The Influence of Liquid Crystalline Phases on Drug Percutaneous Absorption. II. Permeation Studies Through Excised Human Skin

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The influence of liquid crystalline (LC) phases on the percutaneous absorption of a model compound (ploxicromil; PXC) was studied with the use of the phase diagram for the surfactant, oil, and water comprising the vehicles. Two separate sets of vehicles, representing two different tie lines lying in the L_1 + LC phase region, were prepared in which the concentration of LC was varied over the range 0 to 100% along each tie line. *In vitro* permeation studies of PXC from these systems were conducted using excised human skin and the flux values determined as a function of the percentage LC present in the vehicles. In virtually all cases, the flux reached a peak at 5–10% LC and then decreased significantly as the fraction of LC present increased further. The pattern of behavior observed is discussed in terms of current theories describing membrane-controlled and vehicle-controlled diffusion, none of which adequately model the results obtained.

KEY WORDS: liquid crystalline phases; percutaneous absorption; transdermal drug delivery; topical vehicles; phase diagrams; tie lines.

INTRODUCTION

A previous publication (1) outlined the rationale behind the use of liquid crystalline (LC) phases in topical vehicles and their possible effect on drug permeation through skin. The relevant portions of the ternary phase diagram for the polyoxyethylene(20)cetyl ether (Brij 58 or cetomacrogol; $C_{16}E_{20}$):dodecanol ($C_{12}OH$):water system were determined. This system was selected because of the presence of substantial LC regions, the acceptable physical and chemical stability in the absence and presence of the drugs to be studied, and the likely absence of any overt adverse effects when in contact with human skin. A number of tie lines were established within the L_1 + LC phase region. Based on such tie lines, it was then possible to study systematically the effect of increasing concentrations of an LC phase on the percutaneous absorption of drugs dispersed in the L_1 + LC vehicle. Such studies form the basis of this present report, in which proxicromil (PXC), a lipophilic experimental antiasthma agent, was used. Prior to conducting permeation studies through excised human skin, solubility and partitioning studies in a number of systems were undertaken using this compound.

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MATERIALS AND METHODS

Chemicals

Phosphate buffer (67 m*M*, pH 7.4) was prepared by dissolving 1.6 g sodium phosphate monobasic and 7.8 g sodium phosphate dibasic in 1 L water. Trypsin solution was prepared by diluting 250 mg trypsin (Type IX, Sigma Chemical Company, St. Louis, MO) in 100 ml 0.5% sodium bicarbonate in water and adjusting the pH to 8.2–8.6. Proxicromil [FPL 57,787; 6,7,8,9-tetrahydro-5-hydroxy-4-oxo-10-propyl-4H-naphtho(2,3-*b*)-pyran-2-carboxylic acid; PXC] was donated by Fisons PLC, Pharmaceutical Division, Loughborough, England. All other materials were as stated previously (1).

Excised Human Skin

Samples of whole human skin were obtained from the chest within 24 hr of death. The subcutaneous fat was removed and the remaining skin immersed in a water bath at 60°C for 2 min. The stratum corneum plus epidermis (SCE) was separated from the dermis (2) and the SCE was spread, epidermal side down, onto the surface of water contained in a beaker. Using a piece of aluminum foil as a scoop, the sample was transferred to a Styrofoam pad and placed in a desiccator maintained at 25% RH. After 3 days, the dried SCE was removed, wrapped in aluminum foil, and stored at 3°C until needed. Samples of stratum corneum (SC) were prepared as follows: A piece of Whatman No. 1 filter paper on a ceramic saucer maintained at 37°C was soaked with a 0.25% solution of trypsin in 0.5% sodium bicarbonate solution adjusted to a pH of 8.2–8.6. The SCE was placed, epidermal side face down, onto the filter paper for 5 min. After rinsing with distilled water, the epidermal surface was gently rubbed with a cotton-tipped applicator until only the stratum corneum remained as an intact sheet of tissue. The SC was rinsed with distilled water, dried, wrapped in aluminum foil, and stored at 3°C until needed. Prior to use in a permeation study, dried samples of SCE or SC were rehydrated in distilled water for 1 hr.

Preparation of Systems Containing PXC

Based on previous work to characterize the L_1 + LC region of the $C_{16}E_{20}$:$C_{12}OH$:water system (1), two tie lines, designated I and II, were selected for formulation of the donor vehicles. Four ternary component mixtures lying along each tie line, and containing 10, 30, 50, and 75% (w/w) LC, were prepared and 0.15 mg PXC/g was added, a concentration resulting in a system unsaturated with respect to PXC. After equilibration and centrifugation at 25°C, the separated conjugate phases from these four component systems were analyzed and their compositions compared in order to confirm that the L_1 and LC conjugate phases lay on a common tie line. To facilitate preparation of donor vehicles for the actual permeation studies and minimize between-sample variation, a quantity of a four-component mixture containing 0.15 mg PXC/g and sufficient for all studies lying on tie lines I and II was prepared, allowed to reach equilibrium, and separated into the respective L_1 and LC conjugate phases.

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These separated phases were subsequently used as stock solutions that were mixed together, as required, to form a range of dispersed L_1 + LC systems in which the two phases were varied in a known and systematic manner from 0 to 100% LC. In preparing each system, an appropriate amount of each phase was weighed into a small vial, the vial sealed, and the mixture heated until fluid. The mixture was vigorously shaken until blended, then continuously agitated while cooling to 25°C.

Permeation Studies

Plexiglas permeation cells were used that allowed continuous, automated sampling of the receiving compartment. A cell consisted of a stack of Plexiglas plates, each of which had a circular hole drilled through the middle, together with a bolt hole at each corner. The cell was completed by bolting a solid plate, also containing a bolt hole at each corner, to the top and bottom of the stack of drilled plates. By varying the thickness and number of the constituent Plexiglas plates, the volumes of the donor and receiving compartments could be easily varied. In the permeation studies undertaken, the volume of the donor compartment was varied to contain from 80 mg up to 1 g of vehicle, while the volume of the receiving compartment was set at 1.5 ml. A small magnetic stirring bar was placed in the receiving compartment and a sample of SCE or SC placed over the cell opening. The donor compartment, minus, lid, was clamped over the skin sample, a known weight of the formulation added, the top of the donor compartment put in place, and the whole cell fastened together. The cell was immersed in a water bath at 25°C and sited over a magnetic stirrer. A peristaltic pump was used to draw phosphate buffer, at the rate of 0.15 ml/hr, from a reservoir through the receiving compartment, via inlet and outlet ports, into a fraction collector. Samples from the receiving compartment so obtained were analyzed as described below.

Analysis of Formulations and Samples

The L_1 + LC systems were assayed for $C_{16}E_{20}$ and $C_{12}OH$ as described previously (1). PXC was assayed by HPLC using a Waters UV detector. Aqueous samples from permeation studies were injected directly. All other samples were diluted before injection. PXC was eluted using a mobile phase of methanol:0.5% ammonium acetate buffer (73:27) at a flow rate of 2 ml/min. Absorbance was monitored at 254 nm and the retention time was 4 min. The standard curve was linear over the range of concentrations measured. The limit of detectability was 2 ng, corresponding to a 100-μl injection of 0.02 μg/ml. The partition coefficient $K_{LC/L1}$ was determined by measuring the concentration of PXC in each phase and calculating PXC_{LC}/PXC_{L1}.

RESULTS

Analysis of the four systems prepared along tie lines I and II showed that the conjugate L_1 and LC phases had common compositions, thereby confirming the location of the tie lines used. For tie line I, the percentage (w/w) compositions of the L_1 and LC conjugate phases were 2.06% $C_{16}E_{20}$:0.25% $C_{12}OH$:97.60% water and 19.54% $C_{16}E_{20}$:19.56% $C_{12}OH$:60.90% water, respectively. For tie line II, the percentage (w/w) compositions were 0.56% $C_{16}E_{20}$:0.12% $C_{12}OH$:99.32% water and 20.04% $C_{16}E_{20}$:21.30% $C_{12}OH$:58.66% water, respectively. The concentrations of PXC present in each phase as a function of the percentage (w/w) LC present are shown in Fig. 1.

Six permeation experiments were undertaken using L_1 + LC vehicles lying on tie lines I and II (Table I). These permeation studies are further identified as to the cadaver used, where the letters a–e denote different cadavers from which the skin was excised. Flux values were independent of whether SCE or SC was used. Typical permeation profiles from study Ib are presented in Fig. 2 to illustrate the general shape of the amount permeated vs time plots. These data are also qualitatively representative of the other five studies. Typically, there was a gradual increase in the permeation rate over the first 5–10 hr, followed by steady-state conditions that persisted up to 30 hr. Where permeation runs were continued beyond 30–40 hr, the flux frequently exhibited a gradual decline. The steady-state flux (J; μg cm^{-2} hr^{-1}) of PXC through excised human skin was calculated by linear regression analysis of the steady-state phase of the amount permeated vs time profiles.

The relationships between flux and the amount of LC phase present for each of the three studies along tie lines I and II are shown in Figs. 3 and 4, respectively. As the LC content is increased from 0%, the flux quickly reaches a peak at or below 10% LC, then declines progressively as the system approaches 100% LC. The only exception to this pattern is system Ia, but this is due, most likely, to the peak not being found, since unfortunately, no flux determinations

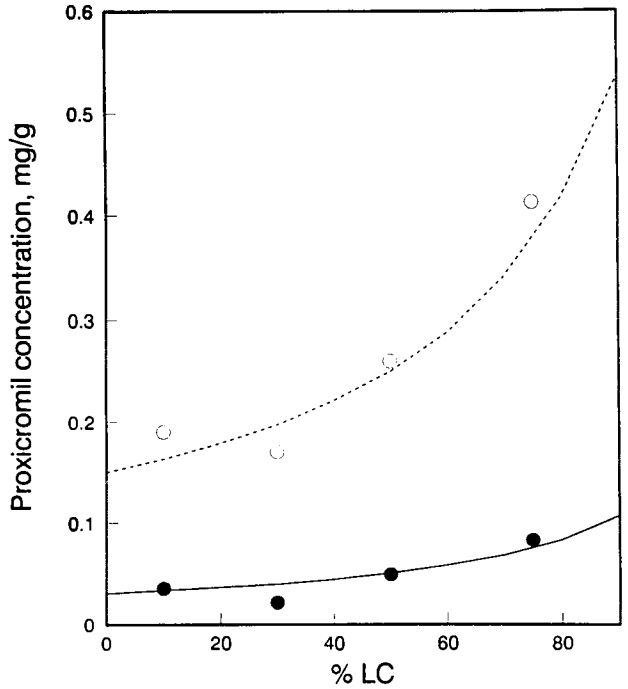

Fig. 1. PXC concentrations in L_1 and LC phases as a function of the percentage (w/w) LC for an unsaturated mixture containing 0.15 mg/g PXC and where $K_{LC/L1}$ = 0.2. Experimental data: L_1 phase, ○; LC phase, ●. Theoretical data: L_1 phase [based on Eq. (2)], - - -; LC phase [based on Eq. (3)], ——.

Table I. Effect of LC on Permeation of PXC Through Excised Human Skin

Study conditions (tie line/cadaver)	Steady-state flux, μg/cm²/hr (95% CI) at % (w/w) LC in formulation									
	0	5	10	15	20	25	30	50	75	100
Ia	0.237 (0.043)	ns	0.156 (0.019)	ns	ns	ns	0.033 (0.006)	0.025 (0.003)	0.399 (0.006)	0.127 (0.002)
Ib	0.146 (0.008)	0.364 (0.300)	0.302 (0.039)	0.238 (0.081)	0.128 (0.006)	0.073 (0.004)	0.131 (0.003)	0.010 (0.001)	ns	0.014 (0.001)
Ic	0.699 (0.033)	1.007 (0.041)	0.849 (0.030)	ns	0.324 (0.024)	0.147 (0.004)	0.126 (0.005)	0.036 (0.003)	0.061 (0.008)	0.020 (0.003)
IIc	0.398 (0.031)	0.423 (0.010)	0.243 (0.005)	0.253 (0.008)	0.177 (0.027)	0.155 (0.041)	0.152 (0.025)	0.042 (0.007)	ns	ns
IId	0.069 (0.067)	ns	0.148 (0.070)	ns	ns	ns	0.029 (0.026)	0.027 (0.004)	0.039 (0.009)	0.027 (0.005)
IIe	0.040 (0.009)	ns	0.164 (0.063)	ns	ns	ns	0.071 (0.007)	0.007 (0.001)	0.054 (0.015)	ns

were carried out between 0 and 10% LC for this particular system.

The effect of the vehicle volume in the donor compartment on the amount of PXC permeated was studied using the L_1 phase from system Ia. Donor cell volumes of 150 μl, 250 μl, and 1 ml resulted in steady-state fluxes of 0.02, 0.13, and 0.30 μg cm^{-2} hr^{-1}, respectively.

DISCUSSION

We have reported previously the determination of a ternary component phase diagram for the system $C_{16}E_{20}$:$C_{12}OH$:water in order to obtain known LC-containing vehicles for studies on the role of LC in the percutaneous absorption of a drug (1). By working with phase systems lying on a tie line within a particular region of the phase diagram, it becomes possible to vary systematically the relative amounts of one or more phases while maintaining their compositions constant. However, this presupposes that the addition of the fourth component, in this case PXC, has no effect on the tie line(s) determined in the ternary component phase diagram. To minimize this possibility and ensure that the compositions of the L_1 and LC phases being

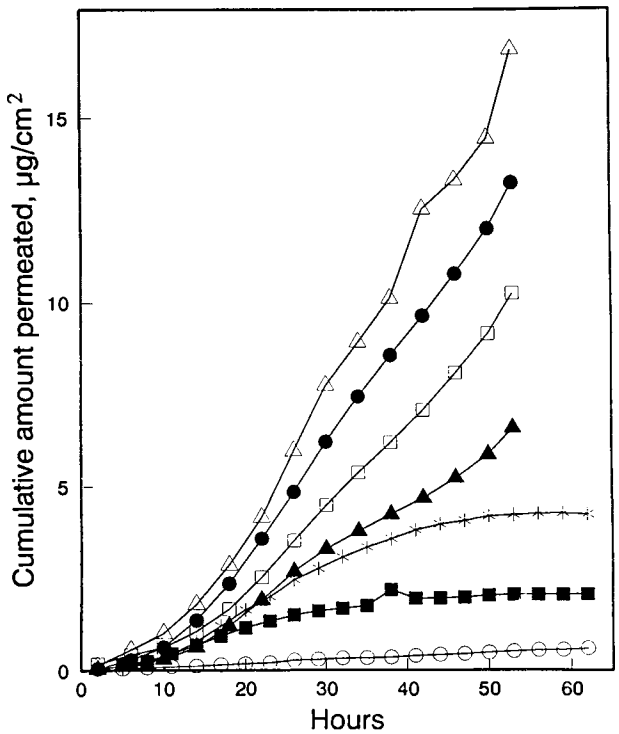

Fig. 2. Typical plots of the cumulative amount of PXC permeating as a function of time through excised human skin from study Ib using L_1 + LC systems. Percentage (w/w) of LC phase in system: 0, ▲; 5, △; 10, ●; 15, □; 20, ✳; 25, ■; 50, ○.

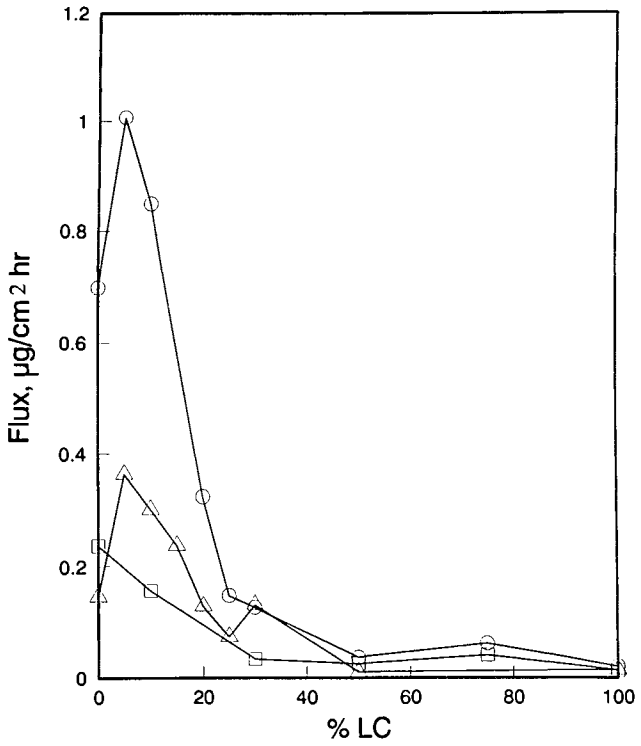

Fig. 3. PXC flux versus percentage (w/w) LC phase in L_1 + LC systems lying along tie line I. Study Ia, □; study Ib, △; study Ic, ○.

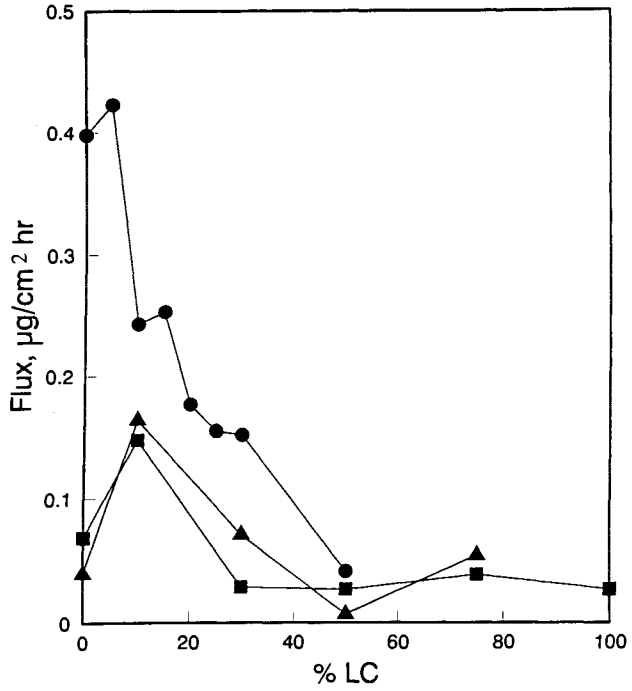

Fig. 4. PXC flux versus percentage (w/w) LC phase in L_1 + LC systems lying along tie line II. Study IIc, ●; study IId, ■; study IIe, ▲.

studied did not vary even as the relative amounts of the two phases were varied, all L_1 + LC mixtures in a particular series of studies were prepared, as described earlier, by combining the single-phase stock solutions in known amounts. No change in phase equilibria or composition of the conjugate phases following mixing was detected.

For such an L_1 + LC system, the total concentration of PXC in the two conjugate phases is given by Eq. (1):

$$C_T = f_{L1}C_{L1} + f_{LC}C_{LC} \quad (1)$$

where C_T is the total concentration of PXC, C_{L1} and C_{LC} represent the concentrations of PXC in each of the conjugate phases, and f_{L1} and f_{LC} are the respective fractions of these phases. By rearranging Eq. (1), the concentration of PXC in each phase can be related to the total concentration, the partition coefficient between the phases ($K_{LC/L1}$), and the volume fractions of each phase. Thus

$$C_{L1} = C_T/(f_{L1} + f_{LC}K_{LC/L1}) \quad (2)$$

and

$$C_{LC} = K_{LC/L1}C_T/(f_{L1} + f_{LC}K_{LC/L1}) \quad (3)$$

These relationships are important since the "effective" concentration of PXC in the vehicle available for permeation may be a function of either C_{L1} or C_{LC}. Figure I shows the theoretical relationship obtained from Eqs. (2) and (3), using an experimentally determined value of $K_{LC/L1}$ = 0.2 and when C_T = 0.15 mg PXC/g system. The experimentally determined points compare well with the predicted curves and are regarded as confirming the validity of the approach taken in using the stock L_1 and LC phases to prepare the L_1 + LC systems described above.

Of necessity, skin samples from a number of different donors, and of limited surface area, were used in the permeation studies. Thus, even though steps were taken to ensure that all L_1 + LC systems fell on either tie line I or tie line II, not all data from the permeation studies were directly comparable because the skin samples came from a number of different cadavers. However, the skin used in studies Ic and IIc did come from the same cadaver. Assuming that the differences in permeability of the skin are independent on the percentage LC along a particular tie line, the results from the other studies (Ia, Ib and IId, and IIe) were normalized to those for Ic and IIc, respectively, so that all three sets of data from each tie line could be averaged and plotted in Fig. 5. This was achieved by taking the flux values from Ic and IIc and calculating the factor which, when used to multiply the flux values from the other studies on tie lines I and II, respectively, produced the smallest standard deviations for the mean flux at each percentage LC studied. With flux data from studies Ia and Ib, the factor was found to be 2.8. while for studies IId and IIe it was 3.0.

The normalized fluxes for the systems prepared along the two tie lines are shown in Fig. 5 as a function of the percentage LC. It is clear that a consistent pattern of behavior exists, with the peak flux occurring when 5–10% LC is present; the flux then decreases significantly as the fraction of LC present increases further. Up to approximately 25% LC, the flux of PXC from systems on tie line I exceeds that from systems prepared on tie line II. These results show that the amount of LC in a formulation and the position of the tie line affect the permeation of PXC through skin. Other factors which may influence a drug's permeation are its solu-

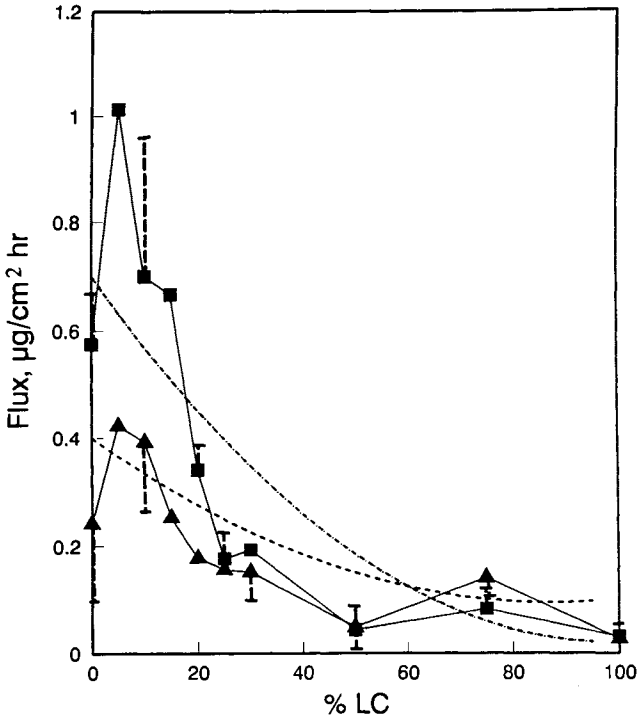

Fig. 5. Comparison of normalized, experimentally determined, fluxes for tie lines I and II with theoretical curves based on Eq. (10). Experimental data: tie line I, ■; tie line II, ▲. Theoretical data: tie line I, - · - ·; tie line II, - - -. Error bars indicate SD.

bility, partition coefficient, and diffusion through the vehicle, as well as the volume of the donor compartment.

Models of Drug Diffusion

Attempts were made to correlate the observations arising from the permeation studies with existing models of drug permeation through skin, which fall into two categories—those dealing with membrane-controlled diffusion and those dealing with vehicle-controlled diffusion. In a membrane-controlled model, the concentration of drug in the vehicle is always uniform. As drug permeates into the skin, membrane-controlled depletion results from a uniform drop in concentration throughout the full thickness of the donor compartment. This is in contrast to depletion for a vehicle-controlled model, where the concentration near the surface of the membrane may be much lower than at the other end of the donor compartment.

Membrane-Controlled Diffusion. Considering membrane-controlled diffusion models, neither the simple model of Blank (3), which characterizes the skin as a homogeneous barrier through which a drug moves by passive diffusion, nor that described by Flynn *et al.* (4), for unidirectional diffusion along two or more parallel pathways, was found to correlate in a satisfactory manner with the data obtained. In the case of the second model, this was felt to be due, at least in part, to the effective concentration in the vehicle at the time of onset of the steady state being significantly lower than the initial concentration. At the beginning of a permeation study, PXC penetrates into the skin. Eventually, a dynamic equilibrium is reached between the skin and the donor compartment. If the total amount of PXC in the donor compartment is insufficient to maintain the initial concentration in the vehicle adjacent to the membrane, then the effective concentration will decrease. For a homogeneous vehicle, the magnitude of the decrease would depend only on the amount of drug initially in the formulation and its distribution between the vehicle and the skin. With heterogeneous vehicles, an additional consideration is the relative degree to which each phase contributes to the decrease in effective concentration.

To estimate the extent to which the effective concentration of PXC will decrease during the equilibration process, an assumption must be made as to the rate of exchange of PXC between the continuous and the dispersed phases. With L_1 systems, the dispersed phase is essentially a dispersion of micelles. Assuming an instantaneous rate of exchange, then a local equilibrium between the continuous phase and the micelles will exist throughout the vehicle. An estimate of the concentration of PXC in the donor compartment at the onset of steady-state flux can be calculated from the skin/water partition coefficient [Eq. (4)] and a mass balance for the system [Eq. (5)], assuming the amount in the receptor at the onset of steady state is negligible:

$$K_{s,w} = C_s/C_w \tag{4}$$

$$C_oV_d = C_dV_d + C_sV_s \tag{5}$$

where V is the volume, C_o is the initial total concentration of PXC in the formulation, and the subscripts s and d represent the skin and donor compartments, respectively. One of the two unknown concentrations in Eq. (5) is eliminated by Eq. (6), which describes the mass balance for PXC in a donor compartment which contains only L_1, and Eq. (7), which describes the distribution coefficient of PXC between the micelles and the water, $K_{m,w}$:

$$C_d = f_mC_m + (1 - f_m)C_w \tag{6}$$

$$K_{m,w} = (C_m/C_w) \tag{7}$$

where f_m is the volume fraction of the micellar phase, and C_m and C_w are the concentrations of PXC in the micellar and continuous phases, respectively. The fraction of the initial concentration remaining in the donor system once a steady state has been reached, C_d/C_o, is found by substituting Eqs. (4), (6), and (7) into Eq. (5) and rearranging. Thus,

$$\frac{C_d}{C_o} = \frac{1}{1 + V_sK_{s,w}/V_d[1 + (K_{m,w} - 1)f_m]} \tag{8}$$

With the aid of suitable parameter estimates, Eq. (8), which assumes that there is no direct partitioning between the micelles and the skin, can be used to interpret the results of the study on the effect of donor volume. The initial total concentration of PXC in the formulation (C_o) was 0.596 mg/ml, while the solubility of PXC in water was 12.6 μg/g at pH 4 (5). With $f_m = 0.065$ in Eq. (6), $K_{m,w}$ is estimated to be 710, while $K_{s,w}$ for PXC between SCE and phosphate buffer at pH 4 can be estimated to be 1000 (6). If the SC is assumed to be 10 μm thick (7), then a reasonable estimate of V_s is 1 μl. Substituting these values into Eq. (8), the percentage initial concentration of PXC remaining in the donor system at equilibrium is calculated to be 0.98 for a donor volume of 1 ml, 0.92 for 250 μl, and 0.88 for 150 μl. If a membrane-controlled permeation model is applicable, the fluxes for these donor compartment volumes should decrease proportionally with C_d/C_o. Thus, relative to the flux from a 1-ml donor volume, the flux from 250- and 150-μl donor volumes would be predicted to be 94 and 90%, respectively. However, the observed flux from the 250- and 150-μl donor volumes were 43 and 7% of the observed flux from 1 ml of donor. Such data indicate that the effective concentration of PXC in the vehicle at the onset of the steady state is lower than predicted, suggesting that the assumption of an instantaneous equilibrium between the dispersed and the continuous phases is not valid.

If the opposite extreme is assumed, i.e., the rate of exchange of PXC between the dispersed and the continuous phases is negligible, then the change in the effective concentration in the formulation after equilibration with the skin will depend only on the concentration of PXC in the continuous phase (C_w), with the concentration in the dispersed phase remaining reasonably constant. Subject to this restriction, the ratio of C_w at equilibrium to that initially ($C_{w,o}$) will be given by

$$C_w/C_{w,o} = 1/[1 + K_{s,w}V_s/(1 - f_m)V_d] \tag{9}$$

Equation (9) implies that the value of C_w will be determined by V_d. Thus, the fractions of the initial concentration of PXC remaining at equilibrium in the donor compartment for volumes of 1 ml, 250 μl, and 150 μl will be 0.48, 0.19, and 0.12, respectively. In this case, fluxes from 250- and 150-μl donor compartments are predicted to be 40 and 26% of that from a

1-ml donor volume, which better reflect the relative fluxes observed from the three donor compartment volumes studied. This implies that a major factor affecting flux is the amount of PXC in the continuous phase.

This approach can be used to help interpret the effect of increasing the percentage LC while holding the volume of the donor compartment constant. Such a situation results in the amount of PXC in the continuous phase decreasing proportionally with the amount of L_1. To account for this, V_d in Eq. (9) must be multiplied by f_{L1}. Therefore, a model accounting for the effect of donor volume and maintaining the assumption that the transfer of PXC from the dispersed to the continuous phase is negligible is given by

$$J = \frac{P_{L1} f_{L1} C_{L1}}{(1 + K_{s,w} V_s / f_{L1} V_d)} + P_{LC} f_{LC} C_{LC} \qquad (10)$$

The theoretical flux values calculated using Eq. (10) are plotted as a function of the percentage LC in Fig. 5 and may be compared to the normalized fluxes for tie lines I and II. Equation (10) correctly predicts that the decrease in flux with increasing percentage LC will be more rapid for low percentage LC formulations than for high percentage LC formulations. However, Eq. (10) does not account for the peak fluxes observed at 5–10% LC and the overall correlation is still poor. Accordingly, consideration was then given to vehicle-controlled diffusion.

Vehicle-Controlled Diffusion. The contribution of vehicle-controlled depletion in L_1 + LC vehicles is complicated by the transfer of PXC, solubilized in the micellar and LC structures, into the continuous phase. As PXC is taken up by the skin from the continuous phase, that portion solubilized in the micelles probably diffuses out of the micelles, but not so rapidly that an instantaneous equilibrium between the micelles and the continuous phase is established. This would explain why vehicles containing small amounts of LC from tie line I exhibit greater fluxes than the corresponding vehicles prepared along tie line II. The L_1 phase from tie line I solubilizes more PXC, presumably because of greater micellar solubilization. The increase in flux from vehicles containing small amounts (10% or less) of LC may be due to this phase serving as an additional reservoir from which PXC may transfer into the continuous phase and enhance the amount permeating. As the concentration of dispersed LC increases beyond 10%, it may be thought of as creating a network of aqueous channels through which PXC must diffuse in order to be available for absorption by the skin. At this point, LC may then begin to function as an obstruction to diffusion through the continuous phase. Thus the effective diffusivity of PXC can be expected to decrease as the percentage LC increases.

In qualitative terms, these three factors (an initial depletion of PXC from the continuous phase, a contribution from PXC partitioning from the dispersed phase into the continuous phase, and the increasing obstruction effect as the percentage LC increases) may well explain the flux vs percentage LC profiles for the two tie lines. Two other factors, not discussed here, that may influence PXC permeation are (i) its ionizability and (ii) any penetration of $C_{16}E_{20}$ or $C_{12}OH$ into the skin.

Other Diffusion Models. A model that adequately correlates the data for transdermal permeation of PXC in L_1 + LC vehicles should account for as many factors as possible. No existing model incorporates all the factors raised in the preceding discussion. The model derived by Ayers and Lindstrom (8), for drug release from suspensions, comes closest to being applicable since the dissolution of solid drug in the vehicle can be a rate-limiting step in the same way as interfacial transport. The development of a model that accounts satisfactorily for the major factors shown to influence the permeation of PXC from L_1 + LC vehicles is the subject of a subsequent paper.

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