

RESEARCH ARTICLE

DESIGN AND EVALUATION OF TRANSDERMAL FILMS CONTAINING KETOPROFEN FOR THE TREATMENT OF ARTHRITIS***Manjula D¹**, Shabaraya AR², Srikanth P³, Suma R¹¹Dayananda Sagar College of Pharmacy, Bangalore, Karnataka, India²Srinivas College of Pharmacy, Mangalore, Karnataka, India³V.L. College of Pharmacy, Raichur, Karnataka, India**Corresponding author's E-mail: manjulad21@rediffmail.com*

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ABSTRACT:

Transdermal drug delivery systems of ketoprofen have been formulated using solvent casting method. matrix type transdermal systems were prepared by using Hydroxy propyl methyl cellulose (HPMC) and ethyl cellulose (EC) polymers by incorporation glycerin and dibutyl phthalate as plasticizers respectively. Drug polymer interactions were studied by FT-IR and differential scanning calorimetry which showed no interaction between drug and the polymers used. All the patches were uniform with respect to physico-chemical evaluation. The drug uniformity in the patch was observed by scanning electron microscopy which showed uniform distribution of drug throughout the patch. The *in vitro* drug release studies indicated that HPMC and EC patches with no permeation enhancer released the drug in an optimum rate. The various permeation parameters such as flux, permeability co-efficient, enhancement ration and diffusion rate constants were determined for all the formulations. The effect of permeation enhancer on the diffusion of ketoprofen across rat skin was determined. The maximum flux of 9.52×10^{-2} mg/cm²/hr was observed with HPMC monolithic system containing 5% v/v d-limonene. A significant improvement of flux was observed with 5% d-limonene than that of 20% oleic acid. The *in vitro* release studies revealed that the release was sustained upto 24 hr and followed zero order kinetics.

Keywords: Ketoprofen, HPMC, EC, d-limonene and Oleic acid.**INTRODUCTION:**

Arthritis is a major syndrome affecting majority of the geriatric patients and generally NSAID'S are advised to reduce pain and inflammation¹. The medications prescribed for the relief of inflammation and associated pain are available as conventional dosages like tablets and capsules. The conventional medications cause GI disturbances and drug level fluctuates considerable making the patient to suffer or the patient is burdened with overdosage². To minimize the GI disturbances and to improve the bioavailability of the drug certain novel dosage forms are being investigated. In the past two decades there has been a commendable growth both in size and to improve bioavailability and patient compliance. Transdermal drug delivery systems (TDDS) are designed to support the passage of drug substances from the surface of skin, through its various layers, into the systemic circulation. Their advantages over conventional dosage forms include improved patient compliance, avoidance of gastric irritation and first-pass effect and controlled therapeutic responses³. Ketoprofen, a non-steroidal anti-inflammatory drug, used in the treatment of arthritis, can be used as a suitable model to develop TDDS because of its short half-life of about 2-3 hr and gastro-intestinal side effects⁴.

MATERIALS AND METHODS:

Ketoprofen was gift sample Themis laboratories Mumbai, HPMC and EC were gift samples from Ajanta Pharmaceuticals Mumbai, d-limonene, oleic acid were obtained from sd-fine chemicals. All the other reagents used were of analytical grade. HPMC and EC are

hydrophilic and hydrophobic polymers respectively, to see their effect on release of ketoprofen through skin, so both the polymers are chosen for the present study.

Drug polymer interaction by FT-IR^{5,6}:

To investigate any possible interaction between the drug and the utilized polymer, IR spectrum of pure drug and its physical mixture was carried out by using FT-IR (Perkin elmer 1600 series USA) the range selected was from 400cm^{-1} to 4000cm^{-1} .

Preparation of monolithic trans dermal systems:

Monolithic transdermal systems of HPMC and EC were prepared by solvent casting method on mercury surface as per mundane et al method⁷. Various formulations with their codes is tabulated in table 1. Polymeric solution was prepared by dissolving the respective polymer in combination of solvents, stirred on magnetic stirrer for 20 min with simultaneous addition of glycerine and dibutyl phthalate as plasticizers for HPMC and EC patches respectively. Specific quantity of drug was dissolved in alcohol and added to the polymeric solution. Finally the resulting solution was poured within a glass bangle of 5cm diameter placed on mercury surface in a petridish. The rate of evaporation of the solvent was controlled by inverting cut funnel over the petridish. After 24 hr the dried patches were taken out and stored in a desiccator. The drug polymer ratio was 1:4 respectively and was kept constant for all the formulations. Various formulations prepared are depicted in table 1.

Table 1: Formulation Codes of Various Monolithic Transdermal Patches Containing Ketoprofen

S.No.	Ingredients (mg/ml)	Formulation codes					
		F1	F2	F3	F4	F5	F6
1	Ketoprofen	50	50	50	50	50	50
2	HPMC	200	200	200	-	-	-
3	EC	-	-	-	200	200	200
4	Dibutyl phthalate	-	-	-	0.0575	0.0575	0.0575
5	Glycerine	0.0585	0.0585	0.0585	-	-	-
6	d-limonene	-	0.0029	-	-	0.0029	-
7	Oleic acid	-	-	0.0111	-	-	0.0111
8	Alcohol	2	2	2	2	2	2
9	Dichloro methane	1	1	1	1	1	1
10	Chloroform	2	2	2	2	2	2

Note: The above formulae gives total area of 19.63 sq. cm

Methodology:

Physical appearance, weight and Thickness uniformity:

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

patches were weighed on afcoset digital balance. The average of five observations was taken. The thickness⁸ was measured by a screw gauge (mitutoyo Japan) at five different random points on the patch. The average of five observations was taken.

Table 2: Physical parameters of the transdermal systems

S.No.	Formulation codes	Physical appearance	Weight (mg)	Thickness (mm)
1	F1	++	272.2(0.49)	0.167(0.0067)
2	F2	++	275.1(0.32)	0.147(0.0044)
3	F3	++	279.5(0.35)	0.129(0.0022)
4	F4	++	291.7(0.42)	0.149(0.0044)
5	F5	++	315.1(0.34)	0.149(0.0102)
6	F6	++	325(0.44)	0.167(0.0067)

Water vapor transmission studies (WVT)⁹:

Glass vials of equal diameter were used as transmission cells. These cells were washed and dried in an oven. About 1gm of fused calcium chloride was taken in the cells and patch of area equivalent to brim of vial (1.36 cm²) was fixed with the help of an adhesive. The cells were weighed accurately and kept in a close desiccator containing

saturated solution of potassium bromide (200ml). The humidity inside the desiccator was measured by a hygrometer and it was found to be 84% RH. The cells were taken out and weighed after 1, 2, 3, 4, 5, 6 and 7 days of storage. The WVT was calculated by taking the difference in the weight of the patches before and at regular intervals of 24 hr for a total period of seven days.

Table 3: Data for water vapor transmission studies for monolithic systems.

S.No.	Formulation codes	Cumulative amount of water vapour transmitted in g ms							WVT rate constant (gm/24hr/sq)
		1 st day	2 nd day	3 rd day	4 th day	5 th day	6 th day	7 th day	
1	F1	0.045	0.089	0.133	0.177	0.221	0.264	0.307	3.307x10 ⁻²
2	F2	0.050	0.105	0.157	0.209	0.26	0.311	0.384	4.137x10 ⁻²
3	F3	0.049	0.099	0.147	0.195	0.243	0.291	0.362	3.900x10 ⁻²
4	F4	0.034	0.069	0.097	0.139	0.176	0.211	0.245	2.600x10 ⁻²
5	F5	0.038	0.076	0.113	0.15	0.188	0.225	0.262	2.820x10 ⁻²
6	F6	0.036	0.072	0.107	0.142	0.174	0.231	0.248	2.671x10 ⁻²

Drug content uniformity¹⁰:

Transdermal films of 1sq.cm area was cut into small piece and transferred into 100ml volumetric flask. 25ml of methanol was added and shaken for 4hr to extract the drug. Finally, suitable dilutions were made using phosphate buffer pH 7.4 and absorbance was measured at 258nm.

In vitro permeation across the rat abdominal skin:

Preparation of the skin¹¹:

The swiss albino rats were sacrificed by decapitation. The fresh abdominal skin was excised from swiss albino rats weighing 170-190g. The abdominal skin of excised hairless rat skin was separated along the epidermal junction and was kept under a steam of 60 °C water for exactly 50 seconds. The heat-treated skin was cleared of its subcutaneous fatty substances and immediately kept in normal saline solution to flatten and smooth. This step maintains the integrity and viability of the skin.

Permeation studies:

A vertically assembled Keshary-Chien12 diffusion cell having downstream volume of 50ml was used. The above skin was mounted on the diffusion cell and receiver compartment was filled with 50ml phosphate buffer of pH 7.4 and the temperature was maintained at 37 °C. The samples were withdrawn every hour (replaced with 1ml fresh buffer to maintain sink condition) and their

concentrations were measured in UV-spectrophotometer at 254nm. The permeation studies were carried out upto 24hr.

RESULTS AND DISCUSSION

Fig 1, 2 and 3 shows the IR spectra of pure drug ketoprofen and the physical mixture of ketoprofen with HPMC polymer and EC polymer. Due to replication of peaks in IR spectra of physical mixture (fig 2 and 3) as that of pure drug ketoprofen (fig1) indicate their compatibility.

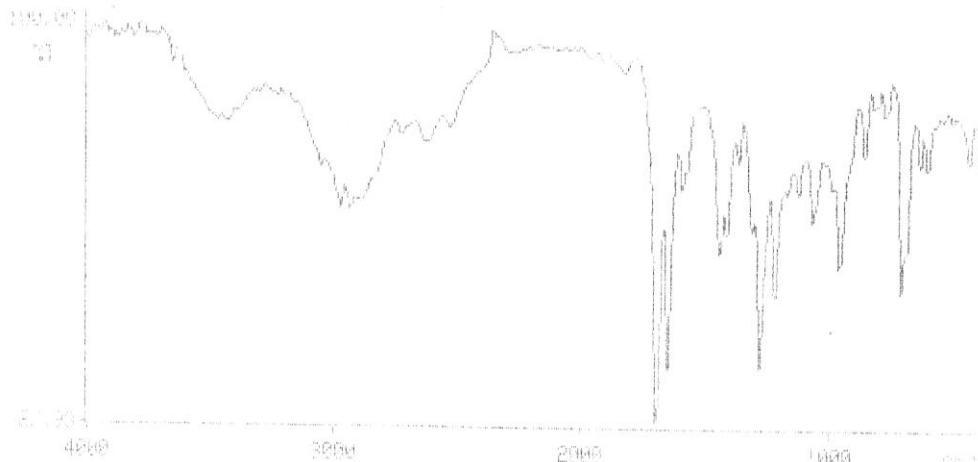


Figure 1: IR of Ketoprofen

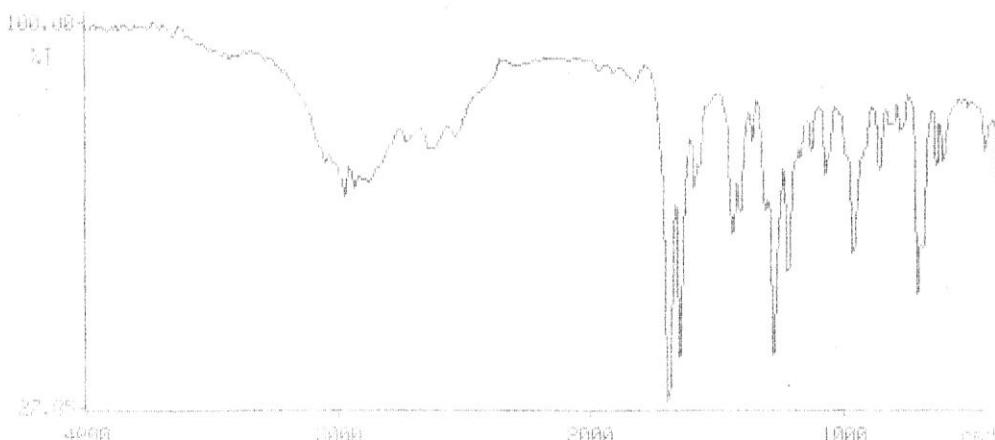


Figure 2: IR of ketoprofen and HPMC mixture

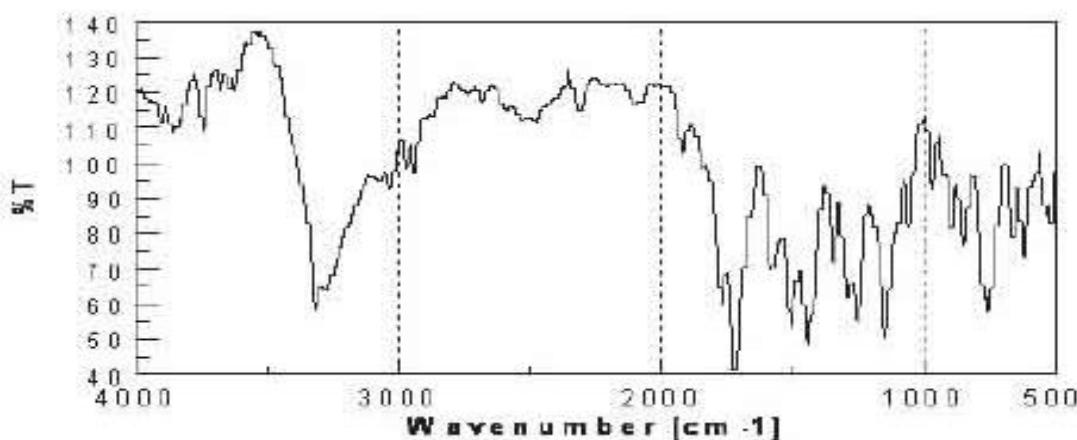


Figure 3: IR of ketoprofen and EC

In the next step, a total of 6 formulations of monolithic and reservoirs were prepared using HPMC and EC polymers as per formulae given in table 1. All the films evaluated for their physical parameters were found to be flexible, smooth and transparent. They were also found to be uniform in their weight and thickness with low SD values as shown in table 2.

The WVT studies (table 3) depicted that all the formulations from F1 to F6 were permeable to water vapour and among all the formulations HPMC containing patches showed good WVT than that of EC patches. The drug content was almost uniform in all the patches with low SD values (table 5).

The *in vitro* release of drug across rat skin from HPMC and EC showed only 57.66%

(F1) and 43.11% (F4) at the end of 24th hr respectively (Fig 4), the flux was calculated from the slope of linear graph and it was found to be 6.13×10^{-2} and 4.59×10^{-2}

mg/cm²/hr, diffusion rate constants were 0.23 and 0.172 mg/hr/cm² respectively (table 5). It was evident from the above result that there was a lower flux, poor drug permeability and less diffusion which might be attributed to tough barrier, stratum corneum of the skin; hence there was a need to incorporate permeation enhancer in the system. Two permeation enhancers namely d-limonene¹³ (5% v/v) and oleic acid¹⁴ (20% v/v) were incorporated and the drug release was studies. Among these systems, patch containing d-limonene in HPMC polymer (F2) showed maximum release, whereas patch containing d-limonene in EC polymer (F5) showed less release at the end of 24hr. In the later study, 20% oleic acid was used as polymer in both HPMC (F3) and EC polymer (F6) among which 20% oleic acid in HPMC polymer showed more release. On the whole, HPMC polymer showed more release than oleic acid (Fig 5).

Table 4: Comparative kinetic values of drug release from trans dermal monolithic and reservoir systems.

S.No.	Formulation codes	Zero order equation		Higuchi's equation	
		N	R	N	R
1	F1	2.3323	0.9968	11.3516	0.9352
2	F2	3.8781	0.895	22.6712	0.9375
3	F3	3.6614	0.898	20.778	0.9517
4	F4	1.7153	0.9952	8.557	0.9546
5	F5	3.1247	0.9963	15.440	0.9477
6	F6	3.0186	0.9981	14.952	0.9501

Table 5: Permeability co-efficient, flux, enhancement ratio and diffusion rate constant of transdermal monolithic system

S.No.	Formulation codes	Permeability co-efficient mg.mm/hr	Flux mg/cm ² /hr	Drug Content	Enhancement ratio	Diffusion rate constant mg/hr/cm ²
1	F1	2.56×10^{-2}	6.13×10^{-2}	98.5 (0.25)	-	0.230
2	F2	4.001×10^{-2}	9.52×10^{-2}	99.1 (0.35)	1.55	0.358
3	F3	3.632×10^{-2}	8.68×10^{-2}	98.9 (0.37)	1.45	0.326
4	F4	1.927×10^{-2}	4.59×10^{-2}	97.2 (0.27)	-	0.173
5	F5	3.402×10^{-2}	8.10×10^{-2}	98.1 (0.36)	1.32	0.305
6	F6	3.326×10^{-2}	7.77×10^{-2}	97.8 (0.41)	1.26	0.292

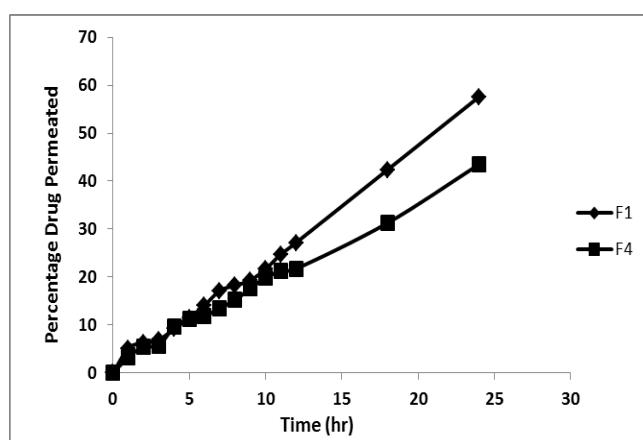


Figure 4: In Vitro Drug Release from Formulations F1 and F2 across Rat Abdominal Skin

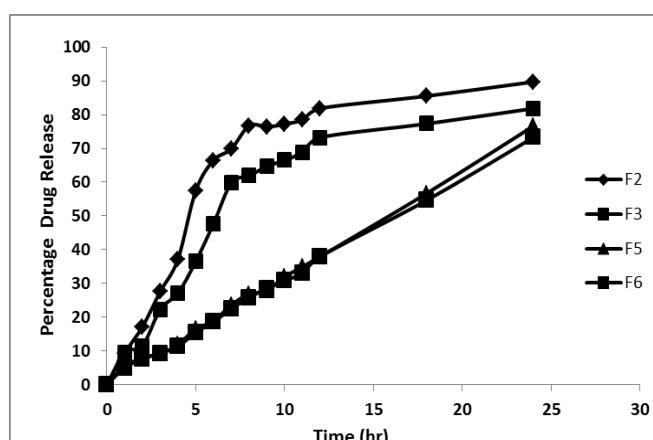


Figure 5: In Vitro Drug Release from Formulations F2, F3, F5 and F6 Across Rat Abdominal Skin

CONCLUSIONS:

The fabricated polymeric films containing ketoprofen had shown uniform thickness, weight variation and drug content. *In vitro* skin permeation profile of the films was fairly uniform. Among two permeation enhancers d-limonene showed significant enhancement of drug permeation than oleic acid. The results of the study indicate the feasibility of formulating rate controlled transdermal therapeutic systems of ketoprofen for effective

management of chronic pain, inflammation associated with rheumatoid and osteoarthritis conditions.

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