PREPARATION AND EVALUATION OF 5, 9-DIMETHYL-2-CYCLOPROPYL-2-DECANOL AS A PENETRATION ENHANCER FOR DRUGS THROUGH RAT SKIN

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ABSTRACT

In the present study a new alcohol derivative of tetrahydrogeraniol (THG), an acyclic monoterpene, has been prepared by using Grignard reagent and methyl cyclopropyl ketone. Penetration enhancing effects of THG and the synthesized derivative 5,9-dimethyl-2-cyclopropyl-2-decanol (DICNOL) on the transdermal penetration of 5-fluorouracil (5-FU) and tramadol hydrochloride (tramadol HCl) across the excised rat skin were studied by an *in vitro* permeation technique using Franz diffusion cells. Azone was used as standard enhancer for comparison. DICNOL and THG significantly enhanced 5-FU and tramadol HCl penetration through rat skin compared with the control. DICNOL enhanced the permeability of 5-FU and tramadol HCl across full thickness skin by about 11 and 20 fold, respectively. Increased partition coefficient and diffusion coefficient values were obtained by these enhancers. The results suggest that the amount of DICNOL in the skin, especially in the stratum corneum, may be related to its penetration enhancing effects.

Keywords: Preparation of 5,9-Dimethyl-2-Cyclopropyl-2-Decanol; Tetrahydrogeraniol; Permeation enhancers; 5-Fluorouracil; Tramadol Hydrochloride.

INTRODUCTION

Recently there has been an increasing interest in using the skin as a port of entry into the body for the drug delivery of therapeutic agents. However, the upper layer of the skin, the stratum corneum (SC), poses a barrier to the entry of many (therapeutic) entities. Thus a key hurdle in the development of transdermal drug delivery systems is achieving a drug flux that is high enough for therapeutic applications without damaging the skin. To overcome this, considerable effort has been applied to identifying flux enhancers. Selection of a flux enhancer is based on the permeation of the therapeutic toxicological profiles. A stable formulation that is amenable to system design is also an important consideration (Hansen *et al*., 1997). Recently, a novel series of penetration enhancers, classed as terpenes or terpenoids has been described (Femenía *et al*., 2005; *Ghafourian et al.,* 2004; Lim *et al*., 2006; William and Barry, 1989). These chemicals may provide a series of safe, naturally occurring penetration enhancers whose toxicities are well documented. Tetrahydrogeraniol (THG) is an acyclic olefinic monoterpene alcohol found in essential oil of geranium, intermediate in terpene synthesis, especially α-tocopherol side chain. It is easily available, convenient and stable in synthesis. It has saturated structure without any double bond and may possess possible enhancing effects.

5-Fluorouracil is a fluorinated pyrimidine antimetabolite. It is sparingly soluble in water; slightly soluble in ethanol; practically insoluble in chloroform, ether and benzene. It is structurally similar to uracil, one of the necessary building blocks in cellular division and growth. Its usefulness is based on uracil being utilized preferentially for nucleic acid biosynthesis in some tumors. Several terpenes have been shown to be effective accelerants for the hydrophilic cytotoxic drug, 5-fluorouracil (William and Barry, 1991a). Tramadol-HCl, a synthetic analgesic, is a white crystalline drug freely soluble in water.

As far as our knowledge is concerned, no one has studied THG as a skin permeation enhancer. Keeping in view the above mentioned points, we synthesized, characterized and evaluated new derivatives of THG as permeation enhancers. The instant study presents the synthesis and effects of 5, 9-dimethyl-2-cyclopropyl-2-decanol (DICNOL), a tetrahydrogeraniol (THG) derivative, on transdermal permeation of 5-FU and tramadol HCl through excised rat skin. The permeation enhancement found with THG and DICNOL was compared with Azone.

MATERIALS AND METHODS

Materials

THG was purchased from Nanjing Perfume Factory and was purified up to contents of 99.9%. Tramadol HCI was obtained from Shi Jia Zhuang No.l Pharmaceutical Factory, 5-FU from Shanghai 12th Pharmaceutical Manufacturing Factory, α-cetyl-γ-butyrolactone from Nantong Pharmaceutical Manufacturing Factory, and Azone was purchased from Guangzhou Zhuji Chemical

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Factory (China). All other chemicals and reagents used were of analytical grade obtained commercially. The Male white rats (Sprague Dawley) were obtained from the Animal House of the Pharmacy Department, University of Peshawar.

Methods of Tetrahydrogeraniol

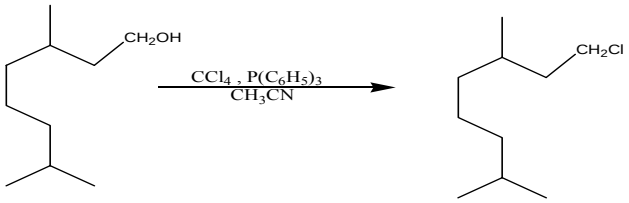
Ten ml of commercial tetrahydrogeraniol (THG) was mixed with 10g of dried silica gel and poured into a droplet column containing 90g of dried silica gel. A boiling chip and 250ml of petroleum ether (60~90°C) were added in a 500ml two-necked flask fitted with a column and a condenser, and connected to the droplet column. The whole assembly was placed on a thermostat and heated. The temperature was adjusted when petroleum ether started boiling (50 °C). Petroleum ether evaporated after boiling and mixed with THG and silica gel of the column and washed the impurities down. Within 25~30 minutes, all the impurities from the THG were washed down, as examined by TLC. In another two-necked flask, 250ml of acetone was taken and replaced with the pet ether flask. Acetone took about two hours to wash down the THG from the silica gel. Acetone was evaporated by rotary evaporator and THG was washed with distilled water under reduced pressure. The purified alcohol (99.9 %), b.p. 112°C/ 1066 Pa was homogeneous as determined by the TLC and GC.

Characterizations

IR spectra were obtained with Perkin Elmer 983 spectrometer. NMR spectra were recorded on PMX-60si instrument. Mass spectra were obtained with ZAB-HS-VG analytical organic mass spectrometry. Gas chromatography was performed with Shimadzu gas chromatographer GC 9A.

Preparation of tetrahydrogeranyl Chloride ($C_{10}H_{21}Cl$)

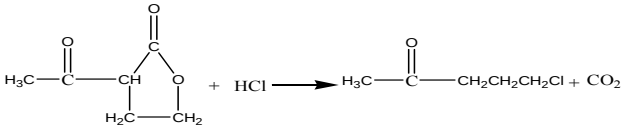
Tetrahydrogeranyl chloride was prepared in the same manner as described in our previous report (Hanif *et al.*, 1998). Briefly, TGH 56 ml (47.04 g, 0.30 mol), dry acetonitrile 150 ml and triphenylphosphine 100 g (0.38mol) were mixed and shaken vigorously at 25°C for 6 h and left overnight. Solvent was removed and the oily precipitate was filtered off with petroleum ether through a column containing dried silica gel. Petroleum ether was evaporated and the oil obtained was distilled to give purified tetrahydrogeranyl chloride; yield: 42 g (80%).



Scheme 1: Preparation of tetrahydrogeranyl chloride

Preparation of 5-Chloro-2-Pentanone

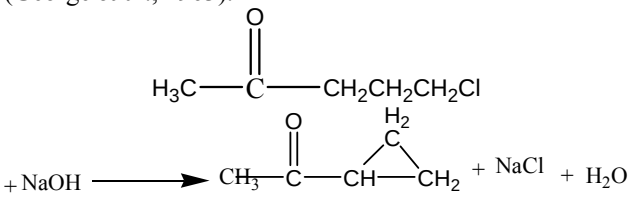
A mixture of 90ml of concentrated HCl, 105ml of water and 76.8 g (0.6mol) of α-cetyl-γ-butyrolactone and a boiling chip were placed in a 500ml distilling flask fitted with a condenser and a receiver immersed in an ice-water bath. Carbon dioxide was evolved immediately. Heating of the reaction mixture does not foam into the condenser. Within 10 minutes, the cooler changed from yellow to orange to black, the effervescence begins to subside and distillation commences. After collection of 180ml of distillate, 90ml of water was added to the distilling flask and another 60ml of distillate was collected. The yellow organic layer from the distillate was separated and the aqueous layer was extracted with 30ml of ether thrice. The ether extracts were combined with organic layer and dried for 1 h over calcium chloride. Saturated calcium chloride layer was formed in the bottom. Ether was decanted and dried with additional calcium chloride. Ether was removed by distillation. The residual crude was 5-chloro-2-pentanone (George *et al*., 1963).



Scheme 2: Preparation of 5-chloro-2-pentanone

Preparation of Methyl Cyclopropyl Ketone

A 250 ml three-necked flask was fitted with a sweep-type stirrer made of iron rod, a reflux condenser and a dropping funnel. A solution of 18 g (0.45 mol) of sodium hydroxide pellets in 18 ml of water was placed in the flask and 36.15 g (34.2 ml, 0.3 mol) of the crude 5-chloro-2-pentanone was added over a period of 15-20 minutes. Boiling was initiated by heating the flask on a thermostat for about 1 h. 37 ml of water was added slowly to the reaction mixture over a 20 minutes period and the mixture was heated under reflux for an additional hour. The condenser was arranged for distillation and a water-ketone mixture was distilled until all the organic layer was removed from the reaction mixture. The aqueous layer of the distillate was saturated with potassium carbonate and the upper layer of methyl cyclopropyl ketone was separated. The aqueous layer was extracted with 15 ml of ether thrice. The ether extracts and ketone layer were combined and dried over calcium chloride. The ether solution was evaporated and the dried ether solution was distilled to give methyl cyclopropyl ketone (George *et al*., 1963).

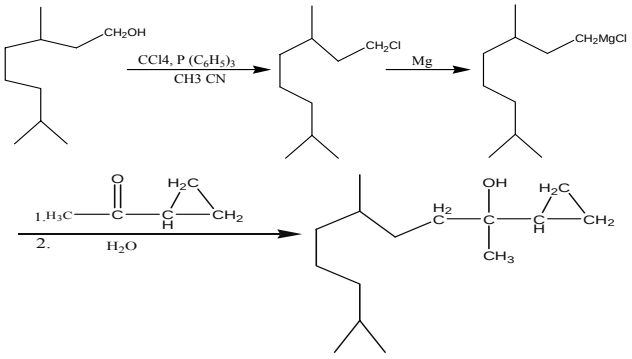


Scheme 3: Preparation of methyl cyclopropyl ketone

Preparation of 5,9-Dimethyl-2-Cyclopropyl-2-Decanol ($C_{15}H_{30}O$)

5, 9-dimethyl-2-cyclopropyl-2-decanol (DICNOL) was synthesized by the preparation of Grignard reagent (Brain *et al*., 1989). 3.5g of magnesium turnings, 6 ml of anhydrous ether and a crystal of iodine were placed in a 500ml four-necked flask. 25.6g (0.145mol) of tetrahydrogeranyl chloride and 100 ml of anhydrous ether were taken in a dropping funnel and dropped slowly into the reaction mixture and stirred. An appropriate water bath was used for heating to reflux. 12.5g (0.148mol) of methyl cyclopropyl ketone and 100 ml of anhydrous ether were taken in the dropping funnel and dropped slowly into the reaction mixture. Reaction was continued for further 6 h; after that we stopped stirring and added saturated solution of ammonium chloride for hydrolysis, until the water layer became clear. We separated the upper oily layer and the lower aqueous layer was extracted with ether thrice. Ether was then evaporated under water aspirator pressure. The oily product was distilled to give 5, 9-dimethyl-2-cyclopropyl-2-decanol (DICNOL) (Brevet of Invention, 1960):

Yield: 15.1 g (58.98%), b.p. 124~125 ^{o}C.
IR (neat) γ 3420, 1150, 2940, 1460, 1380, 1370, 3002, 1020 cm^{-1};
H^1-NMR ($CDCI_3$) δ (PPM) 0.38 (4H, m, $2CH_2$), 0.83-091 (9H, d, J=6.1 Hz, $3CH_3$); 1.00 (3H , s, CH_3), 1.30 (1H, s, OH- D_2O disappearing on deuterium exchange), 1.22-1.60 (1311,m, 3CH, $5CH_2$); MS m/e No M^+, 206 (M-18, 6.2%), 95, 67.



Scheme 4: Synthesis of 5,9-dimethyl-2-cyclopropyl-2-decanol.

Permeation membrane

Male white rats (Sprague Dawley) weighing 150~250 g were sacrificed by a sharp blow on the back of head. Hairs from the abdominal side were carefully clipped, without damaging the underlying skin. Full thickness skin was excised from the abdomen; subcutaneous fat and other extraneous tissues were trimmed. The skin sections were then checked for integrity before subsequent storage in a frozen state (−80 °C) before use. The samples were thawed at room temperature and then floated on normal saline for 12 h before use to ensure full tissue hydration.

In vitro percutaneous penetration

The *in vitro* penetration experiments were performed by mounting fully hydrated skin samples in Franz diffusion cells (PermeGear, Bethlehem, PA, USA), exhibiting a diffusion-available surface area of 0.64 cm^2 and a receptor compartment volume of 5.3 ml. Receptor cells were filled with isotonic normal saline solution that had been degassed by sonication for 5 min (Camlab Transsonic T310, Cambridge, UK). The receptor fluids were stirred at 600 rpm and maintained at 37 ± 0.5°C by the use of a thermostatic water pump (Haake DC10, Karlsruhe, Germany) that circulated water through each chamber jacket. The membranes were initially left in the Franz cells for 12 h in order to facilitate hydration. Subsequently, 1 ml of donor solution was deposited on to each membrane surface. The donor solution consisted of either the saturated solution of 5-FU or tramadol HCl in water. Each donor compartment was covered with a tight layer of Parafilm® in order to minimize evaporation. At appropriate intervals, suitable volumes of the receptor medium was withdrawn and replaced with an equal volume of fresh medium. Diffusion experiments were carried out for 24 h.

To determine the enhancing effect of THG, its derivative DICNOL and Azone, the skins were prepared in the same way and mounted between donor and receptor cells, but in this case the donor cell receives 150 µl of THG, DICNOL or Azone. After 12 h, the excessive enhancer was removed by swabbing with tissue paper and replaced with 1 ml of saturated solution of 5-FU or tramadol HCl solution. Samples were withdrawn and analyzed spectrophotometrically at a wavelength of 266 nm and 271 nm for 5-FU and tramadol HCI, respectively. Blank samples were also run simultaneously and were used as the control for the experiment.

Amount of 5-FU and tramadol HCI in the skin was determined as described in our previous report (Hanif *et al*., 1997). At the end of experiment, the exposed skin was cut, washed carefully with water, blotted dry, weighed and homogenized with 4 ml of ethyl acetate thrice. The homogenates were mixed, filtered and ethyl acetate evaporated to dryness. The residue was reconstituted with 10 ml of water and analyzed for the drug contents.

Data analysis and estimation of permeation parameters

The steady-state flux of 5-FU and tramadol HCl was estimated from the slope of the straight line portion of the cumulative amount absorbed against time profiles. The steady-state permeability coefficient (Kp) was calculated from the flux (J) and the donor concentration (C) using the following expression (Yamane *et al*., 1995):

$$Kp = \frac{J}{C}$$

Enhancement ratio (ER) was then calculated by the following equation (Fuhrman *et al*., 1997):

$$ER = \frac{\text{Kp after enhancement treatment}}{\text{Kp from control}}$$

Apparent partition coefficient (Pc) was expressed by the following equation (Abdullah *et al.*, 1996):

$$PC = \frac{\text{mg of the drug / mg of the skin}}{\text{mg of the drug / mg of the solvent}}$$

Partition ratio (PR) was calculated by the following equation (William and Barry, 1991b):

$$PR = \frac{\text{Pc after enhancer treatment}}{\text{Pc before enhancer treatment}}$$

Apparent diffusion coefficient (D) was calculated by the following equation (William and Barry, 1991b):

$$D = \frac{Kp.h}{Pc}$$

Where Kp is the mean permeability coefficient, Pc is the mean apparent partition coefficient and h is the thickness of the hydrated skin (taken as 3 x 10^{-3} cm). The relative diffusivity ratio (DR) was expressed by the following equation (William and Barry, 1991b):

$$DR = \frac{\text{Diffusion coefficient of drug after treatment}}{\text{Diffusion coefficient of drug before treatment}}$$

RESULTS

5,9-Dimethyl-2-cyclopropyl-2-decanol was synthesized by tetrahydrogeranyl chloride (obtained by the reaction of THG with acetonitrile, triphenylphosphine and carbon tetrachloride) with Grignard reagent and methyl cyclopropyl ketone. The *in vitro* permeation profiles of 5-FU and tramadol HCl are shown in figs. 1 and 2, respectively. The values of permeation parameters obtained in the study are given in tables 1 and 2 for 5-FU; tables 3 and 4 contain the corresponding data for tramadol HCl. In almost all cases, THG as well as DICNOL caused the flux of both drugs to be significantly enhanced over the controls.

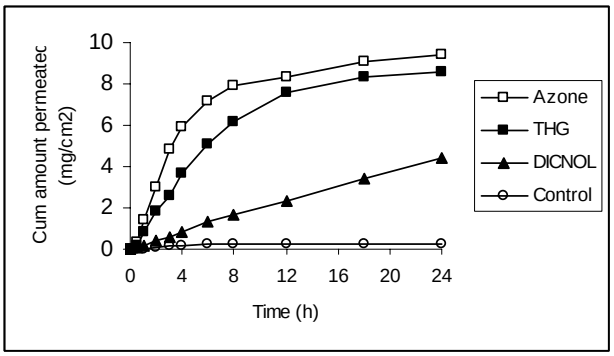


Fig. 1: Time course of the mean permeated amounts of 5-FU in the presence of DICNOL, TGH and Azone. Each point represents the mean ± SD of 5 to 10 determinations.

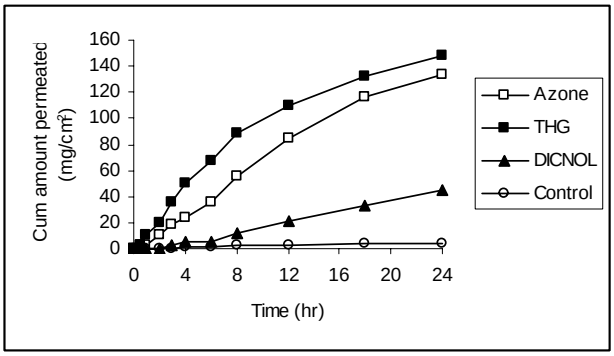


Fig. 2: Time course of the mean permeated amounts of tramadol HCl in the presence of DICNOL and THG. Each point represents the mean ± SD of 4 to 6 determinations.

Table 1 shows the permeation parameters viz. mean fluxes (J), apparent permeability coefficients (Kp), lag-time (LT), steady-state permeation time (SST), and enhancement ratios (ER) of 5-FU before and after treatment with THG, DICNOL and Azone (n = 5~10,

Table 1: Mean fluxes (J), permeability coefficients (Kp), lag-time (LT), steady-state time (SST), and enhancement ratios (ER) of 5-FU before and after treatment with DICNOL, THG, and Azone (n = 5~10, mean ± SD)

Enhancers	Flux µg / cm^2.h	Kp cm / h × 10^{-3}	LT hr	SST hr	ER
Control	18.13±1.35	1.450±0.10	4.0	18.0	----------
DICNOL	204.9±43.49	16.37±3.48	0.5	24.0	1130±*2.40*
THG	875.1±70.14	70.01±5.60	0.1	6.0	48.30±3.87
Azone	1498±90.09	119.9±7.21	0.1	4.0	82.72±4.97

Table 2: Mean apparent partition coefficients (Pc), apparent diffusion coefficients (D), partition ratios (PR) and diffusion ratios (DR) of **5-FU** into fully hydrated skin (n = 5~10, mean ± SD)

Enhancers	Pc x 10^{-3}	D cm^2 / h × 10^{-3}	PR	DR
Control	34.43±4.70	0.135± 0.02	----	----
DICNOL	93.25±8.41	0.53±0.11	2.71	3.93
THG	65.36±4.28	2.89±0.55	1.90	21.50
Azone	92.03±6.54	3.93±0.47	2.70	29.21

Table 3: Mean fluxes (J), permeability coefficients (Kp), lag-time (LT), steady-state time (SST), and enhancement ratios (ER) for tramadol HCl in the absence and presence of DICNOL and THG (n = 4~6 mean ± SD).

Enhancers	Flux µg / cm^2.h	Kp cm / h × 10^{-3}	LT hr	SST hr	ER
Control	60.41± 8.29	0.20± 0.03	6.0	15	----
DICNOL	2075.04± 325.42	4.15± 0.65	4.4	15	20.44± 3.21
THG	11133.21± 1101.93	22.27± 2.20	0.2	6.0	109.7± 10.86
Azone	9449.33±1296.17	18.90± 2.59	0.2	6.0	93.04±12.88

Table 4: Mean apparent partition coefficient (Pc), apparent diffusion coefficients (D), partition ratios (PR) and diffusion ratios (DR) of tramadol HCl into hydrated skin (n=4~6, mean ± SD).

Enhancers	Pc	D	PR	DR
	x 10^{-3}	cm^2 / h × 10^{-3}		
Control	5.77± 0.42	0.11±0.02	-----	-----
DICNOL	12.39± 1.54	1.03± 0.27	2.15	9.72
THG	47.50± 3.37	1.41± 0.11	8.23	13.27
Azone	21.25±3.36	2.67±0.42	3.72	25.17

mean ± SD). As shown in Table 2, treatment of the skin with these enhancers increased the partitioning of the drug into the skin as the mean untreated (control) apparent partition coefficient value of 5-FU is 34.43± 4.70 x10^{-3} only.

As shown in fig. 1, THG was found to cause about 45 fold ($P<0.01$) increase in permeability coefficient of 5-FU. Azone increased it by about 83 fold and DICNOL increased the permeation of 5-FU about 11 fold ($P<0.01$) with a lag time of 30 minutes. The steady-state permeation of 5-FU was observed for 24 h when DICNOL was used as enhancer, while with THG and Azone the steady-state conditions were observed for only 6 and 4 hrs, respectively. The steady state time calculated from penetration experiments apparently relate inversely proportional to the enhancement ratios. As the enhancement ratios increase the corresponding steady state times decrease.

The control values for J and Kp of tramadol HCl in the untreated skin at 37±0.5°C are 60.41±8.29 g/cm^2.h and 0.20±0.03 × 10^{-3} cm/h with a lag time of 6 h respectively. When the skin was treated with DICNOL, no significant effect on lag time was found. It was observed to be 4 h, while with THG, the lag time falls to 10~15 minutes (Table 3). The steady-state conditions were observed for 15 h when DICNOL was used as enhancer, which was probably due to its slow penetration into the skin.

From table 4 it can be seen that both the enhancers has decreased the resistance to the diffusion of tramadol HCl as the mean untreated apparent diffusion coefficient value of the drug is 0.11± 0.02 x 10^{-3} cm^2 /h only.

DISCUSSION

Generally, the skin is considered as a heterogeneous structure, composed of a comparatively lipophilic stratum corneum and hydrophilic viable skin (epidermis and dermis). Therefore, for hydrophilic penetrants, partitioning into the stratum corneum becomes the rate-determining step of skin permeation (Cheon, 1996). Usually, a non-human skin membrane that is sufficiently similar to the human integument is needed so that it might be substituted for human skin in cases of *in vitro* percutaneous absorption and topical bioavailability studies. We have used the Sprague Dawley (SD) rat skin as model membrane for the permeation studies.

The present study was carried out to investigate the penetration enhancing effect of THG and its synthetic derivative viz. DICNOL on the permeation of 5-FU and tramadol HCl through excised rat skin. DICNOL is a THG derivative and was synthesized by the addition of methyl cyclopropyl group on the functional moiety of the hydroxyl group of TGH. THG is an important constituent of Otto of rose, geranium Indian or Turkish geranium and oil of ylang-ylang (Evans, 1989). According to Williams and Barry (1989b) oil of ylang-ylang shows less penetration enhancing activity towards 5-FU with an enhancement ratio of approximately 8; while in our studies its terpene constituent THG increased the penetration of the polar drug, 5-FU, by about 48 ($P<0.01$) fold without any lag-time. The penetration enhancing effects of THG and its new derivative DICNOL were compared to the control and Azone by an *in vitro* penetration technique using excised rat skin and Franz Diffusion cells. Azone caused approximately 83 fold

increase in drug flux and shows good agreement with literature values. It has been reported that Azone caused a 100 fold increase in 5-FU flux across hairless rat skin (Morimoto *et al*., 1986). Although the permeation enhancing effect of THG and its derivative DICNOL was found to be less than that of Azone, however, both the THG and DICNOL significantly enhanced 5-FU penetration through rat skin as compared to the control; moreover, being natural product they may offer a large and useful selection of relatively safe and affective penetration enhancers to aid topical drug delivery. In case of model drug tramadol HCl, the enhancing effect of THG was about 110 fold ($P<0.01$). Azone increased the tramadol HCl flux by 93 fold ($P<0.01$) and DICNOL increased it by 20 fold ($P<0.01$).

The partition and diffusivity ratios calculated suggest that these enhancers increase partition and diffusion of 5-FU and tramadol-HCl into the rat skin. In this study, the role of partitioning phenomenon in the increased drug permeation is less clear. As both drugs are less soluble in enhancers than water, hence a decrease in drug-tissue partitioning after enhancer treatment might be expected. One possibility could be due to the retention of the drugs by the skin, as in this study full-thickness skin was used, while determining drug content. So we can conclude that the increased partition of 5-FU and tramadol HCl cannot be contributed to the solubility of the drugs in enhancers rather it could be due to the structure modification of stratum corneum lipid-bilayers.

The diffusivity ratios calculated from permeation experiments apparently relate linearly to the enhancement ratio, suggesting that the enhanced permeation of the drugs may not only be increasing the partitioning of drug into stratum corneum but also by modifying intracellular lipids, disrupting their highly ordered structure to increase diffusivity ratios (tables 2 and 4). This is in contrast to the results of Chow *et al*. who found that long chain fatty acids had no effect on the diffusivity of hydrocortisone through hairless rat skin and that enhancement entirely arose from partitioning phenomenon (Chow *et al*., 1988). However, 5-FU and tramadol HCl are hydrophilic; with lipophilic enhancers, partitioning phenomenon may be more important in the acceleration of more lipophilic drugs.

These enhancers may act by disrupting the lipid structure of the stratum corneum, thereby increasing the diffusion coefficient of drugs in the membrane as observed by the increased diffusivity ratios calculated from permeation studies (tables 2 and 4). Walker and Smith (1996) suggested that alcohols may influence transdermal penetration by a number of ways, including the enhancement of drug solubility in the stratum corneum and its disruption through extraction of biochemicals by the more hydrophobic alcohols. It is also known that lipid like structures pack tightly together by a mixture of long and short chain lipids or saturated and unsaturated lipids form loosely organized structures (Small, 1984). The most abundant SC lipids are free fatty acids, triglycerides, cholesterol and ceramides. The majority of these lipids, including the free fatty acids have 16 or more carbon atom hydrophobic groups. So one could hypothesize, therefore, that introduction of shorter alcohol chains disrupt the crystalline lipid packing and results in a more fluid and permeable membrane. A general feature of our investigation is the somewhat poor correlation between diffusion- and partition coefficients calculated from permeation experiments. Such mismatches are common in skin work.

CONCLUSIONS

The results from this investigation show that the acyclic monoterpene, tetrahydrogeraniol (THG) and its new alcoholic derivative 5,9-dimethyl-2-cyclopropyl-2-decanol (DICNOL) have the potentials to enhance the percutaneous penetration of 5-FU and tramadol HCl. These results also suggest that natural products such as THG and its derivative DICNOL may offer a useful selection of relatively safe penetration enhancers to aid topical drug delivery.

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