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Formulation of a Transdermal Drug Delivery System of Ketotifen Fumarate

F. V. MANVI, P. M. DANDAGI*, A. P. GADAD, V. S. MASTIHOLIMATH AND T. JAGADEESH
Department of Pharmaceutics, KLES's College of Pharmacy, Nehru Nagar, Belgaum-590 010

Transdermal films of ketotifen fumarate were formulated using combination of eudragit L 100:hydroxypropylmethylcellulose and ethyl cellulose:hydroxypropylmethylcellulose polymeric combinations plasticized with polyethylene glycol 400. Effect of permeation enhancers like dimethyl sulfoxide and propylene glycol at different concentrations were studied on skin permeation kinetics by Keshary-Chein diffusion cell. The films were also evaluated for various physicochemical properties. From *in vitro* diffusion studies it was found that there was increase in permeation rate with increase in permeation enhancer concentration. Both water vapour transmission rate and skin permeation rate followed zero order kinetics. It was concluded that films of eudragit L 100: hydroxy propyl methylcellulose and ethyl cellulose:hydroxypropyl methylcellulose polymeric combinations may be feasible for formulating rate controlled transdermal therapeutic system of ketotifen fumarate for effective control and prophylaxis of allergic asthma.

Ketotifen fumarate (KTF) belongs to tricyclic compounds of benzocycloheptathiophene class[1] is a non-specific, oral mast cell stabiliser. The prominent biochemical and pharmacological activities are H_1 antagonism, phosphodiesterase inhibition and inhibition of calcium flux in smooth muscle preparation. The drug is useful in allergic asthma and rhinitis. The drug has value in prophylaxis of atopic asthma[2]. The incidence of asthma is 2 to 3 times higher in children than that of an adult. Majority of the drug regimen in the treatment of asthma belongs to oral or inhalant class from which a better patient compliance may not be possible. KTF exhibits 50 % oral bioavailability due to hepatic first pass effect and is metabolised to inactive norketotifen and only 1 % of intact drug is excreted through the kidney[2].

Ketotifen fumarate due to its low therapeutic dose and substantial biotransformation in liver becomes it an ideal candidate for design and development of transdermal therapeutic system (TTS). KTF in transdermal formulations provides sustained blood level over a prolonged period, which is required for control of allergic asthma and other allergic syndromes. The present study was undertaken to formulate transdermal films of KTF and to evaluate the effect of enhancers like dimethyl sulfoxide (DMSO) and propylene glycol (PG) on drug release kinetics from prepared film formulations of eudragit L 100: hydroxypropylmethylcellulose and ethyl cellulose:hydroxypropyl methylcellulose (EL 100:HPMC and EC:HPMC) polymeric combinations.

*For correspondence
E.mail: pmdandagi@yahoo.com

MATERIALS AND METHODS

Eudragit L 100 was procured from S. Zhaveir and Co., Mumbai. Ethyl cellulose and polyethylene glycol was purchased from Loba Chemi, Mumbai. hydroxypropyl methylcellulose 400 was obtained from Bal Pharma Ltd. Bangalore) while dimethyl sulfoxide and propylene glycol were supplied by S. D. Fine Chem. Ltd. Mumbai., Ketotifen fumarate was obtained as a gift sample from the Sun Pharmaceuticals Ltd., Silvassa.

Preparation of monolithic matrix film:

Method used for the preparation of film is by solvent casting technique employing a glass substrate[4]. Table 1 shows composition of transdermal films containing KTF. EL 100:HPMC/ EC:HPMC were dissolved in ethanol at room temperature. PEG 400 and penetration enhancers (DMSO

TABLE 1: FORMULATION COMPOSITION OF TRANSDERMAL FILMS.

Formu Code	EL100:HPMC 9:1 (g)	EC:HPMC 3:7 (g)	PEG 400 (ml) 30 % w/w*	DMSO % w/w*	PG % w/w*	KTF (mg)
F_1	1.35 : 0.15		0.4			28
F_2	1.35 : 0.15		0.4	7.5 (102 µl)		28
F_3	1.35 : 0.15		0.4	15.0 (204 µl)		28
F_4	1.35 : 0.15		0.4		5.0 (70 µl)	28
F_5	1.35 : 0.15		0.4		10.0 (140 µl)	28
F_6		0.45 :1.05	0.4			28
F_7		0.45 :1.05	0.4	7.5 (102 µl)		28
F_8		0.45 :1.05	0.4	15.0 (204 µl)		28
F_9		0.45 :1.05	0.4		5.0 (70 µl)	28
F_{10}		0.45 :1.05	0.4		10.0 (140 µl)	28
F_{11}	1.35 : 0.15		0.4	15.0 (204 µl)	10.0 (140 µl)	28

*Based on polymer weight, each transdermal film contains 1.38 mg of KTF per 3.14 square cm area.

and/or PG) were added in concentrations as shown, with continuous mixing. The polymeric solution was obtained by stirring the solution on magnetic stirrer for 30 min. Then the solution was poured in anumbra petridish and dried at 40° for 6 h in an oven. An inverted funnel was placed over the petridish to prevent fast evaporation of the solvent. Films of 20 mm diameter were cut, packed in an aluminium foil and stored.

Evaluation of films:

The thickness of the films were measured by a dial caliper (Mitutoyo). The mean of the five observations were calculated. The tensile strength and percentage elongation of films were determined by using instrument designed in the laboratory[5,6]. The folding endurance of the film was determined by repeatedly folding a small strip measuring 2X2 cm size at same place till it breaks[7]. Data obtained from the above physical evaluation tests were shown in Table 2.

Water vapour transmission (WVT) rate:

For this study vials of equal diameter were used as transmission cells. These cells were washed thoroughly and dried in an oven. About 1.0 g of fused calcium chloride was taken in the cells and the polymeric films measuring 1.54 cm^2 area were fixed over the brim with the help of an adhesive. The cells were weighed accurately and initial weight is recorded, and then kept in a closed desiccator containing saturated solution of potassium chloride (200 ml). The humidity inside the desiccator was measured by a hygrometer, and it was found to be in between 80–90% RH. The cells were taken out and weighed after 1, 2, 3, 4, 5, 6 and 7th d of storage. From increase in the weights the amount of water vapour transmitted and rate at which water vapour transmitted were calculated using formula as shown below[8]. Table 3 shows results of water vapour transmission rate. WVT rate = WL/S, where W is the water vapour transmitted in g, L is the thickness of the film in cm and S is the exposed surface area in square cm.

***In vitro* skin permeation study:**

Freshly excised abdominal skin of 6 to 8 w old mice was used after the skin was immersed in 0.32 N ammonium hydroxide solution to facilitate removal of hair. The skin was fixed on to Keshary-Chein diffusion cell. The receptor medium used 20 % w/v PEG 400 in normal saline solution kept at 37°, being stirred with a magnetic stirrer throughout the experiment. Transdermal KTF films measuring 3.14 cm^2 area were placed in intimate contact with stratum corneum side of the skin. Aliquots from the receptor medium were withdrawn periodically upto 24 h and analysed spectrophotometrically at 301 nm[9].

RESULTS AND DISCUSSION

All the formulations, measured thickness with low stan-

TABLE 2: RESULTS OF THE THICKNESS, TENSILE STRENGTH, PERCENT ELONGATION AND FOLDING ENDURANCE OF THE FILMS.

	Mean Thickness (μm) n=5	Mean Tensile Strength (kg/mm^2) n=3	Mean Percent Elongation at Break (%) n=3	Mean Folding Endurance n=5
F1	241±4.18	2.32±0.07	26.7±2.89	>150
F2	252±5.70	2.89±0.25	61.7±1.44	>200
F3	259±4.18	3.68±0.07	117±3.19	>200
F4	245±7.91	2.83±0.07	54.2±3.82	>200
F5	253±6.70	3.60±0.05	103±2.50	>200
F6	245±3.54	3.55±0.04	15.9±1.44	>200
F7	250±3.54	4.10±0.04	36.7±1.44	>200
F8	259±6.52	4.25±0.04	50.8±1.44	>200
F9	246±4.18	4.21±0.04	38.3±1.44	>200
F10	254±8.99	4.27±0.08	46.7±2.89	>200
F11	261±4.18	4.02±0.07	133±3.19	>200

Values expressed in mean±S.D. n=number of samples.

dard deviation values ensured the uniformity of the films prepared by solvent casting method. The tensile strength of the EC:HPMC films found to be better than EL100:HPMC films, however percent elongation of EL100:HPMC films is greater than EC:HPMC films this may be due to cellulose derivatives which have less film flexibility. The folding endurance of all formulations were found to be satisfactory. WVT rate through the films followed zero-order kinetics. Rate of WVT was more in EC:HPMC films than EL100:HPMC films, may be due to more hydrophilic nature of EC:HPMC film formulations.

Formulation containing EL100:HPMC films shows that there is an increase in permeation rate with increase in concentration of enhancers (F_2 to F_5) in comparison with formulation without enhancers (F_1). Due to slow drug release from these films, the percent of drug permeation was not significant. Formulation F_{11} with DMSO 15 % w/w and PG at 10 % w/w, showed significant increase in skin permeation rate of 13.12 μg/cm^2/h because of synergistic effect of permeation enhancers as shown in Table 3.

Formulations containing EC:HPMC showed there is an increase in permeation rate with increase in concentration of enhancers (F_7 to F_{10}) in comparison to formulation without enhancer (F_6). DMSO at 15 % w/w and PG at 10 % w/w

TABLE 3: RESULTS OF WVT RATE, CUMULATIVE % PERMEATED AND PERMEATION FLUX.

	WVT Rate (g.μ/cm^2.24 h)	Cumulative % Permeated at 24th h n=3	Skin Permeation Rate (Flux, μg/cm^2/h) n=3
F1	2.02	44.7±2.54	8.19±0.47
F2	3.79	47.4±0.53	8.67±0.10
F3	4.14	63.3±2.87	11.7±0.53
F4	2.59	45.7±0.53	8.34±0.10
F5	3.83	61.7±1.85	11.3±0.34
F6	9.30	72.1±1.52	13.2±0.28
F7	10.5	83.4±2 58	15.4±0.48
F8	13.8	95.3±2.41	17.5±0.44
F9	10.0	81.8±1.71	15.0±0.32
F10	10.9	91.4±1.31	16.8±0.24
F11	8.8	71.6±1.84	13.1±0.34

Values expressed in mean±S.D. n=number of samples.

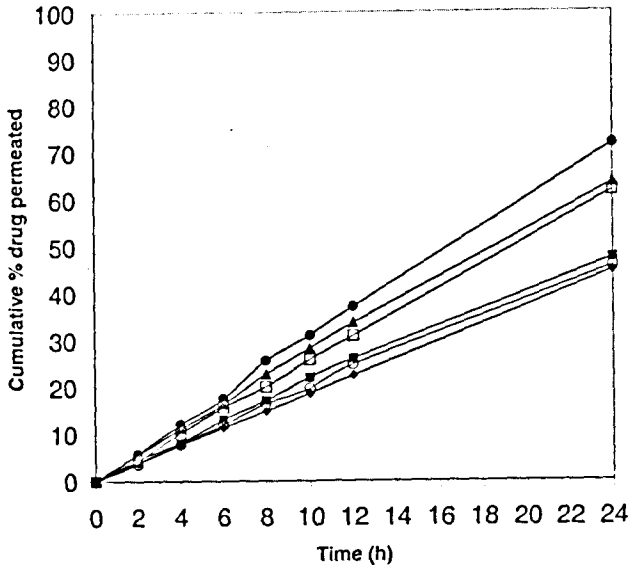

Fig. 1: Plots of cumulative percent drug permeated Vs time for EL100:HPMC formulations.

***In vitro* rat abdominal skin permeation profiles of formulation F_1 (◆), F_2 (▣), F_3 (△), F_4 (○), F_5 (□) and F_{11} (●) containing KTF using EL 100:HPMC polymeric combinations.**

concentration showed significant increase in cumulative drug percent permeation of 95.3 % and 91.4 % for formulation F_8 and F_{10}, respectively at 24 h.

From the above results it was concluded that DMSO and PG enhances the drug diffusivity through skin by affecting the intracellular lipids or proteins and thus increasing the partitioning of the drug in favour of stratum corneum. Decrease in drug release rate (flux) from EL100:HPMC films (F_1 to F_5 and F_{11}) in comparison to EC:HPMC film formulations (F_6 to F_{10}) may be attributed due to the relatively hydrophobic nature of polymers which have less affinity for water, this results in decrease in thermodynamic activity of the drug in the film and decreased drug release. The EC:HPMC films showed higher drug release rate (F_6 to F_8), more permeability of these films may be due to hydrophilic nature which increases the thermodynamic activity of drug.

The graphical representation of cumulative percentage drug permeated as a function of time as shown in figs 1 and 2 were found to be linear with high correlation coefficient (r) values. The linearity indicates that permeation of Ketotifen fumarate from transdermal films followed zero order kinetics.

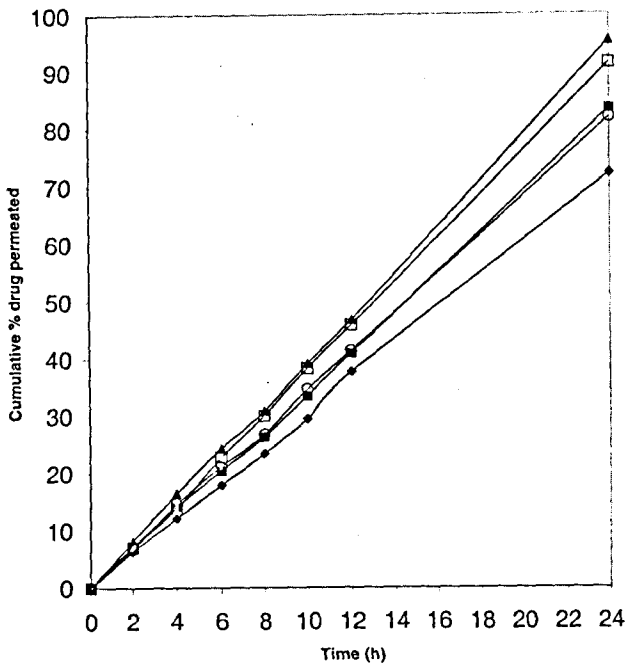

Fig. 2: Plots of cumulative percent drug permeated Vs time for EC:HPMC formulations

***In vitro* rat abdominal skin permeation profiles of formulation F_6 (◆), F_7 (▣), F_8 (△), F_9 (○), and F_{10} (□) containing KTF using EC:HPMC polymeric combinations.**

In conclusion, *in vitro* skin permeation of Ketotifen fumarate shows that films of EC: HPMC is suitable for once a day drug delivery and Eudragit L 100:HPMC films show suitability for a prolonged regimen of controlled drug delivery through transdermal route for a period of more than a day. The results of the study show the feasibility of formulating rate controlled transdermal therapeutic system of Ketotifen fumarate for effective control and prophylaxis of allergic asthma.

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