Absorption of Sunscreens and Other Compounds Through Human Skin *in Vivo*: Derivation of a Method to Predict Maximum Fluxes

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Purpose. The goal of this study was to quantify the transdermally absorbed amounts of the sunscreens octyl dimethyl *p*-aminobenzoic acid, oxybenzone, 4-isopropyl-dibenzoylmethane, 3-(4-methylbenzylidene)-camphor, isoamyl-4-methoxycinnamate, the repellent and plasticizer dibutyl phthalate, the antioxidant 3.5-di-*t*-butyl-4-hydroxyanisol, and the antimicrobial compounds butyl-4-hydroxybenzoate, biphenyl-2-ol, and 2,4,4'-tri-chlor-2'-hydroxydiphenylether (triclosane). Permeabilities P_B and maximum fluxes J_{max} should be correlated with relevant physicochemical properties. ***Methods.*** Saturated solutions of the above-mentioned compounds in a propylene glycol/water mixture were applied to the skin using glass chambers which were fixed to the upper arms of volunteers. Maximum fluxes were calculated from concentration decreases in the vehicle. ***Results.*** A linear relationship between the logarithms of permeabilities P_B of the penetrants (0.02–0.28 cm h^{-1}) and the corresponding octanol/vehicle partition coefficients $PC_{Oct/V}$ (166–186,208) was found. Consequently, the influence of aqueous boundary layers could be neglected. However, the slope of the resulting straight line of 0.38 is considerably smaller than unity indicating that $PC_{Oct/V}$ does not represent the lipophilicity of the stratum corneum adequately. Maximum fluxes range from 0.5 to 130 μg cm^{-2} h^{-1}. A general equation for the calculation of J_{max} was derived based on experimental data taking into account the $PC_{Oct/V}$ and the solubilities c_{sV} of the respective penetrants in the vehicle.

KEY WORDS: transdermal drug delivery; prediction of percutaneous absorption; permeability; maximum flux; sunscreens.

INTRODUCTION

Dermatological and cosmetic preparations may contain agents which are not supposed to penetrate the stratum corneum. These compounds comprise, among others, sunscreens, antioxidants, repellents, and preservatives. As the respective preparations are often applied to large areas of the skin surface, even low penetration rates can cause a considerable amount of penetrant to enter the body. In the case of UV-absorbing chemicals, several attempts have been made to quantify the amount of the respective compound which enters the body via the skin (1,2). An ideal sunscreen should show a high extent of substantivity at the lowest possible level of transdermal penetration (3).

Literature dealing with the percutaneous absorption of drugs provides very few data which result from diffusion experiments with human skin *in vivo*. In these studies various application chambers which allow the application of liquid preparations are used (4–6). However, until now only the established *in vivo* data of homologous nicotinic acid esters have been used for the deduction of generally valid statements about the penetration properties of cutaneously applied agents (6). The intention of this study is to correlate skin penetration data such as permeabilities P_B and maximum fluxes J_{max} with the physicochemical parameters of compounds from different chemical classes in order to reveal a systematic dependence. Such a dependence should allow the prediction of drug penetration rates just by knowledge of their physicochemical properties.

All compounds were applied to the skin in a 30% mixture of propylene glycol and water (v/v) which was selected as vehicle in order to achieve sufficiently high solubilities. For this reason the penetration enhancing activity of propylene glycol had to be investigated.

PRESENTATION OF THE MODEL

Fick's first law has been shown to be applicable to the penetration of agents through the horny layer of the skin. Accordingly, the concentration decrease in the vehicle per time interval (dc/dt) is in direct proportion to the diffusion coefficient (D_B) of the compound in the transport barrier stratum corneum as well as to the partition coefficient ($PC_{B/V}$) between this barrier and the chosen vehicle, the area of application (A), and the concentration in the vehicle (c_V). The thickness of the stratum corneum (h_B) and the applied volume of the vehicle (V_V) are in inverse proportion to the penetration rate.

$$-\frac{dc}{dt} = \frac{D_B \cdot PC_{B/V} \cdot A}{h_B \cdot V_V} \cdot c_V = k_P \cdot c_V \qquad (1)$$

The first order penetration rate constant (k_P) describes the velocity of the penetration process. The term $D_B \cdot PC_{B/V}/h_B$ represents the permeability (P_B). The $PC_{B/V}$ which relevantly influences the permeability is not easily experimentally accessible. Therefore, it is often replaced by the partition coefficient between the model lipid *n*-octanol and the respective vehicle ($PC_{Oct/V}$) which, however, does not usually show a simple linear dependence on the $PC_{B/V}$. Thus, an adequate substitution is possible only in consideration of the interrelation between these two partition coefficients as it has been postulated by Collander (7). Accordingly, Barry (8), Anderson (9), and Itoh (10) deduced the following logarithmic definition of P_B in terms of $PC_{Oct/V}$:

$$\log P_B = \log\left(\frac{D_B}{h_B}\right) + b + a \cdot \log PC_{Oct/V} \qquad (2)$$

The different selectivities in terms of drug partitioning of the two systems n-octanol/vehicle, and stratum corneum/vehicle, respectively, is expressed by the constant a while b is a further correction constant describing the lipophilicity of the selected solvent system.

Yet, the magnitude of the diffusivity D_B in Eq. 2 is still

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unknown. The influence of the molar volume (MV) on D_B can be expressed by an exponential relationship postulated by Cohen and Turnbull (11):

$$\log D_B = \log D_B^0 - \frac{\beta}{2{,}303} \cdot MV \quad (3)$$

In this case D_B^0 stands for the diffusion coefficient of a hypothetical molecule with a molar volume of zero, while β is a further constant. Inserting Eq. 3 in Eq. 2 leads to:

$$\log P_B = \log \left(\frac{D_B^0}{h_B}\right) + b - \frac{\beta}{2{,}303} \cdot MV + a \cdot \log PC_{\text{Oct/V}} \quad (4)$$

Eq. 4 allows the prediction of the permeability of a drug just by knowledge of $PC_{\text{Oct/V}}$ and MV if the constants ($D_B^0/h_B + b$) and β are derived from multiple regression of experimental data. However, these predictable permeabilities which have already been deduced in a similar way from *in vitro* data by Potts and Guy (12), do not provide any information about the actual penetrating amount of drug. Knowledge of the maximum flux of a drug ($J_{\max}$) *i.e.*, the maximum amount of penetrated compound per time and area unit, is of more interest. Maximum fluxes of the permeants may be achieved by application of saturated solutions (concentration in the saturated vehicle is c_{sV}). Simple transformation of Fick's first law results in:

$$\log J_{\max} = \log P_B + \log c_{sV} \quad (5)$$

As the permeability term can be substituted by Eq. 4 maximum fluxes can be calculated only from MV, $PC_{\text{Oct/V}}$, and c_{sV}. It is the goal of this study to examine the applicability of this approach to the experimentally determined *in vivo* data.

MATERIALS AND METHODS

Chemicals

All substances (see Table I) were obtained with a purity >99% and were used as received. Octyldimethyl p-aminobenzoic acid, oxybenzone, 4-isopropyl-dibenzoyl-methane, 3-(4-methylbenzylidene)-camphor, 3,5-di-*t*-butyl-4-hydroxyanisol and dibutyl phthalate, were kindly donated by Merck (Darmstadt, Germany), isoamyl-4-methoxycinnamate by Haarmann and Reimer (Holzminden, Germany), butyl-4-hydroxybenzoate by NIPA-Laboratories GmbH (Norderstedt, Germany), triclosane (2,4,4'-trichlor-2-hydroxydiphenylether) by Ciba Geigy GmbH (Basel, Switzerland), biphenyl-2-ol by Schülke & Mayr (Norderstedt, Germany). 1,2-Propandiol was a gift of BASF AG (Ludwigshafen, Germany). HPLC grade methanol and *n*-octanol were purchased from Merck (Darmstadt, Germany). Water is used freshly distilled.

High-Performance Liquid Chromatography Assay

The concentration of each compound in the collected samples was assayed by a modular HPLC unit (LC-6A, Shimadzu, Duisburg, Germany) equipped with an automatic sample injection module (SIL-6B), system controller (SCL-6B), UV-VIS-spectrophotometer (SPD-6AV), adjustable to variable wavelengths, and an integrator (CR 4AX Chromatopac). The analyses were carried out at ambient temperature with a 123 × 4 mm column packed with LiChrospher® 100 RP-18, 5-μm-particle diameter (E. Merck, Darmstadt, Germany). The mobile phase, consisting of 70 to 90% methanol/water mixtures was pumped at flow rates ranging from 1.5 to 2.0 ml/min. Injection volumes vary between 3 and 50 μl.

Table I. Physicochemical properties

Compound	MP^a (°C)	MV^b (cm^3 mole^{-1})	$c_{sOc}{}^c$ (gl^{-1})	$c_{sV}{}^d$ (gl^{-1})	c_{sV} 25°C^e (gl^{-1})	log $PC_{\text{Oct/V}}{}^f$	log $PC_{\text{Oct/W}}{}^g$
Sunscreens (CTFA)							
octyl dimethyl *p*-aminobenzoic acid	liquid	275	miscible	0.002	0.001	4.67[h]	5.75
4-isopropyl-dibenzoylmethane	47.3	219	571.7	0.003	0.002	5.27	6.51
3-(4-methylbenzylidene)-camphor	68.1	271	317.6	0.023	0.014	4.14	5.13
isoamyl-4-methoxycinnamate	liquid	233	miscible	0.030	0.015	3.83[h]	4.83
oxybenzone	63.3	163	66.7	0.084	0.043	2.90	3.82
Antioxidants							
3,5-di-t-butyl-4-hydroxyanisol	105.4	224	73.6	0.012	0.007	3.79	4.64
Repellent/plasticizer							
dibutyl phthalate	liquid	252	miscible	0.073	0.041	3.43[h]	4.39
Antimicrobial compounds							
butyl-4-hydroxybenzoate	69.2	162	533.4	1.957	1.076	2.44	3.42
triclosane	57.5	153	852.4	0.209	0.088	3.61	4.53
biphenyl-2-ol	58.5	134	73.8	4.432	3.045	2.22	3.07

[a] Melting point determined by differential scanning calorimetry.
[b] Molecular volume calculated by Fedors' increment method.
[c] Solubility in octanol at 32°C.
[d] Solubility in the vehicle, a 30% mixture of propylene glycol and water, at 32°C.
[e] Solubility in the vehicle, a 30% mixture of propylene glycol and water, at 25°C.
[f] Logarithm of octanol/vehicle partition coefficient calculated as octanol/vehicle solubility ratio at 32°C.
[g] Logarithm of octanol/water partition coefficient, experimentally determined at 32°C.
[h] Logarithm of octanol/vehicle partition coefficient calculated from octanol/water partition coefficient at 32°C by Collander's regression analysis.

Concentration of the samples was calculated from peak areas by the external and internal standard method, respectively.

Determination of Physicochemical Properties

Molar Volumes

Molar volumes were calculated using Fedor's incremental method (13).

Solubilities

Each compound was added to the solvent in excess. The resulting suspensions or emulsions were stirred for 48 h at 32°C and then filtered through filter paper. Loss of compounds caused by adsorption to filter material was minimized by choosing a sufficiently high forerun. The concentration of the compounds in the filtrate was measured spectrophotometrically (Lambda 2, Perkin Elmer, Überlingen, Germany) or by means of HPLC.

Partition Coefficients

An experimental determination is not possible due to the partial miscibility of the two solvents. Consequently, partition coefficients were calculated as ratios of the respective solubilities in n-octanol and in the 30% propylene glycol/water mixture. However, this method could not be applied to the liquid compounds which show complete miscibility with *n*-octanol. In order to bypass this problem, partition coefficients between *n*-octanol and water ($PC_{Oct/W}$) were determined experimentally for all compounds. Defined volumes of each phase, with a variable initial amount of the substances in the *n*-octanol phase were placed in stoppered glass tubes and mixed for 24 h at 32°C. The $PC_{Oct/W}$ were correlated to the $PC_{Oct/V}$ of the solid substances. The obtained regression equation allows a calculation of the $PC_{Oct/V}$ for the liquid compounds according to:

$$\log PC_{Oct/V} = -0.56 + 0.91 \cdot \log PC_{Oct/W},\ r^2 = 0.99$$

Percutaneous Transport Studies

In order to quantity the percutaneous absorption, two glass chambers with a suitable area/volume ratio (A = 14–16 cm^2, V_V = 2–6 ml) (5) were fixed to the lateral side of each upper arm of healthy volunteers. The chambers can be filled with liquid preparations by means of a syringe with a flexible cannula (Hamilton, Bonaduz, Switzerland). After pretreatment of the skin with solvent for 1 h, the respective solutions (saturated at 25°C) were filled into the chambers and remained on the skin for 1 h after which they were removed and replaced by fresh solutions of the respective starting concentration. This procedure was repeated six times. The amount of permeant which had penetrated into and through the skin, respectively, was determined indirectly by measuring concentration decreases in the vehicle. The penetration process could not be described by zero order kinetics because of a considerable drug depletion of the vehicle (see Table II). Rather, it had to be considered as a first order process. The reliability of this procedure is proven by results from Le (6) and Stricker (4) whose data indicates that drug depletion of a vehicle applied to human skin *in vivo* proceeds according to first-order kinetics. Thus, the concentration decreases per hour allowed the calculation of penetration rate constants (k_P). Multiplication by the respective application volume (V_V) and division by the area of application (A) led to permeabilities. From these permeabilities, maximum fluxes could be calculated when multiplied by the solubilities in the vehicle at 32°C. Table II lists the penetration parameters which were derived from steady state penetration rates of the last 3 h. Three test series were carried out, each of which included 12 volunteers. Four substances were tested on each volunteer. The selection of one compound as a standard allowed a comparison of compounds from different test series. Within the series, each single compound was rotated systematically to the next application area (top right, bottom right, top left, bottom left) from one volunteer to the next.

A separate study comprising four volunteers was done in order to clarify the influence of the penetration enhancer propylene glycol on the maximum fluxes of oxybenzone and isoamyl-4-methoxycinnamate. Fluxes were measured from water and a 50% mixture of propylene glycol and water both saturated at 25°C and were compared to the fluxes obtained from the 30% propylene glycol/water mixtures. Comparison of two series of data was performed by means of paired and unpaired *t*-tests, respectively.

All *in vivo* experiments followed the tenets of the Declaration of Helsinki. The volunteers provided informed consent to participate.

RESULTS

Table I gives an overview of the determined physicochemical properties of the test compounds. Solubilities as well as partition coefficients cover an interval of four orders of magnitude. The high values of the latter indicate that most of the agents are lipophilic in nature.

Figure 1 shows the courses of the maximum fluxes over a period of 6 h. In general, the maximum flux is high during the first time intervals and then decreases to a constant level. The higher the achieved steady state flux is, the more pronounced these initial effects usually are. Means of the log-transformed flux values of the last 3 h (considered as steady state fluxes) from each volunteer were calculated. Retransformation of the data led to geometric means which were used for further calculations.

Table II lists the concentration decreases in the chambers as percentages, the permeabilities, the maximum fluxes, and the respective standard deviations.

Most of the preparations containing the investigated compounds are normally applied to large areas of the skin. Therefore, the maximum amounts of the permeants which are absorbed per hour assuming treatment of a total skin surface of 1.8 m^2 are also listed in Table II. This extrapolation may be bold, but nevertheless gives an impression of the maximum strain on the organism toxicologic studies may focus on. It becomes evident that indeed considerable amounts may reach the organism.

According to Eq. 4, the permeability seems to be influenced by two variables, the partition coefficient $PC_{Oct/V}$ and the molar volume MV. As a consequence, a multiple regression analysis had to be carried out, the results of which are

Table II. Percutaneous penetration parametes (steady state data)

Compound	Data series no.	Δc_v[a] (%)		P_B[b] (cm h^{-1})		J_{max}[c] (μg cm^{-2} h^{-1})		Amount absorbed per hour over the whole skin surface[d] (mg)
Octyl dimethyl *p*-aminobenzoic acid	1	59.2	+ 11.9 − 9.9	0.259	+ 0.062 − 0.050	0.53	+ 0.13 − 0.10	10
4-Isopropyl-dibenzoylmethane	1	62.2	+ 11.8 − 10.0	0.277	+ 0.083 − 0.064	0.85	+ 0.25 − 0.20	15
3-(4-Methylbenzylidene)-camphor	1	28.1	+ 11.5 − 8.2	0.091	+ 0.035 − 0.026	2.11	+ 0.81 − 0.59	38
Isoamyl-*p*-methoxycinnamate	2	33.6	+ 5.7 − 4.9	0.105	+ 0.028 − 0.022	3.16	+ 0.84 − 0.66	57
	1	19.4	+ 6.4 − 4.8	0.059	+ 0.019 − 0.014	4.93	+ 1.58 − 1.19	89
Oxybenzone	2	18.3	+ 4.6 − 3.7	0.053	+ 0.018 − 0.014	4.44	+ 1.54 − 1.15	80
	3	19.1	+ 7.0 − 5.1	0.050	+ 0.014 − 0.011	4.20	+ 1.19 − 0.92	76
3,5-Di-*t*-butyl-4-hydroxyanisol	3	26.3	+ 6.6 − 5.3	0.072	+ 0.018 − 0.014	0.86	+ 0.21 − 0.17	16
Dibutyl phthalate	3	19.8	+ 8.3 − 5.8	0.052	+ 0.018 − 0.013	3.77	+ 1.28 − 0.96	68
Butyl-4-hydroxybenzoate	2	6.9	+ 3.2 − 2.2	0.016	+ 0.008 − 0.005	32.00	+ 15.61 − 10.50	576
Triclosane	2	24.7	+ 7.3 − 5.7	0.076	+ 0.026 − 0.020	15.86	+ 5.49 − 4.08	286
2-Biphenylol	3	12.4	+ 5.5 − 3.8	0.028	+ 0.012 − 0.008	125.55	+ 51.99 − 36.76	2226

[a] Concentration decrease in the vehicle after one hour expressed as geometric mean ± SD (n = 12).
[b] Permeability expressed as geometric mean ± SD (n = 12).
[c] Maximum flux expressed as geometric mean ± SD (n = 12).
[d] Estimated amount of absorbed compound after treating the whole skin surface (1.8 m^2) with a saturated solution for one hour.

listed in Table III. The correlation between permeability P_B and the partition coefficient $PC_{Oct/V}$ turned out to be statistically significant ($p < 0.001$). However, the relationship between permeability and molar volume was characterized by a regression coefficient ($\beta/2.303$) which did not significantly differ from zero ($p > 0.05$). Consequently, the permeability of these compounds could be exclusively defined by means of the partition coefficient. The high value of r^2 implies that almost 91% of the variability of P_B is caused by $PC_{Oct/V}$. Thus, the permeability is sufficiently predictable in terms of the partition coefficient between n-octanol and the selected vehicle, *i.e.*, it seems to be almost independent of the molar volume. This result has also been reported by other authors (14) but in this case it has to be strictly limited to the examined range of molecular size, which however, includes most drugs. Figure 2 shows log P_B as a function of log $PC_{Oct/V}$, disregarding MV. A linear relationship was achieved which can be mathematically described by the following regression equation:

$$\log P_B = -2.46 + 0.38 \cdot \log PC_{Oct/V},\ r^2 = 0.90 \quad (6)$$

According to Eq. 5 the maximum flux can be defined as follows:

$$\log J_{max} = -2.46 + 0.38 \cdot \log PC_{Oct/V} + \log c_{sV} \quad (7)$$

or:

$$\log J_{max} = -2.46 + 0.38 \cdot \log c_{sOct} + 0.62 \cdot \log c_{sV} \quad (8)$$

or:

$$\log J_{max} = -2.46 - 0.62 \cdot \log PC_{Oct/V} + \log c_{sOct} \quad (9)$$

(Unit of J_{max}: [μg cm^{-2} h^{-1}], unit of c_s: [μg ml^{-1}].)

As expected, a very good correlation between the maximum fluxes determined experimentally and those calculated by Eqs. 7–9 was found.

Figure 3 shows the maximum fluxes of oxybenzone and isoamyl-4-methoxycinnamate versus the added percentage of propylene glycol to the vehicle. Enhancement factors, calculated as ratios of the steady state fluxes from the respective propylene glycol mixture and water as vehicle and significance levels of the enhancing effects calculated from paired and unpaired t-tests, are also listed. Apparently, the maximum fluxes increase with an increasing amount of propylene glycol in the vehicle. Propylene glycol leads to more pronounced flux increases with the more lipophilic compound isoamyl-4-methoxycinnamate than with oxybenzone.

DISCUSSION

Application chambers allow measurement of the quan-

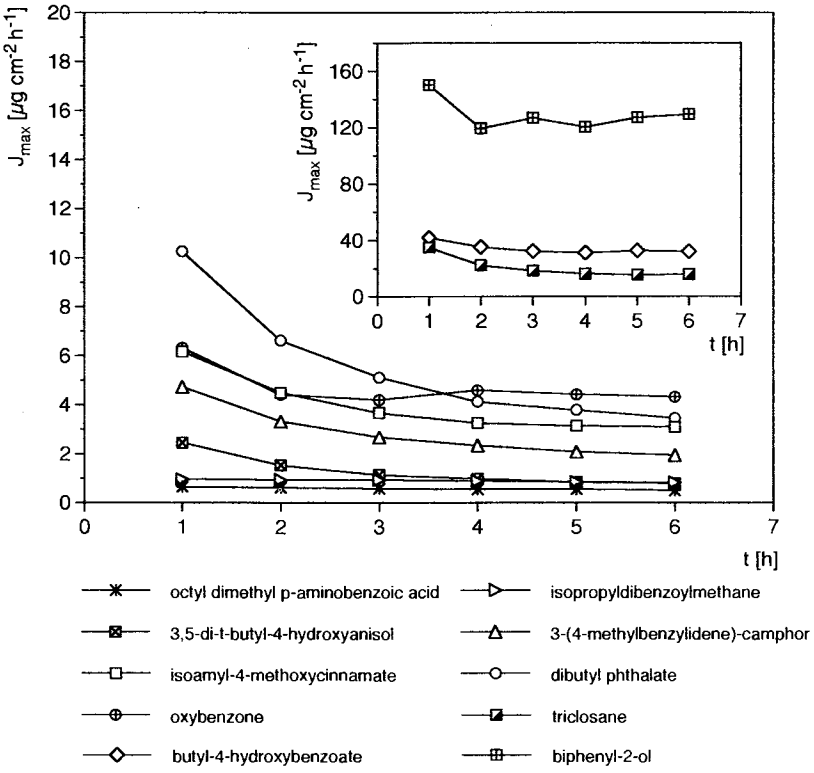

Fig. 1. Time courses of maximum fluxes (J_{max}) from aqueous solutions containing 30% propylene glycol. The inserted plot shows the profiles of the highest fluxes separately. Each point represents the geometric mean of twelve experiments. Standard deviations (about 30%, see Table II) are not included for clarity reasons.

tities of agents which have penetrated into and through the skin under occlusive conditions. However, the degree of metabolism that a compound suffers during its penetration through the skin, as well as the degree of accumulation in special tissues, still remains unknown. To clarify the role of metabolic changes, our experiments would have to be complemented by pharmacokinetic studies on the respective chemical and its metabolites.

The initially high maximum fluxes (see Figure 1) would lead to a lag-time if fluxes were measured in the viable skin (= acceptor compartment). Obviously, this is caused by those amounts of penetrants which are required to saturate the stratum corneum. Drug accumulation in the horny layer is mainly the result of a distribution process. However, specific binding to skin components as for example to the keratin of the corneocytes may contribute to this accumulation process. It has to be emphasized that achievement of a steady state plateau is a sure indication of a balance between the diffusion of the permeant into the stratum corneum and the respective transport out of it into the viable tissue. Interestingly, the level of the initial fluxes correlates with the level of the steady state fluxes, so that the extrapolation of data obtained from early measurements to steady state data would be possible after the necessary regression calculations were carried out. This observation corresponds to that of other authors (15).

In comparison to some other test compounds, sun-

Table III. Results from multiple regression analysis of log P_B upon log $PC_{Oct/V}$ and MV according to Eq. 4

Coefficient	Calculated value ± SD	Statistical significance
log (D_B^0/h_B) + b	−2.48 ± 0.19	($p < 0.001$)
a	0.41 ± 0.07	($p < 0.001$)
β/2.303	−0.001 ± 0.001	n.s. ($p > 0.05$)

[a] $r^2 = 0.91$.

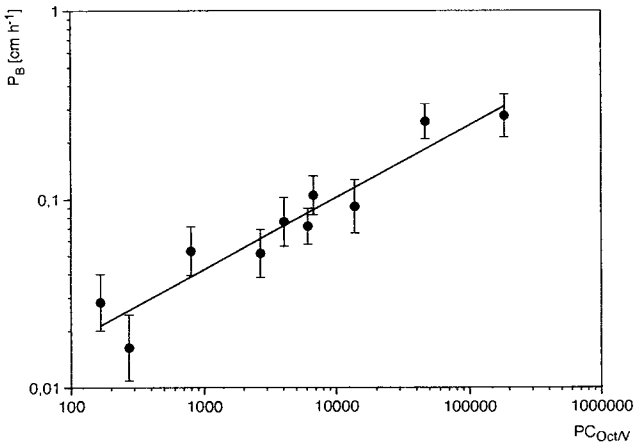

Fig. 2. Relationship between permeability coefficients P_B and octanol/vehicle partition coefficients $PC_{Oct/V}$. Geometric means ± SD (n = 12).

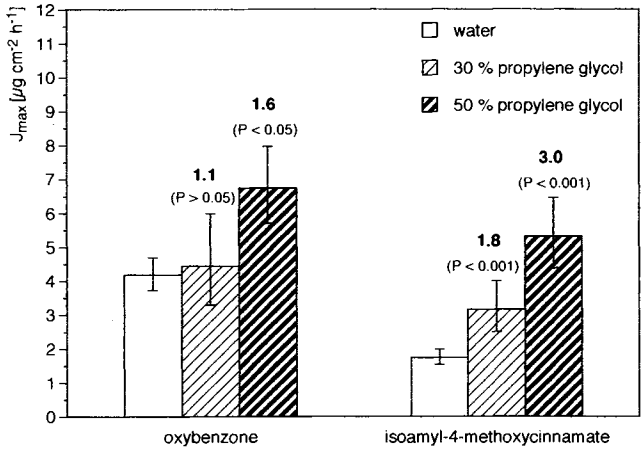

Fig. 3. Maximum fluxes J_{max} of oxybenzone and isoamyl-4-methoxycinnamate obtained from water and aqueous vehicles containing 30 and 50% propylene glycol. Geometric means ± SD (water: n = 4, 50% propylene glycol: n = 4; 30% propylene glycol: n = 12). Enhancement factors of the respective propylene glycol admixtures in comparison to water calculated as ratios of maximum fluxes and significance levels are indicated above the columns.

screens show lower maximum fluxes ranging from 0.5 to 4.4 µg/(cm^2 · h). However, it should be remembered that commercial sunscreen preparations usually contain high concentrations of the respective UV-filters and are repeatedly applied to large areas of the skin while sunbathing. Accordingly, the amounts absorbed during several hours of a sunbath should exceed those amounts which may penetrate the skin during one hour (see Table II).

Several researchers tried to correlate penetration data of drugs with physicochemical properties. However, most of the established relationships are restricted to the prediction of the permeability (6,9,12,14,16–18). Parabolic relationships between the logarithms of P_B and $PC_{Oct/V}$ which have been postulated by Hansch and Clayton (19) are fitted to the results of some studies (17,18). They may be due to the existence of aqueous boundary layers in the vehicle as well as in the viable dermis (20) or to measurements carried before steady state conditions were attained (14). However, in many cases linear relationships between log P_B and $PC_{Oct/V}$ have also been found (6,9,12,14,16).

The results of our *in vivo* study confirm the linear dependence of log P_B on log $PC_{Oct/V}$ over four orders of magnitude. This fact proves that even in the case of very lipophilic permeants, no stagnant layers are present in neither the vehicle nor the viable skin *in vivo*. According to this observation, the considerable convection in the liquid contents we achieved by attaching little stirrers to the application chambers did not lead to a statistically significant increase of the maximum fluxes.

The surprisingly low slope of a = 0.38 shows that the partition coefficient between n-octanol and the vehicle represents the lipophilicity of the horny layer insufficiently. According to the slope, the stratum corneum is an obviously less lipophilic partition compartment in comparison to n-octanol. A correlation of log P_B values of homologous nicotinic acid esters resulting from a similar experimental set-up using water as vehicle with log $PC_{Oct/V}$ shows a slope of a = 0.32 (6) which is in excellent agreement with the slope determined from our experiments. However, in many other *in vitro* studies, higher values of a have been reported (9,12,14,16). If these were employed for calculation of permeabilities and maximum fluxes, they would, of course, lead to values differing significantly from our data. Calculation of diffusion coefficients is not possible because the constant b in Eq. 2 remains unknown.

It seems strange, at first sight, that according to Eqs. 7–9 solubilities in the vehicle apparently play a role in the prediction of maximum fluxes because in the case of true membrane control, the maximum flux should only be influenced by the solubility in the horny layer and should, therefore, be independent of the properties of the chosen vehicle (22). However, the solubility in the vehicle will be necessary to predict J_{max} as long as log $PC_{B/V}$ and $PC_{Oct/V}$ are linked via a Collander coefficient a significantly deviating from unity. The linear correlation of log J_{max} with log c_{sOct} which was postulated by Kasting *et al.* (21) will be worse as a becomes smaller. It should be stated that the validity of the values a and b derived in this study must be limited to flux measurements from similar (aqueous) vehicles. Moreover, maximum fluxes of small polar molecules may be predicted incorrectly by Eqs. 7–9 because their penetration pathway (water-filled pores) differs from that of more lipophilic permeants.

Propylene glycol can be regarded as a penetration enhancer which, after diffusion into the horny layer, may lead to an increase of $PC_{B/V}$, P_B, and J_{max}. Addition of 30% propylene glycol to the aqueous vehicle accelerates the penetration of the lipophilic agent isoamyl-4-methoxycinnamate by a factor of 1.8. More hydrophilic compounds like oxybenzone are not subject to a statistically significant penetration enhancement. In the latter case, a higher concentration in the vehicle (50% propylene glycol) is necessary to enhance penetration by a factor of 1.6. These results indicate a rather moderate influence of propylene glycol on the flux which means that it is only of secondary importance for the presented mathematical deductions.

In conclusion, the prediction of maximum fluxes from aqueous vehicles is possible through the use of deduced regression equations. However, it requires the knowledge of solubility and/or partition data, provided that a possible vehicular influence on the properties of the horny layer can be overlooked.

ABBREVIATIONS

A	treated skin area
a	sensitivity of a solvent system
b	parameter describing the lipophilicity of a solvent system
c_{sB}	solubility in the horny layer
c_{sOct}	solubility in octanol
c_{sV}	solubility in the vehicle
D_B	diffusivity in the horny layer
D_B^0	diffusivity in the horny layer of a molecule with a MV of 0
h_B	thickness of the horny layer
J_{max}	maximum flux
$J_{max\ calc}$	maximum flux calculated from Eqs. 7–9

$J_{max\ exp}$ maximum flux derived from experiments
MV molecular volume
P_B permeability in the horny layer
$PC_{B/V}$ partition coefficient between horny layer and vehicle
$PC_{Oct/V}$ partition coefficient between n-octanol and vehicle
$PC_{Oct/W}$ partition coefficient between n-octanol and water
V_V applied volume

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