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Altered skin permeation of a highly lipophilic molecule: tetrahydrocannabinol

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Summary

The effect of decylmethylsulfoxide (decylMSO) and oleic acid on the skin permeation of the highly lipophilic compound, tetrahydrocannabinol (THC), was investigated. The solvents were propylene glycol (PG)–ethanol (EtOH) and PG–EtOH–H_2O mixtures. For comparison, similar compositions containing the hydrophilic drug 5-fluorouracyl (5FU) were also tested. Twenty-four-hour experiments were performed with diluted solutions of the drugs in Valia-Chien diffusion cells through hairless mouse skin. The results were treated using the Transderm computer program. The results show that the permeability coefficient of THC was: (1) increased by an order of magnitude by water; (2) increased 6 times by 3% oleic acid in PG–EtOH solutions; (3) increased fourteen times by 3% oleic acid in PG–EtOH–H_2O solutions; (4) not affected by decylMSO in PG–EtOH solutions; and (5) decreased 25% by decylMSO in PG–ETOH–H_2O solutions. A different behavior was observed when similar systems containing the hydrophilic 5FU were tested. The permeability coefficient of 5FU was: (1) not affected by presence of water; (2) not affected by oleic acid; (3) not affected by decylMSO in PG–EtOH; and (4) increased 14 times by decylMSO in PG–EtOH–H_2O. These results emphasize that the selective effect of an enhancer is the result of a tridimensional interaction between the drug, the skin, and the enhancer, in a specific environment.

Introduction

Few data related to the effect of enhancers on the skin permeation behavior of highly lipophilic molecules have been reported in the literature (Cooper, 1984; Barry, 1985). The aim of the present investigation was to learn the effect of enhancers on the permeation of tetrahydrocannabinol (THC). THC was selected for the following reasons: (a) THC (Fig. 1) is an excellent model for very lipophilic drugs since it has a water solubility of 2.8 μg/ml and a partitioning coeffi-

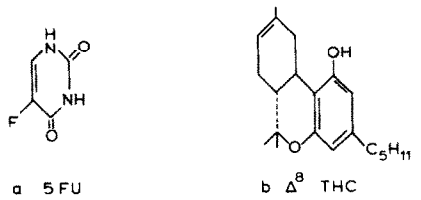

Fig. 1. Chemical structure of: (a) 5-fluorouracyl and (b) Δ^8-tetrahydrocannabinol.

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cient, K_m, (octanol/water) of 6000; and (b) in a recent investigation we have shown that THC is a good candidate for transdermal administration as an antiemetic in cancer chemotherapy (Touitou et al., 1987).

This work focuses on the effect of two enhancers, decylmethyl-sulfoxide (decylMSO), a non-ionic surfactant, and oleic acid, a long-chain unsaturated lipophilic compound, on the skin permeability coefficient of THC from aqueous and non-aqueous solutions of propylene gylcol. Experiments were carried out in an assembly of Valia-Chien diffusion cells.

In order to compare the permeation behavior of the lipophilic THC to a hydrophilic drug, experiments on the skin permeation of 5-fluorouracyl (5FU) in the above-described systems were also performed. 5-FU (Fig. 1) has a water solubility of 12 mg/ml and a partitioning coefficient (octanol/water) of 10^{-2}.

Materials and Methods

Materials

Δ^8-THC was a gift from the laboratories of Professor R. Mechoulam (Hebrew University, Jerusalem). Tritiated Δ^8-THC with a specific activity of 14.8 Ci/mmol and a concentration of 1 mCi/ml was a custom preparation from Kamag-Dimona, Israel. Other materials used were: decylmethylsulfoxide (Cyclo), 5-fluorouracil and propylene glycol (Sigma); 5-fluoro-[6-^{3}H]uracyl with a specific activity of 800 mCi/mmol and a radioactive concentration of 1 mCi/ml was supplied by Amersham (U.K.). The following vehicle compositions were used: propylene glycol (PG)/ethanol (EtOH) 1 : 1 and PG–EtOH/H_2O (7 : 3).

Skin permeability measurements

The experiments were carried out using PG–EtOH and PG–EtOH/H_2O solutions containing either THC or 5FU. Aqueous solutions contained 30% water. The drug concentration used was 0.2 μg/ml, which is below the saturation point of each drug in PG–EtOH. In order to test whether Fick's law is obeyed in these systems, higher concentrations (up to 1 μg/ml drug) were prepared and their permeation courses were measured.

The Valia-Chien cell assembly was used to perform the experiments on permeation of THC and 5FU from various donor compositions through hairless mouse skin at 37 °C. Full thickness abdominal skin excised from 6-week-old male mice was mounted in cells with a surface area of 0.64 cm^2 and half-cell volume of 3 ml. The receiver compartments contained a 50% hydroalcoholic (H_2O/EtOH) solution for ensuring pseudo-sink conditions by increasing the solubility of THC in the medium. During the experiment (24 h), 100 μl samples were mixed with scintillation cocktail (Packard, U.S.A.) and assayed in the Kontron Betamatic Scintillation Counter (Lumitron Scientific Industries). The sample volumes were replaced with fresh solution. The results were treated using the "Transderm" computer program (Touitou and Wartenfeld, 1987).

Each experiment was triplicated. The two-tailed, unpaired Student's t-test was used for determining the statistical significance of the effect of enhancers or water on the permeability coefficient changes. For these analyses, the "Balance" (IBM) computer program was used.

Results

Permeation curves of the cumulative amount of drug that permeated the skin as a function of time were plotted using the "Transderm" program. The curves showed the characteristic skin permeation course: a linear dependency indicative of a steady-state process following a lag time period. The printouts gave the kinetic parameters such as fluxes, permeability coefficients (K_p), lag times, and diffusion coefficients (Touitou and Wartenfeld, 1987). When fluxes vs concentration was plotted, a linear relationship was observed, which indicates that Fick's law is obeyed in these systems. Flux and permeability coefficient values were used in this work to evaluate and compare the skin permeation behavior of the drugs from systems with and without enhancing agents.

THC and 5FU in PG–EtOH solutions without any enhancing agent exhibit relatively low permeation profiles, the calculated K_p reaching values of 9.9×10^{-4} and 2.8×10^{-3} cm · h^{-1}, respec-

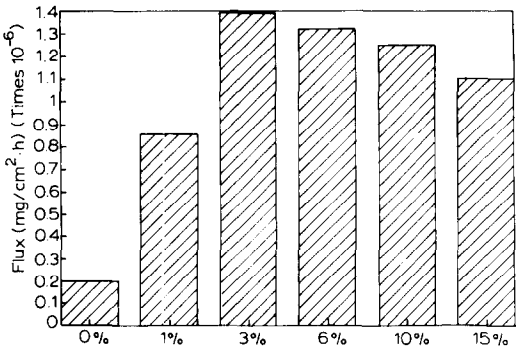

Fig. 2. Effect of oleic acid concentration on the steady-state fluxes of THC through hairless mouse skin from PG–EtOH solutions containing 0.2 μg/ml drug.

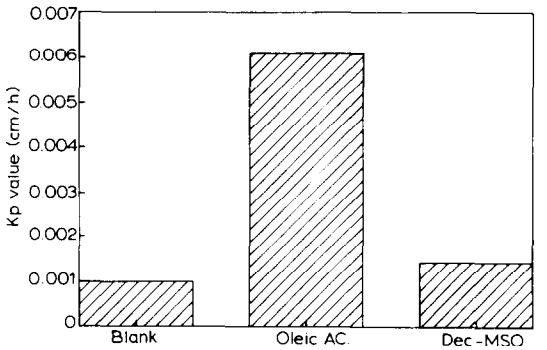

Fig. 3. Effect of oleic acid and decylMSO on the skin permeability coefficient (K_p) of THC in PG–EtOH solutions.

tively. Oleic acid and decylMSO were tested for their potential to improve the skin permeation of these drugs.

In order to choose the optimal concentration of oleic acid as an enhancing agent for THC systems, a series of experiments was conducted with solutions containing oleic acid in a concentration range of 1–15%. THC permeation flux versus oleic acid concentration histograms are given in Fig. 2. A low but statistically significant ($P < 0.01$) increase in flux was seen at 1% oleic acid. The greatest enhancement was measured with oleic acid within the range of 3–10%. The maximum increase in flux was 7-fold relative to THC in PG–EtOH solutions without oleic acid. For example, the flux of a solution containing 0.2 μg/ml THC increased from $1.9\text{–}10^{-7}$ to 13.8×10^{-7} mg · cm^{-2} · h^{-1}. It is interesting to note that statistically, no significant difference was found between the systems containing 3%, 6% and 10% oleic acid. Thus, we have selected 3% (the lowest) as the optimal concentration for continuing this investigation. For decylMSO systems, 1% was the concentration chosen based on our previous studies (Touitou, 1987).

The effect of oleic acid and decylMSO on the permeability coefficients of THC from PG–EtOH solutions is presented in Fig. 3. The histograms clearly indicate that decylMSO does not affect the skin permeation of unsaturated solutions of THC in PG–EtOH. On the other hand, in the presence of oleic acid, the K_p value increased 6-fold, from 9.9×10^{-4} to 6.2×10^{-3} cm · h^{-1}. In order to compare these results with systems containing 5FU, experiments on the effect of oleic acid and decylMSO on the permeation of 5FU in PG–EtOH solutions with compositions similar to the THC systems were performed. The effect of both oleic acid and decylMSO on the permeation of THC versus 5FU is presented by the histograms in Fig. 4. The results show that neither of the two agents tested was effective in increasing the permeation of 5FU from PG–EtOH solutions.

Changes in the vehicle composition may affect the thermodynamic activity of the drug and alter its permeation behavior. To examine this possibility, aqueous systems containing 30% water were prepared and permeation experiments were carried out. For comparing the behavior of the two drugs, compositions containing 5FU were also tested. Fig. 5 illustrates the results of studies with

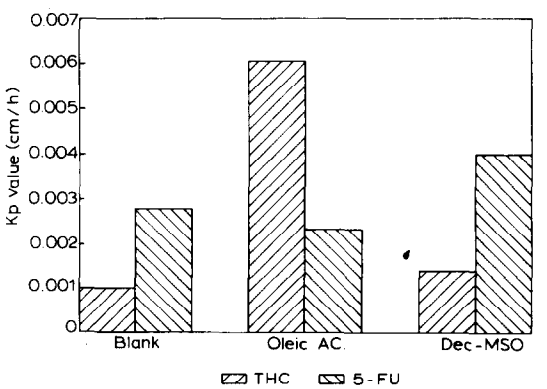

Fig. 4. Effect of oleic acid and decylMSO on the skin permeability coefficients (K_p) of THC and 5FU in PG–EtOH solutions.

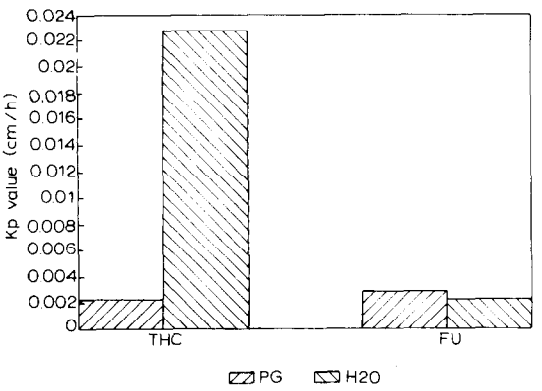

Fig. 5. Effect of water on the permeability coefficients (K_p) of THC and 5FU.

solutions containing 0.2 μg of either THC or 5FU in the vehicle from PG–EtOH/H_2O 7 : 3 without addition of oleic acid and decylMSO. The histograms show that the presence of water in the donor solution during the permeation experiments enhanced by more than 10-fold the K_p value of THC yet had no significant effect on the hydrophilic molecule, 5FU. It is also worthy to note that water drastically shortened the lag time preceding the steady phase in permeation courses of THC from almost 4.45 to 2.15 h.

The influence of oleic acid and decylMSO on skin permeation was also investigated in aqueous solution. The results presented in Fig. 5 and 6 indicate that both water and oleic acid enhanced the skin permeability of THC. However, the effect

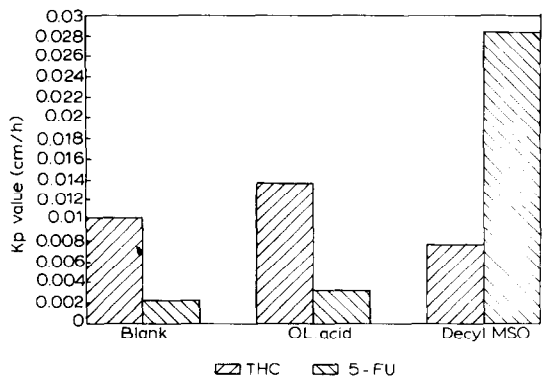

Fig. 6. Effect of oleic acid and decylMSO on the skin permeability coefficients of THC and 5FU from PG–EtOH solutions containing 30% water.

was not additive and only a 14-fold increase in K_p was measured, possibly due to a decrease in the oleic acid activity in aqueous solutions. On the ohter hand, decylMSO had a statistically significant ($P < 0.01$) decreasing effect on the K_p value of THC in aqueous solution, e.g. from 10^{-2} to 7.5×10^{-3} cm · h^{-1}. The histograms in Fig. 6 show that while the permeation coefficient of 5FU in aqueous solutions was unaffected by oleic acid, it was increased 14 times in the presence of decylMSO, i.e. 2×10^{-3} to 2.8×10^{-2} cm · h^{-1}.

Discussion

The effect of the non-ionic surfactant, decylMSO, and the long-chain unsaturated acid, oleic acid, on the highly lipophilic drug THC was investigated in parallel with solutions of the hydrophilic molecule 5FU.

THC in PG–EtOH solution exhibited a low skin permeability. Its K_p value was found to be 3 times lower than that of the hydrophilic drug, 5FU. This finding can be related to the drug's extremely high lipophilicity. THC is so lipid-soluble that it generates a reservoir in the stratum corneum, and the aqueous viable epidermis in which the drug is poorly soluble becomes a significant barrier. Its main portal of entry into the deeper layers of the skin appears to be via lipoidal pathways (Touitou et al., 1987).

The data obtained in the present investigation indicate that the action of these enhancers is selective. The results of the experiments carried out with unsaturated solutions of THC or 5FU in PG–EtOH show that oleic acid enhanced the THC skin permeability, whereas in identical experiments using 5FU instead of THC, no such enhancement was observed. The enhancing effect of oleic acid on THC was intensified in aqueous solutions.

DecylMSO had no effect on either THC or 5FU in PG–EtOH solutions. In aqueous solutions, however, a different behavior was observed. The permeability coefficients of THC were slightly (25%) decreased while those of 5FU increased by 14 times.

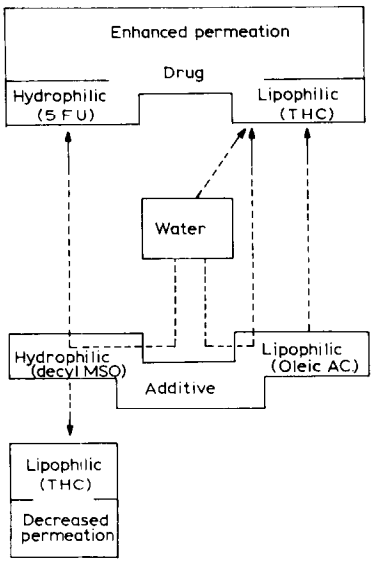

Fig. 7. Selective effect of oleic acid and decylMSO on the skin permeation of the lipophilic THC and the hydrophilic 5FU.

The selective alteration of the skin permeability to 5FU and THC by oleic acid and decylMSO is schematically presented in Fig. 7. To understand this phenomenon, the effect of these agents on both the skin and the drug is considered. Oleic acid in propylene glycol solutions was reported to affect the fluidity of lipidic components of the skin thus facilitating the permeation through lipidic pathways. Other molecules with some degree of lipophilicity like salicylic acid (unionized) showed increased skin permeation mediated by oleic acid (Cooper, 1984). The effect of water can be explained by a favorable change in the thermodynamic acitivity of THC in the aqueous donor solution rather than a hydration effect, since the above parameters that effect the permeation of the lipophilic molecule THC did not interfere with the permeation course of the hydrophilic compound, 5FU.

The effect of decylMSO may be explained as above, considering both the drug and the skin. The lack of effectiveness of decylMSO in non-aqueous solutions suggests that the surfactant is active in a micellar form in water. The surfactant micelles may solubilize lipidic components of the skin and interact with proteins of the stratum cornum (Dugard and Scheuplein, 1973), thus facilitating diffusion through the skin. On the other hand, in micellar solutions of decylMSO, lipophilic compounds such as THC may be entrapped in the hydrophobic core of the micelle, resulting in decreased drug availability to the skin (Touitou, 1987). A study by Dalvi and Zatz (1981) on the effect of non-ionic surfactants on penetration of dissolved benzocaine through excised hairless mouse skin showed that benzocaine permeation was reduced due to its micellar solubilization by the non-ionic surfactants. Another earlier study by Stolar et al. (1960) also reported a marked reduction in in vivo drug percutaneous absorption in the presence of non-ionic surfactants. The results obtained by these authors on salicylic acid skin permeation were explained by increased drug solubility in the vehicle and reduced partitioning of the skin. The decreased permeation of THC versus a significant increase in 5FU skin permeability in aqueous solutions containing decylMSO observed in the present work can be explained if we consider that the apparent permeability coefficient is in fact the result of a number of events, including the process of drug release on the skin surface and the transport through the skin.

DecylMSO may alter the percutaneous absorption by producing either change in the physical parameters of the drug or in the membrane structure. Thus, the rate-limiting step in the overall permeation process may shift from drug transport through the skin to drug release from the vehicle.

In conclusion, the skin permeation of the lipophilic compound THC was altered as follows: (1) enhanced by water; (2) enhanced by oleic acid in PG–EtOH or in PG–EtOH–H_2O; (3) unaffected by decylMSO in PG–EtOH; and (4) decreased by decylMSO in PG–EtOH. These results emphasize that the selective effect of an enhancer is the result of a tridimensional interaction between the drug, the skin, and the enhancer, in a specific environment. This concept is different from the model (Cooper, 1984) that directly relates the selective effect of enhancers to alterations of the lipophilic or hydrophilic structures of the skin without taking into consideration the contribution of the enhancer to a much wider range of processes.

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References

Barry, B.W., Optimizing percutaneous absorption. In Bronaugh, R.L. and Maibach, H.I. (Eds.), *Percutaneous Absorption*, Marcel Dekker, New York, 1985, pp. 489–511.

Cooper, E.R., Increased skin permeability for lipophilic molecules, *J. Pharm. Sci.*, 73 (1984) 1153–1156.

Dalvi, U.G. and Zatz, J.L., Effect of nonionic surfactants on penetration of dissolved benzocaine through hairless mouse skin. *J. Soc. Cosmet. Chem.*, 32 (1981) 87–93.

Dugard, P.H. and Scheuplein, R.J., Effects of ionic surfactants on the permeability of human epidermis: an electrometric study. *J. Invest. Dermatol.*, 60 (1973) 263–269.

Stolar, M.E., Rossi, G.V., and Barr, M., The effect of various ointment bases on the percutaneous absorption of salicylates. *J. Am. Pharm. Assoc. Sci. Ed.*, 49 (1960) 148–158.

Touitou, E., Skin permeation enhancement by *n*-decyl methyl sulfoxide: effect of solvent systems and insights on mechanism of action. *Int. J. Pharm.*, 43 (1988) 1–7.

Touitou, E., Fabin, B., Dany, S. and Almog, S., Transdermal Delivery of Tetrahydrocannabinol. *Int. J. Pharm.*, 43 (1988) 9–15.

Touitou, E. and Wartenfeld, R., Transderm. *Life Sci.*, 40 (1987) 1.