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Determination of partition and binding properties of solutes to stratum corneum

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ABSTRACT

The binding property of a number of relatively hydrophilic solutes to native and delipidized stratum corneum (SC) and their partition coefficients to extracted lipid have been measured by equilibration experiments to expand the current database which consisted of mostly hydrophobic solutes. Using the extended database, quantitative structure property relationships (QSPR) have been proposed for predicting the partition and binding coefficients of both hydrophobic and hydrophilic solutes to the SC protein, and lipid. Solute partition to the SC lipid is best fitted by $PC_{lip/w} = K_{ow}^{0.69}$ and solute binding to the SC protein is best described by $PC_{pro/w} = 4.2K_{ow}^{0.31}$. The two QSPR models of solute partition to the SC lipid and binding to the SC protein have been further combined into a two-phase model to predict the overall partition coefficient of solutes to the stratum corneum ($K_{sc/w}$). Our study not only extends the database of solute partition and binding properties of the SC to include hydrophilic solutes, but also demonstrates that the thermodynamic equilibrium properties of the SC partition and binding can be fitted with good accuracy by combining QSPR models with the multiphase and heterogeneous structures of the SC.

1. Introduction

The stratum corneum (SC), the outermost layer of the skin, constitutes the main rate-limiting barrier to the transport of chemicals across the skin (Scheuplein, 1967; Scheuplein and Blank, 1971; Flynn et al., 1981; Wester and Maibach, 1983). Chemicals must first partition into the SC before entering the deeper layers of the dermis and viable dermis. Driven by applications in drug delivery, cosmetic care and safety assurance, prediction of transdermal permeation and absorption has attracted great attention in recent years (Mitragotri, 2003; Wang et al., 2006; Guoping et al., 2008; Longjian et al., 2010). The thermodynamic equilibrium properties of solute partitioning and binding to the SC play an important role in developing an insight into the SC barrier properties and transdermal permeation mechanisms. In order to accurately predict of transdermal permeation and absorption, it is necessary to understand the partition and binding properties of solutes to the SC.

There has been a continuous interest in predicting solute partition and binding to SC lipid and protein. Early studies considered the partitioning of solutes to the overall SC (Roberts et al., 1977; Saket et al., 1985; Surber et al., 1990a,b; Cleek and Bunge, 1993; Bunge and Cleek, 1995; Pugh et al., 1996; Roberts et al., 1996). Quantitative structure property relationships were developed to relate the observed overall SC partition coefficient $K_{sc/w}$ to the octanol–water partition coefficients (K_{ow}) (Roberts et al., 1977, 1996; Cleek and Bunge, 1993; Bunge and Cleek, 1995; Pugh et al., 1996). Many early studies assumed that the SC lipid as the main pathway of transdermal permeation (Potts et al., 1992; Johnson et al., 1997; Mitragotri, 2002). A great number of experimental and modeling studies have been also reported on the partition properties of solutes to SC lipid (Anderson and Raykar, 1989; Morimoto et al., 1992; Potts and Guy, 1992; Bunge and Cleek, 1995; Johnson et al., 1997; Mitragotri, 2002). There is a good correlation between the overall partition of solutes to the SC and solute partition to the SC lipid. However, with such an approach, binding of solutes to the SC protein has been generally ignored and understanding on the cellular level mechanisms of transdermal permeation is limited (Mitragotri, 2000).

Binding of solutes to the SC protein will affect their storage in the SC and hence availability and permeation to the dermis and viable dermis. There is ever increasing evidence that solutes not only partition into the SC lipid but also diffuse into the SC cornoecytes and bind to the SC proteins (Anderson et al., 1988; Raykar et al., 1988; Anderson and Raykar, 1989; Mitragotri, 2003). Several experimental and modeling studies have been reported on solute binding to SC protein (Anderson et al., 1988; Raykar et al., 1988; Anderson and Raykar, 1989; Nitsche et al., 2006; Chen et al., 2008). It is clear from freeze-fracture, thin-section, histochemical and cytochemical studies that stratum corneum has a heterogeneous two-phase structure comprised of a mosaic of cornified cells containing cross-linked keratin filaments and a continuous intercellular lipid region (Elias and Friend, 1975; Elias et al., 1977, 1979; Elias, 1981). Reported studies

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have further shown that the protein and lipid domains in the SC exhibit different selectivity with respect to solute uptake, resulting in a change of uptake mechanism with increasing solute lipophilicity (Raykar et al., 1988). The heterogeneous structure of the SC was considered using two-phase partitioning models proposed by few recent studies (Raykar et al., 1988; Anderson and Raykar, 1989; Nitsche et al., 2006). These two-phase models still have limited considerations of hydrophilic solutes. Raykar et al. only included one hydrophilic compound (defined as $\log K_{ow} < 0$) in their study. Nitsche et al. reported 9 sets of $K_{sc/w}$ data of 6 different hydrophilic compounds, and no hydrophilic solute for lipid partitioning was included.

In this study, the lipid partition and protein binding properties of several hydrophilic compounds ($\log K_{ow} < 0$) have been measured using equilibration experiments. The measured data of hydrophilic solutes were combined with literature data of hydrophobic solutes to produce a comprehensive database. The expanded database has been used to build quantitative structure property relationships (QSPR) of lipid partition and protein binding properties for both hydrophobic and hydrophilic solutes. A general two-phase model has been further developed and applied to predict the overall partition coefficients of hydrophilic and hydrophobic solutes to the stratum corneum.

2. Materials and methods

2.1. Materials

Skin samples were taken from piglets of about one month old. After removing the hair on the epidermis and the subcutaneous fatty tissue, the skin was divided into smaller pieces of about 36 square centimeters and stored at −26 °C for a maximum of 6 months prior to use (Wagner et al., 2000).

Chemicals used for partition experiments including theophylline, tegafur, thiamazole, cefazolin, cefoperazone, fluorouracil, oxytetracycline were from the National Institute for the Control of Pharmaceutical and Biological Products of China. Methanol used for high-performance liquid chromatographic analysis was of HPLC grade and the other chemicals were analytical grade. All these chemicals were obtained commercially.

Solute concentration for the equilibrium experiments was measured by a high performance liquid chromatography (HPLC) equipped with a SupelocosilTMLC18 column (250 mm × 4.6 mm, 5 μm, Supelco USA) and a Pelliguardmodular guard column LC-18 (250 mm × 4.6 mm, 5 μm, Supelco, USA). An UV–vis detection (HPLC–UV), a Hitachi system (Japan) consisting of two MODEL L-7100 pumps, a MODEL L-7200 auto-sampler and a MODEL L-7420 detector were used. Experimental data were acquired and processed by Weimalong Software (Nanning, PR China). The maximal absorption wavelength of each solute dissolved into 10 mM sodium phosphate buffer solution (pH 7.25–7.35, PBS) was determined using a Tu-1800 UV–Visible spectrophotometer. Fourier transform infrared spectrometry (FTIR) studies were conducted using the Spectrum 400 FT-IR and FT-NIR Spectrometer (PerkinElmer).

2.2. Methods

2.2.1. Preparation of stratum corneum samples

The skin samples obtained above were submerged in water at 60 °C for 2 min. The epidermis layer was then peeled carefully from the dermis with dissection forceps (Kligman and Christophers, 1963). After this treatment, the thin sheet of epidermis were placed (dermal side down) on the surface of PBS with 0.05% trypsin (Sigma Chemical Company) and kept at 37 °C in a sealed petri dish overnight (Anderson et al., 1988). After digestion, the stratum corneum was washed with PBS, and then rinsed in cold hexane to remove exogenous lipids, and lyophilized for 24 h or more to remove all water. Freeze dried stratum corneum samples were kept in a freezer at −18 °C for a maximum of 6 months after treatment (Hansen et al., 2008).

The thickness of the stratum corneum was estimated by measuring the weight and the area of the stratum corneum.

2.2.2. Preparation of delipidized SC samples

Preweighed dry stratum corneum samples were placed in screw-cap glass tubes containing a mixture of chloroform:methanol (2:1, v/v) and gently agitated occasionally for at least 24 h at room temperature (Anderson et al., 1988; Johnson et al., 1997; Hansen et al., 2008). After extraction the delipidized membranes were removed, washed with fresh chloroform: methanol (2:1, v/v) twice and lyophilized to a constant weight.

2.2.3. Preparation of lipid samples

The extraction solvent above was filtered into a preweighed weighing bottle, dried to a constant weight at 30 °C to form a dry lipid film in the inner surface of the lower portion of the bottle (Anderson et al., 1988; Johnson et al., 1997).

The lipid content of the stratum corneum was determined by two methods—by the change in weight of the stratum corneum before and after extraction and by the weight of the lipid film obtained by measuring the increase of the mass of the weighing bottles (Raykar et al., 1988).

2.2.4. FTIR spectra analysis of the sample

Lyophilized untreated and delipidized stratum corneum samples (after 1 and 3 days of extraction respectively) were analyzed with a FTIR spectrometry (between 4000 and 650 cm^{-1}, in the mid-infrared band) to examine the completeness of lipid extraction.

2.2.5. Determination of partition coefficients by equilibration experiments

Accurately weighed stratum corneum, delipidized SC and the lipid film samples were immersed into a known volume and concentration of aqueous solution of desired compounds in PBS and equilibrated for at least 48 h at room temperature. The amount of skin sample, volume and initial concentration of the solution were chosen based on the solute to ensure there was a significant depletion of the solute occurred after equilibration. The initial concentration of the solution was about 8–25 μg/mL which was not very high to make sure the uptake by each phase of SC can be described by a constant partition coefficient and was independent of solute concentration (Anderson et al., 1976; Surber et al., 1990a,b; Wagner et al., 2002). The hydrated stratum corneum and delipidized SC samples were then removed, blotted gently and weighed immediately. Water uptake capacities of both the stratum corneum and the delipidized SC can be calculated by the increase of weight after equilibration. The concentrations of the solutes after equilibration were then measured by HPLC using peak areas against external standards. HPLC conditions for each compound were shown in Table 1.

In order to minimize the loss of solutes due to adsorption to the bottles in the process of equilibration, the same volume of prior solutions were placed into the same weighing bottles without any skin samples and equilibrated about 48 h at the same condition. Then the concentration of the solutions was also measured by HPLC as the initial concentration.

2.2.6. Data regression

Solute binding to protein ($PC_{pro/w}$) and partition to lipid ($PC_{lip/w}$) are usually related to the octanol–water partition coefficient (K_{ow}) through a linear free energy relationship (Anderson et al.,

1988; Kasting et al., 1992; Johnson et al., 1997; Mitragotri, 2002) described by Eqs. (1) and (2). Here α, β ($\log\alpha = c$), ξ and ψ ($\log\xi = \eta$) are constant and the slope of α and ξ reflect the relative selectivity of the protein and lipid domains to the lipophilicity of the solutes measured by the octanol/water partition coefficient. The constants in the equations can be estimated preliminarily by the Least Square Method based on the direct experimental data which have been measured in this study and the other researchers' experiment (Raykar et al., 1988; Anderson and Raykar, 1989; Johnson et al., 1997; Hansen et al., 2008).

$$PC_{pro/w} = \alpha(K_{ow})^{\beta} \quad \text{or} \quad \log PC_{pro/w} = c + \beta \log K_{ow} \tag{1}$$

$$PC_{lip/w} = \xi(K_{ow})^{\psi} \quad \text{or} \quad \log PC_{lip/w} = \eta + \psi \log K_{ow} \tag{2}$$

The best fitted values of the coefficients for Eqs. (1) and (2) were determined by systematic search to minimize the root mean square error (RMSE) between calculated and measured values. The overall solute partition coefficient of the stratum corneum, $K_{sc/w}$ was given by the following two-phase formula

$$K_{sc/w} = \phi_{pro}K_{pro/w} + \phi_{lip}K_{lip/w} + \phi_{w} \tag{3}$$

where the first and second terms represent the contributions of the protein and lipid domains respectively and the third term represents the contribution of the water. φ_{pro}, φ_{lip} and φ_{w} are the volume fractions of protein, lipid and water phase, respectively. $K_{sc/w}$, $K_{pro/w}$ and $K_{lip/w}$ represent the partition coefficients of stratum corneum, protein and lipid phases.

Note here the partition coefficients, $PC_{pro/w}$ and $PC_{lip/w}$ are defined as mass concentration ratios and the partition coefficients $K_{sc/w}$, $K_{pro/w}$ and $K_{lip/w}$ are defined as volumetric concentration ratios. Their relationships are

$$K_{pro/w} = PC_{pro/w}\frac{\rho_{pro}}{\rho_{w}} \tag{4}$$

$$K_{lip/w} = PC_{lip/w}\frac{\rho_{lip}}{\rho_{w}} \tag{5}$$

$$K_{sc/w} = \phi_{pro} \times \frac{\rho_{pro}}{\rho_{w}} \times PC_{pro/w} + \phi_{lip} \times \frac{\rho_{lip}}{\rho_{w}} \times PC_{lip/w} + \phi_{w} \tag{6}$$

where ρ_{pro}, ρ_{lip} and ρ_{w} represent the bulk density of protein, lipid and water. Quoted value of ρ_{pro}, ρ_{lip} and ρ_{w} are 1.37 g/cm^3, 0.9 g/cm^3 and 1 g/cm^3 (Nitsche et al., 2006).

In the literature, the use of the partition coefficient unit is not very consistent, causing the errors in the experimental data. The degree of error depends on the mismatch of the density between the two partition phases. For protein, this can leads to up to 30% errors and for lipid the error is slightly smaller, of 10%. The errors in the SC partition coefficients by mixing the volumetric concentration ratio with the mass concentration ratio depend on the water content. In the worst case scenario of dry SC, the error can reach 26% as pointed out by Nitsche et al. (Nitsche et al., 2006). However, when one considers wide spread of partition coefficient of different solute over several orders of magnitudes, such unit inconsistency induced errors are negligibly small.

SC partition coefficient is an important parameter for skin permeability (Potts and Guy, 1992; Guoping et al., 2008). The mathematical treatment of skin permeability is based on Fick's diffusion theory of homogeneous media. Here the correct form of the SC partition coefficient should be in volumetric concentration ratios. Otherwise, one has to introduce the density into the Fick diffusion equation, if mass concentration is used.

3. Results and discussions

3.1. Stratum corneum thickness, lipid content and water uptake capacity

The measured thickness of the stratum corneum is about 14.5 μm. The measured lipid content ranged from 9% to 35% ($n = 44$) determined by the weight change of the stratum corneum samples after extraction, and the average content is about 23%, which is a little higher than the lipid content of human stratum corneum (The lipid content of human stratum corneum was ca.16% in Raykar's experiment (Raykar et al., 1988).)

Water uptake by the SC can have significant effect on solute partitioning and permeation. The equilibrium water uptake capacities of both untreated and delipidized stratum corneum are shown in Table 2. Approximately 2.99 g and 2.43 g water were absorbed by per gram of dry native and delipidized stratum corneum respectively in the room temperature (25 ± 1 °C). The water uptake capacity of native stratum corneum was comparable to the value derived in other researchers (e.g. 2.91 in Raykar's experiment (Raykar et al., 1988), 2.0 in Scheuplein's experiment (Scheuplein and Blank, 1973), 3.7 in Megrab's experiment (Megrab et al., 1995), 2.75 in Kasting's experiment (Kasting and Barai, 2003; Kasting et al., 2003)).

Raykar et al. (Raykar et al., 1988) examined the solvent property of water using ^{14}C-labeled sucrose and found that the water within the stratum corneum may not differ greatly from bulk water. It was therefore valid to take solute concentrations to be identical in both the aqueous part of the stratum corneum and the adjacent bulk aqueous solution after equilibrium. Yet Hansen et al. (Hansen et al., 2009) reached a different conclusion for caffeine and flufenamic acid. They argue that there was a volume of bound water adjacent to the keratin fibers that exclude dissolved solutes. Yet, how to quantify of the amount of bound water and characterize its thermodynamic property in terms of chemical potential and mobility remains unclear. We adopted Raykar's opinion and assumed the concentration of solutes in both the aqueous of SC and adjacent bulk aqueous solutions after equilibrium were identical.

3.2. FTIR spectra analysis of the sample

To evaluate the degree at which the lipid domain in the SC is extracted by the chloroform–methanol procedure, the FTIR spectra of native and delipidized SC samples were compared. The spectra of native and delipidized stratum corneum are shown in Fig. 1. The absorption band at ~1740 cm^{-1}corresponds to the stretch vibration of aliphatic ester functional groups (Notingher

Table 1
HPLC conditions for each compound.

Compound	Mobile phase	Flow rate (mL/min)	Column temperature (°C)	Detection wavelength (nm)	Injection volume (μL)
Theophylline	MeOH:H_2O (30:70)	1.0	32	272	20
Tegafur	MeOH:H_2O (20:80)	1.0	35	271	20
Thiamazole	MeOH:H_2O (10:90)	1.0	25	252	20
Cefazolin	MeOH:HAc-NaAc(Ph4.0) (30:70)	1.0	35	271	20
Cefoperazone	MeOH:HAc-NaAc(Ph4.0) (30:70)	1.0	35	266	20
Fluorouracil	MeOH:HAc-NaAc(Ph4.0) (30:70)	1.0	35	266	10
Oxyteracycline	MeOH:3%HAc (25:75)	1.0	35	274	20

Table 2
Water uptake in the untreated and delipidized stratum corneum.

Weight of stratum corneum (g)		Water uptake of stratum corneum (g/g dry stratum corneum)	Weight of delipidized stratum corneum (g)		Water uptake of delipidized stratum corneum (g/g dry delipidized stratum corneum)
Dry	Wet		Dry	Wet	
0.0593	0.2313	2.90	0.0874	0.3288	2.76
0.0476	0.1717	2.61	0.0674	0.2555	2.79
0.0553	0.2242	3.05	0.0711	0.2439	2.43
0.0347	0.1645	3.74	0.0268	0.1049	2.91
0.0483	0.1646	2.41	0.0436	0.1498	2.44
0.0447	0.1705	2.81	0.0236	0.0934	2.96
0.0491	0.1783	2.63	0.0435	0.1546	2.55
0.0582	0.2271	2.90	0.0429	0.1461	2.41
0.0571	0.2390	3.19	0.0459	0.1549	2.37
0.10111	0.49893	3.93	0.05631	0.16507	1.93
0.10405	0.43107	3.14	0.08225	0.26570	2.23
0.06171	0.23850	2.86	0.10136	0.30883	2.05
0.10674	0.39222	2.67	0.08315	0.24555	1.95
–	–	–	0.05935	0.19194	2.23
Mean ± SD		2.99 ± 0.44 (N = 13)	Mean ± SD		2.43 ± 0.34 (N = 14)

and Imhof, 2004). The absorption band is at its maximum for intact SC but nearly disappeared after one day of extraction with chloroform–methanol (Fig. 1a and b). There is no noticeable difference between one day extraction and three days extraction (Fig. 1b and c).

3.3. Partition coefficients

Table 3 summarizes the measured data of lipid partition and protein binding of the hydrophilic compounds of this study. Here the data are expressed as mass concentration ratios, i.e. $PC_{pro/w}$, $PC_{lip/w}$ and PC′. For hydrophilic solutes, the amount of the solute partition into lipid was too small to measure. The uptake of relatively hydrophilic solutes is governed mostly by protein domain and their absorption by lipid is generally very low. This is in agreement with the view of Raykar et al. (Raykar et al., 1988).

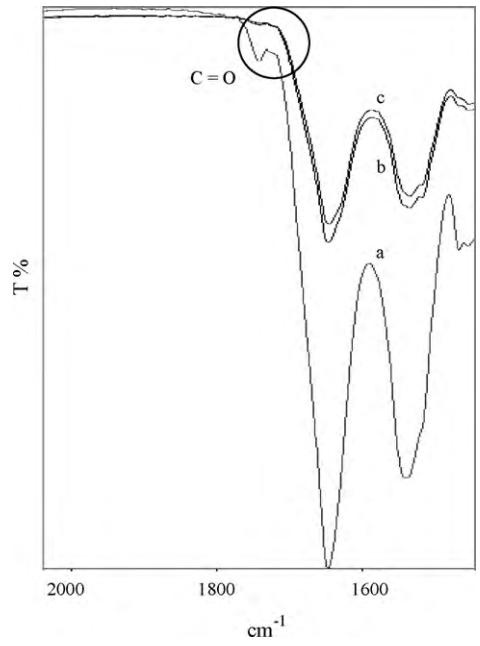

Fig. 1. (a) FTIR spectra of untreated stratum corneum; (b) delipidized stratum corneum after one day of extraction with chloroform–methanol; (c) delipidized stratum corneum after three days of extraction with chloroform–methanol.

3.4. Quantitative structure property relationships

The measured data of hydrophilic solutes of this study are combined with the experimental data (Tables 4 and 5) of hydrophobic solutes reported by other researchers (Raykar et al., 1988; Anderson and Raykar, 1989; Johnson et al., 1997; Mitragotri, 2000; Hansen et al., 2008). Linear regression has been performed for the combined data set. The best fitted relationship of solute binding to SC protein $PC_{pro/w}$ is given by Eq. (7) with a correlation coefficient of R = 0.95. For solute partition to lipid $PC_{lip/w}$, two estimation methods have been frequently quoted (Anderson et al., 1988; Raykar et al., 1988; Johnson et al., 1997; Mitragotri, 2002). One was to set $\xi = 1 (\eta = 0)$ in Eq. (2), implying that the lipophilicity of the lipid closely resembled to octanol. The best fit to the experimental data with this method is at ψ = 0.69 and the correlation coefficient is R = 0.90. The other method considers both ξ and ψ as fitted parameters and the best fitting yielded Eq. (8b) with R = 0.91. Figs. 2 and 3 show the log–log plots of $PC_{pro/w}$ and $PC_{lip/w}$ versus K_{ow} respectively. The equations fitted well to the experimental data.

$$PC_{pro/w} = 5.49(K_{ow})^{0.31} \quad \text{or} \quad \log PC_{pro/w} = 0.74 + 0.31 \log K_{ow} \tag{7}$$

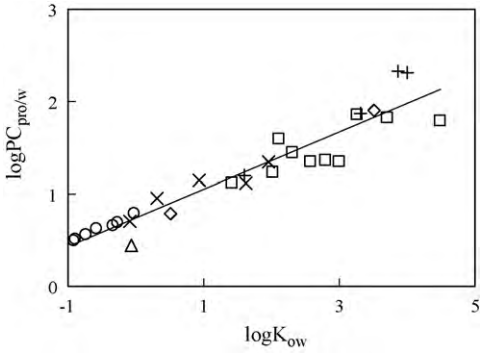

Fig. 2. Log–log plots showing the dependence of $PC_{pro/w}$ upon K_{ow}. Data sets are distinguished as follows: Raykar et al. ((Raykar et al., 1988) (open square (□))); Anderson et al. ((Anderson and Raykar, 1989) (asterisks (×))); Hansen et al. ((Hansen et al., 2008) (open triangle (△))); Surber et al. ((Surber et al., 1990a) (crosses (+))); Surber et al. ((Surber et al., 1990b) (open diamonds (◊))); this study (open circles (○)). Solid line represents Eq. (7) fitted to these data.

Table 3
Partition coefficients of hydrophilic solutes into the stratum corneum.

Compound	MW	$\log K_{ow}$[a]	PC′[b]	N	$PC_{pro/w}$[c]	N	$PC_{lip/w}$[d]	N
Theophylline	180.17	−0.02	1.73 ± 0.45	7	6.03 ± 1.89	7	1.81 ± 0.02	2
Tegafur	200.17	−0.27	1.51 ± 0.52	9	4.90 ± 0.94	5	–	
Thiamazole	114.17	−0.34	1.45 ± 0.38	8	3.39 ± 0.82	4	–	
Cefazolin	454.50	−0.58	1.21 ± 0.26	5	4.17 ± 0.98	7	–	
Cefoperazone	645.67	−0.74	1.16 ± 0.23	7	3.56 ± 1.27	5	–	
Fluorouracil	130.08	−0.89	–	–	3.25 ± 0.09	2	–	
Oxyteracycline	460.44	−0.90[e]	1.10 ± 0.12	2	3.14 ± 0.70	2	–	

[a] Unless noted otherwise, values of $\log K_{ow}$ listed here came from the Hansch's database (Hansch et al., 1995).
[b] Mean ± SD of PC′.
[c] Mean ± SD of $PC_{pro/w}$.
[d] Mean ± SD of $PC_{lip/w}$.
[e] Values of $\log K_{ow}$ obtained from the Sangste's LOGKOW Databank (Sangster, 1994).

$$PC_{lip/w} = (K_{ow})^{0.69} \quad \text{or} \quad \log PC_{lip/w} = 0.69 \log K_{ow} \tag{8a}$$

$$PC_{lip/w} = 1.67(K_{ow})^{0.62} \quad \text{or} \quad \log PC_{lip/w} = 0.22 + 0.62 \log K_{ow} \tag{8b}$$

The best fitted relationship of Eq. (8a) is more robust numerically than Eq. (8b) and is thus used in the following discussions. Substituting Eqs. (7) and (8a) into Eq. (6), the overall solute partition coefficients of the stratum corneum are predicted. Using the experiment data of $K_{sc/w}$ measured in this study and other researchers (Table 6), the quantitative structure property relationship of solute binding to SC protein, expressed by Eq. (7), has been further refined by minimizing the RMSE in the fitted $\log K_{sc/w}$. The optimized relationship of solute binding to SC protein is given by Eq. (9).

$$PC_{pro/w} = 4.2(K_{ow})^{0.31} \quad \text{or} \quad \log PC_{pro/w} = 0.62 + 0.31 \log K_{ow} \tag{9}$$

Eqs. (8a) and (9) combined with Eq. (6) gives a good prediction to the overall stratum corneum partition coefficient of $K_{sc/w}$ with correlation coefficient $R = 0.89$, RMSE = 0.27. Fig. 4 compares the model prediction with the experimental data. The agreement is good.

3.5. Comparison the current model with previous ones

The current model of $K_{sc/w}$ was compared to other models reported by other researchers, Combining Eqs. (6), (8a) and (9) leads

Table 4
Direct determination of $PC_{pro/w}$.

Compound	$\log K_{ow}$[a]	$\log PC_{pro/w}$	Reference
Hidrocotisone hemisuccinate	2.11	1.59	Raykar et al. (1988)
Hidrocotisone hexanoate	4.48	1.79	
Hidrocotisone hydrohexanoate	2.79	1.36	
Hidrocotisone methylpimelate	3.70	1.82	
Hidrocotisone octanoate[b]	5.49	2.74	
Hidrocotisone propionate	3.00	1.34	
Hidrocotisone succinamate	1.43	1.11	
Hidrocotisone dimethylsuccinamate	2.03	1.23	
Hidrocotisone methylsuccinamate	2.58	1.34	
Hidrocotisone hemipimelate	3.26	1.85	
Hidrocotisone pimelamate	2.30	1.45	
Hidrocotisone hemisuccinate	2.11	1.59	
4-dydroxyphenylacetamide	−0.09	0.70	Anderson and Raykar (1989)
4-dydroxybenzyl alcohol	0.32	0.95	
4-dydroxyphenyphenylacetic acid	0.93	1.15	
Methyl 4-dydroxyphenylacetate	1.63	1.11	
p-cresol	1.95	1.34	
Caffeine	−0.07	0.44	Hansen et al. (2008)
Flufenamic acid[b]	5.25	1.31	
Acitretin[b]	6.07	2.71	Surber et al. (1990a)
Progesterone	3.87	2.33	
Testosterone	3.32	1.87	
Estradiol	4.01	2.31	
Hydrocortisone	1.61	1.20	
4-acetamidophenol	0.51	0.79	Surber et al. (1990b)
4-pentyloxyphenol	3.50	1.90	
Theophylline	−0.02	0.78	This study
Tegafur	−0.27	0.69	
Thiamazole	−0.34	0.66	
Cefazolin	−0.58	0.62	
Cefoperazone	−0.74	0.55	
Fluorouracil	−0.89	0.51	
Oxyteracycline	−0.90	0.50	

[a] Unless noted otherwise, values of $\log K_{ow}$ listed here came from the Hansch's database (Hansch et al., 1995). However, for the hydrocortisone esters (Raykar et al., 1988) and methyl-substituted p-cresols (Anderson and Raykar, 1989) studied by Anderson, Raykar, and co-workers were measured by themselves. $\log K_{ow}$ of compounds in this study has been noted in Table 3.
[b] As discussed by Nitsche et al., $PC_{pro/w}$ for highly lipophilic compounds is very sensitive to the residual lipid content of delipidized SC, and therefore subject to high variability and uncertainty; these compounds excluded from final regression of $PC_{pro/w}$ values based on the lipophilicity criterion $\log K_{ow} > 5$.

Table 5
Direct determination of $PC_{lip/w}$.

Compound	log K_{ow}[a]	log $PC_{lip/w}$	Reference
Hidrocotisone hemisuccinate	2.11	1.15	Raykar et al. (1988)
Hidrocotisone hexanoate	4.48	3.20	
Hidrocotisone hydrohexanoate	2.79	1.58	
Hidrocotisone methylpimelate	3.70	2.72	
Hidrocotisone octanoate[b]	5.49	4.20	
Hidrocotisone propionate	3.00	1.84	
Hidrocotisone succinamate	1.43	1.15	
Aldosterone	1.08	0.90	Johnson et al. (1997)
Corticosterone	1.94	1.52	
Estradiol	3.86	2.25	
Lidocaine	2.48	1.38	
Napthol	2.84	2.98	
Progesterone	3.77	3.03	
Testosterone	3.31	1.91	
Caffeine	−0.07	0.33	Hansen et al. (2008)
Flufenamic acid[b]	5.25	1.31	
Theophylline	−0.02	0.26	This study

[a] Unless noted otherwise, values of log K_{ow} listed here came from the Hansch's database (Hansch et al., 1995). However, for the hydrocortisone esters (Raykar et al., 1988) studied by Raykar et al. were measured by themselves. For solutes studied by Johnson et al. were measured by themselves, too.
[b] As discussed by Nitsche et al., $PC_{lip/w}$ for highly lipophilic compounds is very sensitive to the lipid content of samples, and therefore subject to high variability and uncertainty; this compound excluded from final regression of $PC_{lip/w}$ values based on the lipophilicity criterion log K_{ow} > 5.

Table 6
Direct determination of $K_{sc/w}$.

Compound	MW	log K_{ow}[a]	Reported SC/w partition coefficient	log $K_{sc/w}$	Source; basis[b]; temperature (°C)
Water[c]	18.02	−1.38	0.3	−0.06	Scheuplein (1967); $PC_{intrinsic}$; 25
Methanol	32.04	−0.77	0.6	−0.02	
Ethanol	46.07	−0.31	0.6	−0.02	
Propanol	60.10	0.25	2.0	0.13	
Butanol	74.12	0.88	2.5	0.17	
Pentanol	88.15	1.56	5.0	0.34	
Hexanol	102.18	2.03	10	0.55	
Heptanol	116.20	2.72	30	0.96	
Octanol	130.23	3.00	50	1.17	
1a	461.56	1.43	9	0.50	Raykar et al. (1988); $PC_{intrinsic}$; 37
1b	489.61	2.03	12	0.60	
1c	476.57	2.58	22	0.82	
1d hy-hemisuccinate (pH 5.5)[c]	462.54	2.11	11	0.57	
1e (pH 4)	504.62	3.26	68	1.28	
1f	503.64	2.30	25	0.87	
1g hy-6-OH-hexanoate	476.61	2.79	20	0.79	
1h hy-propionate	418.53	3.00	30	0.95	
1i	518.65	3.70	133	1.56	
1j hy-hexanoate	460.61	4.48	208	1.75	
1k hy-octanoate[c]	488.67	5.49	3640	2.99	
1a 4-hydroxyphenyl-acetamide	151.17	−0.09	5	0.33	Anderson and Raykar (1989); $PC_{intrinsic}$; 37
1b 4-hydroxybenzyl alcohol	124.14	0.32	9	0.51	
1c 4-hydroxyphenylacetic acid (pH4)	152.15	0.93	14	0.66	
1d methyl 4-hydroxyphenylacetate	166.18	1.63	13	0.64	
1e p-cresol	108.14	1.95	22	0.83	
beta-Estradiol	272.39	4.01	9.3	1.00	Megrab et al. (1995); PC′; 32
Progesterone	314.47	3.87	104	1.47	Scheuplein et al. (1969); $PC_{intrinsic}$
Pregnenolone	316.49	4.22	50	1.17	
Hydroxypregnenolone	332.49	3.40[d]	43	1.11	
Hydroxyprogesterone	330.47	3.17	40	1.08	
Cortexone (desoxycorticosterone)	330.47	2.88	37	1.05	
Testosterone	288.43	3.32	23	0.86	
Cortexolone	346.47	2.52	23	0.86	
Corticosterone	346.47	1.94	17	0.74	
Cortisone	360.45	1.47	8.5	0.50	
Hydrocortisone	362.47	1.61	7	0.44	
Aldosterone	360.45	1.02[d]	6.8	0.43	
Estrone	270.37	3.13	46	1.13	
Estradiol	272.39	4.01	46	1.13	
Estriol	288.39	2.45	23	0.86	
Resorcinol	110.11	0.80	1.8	0.29	Anderson et al. (1976); PC′; 25
Phenol	94.11	1.47	5.4	0.76	
p-cresol	108.14	1.94	10.6	1.06	
o-cresol	108.14	1.95	10.6	1.06	
m-cresol	108.14	1.96	10.6	1.06	
m-nitrophenol	139.11	2.00	12.1	1.11	

Table 6 (*Continued*)

Compound	MW	log K_{ow}[a]	Reported SC/w partition coefficient	log $K_{sc/w}$	Source; basis[b]; temperature (°C)
p-nitrophenol	139.11	1.91	12.8	1.14	
o-chlorophenol	128.56	2.15	13.8	1.17	
3,4-xylenol	122.17	2.23	16.9	1.26	
p-ethylphenol	122.17	2.47	18.3	1.29	
p-chlorophenol	128.56	2.39	20.4	1.34	
p-bromophenol	173.01	2.59	27.2	1.46	
2-napthol	144.17	2.70	33.4	1.55	
2,4-dichlorophenol	163.00	3.06	45.4	1.69	
Chlorocresol	142.59	3.10	50.4	1.73	
Chloroxylenol	156.61	3.27	60.8	1.81	
Thymol	150.22	3.30	72.7	1.89	
2,4,6-trichlorophenol	197.45	3.69	89	1.98	
Acitretin[c]	326.44	6.07[d]	2.4	1.85	Surber et al. (1990a); log PC; 25
Progesterone	314.47	3.87	2.3	1.75	
Testosterone	288.43	3.32	1.6	1.05	
Diazepam	284.75	2.99	1.8	1.25	
Estradiol	272.39	4.01	2.1	1.55	
Hydrocortisone	362.47	1.61	0.98	0.43	
Caffeine	194.19	−0.07	0.96	0.41	
4-acetamidophenol	151.17	0.51	0.7	0.15	Surber et al. (1990b); log PC; 25
4-cyanophenol	119.12	1.60	0.9	0.35	
4-iodophenol	220.01	2.91	1.8	1.25	
4-pentyloxyphenol	180.25	3.50	1.9	1.35	
PCB (polychlorinated biphenyls)[c]	–	6.40	2.3	1.75	
DDT (1,1,1-trichloro-2,2-bis(p-chloro-phenyl)ethane)[c]	354.49	6.91	2.5	1.95	
Flufenamic acid[c]	281.24	5.25	139	1.60	Wagner et al. (2002); $PC_{intrinsic}$; 32
Ethanol	46.07	−0.31	0.5	−0.27	Cross et al. (2003); PC′
Butanol	74.12	0.88	0.8	−0.07	
Hexanol	102.18	2.03	2.3	0.39	
Octanol	130.23	3.00	16	1.23	
Decanol[c]	158.28	4.57	2393	3.41	
Nicotinamide	122.13	−0.37	1.16	0.07	Kasting et al. (2005); $K^{*}_{sc/w}$; 30
Testosterone	288.43	3.32	25	1.40	
Testosterone	288.43	3.32	6.8	0.84	
Cortisone	360.45	1.47	8.1	0.48	Saket et al. (1985); $PC_{intrinsic}$; 25
Hydrocortisone (HC)	362.47	1.61	6.9	0.43	
Hydrocortisone (HC)	362.47	1.61	7.1	0.44	
Cortisone acetate	402.49	2.10	20	0.80	
HC-21-yl-acetate	404.51	2.19	17	0.74	
HC-21-yl-propionate	418.54	2.80	32.4	0.99	
Cortisone butyrate	430.54	3.13	63.1	1.26	
HC-21-yl-pentanoate	446.59	3.62	126	1.56	
Cortisone hexanoate	458.60	4.11	269	1.88	
HC-21-yl-hexanoate	460.62	4.48	246	1.84	
Cortisone octanoate	486.65	5.09	851	2.38	
HC-21-yl-octanoate	488.67	5.49	813	2.36	
o-Phenylenediamine	108.14	0.15	6.9	0.37	Bronaugh and Congdon (1984); $K^{**}_{sc/w}$; 25
2-Nitro-p-phenylenediamine	153.14	0.53	13	0.57	
4-Amino-2-nitrophenol	154.13	0.96	13	0.57	
N-Nitrosodiethanolamine	134.14	−1.28	1.8	0.11	Bronaugh et al. (1981); $PC_{intrinsic}$; 32
Caffeine	194.2	−0.07	0.65	0.10	Hansen et al. (2008); PC; 32
Flufenamic acid[c]	281.24	5.25	1.21	0.66	
Theophylline	180.17	−0.02	1.73	0.26	This study; PC′; 25
Tegafur	200.17	−0.27	1.51	0.20	
Thiamazole	114.17	−0.34	1.45	0.18	
Cefazolin	454.5	−0.58	1.21	0.10	
Cefoperazone	645.67	−0.74	1.16	0.09	
Oxyteracycline	460.44	−0.90	1.10	0.06	

[a] Unless noted otherwise, values of log K_{ow} listed here came from the Hansch's database (Hansch et al., 1995). However, for the hydrocortisone esters (Raykar et al., 1988) and methyl-substituted p-cresols (Anderson and Raykar, 1989) studied by Anderson, Raykar, and co-workers were measured by themselves. log K_{ow} of compounds in this study has been noted in Table 3.

[b] Type of reported partition coefficient data in the reference. The experiment data can be converted to the same unit by the following equations: PC was defined as (mass of solute absorbed in the hydrated SC per unit mass of the original dry SC)/(w/w solute concentration in the adjacent solution). $K_{SC/w} = \frac{\rho_{hydrated\,SC}}{\rho_w} \times PC \times \frac{1}{1+\nu}$, where $\rho_{hydrated\,SC}$ was the density of the fully hydrated SC and can be expressed as: $\rho_{hydrated\,SC} = \frac{1+\nu}{(w_{pro}/\rho_{pro})+(w_{lip}/\rho_{lip})+(\nu/\rho_w)}$ where w_{pro} and w_{lip} were the density of protein and lipid, ν meant grams of water absorbed by per gram of dry SC. Unless noted, $w_{pro} = 0.90$, $w_{lip} = 0.10$, $\nu = 2.84$ (average value of the experiment data in literatures (Scheuplein and Blank, 1973; Raykar et al., 1988; Megrab et al., 1995; Kasting and Barai, 2003; Kasting et al., 2003)); however, for the measurements of Raykar et al., $w_{pro} = 0.84$, $w_{lip} = 0.16$, $\nu = 2.91$ which was measured by themselves (Raykar et al., 1988); for the measurements of our study, $w_{pro} = 0.77$, $w_{lip} = 0.23$, $\nu = 2.99$.

$PC_{intrinsic}$ = PC-v, and was defined as PC excluded solute contained in the water of hydration.

$K^{*}_{sc/w}$ meant (moles of solute absorbed in the hydrated SC per unit volume of the hydrated SC)/(mol/vol. solute concentration in adjacent solution). $K_{sc/w} = K^{*}_{sc/w}$.

$K^{**}_{sc/w}$ meant (moles of solute absorbed in the dry SC per unit volume of the original dry SC)/(mol/vol. solute concentration in adjacent solution).

$K_{sc/w} = \frac{1}{1+\nu} \times \frac{\rho_{hydrated\,SC}}{\rho_w} \times (K^{**}_{sc/w} \times \frac{\rho_w}{\rho_{dry\,SC}} + \nu)$, where ρ_{drySC} was the density of the dry SC and can be expressed as: $\rho_{dry\,SC} = \frac{1}{(w_{pro}/\rho_{pro})+(w_{lip}/\rho_{lip})}$.

[c] These data were excluded for the same reasons as reference (Nitsche et al., 2006).

[d] log K_{ow} were estimated by the CLOGP Program Vers. 2.0.0. (BioByte, Inc., 1999).

Table 7
Comparison results of the stratum corneum models.

Models	Prediction results	
	R	RMSE
Current model (Eq. (10))	0.89	0.27
Cleek et al. (Eq. (11)) (Cleek and Bunge, 1993; Bunge and Cleek, 1995)	0.89	0.92
Robert et al.(Eq. (12)) (Pugh et al., 1996; Roberts et al., 1996)	0.89	0.55
Raykar et al.(Eq. (13)) (Raykar et al., 1988)	0.88	0.28
Nitsche et al.(Eq. (14)) (Nitsche et al., 2006)	0.88	0.28

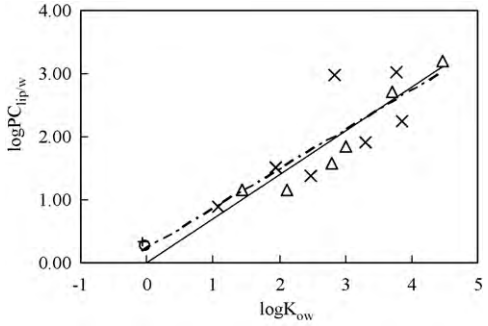

Fig. 3. Log–log plots showing the dependence of $PC_{lip/w}$ upon K_{ow}. Data sets are distinguished as follows: Raykar et al. ((Raykar et al., 1988) (open triangle (△))); Jonson et al. ((Johnson et al., 1997) (ex's (×))); Hansen et al. ((Hansen et al., 2008) (crosses (+))); experimental data in this study (open circles (○)). Solid line represents Eq. (8a) and dashdotted line represents Eq. (8b) fitted to these data.

to the overall stratum corneum partition coefficient expressed as

$$K_{sc/w} = \phi_{pro} \times \frac{\rho_{pro}}{\rho_w} \times 4.23(K_{ow})^{0.31} + \phi_{lip} \times \frac{\rho_{lip}}{\rho_w} \times (K_{ow})^{0.69} + \phi_w \quad (10)$$

The model of this study can be compared to the following two one-phase models proposed by Cleek et al. (Eq. (11)) (Cleek and Bunge, 1993; Bunge and Cleek, 1995) and Roberts et al. (Eq. (12)) (Pugh et al., 1996; Roberts et al., 1996) without breaking down the SC into separate lipid and protein domain. The current model

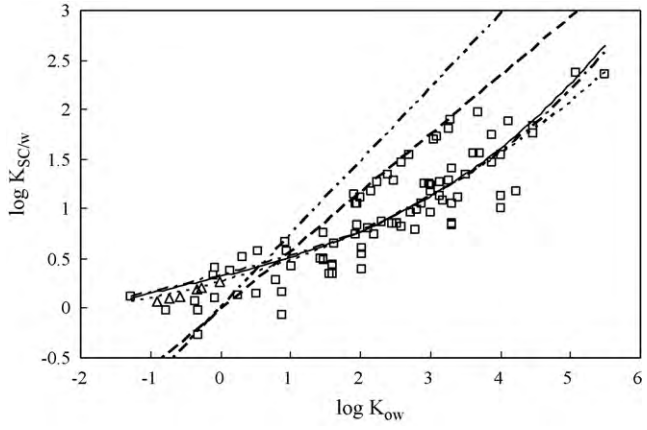

Fig. 4. Log–log plot showing the dependence of $K_{sc/w}$ upon K_{ow}. Data sets are distinguished as follows: experimental data compiled from the literature in reference (Scheuplein, 1967; Scheuplein et al., 1969; Anderson et al., 1976; Bronaugh et al., 1981; Bronaugh and Congdon, 1984; Saket et al., 1985; Raykar et al., 1988; Anderson and Raykar, 1989; Surber et al., 1990a,b; Megrab et al., 1995; Wagner et al., 2002; Cross et al., 2003; Kasting et al., 2005; Hansen et al., 2008) (open square (□)); this study (open triangle (△)). The dotted line represent model in this study (Eq. (10)). The double dashdotted line and dashed line represent Eq. (11) from Cleek et al. and Eq. (12) from Robert et al., respectively. The dashdotted line and solid line represent Eq. (13) from Raykar et al. and Eq. (14) from Nitsche et al., respectively.

was also compared to other two two-phase models. One was fitted directly using Anderson and Raykar et al.' experiment data (Raykar et al., 1988; Anderson and Raykar, 1989) as discussed by Nitsche et al. (see Eq. (13)) and the other proposed by Nitsche et al. (Eq. (14)) (Nitsche et al., 2006).

$$K_{sc/w} = (K_{ow})^{0.74} \quad (11)$$

$$K_{sc/w} = 0.95(K_{ow})^{0.59} \quad (12)$$

$$K_{sc/w} = \phi_{pro} \times \frac{\rho_{pro}}{\rho_w} \times 5.6(K_{ow})^{0.27} + \phi_{lip} \times 0.35(K_{ow})^{0.81} + \phi_w \quad (13)$$

$$K_{sc/w} = \phi_{pro} \times \frac{\rho_{pro}}{\rho_w} \times 5.4(K_{ow})^{0.27} + \phi_{lip} \times 0.43(K_{ow})^{0.81} + \phi_w \quad (14)$$

The comparison results were shown in Table 7 and Fig. 4. In general, the two-phase models gave better prediction than single-phase models. All two-phase models predict non-linear relationship between $\log K_{ow}$ and $\log K_{sc/w}$. The non-linear behaviour reflects the change in mechanism of solute uptake from protein binding dominated for hydrophilic solutes to lipid domain partition dominated for lipophilic solutes. Such non-linear behaviour cannot be predicted from single phase models of homogeneous materials. Compared with reported two-phase models, the model in this study gives similar results but extends to both hydrophobic solutes and hydrophilic solutes.

4. Conclusions

Experiments have been carried out to measure the SC lipid partitioning and protein binding of a number of representative hydrophilic solutes. The partition coefficients of hydrophilic solutes for untreated and delipidized SC have been measured using the equilibrium experiments. An extended database of the thermodynamic equilibrium properties of SC partition and binding has been compiled by combining the newly measured data of hydrophobic solutes of this study with published data of hydrophobic solutes. The extended database has been used to derive quantitative structure property relationships of solute partitioning and binding to the SC. From the QSPR models of SC lipid partition and protein binding, the overall partition coefficient of the SC has been predicted using a multiphase and heterogeneous structure based model.

The thickness of the stratum corneum, water uptake ability for untreated stratum corneum and delipidized stratum corneum, as well as the lipid content of the stratum corneum have been also measured in this study. All these parameters are comparable to the results from published references. The degree of lipid extraction experiment has been determined by the FTIR spectrum analysis. The experimental data showed that the lipid nearly disappeared after one day of extraction with chloroform–methanol and there was no significant difference between one day and three day extraction.

Our study has extended the database of solute partition and binding properties of the SC by considering a number of hydrophilic solutes. It is demonstrated that the thermodynamic equilibrium properties of SC lipid partition and protein binding can be fitted with good accuracy by QSPR models related to octanol–water partition coefficient. It is further demonstrated that the overall SC partition coefficient of both hydrophobic and hydrophilic solutes can be predicted from the QSPR models of SC lipid partition and protein binding by using multiphase heterogeneous structured based model.

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References

Anderson, B., Higuchi, W., Raykar, P., 1988. Heterogeneity effects on permeability–partition coefficient relationships in human stratum corneum. Pharm. Res. 5, 566–573.
Anderson, B.D., Raykar, P.V., 1989. Solute structure–permeability relationships in human stratum corneum. J. Invest. Dermatol. 93, 280–286.
Anderson, R.A., Triggs, E.J., Roberts, M.S., 1976. The percutaneous absorption of phenolic compounds 3. Evaluation of permeability through human stratum corneum using a desorption technique. Aust. J. Pharm. Sci. 5, 107–110.
Bronaugh, R.L., Congdon, E.R., 1984. Percutaneous Absorption of Hair Dyes: Correlation with Partition Coefficients. J. Invest. Dermatol. 83 (2), 124–127.
Bronaugh, R.L., Congdon, E.R., Scheuplein, R.J., 1981. The Effect of Cosmetic Vehicles on the Penetration of N-Nitrosodiethanolamine Through Excised Human Skin. J. Invest. Dermatol. 76 (2), 94–96.
Bunge, A.L., Cleek, R.L., 1995. A new method for estimating dermal absorption from chemical exposure: 2. Effect of molecular weight and octanol–water partitioning. Pharm. Res. 12, 88–95.
Chen, L.J., Lian, G.P., Han, L.J., 2008. Use of "bricks and mortar" model to predict transdermal permeation: model development and initial validation. Ind. Eng. Chem. Res. 47, 6465–6472.
Cleek, R.L., Bunge, A.L., 1993. A new method for estimating dermal absorption from chemical exposure. 1. General approach. Pharm. Res. 10, 497–506.
Cross, S.E., Magnusson, B.M., Winckle, G., Anissimov, Y., Roberts, M.S., 2003. Determination of the Effect of Lipophilicity on the in vitro Permeability and Tissue Reservoir Characteristics of Topically Applied Solutes in Human Skin Layers. J. Invest. Dermatol. 120 (5), 759–764.
Elias, P.M., 1981. Lipids and the epidermal permeability barrier. Arch. Dermatol. Res. 270, 95–117.
Elias, P.M., Brown, B.E., Fritsch, P., Goerke, J., Gray, G.M., White, R.J., 1979. Localization and composition of lipids in neonatal mouse stratum granulosum and stratum corneum. J. Invest. Dermatol. 73, 339–348.
Elias, P.M., Friend, D.S., 1975. The permeability barrier in mammalian epidermis. J. Cell Biol. 65, 180–191.
Elias, P.M., Goerke, J., Friend, D.S., 1977. Mammalian epidermal barrier layer lipids: composition and influence on structure. J. Invest. Dermatol. 69, 535–546.
Flynn, G.L., Dürrheim, H., Higuchi, W.I., 1981. Permeation of hairless mouse skin II: membrane sectioning techniques and influence on alkanol permeabilities. J. Pharm. Sci. 70, 52–56.
Guoping, L., Longjian, C., Lujia, H., 2008. An evaluation of mathematical models for predicting skin permeability. J. Pharm. Sci. 97, 584–598.
Hansch, C., Leo, A., Hoekman, D., 1995. Exploring QSAR: Hydrophobic, Electronic and Steric Constants. American Chemical Society, Washington, D.C.
Hansen, S., Henning, A., Naegel, A., Heisig, M., Wittum, G., Neumann, D., Kostka, K.H., Zbytovska, J., Lehr, C.M., Schaefer, U.F., 2008. In-silico model of skin penetration based on experimentally determined input parameters. Part I: experimental determination of partition and diffusion coefficients. Eur. J. Pharm. Biopharm. 68, 352–367.
Hansen, S., Naegel, A., Heisig, M., Wittum, G., Neumann, D., Kostka, K.H., Meiers, P., Lehr, C.M., Schaefer, U.F., 2009. The role of corneocytes in skin transport revised—a combined computational and experimental approach. Pharm. Res. 26, 1379–1397.
Johnson, M.E., Blankschtein, D., Langer, R., 1997. Evaluation of solute permeation through the stratum corneum: lateral bilayer diffusion as the primary transport mechanism. J. Pharm. Sci. 86, 1162–1172.
Kasting, G.B., Barai, N.D., 2003. Equilibrium water sorption in human stratum corneum. J. Pharm. Sci. 92, 1624–1631.
Kasting, G.B., Barai, N.D., Wang, T.F., Nitsche, J.M., 2003. Mobility of water in human stratum corneum. J. Pharm. Sci. 92, 2326–2340.
Kasting, G.B., Miller, M.M., Talreja, P.S., 2005. Evaluation of stratum corneum heterogeneity. In: Bronaugh, R.L., Maibach, H.I. (Eds.), Percutaneous absorption. Taylor and Francis, New York, pp. 193–212.
Kasting, G.B., Smith, R.L., Anderson, B.D., 1992. Prodrugs for dermal delivery: solubility, molecular size, and functional group effects. In: Sloan, K.B. (Ed.), Prodrugs, Topical and Ocular Drug Delivery. Marcel Dekker, New York, pp. 117–161.
Kligman, A.M., Christophers, E., 1963. Preparation of isolated sheets of human stratum corneum. Arch. Dermatol. 88, 70–73.
Longjian, C., Guoping, L., Lujia, H., 2010. Modeling transdermal permeation. Part I. Predicting skin permeability of both hydrophobic and hydrophilic solutes. AIChE J. 56, 1136–1146.
Megrab, N.A., Williams, A.C., Barry, B.W., 1995. Oestradiol permeation across human skin, silastic and snake skin membranes: the effects of ethanol/water co-solvent systems. Int. J. Pharm. 116, 101–112.
Mitragotri, S., 2000. In situ determination of partition and diffusion coefficients in the lipid bilayers of stratum corneum. Pharm. Res. 17, 1026–1029.
Mitragotri, S., 2002. A theoretical analysis of permeation of small hydrophobic solutes across the stratum corneum based on Scaled Particle Theory. J. Pharm. Sci. 91, 744–752.
Mitragotri, S., 2003. Modeling skin permeability to hydrophilic and hydrophobic solutes based on four permeation pathways. J. Controlled Release 86, 69–92.
Morimoto, Y., Hatanaka, T., Sugibayashi, K., Omiya, H., 1992. Prediction of skin permeability of drugs: comparison of human and hairless rat skin. J. Pharm. Pharmacol. 44, 634–639.
Nitsche, J.M., Wang, T.F., Kasting, G.B., 2006. A two-phase analysis of solute partitioning into the stratum corneum. J. Pharm. Sci. 95, 649–666.
Notingher, I., Imhof, R.E., 2004. Mid-infrared in vivo depth-profiling of topical chemicals on skin. Skin Res. Technol. 10, 113–121.
Potts, R.O., Guy, R.H., 1992. Predicting skin permeability. Pharm. Res. 9, 663–669.
Potts, R.O., Guy, R.H., Francoeur, M.L., 1992. Routes of ionic permeability through mammalian skin. Solid State Ionics 53–56, 165–169.
Pugh, W.J., Roberts, M.S., Hadgraft, J., 1996. Epidermal permeability–penetrant structure relationships: 3. The effect of hydrogen bonding interactions and molecular size on diffusion across the stratum corneum. Int. J. Pharm. 138, 149–165.
Raykar, P.V., Fung, M.C., Anderson, B.D., 1988. The role of protein and lipid domains in the uptake of solutes by human stratum corneum. Pharm. Res. 5, 140–150.
Roberts, M.S., Anderson, R.A., Moore, D.E., Swarbrick, J., 1977. The distribution of non-electrolytes between human stratum corneum and water. Aust. J. Pharm. Sci. 6, 77–82.
Roberts, M.S., Pugh, W.J., Hadgraft, J., 1996. Epidermal permeability: penetrant structure relationships. 2. The effect of H-bonding groups in penetrants on their diffusion through the stratum corneum. Int. J. Pharm. 132, 23–32.
Saket, M.M., James, K.C., Kellaway, I.W., 1985. The partitioning of some 21-alkyl steroid esters between human stratum corneum and water. Int. J. Pharm. 27, 287–298.
Sangster, J., 1994. LOGKOW Databank. Canada, Sangster Res Lab., Montreal Quebec.
Scheuplein, R.J., 1967. Mechanism of percutaneous absorption II. Transient diffusion and the relative importance of various routes of skin penetration. J. Invest. Dermatol. 48, 79–88.
Scheuplein, R.J., Blank, I.H., 1971. Permeability of the skin. Physiol. Rev. 51, 702–747.
Scheuplein, R.J., Blank, I.H., 1973. Mechanism of percutaneous aborption. IV. Penetration of nonelectrolytes (alcohols) from aqueous solution and from pure liquids. J. Invest. Dermatol. 60, 286–296.
Scheuplein, R.J., Blank, I.H., Brauner, G.J., MacFarlane, D.J., 1969. Percutaneous absorption of steroids. J. Invest. Dermatol. 52 (1), 63–70.
Surber, C., Wilhelm, K.P., Hori, M., Maibach, H.I., Guy, R.H., 1990a. Optimization of topical therapy: partitioning of drugs into stratum corneum. Pharm. Res. 7, 1320–1324.
Surber, C., Wilhelm, K.P., Maibach, H.I., Hall, L.L., Guy, R.H., 1990b. Partitioning of chemicals into human stratum corneum: implications for risk assessment following dermal exposure. Toxicol. Sci. 15, 99–107.
Wagner, H., Kostka, K.H., Lehr, C.M., Schaefer, U., 2000. Drug distribution in human skin using two different in vitro test systems: comparison with in vivo data. Pharm. Res. 17, 1475–1481.
Wagner, H., Kostka, K.H., Lehr, C.M., Schaefer, U.F., 2002. Correlation between stratum corneum/water-partition coefficient and amounts of flufenamic acid penetrated into the stratum corneum. J. Pharm. Sci. 91, 1915–1921.
Wang, T.F., Kasting, G.B., Nitsche, J.M., 2006. A multiphase microscopic diffusion model for stratum corneum permeability. I. Formulation, solution, and illustrative results for representative compounds. J. Pharm. Sci. 95, 620–648.
Wester, R.C., Maibach, H.I., 1983. Cutaneous pharmacokinetics: 10 steps to percutaneous absorption. Drug Metab. Rev. 14, 169–205.