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CINEOLE AS SKIN PENETRATION ENHANCER

Z.S. SAIFY*, OZRA AHSAN AND ABDULLAH DAYO
**Faculty of* Pharmacy, *University of* Karachi. *Karachi*
Department of Pharmacy, University of Sindh, Jamshoro, Pakistan

ABSTRACT:

Cineole is a chief constituent of euclyptus oil and constitutes almost 80% of this essential oil. A study was conducted on skin penetration enhancing capacity of cineole (1, 8-cineole) towards the permeation of 5 flurouracil in excised rat skin; it caused almost 83 fold increase in drug permeability co-efficient, the mode of action of acceleration may be described by combined process of partition and diffusion.

INTRODUCTION

The development of transdermal drug delivery system is a new emerging technology in pharmaceutical industry. The potential applications are enormous. However the optimisation of each application requires substantial efforts to design transdermal drug delivery system in such a may that not only enhances the perentenous absorption of drug but also ensures continuous systemic absorbtion without causing skin irritancy. This is usually achieved any incorporation of certain chemicals or derivatives as permeation enhancers in the formulation which act as non toxic promotor for enhancing percuteneous absorbtion. The success of transdermal drug delivery depends on the ability of drug to penetrate stratum corneum barrier (outermost layer of the skin). To reduce this diffusion barrier penetration enhancers are applied which usually disrupts the membrane structure (D. Southwell, 1983, B.W., Bony, 1984, Dis Southwell, 1984, B.J., August, 1986, M., Goodman, 1989, H., Okamoto, 1988).

In the present study 'cineole' which is a chief constituent of Eucalyptus oil and constitutes 80% of this essential oil was studied for it's skin penetration enhancing effects towards the permeation of 5-flurouracil (a model drug) which is usually used in formulation of gel. Ointment etc. Cineole should be free from other volatile aldehydes alcohols and phenols which have irritant properties and which are removed by redistillation of oil.

EXPERIMENT

A diffusion cell assembly was used to determine the permeation of drug through rat skin. The animals were sacrificed and abdominal skin was taken out, the hairs were removed and skin was treated, clipped and mounted between donor and receptor compartments. The donor cell received 1 ml. of saturated solution of 5-flurouracil and kept at normal temperature. The recipient cell was maintained at 37$\pm$5°C. At appropriate time 4 ml of solution was withdrawn from the receiving cell and I ml was taken for analysis using HPLC. After few samples 4 ml of fresh normal saline was added to receiving cell to keep the volume constant. To determine the penetration enhancing effect 150 ml of cineole was added to donor compartment. This experiment was repeated 10 times after

that the samples from receiving cells were analyzed and permeability coefficient at steady rate was evaluated. An enhancement ratio may be used to define the activity of enhancer (A., Osol, 1980).

$$ER = \frac{K_p \text{ after application of penetration enhancer}}{K_p \text{ before application of penetration enhancer}}$$

RESULTS AND DISCUSSION

The mean permeability coefficient of 5-FU before and after treatment of the skin with cineole are shown in Table I and indicated the obvious enhancing effect. The mean control value of K_p of 5-FU in the untreated skin at 37±0.5°C is $1.053\pm0.02\times10^{-3}$ cm/h, with a lag time of 4 hours.

In Fig. I, the total amount of penetrant that appeared in the receptor fluid is plotted as a Function of time. Following skin treatment with a enhancer, the lag time for 5 FU falls. The steady state conditions were observed only for 4-6h when cineole was used as enhancers, which may contribute to accumulation of higher concentrations of 5-FU in receiver compartment and/or the wash up effect of the enhancer in diffusion cell. Cincole clearly increased drug permeation across the skin. ER being 82.87 (Table 1).

Partitioning results are also given in Table I. Treatment of skin with Cineole used generally increased partitioning (more than double) of the drug into the skin as illustrated by the partition ratio, P_R, where:

$$ER = \frac{P_c \text{ after enhancer treatment}}{P_c \text{ with treated skin}}$$

Using the experimentally determined partition coefficients, a diffusion coefficient (D) of 5-FU in skin may be calculated by.

$$D = \frac{K_p.h}{P_c}$$

Where K_p is the mean permeability coefficient and h is the thickness of hydrated stratum comeum (taken as 3×10^{-3}). From diffusion coefficient value it can be seen that use of enhancer has increased the resistance to the diffusion of the drug as mean untreated diffusion coefficient value of 5-FU is $6.76\pm0.4\times10^{-5}$ cm^2/h only.

The solubility of 5-FU in Cineole, as determined, is about 0.43mg/ml. 5-FU is much less soluble in enhancer than in donor phase, water. Solubility of 5-Fu in water is 12.5 mg/ml.

Some essential oils and their *terpene* constiuents have recently been investigated as potential

enhancers. Eucalyptus oil have been used to promote the percuteneous absorption of nicotine (E.S., Newayser., 1998), 5-FU (A.C., William, 1989) and Cineole of benzocaine, procaine, bupranolol, indomethacin, dibucaine and 5-FU (A., Osol, 1980). In present study Cineole was found very active, no any lag time was observed. The enhancer increased the penetration of 5-FU by approx. 83 fold. The partition ratios calculated suggests that the enhancer increase partition of the drug into skin. As the drug is less soluble in enhancer than water, therefore this increased partition of drug may be retention of the drug by skin, as in this study full thickness skin was used to determine drug contents. Therefore enhanced permeation of 5-FU may not only by increasing the partition of the drug into stratum comeum, but also by modifying intercellular lipids, disrupting their highly ordered structure, thus increasing the diffusion of the drug through skin, as observed by comparatively increased diffusion coefficient values.

This study has shown that the cineole may offer a large and useful selection of relatively safe penetration enhancer to aid topical drug delivery. However further studies are required to make the use of cineole as such or in combination with other enhancers in Pharmaceutical preparations.

Table I

Mean Flux, Permeability Coefficient (KP), Enhancement ratios (ER), partition coefficient, (PC) partition ratios, and Diffusion coefficients, with SD, of 5-FU into fully hydrated skins: n=3

Enhancer	Flux $\mu g/cm^2/h$	KP cM/hx10^-3	Er	PC x10 ^-3	PR	D cm/hx10 ^-3
Control	13.0±0.28	1.053±0.02	--	46.94±4.3	1	6.7±0.4
Cineole	223.7±12.4	87.8±0.19	82.87	115.4±5.3	2.45	25.3±1.5

Sheet I

Time (H)	0	0.5	1	2	3	4	6	9	12	18	24
Control	0	0	0	0	0	0	0.32	0.065	0.105	0.174	0.27
Cineole	0	0.608	1.219	2.394	3.733	4.856	7.195	8.594	9.402	11.18	13.59

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