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IMPROVED INPUT PARAMETERS FOR DIFFUSION MODELS OF SKIN ABSORPTION

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Abstract

To use a diffusion model for predicting skin absorption requires accurate estimates of input parameters on model geometry, affinity and transport characteristics. This review summarizes methods to obtain input parameters for diffusion models of skin absorption focusing on partition and diffusion coefficients. These include experimental methods, extrapolation approaches, and correlations that relate partition and diffusion coefficients to tabulated physico-chemical solute properties. Exhaustive databases on lipid-water and corneocyte protein-water partition coefficients are presented and analyzed to provide improved approximations to estimate lipid-water and corneocyte protein-water partition coefficients. The most commonly used estimates of lipid and corneocyte diffusion coefficients are also reviewed. In order to improve modeling of skin absorption in the future diffusion models should include the vertical stratum corneum heterogeneity, slow equilibration processes, the absorption from complex non-aqueous formulations, and an improved representation of dermal absorption processes. This will require input parameters for which no suitable estimates are yet available.

<150 words

Keywords

Partition coefficient, diffusion coefficient, stratum corneum, lipid bilayer, keratin, corneocyte

Abbreviations
A area; C solute concentration; Cor corneocyte; D diffusion coefficient; Der dermis; DMPC dipalmitoyl phosphatidycholine; Epi epidermis; \( f_{\text{hydro}} \) hydrodynamic hindrance factor; \( f_{\text{steric}} \) steric hindrance factor; h thickness; \( J_s \) steady state flux; K partition coefficient; \( k_B \) Boltzmann constant; \( k_{\text{off}} \) desorption rate constant; \( k_{\text{on}} \) adsorption rate constant; \( K_{\text{OW}} \) octanol-water partition coefficient; \( k_P \) permeability coefficient; \( K_{\text{pH}} \) octanol-water distribution coefficient at a defined pH; \( K_{\text{SC/w}} \) SC partition coefficient based on molar concentrations, defined as (moles of solute absorbed in the SC per unit volume of the hydrated SC)/(mol/volume solute concentration in the adjacent solution); \( k_{\text{trans}} \) mass transfer coefficient; Lip lipids; \( MV \) the molar volume; \( MW \) the molar weight; \( N_a \) Avogadro’s number; \( PC_{\text{intrinsic}} \) SC partition coefficient based on mass ratio concentrations and dry SC weight, defined as (weight of solute absorbed in SC per unit weight of the original dry SC)/(wt/wt solute concentration in the adjacent solution); \( PC_{\text{SC/w}} \) partition coefficients based on weight ratio concentrations and hydrated SC weight, defined as (weight of solute absorbed in protein or lipid phase per unit weight of hydrated protein or lipid phase)/(wt/wt solute concentration in the adjacent solution); Pro protein; \( (\Phi_{\text{SC/w}})^{\text{comp}} \) dimensionless SC permeability; Q amount of solute diffusing across the skin membrane; QSA(P)R quantitative structure activity (or permeability) relationship models; R Resistance; \( r \) solute radius assuming a spherical shape of the molecule; \( R \) the ratio of trans-bilayer to lateral diffusivity; SC stratum corneum; T temperature; t time period; \( t_{\text{lag}} \) lag-time; \( \gamma(r_p)dr_p \) pore size distribution as a function of pore radius; \( \gamma_e \) Euler’s constant; \( \Delta c \) concentration gradient; \( \eta_0 \) dynamic solvent viscosity; \( \eta_{\text{cor}} \) dynamic viscosity of the corneocytes; \( \theta \) constant describing pore size distribution; \( \lambda \) ratio of solute to keratin fiber radius; \( \mu \) constant describing pore size distribution; \( \nu \) are the weight fractions of water; \( \rho \) density; \( \sigma \) the ratio of lipid to corneocyte permeability; \( \varphi_{\text{cor}} \) volume fractions of corneocytes; \( \varphi_{\text{lip}} \) volume fractions of lipids; \( \varphi_{\text{pro}} \) volume fractions of protein; \( \omega_{\text{lip}} \) weight fractions of lipids; \( \omega_{\text{pro}} \) weight fractions of proteins
Graphical Abstract

Log-log plots showing the dependence of (A) the lipid-water partition coefficient ($PC_{lip/w}$) and (B) the corneocyte protein-water partition coefficient ($PC_{pro/w}$) upon the octanol-water distribution coefficient ($K_{ow}$). The solid curves (—) represent least squares fits over the entire data sets.
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1. INTRODUCTION

Modeling skin absorption is relevant for percutaneous delivery and risk assessment of occupational and environmental hazards. Applications in pharmaceutics and cosmetics range from estimating permeability to formulation development and optimization. An important motivation to model skin absorption is also to gain fundamental understanding of permeation pathways and permeant-vehicle-skin interactions. The main modeling strategies that have been employed for these purposes are quantitative structure activity (or permeability) relationship models (QSA(P)R), pharmacokinetics models, and diffusion models. As skin absorption is primarily a passive process it can effectively be described by diffusion mathematics. In the simplest case we can assume the skin to be a pseudo-homogeneous membrane. This membrane is exposed on one site to a solute. Under steady state conditions Fick’s first law relates the amount of solute \((Q)\), diffusing across the skin membrane with area \((A)\), and thickness \((h)\), and diffusion coefficient \((D)\), over a time period \((t)\), to a concentration gradient within this membrane \((\Delta c_s)\):

\[
Q = DA t \Delta c_s / h
\]

(1)

The steady state flux \((J_{ss})\) across the membrane is defined as:

\[
J_{ss} = Q / At = D \Delta c_s / h
\]

(2)

As the concentration gradient within the membrane is not easily accessible Eq. 2 is usually expressed as solute concentration in the vehicle \((c_v)\) and a vehicle-skin partition coefficient \((K = c_s / c_v)\):

\[
J_{ss} = Q / At = D K c_v / h
\]

(3)
Eq. 3 assumes perfect sink conditions so that the concentration at the end of the membrane is effectively zero and an according skin-acceptor partition coefficient (i.e. in the \textit{in vitro} setup) can be neglected. Normalizing Eq. 3 for \(c_v\) returns the permeability coefficient \((k_p)\):

\[
k_p = \frac{J_{ss}}{c_v} = \frac{D K}{h}
\]

(4)

It follows that for predicting skin permeability across a homogeneous membrane one has to know the parameters \(D\), \(K\), and \(h\). In most cases the stratum corneum (SC) is the main barrier to absorption. Thus the parameters in Eq. 4 can effectively be substituted by the apparent SC diffusion and SC-vehicle partition coefficients and the SC thickness indicating the apparent path length (denoted as subscripts \(D_{SC}\), \(K_{SC/v}\), \(h_{SC}\)).

A transient expression is provided by Fick’s 2\textsuperscript{nd} law of diffusion:

\[
\frac{\partial C}{\partial t} = D \frac{\partial^2 C}{\partial x^2}
\]

(5)

where \((C)\) is the concentration of a permeating substance at time \((t)\) and position \((x)\) in the membrane. Equation 5 assumes pseudo-homogeneous conditions. Transient models are especially important to describe non-steady state diffusion. Of special interest are models that apply finite dose conditions. In fact these are more relevant to the \textit{in vivo} situation where usually the skin is exposed to a limited dose of a drug, a cosmetic agent, or a harmful compound. Often in these cases a steady state of absorption is never reached as the drug depletes from the skin surface over time (on different time scales caused by evaporation, diffusion, metabolism, and desquamation).

The pseudo-homogeneous membrane models imply that transport characteristics, i.e. partition and diffusion coefficients, do not vary with time and position in the membrane resulting in a single pathway that is taken by all molecules. Although oversimplifying the highly complex skin
absorption process such models were successfully used to explain trans-epidermal water loss (TEWL). As an advancement to this, diffusion models with depth dependent diffusion- and/or partition coefficient were proposed to account for the vertical heterogeneity of the SC.

A steady state expression that integrates parallel diffusion pathways is achieved by adapting Kirchhoff’s rules to the diffusion problem. Parallel diffusion pathways are described as resistors connected in parallel so that the conductivity (or permeability) of the membrane equals the sum of the conductivity of the individual pathways.

\[
k_{P,\text{tot}} = \sum_{n=1}^{N} k_{P,n}
\]

(6)

Accordingly, consecutive diffusion barriers can be modeled as serial resistors. Resistance \( R \) and permeability are related via \( k_r = 1/R \). This is used in multi-layer models that include the viable epidermis and/or the dermis to account for a diffusion hindrance of highly lipophilic compounds by the more hydrophilic skin layers.

\[
R_{\text{tot}} = \sum_{n=1}^{N} R_n
\]

(7)

For example the three-layer model in Figure 1 assumes two parallel pathways across the SC. One is a path along the inter-corneocyte lipids characterized by the resistance \( R_{\text{lip}} \), the other is a trans-corneocyte path with the resistance \( R_{\text{cor}} \). The SC arrangement in which the corneocytes are surrounded by lipids has first been used by Michaels and coworkers for modeling the SC absorption and is commonly referred to as “brick and mortar”. Two further resistors for the epidermis (\( R_{\text{epi}} \)) and dermis (\( R_{\text{der}} \)) are connected in series. Due to the rich vasculature and
lymphatic drainage within the dermis this layer can usually be neglected as a barrier in vivo. However in vitro it may be necessary to explicitly include the dermis for highly lipophilic compounds. Consequently for predicting skin permeability across the membrane in Figure 1 one requires sets of parameters defining the membrane geometry, microscopic partition coefficients between aqueous vehicle, lipid and corneocyte; SC and epidermis; and epidermis dermis (Klip/w, Kcor/w, Ken/SC and Kder/epi) and diffusion coefficients within lipids, corneocytes, epidermis and dermis (Dlip, Dcor, Der and Des) as summarized in Figure 2.

As reviewed recently, shape and structuring of cellular and lipid phase in brick-and-mortar models may differ widely as do offset between the cells and the representation of lipophilic and hydrophilic pathways across the membrane.

Table 1 and 2 summarize published diffusion models. Several models with pseudo-homogeneous representation of the SC (table 1) include multiple skin layers. In contrast, most brick-and-mortar models (table 2) focus on diffusion in the SC and do not explicitly treat the epidermis and/or dermis. It is likewise usually the simpler models that have been applied to investigate specific questions of skin absorption, including effects like variable hydration, adsorption of permeants to a limited number of binding sites, the influence of permeation enhancers or reducers; and clearance kinetics. It is obvious that the computational tools to create complex and realistic models are available. However, these models will require more complex input parameters as well as well-defined data sets for validation to be usable in a meaningful way.

For certain applications it may be useful to use diffusion models to simulate rather than predict transdermal absorption. Simulations use a set of artificial input parameters. Testing serial variations of one input parameter may allow separating the influence of this parameter on a specific aspect of absorption. Simulations may therefore be used for sensitivity testing during model validation or for investigating the influence of parameters that cannot be easily isolated experimentally. In contrast, predictions use experimentally determined or theoretically derived
input parameters to predict the absorption of a specific compound. As outlined above, parameters defining membrane geometry, affinity (partitioning, reversible or irreversible binding), and diffusivity are required.

This review summarizes methods to obtain input parameters for diffusion models of skin absorption. We will touch briefly on experimental as well as fitting methods to obtain input parameters. The major focus will be on approximations that can be used to estimate input parameters from physico-chemical properties of solutes as these are of the highest importance for predicting skin absorption. Necessary requirements for the future in this field will be discussed.

2. Input Parameters for Diffusion Models of Skin Absorption

2.1. Experimentally Derived Input Parameters

Partition coefficients can easily be obtained experimentally from equilibration experiments between a skin membrane (SC, delipidized SC, reconstituted SC lipids, epidermis, or dermis) and a solution of the solute in question. Ideally it is assumed that both phases are not miscible. However, usually partition coefficients into skin membranes are obtained from aqueous solution which violates this assumption. Consequently especially for hydrophilic solutes which are well water soluble differences will be obtained between partition coefficients determined from the decrease of solute concentration in the incubation solution and from extraction of the skin membrane. The difference will be equal to the amount of hydration of the membrane and can be used to estimate the degree of membrane hydration if equal solubility of the solute within the membrane-bound water and bulk water is assumed. The uptake of solutes into water of hydration can also be observed by measuring partition coefficients from a non-aqueous solvent.
which is non-miscible with the membrane (e.g. low viscous paraffin) using skin membranes hydrated to different degrees.

Apparent diffusion coefficients are also accessible in experiments, e.g. by measuring steady-state flux and equilibrium partitioning (Eq. 3). Alternatively the apparent diffusion coefficient can be determined from lag-time \( t_{\text{lag}} \).

\[
D = \frac{h^2}{6 \cdot t_{\text{lag}}}
\]  

(8)

However, the determination of lag-time from steady-state permeation profiles is prone to errors especially for slowly diffusing solutes. Furthermore, as recently pointed out in the excellent review by Mitragotri et al. apparent diffusivities that are determined in either manner from steady-state absorption are suitable only to estimate steady-state flux from the same vehicle but should be used with caution for other vehicles and, importantly, transient calculations. Vice versa, Pirot and coworkers showed that transient diffusion data can be used to extrapolate on skin permeability at steady-state as will be explained below.

The apparent diffusion coefficients can be obtained from non-steady-state data based on desorption measurements. For this purpose a membrane is first equilibrated with a solute and then the cumulative amount desorbed into an acceptor is measured over time maintaining sink conditions in the acceptor. A solution of the diffusion equation (Eq. 5) which is appropriate to evaluate desorption data is given by:

\[
\frac{M_i}{M_{\infty}} = 1 - \frac{8}{\pi^2} \sum_{n=0}^{\infty} \frac{1}{(2n+1)^2} \cdot \exp \left[ -D \frac{(2n+1)^2 \pi^2 t}{h^2} \right]
\]  

(9)

for the following initial and boundary conditions:

\[
C(x,0) = c_0, \ 0 < x < h
\]
\[ C(0,t) = 0 \]
\[ C(h,t) = 0 \]

Non-linear curve fitting of the cumulative amount desorbed \((M_t/M_\infty)\) versus time provides \(D/h^2\) which is a measure of apparent diffusivity within the membrane. Here \(h\) is the membrane thickness assuming \(h\) is equal to the pathlength. All three methods that have been introduced so far can be applied to obtain the apparent diffusion coefficients in different skin membranes, such as the SC, membranes of reconstituted human SC lipids, different keratinous matrices including delipidized SC, callus, hoof/horn, wool, and hair as well as dermis. Especially with reconstituted SC lipid membranes and keratinous membranes the quality of the obtained measurements strongly depends on whether the structural organization of these membranes is representative of the situation within the intact SC in vivo in humans. Also, the analysis assumes that all microscopic equilibration processes are fast compared to the measured diffusivity which is arguable in case of desorption from keratins and crossing the cornified envelope proteins.

Experimental measurements of microscopic diffusion constants are rarely reported in literature. Early analyses compared the corneocyte interior to an aqueous gel taking \(D_{\text{cor}}\) to be roughly one-tenth of \(D_{\text{eq}}\). For compounds with a molecular weight between 300 and 500 Da a value of \(2\cdot10^{-7} \text{ cm}^2/\text{s}\) was considered appropriate. Water is particularly well investigated but also data for a few other solutes are available. Typical values for water diffusion in hard keratins range from \(1\cdot10^{-10} \text{ cm}^2/\text{s}\) (at dry state) to \(1\cdot10^{-7} \text{ cm}^2/\text{s}\) (at hydrated state); in SC corneocytes from \(4\cdot10^{-8} \text{ cm}^2/\text{s}\) to \(1\cdot10^{-5} \text{ cm}^2/\text{s}\) (depending on hydration). Water diffusivities have also been measured by spin-echo NMR measurements of mobile protons in guinea pig footpad SC. Similar measurements in human SC are available for example from. Typically for the diffusion of water the diffusion coefficient depends on hydration due to a self enhancement of diffusion through water.

For phospholipid bilayer systems, notably liposomes, it is known that solute transport is highly anisotropic and size dependent. The structural heterogeneity of the lipid bilayers translates into
spatial variations in partition and diffusion coefficients. For a relatively small set of fluorescent labels (223-856 Da) and molecular oxygen lateral diffusion coefficients in human SC lipids were determined by FRAP (fluorescence recovery after photo-bleaching) and EPR (electron paramagnetic resonance spectroscopy) respectively. For molecular oxygen a value of $3 \times 10^{-7}$ cm$^2$/s was obtained while the values for the fluorescent probes were in the range of $2.34 \times 10^{-8}$ cm$^2$/s (223 Da) to $3.04 \times 10^{-9}$ cm$^2$/s (854 Da). These measurements are usually interpreted as lateral diffusion coefficients within the plane of the lipid bilayers as it is expected that transbilayer crossing is considerably slower. For reference apparent lipid diffusion coefficients obtained for two solutes (flufenamic acid with 281 Da and caffeine with 194 Da) from steady-state permeability measurements with reconstituted SC lipid membranes (which necessarily requires crossing of multiple bilayers) were in a very similar range ($3.09 \times 10^{-8}$ cm$^2$/s and $5.83 \times 10^{-8}$ cm$^2$/s respectively).

Nonetheless it is obvious that experimental input parameters are sometimes gained at considerable expense and not useful for predicting the permeability of a large numbers of compounds (although they have their use during model development and validation). Especially if it is the goal to predict the permeability of a large number of compounds (e.g. as done in: Mitragotri, Johnson et al., Wang et al.) approximations that are derived from physico-chemical properties are the only option.

2.2. **EXTRAPOLATION APPROACHES**

A very elegant way to derive input parameters is to fit an analytical solution of Fick’s law to experimental skin absorption data that can be obtained relatively easily and obtain values describing membrane affinity and diffusivity. Fitted parameters can for example re-enter the same analytical solution and “extrapolate” on the absorption of the same solute at a later time point.

$$c(x,t) = K_{SC/w} \cdot c_i \left[ \frac{1-x}{h} - \frac{2}{\pi} \sum_{n=1}^{\infty} \frac{1}{n} \sin \left( \frac{n \cdot \pi \cdot x}{h} \right) \exp \left( -\frac{D \cdot n^2 \cdot \pi^2 \cdot t}{h^2} \right) \right]$$
Equation 9 is an analytical solution of Equation 5 for the case of a homogeneous single layer membrane with the following initial and boundary conditions:

(i) at $x = 0$, $C = K_{SC/w} C_v$ for $t \geq 0$
(ii) at $c = h$, $C = 0$ for $t \geq 0$, and
(iii) at $0 < x < h$, $C = 0$ for $t = 0$

It expresses the concentration profile of a chemical, i.e. the time and position dependent concentration within the membrane. Fitting Eq. 9 to tape-stripping data yields values for the SC-vehicle partition coefficient $K_{SC/v}$ and the characteristic SC diffusion parameter $D_{SC}/h^2$. Pirot et al. used estimates of $K_{SC/v}$ and $D_{SC}$ obtained from fitting Equation 8 to tape stripping data of a short term exposure (15 min) to extrapolate on steady state concentration depth profiles. This is useful for example when evaluating potentially harmful compounds to minimize the exposure time in in vivo experiments.

A similar approach was followed by Kruese et al. who investigated possibilities of predicting different finite dose experiments (cumulative amount absorbed versus time data obtained in static Franz diffusion cells) using $K_{SC/v}$ and $D_{SC}$ determined from infinite dose permeation data using a homogeneous multi-layer diffusion model. The benefit of the approach is that infinite dose experiments are less challenging concerning experiment and analytics.

The draw-back of fitting procedures is of course the limited usefulness for “unknown solutes”, i.e. solutes for which no permeation data is available.

2.3. **Theoretically Derived Input Parameters**

2.3.1. **Partition Coefficients**

As outlined in the introduction partition coefficients account for jumps in concentration at many interfaces in the skin, including the partition coefficients between vehicle and SC; lipids and corneocytes; SC and epidermis; epidermis and dermis. It is self-evident that membrane affinities are usually predicted from physico-chemical parameters describing solute lipophilicity, i.e. to
replace membrane-donor partition coefficients by solvent-solvent partition coefficients with simple organic lipophilic solvents aiming to mimic the solvent properties of the membrane. Mostly this is the octanol-water partition coefficient \((K_{ow})\) but also mineral oil, olive oil, hexadecane, butadiene, dodecadiene or isopropyl myristate were proposed as suitable model lipids.

### 2.3.1.1. Stratum Corneum Partition Coefficient

For solute partitioning into SC two estimation methods according to a power law (linear free energy relationship) are mostly used.

\[
K_{SC/w} = \alpha (K_{ow})^\beta \text{ or } \log K_{SC/w} = a + \beta \log K_{ow}
\]

(10)

One method is to set \(\alpha = 1\) \((a = 0)\) in Eq. 10 emphasizing the similarity between SC lipids and octanol and fitting Eq. 10 to a database of experimental SC-water partitioning data. Another is to consider both parameters \(\alpha\) and \(\beta\) \((a\ \text{and } \beta)\) for the fitting procedure. Estimates for \(\alpha\) are usually close to 1 while \(\beta\) varies in a broader range between 0.4 and 0.9 depending on the data set used. An exponent \(\beta\) below 1 indicates that the SC lipophilicity is lower than octanol.

A one-phase analysis of partitioning into SC as suggested by Eq. 10 does not reflect the non-linearity seen in the dependence of \(\log K_{SC/w}\) upon \(\log K_{ow}\). These correlations overestimate \(\log K_{SC/w}\) for lipophilic compounds while they underestimate \(\log K_{SC/w}\) for hydrophilic compounds.

In order to separately acknowledge the contributions of lipid and corneocyte phase uptake to the SC partition coefficient Raykar and coworkers derived the following equation:

\[
PC_{intrinsic} = \omega_{pro} \cdot \gamma (K_{ow})^\beta + \omega_{lip} \cdot \epsilon (K_{ow})^\xi
\]

(11)

Here \(PC_{intrinsic}\) refers to the SC partition coefficient based on weight ratio concentrations and dry SC weight, defined as (weight of solute absorbed in SC per unit weight of the original dry SC)/
(wt/wt solute concentration in the adjacent solution). Furthermore, $\omega_{\text{pro}} (= 0.85)$ and $\omega_{\text{lip}} (= 0.15)$ are the weight fractions of the lipid and protein phases constituting the SC. Values for $\gamma$, $\delta$, $\varepsilon$, and $\phi$ were determined by linear regression of partition coefficients into delipidized SC and extracted human SC-lipids upon octanol-water partition coefficients ($\gamma = 0.74$, $\delta = 0.24$, $\varepsilon = 0.15$, and $\phi = 0.91$).

Raykar et al.’s analysis applied to fully hydrated SC assuming that the solvent domain (mainly residing within the corneocytes) has solvent properties of bulk water. Later, Nitsche and coworkers expanded this analysis to quantify the effects of variable hydration.

$$K_{SC/w} = \phi_{\text{cor}} \cdot \omega_{\text{pro}} \cdot \gamma \cdot (K_{ow})^\delta + \phi_{\text{lip}} \cdot \varepsilon \cdot (K_{ow})^\varepsilon$$

(12)

Here $K_{SC/w}$ is the SC partition coefficient based on molar concentrations, defined as (moles of solute absorbed in the SC per unit volume of the hydrated SC)/(mol/V solute concentration in
the adjacent solution). Values for the regression parameters \( \gamma, \delta, \epsilon, \) and \( \omega' \) were determined as (\( \gamma' = 5.4, \delta' = 0.27, \epsilon' = 0.43, \) and \( \omega' = 0.81 \)). Furthermore, \( \varphi_{\text{cor}} \) and \( \varphi_{\text{lip}} \) are the volume fractions of the corneocyte and lipid phases where \( \varphi_{\text{cor}} \) is composed of a protein and a water phase with volume fractions \( \varphi_{\text{pro}} \) and \( \varphi_{\text{w}} \); \( \omega_{\text{pro}} \) and \( \nu \) are the weight fractions of the protein and water phases. All ratios are adjustable according to the hydration state of the membrane. The values for \( \varphi_{\text{cor}} \) and \( \varphi_{\text{lip}}, \omega_{\text{pro}} \) and \( \nu \) required for estimating \( K_{\text{SC}/w} \) for fully (in vitro situation) and partially hydrated skin (in vivo situation) are summarized in Table 3.

Note the different definitions of \( K_{\text{SC}/w}, \ PC_{\text{intrinsic}} \) (and \( \ PC \)) with regards to volume and mass ratios. These coefficients may be converted into each other according to:

\[
PC_{\text{intrinsic}} = PC - \nu
\]

(13)

\[
K_{\text{SC}/w} = \varphi_{\text{pro}} \cdot \rho_{\text{pro}} / \rho_{\text{w}} \cdot PC_{\text{pro}/w} + \varphi_{\text{lip}} \cdot \rho_{\text{lip}} / \rho_{\text{w}} \cdot PC_{\text{lip}/w} + \nu
\]

(14)

\[
K_{\text{pro}/w} = \rho_{\text{pro}} / \rho_{\text{w}} \cdot PC_{\text{pro}/w}
\]

(15)

\[
K_{\text{lip}/w} = \rho_{\text{lip}} / \rho_{\text{w}} \cdot PC_{\text{lip}/w}
\]

(16)
Here $\rho_{\text{pro}}, \rho_{\text{lip}},$ and $\rho_{\text{w}}$ are the densities of the protein, lipid, and water phase. Commonly assumed values for $\rho_{\text{pro}}, \rho_{\text{lip}},$ and $\rho_{\text{w}}$ are 1.37 g/cm³, 0.9 g/cm³, and 1 g/cm³. Furthermore, $PC_{\text{pro/w}}$ and $PC_{\text{lip/w}}$ are the partition coefficients into lipid and protein phase based on weight ratio concentrations and hydrated protein or lipid weight, defined as (weight of solute absorbed in protein or lipid phase per unit weight of hydrated protein or lipid phase)/(wt/wt solute concentration in the adjacent solution). $K_{\text{pro/w}}$ and $K_{\text{lip/w}}$ are the partition coefficients into lipid and protein phase based on molar concentrations and hydrated protein or lipid volume, defined as (moles of solute absorbed in protein or lipid phase per unit volume of hydrated protein or lipid phase)/(mol/V solute concentration in the adjacent solution).

Furthermore, it was discussed whether all corneocyte proteins participate equally to binding absorbed solutes. It was hypothesized that especially under physiological hydration most or all water is bound to SC proteins and therefore not available to dissolve any solute. Consequently only a reduced fraction of corneocyte proteins that is in contact with SC lipids would be exposed to solute and participate in the adsorption. However this hypothesis has not yet been tested for a large dataset of SC partition coefficients.

A major issue that arises with the estimates of $K_{\text{SC/w}}$ and $PC_{\text{intrinsic}}$ in Eq. 11 and 12 is that the values for $\gamma, \delta, \epsilon,$ and $\varepsilon$ were derived for a rather small and homogeneous dataset of experimentally measured partition coefficients into excised SC lipids and isolated corneocyte sheets. Just recently these relationships have been re-investigated. Based on an extensive literature search which was also supplemented by novel experimental measurements especially of hydrophilic solutes a much broader and larger database was collected and improved estimates of $PC_{\text{lip/w}}$ and $PC_{\text{cor/w}}$ were derived. These efforts will be reviewed and summarized within the next sections.
2.3.1.2. Lipid Partition Coefficients

Table 4 presents a comprehensive list of published partition coefficients into SC lipids. Two large datasets of lipid-water partition coefficients were contributed by Raykar et al. who measured equilibrium partition coefficients into solvent extracted lipids from human SC for hydrocortisone esters (HC-esters) with increasing lipophilicity and Johnson who measured several steroids and some other solutes. The same solutes analyzed by Johnson were re-investigated by Mitragotri (plus one additional solute). Mitragotri derived \( PC_{lip/w} \) from permeability and desorption measurements with human skin assuming transport across the SC is by the lipid pathway only. Under this assumption the measured permeability and diffusion coefficients represent permeability and diffusivity within the SC lipids. Thus, taking into account the tortuosity of the lipid path, \( PC_{lip/w} \) was derived (Eq. 4). This analysis over-simplifies SC permeation which is in fact a heterogeneous process with several parallel permeation pathways and repeated partition and diffusion steps. Therefore, Mitragotri’s values have been omitted here. Only recently from our own works and from Wang et al. data for two more hydrophilic solutes (caffeine and theophylline) and a weak acid (flufenamic acid) were added. Still, the dataset presented in Table 4, although spanning a wide range of \( \log K_{ow} \), is heavily dominated by lipophilic data.

Published relationships aiming to predict \( PC_{lip/w} \) from \( K_{ow} \) are summarized in table 5. Similar to Eq. 10 these are power law relationships of \( PC_{lip/w} \) upon \( K_{ow} \):

\[
PC_{lip/w} = \varepsilon (K_{ow})^{\xi}
\]

(17)

Evidently the results for the correlation parameters (\( \varepsilon \) and, if considered, \( \xi \)) depend considerably on the dataset that was used. The difficulty of using data for \( PC_{lip/w} \) that was estimated from permeability data was already discussed above. It shall further be pointed out
that experimental data for \( PC_{lip/w} \) by Raykar et al. in fact only exist for 6 of the 7 HC-esters. In addition, for some of these solutes \( PC_{lip/w} \) was averaged over measured and estimated data. Also, for the more lipophilic esters (1h, HC-21-propionate and onwards) \( PC_{lip/w} \) was calculated according to

\[
PC_{lip/w} = \frac{(PC_{SC/w} - \omega_{cor} \cdot PC_{cor/w})}{\omega_{lip}}
\]  

(18)

using experimental values for \( PC_{SC/w} \), \( PC_{cor/w} \), \( \omega_{lip} \), and \( \omega_{cor} \) rather than measuring \( PC_{lip/w} \) directly.

This procedure was not without problems as for some compounds (e.g. for the more hydrophilic HC-esters, compounds 1a-1g) estimates of \( PC_{cor/w} \) exceeded values of \( PC_{SC/w} \) returning negative values of \( PC_{lip/w} \) which is not feasible.

Nitsche et al. encountered the same problem when they analyzed published SC partition coefficients. As for the majority of these solutes no data for corneocyte and/or lipid partitioning were available they used a published correlation of \( PC_{cor/w} \) upon \( K_{ow} \)

\[
PC_{cor/w} = 5.6 \cdot (K_{ow})^{0.27}
\]  

(19)

to estimate corneocyte phase partitioning. Next they used these estimates of \( PC_{cor/w} \) and experimental values for \( PC_{SC/w} \) to estimate \( PC_{lip/w} \) as described above using mean values for fully hydrated SC for \( \omega_{lip} \) and \( \omega_{lip} \) (table 3).

Due to these problems it was our aim to develop a relationship to predict \( PC_{lip/w} \) strictly avoiding the use of estimated data. After the recent addition of the data for the hydrophilic compounds caffeine and theophylline together with the data by Raykar et al. and Johnson et al. the present analysis includes 17 compounds spanning a wide range of \( \log K_{ow} \) of -0.13 to 5.49 (Table 4). In contrast to Nitsche et al. and Wang et al. we did not a priori exclude the datum for compound 1k (HC-21-octanoate) for lipophilicity reasons. Also, for all ionizable compounds (namely for 1d
Rather than partition coefficients to correct for the ionization state of the compound in the solvent. For compound 1d and lidocaine experimentally measured values for log $K_{\text{pH}}$ exist which were determined at the same pH as $K_{\text{lip/w}}$. Others came from ACD/PhysChem 10.02, Advanced Chemistry Development Inc. (Toronto, Ontario, Canada). The result is a highly significant correlation of log $PC_{\text{lip/w}}$ upon log $K_{\text{pH}}$ ($r^2 = 0.85$) (Table 5, Figure 3). The regression parameters are very similar to those estimated by Wang et al. who used a similarly broad database but did not exclude non-experimentally determined data.

Considering the compositional and structural complexity of SC lipids it may be surprising that partitioning into an isotropic lipid such as octanol is a good surrogate for solute partitioning into SC lipids. Along these lines Johnson investigated whether different liposome systems are more suitable than octanol. Liposomes build organized bilayer systems which should be more similar to the organization of lipids within the SC. Johnson designed SC lipid liposomes (40% (wt/wt) ceramides, 25% (wt/wt) cholesterol, 25% (wt/wt) palmitic acid, 10% (wt/wt) cholesterol sulfate), liposomes of DPPC and DOPC. Surprisingly he could not find a better correlation between any of these liposome systems and SC lipids compared to octanol.

### 2.3.1.3. Corneocyte Protein Partition Coefficients

Similar to the partition coefficients into SC and extracted SC lipids the corneocyte partition coefficient is related to the octanol water partition coefficient (Eqs. 10, 17, and 19), a relationship that was first established by the Anderson group. Particular problems of their work were the small size of the dataset ($n = 16$), the structural similarity of the solutes, and the under-representation of hydrophilic and ionizable solutes ($\log K_{\text{ow}}$ -0.09 to 5.49).

Recently in an attempt to overcome these problems their analysis was re-investigated by two groups (analyses by Wang et al. and Hansen et al.; table 6) and the underlying dataset was greatly increased (31 and 64 data points respectively), the range of compounds was broadened and more hydrophilic solutes were investigated. Also, the suitability of different keratin matrices
to predict the partition coefficient to corneocyte proteins $K_{pro/w}$ was investigated. Apart from delipidized SC, these included delipidized callus, bovine hoof and horn, human nail, human hair, and sheep wool which are structurally and functionally closely related. Delipidized SC, callus, hoof/horn, nail, and wool had been used in the past to evaluate the thermodynamics of keratin swelling in water and to estimate water diffusion coefficients in corneocytes. It was shown that partition coefficients into delipidized SC, callus, and hoof/horn provide suitable estimates for $PC_{pro/w}$. To reconcile the data for hoof/horn with the datasets for delipidized SC and callus log$_{10}PC_{pro/w}$ for hoof/horn was scaled down by a logarithmic factor of 0.6. This data correction reflects the differences between the soft (delipidized SC and callus) and hard keratins (hoof/horn) under the assumption that delipidized SC and callus better represent protein partitioning in intact SC. For nail there were not enough data available to allow meaningful conclusions. The results obtained with hair and wool were considerably different from the other keratin matrices, often including non-linear isotherms which are rarely reported for delipidized SC. Also, binding to hair and wool seemed to be governed by solute molecular weight and ionization state rather than lipophilicity. These differences probably arise from a multitude of reasons, namely (i) varying and often poorly defined experimental conditions under which the results were obtained (data were drawn from the dyeing literature or reports on removal of environmental toxins); (ii) inability of larger molecules (dyes) to penetrate the hair or wool cuticle and reach the keratin protein; and (iii) binding to structures other than keratin, namely melanin or keratin filament associated proteins.

Up to now the separate analyses by Wang et al. and Hansen et al., which in parts differed in the dataset, have never been analyzed completely. Also, in the meantime we have evaluated the partition coefficients of some further solutes (table 7). Therefore any data supplementary to the larger of the two databases (i.e. the Hansen database) is presented in table 7. Again, we did not a priori exclude any data for lipophilicity reasons. A couple of those highly lipophilic compounds that had earlier been excluded from the analysis were in fact weak acids and bases. Therefore, for all ionizable compounds we use distribution coefficients (log$_{10}K_{pH}$) rather than partition
coefficients to correct for the ionization state of the compound in the solvent. If available, experimentally measured values for log$K_{pH}$ were preferred. Others came from ACD/PhysChem 10.02, Advanced Chemistry Development Inc. (Toronto, Ontario, Canada). The complete data from table 7 and the Hansen database was analyzed in Figure 4. For several compounds in the data base log$PC_{pro}$ had been measured at several pH values. To avoid overemphasizing the weight of these compounds on the regression analysis, we took into account those measurements that were taken around or at pH 5.5, reflecting conditions closest to the in vivo environments of the protein. Data for the ionizable compounds are shown again separately in Figure 5.

The results of the regression analysis in Figure 4 are also presented in Table 6. The general relationship between log$PC_{pro/w}$ and log$K_{pH}$ that was established by Raykar et al. is confirmed in the extended analysis. Therefore binding to keratin is largely a lipophilicity- and not a charge driven process. Unanimously all three reports come to the conclusion that the exponent is a little higher than originally predicted by Raykar et al. and probably assumes a value of 0.32 rather than 0.27. Instead, the offset is subject to higher variability. Estimates vary substantially from 4.2 (Wang et al.) to 5.35 (present analysis). The latter value is very close to the value suggested by Nitsche et al. and should be preferred as it currently provides the estimate that is based on the largest and broadest database that has been compiled based on strict inclusion and exclusion criteria without a priori excluding any data.

2.3.2. Diffusion Coefficients
Due to the anisotropic nature of the human skin several microscopic diffusion coefficients play a role in the topical absorption of solutes. It may suffice to consider the individual skin layers as effective media which are characterized by an apparent diffusivity. For example the apparent diffusion coefficient in the SC ($D_{SC}$) averages transverse diffusivity across the SC membrane microstructure. A number of model based estimates of diffusion coefficients in the SC have been developed. Common feature to all of them is an inverse relationship of the diffusion coefficient with permeant size. Early on it could be shown that the diffusion of small compounds in different
cell membranes is similar to the diffusion in polymers suggesting that the relationship between molecular size and diffusion coefficient is exponential rather than linear. The same was proposed to be applicable to solute diffusion in skin. This opened many possibilities to apply diffusion theories originating from polymer research such as free-volume theory, hindered diffusion theory, or scaled particle theory to describe the diffusion in skin. The major concepts that have been applied for this purpose will be summarized below.

2.3.2.1. Poulin-Krishnan Model
For the diffusion in solvents $D$ can be assessed from the Stokes-Einstein equation which was derived from classical continuum theory

$$D = \frac{k_B \cdot T}{(6 \cdot \pi \cdot \eta_0 \cdot r)}$$

(20)

Here $k_B$ is the Boltzmann constant ($1.3806 \cdot 10^{-23}$ J/K), $T$ is temperature, $\eta_0$ is the dynamic solvent viscosity and $r$ is the solute radius assuming a spherical shape of the molecule ($r = (\frac{MV}{N_A}) \cdot \frac{4\pi}{3})^{1/3}$), $MV$ being the molar volume and $N_A$ being Avogadro's number ($6.022 \cdot 10^{23}$ mol$^{-1}$). The size dependence predicted by Eq. 20 is relatively weak. The terms in numerator and denominator can be interpreted in terms of thermal energy and the friction coefficient of the solute. Poulin and Krishnan used Eq. 20 to predict $D_{lip}$ and $D_{cor}$. In this sense they describe diffusion in skin lipids and corneocytes as diffusion processes in layers of solvents, which certainly oversimplifies the situation and underestimates the size dependence of diffusivity in biological membranes. To this end they supplemented $\eta_{lip}$ by the viscosity of olive oil (72 and 43 mPa s at 25 and 37°C respectively). The dynamic viscosity of the corneocytes $\eta_{cor}$ was estimated from experimental data on $D_{cor}$ which was available for tritiated water and methyl nicotinate (24.5 Pa s at 25 °C). These literature values of $D_{cor}$ had mostly been determined from steady state permeability with all implications as discussed above. For toluene they used a different value of $\eta_{cor}$ which was linearly interpolated (16.6 Pa s at 37 °C). Diffusion coefficients estimated in this manner were used in a brick-and-mortar model to predict human abdominal
permeability coefficients for 46 structurally unrelated organic compounds and water. For this purpose, $K_{lip/w}$ of hydrocarbons, amines, ketones, and ethers was set equal to the olive oil-water partition coefficient ($\log K_{o/w} = 1.009 \log K_{ow} - 1.31$, where $\log K_{ow}$ was obtained from the KOWWIN program). For alcohols and acids $K_{ow}$ was used directly as estimated from KOWWIN. $K_{pro/w}$ was estimated from the relationship derived by Anderson and Raykar. For values of lipid, protein, and water volume fractions and lipid and protein diffusion path lengths mean values in human abdominal SC were used as obtained from the literature. A fit of experimental versus predicted $k_P$ produced a highly significant linear correlation ($\log k_{P,exp} = 1.0784 \cdot \log k_{P,pred} + 0.08837$) with $r = 0.95$. Despite these encouraging results the model certainly lacks in rationality in the way the diffusion and partition coefficients are obtained. Therefore it is of limited value as a predictive model.

### 2.3.2.2. Lateral diffusion coefficients in SC lipids

As described above experimental data on lateral diffusion coefficients is available from FRAP and EPR measurements. This data is well expressed by Saffman-Dellbruck diffusion theory which originally had been developed for describing the diffusion of proteins in fluid phase lipid membranes. Key aspect of this theory is a strong size dependence for small solutes whereas for larger solutes a weak size dependence is predicted.

$$D_{lip} = a \cdot MW^{-b} + \left( \frac{k_B \cdot T}{4 \cdot \pi \cdot n_0 \cdot h} \right) \ln \left( \frac{n_0 \cdot h}{n \cdot r_c} \right) - \gamma_e$$

(21)

For reconstituted bilayers of extracted SC lipids Johnson et al. determined the empirical constants $a$ and $b$ were to be $13 \text{ cm}^2/\text{s}$ and $3.75$, respectively. In Eq. 21 $MW$ is solute molecular weight, $h$ is bilayer thickness (or originally the “height” of the protein, which was assumed to span the entire bilayer thickness, i.e. $5.5 \text{ nm}$ in the case of dipalmitoyl phosphatidycholine (DMPC) bilayers, a value that was adopted for SC lipids), $\gamma_e$ is Euler’s constant ($0.5777$), and $r_c$ is solute radius ($r_c$ is related to $MW$ by $r_c = (MW/\pi \cdot h \cdot N_A \cdot \rho)^{1/2}$; all parameters keep their meaning as introduced before). For $n_0$ an empirical value of $2.13$ Pa s was used which can be understood
as the effective SC lipid viscosity. $\eta$ is the viscosity of the solvent (0.7978 mPa s for water at 305 K). Keep in mind that structural parameters that were obtained from DMPC bilayers are probably not fully representative of the SC lipid bilayers. However the complexity of the SC lipid composition and organization makes it difficult to obtain measurements in situ so that the above is probably an adequate substitute.

For extracted SC lipids the transition between strong and weak size dependence occurs at a solute $MW$ of approximately 300 Da. Due to the high degree of order in SC lipids lateral diffusion coefficients measured in excised SC lipid bilayers are considerably smaller than in phospholipid bilayers and the discrimination between large and small molecules is stronger.

Johnson et al. made a case for 120 solutes ($MW$ 18-519 Da, $\log K_{ow}$ -1.38 to 5.49, $\log k_F$ -4.72 to -8.72) that lateral diffusion coefficients sufficiently explained SC permeability. This assumes that corneocytes are impermeable obstacles. As lateral diffusion is typically several orders of magnitude faster than trans-bilayer crossing (evidence is mostly available for phospholipid bilayer systems, e.g. liposomes) a continuous lateral bilayer pathway requires an extraordinarily long pathlength to obtain reasonable lag-times. Nonetheless lag times of water which was the most hydrophilic, smallest and therefore fastest diffusing compound in the database were underestimated considerably (0.3 s) probably due to neglecting corneocyte uptake. There is a body of evidence showing that corneocyte uptake and diffusion plays a role not only for highly water soluble compounds. Also, it must be assumed that for very hydrophilic and charged molecules additional permeation routes, such as the postulated “aqueous pore” pathway will play a role. Nonetheless the study by Johnson and co-workers has a lot of merit both because it is one of the few available sources of experimental values for diffusion coefficients in SC lipids and it inspired the development of a couple of skin absorption models including anisotropic lipid diffusion.

2.3.2.3. **Wang-Kasting-Nitsche model**
The Wang-Nitsche-Kasting model adopts the idea of anisotropic lipid diffusion by differentiating between lateral bilayer diffusion and trans-bilayer crossing. Based on the FRAP and EPR data by Johnson et al. and Hatcher and Platchy they reevaluated the relationship between measured lateral lipid coefficients and molecular weight coming up with a relationship that can be written in a form similar to Eq. 21 as:

\[ D_{lip} = a \cdot MW^b + c \tag{22} \]

The empirical constants have the values \( a = 8.98 \cdot 10^{-3} \text{ cm}^2/\text{s}, b = 2.43, c = 2.34 \cdot 10^{-9} \text{ cm}^2/\text{s}. \) Note that the dependency upon \( MW \) is less pronounced than predicted by Eq. 21. Interesting to note is also the interpretation of constant \( c \) which will set the minimum level of the relationship. It was defined by Mitragotri as the lateral diffusion coefficients of lipid molecules which will limit the diffusion coefficient of molecules which are as large or larger than the lipid molecules (\( MW \approx 400 \text{ Da} \)).

Wang, Kasting, and Nitsche compared two alternative models; one with a continuous lateral diffusion pathway across the entire SC, the other with a discontinuous lateral pathway which requires the permeating solute to hop from one bilayer to the next. For this purpose they defined a mass transfer coefficient \( k_{trans} \). As expected, \( k_{trans} \) decreased with increasing solute size since the difficulty of permeating between adjacent chains in the transitional tight hydrocarbon zones increases with increasing molecular size.

\[ \log k_{trans} = a - b \cdot MW^{1/3} \tag{23} \]

The authors emphasized that the real situation probably lies between the two extremes of fully continuous and fully discontinuous lateral path.
In addition they considered the corneocytes to be permeable. The effective corneocyte diffusion coefficient \( D_{\text{cor}} \) was predicted from classical continuum theory in composite media with fibrous inclusions. Hindered diffusion theory had been used before to explain transdermal absorption results. Peck and coworkers explained the observed high permeability coefficients of hydrophilic solutes (such as urea, mannitol, sucrose, and raffinose) on the basis of a porous pathway and assigned an effective pore radius \((15-25 \text{ Å})\) to this route of absorption.

Wang et al. considered the keratin fibers as being non-accessible for solute diffusion with the non-accessible fiber volume fraction \( \varphi'_\text{fiber} \) being defined as

\[
\varphi'_\text{fiber} = \varphi_\text{fiber} \cdot (1 + \lambda)^2
\]

(24)

Here \( \varphi_\text{fiber} \) is the fiber volume fraction which depends upon hydration (0.19 and 0.60 for fully and partially hydrated corneocytes); \( \lambda \) is the ratio of solute to fiber radius \( \lambda = r_\text{solute}/r_\text{fiber} \) assuming a value of 35 Å for \( r_\text{fiber} \). Binding to keratin fibers was acknowledged by assuming a protein-water partition coefficient. Adsorption and desorption rate constants are assumed to be fast on the time scale relevant for \( D_{\text{cor}} \). Slow desorption processes have been reported in literature and have also recently been integrated into diffusion models of skin absorption. The consequences of slow desorption kinetics will be discussed separately below.

\( D_{\text{cor}} \) was then calculated as

\[
(D_{\text{cor}})_{\text{free}} = D_{\text{aqu}} \cdot (f_{\text{steric}} (\varphi'_\text{fiber}) \cdot f_{\text{hydro}} (\lambda, \varphi_\text{fiber}))
\]

(25)

The diffusion coefficient in water \( D_{\text{aqu}} \) was calculated according to the Wilke-Chang relationship, i.e. in a manner similar to Eq. 21 and 22, assuming that the diffusivity is equal to the diffusivity in bulk liquids (at 30°C).

\[
D_{\text{aqu}} = a \cdot MV^b
\]
For solutes with a molecular volume below or equal to 445.2 the constants in Eq. 26 adopted the values \( a = 1.92 \times 10^{-4} \text{ cm}^2/\text{s} \), and \( b = 0.6 \) and \( r_{\text{solute}} = 0.145 \text{ Å} \cdot \text{MV}^{0.6} \); for large solutes \( a = 3.78 \times 10^{-5} \text{ cm}^2/\text{s} \), \( b = 1/3 \), and \( r_{\text{solute}} = 0.735 \text{ Å} \cdot \text{MV}^{1/3} \). Note that the dependence of diffusivity on solute size is considerably less pronounced than in SC lipids. Similar to lateral lipid diffusivities for larger compounds the size dependence of the aqueous diffusion coefficient is less steep than for smaller compounds. The molecular volume was determined by adding the number of atoms, double/triple bonds and rings in the molecule according to Schroeder’s method.

\[
MV = 7(N_C + N_H + N_O + N_N + 2 \cdot N_DB) + 31.5 \cdot N_Cl + 24.5 \cdot N_F + 38.5 \cdot N_I + 21 \cdot N_S - 7
\]

(27)

The two remaining terms in Eq. 25 are retardation factors due to steric and hydrodynamic hindrance. These are defined as:

\[
f_{\text{steric}}(\varphi_{\text{fiber}}) = 1 - \varphi_{\text{fiber}}
\]

\[
f_{\text{hydro}}(\lambda, 0.19) = 0.9999 - 1.2762 \cdot \lambda + 0.0718 \cdot \lambda^2 + 0.1195 \cdot \lambda^3 \text{ (for fully hydrated skin)}
\]

\[
f_{\text{hydro}}(\lambda, 0.69) = 1.0001 - 2.4497 \cdot \lambda + 1.141 \cdot \lambda^2 + 0.5432 \cdot \lambda^3 \text{ (for partially hydrated skin)}
\]

(28)

The Wang-Nitsche-Kasting model was applied to predict the steady state permeability coefficients of a large database of solutes. Results were expressed as a dimensionless SC permeability \( \left( \frac{P_{\text{SC/\mu}}}{\text{comp}} \right)^{\text{comp}} \) which depends on two dimensionless parameters \( R \) and \( \sigma \). \( R \) denotes the ratio of trans-bilayer to lateral diffusivity \( R = \frac{k_{\text{trans}} \cdot h_s^2}{\delta \cdot D_{\text{lip}}} \) where \( h_s^2 \) depends on hydration (0.132536 cm\(^{-1}\) and 0.141916 cm\(^{-1}\) for fully and partially hydrated SC, respectively). \( \sigma \) denotes the ratio of lipid to corneocyte permeability \( \sigma = \frac{D_{\text{lip}} \cdot K_{\text{lip/\mu}}}{D_{\text{cor}} \cdot K_{\text{cor/\mu}}} \). They could show that within the range of \( R \) that can reasonably be assumed for solutes permeating across human SC
(R and \( k_{\text{trans}} \) typically assume values of \( 1 \leq \log R \leq 4.5 \) and \( -3.5 \leq \log \sigma \leq 1.5 \)) the corneocyte holdup hardly contributes to the total flux through the SC. This is due to the fact that \( k_{\text{trans}} \) and therefore \( R \) is small. In fact \( k_{\text{trans}} \) controls SC permeation for most compounds regardless of their lipophilicity. Nonetheless, uptake into corneocytes was still substantial for a wide a range of solutes as they showed in a companion paper.

### 2.3.2.4. Mitragotri Model

Lateral diffusion equally played a role in the Mitragotri model. The model assumes transport to be confined to the lipid region and the skin appendages. Thus the corneocytes are impermeable and simply serve as obstacles reducing the diffusion area and increasing the path length [12, 13]. The steady state SC permeability was expressed as the sum of the permeability via lateral diffusion, free volume diffusion, diffusion via shunts, and aqueous pores [11].

\[
k_{p,SC} = k_{p,\text{lateral}} + k_{p,\text{free volume}} + k_{p,\text{shunt}} + k_{p,pore}
\]

(29)

Preferences for one or more of the pathways were determined by solute size and lipophilicity. Thus lateral diffusion was relevant for solutes similar or larger in size than the lipid molecules forming the bilayer (> 400 Da). As mentioned above for these solutes the self-diffusion coefficient of the lipids controls solute motion and sets a lower limit to \( D_{\text{lip}} \). Thus \( D_{\text{lip,lateral}} \) was estimated as \( 3 \cdot 10^{-9} \text{ cm}^2/\text{s} \) from the relationship established by Johnson et al.

Free volume diffusion through the SC lipids was relevant for small lipophilic molecules (< 400 Da). An average lipid diffusion coefficient was predicted according to scaled particle theory which describes diffusion as a statistical process. A molecule of a defined size requires the formation of a sufficiently large cavity right next to it created by density fluctuations in the lipid chains. The free volume diffusion coefficient \( D_{\text{lip,free volume}} \) is related to the work required to create such a cavity and can be estimated according to the empirical relationship

\[
D_{\text{lip,free volume}} = a \cdot \exp(-b \cdot r^2)
\]
where \( a = 2 \cdot 10^{-5} \) cm\(^2\)/s, and \( b = 0.46 \). The solute radius \( r \) enters Eq. 30 in Å.

For shunt diffusion across skin appendages such as hair follicles and sweat ducts they estimated a representative diffusion coefficient \( D_{\text{shunt}} = 1 \cdot 10^{-6} \) cm\(^2\)/s. In principle shunt diffusion could also be estimated by Stokes-Einstein or Wilke Chang theory however as it was found to be relevant only for very large hydrophilic solutes \((MW > 100 \text{ kDa})\) the dependence of \( D_{\text{shunt}} \) upon molecular size was ignored. The permeation across skin appendages has been shown by others to be relevant for the absorption of several solutes at very early time points in permeation. Hair follicles furthermore play a role in the absorption of nanoparticles.

Pore diffusion was estimated based on hindered diffusion theory. Pores are imperfections of the lipid bilayers and were shown to be the major “polar pathway” for hydrophilic solutes.

\[
D_{\text{pore}} = \frac{2.6 \cdot 10^{-5}}{r_h} \int_0^r H(\lambda) \gamma(r_{\text{pore}}) dr_{\text{pore}}
\]

(31)

Here \( r_s \) will be the solute molecular radius, \( \gamma(r_{\text{pore}})dr_{\text{pore}} \) will describe pore size distribution as a function of pore radius, where

\[
\gamma(r_{\text{pore}}) = \mu \cdot \exp(-\vartheta \cdot r_{\text{pore}}^2)
\]

(32)

With \( \mu \) and \( \vartheta \) being constants describing pore size distribution and assuming the values \( \mu = 0.024 \) and \( \vartheta = 0.00045 \) for porcine skin. Furthermore the hydrodynamic hindrance factor \( H(\lambda) \) was estimated for \( \lambda < 0.4 \) (with \( \lambda = r_s/r_{\text{pore}} \)), i.e. for small solutes as

\[
H(\lambda) = (1-\lambda)^2 \cdot (1 - 2.104 \cdot \lambda + 2.09 \cdot \lambda^2 - 0.95 \cdot \lambda^3)
\]

(33)
Mitragotri employed the model to predict steady state permeability coefficients of a large number of compounds (the same dataset that had already been evaluated by Johnson et al.) and compared the model with other predictions from the literature, notably the Potts-Guy QSPR-equation which relies on absorption via a single (lipophilic) pathway. While both models performed equally well to predict the permeability of lipophilic solutes only the Mitragotri model correctly expressed the dependence of skin permeability on molecular weight of hydrophilic solutes.

2.4. UNRESOLVED ISSUES
The overview that is presented here gives the impression that a very detailed description of diffusion in the SC is already possible based on the available approximation for partition and diffusion coefficients. Certainly, there is no doubt that the more complex models such as the Wang-Nitsche-Kasting model and the Mitragotri model have greatly moved the field forward, especially improving predictions of the steady-state permeability of hydrophilic solutes by integrating a “polar pathway”. What also becomes clear especially with these two models, which have been discussed in more detail than others, is that there is still “the true nature” of the permeation pathways of lipophilic and hydrophilic solutes is still actively discussed. A number of issues that are important for transdermal absorption have been addressed theoretically. The overview provided in table 1 and 2 shows that computational frameworks are available to tackle questions such as the vertical heterogeneity of SC, slow desorption kinetics from keratin, clearance by dermal blood flow and lymphatic drainage, co-permeation of formulation ingredients, evaporation of volatile formulation components, absorption from finite doses, and absorption from non-aqueous formulations to name but a few.

A phenomenon which is particularly well described qualitatively is the vertical heterogeneity of the SC. However the quantitative consequences, or depth dependent changes in partition and diffusion coefficients and hence permeability are less clear. As noted before describing the SC as a homogeneous membrane is an oversimplification which is however useful for certain purposes. Depth dependent changes of SC morphology have been observed both with the lipids as well as
with the cellular phase of the SC. The progressive degradation of corneodesmosomes towards the skin surface leads to a different cellular cohesion within SC disjunctum and SC conjunctum possibly enhancing corneocyte uptake. Also, within the SC disjunctum lipid conformational ordering is disturbed and lipid fluidity is increased possibly due to a mixing with sebum lipids which spread across the skin surface. An increase in lipid alkyl chain disorder has been correlated to an increase in the permeability of water. Both factors hint that the permeability should be greater in the SC disjunctum than in the SC conjunctum. Interestingly, Mueller et al. reported biphasic steady-state tape stripping profiles for clobetasol propionate applied to human heat separated epidermis in vitro as saturated solutions containing 20% v/v propylene glycol. The curvature of the concentration-depth profile was steeper over the first three tapes than from tape four onwards. This may be interpreted as an increased corneocyte uptake or an increased intercellular solubility and diffusivity within the SC disjunctum which is in line with the morphological changes described above.

However, there are other factors which hint to the opposite. Across the SC a hydration gradient runs from typically 20% at the skin surface to 60% at the SC-epidermal interface in partially hydrated SC, and from 50% to 70% in fully hydrated SC. The inhomogeneous swelling throughout the SC is supposed to be due to an incomplete degradation of filaggrin in the corneocyte layers that are close to the epidermis. Degradation products would typically work as osmotic agents (“natural moisturizing factors”) that increase swelling. It is well known that water is a very efficient enhancer to its own permeation as well as to the absorption of other solutes. This leads to the conclusion that the lower SC layers should be more permeable than the upper layers in partially hydrated SC and that excessive hydration such as through the application of an occlusive dressing should especially affect the permeability in the upper SC layers. It is thus clear that the implications of the observed morphological changes on permeability are probably multi-factorial. Diffusion models may help to improve our understanding in this direction. Anissimov and Roberts have looked at different combinations of depth dependent changes in partition and/or diffusion coefficients. It was shown that variations
in the partition coefficient have a more pronounced effect on the predicted fluxes than changes in the diffusion coefficient.

Another topic which has received much attention recently, are slow equilibration processes which prohibit the use of an effective diffusion coefficient. These can arise from slow desorption kinetics from corneocyte proteins such as keratin, desmosomal proteins and proteins of the cornified envelope. Alternatively, an additional diffusion hindrance by the cornified envelop may also explain slow desorption of solutes from SC. Especially from simulation studies the effects of slow equilibration processes on tissue levels, lag time and the amount permeated over time are well established. Bound substance will be removed from the pool of diffusing solute. Furthermore, slow desorption rate constants will retard the effective corneocyte diffusion and lead to sustained tissue levels. The effect may be significant especially for lipophilic compounds as for these compounds a high protein binding is to be expected. According to chemical equilibrium theory equilibrium binding constants and adsorption \( (k_{on}) \) and desorption rate constant \( (k_{off}) \) are related according to:

\[
P_{\text{pro/w}} = \frac{k_{on}}{k_{off}}
\]

Thus the retardation effect should be more pronounced the more lipophilic a compound is. It is important to realize that the combined effects of increased solute hold-up and decreased effective diffusivity will cancel out in the permeability coefficient. However, the lag-time will certainly be affected. Following the line of thought initiated by Eq. 34 the adsorption and desorption rate constants are connected to a parameter that is typically influenced by lipophilicity in contrast to diffusion coefficients which depend on molecular size. While equilibrium binding to corneocyte proteins is well documented as summarized in the previous chapters, detailed kinetic measurements have only been performed for the desorption of water from SC. Very few further compounds have been investigated at all. For the organophosphorus chemical warfare agent sarin desorption rate constants from powdered human callus are
available, but only into organic solvents which are not representative for the aqueous corneocyte environment. Recently, a desorption rate constant of theophylline has been estimated from fitting infinite dose permeation data across epidermal membrane. The next step in order to test the significance of slow desorption kinetics for predicting dermal absorption will be to obtain reliable desorption data from keratin for a larger number of solutes with varying lipophilicity. According to Eq. 34 it should be possible to correlate adsorption and desorption rate constants to solute lipophilicity which offers possibilities of using such a relationship in a predictive way.

3. CONCLUSIONS

We have reviewed relationships to predict partition and diffusion coefficients in the SC that are required for diffusion models. Microscopic SC models which take into account solute partitioning into lipids and corneocyte are well established. Lately a lot of progress has been made especially concerning the prediction of solute partitioning into corneocytes which was based on a much larger and broader database. The same is repeated here for lipid partition coefficients which greatly solidified the correlations of both parameters upon log $K_{ow}$ and will improve predictions of the macroscopic SC-water partition coefficient.

With diffusion coefficients the situation is more complex. Due to the still ongoing discussion of lipophilic and polar absorption routes across the SC the representation of these pathways varies greatly between individual models which therefore require very different diffusion coefficients or mass transfer coefficients. A plethora of theories has been used to obtain estimates. As a common principle all diffusion and mass transfer coefficients are inversely related to a measure of molecular size. The strength of this size dependence may be different (less pronounced in an aqueous environment than in the highly organized SC lipid bilayers, more pronounced in bilayer crossing than in lateral diffusion). In the future it will be important to develop and improve
estimates also of other input parameters to improve describing observed features such as outlined for the vertical heterogeneity of SC morphology and slow equilibration processes.
4. **Tables and Figures**

4.1. **Tables**

Table 1  Diffusion models with pseudo-homogeneous representation of the SC.

<table>
<thead>
<tr>
<th>Source</th>
<th>Model complexity</th>
<th>Applications</th>
<th>Input data</th>
<th>Phys.-chem.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Skin layers</td>
<td>Non-ss</td>
<td>Special features</td>
<td>Fit exp. data</td>
</tr>
<tr>
<td>Chandrasekaran (1980)</td>
<td>1</td>
<td></td>
<td>Binding</td>
<td>x</td>
</tr>
<tr>
<td>Tang (2002)</td>
<td>1 x</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Pirot (1997)</td>
<td>1 x</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Kalia (2001)</td>
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<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Kubota (1993)</td>
<td>1 x</td>
<td></td>
<td>Binding</td>
<td>x</td>
</tr>
<tr>
<td>Gumel (1998)</td>
<td>1 x</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>George (2004)</td>
<td>1 x</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>George (2005)</td>
<td>1 x</td>
<td></td>
<td>Binding</td>
<td>x</td>
</tr>
<tr>
<td>Anissimov (2009)</td>
<td>1 x</td>
<td></td>
<td>Binding</td>
<td>x</td>
</tr>
<tr>
<td>Frasch (2011)</td>
<td>1 x</td>
<td></td>
<td>Binding</td>
<td>x</td>
</tr>
<tr>
<td>Kasting (2001)</td>
<td>1 x</td>
<td></td>
<td>Finite dose</td>
<td>x</td>
</tr>
<tr>
<td>Kasting (2006)</td>
<td>1 x</td>
<td></td>
<td>Finite dose, Evaporation</td>
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<td>Watkinson (1992)</td>
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<td>Variable D, Enhancer</td>
<td>x</td>
</tr>
<tr>
<td>Anissimov (2004)</td>
<td>1 x</td>
<td></td>
<td>Variable D and/or K</td>
<td>x</td>
</tr>
<tr>
<td>Rim (2005)</td>
<td>1 x</td>
<td></td>
<td>Finite dose, Enhancer, Binding</td>
<td>x</td>
</tr>
<tr>
<td>Anissimov (1999)</td>
<td>2 x</td>
<td></td>
<td>Clearance, Unstirred layers</td>
<td>x</td>
</tr>
<tr>
<td>Anissimov (2001)</td>
<td>2 x</td>
<td></td>
<td>Finite dose, Clearance, Unstirred layers</td>
<td>x</td>
</tr>
<tr>
<td>Chaudhuri (2009)</td>
<td>2 x</td>
<td></td>
<td>Finite dose, Evaporation, Capillary sorption</td>
<td>x</td>
</tr>
<tr>
<td>Krüse (2007)</td>
<td>2 x</td>
<td></td>
<td>Exposure scenarios, Finite dose</td>
<td>x</td>
</tr>
<tr>
<td>Kretsos (2004)</td>
<td>3 x</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Manitz (1998)</td>
<td>3 x</td>
<td></td>
<td>Enhancers &amp; retarders</td>
<td>x</td>
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</tbody>
</table>

non-ss: non-steady state; exp.: experimental; sim.: simulation; pred.: prediction; phys.-chem.: physico-chemical
### Table 2
Diffusion models with brick-and-mortar representation of the SC.

<table>
<thead>
<tr>
<th>Source</th>
<th>Model complexity</th>
<th>Applications</th>
<th>Input data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Skin layers</td>
<td>2D</td>
<td>3D</td>
</tr>
<tr>
<td>Michaels (1975)</td>
<td>1</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Poulin (2001)</td>
<td>1</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Johnson (1997)</td>
<td>1</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Mitragotri (2003)</td>
<td>1</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Wang (2006/07)</td>
<td>1</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Frasch (2003)</td>
<td>1</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Barbero (2005)</td>
<td>1</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Heisig (1996)</td>
<td>1</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Chen (2008)</td>
<td>1</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Naegel (2008)</td>
<td>2</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Rim (2007)</td>
<td>1</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Feuchter (2006)</td>
<td>1</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

cor. access.: corneocytes accessible; non-ss: non-steady state; sim: simulation; pred.: prediction; exp.: experimental; phys.-chem.: physico-chemical
Table 3  Compositional parameters characterizing the SC microstructure according to

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Fully hydrated</th>
<th>Partially hydrated</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\phi_{cor}$ ($=\phi_{pro} + \phi_{w}$)</td>
<td>0.9684</td>
<td>0.9073</td>
</tr>
<tr>
<td>$\phi_{lip}$</td>
<td>0.0316</td>
<td>0.0927</td>
</tr>
<tr>
<td>$\omega_{pro}$</td>
<td>0.90</td>
<td>0.90</td>
</tr>
<tr>
<td>$\nu$</td>
<td>2.75</td>
<td>0.43</td>
</tr>
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</table>
Table 4  List of published values for $P_{lip/w}$.

<table>
<thead>
<tr>
<th>compound</th>
<th>log$K_{ow}$</th>
<th>log$P_{lip/w}$</th>
<th>log$P_{lip/w}$</th>
<th>literature</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>a</td>
<td>b (experim.)</td>
<td>b (calcul.)</td>
<td></td>
</tr>
<tr>
<td>1a, HC-21-succinamat</td>
<td>1.43</td>
<td>1.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1d, HC-21-hemisuccinate</td>
<td>2.11</td>
<td>1.15</td>
<td></td>
<td></td>
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<tr>
<td>1g, HC-21-hydroxyhexanoate</td>
<td>2.79</td>
<td>1.58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1h, HC-21-propionate</td>
<td>3.00</td>
<td>1.84 c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1i, HC-21-methylpimelate</td>
<td>3.70</td>
<td>2.62</td>
<td>2.72 d</td>
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</tr>
<tr>
<td>1j, HC-21-hexanoate</td>
<td>4.48</td>
<td>3.30</td>
<td>3.20 d</td>
<td></td>
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<tr>
<td>1k, HC-21-octanoate</td>
<td>5.49</td>
<td>4.20</td>
<td>4.20 d</td>
<td></td>
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<tr>
<td>aldosterone</td>
<td>1.08</td>
<td>0.90</td>
<td></td>
<td></td>
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<td>hydrocortisone</td>
<td>1.94</td>
<td>1.52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>lidocaine</td>
<td>2.48</td>
<td>1.38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>naphthol</td>
<td>2.84</td>
<td>2.98</td>
<td></td>
<td></td>
</tr>
<tr>
<td>testosterone</td>
<td>3.31</td>
<td>1.91</td>
<td></td>
<td></td>
</tr>
<tr>
<td>progesterone</td>
<td>3.77</td>
<td>3.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>estradiol</td>
<td>3.86</td>
<td>2.25</td>
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<td></td>
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<td>caffeine</td>
<td>-0.13</td>
<td>0.33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>flufenamic acid</td>
<td>2.57 e</td>
<td>1.31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>theophylline</td>
<td>-0.02</td>
<td>0.26</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Unless noted otherwise values for log$K_{ow}$ came from ACD/PhysChem 10.02, Advanced Chemistry Development Inc. (Toronto, Ontario, Canada). For the hydrocortisone esters (Raykar et al. 1988 and Anderson et al. 1988) values for log$K_{ow}$ were measured by themselves. For the data by Johnson (Johnson 1996) values for log$K_{ow}$ were measured by themselves. log$K_{ow}$ for theophylline was taken from the database of experimental log$K_{ow}$ values by Hansch et al. 1995.

b experimental data

c Data for compound 1h, HC-21-propionate, was calculated according to equation 15.

d Data for compounds 1i, 1j, and 1k represent averages over experimental and calculated data.

e For flufenamic acid we use log$K_{pH}$ for pH 7.4 instead of log$K_{ow}$ as $P_{lip/w}$ was measured in phosphate buffer pH 7.4.
Table 5  Comparison of published relationships to predict $PC_{lip/w}$.

<table>
<thead>
<tr>
<th></th>
<th>Data points</th>
<th>Range $logK_{ow}$</th>
<th>$\varepsilon$</th>
<th>$r^2$</th>
<th>$PC_{lip/w}$ data</th>
<th>$PC_{lip/w}$ data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>exp.</td>
<td>calc.</td>
</tr>
<tr>
<td>Raykar et al. '88</td>
<td>3</td>
<td>3.70 - 5.49</td>
<td>0.15</td>
<td>0.91</td>
<td>x</td>
<td>---</td>
</tr>
<tr>
<td>Johnson '96</td>
<td>15</td>
<td>1.08 - 5.49</td>
<td>---</td>
<td>0.76</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Nitsche et al. '06 (Eq. 9)</td>
<td>7</td>
<td>1.43 - 5.49</td>
<td>0.39</td>
<td>0.81</td>
<td>0.98</td>
<td>x</td>
</tr>
<tr>
<td>Nitsche et al. '06 (Eq. 10)</td>
<td>46</td>
<td>-0.07 - 4.90</td>
<td>0.48</td>
<td>0.81</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Wang et al. '10 (Eq. 8a)</td>
<td>15</td>
<td>-0.13 - 4.48</td>
<td>---</td>
<td>0.69</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Wang et al. '10 (Eq. 8b)</td>
<td>15</td>
<td>-0.13 - 4.48</td>
<td>1.66</td>
<td>0.62</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Present analysis</td>
<td>16</td>
<td>-0.13 - 5.49</td>
<td>1.32</td>
<td>0.67</td>
<td>0.85</td>
<td>x</td>
</tr>
</tbody>
</table>

*a Raykar et al. used only their own experimental data (compounds 1i, 1j, and 1k).

*b Johnson used his own and the entire Raykar et al. and Anderson et al. dataset (compounds 1a, 1d, 1g, and 1h calculated data; compounds 1i, 1j, and 1k averaged over calculated and experimental data)

*c In Eq. 9 Nitsche et al. used the entire Raykar et al. and Anderson et al. dataset (as described for Johnson).

*d In Eq. 10 Nitsche et al. used the entire Raykar et al. and Anderson et al. dataset (as described for Johnson). For further compounds they estimated $K_{lip/w}$ from published experimental data on $K_{sc/w}$ and data on $K_{cor/w}$ estimated according to equation 16 using mean values for fully hydrated SC for $\omega_{lip}$ and $\omega_{cor}$ (table 3).

*e Wang et al. used the entire Raykar et al. and Anderson et al. data (as described for Johnson), plus the data by Johnson, Hansen et al., and their own.

*f The present analysis used only experimentally determined data by Raykar et al., Johnson, Wang et al., and our own.
Nitsche et al. predict $K_{lip/w}$. Values for ε reported by Nitsche were corrected for the difference between $PC_{lip/w}$ and $K_{lip/w}$ according to $\varepsilon_{corr} = \varepsilon/0.9$ as $K_{lip/w} = PC_{lip/w} \cdot \rho_{lip}/\rho_w$ with $\rho_{lip} = 0.9$ g/cm$^3$ and $\rho_w = 1$ g/cm$^3$. 
Table 6  Comparison of published relationships to predict $P_{C_{pro/w}}$

<table>
<thead>
<tr>
<th></th>
<th>Data points</th>
<th>Range log$K_{ow}$</th>
<th>Range log$K_{ph}$</th>
<th>$\varepsilon$</th>
<th>$r^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raykar et al. '89</td>
<td>16 $^a$</td>
<td>-0.09 to 5.49</td>
<td>---</td>
<td>5.6</td>
<td>0.27</td>
</tr>
<tr>
<td>Wang et al. '10</td>
<td>31 $^b$</td>
<td>-0.90 to 4.48</td>
<td>---</td>
<td>4.2</td>
<td>0.31</td>
</tr>
<tr>
<td>Hansen et al. '11</td>
<td>64 $^c$</td>
<td>---</td>
<td>-4.67 to 5.49</td>
<td>4.47</td>
<td>0.32</td>
</tr>
<tr>
<td>Present analysis</td>
<td>71 $^d$</td>
<td>---</td>
<td>-4.67 to 5.49</td>
<td>5.35</td>
<td>0.32</td>
</tr>
</tbody>
</table>

$^a$ Raykar et al. used only their own experimental data. All experiments were performed with delipidized SC.

$^b$ Wang et al. used their own experimental data, the entire Raykar et al. and Anderson et al. dataset, the data from Hansen et al. and Surber et al. All experiments were performed with delipidized SC.

$^c$ Hansen et al. used their own experimental data, the entire Raykar et al. and Anderson et al. dataset, Surber et al., as well as the data from Hagedorn-Leweke et al., and Sobue et al. These included data obtained with delipidized SC, callus, and hoof/horn.

$^d$ The present analysis used all data analyzed in Hansen et al. supplemented by unpublished data by the authors and the data by Wang et al., Mohorcic et al., and Romonchuk et al. These included data obtained with delipidized SC, callus, and hoof/horn. For those compounds which had been inspected at several pH values the data that were obtained closest to pH 5.5 were used.
Table 7  
Supplement to the extended database of keratin binding published in .

<table>
<thead>
<tr>
<th>Substance</th>
<th>MW</th>
<th>log(K_{ow})</th>
<th>Keratin</th>
<th>Vehicle</th>
<th>(T) [°C]</th>
<th>log(PC_{pro/w})</th>
<th>Literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>metformine</td>
<td>129</td>
<td>-3.82</td>
<td>Hoof/horn</td>
<td>Tris 7.5</td>
<td>32</td>
<td>-0.37</td>
<td>b</td>
</tr>
<tr>
<td>propranolol</td>
<td>259</td>
<td>1.3</td>
<td>Hoof/horn</td>
<td>Soer 7.4</td>
<td>32</td>
<td>1.60</td>
<td>b</td>
</tr>
<tr>
<td>flufenamic acid</td>
<td>281</td>
<td>3.8</td>
<td>Hoof/horn</td>
<td>Soer 5.5</td>
<td>32</td>
<td>2.17</td>
<td>b</td>
</tr>
<tr>
<td>caffeine</td>
<td>194</td>
<td>-0.13</td>
<td>Hoof/horn</td>
<td>Soer 7.4</td>
<td>32</td>
<td>-0.12</td>
<td>b</td>
</tr>
<tr>
<td>theophylline</td>
<td>180</td>
<td>-0.04</td>
<td>Hoof/horn</td>
<td>Soer 7.4</td>
<td>32</td>
<td>-0.10</td>
<td>b</td>
</tr>
<tr>
<td>theophylline</td>
<td>180</td>
<td>-0.20</td>
<td>Delip. SC</td>
<td>PBS 7.4</td>
<td>25</td>
<td>0.78</td>
<td></td>
</tr>
<tr>
<td>tegafur</td>
<td>200</td>
<td>-0.81</td>
<td>Delip. SC</td>
<td>PBS 7.4</td>
<td>25</td>
<td>0.69</td>
<td></td>
</tr>
<tr>
<td>thiamazole</td>
<td>114</td>
<td>-2.74</td>
<td>Delip. SC</td>
<td>PBS 7.4</td>
<td>25</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td>cefazoline</td>
<td>455</td>
<td>-2.58</td>
<td>Delip. SC</td>
<td>PBS 7.4</td>
<td>25</td>
<td>0.62</td>
<td></td>
</tr>
<tr>
<td>cefoperazone</td>
<td>646</td>
<td>-2.28</td>
<td>Delip. SC</td>
<td>PBS 7.4</td>
<td>25</td>
<td>0.55</td>
<td></td>
</tr>
<tr>
<td>5-fluorouracil</td>
<td>130</td>
<td>-0.89</td>
<td>Delip. SC</td>
<td>PBS 7.4</td>
<td>25</td>
<td>0.51</td>
<td></td>
</tr>
<tr>
<td>oxytetracycline</td>
<td>460</td>
<td>-2.34</td>
<td>Delip. SC</td>
<td>PBS 7.4</td>
<td>25</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td>methyl paraben</td>
<td>152</td>
<td>1.83</td>
<td>Delip. SC</td>
<td>PBS 7.4</td>
<td>32</td>
<td>1.03</td>
<td></td>
</tr>
<tr>
<td>4-cyanophenol</td>
<td>119</td>
<td>1.45</td>
<td>Delip. SC</td>
<td>PBS 7.4</td>
<td>32</td>
<td>1.19</td>
<td></td>
</tr>
</tbody>
</table>

\(a\) exp. value determined at pH 7.4

\(b\) corr. value; log\(PC_{pro/w}\) values measured with BHH were corrected for the difference in offset obtained for different keratin matrices by subtracting a constant value of 0.6.

\(c\) Hansen et al. Unpublished data

\(d\) For propranolol, flufenamic acid, tegafur, cefazoline, cefoperazone, 5-fluorouracil, and oxytetracyclin we used log\(K_{ph}\) for pH 7.4 instead of log\(K_{ow}\) as \(PC_{pro/w}\) was measured in phosphate buffer pH 7.4.
4.2. Figures

**Figure 1** A three-layer brick-and-mortar skin model considering inter- and trans-cellular pathways across the SC is transcribed into a circuit with parallel and serial resistors. (Not drawn to scale)

**Figure 2** Parameter set required for the three-layer brick-and-mortar model depicted in Figure 1 with microscopic partition and diffusion coefficients in the SC. $K_{lip/w}$, $K_{cor/w}$, $K_{epi/SC}$, and $K_{der/epi}$ are the partition coefficients between lipids and aqueous vehicle, corneocytes and aqueous vehicle, epidermis and SC, dermis and epidermis. $\phi_{lip}$ and $\phi_{cor}$ are the volume fractions of lipids and corneocytes within the SC, the apparent partition coefficient between SC and aqueous vehicle is defined as $K_{SC/w} = \phi_{lip} K_{lip/w} + \phi_{cor} K_{cor/w}$. $D_{lip}$, $D_{cor}$, $D_{epi}$, and $D_{der}$ are the diffusion coefficients in lipids, corneocytes, epidermis and dermis. (Not drawn to scale)

**Figure 3** Log-log plot showing the dependence of $PC_{lip/don}$ upon $K_{pH}$. Only experimental values of $\log PC_{lip/don}$ are considered. Filled squares (■) represent experimental data by Raykar et al. Open circles (○) represent experimental data by Johnson. Filled triangles (▲) represent experimental data by Hansen et al. Open stars (★) represent experimental data by Wang et al. The solid curve (—) represents a least squares fit.

**Figure 4** Log-log plot showing the dependence of $PC_{pro/w}$ upon $K_{pH}$. Filled squares (■) represent data obtained with hoof/horn, $\log PC_{pro/w}$ values were corrected for the difference in offset obtained for different keratin matrices by subtracting 0.6. Open circles (○) represent data
obtained with callus. Open triangles (▲) represent data obtained with delipidized SC. The solid curve (−) represents a least squares fit over the entire data set of 71 data points.

**Figure 5** Log-log plot showing the dependence of $PC_{\text{pro/w}}$ upon $K_{\text{pH}}$. Only acids and bases are considered. Filled symbols represent acids, open symbols represent bases. Squares (■,□) represent data obtained with BHH, $\log PC_{\text{pro/w}}$ values were corrected for the difference in offset obtained for different keratin matrices by subtracting a constant value of 0.6. Triangles (▲,▲) represent data obtained with DSC. The solid curve (−) represents a least squares fit over the entire data set of 71 data points.
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Figure 5  Log-log plot showing the dependence of $PC_{\text{pro/w}}$ upon $K_{\text{pH}}$. Only acids and bases are considered. Filled symbols represent acids, open symbols represent bases, partially filled symbols represent solutes with both acidic and basic groups. Squares (■, □) represent data obtained with BHH, log$PC_{\text{pro/w}}$ values were corrected for the difference in offset obtained for different keratin matrices by subtracting a constant value of 0.6. Triangles (▲, △) represent data obtained with DSC. The solid curve (−) represents a least squares fit over the entire data set of 71 data points.
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