Effect of Dimethyl Sulfoxide on Drug Permeation Through Human Skin

The effect of the presence of dimethyl sulfoxide (in admixture with water) on the sorption and permeation rate of scopolamine base in human skin in vitro has been measured as a function of drug concentration in aqueous solution. The equilibrium sorption of scopolamine by skin from solution appears to be unaffected by the presence of even high concentrations of dimethyl sulfoxide in the solution phase. In the absence of a transdermal gradient of DMSO (or water), the permeability of skin to scopolamine in the presence of DMSO is about twofold higher than in its absence, suggesting that the diffusivity of scopolamine in the stratum corneum is somewhat elevated by the solvating action of DMSO.

When, however, a gradient of DMSO concentration is impressed across the skin (irrespective of whether that gradient is of the same or opposite sign to that of the drug), the permeability of the skin to scopolamine is increased by one to two orders of magnitude. Microscopic examination of the skin subjected to such treatment reveals marked swelling, distortion, and intercellular delamination of the stratum corneum, which is only partially reversible following complete extraction with water. These effects are believed due to development of very high osmotic stresses produced within the stratum corneum, as both water and DMSO are transported into the tissue.

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This paper is the third in a series devoted to the measurement and interpretation of the transport of relatively small, biologically active molecules though intact human skin, whose objective has been to explain the often puzzling barrier properties of skin on rational, physicochemical principles of solution thermodynamics and molecular diffusion kinetics.

For many years, certain super solvents such as dimethyl sulfoxide (DMSO) have been recognized as exceedingly skin-permeable substances and have been shown to greatly elevate the permeability of skin to many compounds to which intact human skin is normally an effective barrier. These observations have evoked numerous hypotheses about the role of substances such as DMSO on skin permeation, some of which call upon active transport mechanisms, or coupled-flow, piggyback diffusion processes, which have few, if any, counterparts in passive membrane transport systems.

In the studies herein reported, we have found that the effects of DMSO on skin permeability in vitro are entirely consistent with accepted theories of solution diffusion models of membrane transport, when changes in penetrant activity with changes in solvent composition are properly allowed for, and when changes in tissue microstructure accompanying osmotic shock are duly considered.

CONCLUSIONS AND SIGNIFICANCE

The principal barrier to the transport of drugs and other relatively small molecules through intact human skin is localized with the stratum corneum, which is comprised of dead, keratinized, partially desiccated epidermal cells. Drug permeation through the stratum corneum occurs principally by a passive diffusion process independent of metabolic assistance.

The permeation of scopolamine through human stratum corneum in vitro is greatly elevated by the action of dimethyl sulfoxide, the enhancement being dependent on the presence, magnitude, and direction of the impressed DMSO concentration gradient, relative to that of the drug. The mechanism of action of DMSO in enhancing scopolamine transport through human skin is entirely consistent with the accepted theory of a passive diffusion model for drug transport, provided changes in scopolamine activity with changes in solvent composition are accounted for, and when the marked distortion and intercellular delamination of the stratum corneum accompanying high osmotic stresses are considered. These observations may, it is believed, lay the groundwork for rational selection of mixed solvent systems for enhancement of drug permeation through skin in vivo and, as well, provide a basis for the design of safe and more effective agricultural chemical formulations.

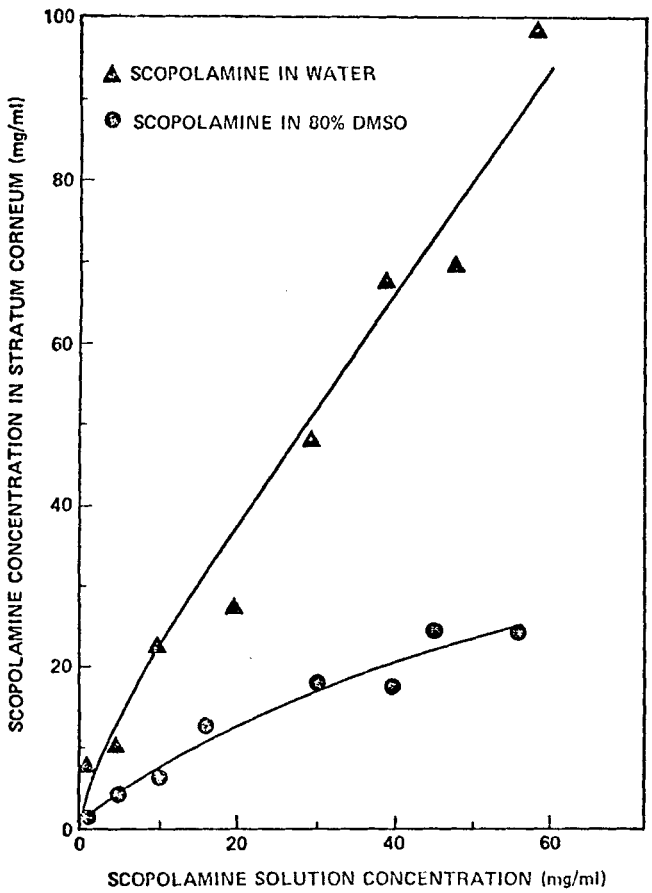

Fig. 1. Scopolamine sorption isotherms in human stratum corneum.

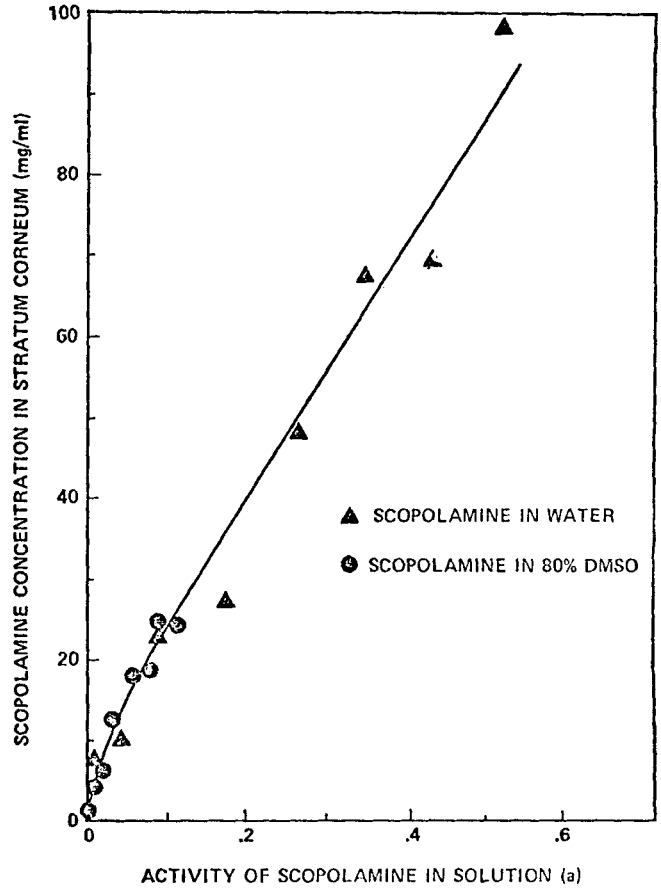

Fig. 2. Normalized scopolamine sorption isotherms in human stratum corneum.

The permeation of drugs and other micromolecules through intact human skin occurs principally by Fickian diffusion, with the gradient in drug concentration across the entire skin being localized within the stratum corneum (Scheuplein and Blank, 1971). The transdermal permeation rates are generally small, and a variety of organic liquids have been used as vehicles to accelerate the penetration of topically applied pharmacologically active or chemotherapeutic substances through the skin. Of these liquids, the best known is dimethyl sulfoxide (DMSO), which has been found to enhance the transdermal penetration of water (Baker, 1968), fluocinolone acetonide (Stoughton and Fritsch, 1964), barbiturates (Horita and Weber, 1964), and other substances (Kligman, 1965).

The ability of DMSO to enhance the permeation rate of micromolecules across human skin appears to be dependent upon the concentration of DMSO, the mode of application whether as a stratum corneum pretreatment or as a vehicle for the drug, and on the time of contact with the tissue (Astley and Levine, 1976; Elfbaum and Laden, 1968). The purpose of this study was to determine the effect of DMSO (in admixtures with water) on the sorption and permeation rate of scopolamine base in human skin in vitro, in an effort to reexamine and more clearly understand the mechanism of action of DMSO in enhancing drug transport through human skin.

EXPERIMENTAL

Details of the apparatus and experimental technique have been previously described by Chandrasekaran et al. (1976) and Michaels et al. (1975). Skin was obtained from Caucasian cadavers, excised from the inner surface of the thigh; samples were preserved in heat sealed plastic bags, stored at 4°C prior to use. The epidermis was separated from the remaining layers of tissue by stirring the skin for 60 s in water at 60°C. The stratum corneum was subsequently isolated by digesting the epidermis with 0.10% trypsin in 0.05 M tris·hydrochloric acid *p*H 7.9, for 45 min followed by rinsing with water.

Equilibrium sorption isotherms were determined by equilibration of a measured weight of isolated stratum corneum in a relatively large volume of radiolabeled scopolamine solution of known concentration for 24 hr at 30 ± 0.1°C, removing the stratum corneum from the solution, digesting it in a proteolytic solvent, and scintillation counting the resulting solution for total drug present in the tissue.

Permeation measurements were conducted in glass permeation cells, with concentrated radiolabeled drug being confined in one compartment in contact with the stratum corneum surface of the tissue and drug free solution in the other compartment. Experiments were conducted both in the absence of a transdermal gradient of DMSO (or water) and in the presence of a gradient of DMSO concentration either in the same or opposite direction to that of the drug. Periodic sampling of the two compartments, and assay of drug content by scintillation counting and DMSO content by gas chromatography, permitted determination of the amount and rate of permeation as a function of time.

RESULTS AND CONCLUSIONS

Sorption Experiment (Cadaver 1)

The sorption isotherms for stratum corneum in equilibrium with scopolamine present in either aqueous solutions or in 80% DMSO/20% water solutions are shown in Figure 1. It is apparent that at equivalent concentrations of scopolamine in solution, the stratum corneum in equilibrium with the 80% DMSO solution contains about one quarter of the drug present under equilibrium with the

Table 1. Equilibrium Dual Mode Sorption Coefficients

Solution conditions	Partition coefficient K_D	Langmuir's isotherm constants C_1' (mg/ml)	b (ml/mg)
Scopolamine in water	1.4	10.5	0.36
Scopolamine in 80% DMSO	0.3	10.5	0.08

pure aqueous solution. However, scopolamine is five times more soluble in 80% DMSO/20% water solutions compared with pure water, with saturation concentrations of 502 and 100 mg/ml, respectively, in the two solvents. In Figure 2, the concentration of scopolamine in the stratum corneum is replotted against the activity (or percent saturation) of scopolamine in the solution phase contacting the skin; under these conditions, the amount of drug present in the stratum corneum at equilibrium is the same for both aqueous and 80% DMSO solutions with equivalent activities of scopolamine.

The equilibrium sorption isotherms were analyzed using the dual mode sorption model, shown previously to be valid and useful in the analysis of the permeation characteristics of scopolamine through human skin in vitro (Chandrasekaran, 1976). The results are presented in Table 1 and show that in the presence of 80% DMSO, the drug partition coefficient and Langmuir affinity parameter are lowered by a factor of 4.5, but the Langmuir saturation parameter remains constant.

Permeation Experiment (Cadaver 1)

The results of the permeation of scopolamine through stratum corneum (cadaver 1) from both aqueous and 80% DMSO donor solutions into receptor solutions of the same respective solvent are presented in Table 2. In the presence of DMSO, the steady state flux of scopolamine appears to be lower compared to the control experiment. Using the partition coefficients computed from the sorption isotherm, and the measured thickness of the stratum corneum at the termination of the experimentation, the steady state diffusivity was now determined by dividing the measured steady state in vitro transdermal flux by the computed gradient in the stratum corneum of dissolved drug. From aqueous solutions, the diffusivity of scopolamine in stratum corneum approximates 6×10^{-10} cm^2/s and is in good agreement with results published earlier (Chandrasekaran, 1976), whereas from 80% DMSO solutions, the steady state diffusivity approximates 15×10^{-10} cm^2/s, indicating a decrease in the transport resistance offered by the stratum corneum in the presence of DMSO.

Permeation Experiment (Cadaver 2)

The permeation characteristics of scopolamine through stratum corneum (cadaver 2) are presented in Table 3. The flux of scopolamine with water in the two compartments of the permeation cell approximates 6.8 μg/cm^2 hr, whereas at a similar concentration of scopolamine of 11.5 mg/ml, the flux with 80% DMSO in both compartments is 3.0 μg/cm^2 hr. The results of normalizing these flux values for skin thickness and the activity of scopolamine in the donor solution are shown in Table 3. Under the experimental conditions of having water in both the compartments, the normalized flux approximates 0.3 μg/cm hr, whereas with 80% DMSO the normalized flux is 0.7 μg/cm hr. The 2.3 fold increase in the normalized flux in the presence of DMSO directly reflects a 2.3 fold increase in the scopolamine diffusivity through the stratum corneum; this enhancement compares well with the 2.5 fold increase in drug diffusivity measured previously using stratum corneum from cadaver 1.

Analysis of the fluxes, under conditions when a gradient of DMSO concentration is impressed across the stratum corneum, is more complex, and the variables measured are shown in Figure 3. The presence of 80% DMSO on one side of the stratum corneum vs. water on the other side causes an osmotic pressure gradient of about 320 atm; when a DMSO gradient of opposite sign to that of scopolamine is impressed across the skin, bulk flow of water into the receptor solution decreases the donor solution volume by about 3 ml in 9 hr (Figure 3*a*, C). This bulk flow of water was greater than the permeation rate of drug, resulting in an increase in the scopolamine concentration in the donor compartment solution (Figure 3*b*, C). At the same time, DMSO migrated from the receptor into the donor solution, resulting in a gradual increase in the DMSO concentration in the scopolamine rich donor solution (Figure 3*c*, C). A consequence of this rise in the DMSO concentration was the increase in drug solubility

Table 2. Permeation of Scopolamine Through Stratum Corneum In Vitro (Cadaver 1)

Donor/receptor combination	Nature of donor solution	Scopolamine concentration in donor (mg/ml)	Nature of receptor solution	Scopolamine flux, J (μg/cm^2 hr)	Average scopolamine diffusion coefficient, D_{ss} cm^2/s $\times 10^{10}$
A	Water	18.9	Water	9.4	6
	Water	4.9	Water	2.0	
B	80% DMSO	20.5	80% DMSO	6.8	15
	80% DMSO	5.3	80% DMSO	1.7	

Table 3. Permeation of Scopolamine Through Stratum Corneum In Vitro

Donor/receptor combination	Nature of donor solution	Nature of receptor solution	Scopolamine concentration in donor (mg/ml)	Average scopolamine flux, J (μg/cm^2 hr) Time — (5 → 9 hr)	Scopolamine activity at $t = 0$*
A	Water	Water	11.7	6.8	0.117
B	80% DMSO	80% DMSO	11.5	3.0	0.023
C	Water	80% DMSO	11.7	35.1	0.117
D	80% DMSO	Water	11.5	13.7	0.023

* Calculated using 100 mg/ml as saturation for scopolamine in water and 502 mg/ml as saturation for scopolamine in 80% DMSO.
† Computed as $J = Jl/\Delta a$.

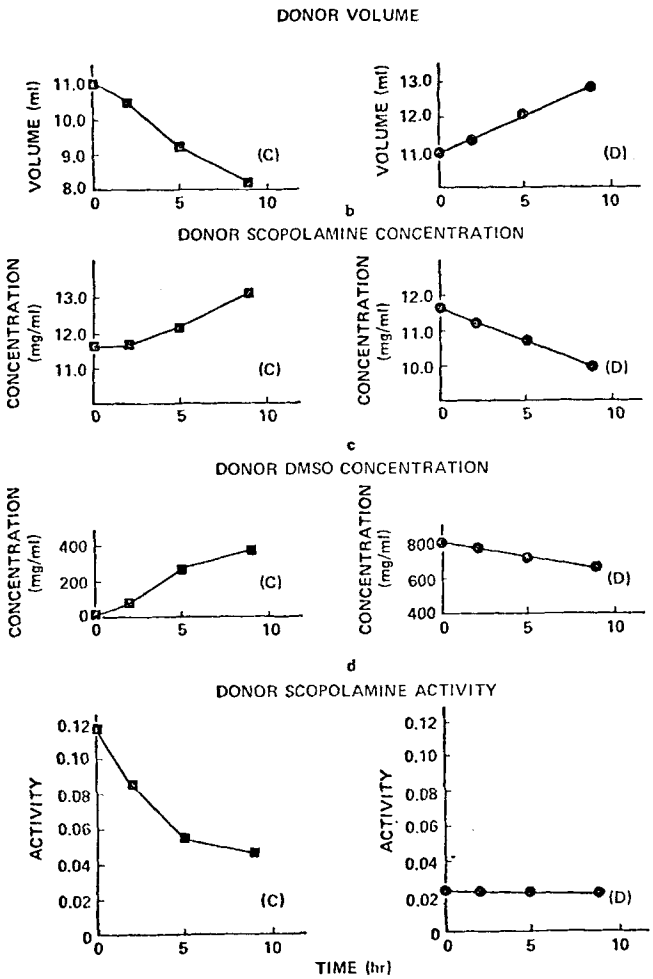

Fig. 3. Variation of volume, concentration, and activity with time.

in the donor solution, resulting in a net decrease in scopolamine activity (Figure 3*d*, C).

The opposite phenomenon occurred when the impressed gradient of DMSO was in the same direction as that of scopolamine; there was bulk flow of water from the receptor into the scopolamine donor solution and, consequently, dilution of the concentration of scopolamine (Figures 3*a* and 3*b*, D). Simultaneously, DMSO permeated from the donor to the receptor compartment, resulting in a decrease in the DMSO concentration in the donor solution (Figure 3*c*, D). The decrease in DMSO concentration offset the decrease in scopolamine concentration, resulting in an almost constant activity level of scopolamine in the donor solution (Figure 3*d*, D).

The representative transport fluxes of scopolamine during the experimentation described above are shown in Figure 4. The permeation rate of scopolamine is time dependent and, more surprisingly, the flux of drug, under conditions when the impressed concentration gradient of DMSO is of opposite sign to that of the drug, is about two to three times greater, compared to when the gradient of drug and DMSO are in the same direction. However, in either case, the permeability of the skin to scopolamine is increased by at least one order of magnitude compared to the permeation rate in the absence of a transdermal gradient of DMSO.

(Cadaver 2)

Scopolamine activity gradient, Δa	Stratum corneum thickness l (cm)	Average normalized flux, $\bar{J}t$ (μg/cm hr) Time — (4 → 14 hr)
0.114	0.00432	0.3
0.023	0.00508	0.7
0.049	0.00534	3.8
0.022	0.00737	4.5

These fluxes were normalized with respect to the skin thickness and activity (percent saturation) gradients of scopolamine across the stratum corneum during the permeation experiments. The results of these computations are presented in Figure 4 and Table 3. After a time period of about 4 hr, the normalized fluxes are quite similar at approximately 4 μg/cm hr and appear independent of whether the impressed gradient of DMSO concentration is of the same or opposite sign to that of the drug.

This apparent independence of the direction of the DMSO concentration gradient on its ability to enhance the permeation rate of scopolamine is surprising. These results suggest an alteration in the stratum corneum microstructure caused by the presence of a DMSO concentration gradient. Photomicrographs of stratum corneum cross sections after exposure to water, 80% DMSO, and a concentration gradient of 80% DMSO are shown in Figure 5. The tissues were prepared using the routine paraffin embedding procedure, namely, the tissues were placed in 10% buffered formalin, dehydrated with graded alcohol, cleared in xylene, and infiltrated with paraffin. Marked swelling, distortion, and intercellular delamination are apparent in the stratum corneum only when it is subjected to a concentration gradient of DMSO; these changes are partially reversible following complete extraction of the tissue with water (Figure 6). These effects may be caused by the development of very high osmotic stresses produced within the stratum corneum as both water and DMSO are transported into the tissue.

These permeation experiments were repeated using a microporous polypropylene membrane, chemically unaffected by DMSO, in the place of human stratum corneum; the results are presented in Table 4. It is apparent that

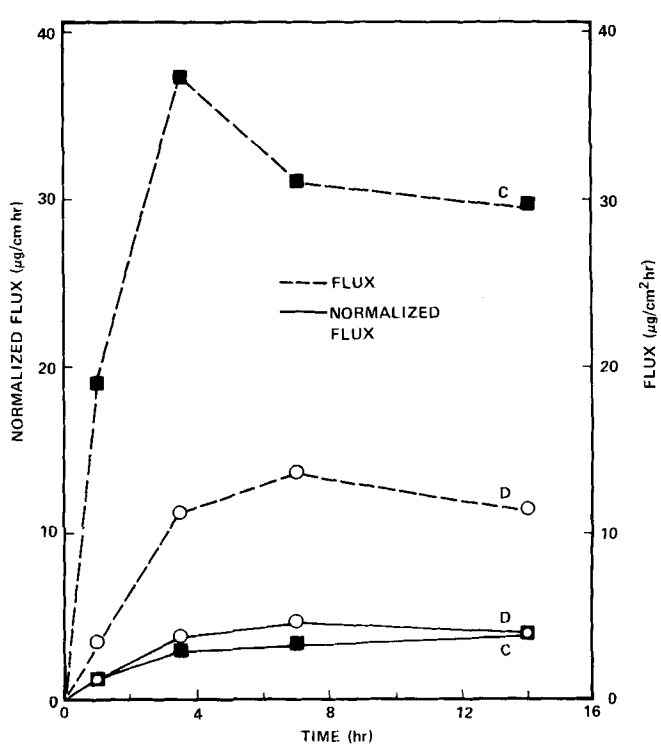

Fig. 4. Scopolamine fluxes through human stratum corneum.

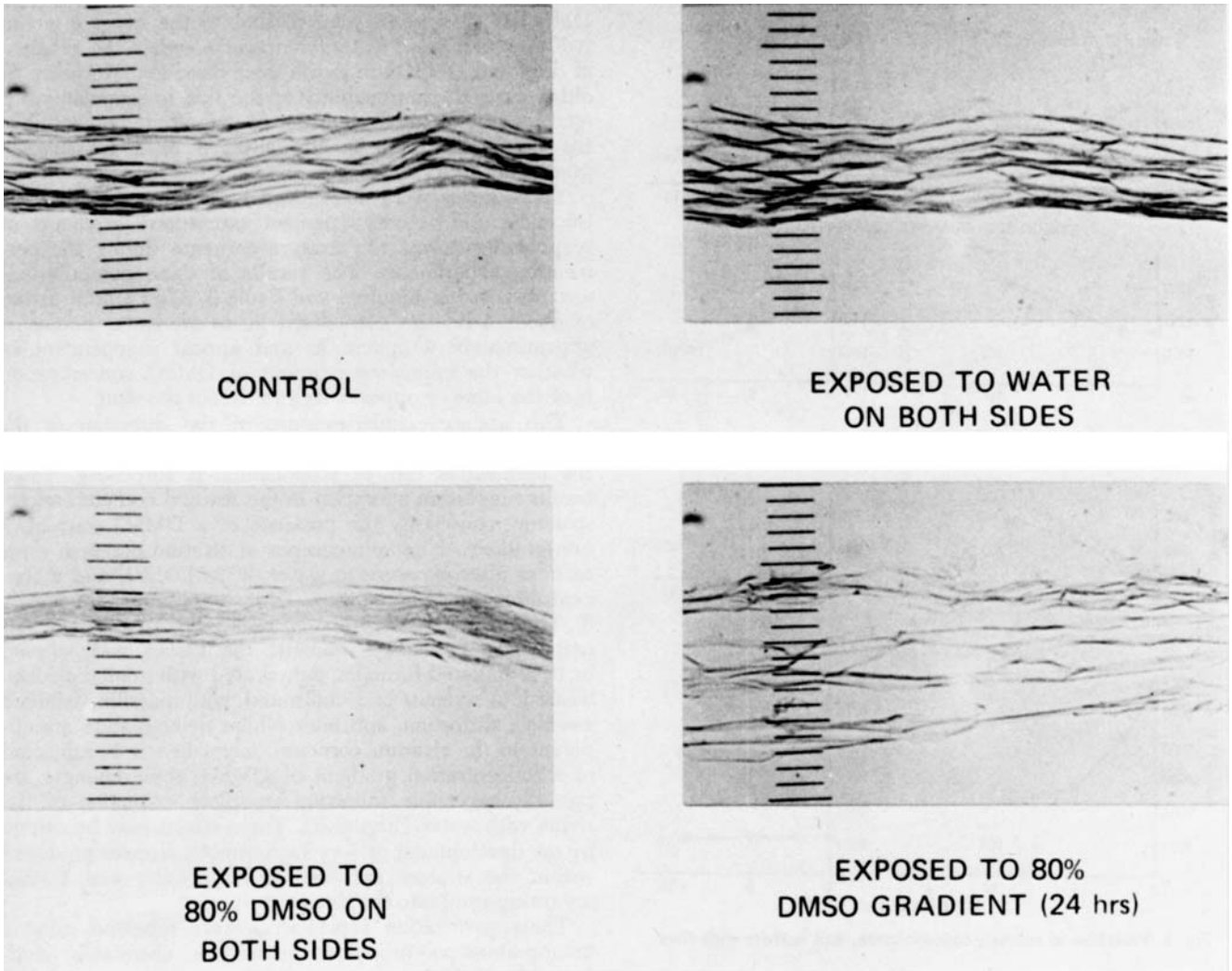

Fig. 5. Photomicrograph of stratum corneum, effect of DMSO exposure.

the normalized fluxes of scopolamine in the presence of DMSO, irrespective of whether a concentration gradient is impressed or not, is about 1.5 to 2 fold greater compared to the drug flux from pure aqueous solutions. These results suggest that for scopolamine transport in microporous membranes which are chemically unaffected by DMSO, the drug diffusion coefficient is enhanced about 1.5 to 2 fold in the presence of DMSO; this increase compares favorably with the value obtained for scopolamine permeation through human stratum corneum in the presence of 80% DMSO/water solution, but without a DMSO concentration gradient.

DISCUSSION

The penetration of micromolecules through the skin is a passive diffusion process independent of metabolic assistance, with the relative impermeability of the tissue residing within the stratum corneum. Over the years, numerous studies have been performed concerning the enhancement of skin permeability by dimethyl sulfoxide. However, there has been little agreement regarding the mechanism of action and the extent or degree of reversibility of this effect.

The results of this study show that in the absence of a transdermal gradient of dimethyl sulfoxide, the permeability of the stratum corneum to scopolamine in the presence of DMSO is about twofold higher than in its absence. Under similar experimental conditions, equivalent enhancements were observed in the permeation of scopolamine through microporous polypropylene membrane, suggesting that the diffusivity of scopolamine both in the stratum corneum and in aqueous solution is elevated about twofold in the presence of high concentrations of DMSO.

However, when a DMSO concentration gradient is impressed across the stratum corneum, irrespective of whether

Table 4. Scopolamine Fluxes Through Microporous Polypropylene Normalized for Activity Gradient and Membrane Thickness

Donor/receptor combination	Nature of donor solution	Nature of receptor solution	Scopolamine activity gradient, Δa	Membrane thickness l (cm)	Normalized flux, $\bar{J}^*$ (μg/cm hr)
A	Water	Water	0.104	0.00254	25.8
B	80% DMSO	80% DMSO	0.022	0.00254	41.6
C	Water	80% DMSO	0.051	0.00254	44.0
D	80% DMSO	Water	0.021	0.00254	47.5

* Computed as $\bar{J} = Jl/\Delta a$.

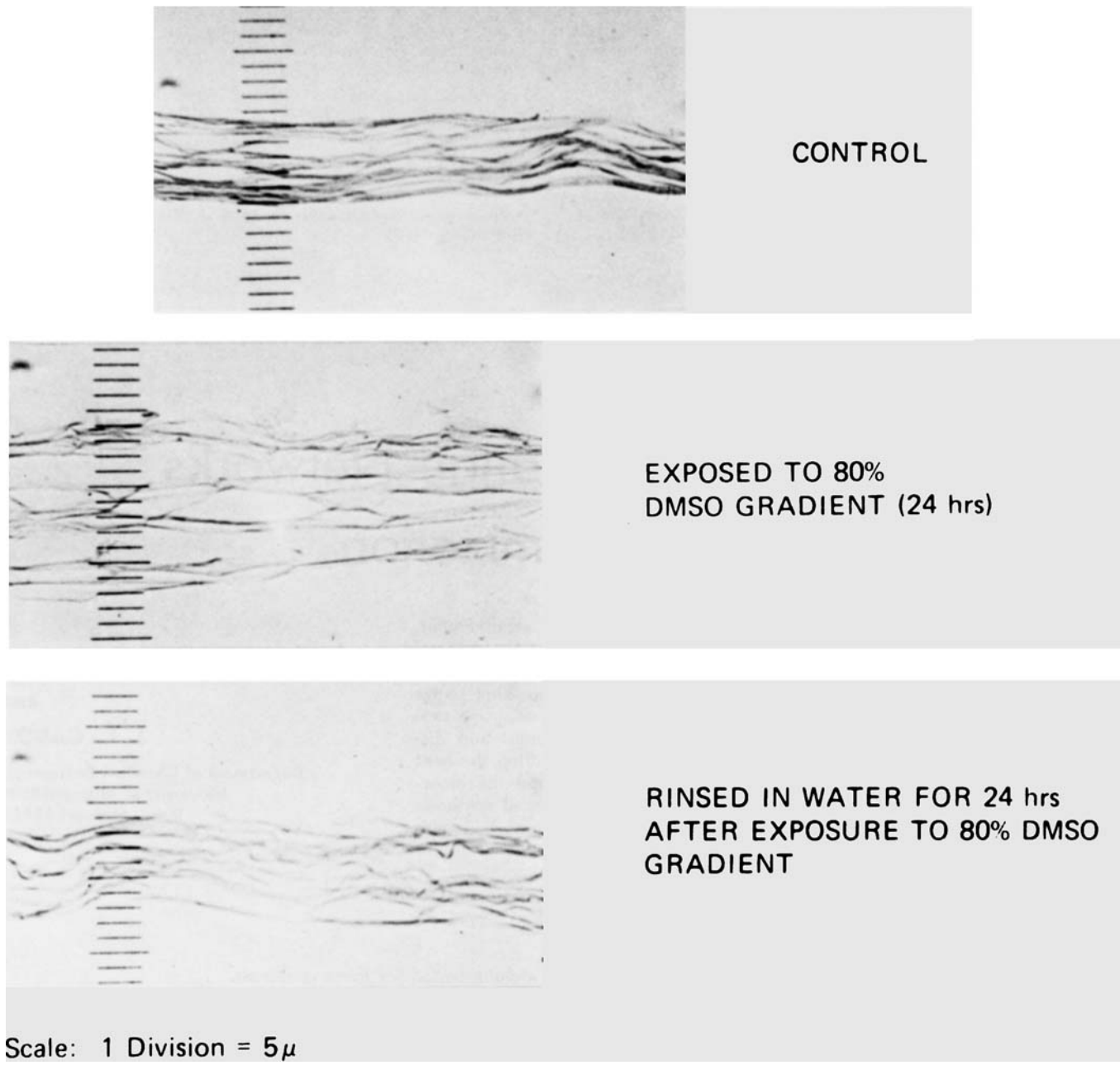

Fig. 6. Photomicrographs of stratum corneum, reversibility after DMSO exposure.

the gradient is in the same or opposite direction to that of the drug, the skin permeability to scopolamine is increased by more than one order of magnitude. In contrast, the permeability of microporous polypropylene to scopolamine is elevated only twofold by the presence of DMSO and appears independent of the existence or direction of an impressed DMSO concentration gradient. Hence, the marked enhancement of skin permeability to scopolamine in the presence of a DMSO gradient is probably not due to facilitated or sweep diffusion of scopolamine. More likely, the development of high osmotic stresses produced within the stratum corneum by the transport of water and DMSO into the tissue causes swelling, distortion, and intercellular delamination of the stratum corneum, resulting in a marked decrease in its transport resistance to scopolamine.

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NOTATION

a = activity
b = Langmuir's affinity constant
C = concentration
C_l^* = Langmuir's saturation constant
D_{ss} = steady state diffusion coefficient
J = flux
$\overline{J}$ = normalized flux
K_D = partition coefficient
l = membrane thickness
t = time

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Synthesis of Heat Exchange Networks by Mixed Integer Optimization

Process synthesis involves manipulation of the process arrangement, while studying the variables of each arrangement, to arrive at the optimal process. If each process arrangement is treated as a discrete variable, process synthesis becomes a mixed integer optimization problem. This paper examines the synthesis of heat exchanger networks using the adaptive random search procedure, which can be used to search continuous and discrete independent variables simultaneously. The means of handling the heat exchanger arrangement as a discrete variable is discussed, and the incorporation of various synthesis heuristics is presented. The results of synthesis of 2 × 2, 2 × 3, and 3 × 3 networks are presented and compared with other methods of synthesis.

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Synthesis of heat exchange networks is usually treated as a discrete optimization problem. Recent studies of these systems have successfully utilized branch and bound techniques to reduce the computational effort (Lee et al., 1970; Pho and Lapidus, 1973; Rathore and Powers, 1975). Each of these studies has been concerned with finding the optimal arrangement of the network and has not considered optimization of the individual exchangers. Improvement in the economics and different optimal arrangements might result if the quantity of heat transferred in each exchanger is optimized along with the order of the exchangers. The optimization problem then becomes mixed integer, and suitable algorithms have not been demonstrated for these problems.

The adaptive random search procedure has been successfully applied to the mixed integer reliability problem (Campbell and Gaddy, 1976). The purpose of this study is to examine heat exchanger synthesis as a mixed integer optimization problem using the adaptive random search. Examples from the literature were chosen for study so that a comparison between optimal networks could be made to evaluate any advantage in treating synthesis problems as mixed integer. The reliability and efficiency of the adaptive random search are measured and reported for three problems solved previously by Lee et al. (1970) and Pho and Lapidus (1973).

CONCLUSIONS AND SIGNIFICANCE

The adaptive random search with heuristics was found to be an effective method for solving heat exchanger synthesis problems. Simultaneous optimization of the heat transfer and exchanger sequence resulted in improved economics for two of the three examples considered.

As might be expected for more complicated problems, the search region for the mixed integer synthesis problem was found to be very poorly behaved. To aid the search, in these cases, heuristics are employed to reduce the computational effort. Termination of a stream at its desired temperature, when possible in an exchanger, was found to speed the search without impairing the accuracy.

The use of heuristics with the adaptive random search resulted in perfect reliability in solving each of the examples. Only slightly more computer time is required to solve these problems as mixed integer. The method is quite simple to apply to synthesis problems and should receive broad application to more complicated systems.

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