International Journal of Pharmaceutics, 43 (1988) 1–7
Elsevier

IJP 01437

Research Papers

Skin permeation enhancement by *n*-decyl methyl sulfoxide: effect of solvent systems and insights on mechanism of action

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(Received 6 August 1987)
(Modified version received 17 September 1987)
(Accepted 30 September 1987)

Key words: *n*-Decyl methyl sulfoxide; Skin permeation; Idoxuridine; 5-Fluorouracil; Azone; Enhanced permeability

Summary

n-Decyl methyl sulfoxide (decylMSO), was investigated for its permeation enhancement properties in aqueous and propylene glycol (PG) solutions in vitro through hairless mouse skin. 5-Fluorouracil (5-FU) and idoxuridine (IDU) were selected for this study because of their respective hydrophilic and hydrophobic characteristics. In aqueous solutions of decylMSO, a concentration-dependent enhancement was noted for both drugs. At a concentration of 1% decylMSO, 200- and 46-fold K_p increases were found for 5-FU and IDU, respectively. On the other hand, in PG solutions practically no enhancement was observed except at high concentrations, where a relatively small increase in the permeability coefficient occurred. In these systems maximum enhancement was measured at a concentration of 15% decylMSO, where K_p values increased for the respective drugs by only 7- and 10-fold. In contrast to decylMSO, Azone was very effective at increasing IDU permeation from PG solutions, even at concentrations as low as 0.5%; at 5% Azone, a maximum enhancement of 3 orders of magnitude was observed. These results point toward different mechanisms of action for Azone and decylMSO. DecylMSO activity in aqueous solutions may be related to its generation of micelles which solubilize lipophilic components in the skin, thus facilitating the transport of molecules. Lipophilic drugs may be entrapped in the surfactant micelles, leading to a decrease in drug availability.

Introduction

n-Decyl methyl sulfoxide (decylMSO) is a derivative of the homologue series of alkyl methyl sulfoxides reported to enhance skin permeability of chemicals (Sekura and Scala, 1972). DecylMSO was shown to increase penetration through the skin of methyl nicotinate and thiourea (Sekura and Scala, 1972), salicylate ion (Cooper, 1984), 5-fluorouracil (5-FU; Touitou and Abed, 1985) and naproxen (Chowhan and Pritchard, 1978). Clinically it was proven to enhance the skin penetration of tetracycline hydrochloride, generating a formulation that was effective in the treatment of acne (Wechsler et al., 1978). The enhancing effect of decylMSO was observed with concentrations ranging between 0.15% and 40% in various media; Chowhan and Pritchard (1978) reported that 1% decylMSO incorporated in an aqueous cream increased the flux of naproxen through various types of skin in vitro. Touitou and Abed (1985) found that only high concentrations

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of decylMSO (> 10%) were able to increase the skin permeation of 5-FU from propylene glycol (PG) systems.

Results were presented on increased penetration of salicylic acid at pH 9.9 and of urea, and only a slight effect was reported on salicylic acid permeability at pH 2.65 and on 1-pentanol (Cooper, 1984). These results were claimed to be related to a mechanism by which decylMSO alters mainly the polar pathway, and any possible alteration of the lipid route due to the presence of micelles in aqueous systems was completely ignored (Cooper, 1984).

DecylMSO is an amphiphilic molecule; thus, the medium used should be of major importance in determining the system behavior. No studies have attempted to evaluate the effect of solvents on the concentration-dependent decylMSO enhancement.

The purpose of the present work was to investigate the concentration-dependent enhancing properties of decylMSO in the presence of two media, water and propylene glycol, and to shed more light on the selective enhancement effect. Two molecules were selected as models for drugs having different lyophilic characteristics: 5-FU (hydrophilic) idoxuridine (IDU) (more hydrophobic). The permeation patterns and the kinetic parameters were determined in vitro, in the presence of various concentrations of decylMSO in aqueous and propylene glycol solutions, through hairless mouse skin. For comparison, the concentration-dependent enhancement effect of dodecylazacycloheptanone (Azone) on the skin permeation of IDU from propylene glycol solutions was also studied.

Materials and Methods

Materials

5-FU, IDU and PG were purchased from Sigma; decylMSO was supplied by Cyclo (U.S.A.). 5-fluoro-[6-^{3}H]uracil and [^{3}H]IDU with specific activities of 0.8 and 5 Ci/mmol, respectively, were obtained from Amersham. Their radioactivity concentration was 1 mCi/ml.

Dodecylazacycloheptanone (Azone) was a gift of Nelson Research (U.S.A.).

Methods

Skin permeation measurements

Permeation experiments were assessed using a horizontal diffusion cell assembly described previously (Touitou and Abed, 1985). Full-thickness hairless mouse skin was excised from the abdomen of 6–8-week-old male mice (Hadassah Hospital, Jerusalem), was examined carefully for integrity, and was mounted in diffusion cells with the epidermis towards the donor compartment.

The skin was cut (effective diffusion surface area 0.78 cm^2) and mounted with the stratum corneum towards the donor compartment, which contained 3 ml drug solution. Various systems containing [^{3}H]5-FU or [^{3}H]IDU, diluted with unlabelled drug, were tested. The final drug concentration was 1.5 mg/ml. The receiver compartment contained 3 ml of pH 7.2 phosphate buffer solution. Pseudo-sink conditions were maintained throughout the experiments which took place over a period of 30 h at 23 ± 1° C. At times 0, 1, 2, 4, 6,... 30 h, 100-μl samples were withdrawn from the receiver and replaced by 100 μl samples of buffer solution.

Drug concentrations were determined by radioactive counting using a Kontron Betamatic liquid scintillation counter (Lumitron Scientific Instruments). Experiments were triplicated.

Rheological measurements

Viscometric measurements were performed using the Ferranti portable viscometer model VL. All measurements were conducted at room temperature (23 ± 1° C). The cylinders used were VL-A for decylMSO concentrations ranging from 0.025 to 2.5% and VH-A for 5 to 15% decylMSO solutions.

Surface tension measurements

Surface tension was measured on freshly prepared decylMSO aqueous solutions using a Fisher semi-automatic Surface Tensiometer Model 21 by the method of Mittal (1972). Solutions containing decylMSO in the concentration range of 10^{-6} to $5 \cdot 10^{-1}$ M were tested.

Data treatment and statistics

Data computation was carried out using a computer program (Touitou and Wartenfeld, 1987) which manipulates data of skin permeation experiments. The program plots, directly from the sample counts, the cumulative amounts of drug permeating the skin vs time and calculates the kinetic parameters such as permeability coefficient, flux, etc. (Touitou, 1986).

The "Balance" (IBM) computer program was used to perform Student's *t*-tests (two-tailed) for comparing permeability coefficients from various experiments; $P \leqslant 0.01$ was considered significant.

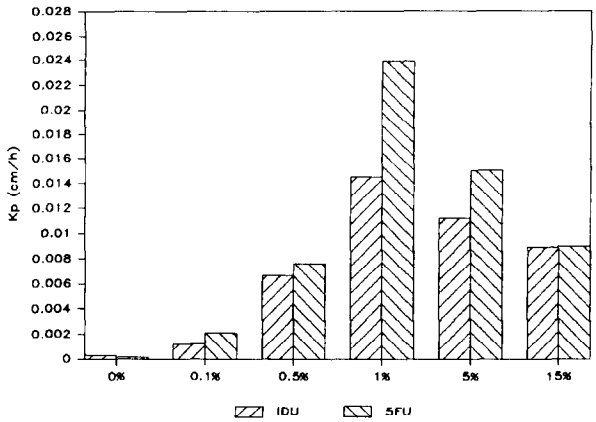

Fig. 1. Effect of various concentrations of decylMSO on the skin permeation of 5-FU and IDU from aqueous solutions containing 1.5 mg/ml drug.

Results and Discussion

The effect of decylMSO on the skin permeation of 5-FU and IDU from water and PG was studied; the two drugs selected have different lyophilic characteristics (Table 1). The more hydrophobic molecule, IDU, has a partitioning coefficient (octanol/water) 30 times greater than 5-FU.

DecylMSO in concentrations ranging from 0.1 to 15% was added to the aqueous and PG solutions of 5-FU and IDU, and their effect on skin permeability was tested.

The permeation profiles of 5-FU and IDU through hairless mouse skin from water and PG showed classical courses with lag times and steady-state phases. The permeability coefficients, K_p, computed using the transdermal program described in Materials and Methods, were further used to compare the effect of various concentrations of decylMSO on the skin permeation behavior of the drugs.

The effect of increasing concentrations of decylMSO in water on the permeability coefficient of the hydrophilic molecule 5-FU is shown in Fig. 1. The histogram clearly indicates that in the concentration range tested, 0.1 to 15%, the permeation of 5-FU was enhanced by decylMSO, and the degree of enhancement is highly concentration-dependent; the strongest effect was seen at 1% decylMSO, where a 200-fold increase in the K_p value was measured relative to the control (no decylMSO), i.e. from 1.2×10^{-4} to 2.4×10^{-2} cm/h. However, the histogram illustrates that at 5% and up, the enhancement decreases.

In order to test whether the enhancing effect is exercised only on hydrophilic molecules, similar experiments were performed with aqueous solutions of the more hydrophobic drug, IDU.

It can be observed (Fig. 1) that a picture similar to 5-FU systems was obtained in the concentration range tested, with the 1% decylMSO system being the most effective. The decrease of enhancement following the increase in decylMSO concentration above 5% was also present. Nevertheless, the maximum increase observed with IDU solutions was 46-fold relative to the control (IDU aqueous solutions without surfactant), i.e. from 3.2×10^{-4} to 1.5×10^{-2} cm/h, respectively. A number of factors may have contributed to the decrease in the enhancement effect with increasing concentrations of decylMSO observed in the aqueous solutions of both drugs. One parameter which may have had an important contribution was the viscosity of the various decylMSO solutions. In

TABLE 1

Physical characteristics of 5-FU and IDU

Drug	Solubility at 25 °C (mg/ml)				K_m (oct/H_2O)
	H_2O	EtOH	PG	$CHCl_3$	
5-FU	12	10	2.2	Insol.	0.01
IDU	2.0	2.6	1.8	0.003	0.3

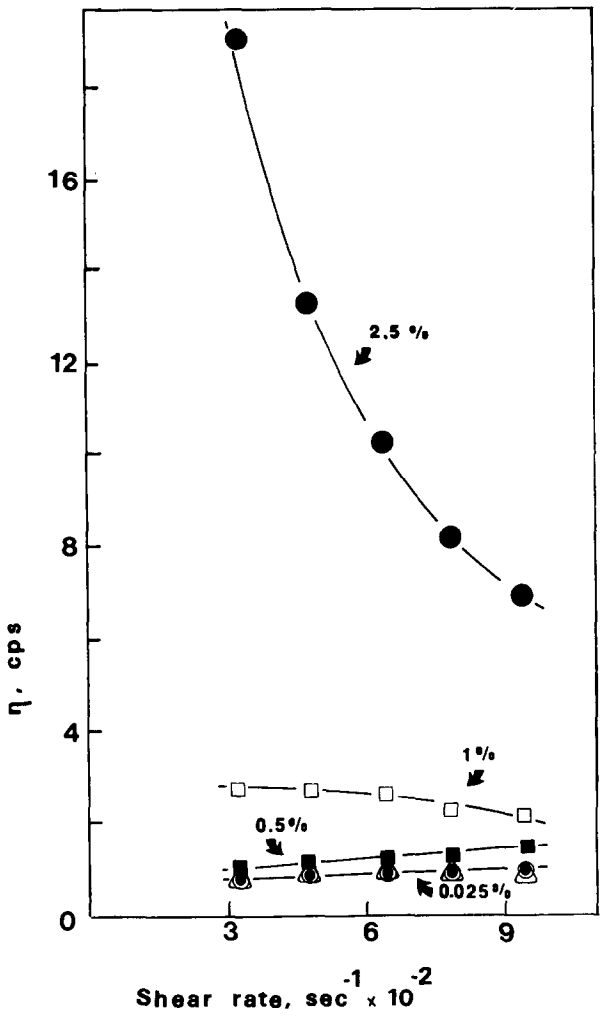

Fig. 2. Rheograms of aqueous solutions containing various concentrations of decylMSO (0.025–2.5% w/v) tested at 23° C.

order to test this possibility, the viscosity of aqueous solutions containing increasing concentrations of decylMSO was measured. The rheograms are given in Figs. 2 and 3. Fig. 2 shows that the viscosity rises when the decylMSO concentration increased from 1 to 2.5%, i.e. at a shearing rate of 300 s^{-1}, the viscosity increased from 3 to 20 cps. At higher concentrations of decylMSO, a sharp viscosity increase was observed at 15% decylMSO. This behavior corresponds to the decrease in the enhancing effect found at the higher concentrations. The observation that the decrease in the

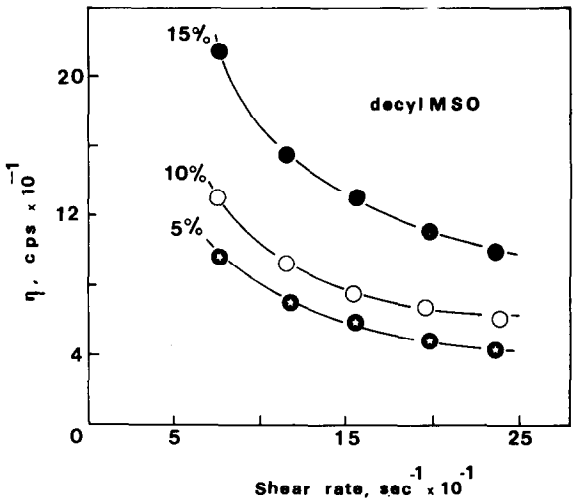

Fig. 3. Rheograms of aqueous solutions containing higher concentrations of decylMSO (5–15% w/v) tested at 23° C.

enhancement effect was seen for both 5-FU and IDU systems supports the idea that the impediment in enhancement at high concentrations of decylMSO was caused by a decrease in drug availability at high viscosities.

Figs. 4 and 5 illustrate the effect of increasing concentrations of decylMSO on the permeability coefficients of 5-FU and IDU from PG solutions. Fig. 4 shows that the permeability of 5-FU is not affected up to a very high concentration of enhancer. Even then, the enhancement, though statistically significant, is only 7-fold relative to the

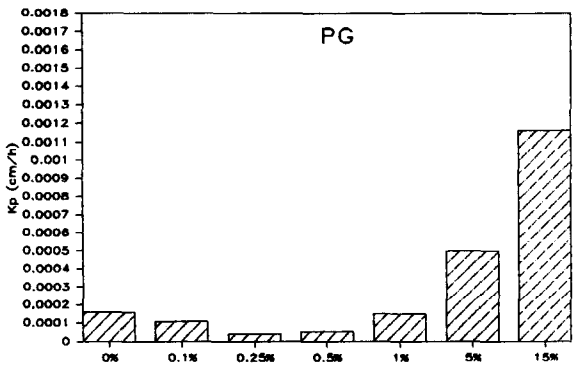

Fig. 4. Effect of various concentrations of decylMSO on the skin permeation of 5-FU from solutions containing 1.5 mg/ml drug in PG.

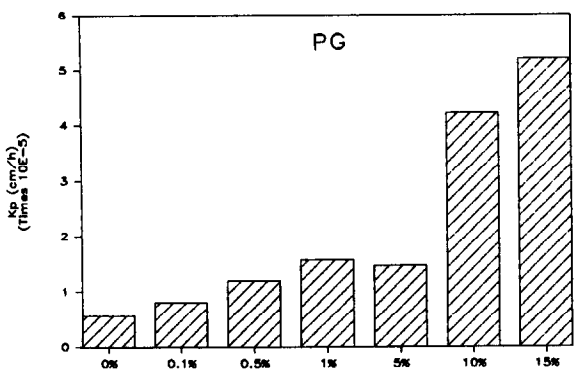

Fig. 5. Effect of various concentrations of decylMSO on the skin permeation of IDU from solutions containing 1.5 mg/ml drug in PG.

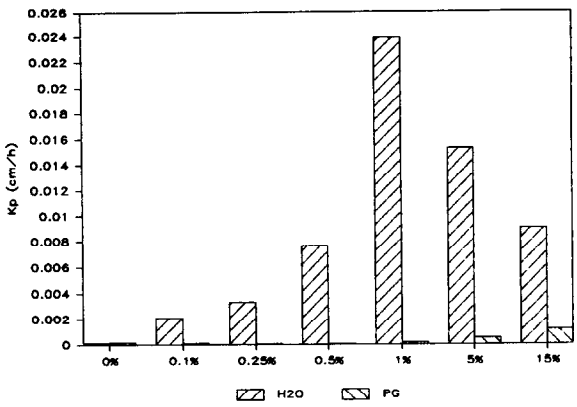

Fig. 6. The concentration-dependent effect of decylMSO on the permeability coefficient of 5-FU from H_2O and PG solutions.

control (no decylMSO). For IDU systems the permeability coefficient of the control solution is 30 times smaller than for 5-FU, i.e. 5.2×10^{-6} vs 1.6×10^{-4} cm/h for IDU and 5-FU solutions, respectively. The picture presented in Fig. 5 is almost identical to that in Fig. 4; in the IDU/PG system, similar to the 5-FU/PG system, decylMSO affects the drug permeability only at high concentrations (> 10%); moreover, at concentrations as high as 15% decylMSO, only a 10-times increase in the permeability coefficient was observed.

As can be seen from the results presented above, the concentration-dependent effect of decylMSO changed according to the media used. To emphasize this difference, the permeability coefficients at selected decylMSO concentrations, in PG vs water for both drugs, were illustrated (Figs. 6 and 7). The histograms clearly show that in PG solutions decylMSO has practically no effect on the permeation of the drug tested when compared to the aqueous solutions.

Further, it was interesting to learn if the behavior exhibited by decylMSO in PG solutions is characteristic of this enhancing agent or is present for other enhancers, e.g. Azone, which have also been stated to affect the permeation of polar drugs (Sugibayashi et al., 1985). In order to test this, increased concentrations of Azone were added to IDU-PG systems, and the results are illustrated in Fig. 9.

From the histograms shown in Fig. 8, it can be clearly seen that the flux of IDU was increased 7-fold at concentrations of Azone as low as 0.5%. The optimal concentration of Azone was found to be 5% in PG solution, at which an enhanced delivery of IDU by more than 3 orders of magnitude was measured relative to the control, i.e. from 1.3×10^{-5} to 4.2×10^{-2} $mg \cdot cm^{-2}$ h^{-1}. These results indicate that Azone, in contrast to decylMSO, is very effective in enhancing the skin permeation of IDU from PG solutions. Similar high permeation enhancement by Azone in PG solutions was reported with metronidazole (Wotton et al., 1985) and trifluorothymidine (Sheth et

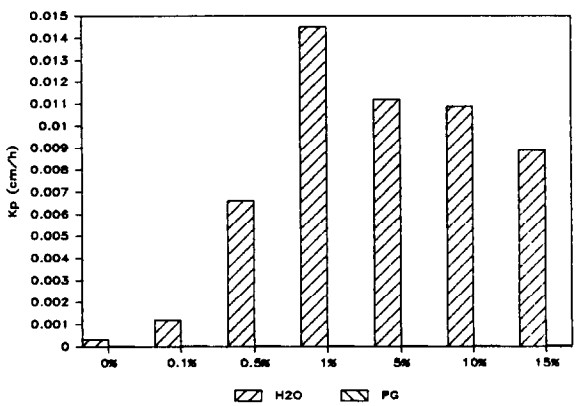

Fig. 7. The concentration dependent effect of decylMSO on the permeability coefficient of IDU from H_2O and PG solutions.

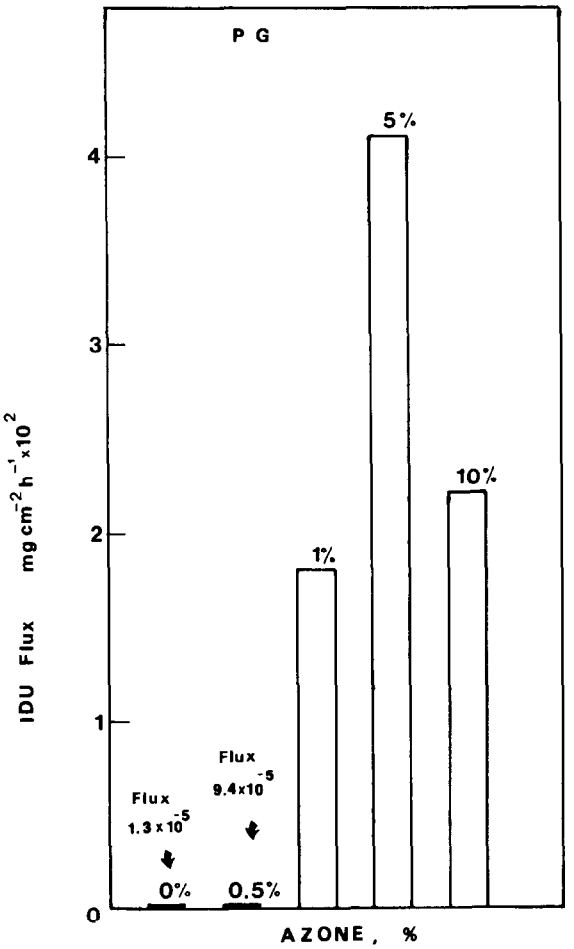

Fig. 8. Effect of various concentrations of Azone on the skin permeation fluxes of IDU from solutions containing 1.5 mg/ml drug in PG.

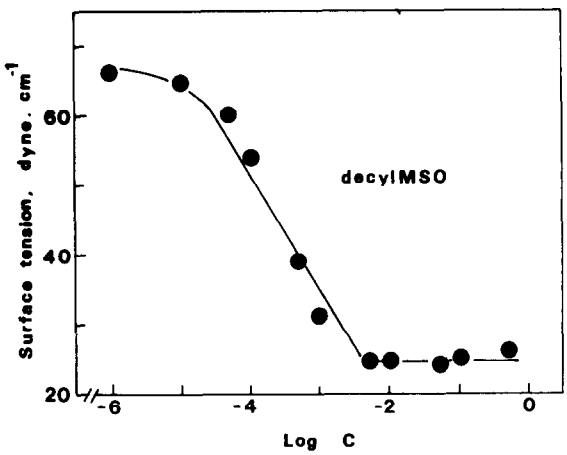

Fig. 9. Surface tension vs log concentrations of decylMSO in aqueous solutions tested at 23° C by means of a Fisher surface tensiometer.

al., 1986). The results presented here indicate that decylMSO and Azone affect the skin transport of drugs by different mechanisms.

It can be concluded that for decylMSO to exercise its enhancement effect, an aqueous medium is necessary. Although we found that in aqueous solutions decylMSO is active at relatively low concentrations, its effect increased at concentrations higher than 0.1%. These observations suggest that the activity of decylMSO, a surface-active molecule, may be related to its property of generating micelles in aqueous solutions. In order to test this supposition, the surface activity of aqueous solutions containing decylMSO in a concentration range of 10^{-6} to 5×10^{-1} M was measured. The surface tension vs concentration curve given in Fig. 9 shows a sharp break corresponding to a CMC value of 5×10^{-3} M (0.12%). Comparing this CMC value with the concentrations that enhance the skin permeation of 5-FU and IDU in aqueous solutions, it can be concluded that the enhancement occurs at decylMSO concentrations higher than the CMC.

The above results show that the mechanism of drug permeation enhancement by decylMSO is related to the micelle formation of the surface-active molecule in water and is influenced by other properties such as increased viscosity at high concentrations. However, lipophilic drugs may be trapped in the surfactant micelles, with the final effect being decreased drug availability (Dalvi and Zatz, 1981). Stolar et al. (1960) and Dalvi and Zatz (1981), testing the penetration of salicylic acid and benzocaine, respectively, in the presence of non-ionic surfactants, both found a marked reduction in the penetration flux. In the latter case, the authors reported that the flux was inversely related to the surfactant concentration and concluded that the penetration of benzocaine was proportional to the free drug concentration. To summarize, the non-ionic surfactants reduced drug penetration because of micellar solubilization,

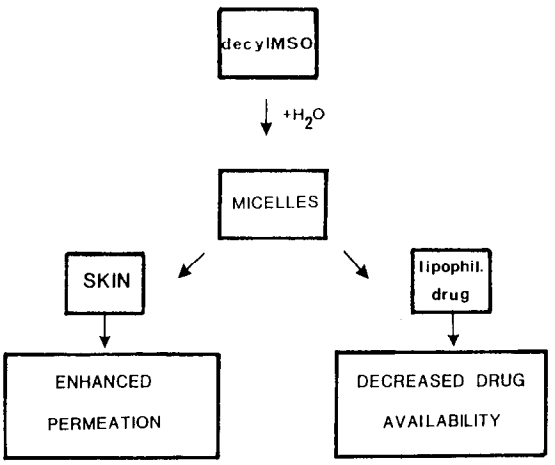

Fig. 10. Schematic representation of the potential effects of decylMSO during the process of drug permeation through the skin.

consequently reducing the number of molecules available for transport.

Fig. 10 schematically presents the possible effects of decylMSO that are related to the drug and the skin: the surfactant micelles, which may solubilize lipophilic components in the stratum corneum, can facilitate the transport of molecules. The lack of permeation enhancement of lipophilic molecules by surfactants may be explained by a decrease in drug availability. When considering the mechanism of action of an enhancing agent, the effect must be related to both the drug and the skin — and not only to the skin.

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