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Skin penetration of organic compounds from aqueous and lipophilic vehicles

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Background

In occupational settings skin is frequently exposed to chemicals dissolved in non-aqueous vehicles or to highly lipophilic compounds dissolved in water. Unfortunately, there are few experienttal data available for either of these two situations. The purpose of this study was to compare skin penetration rates of lipophilic compounds from water and one or more lipophilic vehicles.

Typically, the rate of solute penetration from water through skin is proportional to the solute's concentration in water (C_W) as long as C_W is less than the solute's solubility in water (S_W). The steady-state flux across the skin from water ($J_{SS,w}$) is often described by the product of C_W and the permeability coefficient for dermal absorption from water ($K_{p,w}$). Unless super saturation is stabilized, the maximum steady-state flux ($J_{SS,max}$) occurs when $C_W = S_W$ and $J_{SS,w} = J_{SS,max}$ even if $C_W > S_W$.

The permeability coefficient $K_{p,w}$ is affected by both the lipophilic character and size of the penetrating solute, which are frequently approximated by the octanol-water partition coefficient (K_{OW}) and molecular weight (MW). Several structure-activity relationships for estimating $K_{p,w}$ have been derived using K_{OW} and MW. The equation developed by Potts and Guy[1]:

$$\log K_{pw}[\text{cnh}^{-1}] = -2.73 + 0.7 \log K_{OW} - 0.0061 MW \qquad (1)$$

is one of the most widely used. In their critical review of permeability coefficient data measured *in vitro* in human skin from water, Vecchia and Bunge[2] concluded that the Potts and Guy equation provided reasonable estimates of the existing data. However, because there are almost no data for compounds with $\log K_{OW} < -1$ or $\log K_{OW} > 4$, using the Potts and Guy (or any other structure-activity relationship) beyond these limits is unsupported by data and may produce estimates that are incorrect.

There are many experimental challenges that make reliable and reproducible determination of $K_{p,w}$ difficult for compounds with $\log K_{OW} > 4$. Basically, measuring steady-state flux of a lipophilic solute from water is difficult because its water solubility is low, its absorption rate into the lipophilic stratum corneum is relatively large, and its low solubility in the more hydrophilic viable epidermis limits mass transfer from the stratum corneum into these tissues. The difficulty in measuring $K_{p,w}$ increases as $\log K_{OW}$ increases and S_W decreases. Because the solubility of a

lipophilic solute in a lipophilic vehicle (S_V) would be much larger than S_W, it should be possible to measure steady-state flux from a lipophilic vehicle provided it did not significantly damage the skin.

As long as a nonaqueous vehicle v does not damage the skin, steady-state flux through skin from it ($J_{ss,v}$) should be related to the solute concentration C_V as $J_{ss,v} = K_{p,v} C_V$, in which $K_{p,v}$, the permeability coefficient from vehicle v, is not the same as the permeability coefficient from an aqueous vehicle $K_{p,v}$. If water and a nonaqueous vehicle (v) do not alter the skin barrier significantly, then, based on thermodynamic arguments we expect that the maximum flux would be the same from both and related to solute solubility in each. That is,

$$J_{ss},\text{max} = K_{p,w} S_W = K_{p,v} S_V \qquad (2)$$

If so, then we can estimate $K_{p,v} = K_{p,w} S_W / S_V$ using an estimate of $K_{p,w}$ (e.g., using Eq. 1). Alternatively, we could estimate Kp,w of a highly lipophilic compound from the steady-state flux determined in a nonaqueous vehicle and the water solubility (i.e., $K_{p,w} = J_{ss,v}/S_W$).
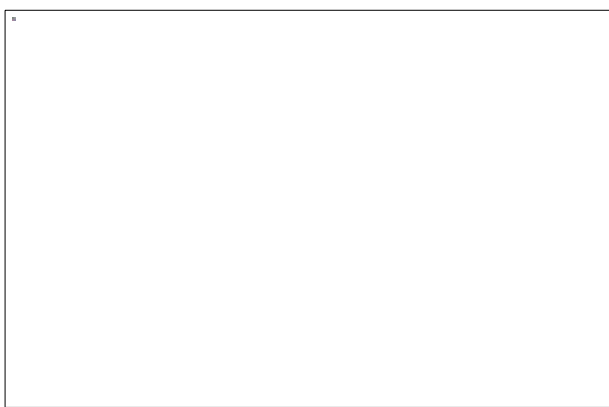
Our goal was to test the hypothesis represented by Eq. (2) and its limitations by comparing solute penetration rates through skin from aqueous and nonaqueous vehicles. In particular, we were interested in finding nonaqueous vehicles that would have little or no effect on the skin barrier. Here we describe a preliminary study of three test compounds, 4-cyanophenol (CP), methyl paraben (MP), and phenanthrene (PN), for which $\log K_{ow}$ = 1.6, 2.0, and 4.46, respectively, applied to skin in water and in one or more of three different lipophilic vehicles. Properties of these compounds are listed in Table 1.

Methods

Steady-state flux of the test compounds through heat-separated human skin (i.e., the epidermal membrane) was measured in flow-through diffusion cells from water and one or more of selected lipophilic vehicles. The lipophilic vehicles studied were decane, mixtures of decane and a light mineral oil (MO), and two light silicone oils (SO). The mineral oil (Fisher Scientific) had a viscosity that was not more than 33.5 cSt at 40°C. (For comparison, the viscosity of water is 0.66 cSt at 40°C). Mixtures of decane and mineral oil (100:0, 75:25, 50:50 by volume) were studied. The viscosity of the 50:50 decane:MO mixture (DMO) was ~ 7.5% of the viscosity of the MO. The two silicone oils (a gift from Dow Corning Corporation, Midland, MI), designated as SO1.5 and SO2, had viscosities of 1.5 and 2.0 cSt, respectively and specific gravities of 0.872 and 0.850, respectively.

Frozen human cadaver skin was acquired from LifeCell (The Woodlands, TX) or NDRI (Philadelphia, PA) and kept frozen at < -60°C until used. Skin was heat separated, clamped into Franz-type vertical diffusion cells (PermeGear, Bethlehem, PA) and equilibrated with recaptor solution for several hours. The diffusion area was 0.64 cm^2 and the average temperature of the

cells was 32°C. The receptor solution was 0.01 M phosphate buffered saline, circulated at a flow rate of 1.5 mL h^{-1}. Bovine serum albumin (4% by weight) was added to the receptor solution in experiments with PN to insure adequate solubility. Donor solutions of either MP or CP were saturated and contaminated with excess chemical. The concentration of CP or MP in the receptor solution was determined by HPLC with a diode array detector (254 nm). Donor solutions of PN were sub-saturated and contained tracer quantities of ^{14}C-PN. The amount of ^{14}C-PN in the receptor was determined by liquid scintillation counting. $K_{p,v}$ of ^{14}C-PN was calculated from the $J_{ss,v}$ and C_v for ^{14}C-PN. Donor solutions of PN in water were replaced frequently during the experiment to insure that absorption into the skin did not change the donor concentration significantly.

Results

Prior to this study, we had measured dermal penetration of CP or MP from decane, tetradecane, or hexadecane vehicles. In these experiments we found that decane increased chemical flux through skin relative to water, while solubility of CP or MP in these very lipophilic tetradecane and hexadecane made steady-state flux measurements difficult. Although the light mineral oil (MO) did not appear to enhance chemical flux, its relatively large viscosity produced unstirred layers in the donor solution that reduced the steady-state flux. Also, comparisons of results within and between subjects showed that subject-to-subject variation was significant.

Steady-state flux (J_{ss}) from saturated solutions of MP and CP are shown in Figures 1 and 2, respectively. As expected, mixtures of decane:MO, which have the advantage of being less viscous than MO alone, affected skin barrier function less than decane alone (see Figure 1, Subject A). In the same subject, J_{ss} from saturated solutions of MP in water, SO1.5 and SO2 were the same. However, for saturated solutions of CP in water and SO, JSS was consistently larger from water by a factor of ~10. J_{ss} was almost the same from SO1.5 and SO2 (Figure 2). We do not know why and confirmatory experiments are in progress. One difference between MP and CP is that CP ionizes in water.
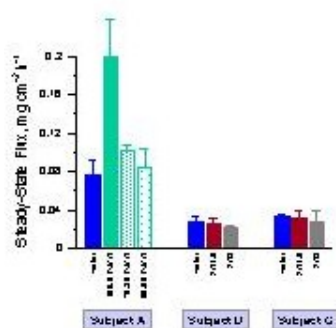

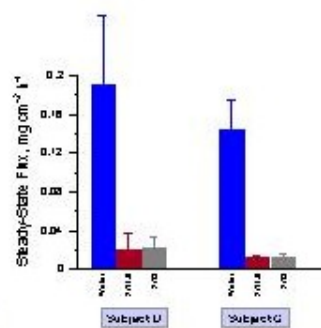Figure 1. Flux from saturated MP solutions   Figure 2. Flux from saturated CP solutions

Table 2 lists the permeability coefficients of PN ($K_{p,v}$) along with estimated maximum flux of PN from each vehicle (i.e., $K_{p,v} S_v$) measured from water, DMO, SO1.5 and SO2. Although Kp,w in Subject D was 160-fold larger than $K_{p,v}$ from the 50:50 decane: MO (DMO) vehicle, the estimated maximum flux (i.e $K_{p,v} S_v$) from water was only about 3.4 times larger than from DMO. $K_{p,w}$ estimated from $K_{p,v}$ for DMO was 4-fold smaller than $K_{p,w}$ measured from water. This was probably because the viscous DMO presented an additional mass transfer resistance. The estimated maximum flux and the $K_{p,w}$ estimated from DMO might be smaller than measured from water because the donor solution was stirred and DMO is more viscous.

Table 2. $K_{p,v}$ for PN from Various Vehicles

Vehicle	Subject	[a] $K_{p,v} \times 10^3$ cm h^{-1}	[b] n	[c] S_v mg mL^{-1}	[d] $K_{p,v} S_v$ µg cm^{-2} h^{-1}	[e] $K_{p,v} S_v / S_w$ cm h^{-1}
Water	D	44 ±0.4	2	0.00115	0.051 ±0.0005	0.044 ±0.0004
DMO	D	0.28 ±0.11	2	0.053	0.015 ±0.006	0.013 ±0.005
SO1.5	D	0.73 ±0.60	5	10.6	7.7 ±6.4	6.7 ±5.6
	E	0.24 ±0.10	6		2.5 ±1.1	2.2 ±1.0
	G	0.324	1		3.4	3.0
SO2	D	1.00 ±0.53	6	13	13 ±6.9	11 ±6.0
	E	0.33 ±0.21	6		4.3 ±2.7	3.7 ±2.3
	G	0.27 ±0.16	2		3.5 ±2.1	3.0 ±1.8

[a] Mean ±confidence interval; [b] Number of replicates;
[c] PN solubility measured at 32°C except for water, which was at 25°C;
[d] Estimated maximum flux; [e] Estimated using Eq. (1)

The estimated maximum steady-state flux of PN from the two silicone oils was approximately 100 times larger than from water and approximately 500 times larger than from DMO. $K_{p,w}$ values estimated from $K_{p,v}$ for the SO1.5 and SO2 were similar to each other and about 70 to 250 times larger than $K_{p,w}$ measured from water. This difference is probably due in part to a mass transfer resistance in the aqueous donor solution. Silicone oil solubility in skin is expected to be very small. Consequently, it seems unlikely that silicone oil could enhance flux by changing PN diffusion or solubility in the skin. These results are preliminary and in some cases the number of replicates is small. Experiments comparing PN flux from saturated solutions of PN in water, DMO and SO are currently underway.
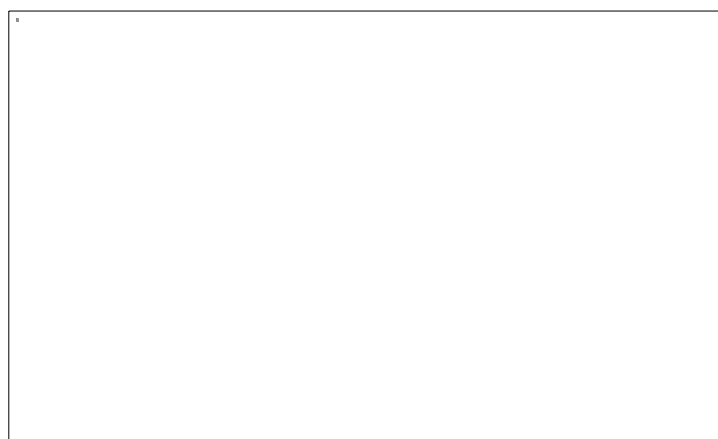
Summary

Table 3 summarizes $K_{p,w}$ values estimated from $K_{p,v}$ for the three test compounds from DMO, SO1.5 and SO2. Except for PN, $K_{p,w}$ values estimated from $K_{p,v}$ were all smaller than predictions from Eq. (1). For MP, $K_{p,w}$ values estimated from $K_{p,v}$ are the same as measured from water. For CP, $K_{p,w}$ values estimated from $K_{p,v}$ are significantly smaller than measured from water. For PN, $K_{p,w}$ values estimated from $K_{p,v}$ are similar for the two silicone oils, which are both larger than measured from water and DMO. This was expected because PN has little solubility in water and DMO is viscous. However, the estimated $K_{p,w}$ for SO1.5 and SO2 was large and larger than predicted by Eq. (1)

References

1.   Potts, R.O. and Guy, R.H., 1992. Predicting skin permeability. Pharm Res, 9, 663-669.

2.   Vecchia, B.E., and Bunge, A.L., 2002. Skin absorption databases and predictive equations. In: Transdermal Drug Delivery Systems (J. Hadgraft and R.H. Guy, eds.), Marcel Dekker, New York, pp. 57-141.

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