Effect of Bilayer Disruption on Transdermal Transport of Low-Molecular Weight Hydrophobic Solutes

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Purpose. Applications of transdermal drug delivery are limited by low skin permeability. Several chemicals have been used to enhance transdermal drug transport, many of which enhance skin permeability by disordering lipid bilayers. The objective of this study was to develop a mathematical model to describe the effect of bilayer disrupting agents on skin permeability to low molecular weight hydrophobic drugs.

Methods. I predicted solute partition and diffusion coefficients in the lipid bilayers of the stratum corneum using scaled particle theory, which calculates these coefficients based on the work required to create a cavity to incorporate the solute in the lipid bilayer.

Results. Model equations predicted that no significant permeability enhancement would be observed for small solutes (MW < 100). Thereafter, the enhancement, *E,* increases with solute cross-sectional area. The resulting equation to predict the enhancement of skin permeability is given by $E = \exp[\alpha(r^2 - 8.7)]$, where r is solute molecular radius in angstroms and α is the degree of bilayer disorder. Predictions of the model were compared with the experimental data collected from several studies.

Conclusions. The model predictions compare well with the experimental data.

KEY WORDS: transdermal; modeling; chemical enhancer; diffusion; scaled particle theory; enhancers.

INTRODUCTION

Transdermal drug delivery (TDD) offers several advantages over injections (1). However, applications of TDD are limited by low skin permeability of the stratum corneum (SC), the uppermost layer of the skin. Several enhancers including chemical agents (2–3), ultrasound (2–5), and electric fields (6,7) have been used to enhance transdermal drug transport. The objective of this study was to predict the effect of enhancers that increase skin permeability through bilayer disruption. Development of models to predict transdermal transport from the first principles has been limited by the complex nature of solute transport in lipid bilayers of the SC. Transdermal transport of drugs (especially low molecular weight hydrophobic drugs) occurs through the intercellular lipid bilayers of the SC. Lipid bilayers exhibit a strong structural heterogeneity that results in spatial variations in solute partition and diffusion coefficients within the lipid bilayers (8–10). Such features of solute transport in lipid bilayers have been identified through molecular simulations (11,12). However, applications of such simulations to the SC lipid bilayers have been limited by the slow dynamics and structural heterogeneity in these systems. We recently developed a model based on scaled particle theory that allows calculation of solute partition and diffusion coefficients in the lipid bilayers (13). Specifically, the scaled particle theory allows calculation of the work required to create a cavity for solute incorporation in the lipid bilayers. This calculation was used to predict solute partition coefficient in the lipid bilayers. Similarly, scaled particle theory was also used to predict the work required to create a cavity for solute diffusion in the lipid bilayers. These two calculations, that is, partition coefficient and diffusion coefficient, were combined to predict bilayer permeability. In the present study we extended these calculations to describe the effect of bilayer disrupting agents on skin permeability. Predictions of the model are compared with experimental data from the literature.

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THEORETICAL ANALYSIS

Passive Skin Permeability

First the model used to predict the passive skin permeability to low molecular weight hydrophobic drugs (unpublished data) is summarized. This model serves as the foundation for the calculations described in the present study. The model assumes that transdermal drug transport occurs primarily through the lipid bilayers of the SC. In other words, the model is applicable for low molecular weight (MW < 500 Da) hydrophobic ($K_{o/w}$, octanol-water partition coefficients > 10) solutes. In this model, skin permeability, P, is related to solute diffusion coefficient, D_b, and partition coefficient, K_b, in lipid bilayers by the following equation:

$$P = \frac{D_b K_b}{\tau^* L} \tag{1}$$

where L is the SC thickness (13 μm) and τ^* is the tortuosity associated with transdermal drug transport. Solute partition coefficient in the SC lipid bilayers, K_b, was related to solute partition coefficient between octanol and water, $K_{o/w}$ by the following equation.

$$K_b = K_{o/w}^{0.7} \tag{2}$$

Similarly, solute diffusion coefficient in the SC lipid bilayers, D_b, was related to solute radius, r, by the following equation.

$$D_b = D_0 \exp(-Ar^2) \tag{3}$$

where D_o is the solute diffusion coefficient in a model isotropic solvent, r is the van der Waals radius of the solute in angstroms, and A is a constant, the value of which was found to be 0.46. Eq. (1)–(3) were combined to obtain a working correlation between skin permeability, solute radius, and $K_{o/w}$ as follows.

$$P = 5.6 \times 10^{-6} K_{o/w}^{0.7} \exp(-0.46\, r^2) \tag{4}$$

where P is in centimeters per second and r is in angstroms. Next, we discuss extension of this equation to predict the effect of bilayer disrupting agents on skin permeability.

Effect of Bilayer Disrupting Agents on Skin Permeability

Let's assume that an area fraction, f, of the bilayers is "affected" by the enhancer. No assumption about the "de-

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gree" of the effect of disruptors on bilayer structure has been made at this point. In that case, the solute partition coefficient in the presence of bilayer disruptors, $K_b^{enhancer}$, can be given by the following expression:

$$K_b^{enhancer} = (1 - f)K_{o/w}^{0.7} + fK_o \quad (5)$$

where K_o is the solute partition coefficient in the disordered region of the bilayer. Hence, the enhancement of partition coefficient, E^K, can now be obtained by dividing Eq. (5) by Eq. (2).

$$E^K = (1 - f) + f\frac{K_o}{K_{o/w}^{0.7}} \quad (6)$$

The contribution of the term $K_o/K_{o/w}^{0.7}$ to the enhancement of partition coefficient depends on two components: i) physical or steric component, that is, the effect of bilayer disrupting agents on the free volume in the bilayer; and ii) chemical effect, that is, the effect of the enhancer on the chemical environment in the SC lipid bilayers. In the following paragraphs both components are discussed.

In the absence of bilayer disrupting agents, solutes tend to partition near the center of the bilayer due to the existence of a large free volume fraction in this region (comparable to isotropic solvents such as octanol) (10). Thus, relatively little volume fraction of the bilayer is occupied by the solute. Disordering of lipid chains due to enhancers should increase the free volume fraction throughout the bilayer, thereby making a larger fraction of the bilayer available for solute partitioning. This should increase the solute partition coefficient. The volume fraction in the lipid bilayer that is available for solute partitioning depends on its radius. For a solute possessing a radius of 3 Å, the volume fraction that is available for solute partitioning (averaged over the entire bilayer; a model dipalmitoyl phosphatidylcholine bilayer was used for calculations) is about 0.004 (for details of these calculations, see Ref. 13). If the bilayer is completely disordered, the available volume fraction becomes comparable to that of an isotropic solvent (for a solute of 3 Å radius this value is about 0.012; see Ref. 13). Thus, the available free volume fraction increases by a factor of about three due to complete bilayer disruption. Hence, about threefold enhancement in partition coefficient can be observed solely due to steric effects if the bilayer is completely disordered, that is, $f = 1$. Such enhancing effects of bilayer fluidizers on solute partition coefficients (≈2.5-fold) have indeed been reported in the literature (14). This enhancement, though significant, is much smaller compared to that in the diffusion coefficient, as will be explained later. In view of this, the steric contribution to the enhancement of the partition coefficient is neglected in this study. However, it should be realized that the steric contribution to the enhancement of partition coefficient may become significant for large solutes.

The second contribution to the enhancement of the partition coefficient may originate from the change in the chemical environment within the lipid bilayer. The chemical contribution to the partition coefficient depends on the difference between the solute chemical potential outside and inside the SC lipid bilayer. A bilayer disrupting agent may affect solute chemical potential inside as well as outside the bilayer, thereby altering the solute partition coefficient. However, for most bilayer disrupting agents discussed in this study the contribution of the chemical component can be neglected for the reasons discussed next. Most bilayer disruptors discussed in this study (for example, linoleic acid) are dissolved in appropriate solvents (for example, ethanol). The concentration of the bilayer disrupting agent in the formulation is relatively small compared to that of the solvent (a typical concentration of a bilayer disrupting agent is 1% w/v). Hence, as a first approximation, we assume that the disrupting agent itself does not induce a significant change in the chemical environment within the bilayer compared to that induced by the solvent itself. Note that many solvents used to dissolve the enhancers (for example, ethanol) can readily partition into the bilayer and alter the chemical environment therein. In all the cases discussed in this article, the effect of the solvent alone on skin permeability was also measured. The enhancement induced by the bilayer disrupting agent was then calculated by taking the ratio of the skin permeability in the presence of bilayer disrupting agent + solvent to that in the presence of the solvent alone. By doing so, the effect of the solvent was canceled.

The discussion presented in the above paragraphs shows that the steric as well as the chemical contribution to the enhancement of the partition coefficient can be neglected when the enhancements are defined with respect to those observed in the presence of the solvent alone. This leads to $K_o \approx K_{o/w}^{0.7}$, thereby leading to $E^K \approx 1$.

Effect of Bilayer Disrupting Agent on Solute Diffusion Coefficient

In the presence of enhancers, the diffusion coefficient in lipid bilayers, $D_b^{enhancer}$, can be given by the following expression:

$$D_b^{enhancer} = (1 - f)D_b + fD^{disrupt} \quad (7)$$

where f is the area fraction of the bilayers disrupted by the enhancer, $D^{disrupt}$ is the solute diffusion coefficient in the disrupted lipid bilayers, and D_b is the solute diffusion coefficient in undisrupted lipid bilayers. D_b as well as $D^{disrupt}$ depend on the available free volume within the bilayer. Because the free volume fraction is lowest near the bilayer interface, lowest diffusion coefficients are observed in this region of the bilayer. A slight increase in the free volume fraction is expected to induce a dramatic enhancement of diffusion coefficients. Specifically, an increase in the free volume fraction from 0.35 (typical free volume fraction in the interfacial region) to 0.7 (typical free volume fraction in disordered organic solvents) is expected to increase the diffusion coefficient of a solute (3 Å in radius) by more than 1000-fold (13). Hence, the contribution of the second term in Eq. (7) is expected to be much higher than that of the first term. Equation (7) can then be approximated as follows:

$$D_b^{enhancer} = fD^{disrupt} \quad (8)$$

Because the general mechanism of solute diffusion through disordered lipid bilayers is expected to be similar to that through normal bilayers (that is, jumps through free volume pockets), the solute diffusion coefficient in disrupted lipid bilayers, $D^{disrupt}$, can be described by an equation similar to that used for describing solute diffusion in undisrupted lipid bilayers (that is, Eq. [3]) as follows:

$$D^{disrupt} = D_o \exp(-A'r^2) \quad (9)$$

where D_o is the solute diffusion coefficient in an isotropic liquid such as octanol, and A' is a constant. The value of A' primarily depends on the free volume fraction in the disrupted lipid bilayers. Mathematically this dependence can be described as follows:

$$A' = \left\langle \frac{1}{R^2\phi}\left(\frac{1-\chi/\phi}{\kappa}+\frac{\chi/2\phi}{\kappa^2}+\frac{\chi}{2\phi}-1\right) - \frac{1}{R^2\psi}\left(\frac{1-\xi/\psi}{a_f}+\frac{\xi/2\psi}{a_f^2}+\frac{\xi}{2\psi}-1\right)\right\rangle_{disrupted\_bilayer}$$

R is the radius of the lipid chain and a_f is the free area per lipid molecule in the bilayer. ψ, ξ, ϕ, and ψ are structural parameters that are related to lipid order parameter, $S_{CD}(z)$ (13). The suffix *disrupted_bilayer* indicates that the average is calculated over the entire thickness of the disrupted lipid bilayer.

The enhancement of the solute diffusion coefficient due to bilayer disruption, E^D, can now be calculated using Eqs. (3) and (9) as follows:

$$E^D = \frac{D_b^{enhancer}}{D_b} = f\exp(\alpha r^2) \qquad (10)$$

where $\alpha = A - A'$. Physically, α quantifies the change in the bilayer structure due to disrupting agents (that is, the quality of bilayer disruption). If the structure of the disrupted bilayers becomes comparable to that of the model isotropic solvent (that is, octanol), the value of A' should be zero, thereby leading to $\alpha = 0.46$. However, because the structure of disrupted bilayers could be even less dense than that of octanol (due to lipid removal), values of α slightly larger than 0.46 are also theoretically feasible. The value of f quantifies the area fraction of bilayers disordered by the enhancer (quantity of bilayer disruption). The value of f ranges from 0 to 1. Next, model predictions are compared with the literature data.

RESULTS AND DISCUSSION

Effect of Bilayer Disrupting Agents on Solute Partition and Diffusion Coefficients

Equations (6) and (10), respectively, predict the effect of bilayer disruptors on solute partition and diffusion coefficients. However, direct measurements of the effect of bilayer disrupting agents on these properties have not been reported in the literature because such measurements are not easy to perform. Note that several measurements of solute partitioning into the SC have been performed (15); however, interpretation of partition coefficients measured this way is difficult. Recently an easy-to-use method for measuring solute partition and diffusion coefficients in the SC lipid bilayers (16) was developed. This method was also used to determine the effect of a model disrupting agent, therapeutic ultrasound (1 MHz), on partition and diffusion coefficients of five model drugs—corticosterone, testosterone, aldosterone, napthol, and lidocaine—in the SC lipid bilayers (17). The data obtained from that study are compared with the model predictions presented in this study. Previously, it was shown that ultrasound at a frequency of 1 MHz increases transdermal transport primarily through affecting the skin structure and not through convection (4). Hence, the data obtained with therapeutic ultrasound can be compared with the model predictions, even though therapeutic ultrasound is clearly a different type of enhancer than chemicals.

Figure 1 shows the relationship between partition coefficients of five solutes in the presence and the absence of therapeutic ultrasound. The figure shows that solute partition coefficients in the presence of ultrasound are comparable to those in the absence of ultrasound (a mild bilayer disruptor). The line corresponds to the equality between the two partition coefficients. A careful look at the data in Fig. 1 reveals that partition coefficients of some solutes are increased by as much as 50% and those of some solutes are reduced by the same magnitude. However, as will be shown later, this alteration of the partition coefficient is relatively insignificant compared with that of diffusion coefficient. Fundamentally, the lack of a significant effect of ultrasound on the solute partition coefficient is understandable because the solutes tend to partition near the bilayer center where the lipid chains are relatively disordered even in the absence of a bilayer disrupting agent (18). Hence, ultrasound-induced bilayer disruption is unlikely to provide any additional benefit to solute partitioning. Similar arguments can also be made regarding the effect of chemical enhancers under the conditions described in the theoretical section.

Equation (10) predicts that the enhancement of the solute diffusion coefficient increases exponentially with solute cross-sectional area. This prediction was also tested for the effect of therapeutic ultrasound on solute diffusion coefficients in the SC lipid bilayers (taken from Ref. [17]). Figure 2 shows the variation of enhancement of diffusion coefficient, E^D, with solute radius for the same five solutes that were shown in Fig. 1. The enhancement of the diffusion coefficient indeed increases with solute area. The line shows the fit of Eq. (10) to the experimental data. The model fits the data reasonably well ($r = 0.91$). The fitted values of f and α are, respectively, 0.27 and 0.2. Because the theoretical maximum

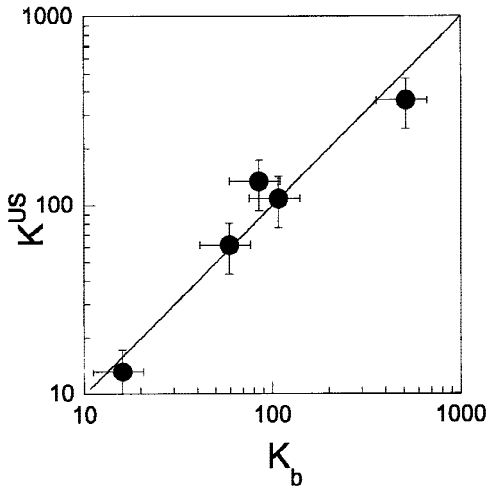

Fig. 1. Comparison of solute partition coefficients in the presence (y-axis) and absence (x-axis) of therapeutic ultrasound (1 MHz, 2 W/cm^2). The data were collected from Ref. (17). Methods for measuring partition coefficients are described in Ref. (16). The data shown in the figure correspond to five solutes—corticosterone, testosterone, aldosterone, napthol, and lidocaine. Error bars correspond to standard deviation.

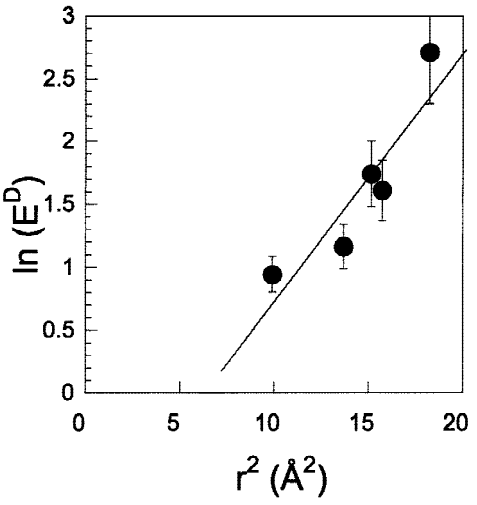

Fig. 2. Variation of the enhancement of the solute diffusion coefficient in the SC lipid bilayers induced by ultrasound application (1 MHz, 2 W/cm^2) with solute radius. The data were collected from Ref. (17). The line corresponds to best fit of Eq. (10) with the data (r = 0.91). The data shown in the figure correspond to five solutes—corticosterone, testosterone, aldosterone, napthol, and lidocaine. Error bars correspond to standard deviation.

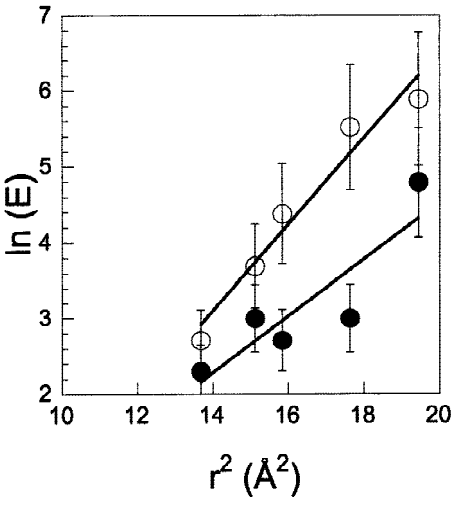

Fig. 3. Variation of enhancement of skin permeability with solute size. Closed circles correspond to the enhancement induced by LA/EtOH alone (5% linoleic acid in 1:1 ethanol: PBS). Open circles correspond to the enhancement induced by LA/EtOH and ultrasound (1 MHz, 2 W/cm^2). Data correspond to five drugs (corticosterone, estradiol, testosterone, dexamethasone, and lidocaine). Error bars correspond to standard deviation. The data were taken from Ref. (19). Lines correspond to the fit of Eq. (12) to the data (r = 0.97 for open circles and 0.89 for closed circles). Fitted values of α and ϕ are described in the text as well as in Table I.

value of f is 1, the data suggest that application of ultrasound disorders only a fraction of lipid bilayers. Furthermore, the experimentally obtained value of $\alpha = 0.2$ suggests that the bilayers are not completely disordered due to ultrasound application. Next, the model predictions are compared with experimental data on permeability enhancement.

Effect of Bilayer Disordering Agents on Skin Permeability

Equations (1) and (10) can be combined to calculate the permeability enhancement, E, as follows:

$$E = f\left(\frac{\tau^*_{passive}}{\tau^*_{enhancer}}\right)\exp(\alpha r^2) \tag{11}$$

where $\tau^*_{enhancer}$ is the tortuosity of transdermal transport in the presence of disruptors and $\tau^*_{passive}$ is the tortuosity of transdermal transport in the absence of disruptors. Note that E^K has been assumed to be unity for the reasons discussed earlier. Equation (11) can be rewritten as follows:

$$E = \phi \exp(\alpha r^2) \tag{12}$$

where $\phi = f(\tau^*_{passive}/\tau^*_{enhancer})$. In the event that the enhancer does not affect the tortuosity of transdermal transport, ϕ simply denotes the fraction of bilayers disordered, f. The parameters ϕ and α, respectively, measure the "quantity" and "quality" of bilayer disruption.

Equation (12) suggests that the permeability enhancement induced by bilayer disruptors increases strongly with the solute radius. This prediction is consistent with previous experimental observations. Specifically, Johnson *et al.* measured the effect of linoleic acid (dissolved in ethanol: PBS, referred to as LA/EtOH hereafter) with or without therapeutic ultrasound on transdermal transport of various solutes including estradiol, dexamethasone, lidocaine, testosterone, and corticosterone (19). Their data are summarized in Fig. 3. Open circles correspond to the enhancement obtained by ultrasound in combination with LA/EtOH (calculated relative to EtOH: PBS without ultrasound). Closed circles correspond to the enhancement induced by LA/EtOH alone (calculated relative to EtOH: PBS). Lines correspond to fits of Eq. (12) to corresponding data. The fitted value of ϕ is 0.055 in the case of LA/EtOH alone and about 0.008 in the presence of ultrasound-LA/EtOH. Corresponding values of α for LA/EtOH and ultrasound-LA/EtOH are respectively 0.37 and 0.56. Because a larger value of α indicates a larger degree of bilayer disordering, these data show that application of ultrasound-LA/EtOH disorders lipid bilayers to a larger extent than that induced by the application of LA/EtOH alone. Also compiled were literature data on the effect of several other enhancers including capric acid (19), lauric acid (19), neodecanoic acid (20), therapeutic ultrasound (4), lauryl alcohol (21), azone (three different studies [21–23], dodecyl-2-(N,N-Dimethylamino)propionate (DDAIP [22]), and five azone analogs (N-dodecyl-2-pyrrolidinone [analog I], N-dodecyl-2-piperdinone [analog II], N-dodecyl-N-(2-methoxyethyl) acetamide [analog III], N-(2,2-dihydroxyethyl) dodecylamine [analog IV], and 2-(1-nonyl)1,3-dioxolane [analog V]) (23) on transdermal transport of several low-molecular weight hydrophobic solutes. In each case, the enhancement was calculated relative to the permeability obtained from the solvent used for dissolving the enhancer. These data fitted well to Eq. (12). Corresponding values of α and ϕ for these data are shown in Table I. Although most of these data were obtained using human skin, some were obtained using animal skin. However, these data can still be analyzed using the current model because the difference in the geometry of different skins can be accounted by ϕ and the difference in the effect of enhancers on different skin models can be accounted by α.

The values of ϕ and α for various enhancers shown in Table I are strongly correlated. This correlation is shown in Fig. 4 (r = 0.96). Fundamentally, this correlation suggests

Table I. Summary of ϕ and α Values Obtained from the Literature Data

Enhancer	ϕ	α	Enhancement data collected from Ref.
Passive	1.00	0.00	
2-(1-nonyl)1,3-dioxolane	0.68	0.056	23
N-dodecyl-N-(2-methoxyethyl)acetamide	0.28	0.19	23
N-(2,2-dihydroxyethyl)dodecylamine	0.16	0.19	23
Ultrasound alone	0.20	0.22	17
Azone I	0.21	0.22	23
N-dodecyl-2-piperdinone	0.25	0.22	23
Capric acid	0.20	0.23	20
Neodecanoic acid	0.11	0.27	20
N-dodecyl-2-pyrrolidinone	0.10	0.31	23
LA/EtOH	0.05	0.36	19
Lauric acid	0.05	0.36	20
Azone II	0.02	0.42	21
Lauryl Alcohol	0.004	0.50	21
Dodecyl 2-(N,N-Dimethylamino)propionate	0.022	0.53	22
Ultrasound + LA/EtOH	0.0078	0.58	19
Azone III	0.0016	0.61	22

Note. The same enhancer may possess different values of α and ϕ depending on the application method for the enhancer. In addition, the solvent used to dissolve the enhancer may also affect these parameters.

that the enhancers that strongly affect the bilayer structure (that is, a high value of α) affect a smaller fraction of the bilayers (that is, a lower value of ϕ). This is an important outcome of this model. Fundamentally, this may be explained based on the heterogeneity of transdermal drug transport. Specifically, transport of drugs across the skin has been known to be heterogeneous (15). This may generate localized transport regions in the skin. When bilayer disruptors are added to the formulation, they are likely to penetrate preferentially into these permeable regions. Enhanced penetration of bilayer disruptors should further increase transport in this area, thus increasing the heterogeneity of transdermal transport even further. In addition, certain enhancers such as oleic acid are known to pool in the SC (24). Such localization of enhancers may also contribute to heterogeneity of skin permeability. Increased heterogeneity should lead to the localization of the drug. Hence, stronger enhancers are likely to induce higher localization of the drug. However, as will be presented in the next paragraph, the beneficial effect of strong enhancers dominates the negative effect of drug localization. As a result, the enhancement increases with increasing potency of the enhancer.

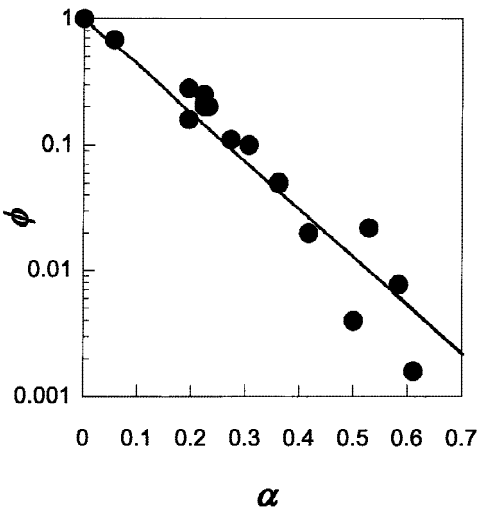

Fig. 4. Relationship between α and ϕ for enhancers analyzed in this study. The data were taken from Table I. These data were obtained by fitting literature data to Eq. (12). Sources of these data are listed in Table I. The line corresponds to the best fit that was forced to go through the point ($\alpha = 0, \phi = 1$) ($r = 0.98$). The resulting equation was $\phi = \exp(-8.7\alpha)$.

The correlation between ϕ and α is given by $\phi = \exp(-8.7\alpha)$ (from Fig. 4). By combining this equation with Eq. (12) one obtains:

$$E = \exp[\alpha(r^2 - 8.7)] \tag{13}$$

Two trends are clear from this equation. No enhancement can be observed for solutes having a radius, r, such that $r^2 = 8.7$ (that is, $r \sim 2.9$ Å or solute molecular weight of approximately 100 Da) regardless of the potency of the enhancer. This prediction is consistent with the literature data (25). Second, the equation predicts that the enhancement increases strongly with solute radius. Figure 5 shows a comparison of the predictions of Eq. (13) with the literature data. These data correspond to about 14 different enhancers listed in Table I. The line shows predictions of Eq. (13). Figure 5 shows that the experimental data indeed show a behavior similar to that predicted by the model. That is, the enhancement induced by these enhancers increases with solute size, and no significant enhancement is observed for solutes having a molecular weight less that about 100 Da. A significant scatter is observed in the data. This may be attributed to the error in the data as well as to the assumption that the effect of bilayer disruptors on solute partition coefficient is minimal. Additional factors such as specific interactions between the solute and lipid bilayers may also be responsible for the scatter. These issues should be further investigated in future studies.

Implications of the Model and Future Studies

The model developed in this article offers a simple equation to analyze the effect of enhancers on transdermal drug

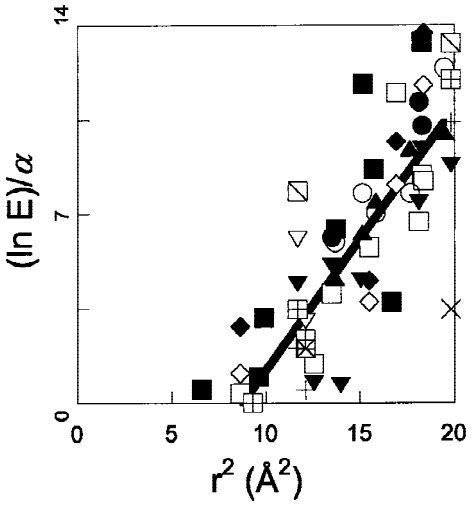

Fig. 5. Variation of the enhancement of skin permeability with solute size. Each symbol corresponds to data for a separate enhancer taken from the literature. A list of references is shown in Table I. For each enhancer, enhancement data were obtained for at least three solutes from the same study. This data were fitted to Eq. (12) to obtain the values of α and ϕ for each enhancer. These values of α were used to calculate the values of $(1nE)/\alpha$ for each solute used with corresponding enhancers. These data were then plotted in Fig. 5. Symbols are as follows: ultrasound + LA/EtOH (▲), LA/EtOH (○), azone analog I (▽), DDAIP (●), azone (▼), lauryl alcohol (⊡), ultrasound alone (■), capric acid (♦), azone analog III (⊞), azone analog II (⧅), azone analog IV (+), azone analog V (X), lauric acid (◇), neodecanoic acid (□).

transport. The model also offers a quantitative parameter to compare various enhancers. The parameter, α, quantifies the effect of bilayer disruptors on transdermal drug transport. α allows one to compare a variety of bilayer disrupting agents on the same scale. Enhancers possessing a higher value of α possess a larger enhancing potential. The model also describes the size-dependence of permeability enhancement due to bilayer disruptors. The model predicts that the enhancement induced by bilayer disruptors increases exponentially with the square of the solute radius. Furthermore, no significant enhancement can be observed for solutes having a molecular weight less than about 100 Da. Both these predictions are consistent with experimental observations. The model equations can be further developed to include specific interactions between the solute and the lipid bilayers. Furthermore, additional factors such as solute shape can also be incorporated in the model.

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