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Research Article

APPLICATION OF PERMEATION ENHANCER IN DIFFERENT MODES AND THEIR EFFECT ON *IN VITRO* PERMEATION OF KETOPROFEN ACROSS EXCISED RAT ABDOMINAL SKIN

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ABSTRACT

Transdermal route offers inherent advantages over other conventional routes for the delivery of drugs with systemic activity. Transdermal drug delivery provides a continuous mode of administration at rates approaching zero-order similar to that provided by an intravenous infusion.The greatest obstacle is the stratum corneum, the outermost layer of the skin, which is considered to form a primary rate –limiting barrier to the permeation of the drugs across the skin. Permeation enhancers are the substances that facilitate the absorption of penetrant through the skin by temporarily diminishing the impermeability of the skin. In the present study 4% d-limonene was selected as permeation enhancer and incorporated in the transdermal film in three different modes 1) permeation enhancer was incorporated in monolithic system 2) permeation enhancer was incorporated in the rate-controlling membrane 3) permeation enhancer was applied directly onto the skin 10min prior to the study and studied their influence on ketoprofen drug release from the selected transdermal film.The results revealed that highest percentage (92%) of drug release was observed *in vitro* across rat abdominal skin when we applied permeation enhancer directly on to the skin.

Keywords: Permeation enhancer, d-limonene and Hydroxy propyl methyl cellulose.

INTRODUCTION

Optimum therapeutic outcomes require not only proper drug selection but also effective drug delivery. The human skin is a readily accessible surface for drug delivery. Over the past three decades developing controlled drug delivery has become increasingly important in the pharmaceutical industry. The pharmacological response, both the desired therapeutic effect and the undesired adverse effect, of a drug is dependent on the concentration of the drug at the site of action, which in turn depends upon the dosage form and the extent of absorption of the drug at the site of action[1]. Tablets and injections have been the traditional way to take medications; new options are becoming increasingly popular. One highly successful alternative delivery method is the transdermal. Skin of an average adult body covers a surface of approximately 2 m^2 and receives about one-third of the blood circulating through the body.

The polymeric technologies have been honed and refined over the past several years and currently great interest has been focused on the development of novel drug delivery systems[2]. Treatment of chronic diseases such as asthma, rheumatoid arthritis by transdermal route of drug administration might prove to have several advantages over other routes of drug administration[3] .Transdermal route offers inherent advantages over other conventional routes for the delivery of drugs with systemic activity because it by-passes the first pass metabolism, avoids inactivation of drugs by p^H effects and enzymes present in gastrointestinal tract, which otherwise happens on oral administration. Transdermal drug delivery provides a continuous mode of administration at rates approaching zero-order similar to that provided by an intravenous infusion. The greatest obstacle is he stratum corneum, the outermost layer of the skin, which is considered to form a primary rate-

limiting barrier to the permeation of the drugs across the skin. Despite this limitation, several techniques have been developed to overcome the impervious nature of the stratum corneum by the use of permeation enhancer [4].

Permeation enhancers are the substances that facilitate the absorption of penetrant through the skin by temporarily diminishing the impermeability of the skin. After preliminary studies,4% d-limonene was selected as permeation enhancer [5] and incorporated and applied in different modes and investigated their influence on drug permeation across the rat abdominal skin.

MATERIALS AND METHODS

Ketoprofen was obtained as gift sample from Themis Laboratory, Mumbai. It is a non-steroidal anti-inflammatory drug, which can be used as a suitable model to develop transdermal drug delivery system because of its short biological half-life of about 2 hrs and gastrointestinal side effects. Because of its ionization at the p^H of skin and high dose requirement of 100-200mg daily, the flux value need a considerable improvement[6]. Hydroxy propyl methyl cellulose (HPMC), Ethyl cellulose (EC), d-limonene were obtained from Supra Laboratories, Hyderabad and Rolex Chemical Industries ,Mumbai and the remaining chemicals and reagents are of analytical grade were used.

The polymeric patches of HPMC and EC (2%) were prepared using mercury surface adopting method [7] . Glycerol and dibutyl phalate were used as plasticizers (30% w/w polymer) in HPMC and EC patches respectively. Alcohol , dichloromethane and chloroform in the ratio of 2:1:2 were used as solvent mixture. The casted films were dried at room temperature for 24 hrs. In our preliminary studies all patches were subjected to in vitro drug release using Keshary-Chiene diffusion cell[8] employing phosphate buffer of p^H 7.4[9] as diffusion medium at 32^0 C .Swiss albino rats were used as experimental animals, whose abdominal skin was prepared according to Flynn et al[10] . The samples were collected periodically and analysed for drug content. At the end of 24 hrs the formulation (HPMC patch) F_0 has shown 57.66% drug release which was highest among various formulations without penetration enhancer.(Table.1) . The permeability coefficient, flux, diffusion rate were also calculated and showed in Table .2

In our next phase of studies , only F_0 formulation was selected and incorporated d limonene and oleic acid of different concentrations . Finally 4% d-limonene has given promising results and hence, it was selected as permeation enhancer in further studies. The drug release studies were carried out upto 24 hrs and named as F_1 that showed 89.65% drug release with an initial release of 66.56% within 6 hrs.(Table.1).

In subsequent studies EC was selected as rate controlling membrane(RCM) and named as F_2. An attempt was made and incorporated the penetration enhancer in RCM. The drug release studies indicates that 74.65% drug release at the end of 24 hrs.(Table.1).

In the later investigation , the permeation enhancer was applied directly onto the excised rat abdominal skin 10 min prior to diffusion studies. Highest percentage of drug release (92%) at the end of 24 hrs was observed and it was named as F_3.

RESULTS AND DISCUSSION

The percentage drug release, the flux, diffusion rate and permeability co-efficient are given Table 1 &2 . As indicated in fig 1 , it was observed that among three modes of application of penetration enhancers, the F_3 system has showed highest percentage of drug release (92%) with improved flux, diffusion rate and permeability co-efficient (Table 2). This might be due to delipidization of stratum corneum by d-limonene prior to drug diffusion and more amount of drug was penetrated through modified stratum corneum. Hence, the flux, diffusion rate and permeability co-efficient were improved in F_3 system. The results suggested that penetration enhancer can be applied onto the skin before placing the transdermal patch so that it can improve the therapeutic response.

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Table 1: *In vitro* percentage of drug release across excised rat abdominal skin from ketoprofen trandermal patches with or without penetration enhancer

Time (hrs)	F0	F1	F2	F3
1	5.06	9.50	5.38	11.98
2	6.05	17.23	9.54	19.95
3	6.9	27.74	12.92	30.02
4	9.33	37.27	14.53	40.15
5	11.57	57.02	17.63	48.26
6	14.09	66.56	20.53	67.17
7	17.1	69.93	24.25	70.53
8	18.16	76.65	27.52	74.50
9	19.30	76.20	30.64	77.52
10	21.75	77.15	33.64	80.66
11	24.69	78.52	36.68	83.66
12	27.12	81.96	40.87	85.61
18	42.58	85.73	54.07	88.72
24	**57.66**	**89.65**	**74.65**	**92.00**

Note :o time =o%drug release

Table 2: Permeability coefficient, drug flux and diffusion rate of ketoprofen from transdermal patches of F0, F1,F2 and F3

Formulation Code	Permeability coefficient (cm/hr)	Flux ($mg/cm^2.hr$)	Diffusion rate (mg/hr)
F0	$2.560x10^{-2}$	$6.13x10^{-2}$	0.230
F1	$4.001x10^{-2}$	$9.52x10^{-2}$	0.358
F2	$3.330x10^{-2}$	$7.93x10^{-2}$	0.298
F3	**$4.104x10^{-2}$**	**$9.77x10^{-2}$**	**0.367**

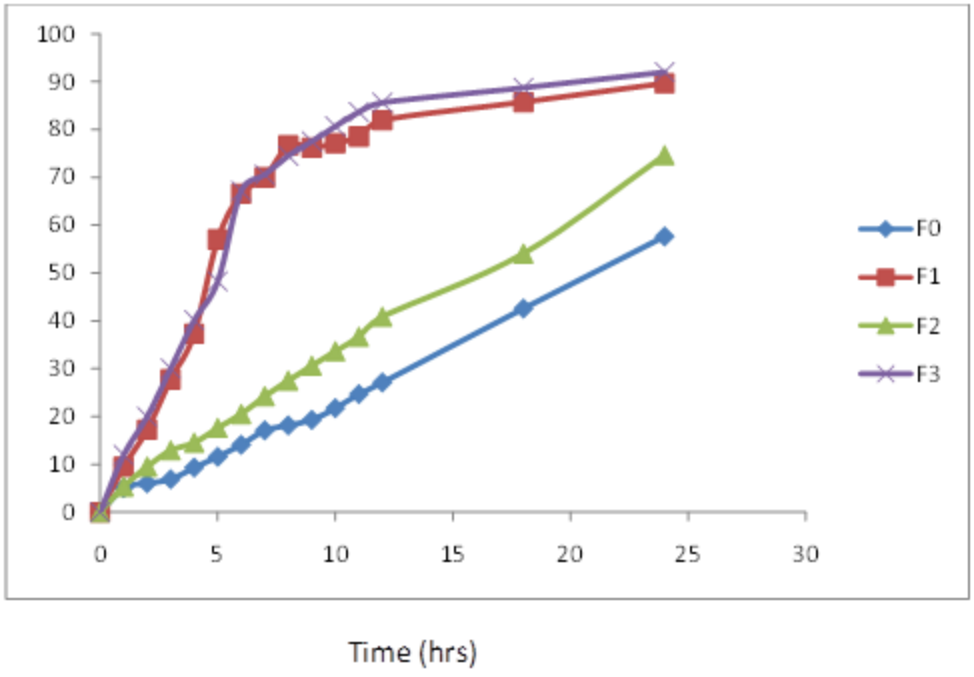

Fig. 1: Invitro cumulative % drug release profile from ketoprofen transdermal pateches (F0, F1, F2 & F3).

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