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Phase volume and partitioning effects on drug delivery from topical emulsions

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The distribution of drugs or preservatives between the phases of emulsions and the respective influences thereof on oral absorption and on microbial preservation have been discussed in the literature (Attwood and Florence, 1983). Here we report on a comparable phenomenon and give appropriate equations describing the apparent permeability of a membrane (e.g., the skin) to a drug (e.g., hydrocortisone (HC)) under the enhancing action of an emulsified, insoluble enhancer (e.g., 1-dodecylazacycloheptan-2-one or Azone^{TM}) present as the internal phase of an oil-in-water (o/w) emulsion. Experimental data which fit well to the proposed model have been reported recently (Hou and Flynn, 1989). Specifically, it was found that the pseudo-steady state flux of HC systems formulated to contain a fixed, total drug concentration decreased systematically as the amount of Azone in the emulsions was increased from 0.1 to 10%. Over this composition range the intrinsic permeability of the skin actually reached and remained at a high, apparently maximal value. This latter point was established in complementary experiments in which the skin was treated with the Azone emulsions but the permeability was assessed following the removal of the Azone by rinsing. Under this circumstance the permeability to HC remained steady and high. The disparity apparent in the Azone concentration dependencies of HC's permeability with and without Azone present is explained by the fact that HC partitions into the Azone phase and, in doing so, lowers the thermodynamic activity of HC in the emulsion. The partition coefficient for HC between Azone and water was found to be 331. The reduction in activity thus should be dramatic as the fractional volume of Azone in the emulsion is increased, as was observed. The effect of this on permeability is straightforward. The lowering of activity reduces HC's partitioning into the skin's surface, the first step in the establishment of the gradient of concentration of this permeant across the skin. The flux from the emulsions falls off accordingly. One can write general equations which quantitatively describe the partitioning phenomenon and how it interacts with permeability. In the first part of our analysis, we will present equations relating thermodynamic and kinetic variables for the mass transfer of hydrocortisone through skin from the two phase emulsion. In the second part, we will account for the effect of phase volume.

Equilibria are assumed to exist for the distribu-

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tion of HC among the three phases involved in the mass transfer of the drug across the skin, namely, the Azone and the aqueous phases (subscripts 1 and 2, respectively, in the following equations) of the emulsion, and the surface of the stratum corneum* (subscript sc) which is the effective diffusion barrier. Hence the activity of HC in the three phases is identical:

$$a_{sc} = a_1 = a_2 \tag{1}$$

In general, for equilibrium between two phases:

$$a_i = a_j \tag{2}$$

$$\gamma_i C_i = \gamma_j C_j \tag{3}$$

where γ is the activity coefficient, C, concentration; and since in general

$$a = \gamma C \tag{4}$$

Rearranging Eqn 3 we have

$$\frac{C_i}{C_j} = \frac{\gamma_j}{\gamma_i} \tag{5}$$

By definition,

$$\frac{C_i}{C_j} = K_{ij} \tag{6}$$

where K_{ij} is the partition coefficient. In terms of the above variables, the steady-state flux of HC through the skin is given by (Higuchi, 1960):

$$J = \frac{D}{h} C_{sc} = \frac{D a_{sc}}{h \gamma_{sc}} \tag{7}$$

where D is the effective diffusion coefficient, and h, the effective thickness of the stratum corneum. But the activities are identical in the three phases (Eqn 1), so

$$J = \frac{D}{h}\frac{a_{sc}}{\gamma_{sc}} = \frac{D}{h}\frac{a_1}{\gamma_{sc}} = \frac{D}{h}\frac{a_2}{\gamma_{sc}} \tag{8}$$

Substituting $\gamma_i C_i$ for a_i ($i = 1,2$):

$$J = \frac{D}{h}\frac{\gamma_1}{\gamma_{sc}} C_1 = \frac{D}{h}\frac{\gamma_2}{\gamma_{sc}} C_2 \tag{9}$$

$$J = P_1 C_1 = P_2 C_2 \tag{10}$$

where

$$P_i = \frac{D}{h}\frac{\gamma_i}{\gamma_{sc}} \tag{11}$$

is the permeability coefficient with respect to the i-th phase (or more appropriately, in terms of the i-th phase variables); $i = 1$ being the Azone phase and $i = 2$ being the aqueous phase. In the following, the intrinsic permeability that we will be referring to is P_2, as given in Eqn 10. Also, note that γ_i/γ_{sc} is the partition coefficient between the stratum corneum and the i-th phase of the emulsion.

Let V_1 and V_2 be the volumes of the Azone phase and the aqueous phase, respectively, in the emulsion and C_1 and C_2 be HC's respective concentrations in these two phases. The partition coefficient of HC between the two phases would be:

$$K = \frac{C_1}{C_2} \tag{12}$$

and therefore:

$$C_2 = \frac{C_1}{K} \tag{13}$$

Let C_e be the concentration of HC in the emulsion based on the total volume of the emulsion. The total amount of HC in the emulsion is the sum of the amounts in the two phases:

$$C_e(V_1 + V_2) = C_1 V_1 + C_2 V_2 \tag{14}$$

* Here meaning specifically the first molecular depth of the stratum corneum. Overall there will be a gradient across the stratum corneum and at all locations deeper than the surface the activity of hydrocortisone will be less than in the applied phase.

and it follows that:

$$C_1 = \frac{C_e(V_1 + V_2) - C_2V_2}{V_1} \quad (15)$$

By substituting for C_1 in Eqn 13 and rearranging, one obtains C_2 in terms of the total drug 'concentration', C_e; the partition coefficient, K; and the individual volumes of the emulsion's phases:

$$C_2 = \frac{C_e(V_1 + V_2)}{KV_1 + V_2} \quad (16)$$

or:

$$C_2 = \frac{C_e}{(K - 1)\,\alpha + 1} \quad (17)$$

where α is the volume fraction of Azone in the emulsion, i.e.:

$$\alpha = \frac{V_1}{V_1 + V_2} \quad (18)$$

McNutly and Karel (1973) reported a similar equation for the release of flavor from o/w emulsions placed in the mouth.

The observed pseudo-steady state flux through the skin, J_e, under the circumstance that the donor medium remains well mixed is:

$$J = \frac{V}{A}\left(\frac{dC}{dt}\right) \quad (19)$$

where V is the volume of the receiver compartment; A, the area for diffusion; and dC/dt is the rate of increase in concentration of the permeant in the receiver compartment of a two-chambered diffusion cell.

The effective overall permeability coefficient (permeability coefficient without regard for the heterogeneity of the system) is:

$$P_e = \frac{J}{C_e} \quad (20)$$

and thus

$$P_e = \frac{V}{A}\frac{dC/dt}{C_e} \quad (21)$$

We assume that the emulsion is well mixed and that distributioning of the drug within the emulsion and between the emulsion and the skin's surface is facile and much faster than the permeation of the drug across the skin. Hence, the drug in the emulsion should exhibit a uniform thermodynamic activity which can be referenced to the prevailing concentration in the aqueous, continuous phase if one knows the partition coefficient of the drug between the two phases of the emulsion and also the respective volumes of the phases. The permeability coefficient normalized for reduced activity as the result of intra-vehicle partitioning is derived beginning with:

$$P_2 = \frac{V}{A}\frac{dC/dt}{C_2} \quad (22)$$

where C_2 again is the prevailing aqueous phase concentration and P_2 is the true or intrinsic permeability coefficient. Substituting Eqn 17 for C_2, we have:

$$P_2 = \frac{V}{A}\frac{dC/dt}{C_e}[(K-1)\,\alpha + 1] \quad (23)$$

and thus it follows that:

$$P_2 = P_e[(K - 1)\,\alpha + 1] \quad (24)$$

or

$$P_e = \frac{P_2}{(K - 1)\,\alpha + 1} \quad (25)$$

The same factor relates the flux from emulsions to that from an aqueous solution of the same total drug concentration. The observed pseudo-steady state flux is given by:

$$J = P_2C_2 \quad (26)$$

$$J = \frac{P_2 C_e}{(K - 1)\,\alpha + 1} \tag{27}$$

But

$$J_0 = P_2 C_e \tag{28}$$

where J_0 is the flux when there is no Azone, i.e. $\alpha = 0$. So:

$$J = \frac{J_0}{(K - 1)\,\alpha + 1} \tag{29}$$

Hence the flux through the skin is lowered by a factor of $(K - 1)\,\alpha + 1$ if the applied phase is an emulsion with discontinuous phase volume fraction α. J obviously equals J_0 when $\alpha = 0$ or when one has a simple solution of the drug in water. It can be seen from Eqn 24 that the effective permeability coefficient, P_e, has to be multiplied by the factor, $(K-1)\,\alpha + 1$, to obtain the actual (partitioning-adjusted) permeability coefficients, P_2.

It is instructive to consider the effect of partitioning on flux or apparent permeability for various regimes of the partition coefficient, K. From Eqn 25, we see that, as a first case, if $K=1$, $P_c = P_2$; there is no partitioning effect. In this unique instance the activity coefficients of the drug in the water and oil phases are equal and the activity is unaffected by shifts in the fractional volumes of the phases. In the second case we assume $K > 1$. If $K > 1$, $(K - 1)\,\alpha + 1 > 1$, it necessarily follows that $P_c < P_2$; the drug's activity through the system is less than it would be if the system was strictly aqueous. On the other hand (third case), if $K < 1$, $(K - 1)\,\alpha + 1 < 1$, then $P_c > P_2$. In this situation the activity through the system is elevated over that when the system is strictly aqueous. The fourth case is a special sub-case of the third. In the limit of $K = 0$, $P_c = P_2/[1 - \alpha]$. In the latter two cases, P_e becomes increasingly larger than P_2 as α is increased. This is because the amount of drug per emulsion volume is constant and as the aqueous phase volume decreases, the concentration of the drug in the aqueous phase, which reflects the activity in this phase, increases up to the limit of its solubility in this phase. In Fig. 1a we have plotted the calculated relative permeabilities P_c/P_2 or equivalently, relative fluxes J/J_0, against α for various cases of K, including that for HC in Azone emulsions where K=331 [2]. We have included a range of α values from 0.001 to 1 but this is only to show the extremes as described by the equation. Due to some co-miscibility of the vehicle solvents, emulsions may not exist throughout this range. The agreement between experimental permeability data (Hou and Flynn, 1989) and prediction in the case of Azone is shown in Fig. 1b for mouse skin and Fig. 1c for human epidermis.

The point at which the aqueous phase attains saturation as the phase volume ratio, α, is increased systematically from some arbitrary starting point (cases 3 and 4) depends on the amount of drug initially present in the system. Suppose C_e is equal to βS_2, where S_2 is the aqueous solubility of the drug and β indicates the prevailing fractional aqueous saturation. As such, β takes values of $0 < \beta \leq 1$. Substituting this for C_e and S_2 for C_2 in Eqn 17 yields:

$$S_2 = \frac{\beta S_2}{(K - 1)\,\alpha + 1} \tag{30}$$

When solved for α, we obtain the oil phase volume fraction at which the aqueous phase drug concentration reaches saturation and thus the point where the flux should reach its theoretical thermodynamic maximum (maximum determined by unit thermodynamic activity in the vehicle, presuming there is no supersaturation):

$$\alpha_2 = \frac{\beta - 1}{K - 1} \tag{31}$$

Eqn 31 is plotted as a function of β for various values of K in Fig. 2. Notably, Eqn 31 suggests that $\alpha_2 > 1$ when $\beta < K$. However, this apparent anomaly actually describes a situation where saturation is unachievable and α_S is without meaning. Thus, for saturation to be reached, it is necessary that β be greater than K and $K < 1$. The relative permeability and/or flux is plotted as a function of α for $K = 0.1$ in Fig. 3, in this instance showing the limiting effect of solubility. It will be noted that

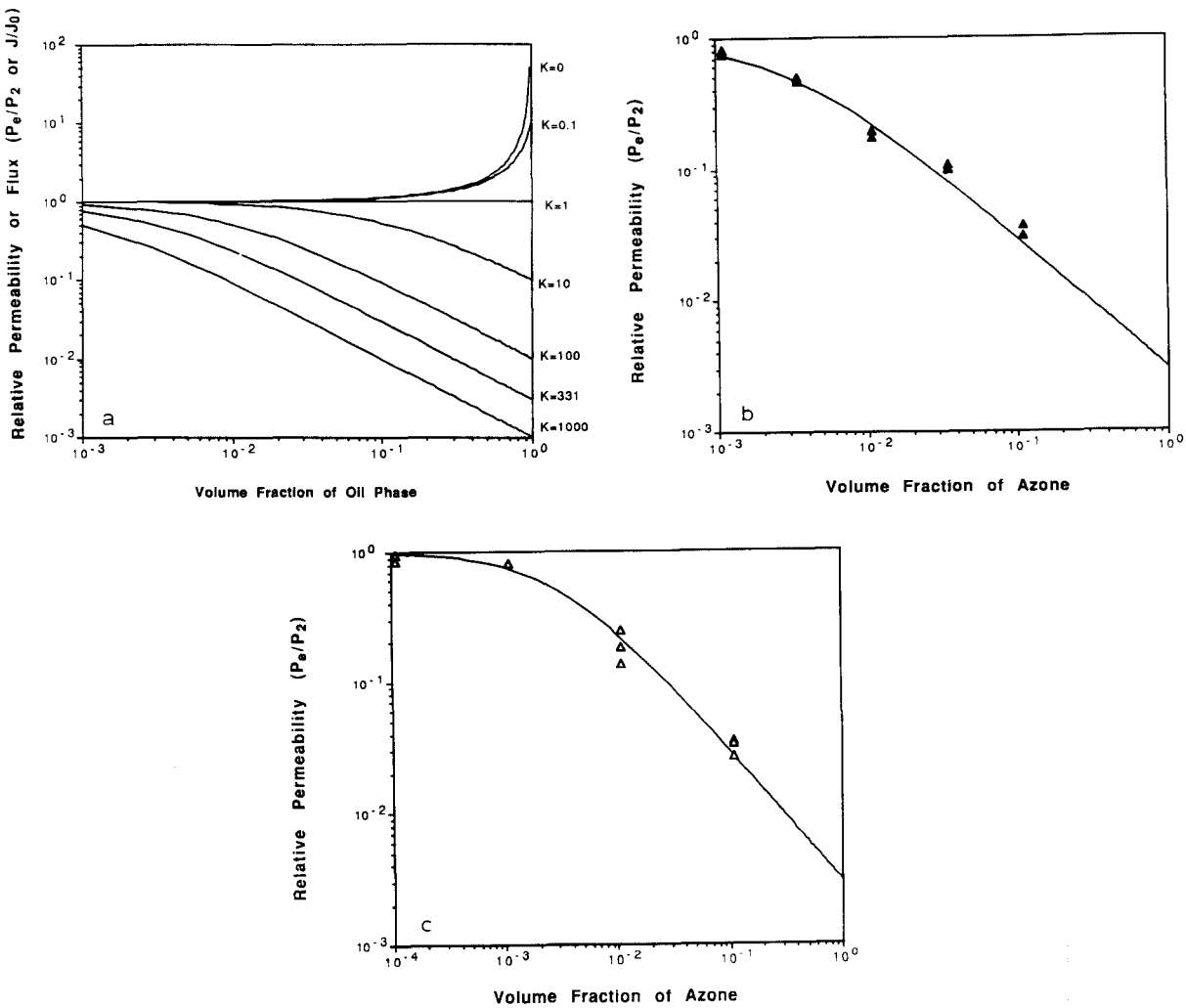

Fig 1. Effect of solute partitioning in emulsion phases on permeability or flux. (a) Prediction for various partition coefficients, K. (b) Permeation of mouse skin by hydrocortisone in Azone emulsions. (c) Human epidermis. In panels b and c, the symbols represent relative permeabilities calculated by taking the ratio of experimental P_e and P_2 values. P_2 is given by the permeability observed after pretreating the skin with 0.1% Azone and rinsing (0.0661 and 0.00119 cm h^{-1} for mouse skin and human epidermis, respectively). The solid curves are the predicted values using K=331.

the less the initial fractional solubility is, the higher is the value of α_2, which falls at the intersection of the curve with each β-dependent plateau line.

For $K > 1$, we consider the effect of saturation with respect to the Azone (internal) phase as α decreases. Since

$$C_1 = KC_2 = \frac{KC_e}{(K-1)\,\alpha + 1} \tag{32}$$

we substitute the solubility of the drug in the internal phase, S_1, for C_1, and βS_1 for C_e. We have

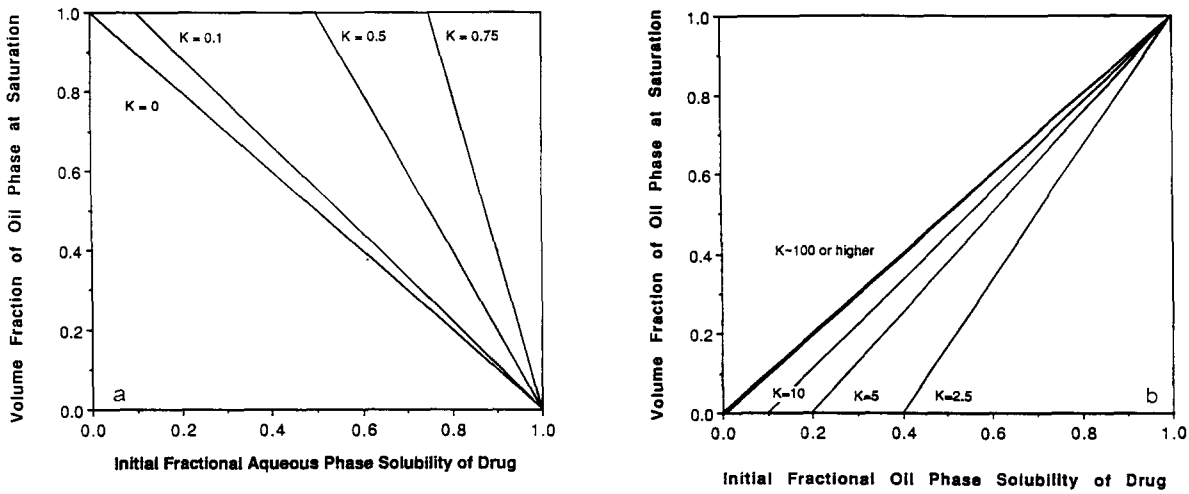

Fig. 2. (a) A plot of Eqn 20 for various K values: oil phase volume fraction (α_2) at which the aqueous phase drug concentration reaches saturation or the flux reaches maximum (for the same total drug concentration based on emulsion volume) as a function of the ratio of the overall drug concentration based on the emulsion total volume to aqueous solubility ($\beta = C_e/S_2$, see Eqn 19). (b) A similar plot of Eqn 33 for $K > 1$.

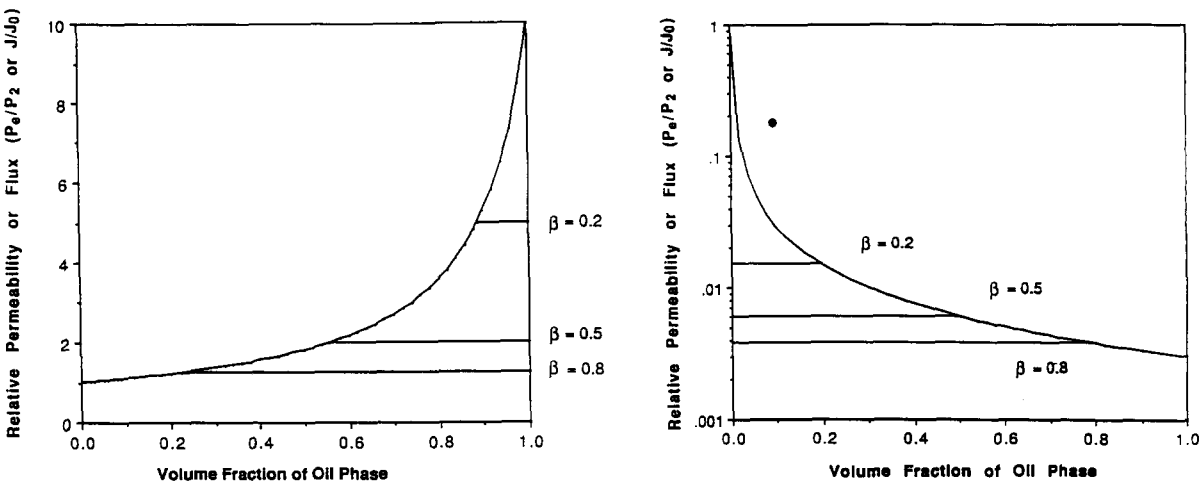

Fig. 3. (a) Limiting effect of the drug aqueous solubility on the effect of its partitioning in emulsion phases with $K < 1$. The case of $K = 0.1$ is shown here. (b) Limiting effect of the drug oil phase solubility on the effect of its partitioning in emulsion phases with $K > 1$. The case of $K = 331$ (Azone) is shown here.

$$\alpha_1 = \frac{\beta K - 1}{K - 1} = \frac{\beta - 1/K}{1 - 1/K} \tag{33}$$

Note that $\beta K > 1$ or $\beta > 1/K$ otherwise α_1 is negative and saturation would never be reached. Eqn 33 is plotted as a function of β for various values of K in Fig. 2b. The relative permeability and/or flux is plotted as a function of α for $K = 331$ (Azone case) in Fig. 3b.

In the real world of use of topical emulsions the relative amounts of an emulsion's phases change at rates determined by the individual volatilities of the phases and capacities for absorption of the phases into the skin after it is applied to the skin. Clearly, from the discussions above, these compositional shifts must be accompanied by complex shifts in activity of the formulated drug. Whether partitioning into the skin at any moment is heightened or lessened depends on the partitioning characteristics of the drug, the drug's solubility characteristics, and the momentary phase volume fraction of the emulsion. All of this is outside of influences of the emulsion on the skin itself.

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