Vol. 13 (2010) 19-24

The Influence and Compatibility of Vegetable Oils and other Additives on Release of Ketoprofen from Transdermal Films

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The vegetable oils used as skin permeation enhancers were selected on the basis of compatibility studies data. A total of eight monolithic systems were prepared by using different concentrations of drug-polymers-permeation enhancers. The permeation parameters, flux, permeability coefficient, enhancement ratio and diffusion rate constants were determined. The maximum flux of 9.08 x 10^{-2} mg/cm^2.h was observed with hydroxy propyl methyl cellulose monolithic system containing 30% w/w olive oil. Further improvement of flux was observed, when 30% w/w olive oil was applied directly onto the skin prior to the studies. The release was sustained up to 24 hours with zero-order kinetics and diffusion controlled mechanism. The 30% w/w olive oil formulation showed promising results with *in vivo* results showing significant analgesic and anti-inflammatory activities (P < 0.01) with no hypersensitivity reactions. Stability studies and scanning electron microscopy studies were also conducted.

Keywords: Vegetable oils, flux, ketoprofen, polymers

INTRODUCTION

Drug delivery into the skin may produce both local effects in dermatology and treatment for systemic disease states. The latter has been brought into sharp focus in recent years through efforts to develop transdermal delivery devices. The transdermal route of drug delivery is gaining favour with the demonstration of percutaneous absorption of a large number of drugs. Vegetable oils may alter skin permeation through three different mechanisms namely; increasing occlusion, widening the polar pathway and widening the non-polar pathway [1]. In addition, it has been found that vegetable oils in general produce virtually no skin irritation or sensitization problems.

The objective of the present study was to enhance drug release by using various vegetable oils as permeation enhancers for the transdermal drug delivery system. Infrared (IR) absorption spectroscopy and differential scanning calorimetry (DSC) were used to investigate any possible interaction between the drug and the utilized polymers.

MATERIALS AND METHODS

Ketoprofen was a gift from Torrent Pharmaceutical Ltd., Gujarat, India. The vegetable oils were purchased from S.D. Fine Chemicals, (Boisar, India). The polymers used were from Central Drug House Pvt. Ltd. (Mumbai, India.). All other chemicals and reagents were of analytical grade.

Preparation of transdermal films

Monolithic transdermal systems of hydroxypropyl methylcellulose (HMPC) and ethyl cellulose (EC) were prepared with a drug-polymer ratio of 1:4 for all the formulations. The solutions were stirred for 20 min using a magnetic stirrer. Glycerin and dibutyl phthalate (35% w/w of polymer) were used as plasticizers for HPMC and EC films respectively.

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Table 1: Formulae of monolithic transdermal systems containing ketoprofen

Ingredients (mg/ml)	Formulations								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Ketoprofe (mg)	50	50	50	50	50	50	50	50	50
HPMC (mg)	200	-	200	200	200	200	200	200	200
EC (mg)	-	200	-	-	-	-	-	-	-
Dibutylphthalate (ml)	-	0.067	-	-	-	-	-	-	-
Glycerin (ml)	0.055	-	0.055	0.055	0.055	0.055	0.055	0.055	0.055
Olive oil (ml)	-	-	0.0165	-	-	-	-	-	0.0165
Linseed oil (ml)	-	-	-	0.016	-	-	-	-	-
Castor oil (ml)	-	-	-	-	0.016	-	-	-	-
Sunflower oil (ml)	-	-	-	-	-	0.016	-	-	-
Coconut oil (ml)	-	-	-	-	-	-	0.0156	-	-
Cottonseed oil (ml)	-	-	-	-	-	-	-	0.0165	-

The specified quantity of drug was dissolved in alcohol and added to the respective polymer solution. The solutions were stirred and poured within a glass bangle of 5 cm diameter placed on mercury surface in a petridish. The rate of evaporation of the solvent was controlled by inverting a cut funnel over the petridish. After 24 h, the dried films were taken out and stored in a dessicator. Films F3, F4, F5, F6, F7 and F8 (Table 1) contained olive oil, linseed oil, castor oil, sunflower oil, coconut oil and cottonseed oil respectively in different concentrations (10%, 20% and 30% w/w of drug) as permeation enhancers. The films were prepared by incorporating them along with plasticizer [2]. In all cases, 30% w/w concentration of permeation enhancer showed good release and this concentration was used in further studies. During the experiments, a permeation enhancer was applied directly to the skin 10 minutes before experiment, giving a total area of 19.63 cm^2. each. (A total of eight monolithic systems were developed as shown in Table 1.

Evaluation parameters: The transdermal films were evaluated for physical parameters such as appearance, surface texture, weight variation, thickness and size, folding endurance [3], surface pH, drug content, water vapour absorption (WVA), water vapour transmission (WVT) and stability [4,5,6] and scanning electron microscopy (SEM) studies [7]. *In vitro* drug release across the rat abdominal skin was determined in each film spectrophotometrically at 258.7 nm in phosphate buffer (pH 7.4).

Water vapour absorption studies [8]: For the determination of water vapour absorption studies of polymer films, 3.14 cm^2 area was taken and weighed, then placed on wire gauze which was kept in a dessicator containing a saturated solution of potassium bromide (200 ml). The humidity inside the dessicator was maintained at 84% RH. The films were weighed after 1, 2, 3, 4, 5, 6, and 7 days of storage. The WVA was calculated by taking the difference in the weight of the film before and after the study at regular intervals of 24 h for a total period of seven days.

Water vapour transmission studies [9]: Glass vials were used as transmission cells. They were washed and dried in an oven maintained at 37 °C. About 1 g of fused calcium chloride was placed in the cells and a film of area equivalent to brim of vial (1.36 cm^2) was

fixed with the aid of an adhesive. The WVT was calculated by taking the difference in the weight of the cells before and after study at regular intervals of 24 h for a total period of seven days.

In vitro permeation across the rat abdominal skin [10, 11]: Swiss albino rats weighing 170 to 190 g were sacrificed by decapitation. The hairless abdominal skin was excised together with the epidermal junction and placed in a water bath at 60 °C for 50 s. The heat-treated skin was cleared of its subcutaneous portion and immediately placed in normal saline solution to maintain the integrity and viability of the skin.

Vertically assembled Keshary-Chien diffusion cells having a down stream volume of 50 ml were used. The skin was mounted on the diffusion cell and the receiver compartment filled with 50 ml phosphate buffer (pH 7.4) maintained at 37 °C. The samples were withdrawn every hour, replaced with fresh buffer to maintain sink condition and their concentrations measured spectrophotometrically at 258.7 nm.

All the eight monolithic systems (F1 to F8) were subjected to the stability studies at two different temperatures of 37 °C and 45 °C. They were observed for changes in colour, appearance, flexibility and drug content at a regular interval of one week for one month.

Anti-inflammatory activity: Twelve albino rats of either sex weighing between 170-200 g were divided into two groups of six animals each. The ventral surface of the animals was depilated. One group was treated as control and other group as test. The test film (F3) containing the dose of ketoprofen equivalent to 9 mg/kg body weight, calculated on the basis of surface area of the animal under study was stuck on the animal and a backing laminate of aluminium foil placed over the film with the support of adhesive tape. A 2% v/v formalin solution was used as chronic inflammogen to induce inflammation. A mark was made on hind paw behind tibiotarsal junction, so that every time the paw was dipped in the mercury column up to the fixed mark to ensure constant paw volume. After one hour, the inflammogen was injected subcutaneously into the paw of all animals. The paw volumes of all the animals were measured by using plethysmograph at selected time intervals. From the results obtained the percentage reduction in oedema volume was calculated. The anti-inflammatory activity of the formulation was statistically analyzed using the Student‘t’ test’.

Analgesic activity: Twelve albino mice of either sex weighing 20-30 g were selected and divided into two groups each having six mice. The ventral surface of the animals were depilated and divided into group-I (control) and group-II (test). The selected test film (F3) containing the dose of ketoprofen equivalent to 13 mg/kg body weight, calculated on the basis of surface area of the body was stuck on the animal and a backing laminate of aluminum foil was placed over the film and supported by an adhesive tape. Acetic acid 0.6% v/v was injected intra peritonially (1 ml/ 100 g of body weight of animal) to both groups and the numbers of writhes were noted. The activity of the formulation was statistically analyzed by Student‘t’ test.

RESULTS AND DISCUSSION

The IR spectral data and DSC studies showed that there was no interaction between drug and utilized polymers. All the films were found to be flexible, had a smooth surface texture and were transparent and uniform in weight and thickness. The surface pH values were found to be between 7.2 -7.5 in all the formulations, which indicated that they were compatible with skin. All the systems were permeable to water vapour at 84% RH and followed zero-order kinetics.

Table 2: Diffusion rate, permeability coefficient, flux, enhancement ratio and permeability rate of transdermal monolithic systems

Formulation codes	Diffusion rate (mg/h)	Permeability coefficient (cm/h)	Flux ($mg/cm^2.h$)	Enhancement ratio	Permeability rate (mg/h.cm)
F1	0.189	6.49×10^{-3}	5.50×10^{-2}	-	9.35×10^{-4}
F2	0.132	4.42×10^{-3}	3.84×10^{-2}	-	6.51×10^{-4}
F3	0.311	10.7×10^{-3}	9.08×10^{-2}	1.65	15.45×10^{-4}
F4	0.290	9.9×10^{-3}	8.45×10^{-2}	1.54	14.37×10^{-4}
F5	0.220	7.6×10^{-3}	6.42×10^{-2}	1.17	10.91×10^{-4}
F6	0.277	9.4×10^{-3}	8.07×10^{-2}	1.47	13.72×10^{-4}
F7	0.253	8.7×10^{-3}	7.45×10^{-2}	1.35	12.66×10^{-4}
F8	0.273	9.3×10^{-3}	7.88×10^{-2}	1.43	13.40×10^{-4}
F9	0.325	11.2×10^{-3}	9.47×10^{-2}	1.72	16.10×10^{-4}

The *in vitro* release of drug across rat skin from HPMC and EC films showed only 53.63% (F1) and 36.50% (F2) at the end of 24 h respectively. The flux was calculated from the slope of linear graph and found to be 5.50×10^{-2} and 3.84×10^{-2} $mg/cm^2.h$ while the diffusion rate constant was 0.189 and 0.132 mg/h respectively. Poor drug release was observed which might be attributed to tough barrier, the *stratum corneum* of skin, which contributes to low diffusivity. It was evident from the above results that there was a lower flux and lower diffusion rate through rat skin. Hence, there is a need to incorporate a permeation enhancer in the system. The HPMC film gave better release than EC film. Consequently, the HPMC film was selected for incorporation of various vegetable oils as permeation enhancers.

In the other studies, six vegetable oils namely olive oil, linseed oil, cottonseed oil, sunflower oil, coconut oil and castor oil were selected and used in various concentrations of 10% w/w, 20% w/w and 30% w/w. The oil concentration of 30 % w/w showed good release from F1 in all the cases. The kinetic values of drug release were determined using P-STAT package (P-STAT Inc, USA). The drug release profiles of all monolithic systems were approximately linear with correlation coefficients of 0.9829 - 0.9977. The results confirmed that, all the systems followed zero order kinetics, which is desirable for controlled delivery of drugs.

Olive oil (30%) containing HPMC monolithic system (F3) showed good release when compared to other vegetable oils as permeation enhancers with maximum flux of 9.08×10^{-2} $mg/cm^2.h$ was observed (Table 2). A significant improvement of flux was observed in the order, olive oil > linseed oil > sunflower oil > cottonseed oil > coconut oil > castor oil.

The formulations released in the order, F3 > F4 > F7 > F5 > F8 > F6 > F1 > F2 as shown in Figure 1. The highest drug release was observed when permeation enhancer was applied directly onto the skin 10 min before the study. The selected monolithic system showed significant anti-inflammatory activity. The oedema reduction for system F3 was 51.13% at the end of 18 h ($p < 0.05$).

It also showed good analgesic activity up to 24hrs. The data was analyzed by using P-STAT package (P-STAT, Inc. New Jersey USA) and showed significant analgesic activity at $p < 0.01$ and $p < 0.001$.

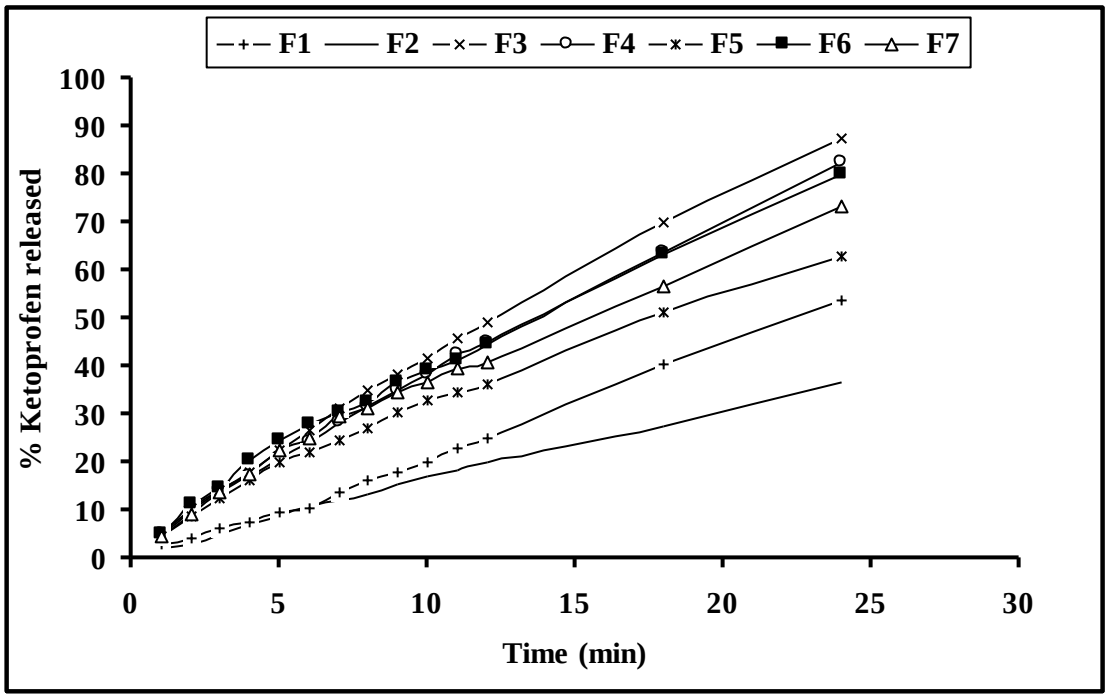

Figure 1: Comparison of *In vitro* release profiles of ketoprofen from different HPMC monolithic systems.

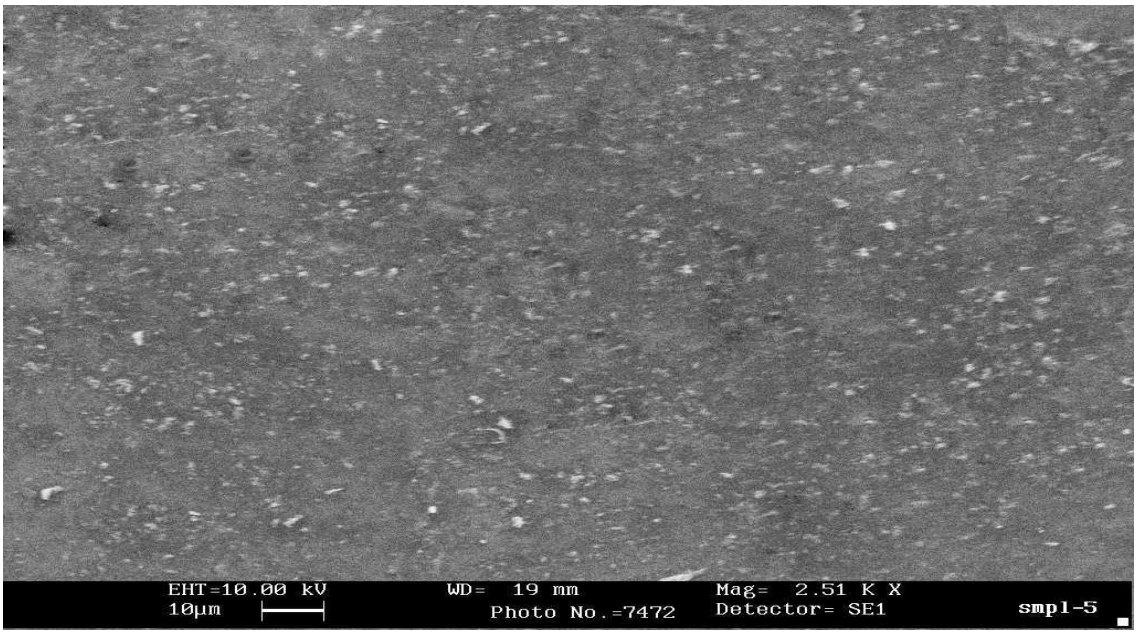

Figure 2: Scanning electron microscopy photograph of F3 formulation

No hypersensitivity reactions were observed implying safety for topical application. SEM studies revealed that the drug was uniformly distributed in the selected formulation (F3) as shown in Figure 2. All the films were stable at 37 °C and at 45 °C with respect to their physical parameters and drug content

CONCLUSION

The present studies have shown promising results of using vegetable oils as permeation enhancers. There is need for further pharmacodynamic and pharmacokinetic evaluation of the formulations. Toxicity studies need to be conducted in order to evaluate the safety and efficacy of the selected formulation

ACKNOWLEDGEMENT

The authors are grateful to the Sipra laboratories, India, for conducting the FT-IR and DSC studies and also to the central drug laboratory, India, for the SEM studies.

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