end of 24<sup>th</sup> hour the in vivo drug release showed 98.69% release.

The correlation between the results obtained by the in vitro and in vivo techniques was very good. To ensure the correlation between the in vitro and in vivo release pattern, the regression analysis was carried out. Figure 9 exhibits the correlation between the in vitro and in vivo release pattern.

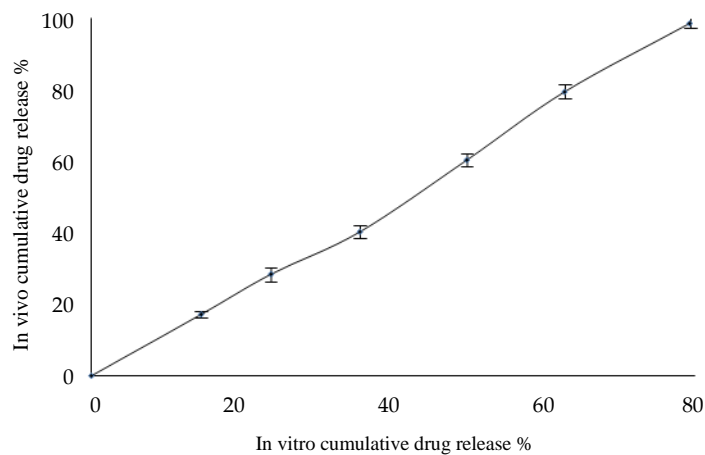
Paw edema induced by carrageen was effectively suppressed by MX patch. The result obtained in this study showed that the paw edema inhibition percentage was 47.38% ( $p<0.05$ ) for animal treated with MX patch and 48.04% ( $p<0.05$ ) for animal treated with diclofenac sodium patch. Table 5 and Figure 10 lists the antiinflammatory activity data for formulation MX-2.



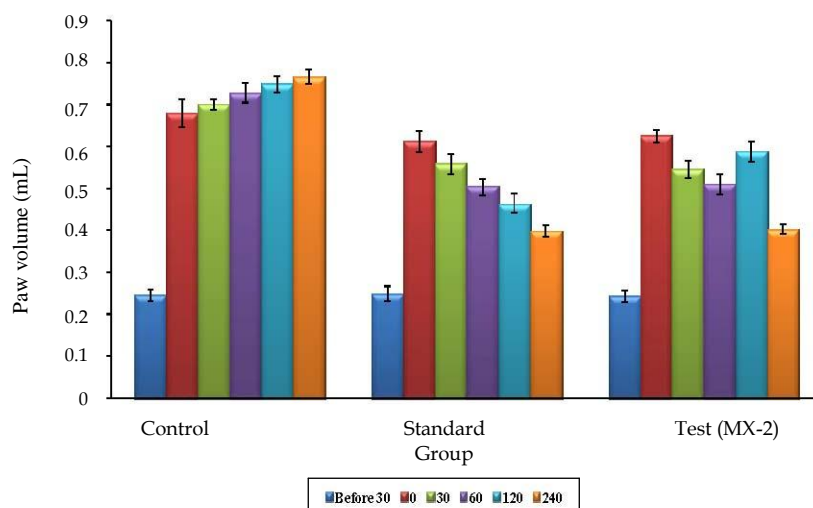
**Fig. 7:** In vitro skin permeation drug release of various biological skin membrane of MX-2.



**Fig. 8:** Comparison of drug release from formulation MX-2 across shed snake skin, porcine ear skin and in vivo drug release.



**Fig. 9:** In vitro-in vivo correlation graph of MX-2.



**Fig. 10:** Antiinflammatory activity data for formulation MX-2.

The formulation (MX-2) was subjected to accelerated stability testing at 4°C, 40°C and 60°C for 90 days. The formulation was found to be stable with respect to MX assay when analysed by HPLC. Period of expiry was found to be 186 days at 25°C which showed all stable.

**Table 5:** Antiinflammatory activity data for formulation MX-2.

Time (min)	Paw volume (mL)			% Inhibition	
	Control	Standard	Test (MX-2)	Standard	Test (MX-2)
Before 30	0.245±0.013	0.249±0.018	0.243±0.014	-	-
0	0.680±0.033	0.611±0.025 <sup>ns</sup>	0.625±0.015 <sup>ns</sup>	10.14	8.08
30	0.700±0.013	0.558±0.025 <sup>ns</sup>	0.545±0.02 <sup>ns</sup>	20.28	22.14
60	0.728±0.023	0.503±0.020*	0.510±0.023*	30.42	29.46
120	0.749±0.019	0.465±0.023*	0.588±0.024*	37.91	39.25
240	0.766±0.017	0.398±0.014*	0.403±0.012*	48.04	47.38

Note: All values expressed as mean±SD. \*  $p < 0.05$  vs control; ns = non significance.

## DISCUSSION

Transdermal delivery offers several advantages over oral routes for controlled drug delivery viz., bioability of drug for a longer time than the oral dosage forms, evading of hepatic first-pass metabolism, avoid the chemical or metabolic degradation, the delivery of the API can be immediately discontinued (e.g., upon occurrence of adverse reactions).

The observed partition coefficient is in good agreement with those reported in the literature (Diez *et al.* 1991). There is an optimum log K value for most compounds which partitions through lipophilic membranes. Compounds with values below these optimum log K values do not partition readily into the stratum corneum, while compounds with higher values of log K are so lipophilic that they remain dissolved in the stratum corneum.

There were no significant differences in the IR peaks, melting point in DSC analysis and the presence of polymers used in the study, which indicate that the polymers do not interact with the drug. It is well known that popular polymers such as PVP, EC and HPMC are compatible with a number of drugs (Rama Rao and Diwan 1998; Wade and Weller 2000).

The thicknesses of all batches are nearly similar which indicates the physical uniformity of prepared patches. The drug content analysis of the prepared formulation has shown that the process adopted for casting the films in this investigation is capable of giving films uniform drug content and minimum intra batch variability. Folding endurance values of all formulations indicates good strength and elasticity and can maintain the integrity with general skin folding.

The moisture uptake of MX is a function of HPMC, PVP/EC ratios. This may be attributed to the higher polydispersity index and solubility parameter of HPMC and PVP as compared to those of EC. Thereby, it has a high affinity for water and induces higher moisture uptake as the HPMC, PVP ratio in the films increased (Limpongsa and Umprayn 2008). The formulation MX-2 (2% HPMC) gives higher value of moisture loss, which is due to its hydrophilic nature and formulation. MX-3 (1% EC) gives low value, which is due to its hydrophobic nature. The tensile testing gives a sign of the strength and elasticity of the film by tensile strength (TS) and elongation at break (E/B). A soft and weak polymer is characterised by a low TS and E/B; a hard and brittle polymer is defined by a moderate TS and low E/B; a soft and tough polymer is characterised by a moderate TS and high E/B; whereas a hard and tough polymer is characterised by a high TS and E/B

(Sakellariou and Rowe 1995). The results revealed that as the concentration of HPMC increased, the tensile strength was found to be increased but elongation at break values decreased. An inverse relation was observed between TC and E/B. These observations indicate that formulation MX-2 patches were found to be strong, not brittle and flexible. The formulations MX-4 (2% EC) have shown lowest values of TS and percentage elongation respectively, when compared with other formulations and it is clearly found that the TS and the percentage elongation increase as the polymer content in the patch decrease. The formulation MX-2 has shown maximum water vapor transmission. All formulations were permeable to water vapor.

In vitro release test is widely used because of its simplicity and reproducibility. Moreover, it has been shown that drug diffusion through matrix was influenced by the drug-polymer interaction. However, in vitro tests are very useful in the quality control of finished TDDS. Drug released in 24 h was found to be the highest for formulation MX-2 and diffusion mechanism involved in the drug release was of non-fickian diffusion type. Hence formulation MX-2 was selected as the optimised formulation by virtue of its drug release kinetics.

The in vitro skin permeation of MX-2 was performed using various biological membranes such as shed snake skin and porcine ear skin which showed drug diffusion up to 24 h. Furthermore, there was no significant difference among the different barriers used. The drug diffusion of MX from shed snake skin at all the concentrations tested was found to be more in comparison to porcine ear skin. As the porcine ear has more fat deposition and thickness, it might have hampered the drug release through the membrane. This confirmed that shed snake skin is more permeable than porcine ear skin.

Since patch is applied on the skin, its propensity to produce skin irritation should be confirmed. The results indicated a non-irritating level, thus, MX-patch is expected to be applied on skin without skin irritation. In vivo study carried out in rabbit revealed that the consistent in vitro release pattern of the formulation MX-2 was reproducible even in biological environment. The sustained response following transdermal administration was due to controlled and continuous release of drug into the systemic circulation over an extended period. They are well correlated, so the release pattern has followed the predicted zero order kinetics in biological systems also.

Foot edema induced by carrageen was effectively suppressed by MX patch. The result obtained in this study showed that the paw edema inhibition percentage was almost similar for animal treated with MX patch and for animal treated with diclofenac sodium patch.

Less degradation and good physical appearance was observed on performing the stability studies and period of expiry was found to be 186 days at 25°C and could be assigned to the TDDS.

## CONCLUSION

The transdermal formulation and the prototype patch were shown to be efficacious, safe, stable and non-irritant to skin. The formulation MX-2 (2% HPMC) has shown optimum release in concentration dependent manner. The obtained results are encouraging for further studies, which deals with the application of the presently reported findings to human skin permeation, involving in vivo tests.

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