Skin Permeation Enhancement in Aqueous Solution: Correlation With Equilibrium Enhancer Concentration and Octanol/Water Partition Coefficient

S. Kevin Li[1,*] Correspondence information about the author S. Kevin Li Email the author S. Kevin Li

,

Doungdaw Chantasart[2]

DOI: https://doi.org/10.1016/j.xphs.2018.08.014

|

Article Outline

Jump to Section

Abstract

The effectiveness of skin penetration enhancers and the enhancer concentration required for effective skin permeation enhancement are difficult to predict. A comprehensive quantitative structure-enhancement relationship of chemical penetration enhancers for skin permeation is not currently available. The present study (a) investigated the relationship between skin permeation enhancement and chemical enhancer concentration and (b) examined a simple quantitative structure-enhancement relationship for predicting skin permeation enhancement to guide enhancer formulation development. In the present analysis, data from previous skin permeation studies that used the symmetric/equilibrium configuration and skin parallel pathway model were summarized to determine the relationship between enhancement factor and enhancer concentration. Under the equilibrium conditions, semilogarithmic linear relationships between enhancement factor (*E*) and enhancer aqueous concentration (*C*) were observed and an enhancer potency parameter (α) was defined. A correlation between the potency parameter α and enhancer octanol/water partition coefficient (*K*oct) was obtained. The enhancement factor relationship was derived: Log $E = 0.32 \cdot C \cdot K\text{oct}$. The results suggest that a "threshold" of ($C \cdot K\text{oct}$) > 0.5 M is required to induce effective skin permeation enhancement under these conditions. Consistent with the analyses in previous studies, the data suggest that octanol represents the skin barrier microenvironment for the penetration enhancers.

Keywords:
skin, permeability, transdermal, transport, chemical enhancer, flux enhancement, structure-activity relationship, quantitative structure-enhancement relationship (QSER)

Jump to Section

Introduction

Chemical penetration enhancers for topical and transdermal drug delivery have been studied extensively in the past several decades.[1, 2, 3] Typical enhancer studies, particularly in the pharmaceutical industry, have been skin permeation screening to match potential enhancers with drug candidates in transdermal or dermatological formulations. In these studies, the enhancers were evaluated when the test enhancer solutions with the drug were applied on the stratum corneum (SC) whereas the dermis side was in contact with the receiver solution that was usually buffered saline. Although this experimental approach is adequate in assessing the effects of skin penetration enhancers on the delivery of a particular drug and mimics the practical situation of skin delivery in practice, some aspects of enhancer mechanisms could not be systematically evaluated. Previous studies on the quantitative structure-enhancement relationship (QSER) of chemical enhancers have improved our knowledge in the field of skin penetration enhancers,[3, 4, 5] but the effects of these chemicals are still not easy to predict. Among these studies, a systematic approach was to investigate the mechanisms of action of skin penetration enhancers (a) under

symmetric and equilibrium conditions (i.e., same enhancer conditions in the donor and receiver chambers in equilibrium with the SC), (b) with corrections for the changes in the chemical potential (activity) of the permeant in the enhancer solution with respect to that in the buffer solution (the control) to assess the effects of permeant activity alteration upon skin permeation in the presence of the enhancers, and (c) with model analyses to delineate the effects of permeation enhancement on transport across the lipoidal and pore transport pathways and only the lipoidal pathway was assessed.[6, 7]

In this systematic and mechanistic approach,[6, 7] different from the asymmetric enhancer configuration (the test enhancer solution on the SC side and buffered saline on the dermis side), the symmetric and equilibrium conditions avoid the complex situation of an enhancer concentration gradient across the skin, in which the local permeation enhancement varies with the position within the membrane that makes mechanistic analyses of the data difficult. The correction of the changes in thermodynamic activities of the permeant in the enhancer solution with respect to that in the buffer solution (the control) when the thermodynamic activity of the permeant is altered in the presence of the enhancers allows direct comparison of flux enhancement at the same permeant thermodynamic activity. The parallel pathway model of lipoidal and pore transport pathways provides the framework to delineate the effects of the chemical enhancers on these 2 distinct pathways for understanding the mechanisms of the enhancers, particularly, the mechanism of action of chemical enhancers on the lipoidal pathway of the SC in skin permeation. With these strategies, the permeability enhancement factor, the ratio of the permeant flux with the enhancer solution to that of the control (without the enhancer), was calculated, and the enhancer concentrations to induce 10× flux enhancement at the same permeant thermodynamic activity (E = 10 concentrations) were determined. These enhancer concentrations were then compared to establish QSER of the chemical penetration enhancers. The results in these previous studies showed that the concentrations of the enhancers to induce 10× enhancement were related to the lipophilicities of the enhancers and the intrinsic potencies of these enhancers were relatively similar. However, enhancer concentrations other than E = 10 (and E = 4 in some cases) have not been analyzed.

Another method to evaluate skin penetration enhancers under the skin-enhancer equilibrium condition, particularly for highly lipophilic enhancers, was the direct equilibration of the skin with the liquid enhancers (or enhancers dissolved in an organic solvent) and subsequent skin transport experiments with buffered saline as donor and receiver solutions in the diffusion cells.[8, 9] This approach was based on the assumption that the depletion of the enhancers from the skin to the aqueous solution in the diffusion cell chambers was minimal, and essentially constant enhancer concentration could be maintained in the SC due to the high lipophilicity of the enhancers. The direct equilibration approach provided the condition that the enhancers in the SC were always at saturation with the solution in the diffusion cell chamber. Otherwise, due to the low aqueous solubilities and extensive depletion of highly lipophilic enhancers in

the aqueous phase in the diffusion chamber, the equilibrium condition would be difficult to achieve. Or, an aqueous reservoir system (e.g., micelles or cyclodextrins) for the enhancers in the diffusion cell would be required, and the assessment of the interactions between the reservoir system and skin would be needed.[10, 11] Employing the direct equilibration enhancer approach, a series of studies were completed to investigate QSER of highly lipophilic chemical enhancers and determine the maximum enhancement effects of the enhancers when the SC was saturated with the enhancers (i.e., at enhancer solubility in the SC lipids and the thermodynamic activity equivalent to the enhancer pure state).[8, 9]

The present study collected data from the previous skin permeation studies of penetration enhancers that used the symmetric/equilibrium configuration and skin parallel pathway model and then analyzed the data to derive a relationship between skin permeation enhancement factor and enhancer concentration. The objectives were to (a) investigate the relationship between skin permeation enhancement and chemical enhancer concentration for QSER and (b) examine a QSER of enhancer concentration and octanol/water partition coefficient to predict skin permeation enhancement. An important goal was to provide guidance to semiquantitatively predict permeation enhancement of the SC lipoidal pathway under the influence of the chemical enhancers using enhancer concentrations and the general physiochemical properties of the enhancers such as *K*oct. The “threshold” enhancer concentration required to induce permeation enhancement was also investigated.

Jump to Section

Experimental

Jump to Section

Model and Equation

According to previous studies,[12, 13, 14] skin permeation enhancement is related to enhancer concentration and the relationship can be expressed as:

(1) $$Log\ E = \alpha C$$

where *E* is the enhancement factor of the lipoidal pathway in the SC under the influence of the chemical enhancer, *C* is the concentration of the enhancer in the aqueous medium in equilibrium with the skin, and α is the enhancer potency parameter. A higher α value indicates a lower enhancer concentration is required to induce the same permeation enhancement effect for the chemical enhancer, and hence, higher effectiveness of the enhancer. In the absence of the enhancer, when *C* = 0, enhancement factor = 1. The enhancer potency parameter α can be further expressed as the intrinsic potency of the enhancer (α’) and enhancer octanol/water partition coefficient (the intrinsic potency was later found to be a relatively constant value for the studied enhancers, see Results and Discussion section):

(2) $$Log\ E = \alpha' (Koct^n)\ C$$

where *K*oct is the octanol/water partition coefficient of the enhancer and *n* is the coefficient of the linear free energy relationship between the SC lipid microenvironment and octanol, similar to the relationships commonly used for isotropic solvents.[15] The coefficient accounts for the difference between the polarities of the environment in octanol and SC lipid microenvironment for the partitioning of the enhancer. To assess the effect of enhancer lipophilicity on its potency, parameters *n* and α' were obtained using:

(3) $$Log\ \alpha = n\ Log\ Koct + Log\ \alpha'$$

As solute partitioning into lipid bilayer is also related to bilayer free volume and solute molecular size,[16]enhancer molecular weight (MW) can affect its partitioning into SC lipid lamella. Including the effect of MW on enhancer partitioning into SC lipid microenvironment, the effect of MW can be described as follows:

(4) $$Log\ \alpha = n\ Log\ Koct + \beta\ MW + \gamma$$

where *β* is the coefficient for MW and *γ* is constant.

Jump to Section

Data Collection and Analysis

Enhancement factor data were collected from previous studies of chemical penetration enhancers that used the symmetric/equilibrium configuration and skin parallel pathway model. Only data meeting these experimental criteria were used. These penetration enhancers have logarithm of octanol/water partition coefficient (Log *K*oct) ranging from −1 to 5 and MW from 46 to 320 Da. Data of short-chain alkanols were obtained from skin permeation studies of hydrocortisone, β-estradiol, and estrone across hairless mouse skin (HMS) by Ghanem et al. and Kim et al.[12, 13] Data of pyrrolidones were obtained from Yoneto et al.[17] using corticosterone and HMS in a similar experimental setting. Data of alkanols of medium-chain lengths and with *cis*- and *trans*-double bonds were from Chantasart et al. and He et al.[18, 19] Data of amides, diols, dioxolanes, glucosides, monoglycerides, and piperidinones were obtained from Warner et al.[14, 20] and data of azones were from He et al.[19, 21] Data of branched chain alkanols were from Kim et al. and Chantasart et al.[13, 18] Data of alkanols, octyl-pyrrolidone, and terpenes from studies using human epidermal membrane (HEM) were obtained from Chantasart et al.[22, 23] Enhancement factor data of lipophilic enhancers and fatty acids were from previous studies with direct equilibration of skin and enhancers to saturate the skin with the enhancers. These single-point concentration data at saturation in HEM were obtained from Ibrahim and Li.[8, 24]

The data were analyzed for the relationship between enhancement factor and enhancer concentration. For each enhancer, the logarithms of the enhancement factors (for the lipoidal transport pathway after

corrections for the activity coefficients) were plotted against the aqueous enhancer concentrations. Linear regression analyses and statistics were performed using Microsoft Excel (Redmond, WA) on the enhancement factor versus concentration relationships (Eq. 1) by setting y-intercept = 0. The linear least squares slopes (the enhancer potency parameter α) and R^2 of the regression analyses are presented. All α values were used in the analyses of the present study regardless of the R^2 values. To compare the data, plots of the logarithms of the enhancement factors versus concentrations of the enhancers with and without adjustment using *K*oct are presented.

Jump to Section

Results and Discussion

Jump to Section

Correlations Between Enhancement Factor and Enhancer Concentration

Table 1, Table 2 summarize the results of the linear least squares regression analyses of Log *E* versus concentration of the enhancers (Eq. 1). The regression analysis of each enhancer shows good correlation between Log *E* and enhancer concentration with $R^2 > 0.85$ for most enhancers. The slopes α of log *E* versus concentration for the enhancers ranged from 10^{-1} to 10^{4}, up to 5 orders of magnitude differences in the effectiveness of the chemicals as skin penetration enhancers.

Table 1 Summary of Enhancers, Enhancer Lipophilicities (as Log *K*oct) and MW, and Results of "Log *E*versus *C*" Regression Analyses. Enhancer Data Are Obtained From Skin Permeation Experiments With HMS

Class	Chemical	MW	Log *Koct*	α, Slope of Log *E* versus C[a]	R^2[a]	Number of Data Points[b]
Alcohol	1-Ethanol	46	−0.30	0.22	0.979	6
Alcohol	1-Propanol	60	0.25	0.79	0.980	4
Alcohol	1-Butanol	74	0.84	4.2	0.941	4
Alcohol	1-Pentanol	88	1.51	13.2	0.932	4
Alcohol	1-Hexanol	102	2.08	50	0.961	4
Alcohol	1-Heptanol	116	2.54	152	0.980	5

Alcohol	1-Octanol	130	3.13	612	0.974	4
Alcohol	1-Nonanol	144	3.52	1935	0.968	4
Alcohol	Isopropanol	60	0.05	0.51	0.990	5
Alcohol	2-Hexanol	102	1.83	22.3	0.945	5
Alcohol	2-Heptanol	116	2.43	69	0.959	5
Alcohol	2-Octanol	130	3.03	259	0.735	4
Alcohol	2-Nonanol	144	3.48	1102	0.250	4
Alcohol	3-Hexanol	102	1.81	18.2	0.980	4
Alcohol	3-Heptanol	116	2.42	58	0.921	4
Alcohol	3-Octanol	130	2.94	200	0.950	3
Alcohol	3-Nonanol	144	3.47	711	0.862	4
Alcohol	4-Heptanol	116	2.32	55	0.942	4
Alcohol	4-Octanol	130	2.88	188	0.985	4
Alcohol	4-Nonanol	144	3.46	585	0.939	4
Alcohol	5-Nonanol	144	3.42	524	0.964	5
Aromatic ring: alcohol	2-Phenylethanol	122	1.57	16.4	0.989	4
Alcohol	*cis*-3-Penten-1-ol	86	1.08	4.6	0.892	3
Alcohol	*cis*-3-Hexen-1-ol	100	1.63	17.6	0.965	4
Alcohol	*cis*-3-Octen-1-ol	128	2.71	193	0.994	3
Alcohol	*cis*-3-Nonen-1-ol	142	3.25	555	0.999	3

Alcohol	*trans*-3-Hexen-1-ol	100	1.76	19.0	0.847	4
Amide/Alcohol	*trans*-Hydroxyproline-*N*-decanamide-*C*-ethylamide	131	2.86	222	0.894	3
Amide	*N,N*-Dimethylhexanamide	143	1.36	11.9	0.944	5
Amide	*N,N*-Dimethylheptanamide	157	1.89	36	0.902	5
Amide	*N,N*-Dimethyloctanamide	171	2.59	144	0.991	5
Amide	*N,N*-Dimethylnonanamide	185	3.00	596	0.978	5
Azone	1-Butyl-2-azacycloheptanone	169	1.80	35	0.912	3
Azone	1-Hexyl-2-azacycloheptanone	197	2.91	230	0.853	4
Azone	1-Octyl-2-azacycloheptanone	225	4.04	2315	0.998	4
Diol	1,2-Hexanediol	118	0.78	5.0	0.978	4
Diol	1,2-Octanediol	146	2.08	54	0.954	5
Diol	1-2-Decanediol	174	3.23	770	0.970	5
Dioxolane	2-(1-Butyl)-2-methyl-1,3 dioxolane	144	2.07	78	0.756	3
Dioxolane	2-(1-Hexyl)-2-methyl-1,3 dioxolane	172	3.51	794	0.118	3
Glucoside	1-Octyl-β-D-glucopyranoside	292	1.94	61	0.622	3
Glucoside	1-Decyl-β-D-glucopyranoside	320	3.14	655	0.953	5
Monoglyceride	1,2-Dihydroxypropyl octanoate	218	2.6	165	0.958	4
Monoglyceride	1,2-Dihydroxypropyl decanoate	246	3.4	1482	0.709	4

Piperidinone	1-Butyl-2-piperidinone	155	1.39	11.7	0.761	4
Piperidinone	1-Hexyl-2-piperidinone	183	2.3	135	0.910	4
Piperidinone	1-Octyl-2-piperidinone	211	3.41	929	0.918	5
Pyrrolidone	1-Ethyl-2-pyrrolidone	113	−0.04	0.38	0.956	4
Pyrrolidone	1-Butyl-2-pyrrolidone	141	1.02	2.7	0.993	4
Pyrrolidone	1-Hexyl-2-pyrrolidinone	169	2.1	37	0.981	4
Pyrrolidone	1-Octyl-2-pyrrolidinone	197	3.05	517	0.989	5

View Table in HTML

aLinear regression slopes and R^2 (forcing *y*-intercept = 0).

bNumber of concentration data points in the linear regression analysis.

Table 2 Summary of Enhancers, Enhancer Lipophilicities (as Log *K*oct) and MW, and Results of "Log *E*versus *C*" Regression Analyses. Enhancer Data Are Obtained From Skin Permeation Experiments With HEM

Class	Chemical	MW	Log *K*oct	α, Slope of Log *E*versus C[a]	R^2[a]	Number of Data Points[b]
Alcohol	1-Hexanol	102	2.08	42	0.753	4
Alcohol	1-Heptanol	116	2.54	152	0.265	4
Alcohol	1-Octanol	130	3.13	512	0.966	3
Alcohol	4-Octanol	130	2.88	145	0.821	4
Aromatic ring: alcohol	2-Phenylethanol	122	1.57	17.4	0.916	4
Terpene	Thymol	150	2.52	338	0.829	4
Terpene	Menthol	156	3.38	372	0.696	3
Terpene	Menthone	154	2.87	262	0.766	3

Terpene	Carvacrol	150	2.52	355	0.591	4
Terpene	Cineole	154	3.13	148	0.878	3
Pyrrolidone	1-Octyl-2-pyrrolidinone	197	3.05	404	0.931	4
Aromatic ring: alcohol	Benzyl alcohol	108	1.06	–[c]	–[c]	–[c]
Aromatic ring: alcohol	2-Phenoxyethanol	138	1.16	–[c]	–[c]	–[c]
Aromatic ring: aminobenzoate	Padimate O	277	5.76	–[c]	–[c]	–[c]
Aromatic ring: hydroxyanisole	Butylated hydroxyanisole	180	3.14	–[c]	–[c]	–[c]
Aromatic ring: salicylate	2-Ethylhexyl salicylate	250	5.97	–[c]	–[c]	–[c]
Aromatic ring: salicylate	Salicylaldehyde	122	2.0	–[c]	–[c]	–[c]
Ester	Isopropyl myristate	270	7.3	–[c]	–[c]	–[c]
Fatty acid	Decanoic acid	172	4.02	–[c]	–[c]	–[c]
Fatty acid	Undecanoic acid	186	4.51	–[c]	–[c]	–[c]
Fatty acid	Lauric acid	200	5.0	–[c]	–[c]	–[c]
Fatty acid	Tridecanoic acid	214	5.49	–[c]	–[c]	–[c]
Fatty acid	Myristic acid	228	5.98	–[c]	–[c]	–[c]
Fatty acid	Pentadecanoic acid	242	6.47	–[c]	–[c]	–[c]
Fatty acid	Palmitic acid	256	6.96	–[c]	–[c]	–[c]
Fatty acid	Stearic acid	284	7.94	–[c]	–[c]	–[c]

Fatty acid	Linoleic acid	280	7.51	–[c]	–[c]	–[c]
Fatty acid	Oleic acid	282	7.64	–[c]	–[c]	–[c]
Fatty acid	Ricinoleic acid	298	6.19	–[c]	–[c]	–[c]
Alcohol	1-Undecanol	172	4.2	–[c]	–[c]	–[c]
Alcohol	Oleyl alcohol	268	7.0	–[c]	–[c]	–[c]
Azone	Laurocapram	281	6.28	–[c]	–[c]	–[c]

View Table in HTML

[a]Linear regression slopes and R^2 (forcing *y*-intercept = 0).

[b]Number of concentration data points in the linear regression analysis.

[c]Not available. Only single-point concentration data at saturation in HEM are available.

Figure 1 shows the correlation between the potency parameters α and Log *K*oct values of the enhancers (Eq. 3). The data suggest a strong correlation between the effectiveness of the enhancers (based on potency parameter α) and the lipophilicities of the enhancers (indicated by their Log *K*oct), supporting the relationship described in Equation 2. The regression of $e^{2.15}$ is equivalent to $10^{0.933}$ in the logarithmic scale. The $10^{0.933}$ value suggests that the *n* value in Equations 2 and 3 is close to unity. Despite that the HEM data (triangle symbols in the plot) show larger variability compared to the HMS data, both sets of data demonstrate similar trends and the significant impact of the lipophilicities of the enhancers on their effectiveness to enhance skin permeation.

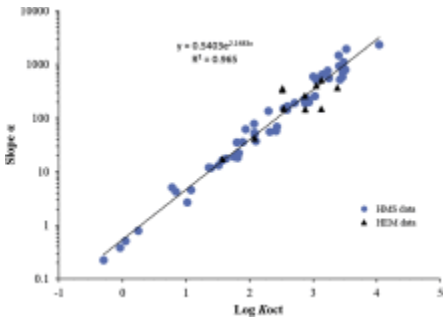

Figure 1

Correlation between the enhancer potency (slope α of Log *E* vs. *C*) and Log *K*oct. Each data point represents an individual penetration enhancer. Note that $e^{2.15} = 10^{0.933}$ in the logarithmic scale.

View Large Image | View Hi-Res Image | Download PowerPoint Slide

The ability of a penetration enhancer partitioning and diffusing into the SC could affect the effectiveness of the enhancer. In addition to enhancer lipophilicity, molecular charge and MW, which govern enhancer partition and diffusion behaviors in lipids, could affect enhancer potency. The molecular shape and size of an enhancer also affect its intercalation in the SC intercellular lipids and enhancer-induced lipid fluidization. The majority of the penetration enhancers in Table 1, Table 2 are uncharged, so possible effects of molecular charges on enhancer potency could not be systematically investigated in the present study. For enhancer molecular size, the influence of MW on enhancer potency was examined using regression analyses of Equation 4. No significant effect of MW on enhancer potency in addition to that of Log *K*oct was found: *n* and R^2 obtained using Equation 4 (*n* = 0.91, R^2 = 0.970) are essentially the same as those of Equation 3 (Fig. 1).

Jump to Section

Correlations Between Enhancement Factor and Enhancer Concentration With Koct

With the correlation between α and Log *K*oct for the enhancers in Figure 1, the concentrations of the enhancers were multiplied by their respective *K*oct values to determine their equilibrium concentrations in the lipid phase at the aqueous enhancer concentration conditions. Figure 2 illustrates the effect of enhancer lipophilicity (based on their *K*oct) on skin permeation enhancement by comparing the relationships of "Log *E* versus *C*" and "Log *E* versus *C* · *K*oct." The figure shows the large data scattering of "Log *E* versus *C*" over the enhancer concentration range between 0.0002 and 5 M "collapses" to the narrower range between 0.3 and 6 M when *C* · *K*oct was used as the *x*-axis in the analysis. The data suggest that the general condition of *C* · *K*oct = 0.3 to 6 M is required to induce significant permeation enhancement under the conditions of the enhancers studied. There is no significant difference between the HEM and HMS data. The variability in the "Log *E* versus *C* · *K*oct" relationships for the enhancers could be attributed to the different intrinsic potencies of the enhancers.

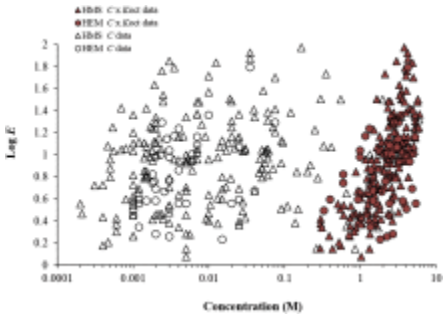

Figure 2

Correlation between Log *E* and enhancer concentration *C* · *K*oct (i.e., *x*-axis concentration = *C* · *K*oct) compared to the results without *K*oct (i.e., *x*-axis concentration = *C*). Each data point represents a concentration condition of an enhancer.

View Large Image | View Hi-Res Image | Download PowerPoint Slide

Jump to Section

Enhancement Factor, Enhancer Concentration, and Koct for Each Enhancer Class

The “Log *E* versus *C* · *K*oct” relationships were further examined based on their chemical classes and structures. Figure 3 examines the relationships between Log *E* and *C* · *K*oct of alkanols with short- to medium-chain lengths. The 1-alkanol data show good predictivity of *C* · *K*oct on permeation enhancement with essentially the same intrinsic potencies (α′) for the alkanol homologous series. The data also suggest an effect of alkyl chain branching (2-, 3-, and 4-alkanols) on permeation enhancement. Branching of the alkyl chain leads to less effective enhancers compared to 1-alkanols. This observation is consistent with a previous study using the *E* = 10 approach.[18] Although 2-alkanols show a trend of lower Log *E* values compared to 1-alkanols, most 2-alkanol data points still overlap with those of 1-alkanols. The data of 3-alkanols, 4-alkanols, and 5-alkanols show a clear deviation from those of 1-alkanols, but there is no noticeable difference between 3-alkanols, 4-alkanols, and 5-alkanols in the figure. The Log *E* values of *cis*- and *trans*-alken-1-ols are not significantly different from those of 1-alkanols, which is consistent with the results in a previous study using the *E* = 10 approach.[19] The lack of the C=C double bond effect of the enhancers on skin permeation enhancement could be due to the alkyl chain lengths (C5-C9) examined and the *C* · *K*oct strategy used in the present study.

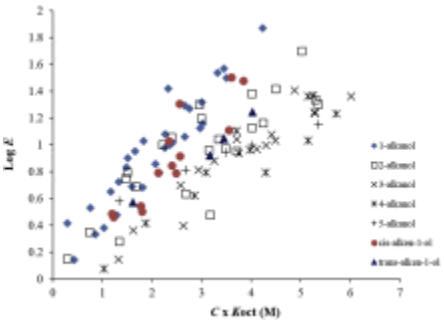

Figure 3

Relationship between permeation enhancement and *C* · *K*oct for alkanols and the effect of alkyl chain branching (branched alkanols: 2-, 3-, 4-, and 5-alkanols) and C=C double bonds (*cis*- and *trans*-alken-1-ols). Each data point represents a “*C* · *K*oct” condition of an enhancer.

View Large Image | View Hi-Res Image | Download PowerPoint Slide

Figure 4 compares the relationships between permeation enhancement factor and enhancer concentration (*C* · *K*oct) for homologous series of enhancers of different polar head groups. The data show larger uncertainties of using *C* · *K*oct to predict the permeation enhancement effect for the enhancers. The majority of the data points overlap with those of 1-alkanols. The diols show some data

scattering to the higher Log *E* values, and the pyrrolidones and azacycloheptanones show data scattering to the lower Log *E* values relative to 1-alkanols. Most enhancers follow the permeation enhancement relationship: Log $E = 0.32 \cdot C \cdot K\text{oct}$, that the condition of $C \cdot K\text{oct} > 0.5$ M is required for effective permeation enhancement (e.g., $E > 2$).

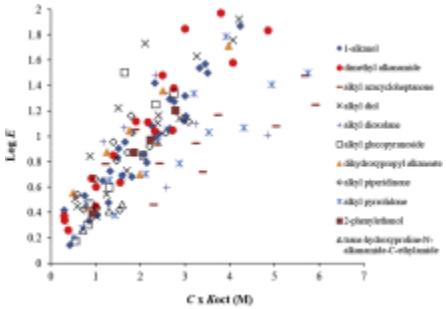

Figure 4

Relationships between enhancement factor and $C \cdot K\text{oct}$ for the studied penetration enhancers compared with alkanol data. Each data point represents a "$C \cdot K\text{oct}$" condition of an enhancer.

View Large Image | View Hi-Res Image | Download PowerPoint Slide

Jump to Section

Comparison Between HMS and HEM Enhancement Factors and Data Regression Analyses

Figure 5 presents the relationships between enhancement factor and concentration ($C \cdot K\text{oct}$) for HEM and HMS and all the enhancers studied. The results of previous skin permeation studies using the direct equilibration method (liquid enhancers or enhancers in an organic solvent saturating the HEM SC for the permeation experiments)[8, 24] are also presented in the figure for comparison. The HEM data of alkyl chain enhancers that have similar chemical structures to those in the HMS studies are consistent with those of HMS. Larger deviations and variability were observed with the HEM data of ring-structure enhancers (e.g., the terpenes and 2-phenylethanol) compared to the enhancers in the HMS studies. The data of highly lipophilic enhancers from the direct equilibration studies with HEM (data of enhancers saturated in HEM) are not substantially different from those of the less lipophilic enhancers in the HMS studies.

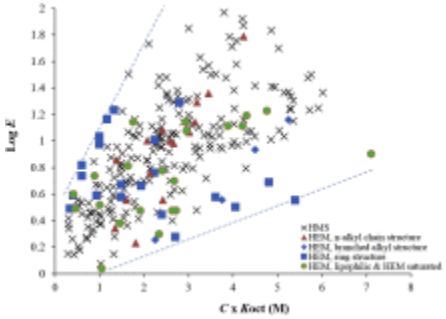

Figure 5

Relationships between enhancement factors and concentration ($C \cdot K$oct) of all studied enhancers including data of lipophilic enhancers when they were saturated in HEM. Each data point represents a "$C \cdot K$oct" condition of an enhancer. The dotted lines bracket the data.

View Large Image | View Hi-Res Image | Download PowerPoint Slide

In the regression analysis using Equation 2 and all the enhancers (including the data from enhancers saturated in HEM), n = 0.94 was determined. This value is larger than the coefficient of 0.7-0.86 for Log Koct to account for the difference between the polarities of octanol and the SC lipid-partitioning domain for skin permeation.[25, 26, 27] Different from skin permeation in which octanol is more lipophilic than the SC partitioning domain, the n = 0.94 value in the present study suggests that the SC microenvironment for the enhancer action to induce permeation enhancement is similar to octanol.[6, 20] Assuming that the skin lipid domain can be described by octanol (n = 1.0 in Eq. 2), linear least squares regression analyses were performed using the data in Figure 5. Table 3 presents the results of the regression analyses.

Table 3 Linear Least Squares Regression Analyses of "Log E versus $C \cdot K$oct" for the Enhancers Studied in Figure 5 Under the Assumption That n = 1.0 in Equation 2 With and Without Forcing y-intercept = 0

Skin Permeation Experimental Data	Slope (α')	y-Intercept	R^2
HMS data only (crosses in Fig. 5)	0.336	–[a]	0.370
	0.227	0.365	0.529
HMS and HEM data without data of enhancers saturated in HEM (all data except circles in Fig. 5)	0.327	–[a]	0.229
	0.203	0.409	0.441
All HMS and HEM data (all data in Fig. 5)	0.320	–[a]	0.196
	0.195	0.416	0.423

View Table in HTML

aNot applicable, linear regression forcing y-intercept = 0.

Jump to Section

Enhancer Concentration and Koct to Predict Skin Permeation Enhancement

A main finding in the present study is the importance of *K*oct as a parameter to predict the effects of penetration enhancers. Enhancer *K*oct (i.e., lipophilicity) can be used to assess enhancer potency. This is consistent with the finding that enhancer effects are related to enhancer concentration in the SC barrier,[28] and hence enhancer partitioning into the SC lipids and enhancer lipophilicities. Particularly, a correlation was found between the enhancer potency parameter α and enhancer *K*oct (Fig. 1). Using this correlation, the potency of an enhancer for skin permeation enhancement under the conditions studied can be predicted. The R^2 value of the regression analysis in Figure 1 suggests satisfactory predictivity.

Under the conditions in the present study, skin permeation enhancement can also be predicted by the thermodynamic activity of the enhancer in the formulation and its equilibrium activity in octanol (i.e., $C \cdot K\text{oct}$). The values of $C \cdot K\text{oct}$ were shown to correlate with skin permeation enhancement. The higher the aqueous enhancer concentration in the chamber (or formulation) and the higher its lipophilicity, the higher is the skin permeation enhancement. This correlation suggests that $C \cdot K\text{oct}$ can be a predictor of skin permeation enhancement. The significance of *K*oct suggests that octanol could mimic the microenvironment for the enhancer action in the SC. According to Table 3, the equation derived from the present analysis for skin permeation enhancement is $\text{Log } E = 0.32 \cdot C \cdot K\text{oct}$.

Specifically, the relationship of "$\text{Log } E = 0.32 \cdot C \cdot K\text{oct}$" suggests that the condition of $C \cdot K\text{oct} > 0.5$ M is needed for an enhancer to induce adequate permeation enhancement. Although the concentration of 0.5 M in this analysis is empirical, mechanistic insights can be deduced from this value. Assuming that the equilibrium $C \cdot K\text{oct}$ concentration is representative of the enhancer concentration in the SC intercellular lipids, the "threshold" value of 0.5 M (or 10% [w/w] for an enhancer with MW of 200 Da) implies that relatively high enhancer concentration is needed in the SC to induce effective permeation enhancement under the conditions studied. This value is not highly dependent on the chemical structures among the enhancers examined in the present study (Fig. 5) as the data scatter of this "threshold" value (e.g., ~0.5-3 M for $E = 2$) is within an order of magnitude from each other. This suggests that the differences in the intrinsic potencies of the enhancers are generally small. There is also a general trend that the *n*-alkyl chain enhancers are more effective than branched alkyl chain enhancers and some carbon ring-structure enhancers (e.g., menthol and cineole). The disruption of SC lipid lamellar packing is a major mechanism of skin penetration enhancers.[28, 29, 30, 31] The enhancement effect is therefore related to the intercalation of the enhancers in the SC lipid structure and the amounts of the enhancers embedded in the lipids.[28] The *n*-alkyl chain enhancers could be more disruptive to the structural order of the SC intercellular lipid lamella compared to the branched alkyl and ring-structure enhancers when the enhancers partition and

intercalate in the lipids. It is also possible that the branched alkyl and ring-structure enhancers do not partition into lipid lamella as well as the *n*-alkyl chain enhancers do.

Jump to Section

Considerations for Using Enhancer Concentration and Koct as Predictors of Skin Permeation Enhancement

Considerations should be given to the limitations of predicting permeation enhancement using the "Log *E* versus *C* · *K*oct" relationship. First, symmetric and equilibrium conditions were used in the skin permeation experiments to determine the enhancement factors analyzed in the present study. In transdermal delivery in practice, an asymmetric condition is normally encountered, in which the enhancers are only applied to the skin in the donor chamber. The asymmetric condition would likely result in a lower enhancement factor compared to that under the symmetric condition. The difference between enhancer-induced skin permeation effects under the asymmetric and symmetric conditions was examined previously.[32] In this previous study, a correlation between the enhancement factors under the asymmetric and symmetric conditions was observed, with ~2-3× lower flux enhancement under the asymmetric condition. The enhancement factor estimated using the "Log *E* versus *C* · *K*oct" relationship in the present study therefore could overestimate the permeation enhancement effect under the asymmetric enhancer condition in practice.

Skin permeation after formulation application in practice is in transient state. Steady-state permeation normally cannot be achieved due to the transport lag time, drug and enhancer depletion, and other changing conditions in the topical and transdermal formulations. The present analysis used steady-state permeation data. As skin permeation enhancement is related to the concentration of the enhancer in the SC, drug permeation is affected by enhancer permeation kinetics (e.g., from the formulation to its site of action in SC). The analysis did not take into account the diffusion of enhancers in the SC. The analysis also did not consider the changes in enhancer concentration in the formulation due to possible enhancer depletion when a finite dose of an enhancer is used. Enhancer depletion could be important for lipophilic enhancers due to their high skin uptake.

The permeation enhancement factors predicted from the correlation in the present study could be limited to permeants of certain physicochemical properties. The model permeants in the enhancer analysis were moderately lipophilic with MW in the ~270-360 Da range. Permeant molecular size (or MW) could affect enhancer-induced permeation enhancement.[33] For example, skin permeation enhancement was found to be a function of permeant MW (see Supplementary Material).[7] The same trend was observed in skin permeability enhancement results from molecular dynamics simulations.[28] Therefore, permeants of MW different from the ~270-360 Da range would likely deviate from the "Log *E* versus *C* · *K*oct" relationship in

the present study. In addition to MW, permeant lipophilicity dictates the pathway for its skin permeation. The SC intercellular lipids are the predominant pathway for the permeation of lipophilic permeants whereas the pore pathway is the predominant permeation pathway for polar and ionic permeants. Skin permeation enhancement of the pore pathway was not determined in the present analysis, and therefore, the "Log *E* versus *C* · *K*oct" relationship should not be applied to polar and ionic permeants.

Aqueous media were the donor and receptor solutions in the skin permeation studies in the present analysis for the permeability-enhancing effects and baseline permeability values. The results are therefore only appropriate for drug delivery systems that provide skin occlusion when the skin is fully hydrated. In addition, the skin permeation studies did not include nonaqueous vehicles and cosolvents. The "Log *E* versus *C* · *K*oct" relationship is therefore expected to be for aqueous formulations. For skin permeation of a nonaqueous formulation, the vehicle (or cosolvent) alters the thermodynamic activity of the enhancer and hence affects the partitioning tendency of the enhancer from the vehicle into the SC. In this case, the vehicle can result in lower concentration of the enhancer at its site of action in the SC.

The variability in the "Log $E = 0.32 \cdot C \cdot K$oct" relationship (Fig. 5 and Table 3) suggests errors up to an order of magnitude in predicting permeation enhancement using this simple relationship. A number of factors contribute to this variability, which could be minimized. The present analysis was based on both experimental and calculated *K*oct values in the literature, so the uncertainties related to these literature values contribute to the variability in Figure 5. For the direct equilibration experimental approach,[8] both experimental and calculated aqueous solubility values in the literature were used and the uncertainties related to these literature values further contribute to the variability. Considering the simplicity of the "Log $E = 0.32 \cdot C \cdot K$oct" relationship, which does not take into account possible differences between the intrinsic potencies of the enhancers, the observed variability in the correlation is not surprising. Nevertheless, this relationship provides guidance to the effects of chemical penetration enhancers in formulation development.

Jump to Section

Conclusion

To address the question whether penetration enhancer effects can be predicted by enhancer concentration and enhancer physicochemical properties, the present study investigated the relationships between skin permeation enhancement and enhancer concentration for more than 40 chemical penetration enhancers from previous skin permeation studies under symmetric/equilibrium conditions. Good correlations were observed between the logarithms of enhancement factors and concentrations of the enhancers studied. A correlation between the enhancer potency parameter α and enhancer *K*oct was observed. This suggests that octanol represents the skin barrier microenvironment for the enhancers,

consistent with the results in previous studies. Whereas enhancer *K*oct was an effective predictor of enhancer potency, no significant effect of enhancer MW on enhancer potency was observed. Data of more than 15 penetration enhancers under the SC saturation condition were also investigated. Together with the data obtained under the symmetric/equilibrium conditions, a simple QSER between enhancement factor and enhancer concentration was derived: Log $E = 0.32 \cdot C \cdot K\text{oct}$, which could be used to predict skin permeation enhancement. The "threshold" enhancer concentration for skin permeation enhancement was determined: $C \cdot K\text{oct} > 0.5$ M. When using the "Log *E* versus $C \cdot K$oct" relationship, consideration should be given to the effects of symmetric versus asymmetric enhancer configurations, aqueous versus cosolvent media, steady state versus non-steady-state conditions, and equilibrium enhancer condition versus diffusing and depleting enhancers. Limitations should also be considered such as the uncertainties in the prediction (errors up to an order of magnitude) and that the "Log *E* versus $C \cdot K$oct" relationship is limited to permeants using the SC lipoidal pathway for skin permeation.

Acknowledgments

The authors thank Drs. Kevin S. Warner, Ning He, Kunio Yoneto, Abdel-Halim Ghanem, and Sarah A. Ibrahim for their contributions to the skin penetration enhancer studies and Dr. William I. Higuchi for his contribution and the conception of the idea in the original penetration enhancer project. The skin penetration enhancer studies were supported in part by NIH Grants GM 043181 and GM 063559.

There is no personal, financial, or non-financial conflict of interest. The data presented in this paper can be available upon request to the corresponding author.

Jump to Section

Supplementary Data

Supplemental Materials

Jump to Section

References

1. Asbill, C.S. and Michniak, B.B. **Percutaneous penetration enhancers: local versus transdermal activity.** *Pharm Sci Technolo Today*. 2000; 3: 36–41
   - View in Article
   - Google Scholar
2. Williams, A.C. and Barry, B.W. **Penetration enhancers.** *Adv Drug Deliv Rev*. 2004; 56: 603–618
   - View in Article

|

- Google Scholar

3. Karande, P., Jain, A., Ergun, K., Kispersky, V., and Mitragotri, S. **Design principles of chemical penetration enhancers for transdermal drug delivery.** *Proc Natl Acad Sci U S A*. 2005; 102: 4688–4693

- View in Article

|

- Google Scholar

4. Vavrova, K., Zbytovska, J., and Hrabalek, A. **Amphiphilic transdermal permeation enhancers: structure-activity relationships.** *Curr Med Chem*. 2005; 12: 2273–2291

- View in Article

|

- Google Scholar

5. Chantasart, D. and Li, S.K. **Structure enhancement relationship of chemical penetration enhancers in drug transport across the stratum corneum.** *Pharmaceutics*. 2012; 4: 71–92

- View in Article

|

- Google Scholar

6. Li, S.K. and Higuchi, W.I. **Quantitative structure-enhancement relationship and the microenvironment of the enhancer site of action.** in: N. Dragicevic, H.I. Maibach (Eds.) **Percutaneous Penetration Enhancers Chemical Methods in Penetration Enhancement: Modification of the Stratum Corneum**. Springer-Verlag, New York; 2015: 55–67

- View in Article

|

- Google Scholar

7. Li, S.K. and Higuchi, W.I. **Mechanistic studies of permeation enhancers.** in: N. Dragicevic, H.I. Maibach (Eds.) **Percutaneous Penetration Enhancers Drug Penetration Into/Through the Skin: Methodology and General Considerations**. Springer-Verlag, New York; 2017: 119–136

- View in Article

|

- Google Scholar

8. Ibrahim, S.A. and Li, S.K. **Effects of chemical enhancers on human epidermal membrane: structure-enhancement relationship based on maximum enhancement (*Emax*).** *J Pharm Sci*. 2009; 98: 926–944

- View in Article

|

- Google Scholar

9. Ibrahim, S.A. and Li, S.K. **Effects of solvent deposited enhancers on transdermal permeation and their relationship with *Emax*.** *J Control Release*. 2009; 136: 117–124

- View in Article

|

- Google Scholar

10. Shaker, D.S., Ghanem, A.H., Li, S.K., Warner, K.S., Hashem, F.M., and Higuchi, W.I. **Mechanistic studies of the effect of hydroxypropyl-β-cyclodextrin on in vitro transdermal permeation of corticosterone through hairless mouse skin.** *Int J Pharm*. 2003; 253: 1–11

- View in Article

|

- Google Scholar

11. Warner, K.S., Shaker, D.S., Molokhia, S. et al. **Silicone elastomer uptake method for determination of free 1-alkyl-2-pyrrolidone concentration in micelle and hydroxypropyl-β-cyclodextrin systems used in skin transport studies.** *J Pharm Sci*. 2008; 97: 368–380

- View in Article

|

- Google Scholar

12. Ghanem, A.H., Mahmoud, H., Higuchi, W.I., Liu, P., and Good, W.R. **The effects of ethanol on the transport of lipophilic and polar permeants across hairless mouse skin: methods/validation of a novel approach.** *Int J Pharm*. 1992; 78: 137–156

- View in Article

|

- Google Scholar

13. Kim, Y.H., Ghanem, A.H., Mahmoud, H., and Higuchi, W.I. **Short chain alkanols as transport enhancers for lipophilic and polar/ionic permeants in hairless mouse skin: mechanism(s) of action.***Int J Pharm*. 1992; 80: 17–31

- View in Article

|

- Google Scholar

14. Warner, K.S., Li, S.K., and Higuchi, W.I. **Influences of alkyl group chain length and polar head group on chemical skin permeation enhancement.** *J Pharm Sci*. 2001; 90: 1143–1153

- View in Article

|

- Google Scholar

15. Leo, A., Hansch, C., and Elkins, D. **Partition coefficients and their uses.** *Chem Rev*. 1971; 71: 525–616

- View in Article

|

- Google Scholar

16. Xiang, T.X. and Anderson, B.D. **The relationship between permeant size and permeability in lipid bilayer membranes.** *J Membr Biol*. 1994; 140: 111–122

- View in Article

|

- Google Scholar

17. Yoneto, K., Ghanem, A.H., Higuchi, W.I., Peck, K.D., and Li, S.K. **Mechanistic studies of the 1-alkyl-2-pyrrolidones as skin permeation enhancers.** *J Pharm Sci*. 1995; 84: 312–317

- View in Article

|

- Google Scholar

18. Chantasart, D., Li, S.K., He, N., Warner, K.S., Prakongpan, S., and Higuchi, W.I. **Mechanistic studies of branched-chain alkanols as skin permeation enhancers.** *J Pharm Sci*. 2004; 93: 762–779

- View in Article

|

- Google Scholar

19. He, N., Warner, K.S., Chantasart, D., Shaker, D.S., Higuchi, W.I., and Li, S.K. **Mechanistic study of chemical skin permeation enhancers with different polar and lipophilic functional groups.** *J Pharm Sci*. 2004; 93: 1415–1430

- View in Article

|

- Google Scholar

20. Warner, K.S., Li, S.K., He, N. et al. **Structure-activity relationship for chemical skin permeation enhancers: probing the chemical microenvironment of the site of action.** *J Pharm Sci*. 2003; 92: 1305–1322

- View in Article

|

- Google Scholar

21. He, N., Li, S.K., Suhonen, T.M., Warner, K.S., and Higuchi, W.I. **Mechanistic study of alkyl azacycloheptanones as skin permeation enhancers by permeation and partition experiments with hairless mouse skin.** *J Pharm Sci*. 2003; 92: 297–310

- View in Article

|

- Google Scholar

22. Chantasart, D., Sa-Nguandeekul, P., Prakongpan, S., Li, S.K., and Higuchi, W.I. **Comparison of the effects of chemical permeation enhancers on the lipoidal pathways of human epidermal membrane and hairless mouse skin and the mechanism of enhancer action.** *J Pharm Sci*. 2007; 96: 2310–2326

- View in Article

|

- Google Scholar

23. Chantasart, D., Pongjanyakul, T., Higuchi, W.I., and Li, S.K. **Effects of oxygen-containing terpenes as skin permeation enhancers on the lipoidal pathways of human epidermal membrane.** *J Pharm Sci*. 2009; 98: 3617–3632

- View in Article

|

- Google Scholar

24. Ibrahim, S.A. and Li, S.K. **Efficiency of fatty acids as chemical penetration enhancers: mechanisms and structure enhancement relationship.** *Pharm Res*. 2010; 27: 115–125

- View in Article

|

- Google Scholar

25. Potts, R.O. and Guy, R.H. **Predicting skin permeability.** *Pharm Res*. 1992; 9: 663–669

- View in Article

|

- Google Scholar

26. Mitragotri, S. **Modeling skin permeability to hydrophilic and hydrophobic solutes based on four permeation pathways.** *J Control Release*. 2003; 86: 69–92

- View in Article

|

- Google Scholar

27. Nitsche, J.M., Wang, T.F., and Kasting, G.B. **A two-phase analysis of solute partitioning into the stratum corneum.** *J Pharm Sci*. 2006; 95: 649–666

- View in Article

|

- Google Scholar

28. Lundborg, M., Wennberg, C.L., Narangifard, A., Lindahl, E., and Norlen, L. **Predicting drug permeability through skin using molecular dynamics simulation.** *J Control Release*. 2018; 283: 269–279

- View in Article

|

- Google Scholar

29. Suhonen, M.T., Bouwstra, J.A., and Urtti, A. **Chemical enhancement of percutaneous absorption in relation to stratum corneum structural alterations.** *J Control Release*. 1999; 59: 149–161

- View in Article

|

- Google Scholar

30. Engelbrecht, T.N., Schroeter, A., Hauss, T., and Neubert, R.H. **Lipophilic penetration enhancers and their impact to the bilayer structure of stratum corneum lipid model membranes: neutron diffraction studies based on the example oleic acid.** *Biochim Biophys Acta*. 2011; 1808: 2798–2806

- View in Article

|

- Google Scholar

31. Anjos, J.L., Neto Dde, S., and Alonso, A. **Effects of 1,8-cineole on the dynamics of lipids and proteins of stratum corneum.** *Int J Pharm*. 2007; 345: 81–87

- View in Article

|

- Google Scholar

32. Chantasart, D. and Li, S.K. **Relationship between the enhancement effects of chemical permeation enhancers on the lipoidal transport pathway across human skin under the symmetric and asymmetric conditions in vitro.** *Pharm Res*. 2010; 27: 1825–1836

- View in Article

|

- Google Scholar

33. Mitragotri, S. **Effect of bilayer disruption on transdermal transport of low-molecular-weight hydrophobic solutes.** *Pharm Res*. 2001; 18: 1018–1023

- View in Article

|

- Google Scholar