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EFFECT OF PENETRATION ENHANCERS ON THE IN VITRO TRANSPORT OF EPHEDRINE THROUGH RAT SKIN AND HUMAN EPIDERMIS FROM MATRIX BASED TRANSDERMAL FORMULATIONS

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ABSTRACT

The potential of skin as a site for administration of systemically active Ephedrine HCl (EH) has been recognised. The effect of penetration enhancers, i.e., Dimethyl sulfoxide (DMSO), Dimethyl acetamide (DMA), Dimethyl formamide (DMF) and Azone on the in-vitro transport of EH from matrix based transdermal formulations through full thickness rat skin and human epidermis was investigated. The highest flux with minimum time lag through rat skin and human epidermis was observed from the batch containing Azone as penetration enhancer.

INTRODUCTION

Vehicles are often compared in permeation studies with drug formulations and solvents may be used to accelerate percutaneous absorption[1,2]. The penetration enhancers have been found to enhance the permeability of skin[3,4]. In this study, we have incorporated the drug with penetration enhancers e.g., DMSO DMF, DMA and Azone in the polymeric matrix followed by an adhesive overlay to get transdermal formulations and study their effects on the in-vitro transport of the drug, EH, through full thickness rat skin and human epidermis.

MATERIALS AND METHODS

Materials :- Ephedrine HCl, polyvinyl pyrrolidone, polyvinyl alcohol, agar, dimethyl formamide and polyoxyethylene sorbitan monolaurate (tween^{R}20) were received from Central Drug House, Delhi. Polyethyleneglycol 400 (PEG 400) dimethylacetamide, dimethyl sulfoxide, rubber solution no. 4 and Azone were obtained from S.D. Fine Chem, Bombay, Searle Company, U.K., Sarabhai M. Chemicals, Baroda, Dunlop India and Nelson Research and Development, California, U.S.A., respectively. All other reagents used were of analytical grade.

Preparation of transdermal patches :

The mixture for transdermal patches was prepared as described by Sakya and Singh[5]. The mixture was cooled to room temperature and penetration enhancer at

the rate of 0.18 g/patch was mixed with thorough agitation at this stage. The rest of the procedure for the preparation of transdermal patches was similar as described earlier[5]. Thus, ten patches were prepared and each patch had 2.9 cm diameter, 2.5 mm thickness and 406.4 mg of EH. Five batches (A,B,C,D and E) of the transdermal patches were prepared. The control batch A was prepared without penetration enhancer while batches B,C,D, and E contained DMSO, DMF, DMA and Azone, respectively as penetration enhancer.

In-vitro transport studies through rat skin and human epidermis :

The full thickness rat skin was prepared following the method of Singh[6] and human epidermis by the method of Kligman and Christophers[7]. The in-vitro transport study through rat skin/human epidermis was performed following the method of Sakya and Singh[5]. The drug content of the samples was assayed colorimetrically at 570 nm following the method of Sekhon et. al.[8]. Three sets of experiments were run for each batch of the formulation.

RESULTS AND DISCUSSION

The results of the steady state flux, lag time and enhancement factor through rat skin from transdermal patches have been shown in table 1. The highest steady state flux of 1.31 $\pm$ 0.12 mg/cm^2/h with the minimum lag time of 1.46 h was observed by the formulation E. The enhancement factor of 337.6% through rat skin was also demonstrated by the formula-

TABLE 1

Steady state flux and lag time of Ephedrine HCl through rat skin from transdermal formulations. The results have been expressed as mean ± S.D. of three determinations.

Formulation	Steady state flux ($mg/cm^2/h$) Mean ± S.D.	lag time (h) Mean ± S.D.	Enhancement factor[a] (%)
A	0.388±0.024	7.70±6.12	-
B	0.446±0.065	4.90±0.61	114.94
C	1.247±0.374	5.06±3.30	321.39
D	0.563±0.075	12.66±2.40	145.10
E	1.310±0.120	1.47±0.42	337.60

$$^{a}\text{Enhancement factor (\%)} = \frac{(\text{Steady state flux})_{\text{enhancer}}}{(\text{Steady state flux})_{\text{control}}} \times 100$$

TABLE 2

Steady state flux and lag time of Ephedrine HCl through human epidermis from transdermal formulations. The results are expressed as mean ± S.D. of three determinations.

Formulation	Steady state flux ($mcg/cm^2/h$) Mean ± S.D.	Lag time (h) Mean ± S.D.	Enhancement factor[a] (%)
A	6.40±0.36	12.96±1.95	-
C	70.95±24.89	17.20±1.31	1108.50
E	84.80±5.28	3.53±0.42	1325.00

$$^{a}\text{Enhancement factor (\%)} = \frac{(\text{Steady state flux})_{\text{enhancer}}}{(\text{Steady state flux})_{\text{control}}} \times 100$$

tion of batch E in comparison to control. Thus, the comparative flux and enhancement factor through rat skin were found in the following order :

$$E > C > D > B > A.$$

The results of transport study of EH through cadaver epidermis are given in Table 2. The highest steady state flux of 84.80 mcg/cm^2/h with the minimum lag time of 3.53 h through cadaver epidermis was exhibited by the formulation E. Table 2 also shows that the steady state flux is 1325% and 1108% greater from the batches E and C respectively than the control A.

The permeation enhancing effect of Azone is dependent upon the nature of the drug. Azone seeme to change the diffusivity of the model drug EH, in the stratum corneum but not so effective in terms of the diffusivity in the dermis. This explains in part, the greater enhancement of EH flux due to Azone in comparison to control through epidermis than full thickness skin. Such trend has also been observed elsewhere[9].

CONCLUSION

The various permeation enhancers, e.g., DMSO, DMA, DMF and Azone were included into matrix based transdermal formulations to enhance to flux of EH through full thickness rat skin and human epidermis. The highest flux and the minimum lag time to reach the steaty state transport through both the rat skin and human epidermis were found from the batch E containing

Azone as penetration enhancer. The full thickness rat skin was also found to be more permeable to EH than the human epidermis.

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