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MICROEMULSIONS AS TOPICAL DRUG DELIVERY VEHICLES. I. CHARACTERIZATION OF A MODEL SYSTEM.

David W. Osborne
PMTS Fluids/Ointments R&D
The Upjohn Company,
Kalamazoo, MI 49001
USA

and

Anthony J.I. Ward and Kilian J. O'Neill
Chemistry Department
University College
Belfield, Dublin, 4,
IRELAND

ABSTRACT

The microemulsion region formed by the water/octanol/dioctyl sodium sulfosuccinate (DSS) was characterized by determination of the phase boundaries, water self diffusion coefficients, and in vitro transdermal permeation for radiolabeled water. The 58:42 ratio of DSS:octanol can incorporate greater than 70% water. It is found that the average self diffusion values for water increase ten-fold as the water content increases from 15 to 58% by weight. Values for normalized in vitro transdermal flux of water from the microemulsion showed a similar trend increasing five-fold over the

same water content range. This study shows that delivery of the polar water portion of this microemulsion system is highly dependent upon the composition of the microemulsion.

INTRODUCTION

The addition of a surface active agent to a drug delivery vehicle can result in improved drug stability and clinical potency, increased drug absorption and decreased drug toxicity (1). If the drug vehicle containing a surfactant is further optimized to form a microemulsion system, the additional advantages of a transparent vehicle, maximized solubilization of a poorly soluble drug, and thermodynamic stability are realized (2). These advantages stem from microemulsions having an apparent particle size in the range of 100-1000 A compared to the 5,000-10,000 A minimum particle size typical of macroemulsions. While the use of microemulsions as drug delivery vehicles (3,4) and more specifically for topical drug delivery (5-10) have been discussed in the literature, the pharmaceutical industry has yet to fully utilize this technology.

In an attempt to gain insight into the characteristics and properties of a microemulsion vehicle that are fundamental to the topical delivery of drugs, the water in oil (W/O) microemulsion region of the water/octanol/dioctyl sodium sulfosuccinate (DSS) system was investigated. The DSS (also know as Aerosol-OT, AOT, and docusate sodium) system was selected because the microemulsion formed extends to greater than 70% water for the 58:42 ratio of

DSS:octanol. Thus, the effect that microemulsion composition, i.e. amount of water incorporation, has on the delivery of the internal phase can be investigated. Since water is the internal phase of this system, the first step in characterizing the vehicle was to determine how water would be released from the microemulsion and made available for transport across the skin barrier. Since w/o microemulsions would be most likely used to solubilize polar drugs, release of a hydrophilic drug from this model vehicle will be described in a later study.

EXPERIMENTAL

Materials used for the phase behavior characterization, and the in vitro transdermal studies were used as received and include dioctyl sodium sulfosuccinate USP from American Cyanamid Company (Bridgewater, NJ), and 1-Octanol (Aldrich 99%). USP purified water was treated in a millipore MILLI-Q^{R} filtration system prior to use, while tritiated water (5mCi/ml) was obtained from Amersham Corporation (Arlington Heights, IL). For the self-diffusion coefficient measurements using the NMR technique described below, the dioctyl sodium sulfosuccinate USP was further purified by the method according to Eicke (11).

The in vitro skin permeation studies were conducted on an apparatus as described by Holland et.al. (12). This flow through cell design has a small volume receiving chamber and a skin surface dosing area of 2 cm^2. Unlike the method described by Holland, 0.9% NaCl in distilled water solution was used as the

receiving media (flow rate 1.66 ml/hour), and no attempts were made at maintaining skin viability. Fresh, full thickness samples of human skin were obtained from radical mastectomy cases within 24 hours of the operation, and used for the studies within 48hrs. During the time between tissue procurement and use, the skin was soaked in saline and packed in wet ice. The skin was thoroughly rinsed with purified water and the subcutaneous fat was removed prior to mounting in the diffusion cell. After mounting, MILLI-Q^R water was used to maintain skin hydration and to eliminate potential osmotic effects until dosing. The receiving media was thermostated at 35^{o}C. Microemulsion samples for the skin permeation study were prepared by adding 25 microliters of the 50 mCi/ml tritiated water to a tared reaction vial. The appropriate amount of MILLI-Q^R water was then added and mixed, prior to the addition of 58/42 by weight DSS/octanol solution which was then periodically mixed over the next 24 to 72 hours prior to dosing. Amounts were used that would combine for a total sample weight of 2.5 grams. An infinite dose using 500 microliters of microemulsion was placed on the skin surface. The saline receiving fluid was collected directly into the scintillation vials. After addition of Amersham PCS fluid, the samples were counted using a Packard TRI-CARB 2000CA Liquid Scintillation Analyzer.

Phase behavior determinations were completed by the use of the laboratory robotics system described elsewhere (13). Again, the DSS was dissolved in octanol prior to the addition of water

(where possible) to facilitate the samples reaching equilibrium. Phase uniformity was checked using polarized light microscopy.

Water self-diffusion coefficients were measured using the Pulsed Field Gradient Fourier Transform (PFGFT) NMR technique (14), on a JEOL FX90Q multinuclear spectrometer which can produce field gradients in the range of 1-5 gauss/cm by use of the homospoil coil under software control.

RESULTS AND DISCUSSION

As seen in figure 1, the phase behavior for the water/octanol/DSS system is characterized by an extension toward the water corner for a rather narrow range of octanol:DSS mixtures. Also noteworthy are the effect of the liquid crystalline phases on the shape of the high DSS side of the microemulsion boundary. The ability of the 58:42 DSS:octanol weight ratio to incorporate greater than 70 % water makes this system very useful in evaluating the effect of microemulsion composition on transdermal flux. For this initial study, the advantages of the phase behavior and understanding of octanol's skin permeability (15,16) outweigh the practical limitation that octanol is generally too irritating to be used topically (8). Due to the presence of the three phase regions at high water content, the 58:42 DSS:octanol weight ratio does not become saturated with water until the addition of 84% (wt/wt) water. Experimentally, saturation is denoted by essentially pure water being one of the excess phases when water is added to greater than 84% as shown in figure 1.

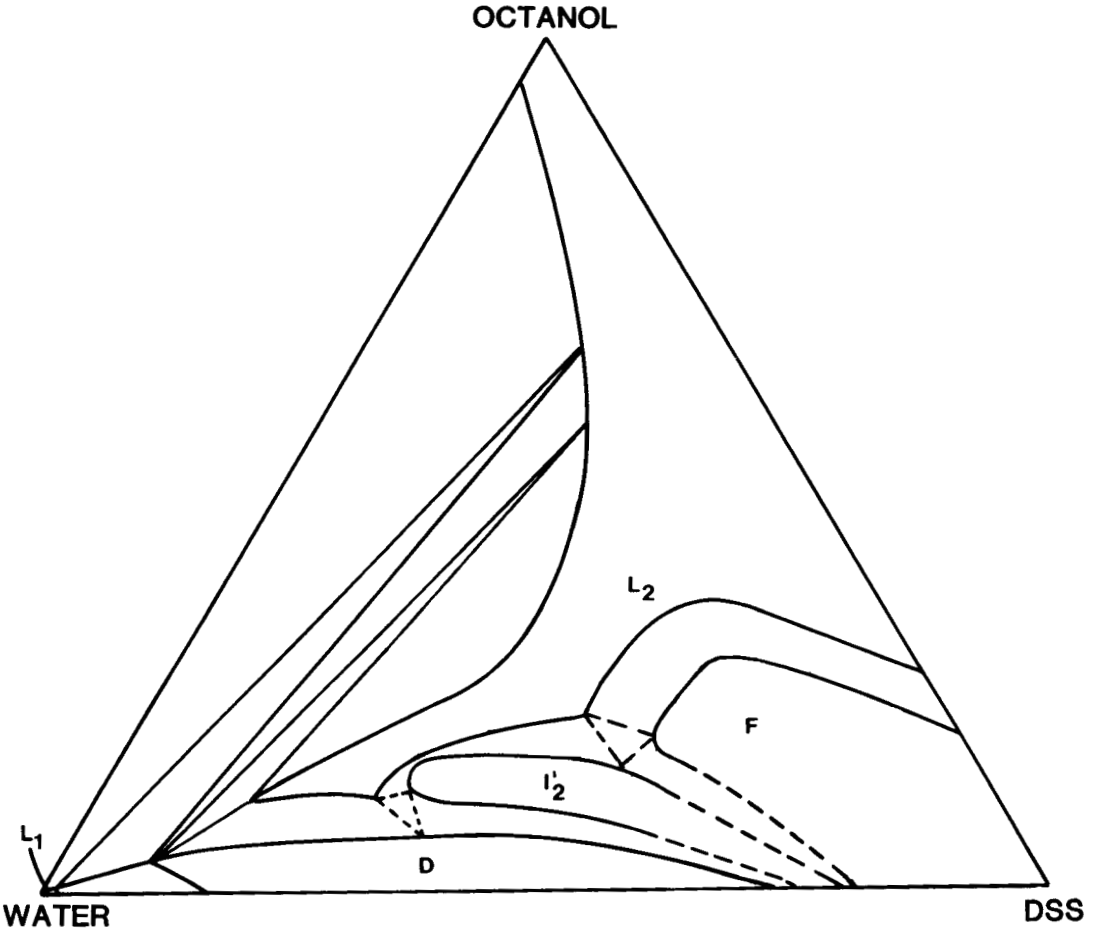

Figure 1. Phase behavior at 25°C of the system water/octanol/dioctyl sodium sulfosuccinate. Phases are labeled by L_1, normal micellar; L_2 inverse micellar; D, lamellar liquid crystalline; I_2, cubic liquid crystalline; and F, reversed hexagonal liquid crystalline.

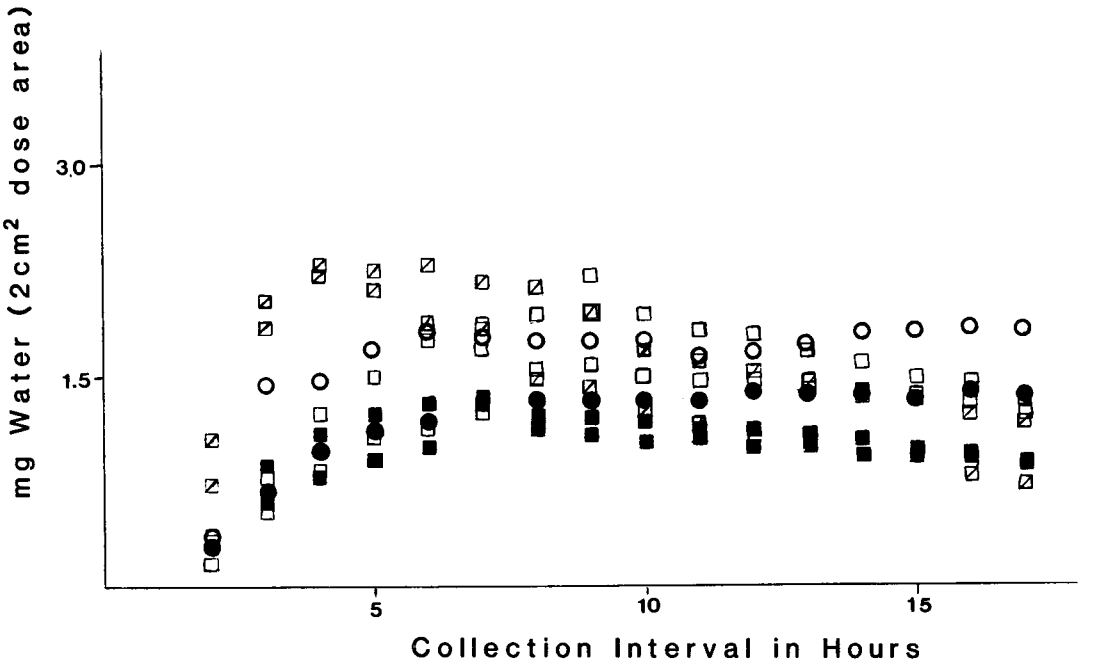

Figure 2. In vitro transdermal data for the microemulsion system having the composition 15% water, 49% DSS, and 36% octanol (squares) compared to water transport (circles). Data represented by slashed squares is for the microemulsion system without water transport values for skin from the same donor.

Figures 2-5 show the percutaneous transport plots for the microemulsions formed by adding 15,35,58, and 67% water to a 58/42 weight ratio of DDS:octanol. Each plot uses squares for denoting transport from the microemulsion, while the circles represent flux for neat water. Circles and squares shaded the same indicate skin obtained from the same donor. By graphing the amount (mg) of water that permeates the skin as a function of time, the steady state flux value can be directly obtained from the data plateau which should be level after the initial lag time, i.e. the mg of

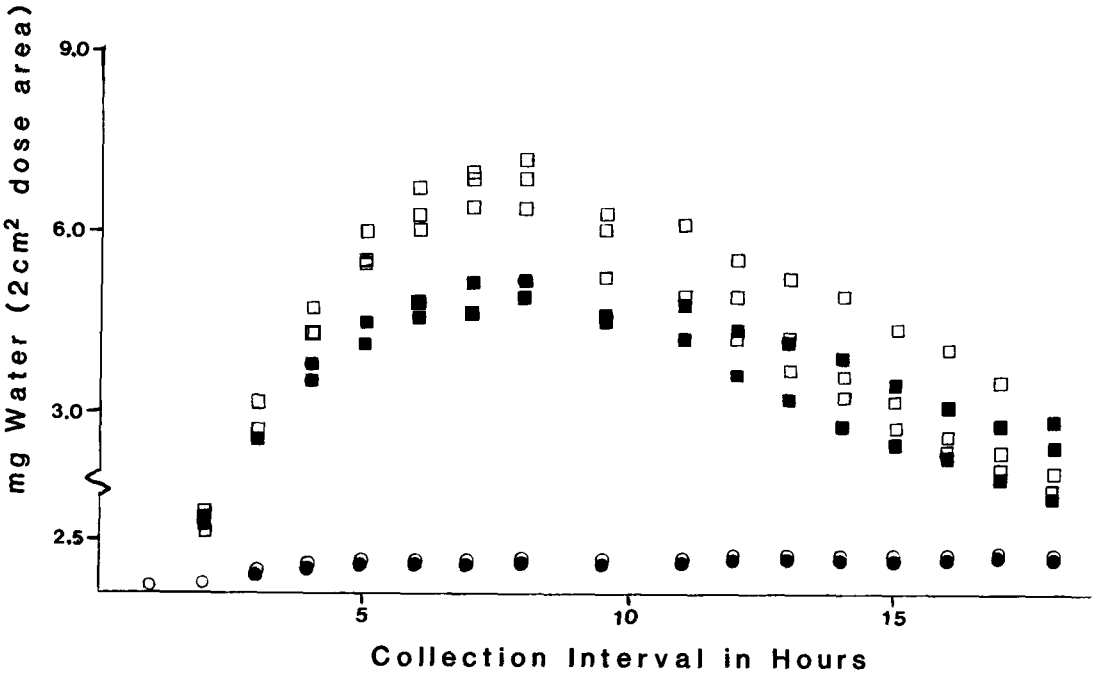

Figure 3. In vitro transdermal data for the microemulsion system having the composition 35% water, 38% DSS, and 27% octanol (squares) compared to water transport (circles).

water that permeates is constant for each equally spaced time interval. As seen for the circles on figures 2-5, the level plateau indicating steady state flux is realized for the skin samples that were treated with neat water. The compilation of the values in Table 1 give an average effective membrane permeability coefficient value of 0.98 X 10^{-3} cm/hr which compares favorably to the values determined by Bronaugh et.al. (17) for human abdominal skin (P_e = 1.54 $\pm$ 0.14 X 10^{-3} cm/hr).

Although some of the microemulsion plots have a level plateau, most show a distinct flux decrease or tailing effect

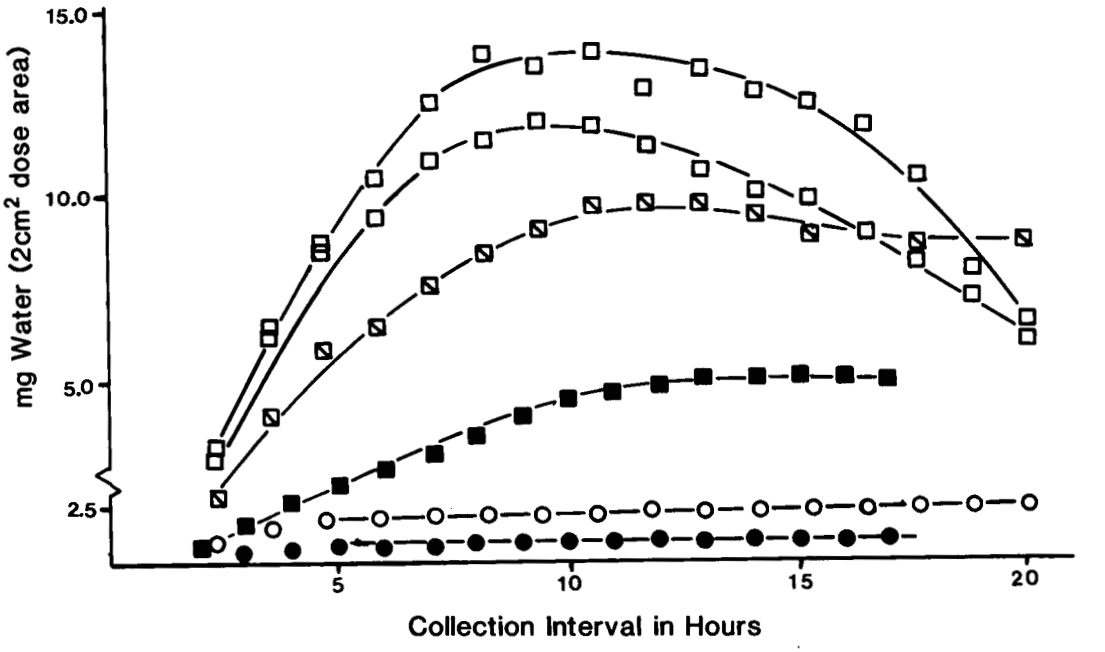

Figure 4. In vitro transdermal data for the microemulsion system having the composition 58% water, 24% DSS, and 18% octanol (squares) compared to water transport (circles). Data represented by slashed squares is for the microemulsion system without water transport values for skin from the same donor.

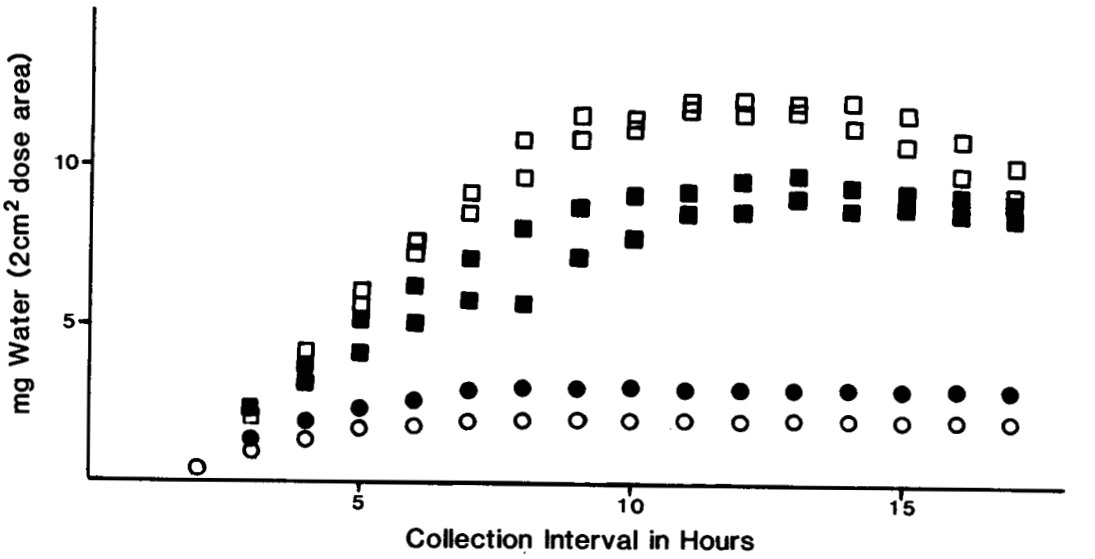

Figure 5. In vitro transdermal data for the microemulsion system having the composition 67% water, 19% DSS, and 14% octanol (squares) compared to water transport (circles).

TABLE 1.

Water Absorption Through Excised Human Breast Skin.

Skin Donor No.	Permeability Coefficient X 10^3 (cm/hr)
089	1.20
111	0.61
134	0.87
169	0.45
232	0.80
234	0.90
334	0.90
345	0.70
392	0.90
457	1.55
459	1.80
659	1.40
717	1.05
750	0.90
773	1.50
811	0.50
Average	0.98

after reaching a peak flux value. This indicates an increase in the barrier properties of the skin with time and is seen for each of the 15,35,58, and to a lesser extent for the 67% water samples. Although the degree of tailing does not appear to be dependent upon the composition of the microemulsion, it is dependent upon the permeability of the skin sample used. In figure 6 it is evident that the degree of tailing dramatically increases as the skin's water permeability increases. Note that these extremes in tailing are for identical doses of the 58% water microemulsion. It is seen that the skin permeability is more significant than vehicle composition in producing this tailing effect.

The relationship between the flux decrease and water permeability of the skin provides the basis for the explanation of

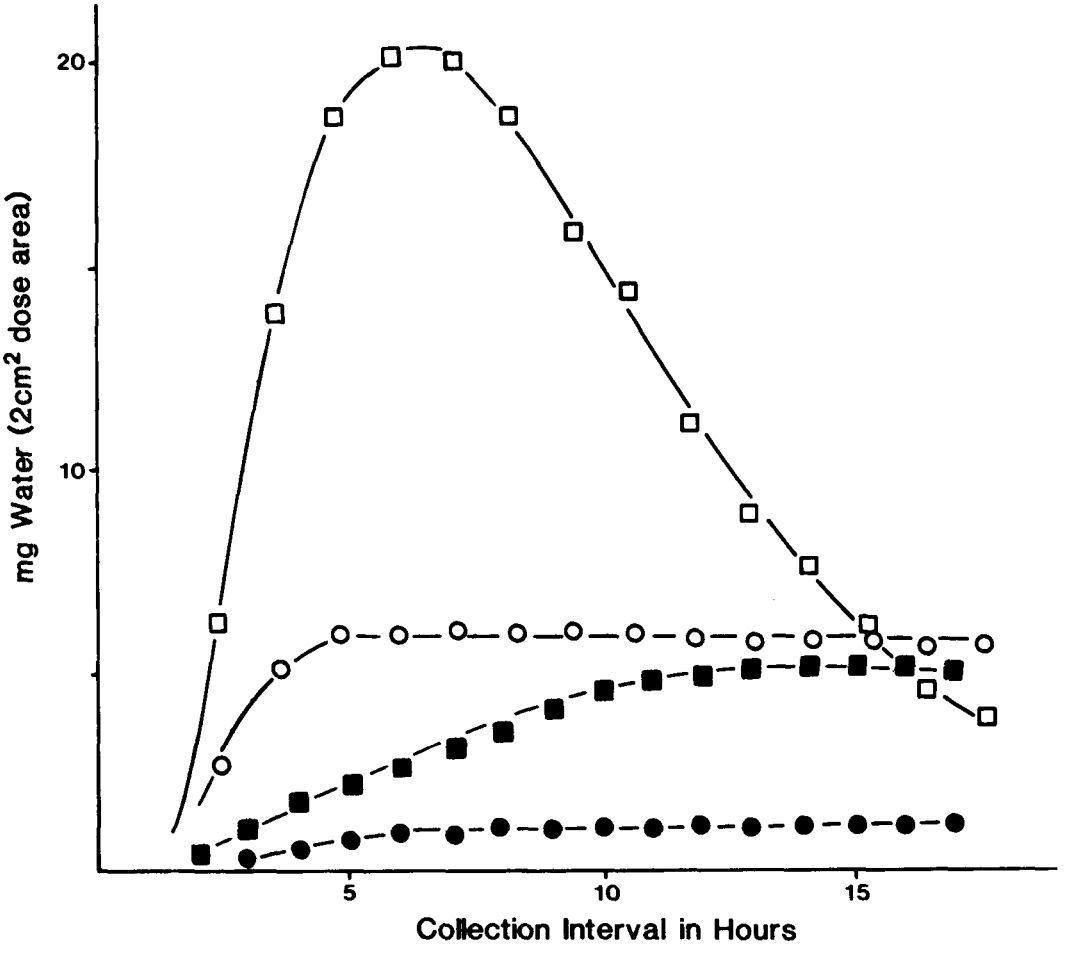

Figure 6. In vitro transdermal data for the microemulsion system having the composition 58% water, 24% DSS, and 18% octanol (squares) compared to water transport (circles). Note the correlation between tailing and the skin specimens water permeability.

this characteristic microemulsion behavior. Since the skin used in this study is fully hydrated, its water permeability is maximized. When an infinite dose of the microemulsion is brought into contact with the hydrated stratum corneum, the microemulsion vehicle apparently pulls water from the stratum corneum,

TABLE 2.

Water Self Diffusion and Normalized in vitro Transdermal Flux Values for the Microemulsion formed by addition of water to a 58/42 weight ratio of DSS/Octanol.

% Water	X_{water}	D/Dw	Normalized Flux (average)
15	0.68	0.035	0.89, 0.78 (0.84)
35	0.87	0.072	2.9, 2.1 (2.5)
45	0.91	0.100	
52	0.93	0.200	
58	0.94	0.353	4.9, 5.4 (5.2)
67	0.96	0.363	6.2, 2.9 (4.5)

indicating that the chemical potential of water in the microemulsion is less than the chemical potential of water in the stratum corneum. This dehydration of the stratum corneum eventually results in the observed increase in barrier function. The more permeable the skin to water, the faster dehydration occurs, and the more severe the tailing during the time frame of the study. Since significant differences in the amount of tailing is not observed between the 15% water and 58% water formulations, it appears that the microemulsions in this concentration range are capable of further incorporating available water from the stratum corneum, but that the rate at which that additional water is made available is controlled by the stratum corneum.

Transdermal flux values normalized against water flux for a separate punch of the same skin sample are given in Table 2 with water self-diffusion coefficients for the same microemulsion compositions. As seen, increasing the amount of water in the system both increases the transdermal flux of the water, and

increases the average self-diffusion of water in the system. The value of D/D_W is a unitless value of the self-diffusion coefficient of water in the microemulsion is divided by the self-diffusion coefficient for water in water. Therefore a D/D_W value of 0.100 means that, on the average, water in the 45% water microemulsion environment diffuses at one-tenth the rate that a water molecule would diffuse in a purely aqueous environment. The initially low values for D/D_W and its subsequent increase with addition of water can be directly attributed to binding of the water molecules to the surfactant headgroup. Thus, the initial molecules of water added to the system are tightly held to the DSS headgroup and will diffuse through the system at the rate that the surfactant diffuses through the system, i.e. presumably at a slower rate than water in an aqueous environment. As the primary solvation sites around the DSS become occupied, free water will begin being incorporated in the system, and D/D_W will increase, approaching unity (figure 7).

The values for normalized flux show a similar trend (Table 2) except enhanced percutaneous absorption of water occurs for the microemulsion systems studied which contain greater than 15% water. Since the vehicle obviously affects the skin barrier, traditional thermodynamic arguments cannot be used to describe increased water flux as water saturation is being approached. Rather, the source of percutaneous enhancement must be determined. To do this a number of pretreatment studies were undertaken. Results from these studies are given in Table 3. As shown, neither Octanol nor DSS pretreatment of the skin caused

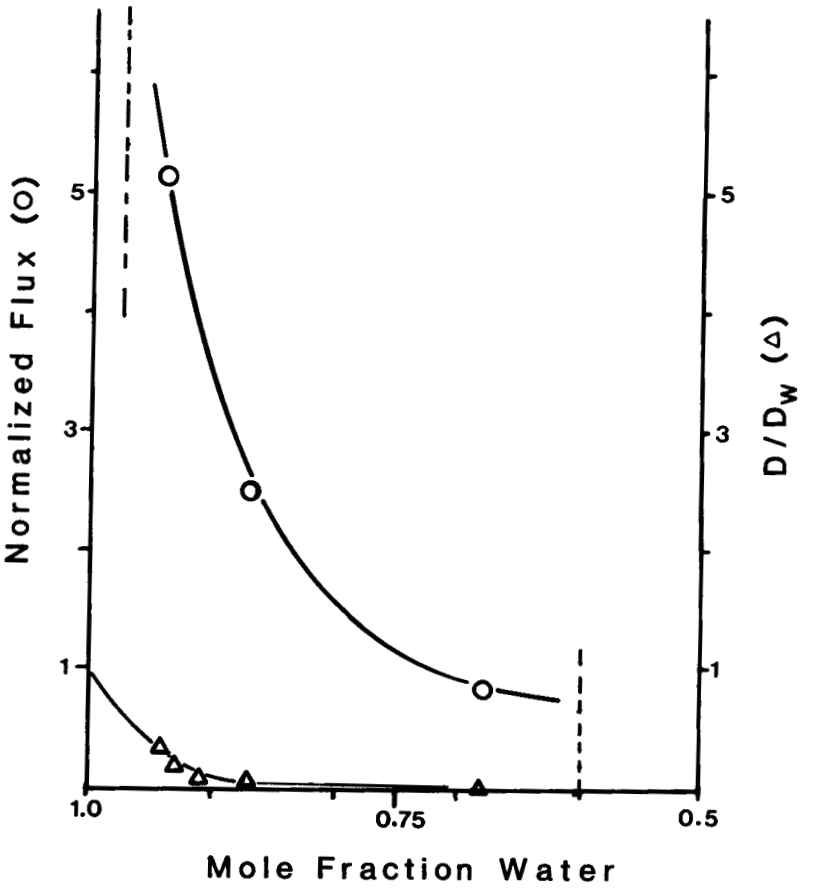

Figure 7. Plot of normalized flux and water self diffusion against mole fraction of water. The mole fraction of water at which the 58/42 ratio of DSS/octanol becomes saturated with water is denoted by (- · - · -), while the mole fraction of water corresponding to six moles of water per mole DSS is denoted by (-----).

TABLE 3.

Normalized in vitro Transdermal Flux Values for Neat Water Following Pretreatment.

Substance	Duration (hours)	Normalized Flux
Octanol	0.5 - 6	1.7
DSS (from EtOH)	2	2.1
DSS/Octanol 58/42	1 - 6	3.8
	18 - 22	7.3

enhancement of the magnitude seen for the high water microemulsions. However, the combination of DSS and octanol did result in percutaneous enhancements for water of the magnitude found for the microemulsions. From these results, it appears that the microemulsion structure itself does not result in enhanced delivery across the skin barrier. Two of the microemulsion's components, when used in combination, do serve as penetration enhancers. Thus, for this system enhancement is dependent upon a synergistic effect between DSS and octanol, but not upon the vehicle's microemulsion structure. This result may imply that for this fluid microemulsion the vehicle/stratum cornuem interface dominates the water transport process. It must also be noted that pretreatment of hydrated skin with DSS/octanol, will result in a certain level of DSS/octanol hydration. Thus, it is impossible to assess the role of "bound" water molecules on the DSS involved in the synergistic behavior of DSS/octanol as observed in the pretreatment.

CONCLUSIONS

A number of factors influence the percutaneous absorption of water when delivered from a microemulsion vehicle. First, for low-water content microemulsions applied in infinite dose, the vehicle will actually dehydrate the skin sufficiently to increase the skin barrier. Because the rate of this dehydration process is stratum corneum controlled, only the most water permeable skin specimens were significantly influenced by this effect. The lowest

water content microemulsions also contained primarily water bound to the surfactant headgroup. Bound water diffuses within/from the vehicle more slowly than the free water characteristic of the high-water microemulsions. The combination of these two effects account for low transdermal water flux values from low-water microemulsions. Secondly, percutaneous absorption enhancement from the high-water microemulsions could be explained in terms of enhancement resulting from a synergistic effect between DSS and Octanol. For this system, it does not appear that the microemulsion structure results in percutaneous absorption enhancement beyond the enhancement resulting from the hydrated DSS/Octanol enhancement.

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