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Fit of fluxes of sunscreens and other compounds from propylene glycol:water (30:70) through human skin and silicone membrane to the Roberts–Sloan equation: The effect of polar vehicle (or water) solubility

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Synopsis

It would be useful to develop a surrogate for animal skin, which could be use to predict flux through human skin. The fluxes (and physicochemical properties) of sunscreens and other compounds from propylene glycol (PG):water (AQ), 30:70, through human skin have previously been reported. We measured the fluxes of several of those sunscreens and other compounds from PG:AQ, 30:70, through silicone membrane and fit both sets of data to the Roberts–Sloan (RS) equation to determine any similarities. For both sets of data, the fluxes were directly dependent on their solubilities in a lipid solvent [octanol (OCT), in this case] and in a polar solvent (PG:AQ, 30:70, or AQ in this case) and inversely on their molecular weights. The fit of the experimental (EXP) fluxes through human skin *in vivo* to RS was excellent: $r^2 = 0.92$ if the vehicle (VEH) PG:AQ, 30:70 was the polar solvent (RS^1) or $r^2 = 0.97$ if water was the polar solvent (RS^2). The fit of the EXP fluxes through silicone membrane to RS was good: $r^2 = 0.80$ if the VEH PG:AQ, 30:70, was the polar solvent (RS^1) or $r^2 = 0.81$ if water was the polar solvent (RS^2). The correlations between their EXP fluxes through human skin *in vivo* and their EXP fluxes through silicone membrane were good ($r^2 = 0.85$). In addition, the correlation between EXP fluxes from PG:AQ, 30:70, through human skin *in vivo* and their fluxes calculated from the coefficients of the fit of solubilities, molecular weights and fluxes from water through silicone membranes from a previous $n = 22$ database to RS was even better ($r^2 = 0.94$). These results suggest that flux through human skin can be calculated from flux through a silicone membrane.

INTRODUCTION

Human skin is an effective barrier to the absorption of many of the chemicals with which it comes in contact. This efficiency has been considered to be a challenge to many in the

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scientific community who have attempted to use topical delivery of drugs as a means to treat local as well as systemic disease states (1). To identify those physicochemical properties of drugs that predict good topical delivery, flux (J) into (dermal delivery) and through skin (transdermal delivery) and various experimental (EXP) physicochemical properties of drugs have been collected (2–5). Qualitative analysis of those physicochemical properties of drugs that affect flux values has shown that those drugs that exhibit higher lipid (S_{LIPID}) and aqueous solubilities (S_{AQ}) and lower molecular weights (MW) give the higher flux values (2–10), regardless of whether a lipid (2,6–8) or an aqueous vehicle (VEH) is used (3,4,9,10).

This dependence of flux on solubilities in both lipid and aqueous phases is due to the presence of ceramides in what is usually characterized as the lipid matrix in which the corneocytes of the stratum corneum (SC) are embedded. The ceramides have polar functional groups attached to long-chain lipid alkyl groups and are arranged in bilayers. The polar functional groups have water molecules associated with them (11), so that to effectively pass through the bilayers that comprise the lipid matrix of the SC, drug molecules must actually pass through alternating layers of lipid and associated water layers (the biphasic solubility model) (6,12), and exhibit some solubility in each layer. Thus, any dependence on the water solubility of the permeant is not dependent on its solubility in an aqueous VEH (or any VEH) but is dependent on its solubility in an aqueous (or polar) phase within the lipid matrix of the SC—the assumed rate limiting barrier to flux.

The qualitative relationship between lipid and aqueous solubilities has been quantified using an extrapolation of Fick's law: eq (1) (2–4):

$$J = D/L(C_{M1} - C_{Mn}) \quad \text{eq (1)}$$

In equation (1), the driving force for diffusion of a drug through a membrane is the concentration gradient between the first few layers of the membrane (C_{M1}) and the last few layers (C_{Mn}) (12,13). If it is assumed that C_{Mn} approaches zero and that C_{M1} has reached its maximum value (the solubility of the drug in those first few layers of skin—S_{M1}) (12–17), then the maximum flux, J_M, is dependent on S_{M1}. Since S_{M1} is difficult to measure, the product of the solubility of the drug in the VEH, S_{VEH}, and the partition coefficient between the first few layers of skin, M1, and the VEH, $K_{M1:VEH}$ or $(K_{LIPID:VEH})^y \cdot c$ (12,15), gives an estimate of S_{M1}. If the lipid, LIPID, is octanol (OCT), and the VEH is water, AQ, expansion of K as solubilities, combined with the solubility in the VEH term, S_{AQ}, gives $\log S_{M1} = y \log S_{OCT} + (1 - y) \log S_{AQ} + \log c$. Insertion of this identity into Fick's law ultimately gives one form of the RS equation: eq (2) (3,4) where water is the VEH and the lipid is OCT. It can be shown that the same equation results if a lipid VEH is used (2).

$$\log J_{MAQ} = x + y \log S_{OCT} + (1 - y) \log S_{AQ} - z\,MW \quad \text{eq (2)}$$

The RS equation not only tells the investigator what properties to optimize to increase flux, but it also tells the investigator what properties to optimize to decreased flux (the only

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clinically relevant measurement)—decrease S_{LIPID} and S_{AQ} and increase MW. On the other hand, partition coefficients, K, and permeability coefficients, P (J/concentration in the VEH, C_{VEH}), which are the basis for the Potts–Guy type analyses, are not useful parameters from which to design molecules exhibiting increased, or in this case decreased, flux (15). However, solubility-based parameters are because they are independent parameters that predict S_{MI}. As the potential hazards from the topical absorption of sunscreens and other compounds becomes better recognized and understood (18,19), the practical aspect of designing sunscreens and other compounds found in cosmetic formulations so that they are not absorbed becomes more important. The topical absorption of sunscreens and other compounds have been studied by numerous investigators (20); however, the study of the *in vivo* absorption of sunscreens and other compounds from the VEH PG:AQ, 30:70, (J_{MHVEH}) reported in 1995 remains the largest database containing sunscreens and other compounds found in cosmetic formulations obtained under the same EXP conditions ($n = 10$) (21). The structures are shown in Figure 1. The authors recognized the dependence of EXP J_{MHVEH} on $K_{OCT:VEH}$ and S_{VEH}. In fact, their equation (8) is very similar to the RS equation with a dependence of J_{MAX} on the solubilities of the permeants in OCT, S_{OCT}, and the VEH, S_{VEH}, except that the coefficient ($y = 0.38$) to the parameter log S_{OCT} was quite different from what we have found (see below) because molecular volume, MV (or MW), was disregarded. In addition, the correlation between the product of $(K_{OCT:VEH})^{y} \cdot c$ and S_{VEH}, S_{MI}, and maximum flux was not recognized, which is an important concept for the design of new drugs with increased (or decreased) topical delivery (15).

Here, we first report the fit of the physicochemical data for the components of the sunscreens and other compounds database $n = 10$ to the RS equation and the correlation of log J_{MHVEH} with MW, log S_{OCT} and either log S_{VEH} or log S_{AQ}.

We also recently correlated EXP flux values for the delivery of drugs through human skin *in vitro* from water (EXP J_{MHAQ}) with EXP flux values for their delivery through a silicone membrane from water (EXP J_{MPAQ}): $n = 11$, $r^2 = 0.82$ (22). The conclusion was that EXP J_{MHAQ} could be predicted by EXP J_{MPAQ}. The unexpected finding that both EXP J_{MHAQ} and EXP J_{MPAQ} depended on S_{AQ} as well as S_{LIPID} (S_{OCT}) (23), when it has been assumed that a silicone membrane presented only a lipid barrier to permeation, was rationalized based on the fact that silicone membranes absorb small amounts of water (24). It should be noted that only a few VEHs such as water, methanol, and PG do not interact with silicone membrane (25,26) so that PG:AQ, 30:70 (21) and water VEHs (22,23) can be used in the study of flux through silicone membrane without raising concerns about VEH effects on J_{MPAQ}.

Here, we next report (i) the EXP flux values of selected members ($n = 7$) that were available to us from the *in vivo* sunscreens and other compounds database through silicone membranes from the same PG:AQ (30:70) VEH, EXP J_{MPVEH}, used in the *in vivo* study (21), instead of from a water VEH (22,23) (ii) the fit of the physicochemical data for selected members of the sunscreen database ($n = 7$) and a homolog of 2 (2′) to the RS equation (iii) correlations of solubilities and MW data with EXP J_{MPVEH} data, and (iv) the correlation between EXP J_{MPVEH} and EXP J_{MHVEH}.

Finally, we report calculated J_{MPVEH} values (CALC J_{MPVEH}) using the previously determined coefficients from the fit of EXP J_{MPAQ} data ($n = 22$, where $S_{LIPID} = S_{OCT}$) to the RS equation ($x = -2.046$, $y = 0.667$, $z = 0.00374$, $r^2 = 0.88$) (23) to determine if J_{MPAQ} coefficients could be used to calculate J_{MHVEH} accurately.

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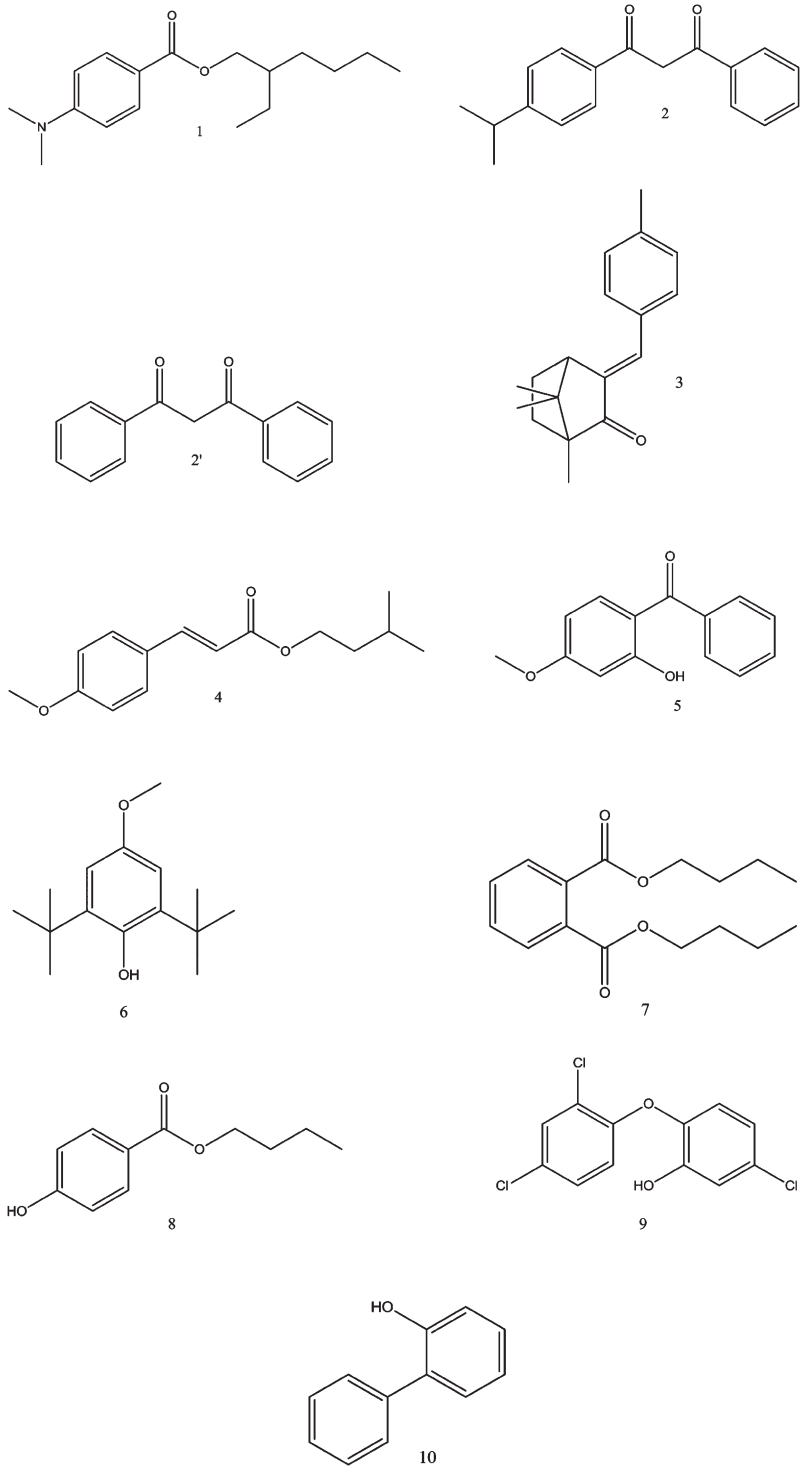

Figure 1. Structures of sunscreen components.

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METHODS

Data from Hagedorn-Leweke and Lippold's Tables (21) have been modified. MWs have been used instead of MV (14). Solubilities (c_{sOc} and c_{sV}) have been converted to mM amounts (S_{OCT} and S_{VEH}, respectively), fluxes (J_{MAX}) have been converted to μmol $cm^{-2} \cdot h^{-1}$ (J_{MHVEH}) and partition coefficients ($PC_{OCT:V}$ and $PC_{OCT:W}$) are now $K_{OCT:VEH}$ and $K_{OCT:AQ}$, respectively. S_{OCT} for oils that are miscible with OCT have been calculated from log S_{VEH} + log $K_{OCT:VEH}$ (16,17). S_{AQ} have been calculated from log S_{OCT} − log $K_{OCT:AQ}$ (Table I).

Diffusion cell experiments to determine the EXP flux values of selected members of the *in vivo* sunscreens and other compounds database through nonreinforced silicone membranes (Pillar Surgical, La Jolla, CA) from a PG:AQ (30:70) VEH (J_{MPVEH}) were run in the same way as previously described in detail (23). Briefly, the silicone membranes were kept in contact with PG:AQ, 30:70, receptor phase for at least 3 h before application of the PG:AQ, 30:70, donor phase to ensure an equilibrium concentration of water (and PG) throughout the 0.254-mm thick membrane (24). Suspensions (at least 10-fold excess of the permeant solubility in VEH) were prepared 1 h before they were applied to the membranes. After 20 h of the first application period, fresh suspensions were applied and samples of the receptor phases were taken every 3 h (for 5, 8, and 9) or every 1 h if the solubility of the permeant in the receptor phase was too low to ensure that sink conditions were maintained for 3 h [for 1, 2′ (the structure is shown in Figure 1), 3, and 7]. The receptor phases were changed each time a sample was taken. Five samples were analyzed during the steady state of the first application period (48 h total) of the experiments (20, 23, 26, 29, and 33 h for 5, 8, and 9; 23, 24, 25, 26, and 27 h for 1, 2′, 3, and 7). For

Table I
MW, Solubility in PG:AQ, 30:70 (S_{VEH}), Solubility in OCT (S_{OCT}), Partitions Coefficient Between OCT and VEH ($K_{OCT:VEH}$), Partition Coefficient Between OCT and AQ ($K_{OCT:AQ}$), and Solubility in Water (S_{AQ}) for Compounds in the Sunscreens and Other Compounds Database

	MW	log S_{VEH}[a,b]	log $K_{OCT:VEH}$[a]	log S_{OCT}[b,c]	log $K_{OCT:AQ}$[a]	log S_{AQ}[b,d]
1	277	–2.14	4.67	2.53	5.75	–3.22
2	266	–1.95	5.27	3.33	6.51	–3.18
2′[e]	224	–1.21[e]	3.48[f]	2.27[e]	4.43[g]	–2.16
3	254	–1.47[h]	4.14	2.67	5.13	–2.46
4	248	–0.92	3.83	2.91	4.83	–1.92
5	228	–0.43	2.90	2.46	3.82	–1.36
6	236	–1.29	3.79	2.49	4.64	–2.15
7	278	–0.58	3.43	2.85	4.39	–1.54
8	193	–1.01	2.44	3.45	3.42	0.03
9	289	–0.14	3.61	3.47	4.53	–1.06
10	170	1.42	2.22	3.64	3.07	0.57

[a]Data from Ref. (21).
[b]Units of mM.
[c]Calculated from EXP log S_{VEH} + EXP log $K_{OCT:VEH}$.
[d]Calculated from EXP log S_{OCT} – EXP log $K_{OCT:AQ}$.
[e]2′ was not part of Ref. (21) database, so values were measured experimentally.
[f]Estimated from EXP log S_{OCT} – log S_{VEH}.
[g]Calculated from log $K_{OCT:VEH}$ by Colander's regression analysis.
[h]Experimental value measured here.

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6, the flux value was so low and the ε_{VEH} was so low that samples were collected about every 12 h for a total of four samples over the 48 h first application period. Samples were quantitated using ultraviolet (UV) spectroscopy and the EXP UV λ_{MAX} and ε_{VEH} values determined for each permeant in the receptor phase (Table III) (23).

After the first application period of 48 h, the donor phases were removed, the membranes were washed 3 times with 5 ml of methanol (25,26) and contact between fresh receptor phase and the membranes were re-established. After 24 h of leaching the initially applied permeant from the membranes into the receptor phases, the receptor phases were changed every 2–8 h to allow more efficient leaching of the permeant out of the membranes. Suspensions of theophylline (ThH) in PG (ThH/PG) were then applied as a second application and samples were taken at 6, 24, and 49 h using the same UV analysis procedures as for the first application where UV_{MAX} = 270 nm, $\varepsilon = 1.02 \times 10^4$ L mol^{-1} for ThH (27).

The solubilities for 2′ and 3 were determined as previously described (23). The solubility of 3 in PG:AQ, 30:70, was repeated because we noticed a decrease in the intensity of its λ_{MAX} at 307 nm with time so that the apparent ε_{VEH} decreased. A decreased apparent ε_{VEH} would lead to increased calculated solubilities for a measured absorbance in the UV of 3.

Flux values were obtained by plotting the cumulative amount of each permeant in the receptor phase versus time. The slope of the plot in μmol h^{-1} was divided by the area of the membrane (4.9 cm^2) to give flux in μmol cm^{-2}·h^{-1}.

Regression analyses and correlations were performed using SPSS 19.

RESULTS AND DISCUSSION

SUNSCREENS AND OTHER COMPOUNDS DATABASE FIT TO THE RS EQUATION

When the EXP log J_{MHVEH}, MW, log S_{OCT}, and log S_{VEH} values from Tables I and II were fit to the RS equation using the SPSS 19 statistical software package from IBM, the parameter coefficient estimates for n = 10 (not including 2′) were $x = -1.550$, $y = 0.591$, $z = 0.00652$, $r^2 = 0.92$ for RS^1. When log S_{AQ} instead of log S_{VEH} values were used in the fit to the RS equation, an equally good fit was observed: $r^2 = 0.97$, $x = -2.159$, $y = 0.481$, $z = 0.00065$ for RS^2. The plots of EXP log J_{MHVEH} versus log J_{MHVEH} calculated from RS^1 (where the polar parameter is PG:AQ, 30:70) and RS^2 (where the polar parameter is water), CALC^1 log J_{MHVEH} and CALC^2 log J_{MHVEH}, respectively, are given in Figure 2. A plot of EXP log J_{MHVEH} versus MW showed a poor dependence on MW ($r^2 = 0.49$). However, we have retained the dependence of J_{MHVEH} on MW because of the physical significance of MW found for larger data sets (3,4) and its theoretical basis (2,12,15). A plot of EXP log J_{MHVEH} versus log S_{AQ} ($r^2 = 0.94$) gave a better fit than a plot of EXP log J_{MHVEH} versus log S_{VEH} ($r^2 = 0.75$), and a plot of EXP log J_{MHVEH} versus log S_{OCT} also gave a poor fit ($r^2 = 0.52$) (plots not shown).

When estimated values of the coefficients obtained when S_{VEH} was the independent variable in the fit of the solubility, flux and MW data to RS were used to calculate log J_{MHVEH} (CALC^1 log J_{MHVEH}) (Table II), the residual error for calculating log J_{MHVEH} (Δ log J_{MHVEH} = EXP log J_{MHVEH} − CALC^1 log J_{MHVEH}) (Table II) was 0.178 ± 0.14 log units. Similarly, when the estimated values of the coefficients obtained when S_{AQ} was the

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Table II
Experimental Log Fluxes from VEH (PG:AQ, 30:70) Through Human Skin *In vivo* (EXP log J_{MHVEH}), Log Fluxes from VEH Through Human Skin *in vivo* Calculated from Fit of Solubililty and MW Data to the RS Equation RS[1] (CALC[1] log J_{MHVEH}), Absolute Values for the Differences Between EXP log J_{MHVEH} and CALC[1] log J_{MHVEH} (Δ log J_{MHVEH}), EXP log Fluxes from VEH (PG:AQ, 30:70) Through Silicone Membrane (EXP log J_{MPVEH}), Log Fluxes from PG:AQ, 30:70 Through Silicone Membrane Calculated from the RS Equation RS[1] (CALC[1] log J_{MPVEH}), and the Absolute Values for the Differences Between EXP log J_{MPVEH} and CALC[1] log J_{MPVEH} (Δ log J_{MPVEH})

	EXP log J_{MHVEH}[a,b]	CALC[1] log J_{MHVEH}[b,c]	Δ log J_{MHVEH}[b]	EXP log J_{MPVEH}[b]	CALC[1] log J_{MPVEH}[b,d]	Δ log J_{MPVEH}[b]
1	–2.72	–2.74	0.02	1.84	2.12	0.28
2	–2.50	–2.11	0.39			
2′				–1.65	–1.65	0.00
3	–2.08	–2.23	0.15	–1.94	–1.66	0.28
4	–1.79	–1.83	0.04			
5	–1.72	–1.76	0.04	–1.04	–1.35	0.31
6	2.44	–2.14	0.30	–2.08	–1.60	0.47
7	–1.87	–1.92	0.05	–1.64	–1.51	0.14
8	–0.78	–1.18	0.40	–0.29	–0.44	0.15
9	–1.25	–1.44	0.19	–0.87	–1.03	0.16
10	–0.13	+0.07	0.20			

[a]Ref. (21).
[b]Units of μmol cm^{-2} h^{-1}.
[c]Calculated from log $J_{MHVEH} = -1.550 + 0.591 \log S_{OCT} + 0.409 \log S_{VEH} - 0.00652$ MW.
[d]Calculated from log $J_{MPVEH} = -1.198 + 0.760 \log S_{OCT} + 0.240 \log S_{VEH} - 0.00842$ MW.

independent variable in the fit of the data to RS were used to calculate log J_{MHVEH} (CALC[2] log J_{MHVEH}), the corresponding Δ log J_{MHVEH} was 0.126 ± 0.065 log units (data not shown). These Δ log J_{MHVEH} are better than those obtained for larger databases of series of prodrugs, various drugs, and other solutes (2–4,22,23). Although r^2 and CALC[2] Δ log J_{MHVEH} are somewhat better using the RS[2] equation, RS[1] predicted the rank order of fluxes of the components of sunscreens better (8/10 versus 5/10) than did RS[2], so a choice

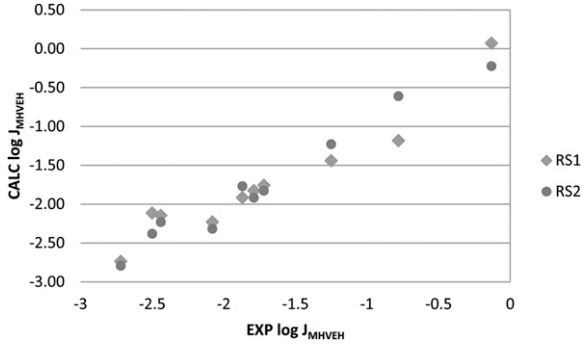

Figure 2. CALC vs. EXP log J_{MHVEH}: RS[1], CALC[1] log $J_{MHVEH} = -1.550 + 0.591 \log S_{OCT} + (1 - 0.591) \log S_{VEH} - 0.0065$ MW, $r^2 = 0.92$; RS[2], CALC[2] log $J_{MHVEH} = -2.159 + 0.481 \log S_{OCT} + (1 - 0.481) \log S_{AQ} - 0.000652$ MW, $r^2 = 0.97$.

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between the two equations and whether S_{VEH} or S_{AQ} is the better descriptor of solubility in the polar phase of SC cannot be made until further data are available.

The *y* coefficient (from y log S_{LIPID}) from RS[1] gives a value of 0.59 with the polar phase being the VEH, PG:AQ, 30:70. This is lower than what has been seen *in vivo* with the lipid mineral oil (MO) as VEH (0.72) (28) but is similar to what has been seen *in vitro* with water as the VEH (0.54) (4). This difference could be due to the interaction of the VEH with the skin. In the present case, PG may permeate the skin and alter the solubilizing capacity of the skin making it more PG-like (more polar) than lipid-like (17). Hence calculation of J_{MHVEH} becomes less dependent on a polar descriptor: [(1 – y) log S_{POLAR} = 0.28 log S_{AQ}] if MO is the VEH and more dependent, (0.41 log S_{VEH}) if PG:AQ (30:70) is the VEH (see above).

FLUX OF SUNSCREENS AND OTHER COMPOUNDS THROUGH SILICONE

The molar absorptivities (ε) for the eight compounds used in the diffusion cell experiments at their λ_{MAX} in the PG:AQ, 30:70, VEH (VEH) are given Table III. These ε were used to calculate the amount of each compound in their respective receptor phases. The new EXP solubility and partition coefficient values for compounds 2′ and 3 are given in Table I. The EXP flux values for the delivery of selected sunscreens and other compounds (1, 3, 5, 6, 7, 8, and 9) from Hagedorn-Lewke and Lippold (21) (n = 7) and 2′ through silicone membrane from PG:AQ, 30:70 (EXP log J_{MPVEH}) are given in Table II. Neither PG, water, nor methanol are known to irreversibly change the properties of silicone membranes like ethanol, propanol, and butanol do (25,26). Those reports are supported in these experiments where the second application fluxes of ThH from PG were not different from the reported control value of 0.00208 ± 0.00068 μmol $cm^{-2}h^{-1}$ (23) obtained after an initial application of water.

When EXP log J_{MPVEH}, MW, log $S_{OCT,}$ and log S_{VEH} values from Tables I and II were fit to the RS equation using the SPSS 19 statistical software package, the estimated

Table III
Molar Absorptivities (ε_{VEH}) and λ_{MAX} Values in PG:AQ, 30:70, the VEH for the Compounds Evaluated in the Diffusion Cell Experiments

	Compound	λ_{MAX}	ε_{VEH}[a]
1	Octyl 4-dimethylaminobenzoic acid	314	1.23 ± 0.01
2	4-Isopropyldibenzoylmethane		
2′	Dibenzoylmethane	347	1.95 ± 0.04
3	3-(4-Methylbenzylidene) camphor	307	2.22 ± 0.03
4	Isoamyl 4-methoxycinnamate		
5	Oxybenzone	290	1.46 ± 0.07
6	3,5-di-t-butyl-4-hydroxyanisole	283	0.29 ± 0.006
7	Dibutyl phthalate	228	0.85 ± 0.03
8	Butyl 4-hydroxybenzoic acid	256	1.62 ± 0.03
9	Triclosane	280	0.45 ± 0.04
10	Biphenyl-2-ol		

[a]L $mol^{-1} \times 10^{4}$.

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parameter coefficients for selected sunscreens and other compounds (n = 7) and 2′ were x = –1.198, y = 0.760, z = 0.00842, r^2 = 0.798, RS[1]. When log S_{AQ} instead of log S_{VEH} values were used in the fit to the RS equation, an equally good fit was observed: x = –1.877, y = 0.722, z = 0.0043, r^2 = 0.805, RS[2]. A similar dependence of maximum fluxes through silicone membranes from water (J_{MPAQ}) on solubility in water (or solubility in a different polar solvent, which is the VEH in this case), in addition to solubility in a lipid has been observed before for two much larger databases (n = 32 where isopropyl myristate (IPM) was the lipid, and n = 22, where OCT was the lipid) (23) when fit to the RS equation. In those cases, the fit of the same databases to an equation where flux, J_{MPAQ}, only depended on the solubility of the permeant in a lipid surrogate (IPM or OCT) for solubility in the silicone membrane (14) was much worse (23). Again, a plot of EXP log J_{MPVEH} versus MW gave a very poor fit (r^2 = 0.15), while a plot of EXP log J_{MPVEH} versus log S_{AQ} (r^2 = 0.80) gave a much better fit than versus log S_{VEH} (r^2 = 0.31) and a plot of EXP log J_{MPVEH} versus log S_{OCT} gave a poor fit (r^2 = 0.55).

The correlation between EXP log J_{MHVEH} and EXP log J_{MPVEH} was quite good (r^2 = 0.86, plot not shown). The value for the y coefficient from the fit of the EXP log J_{MHVEH} to the RS equation was lower that from the fit of the EXP log J_{MPVEH} to the RS equation. This is expected because of the generally assumed more lipid-like nature of silicone, which leads to a higher y value. It should also be noted that flux through silicone was always somewhat higher than through human skin *in vivo* (Table II).

When estimated values of the coefficients obtained when S_{VEH} was the independent variable in the fit of the solubility, flux, and MW data for the n = 7 plus 2′ database to RS were then used to calculate log J_{MPVEH} (CALC[1] log J_{MPVEH}) (Table II), the residual error for calculating log J_{MPVEH} (Δ log J_{MPVEH} = EXP log J_{MPVEH} – CALC[1] log J_{MPVEH}) (Table II) was 0.219 ± 0.142 log units. Similarly, when the estimated values of coefficients obtained when S_{AQ} was the independent variable in the fit of the data to RS were used to calculate log J_{MPVEH} (CALC[2] log J_{MPVEH}), the corresponding Δ log J_{MPVEH} was 0.224 ± 0.135 log units (data not shown). A plot of these CALC[1] and CALC[2] log J_{MPVEH} versus the EXP log J_{MPVEH} is shown in Figure 3. Again, RS[1] predicted the rank order of fluxes of the components of sunscreens better (5/8 versus 2/8) than did RS[2].

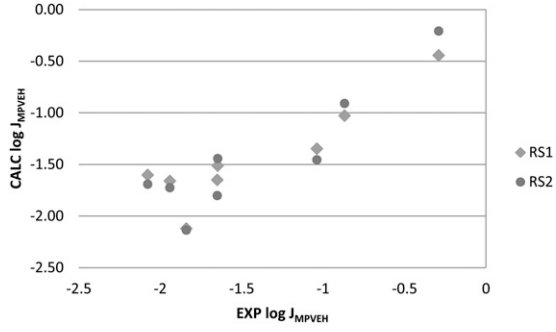

Figure 3. CALC vs. EXP log J_{MPVEH}: RS[1], CALC[1] logJ_{MPVEH} = –1.198 + 0.760 logS_{OCT} + (1 – 0.760) log S_{VEH} – 0.00842 MW, r^2 = 0.80; RS[2], CALC[2] log J_{MPVEH} = –1.877 + 0.722 logS_{OCT} + (1 – 0.722) log S_{AQ} – 0.0043 MW, r^2 = 0.81.

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Calculated log J_{MPAQ} values (CALC log J_{MPAQ}) for the seven compounds in the silicone membrane experiments (1, 3, 5, 6, 7, 8 and 9) and 2, 4, and 10 were also obtained using the following previously reported (23) coefficients to the RS eq(3), where $S_{LIPID} = S_{OCT}$ and the VEH was water instead of PG:AQ, 30:70 ($n = 22$).

$$\text{CALC log } J_{MPAQ} = -2.046 + 0.667 \log S_{OCT} + 0.333 \log S_{AQ} - 0.00374 MW \quad \text{eq (3)}$$

There was a very good correlation between these CALC log J_{MPAQ} for the compounds in this database and their EXP log J_{MHVEH} ($r^2 = 0.945$, $n = 10$, Figure 4), which was somewhat better than the correlation between EXP log J_{MPVEH} and EXP log J_{MHVEH} ($r^2 = 0.86$, $n = 7$). Thus, regardless of whether log J_{MHVEH} are calculated from equations obtained from the fit of log J_{MPVEH} or log J_{MPAQ} to RS, reasonably accurate results can be expected. This result is not unexpected in view of the fact that it was not possible to determine whether S_{VEH} or S_{AQ} was the better descriptor of the solubility of permeants in the polar phase of the lipid matrix of SC.

CONCLUSION

When (i) the maximum fluxes of potential sunscreens and other compounds from PG:AQ, 30:70 through human skin *in vivo* or through silicone membranes, (ii) their solubilities in the lipid solvent OCT and the polar solvents PG:AQ, 30:70, or water, and (iii) their MW were fitted to an expanded Fick's law based on solubilities instead of partition coefficients, the coefficients to the lipid solubility parameter were only as large as or slightly larger than the coefficient to the polar solubility (PG:AQ, 30:70, or water) parameter. However, correlations of the flux values through either membrane with solubilities in PG:AQ, 30:70, or water were better than their correlations with solubility in the lipid OCT. Qualitatively, the flux values were higher for the permeants that were more soluble in OCT and in water and had lower MWs. Thus, decreasing the solubility in OCT and in

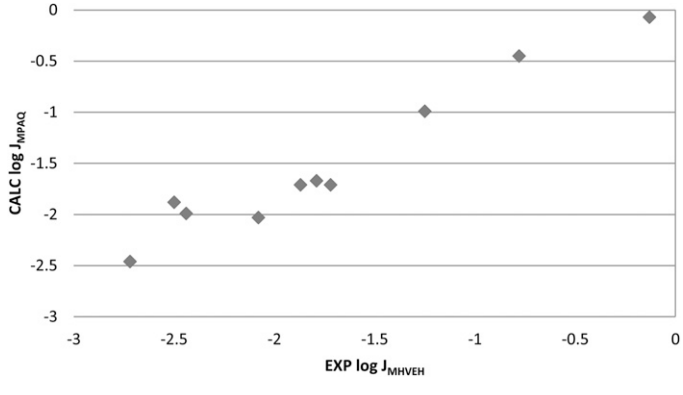

Figure 4. CALC log J_{MPAQ} vs. EXP log J_{MHVEH}: RS CALC log $J_{MPAQ} = -2.046 + 0.667 \log S_{OCT} + (1 - 0.667) \log S_{AQ} - 0.00374$ MW, $r^2 = 0.94$.

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water (and hence S_{MI}) (15) and increasing the MWs (28) should decrease the topical absorption of sunscreens and other compounds and lead to safer sunscreen formulations.

In addition, because of their similar dependencies on solubilities in a lipid solvent, OCT, and in a polar solvent, PG:AQ, 30:70 or water, and inversely on MWs, there was a reasonably substantial correlation between fluxes through human skin *in vivo* and fluxes through silicone membranes similar to that which had previously been observed with fluxes through human skin *in vitro* (22). Thus, flux values of sunscreens and other compounds from PG:AQ, 30:70, through human skin *in vivo* were accurately calculated from the coefficients of the fit of their solubilities in the lipid OCT and water, their MW and their flux values from water through silicone membrane to the RS equation (23).

Finally, it should be noted that these results are consistent with the results from other databases fit to RS equation although the coefficients to the independent variables may be slightly different depending on the membrane and VEH. Regardless of whether the database comprised MW, lipid, and aqueous solubilities and fluxes through human skin *in vitro* from water, $n = 185$, $r^2 = 0.84$ (4), fluxes through human skin *in vivo* from MO, $n = 10$, $r^2 = 0.93$ (29), fluxes through hairless mouse skin from water, $n = 32$, $r^2 = 0.90$ (30), fluxes through hairless mouse skin from isopropyl myristate, $n = 42$, $r^2 = 0.94$ (2), the fit to the RS equation is good.

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