Modeling of composite sorption isotherm for stratum corneum

Ivan Argatov a, b, c, Johan Engblom a, b, Vitaly Kocherbitov a, b, * 

a Faculty of Health and Society, Malmö University, SE-205 06 Malmö, Sweden 
b Biofilms – Research Center for Biointerfaces, Malmö University, SE-205 06 Malmö, Sweden 
c Institut für Mechanik, Technische Universität Berlin, 10623 Berlin, Germany

1. Introduction

Stratum corneum (SC) is the very outer skin layer, whose most important function is to provide an efficient biobarrier to the loss of body water and, generally, to molecular diffusion of chemicals from the environment [1]. The SC can be regarded as a biological composite material [2], primarily, formed by corneocytes (i.e., dead keratin filled cells) embedded in a lipid matrix [3]. A significant body of evidence points to an involvement of the morphology of the SC in facilitating its exceedingly low permeability to water transport [4].

Sorption isotherm is a functional relationship between water content in a material sample and equilibrium relative humidity of the surrounding environment kept under constant temperature [5]. Usually [6], sorption isotherms are given in terms of water activity, \(a_w\), and absorption ratio, \(r_w\), defined as the ratio of the mass of absorbed water to the mass of dry material sample. An accurate modeling of sorption isotherm for stratum corneum is needed for and applied in solving the problem of water diffusion through the stratum corneum membrane, which is of paramount importance for understanding barrier functions of skin [7, 8].

The role of lipids on the water sorption of keratinized tissues like SC was studied in a number of papers [9–11], and the sorption isotherm data for SC were modeled by utilizing the BET (Brunauer–Emmett–Teller) and GAB (Guggenheim–Anderson–de Boer) models, however, without distinguishing the individual contribution of lipids to the SC sorption isotherm. On the other hand, it is known that the lipid content in SC may vary both in healthy [12] and diseased [13] tissues. Therefore, it is of substantial practical utility for applications in biomedicine [14–16] and cosmetology [11, 17] to develop a composite sorption isotherm model for SC that allows highlighting the effect of the lipid content on the variance of the SC sorption isotherm.

Let us recall [18] Onsager’s generalization [19] of Fick’s law [20] developed in the framework of the irreversible thermodynamics approach, which can be written as

\[
J_z = -D(z) \frac{C_w}{RT} \frac{\partial \mu}{\partial z}
\]

Here, \(J_z\) is the flux density (flux per unit area) in the direction of the \(z\) axis, \(C_w\) is the concentration of water (mass/volume), \(R\) and \(T\) are the universal gas constant and the temperature, respectively, \(D(z)\) is the so-

Equilibrium water sorption in stratum corneum (SC) is considered by treating it as a biocomposite with two main phases, namely, corneocytes and lipids. To validate the rule of mixtures for the individual phase sorption isotherms, a new flexible fitting model is introduced by accounting for characteristic features observed in the variations of the thermodynamic correction factors corresponding to the individual sorption isotherms. The comparison of the model fitting performance with that of the five-parameter Park’s model shows a remarkably good ability to fit experimental data for different types of sorption isotherms. The effect of the lipids content on the variance of the composite sorption isotherm of stratum corneum is highlighted. The sensitivity analysis reveals that for the typical water content 20–30 wt%, which corresponds to the SC in a stable condition, the sensitivity of the composite sorption isotherm to the variation of the lipids content on dry basis is predominantly positive and sufficiently small. The good agreement observed between the experimental sorption isotherm for SC and the composite isotherm, which is based on the rule of mixtures for the individual phase sorption isotherms, yields a plausible conclusion (hypothesis) that the corneocytes-lipids mechanical interaction during unconstrained swelling of the SC membrane in the in vitro laboratory experiment is negligible.
called thermodynamic diffusion coefficient, and \( \mu \) is the chemical potential, which is related to the water activity via the relation \( \mu = \mu_0 + RT \ln a_w \).

Thus, in view of Eq. (1), the Fick's diffusion coefficient, \( D \), can be expressed in terms of the thermodynamic diffusion coefficient as follows:

\[
D = D_0 \frac{\partial a_{\text{w}}}{\partial a_{\text{w}}} 
\]

The simple formula above shows that the sorption isotherm, which gives the relation between \( a_w \) and \( C_{\text{w}} \), is needed to establish the relation between the Fick and thermodynamic diffusivities, \( D \) and \( D_0 \). It is to note that thermodynamic aspects of the sorption/desorption process have been considered in detail elsewhere [21,22].

Considering equilibrium water sorption by SC and its phases, we introduce the following absorbed mass ratios:

\[
r_{\text{w}} = \frac{m_{\text{w}}}{m_0}, \quad r_i = \frac{m_i}{m_0}, \quad r_{\text{w},\text{SC}} = \frac{m_{\text{w},\text{SC}}}{m_0} = \frac{m_{\text{w}} + m_1}{m_0}, 
\]

Here, \( m_{\text{w}} \), \( m_i \), and \( m_{\text{w},\text{SC}} \) are the masses of absorbed water by corneocytes, lipids, and stratum corneum, respectively, whereas their masses on dry basis are denoted respectively as \( m_0 \), \( m_1 \), and \( m_{\text{w},\text{SC}} \).

By taking into account the first two formulas (Eq. (3)), we can represent the third relation (Eq. (3)) in the form of a rule of mixtures as

\[
r_{\text{w},\text{SC}} = \omega_{\text{w}} r_{\text{w}} + \omega_1 r_1,
\]

where \( \omega_{\text{w}} = m_0/m_{\text{w},\text{SC}} \) and \( \omega_1 = m_1/m_{\text{w},\text{SC}} \) are the mass fractions of corneocytes and lipid phases, respectively.

There is another approach used in the literature (see, e.g., [23,24]), for modeling sorption isotherms of multicomponent systems, which is based on the relation \( a_w = \prod a_{\text{w},j} \) deduced by Ross [25] from the Gibbs–Duhem equation under the assumption that the activity coefficients of individual components are the same as those in the respective binary mixtures with water. We note, however, that Ross' relation is used for a different physical situation, namely, one-phase multicomponent mixture, while our approach describes equilibrium between two phases (see the graphical abstract). Consequently, the additivity types are different in these two cases.

In what follows, we are going to verify the composite isotherm formula (4) based on the published data (see Fig. 1a) for sorption by the pig stratum corneum, extracted lipids, and isolated corneocytes, which were obtained by means of sorption microcalorimetry [26] at 25 °C. It is to note that the near room-temperature regime is one of the most natural temperature regimes for SC in vivo conditions. We also note that, according to the source paper [26], each of the experimental isotherms shown in Fig. 1a is retrieved from a single test, and therefore, the curves are given without error bars. Correspondingly, the fitting results will be presented without uncertainty errors appearing due to the variability of data.

One of the main difficulties in analyzing the sorption isotherms of SC and its phases is that their sorption isotherm curves belong to different types. To be more precise, according to the classification proposed in the literature [27], the sorption isotherms of SC and corneocytes can be attributed to one class of sigmoid-shaped isotherms (type II), whereas the sorption isotherm of lipids is of type III. Therefore, in spite of the existence of a huge number of analytical models for water sorption isotherms of different materials [6,28], we still need a sufficiently flexible sorption isotherm fitting model to implement a unified numerical treatment of the sorption isotherms under consideration.

Based on the analysis of isotherm equations, described according to the isotherm classification scheme [29], a flexible rational expression for modeling all types of sorption isotherm was suggested by Hinz [30] in the form

\[
r_w = r_{w,\text{max}} \sum_{i=1}^{n} f_i \left( \frac{a_w / \beta_i}{a_w / \beta_i + 1} \right) ^{k_i}.
\]

where \( r_{w,\text{max}} \) is a parameter indicating asymptotic sorption at high water activity, and \( f_1, \ldots, f_N \) are weighting coefficients, such that \( \sum_{i=1}^{n} f_i = 1 \). We observe that in the simple case \( n = m_1 = 1 \), formula (5) contains five fitting constants, namely, \( k_1 = r_{w,\text{max}} q_{w,1}^{-1} q_{w,1}^{-1} \), \( k_2 = p_11 \), \( k_3 = a_{w} \), \( k_4 = \beta_1 \), and \( k_5 = \gamma_1 \), and reduces to the five-parameter formula

\[
r_w = k_1 \left( \frac{a_w}{\beta_1} \right) ^{k_2}.
\]

This example shows the limitations of the parameter-model-based approach [30], since the model complexity (measured, for instance, by the number of degrees of freedom) cannot be simply increased step by step. Indeed, the number of fitting parameters in Hinz’s formula (Eq. (5)) does not increase one by one, while starting from a rather large number of fitting constants. It still may be argued that some parameters (e.g., exponents in formula (6)) can be fixed and thus eliminated from the fitting constants, namely, \( k_1, k_2, k_3, k_4, k_5 \). We observe that in the simplest case \( n = m_1 = 1 \), formula (5) contains five fitting constants, namely, \( k_1 = r_{w,\text{max}} q_{w,1}^{-1} q_{w,1}^{-1} \), \( k_2 = p_11 \), \( k_3 = a_{w} \), \( k_4 = \beta_1 \), and \( k_5 = \gamma_1 \), and reduces to the five-parameter formula

\[
r_w = k_1 \left( \frac{a_w}{\beta_1} \right) ^{k_2}.
\]

This example shows the limitations of the parameter-model-based approach [30], since the model complexity (measured, for instance, by the number of degrees of freedom) cannot be simply increased step by step. Indeed, the number of fitting parameters in Hinz’s formula (Eq. (5)) does not increase one by one, while starting from a rather large number of fitting constants. It still may be argued that some parameters (e.g., exponents in formula (6)) can be fixed and thus eliminated from the model during pre-fitting, however, with the expense of using significantly more computational efforts.

Further, starting from thermodynamic considerations of absorption in polymer+water systems, D’Arcy and Watt [31] suggested a five-
parameter composite isotherm in the form

\[
r_w = \frac{k_w s c_{w}}{1 + k_{aw} s c_{w}} + k_{aw} + k_{aw} s c_{w},
\]

(7)

which has been argued to have general applicability to a wide range of heterogeneous protein systems [32]. Why Eqs. (5)–(7) did not become popular in modeling sorption isotherms? The answer to this question is twofold. On the one hand, they are not physically motivated, and the fitting constants lack even a clear geometrical interpretation. On the other hand, in their practical implementation it is difficult to get a grasp of the isotherm curve evolution in response to variations of the fitting parameters involved, beyond the limited insight provided by the empirical modeling method.

Very recently, an empirical model for sorption by glassy polymers, which is capable of a postpredictive assessment of thermodynamic parameters, has been introduced [33] and shown to be effective in the analysis of sorption isotherms for both stratum corneum and isolated corneocytes, but the case of lipids requires a special consideration. Nonetheless, while the frameworks of the three-parameter models Frenkel–Halsey–Hill (FHH) and Guggenheim–Anderson–de Boer (GAB) are advocated to be useful [34,35] for describing the thermodynamics of water interactions with stratum corneum, there is still a lack of understanding about a unified approach to constructing isotherm equations for the SC phases.

Another strong motivation for this study is the viewpoint on sorption isotherm as an auxiliary analytical tool needed for solving the diffusion problems for SC, as it is seen from formula (2). Since the definition of the thermodynamic correction factor for the water diffusivity [36] employs the operation of differentiation of the sorption isotherm, this imposes higher requirements on the fitting error, as it is usually increases after the differentiation of the fitting relation [37].

The rest of the paper is organized as follows. In the next section, we outline the methodology of our phenomenological approach, which is capable of describing sorption isotherms of different types. The section “Results” presents the analysis of the fitting accuracy and efficiency of the proposed five-parameter fitting model. The sensitivity analysis of the developed analytical modeling framework is illustrated on the previously published data. Finally, the flexibility of the phenomenological fitting model and the parametric analysis of the SC sorption isotherm model are presented as supplementary information.

2. Methodology

Considering stratum corneum as a biocomposite material [2], we would like to investigate the impact of its two main phases (corneocytes and lipids) on water sorption by stratum corneum under constant temperature. Let us recall that \( \omega_{d} \) and \( \omega_{l} \) denote respectively the mass fractions of corneocytes and lipids within dry stratum corneum. Moreover, let \( \rho_{d} \) and \( \rho_{l} \) be the corresponding densities of the dry phases. Then, the density of dry stratum corneum can be calculated as follows [3]:

\[
\rho_{s}^{DC} = \left( \frac{\omega_{d} \rho_{d} + \omega_{l} \rho_{l}}{\rho_{d}} \right)^{-1}.
\]

(8)

In many cases, sorption isotherms are expressed in terms of water weight fraction, defined as the mass of absorbed water divided by the mass of the whole system including the water. In what follows, \( x_{w} \) and \( x_{w}^{DC} \) will denote the corresponding weight water fractions, which are determined as the weight fraction of water in corneocytes, lipids, and stratum corneum, respectively. Also, it is convenient to characterize absorbed water in terms of volume fractions, which will be denoted as \( \phi_{w} \), \( \phi_{w}^{DC} \), and \( \phi_{w}^{SC} \). Under the assumption of volume additivity, we have the following relations:

\[
\begin{align*}
\phi_{w} &= \frac{\rho_{d}^{DC} x_{w} + \rho_{l}^{DC} x_{w}^{DC}}{\rho_{d}^{DC}}, \\
\phi_{w}^{DC} &= \frac{\rho_{d}^{DC} x_{w}^{DC}}{\rho_{d}^{DC}}, \\
\phi_{w}^{SC} &= \frac{\rho_{d}^{DC} x_{w} + \rho_{l}^{DC} x_{w}^{DC}}{\rho_{d}^{DC}}.
\end{align*}
\]

(9)

Here, \( \rho_{w} \) is the density of water. The concentration (mass/volume) of water in a biopolymer system under consideration is given by the formula \( C_{w} = \rho_{w} \phi_{w} \) with an appropriate choice of the water volume fraction according to one of formulas (Eq. (9)).

Interestingly, though the sorption isotherm relates water content to water activity (relative humidity) at equilibrium, it is involved in the relation of the Fick’s diffusion coefficient, \( D \), to the thermodynamic diffusion coefficient, \( D_{T} \), as \( D = D_{T} \Delta \Gamma \) via the thermodynamic correction factor that, in view of Eq. (2), can be evaluated as [36].

\[
\Delta \Gamma = \frac{\partial \ln a}{\partial \ln C_{w}} = \frac{C_{w} \partial a}{\partial C_{w}} \frac{\partial a}{\partial \phi_{w}} = \frac{\phi_{w}}{\rho_{w}} \left( \frac{\partial \phi_{w}}{\partial \ln \rho_{w}} \right)^{-1},
\]

(10)

where the derivatives are evaluated at constant temperature, and, of course, we assume that \( \rho_{w} = \text{const.} \).

We observe that since the operation of differentiation is involved in the definition of \( \Delta \Gamma \), the accuracy of its numerical evaluation strongly depends on both the quality of experimental data and the fitting efficiency of the employed sorption isotherm model. Fig. 1b shows typical behavior of the thermodynamic correction factors for stratum corneum, extracted lipids, and isolated corneocytes, which are evaluated from the sorption isotherms presented in Fig. 1a.

The main idea behind our approach to modeling sorption isotherms is to give a systematic account of the main features observed in experiment-based variations of the thermodynamic correction factor \( \Delta \Gamma \) as a function of the water activity \( a_{w} \). In this way, regarding the last relation in Eq. (10) as a first-order ordinary differential equation and separating the variables, we arrive at the equation \( \Delta \Gamma(a_{w}) a_{w}^{-1} da_{w} = \phi_{w}^{-1} d\phi_{w} \), which after integration provides the following formula:

\[
\phi_{w} = K_{1} a_{w} \exp \left\{ -\int_{a_{w}}^{1} 1 - \frac{\Delta \Gamma(a) \partial a}{\Delta \Gamma(a) \partial a_{w}} \partial a \right\}. 
\]

(11)

Here, \( K_{1} \) is a constant of integration, and \( a \) is the integration variable. Thus, by representing \( \Delta \Gamma(a_{w}) \) with a sufficiently flexible analytical approximation, we can obtain a corresponding analytical approximation for the sorption isotherm.

2.1. Phenomenological sorption isotherm fitting model

By inspecting the variation of the thermodynamic correction factor for SC and its main phases (see Fig. 1b), we identify the following two main features: (i) there is a local maximum, and (ii) \( \Delta \Gamma(a_{w}) \) approaches zero as \( a_{w} \) tends to unit. Keeping this mind in mind, we suggest the following approximation:

\[
\Delta \Gamma(a_{w}) = K_{2} (1 - a_{w})^{K_{3}} \text{RBF} \left(a_{w} - K_{4}, K_{5}\right).
\]

(12)

Here, \( K_{2}, K_{3}, K_{4}, \) and \( K_{5} \) are fitting coefficients, RBF \( (x, \sigma) \) is a radial basis function, whose value depends only on the absolute modulus \( |x| \), and \( \sigma \) is a shape-controlling parameter. In particular, one can make use of the Gaussian radial basis function

\[
\text{RBF} \left(x, \sigma\right) = \exp\left(-\frac{x^{2}}{2\sigma^{2}}\right).
\]

(13)

We note that in the case of lipids, with a reasonable compromise of accuracy and simplicity, formula (12) can be reduced to
\( \mathcal{F}_T (a_w) = K_5 (1 - a_m)^{K_5} \) \hspace{1cm} (14)

It is also to note here that for the Flory–Huggins model, \( a_w = \phi_w \exp (1 - \phi_w + \chi (1 - \phi_w)^2) \), which is simplified for infinite length polymer chains, the thermodynamic correction factor is given by \( \mathcal{F}_T = (1 - \phi_w) (1 - 2\phi_w) \). The latter formula shows that \( \mathcal{F}_T \) is a monotonically decreasing function of \( \phi_w \), and thus of \( a_w \), such that \( \mathcal{F}_T \rightarrow 0 \) and \( \mathcal{F}_T \rightarrow 0 \) as \( a_w \to 0 \) and \( a_w \to 1 \), respectively, for all values of the Flory–Huggins interaction parameter \( \chi \in (0,0.5) \). Without dwelling on further details, it is to be mentioned that the GAB model (for a range of the model parameters used in characterizing water sorption in stratum corneum) exhibits a single maximum variation of the factor \( \mathcal{F}_T \) that, however, does not vanish in the limit as \( a_w \to 1 \).

In contrast to the empirical parametric models, which directly relate two variables \( a_w \) and \( \phi_w \) by some analytical expression with a number of fitting parameters, the presented phenomenological model relates \( a_w \) and \( \phi_w \) by the exact relation (Eq. (11)) via the thermodynamic correction factor \( \mathcal{F}_T \), for which we suggest different parametric approximations. That is why, while in many cases certain parameters of empirical models can be related to the physico-chemical parameters of the adsorption, it would be difficult to do the same for the fitting constants in formulas (12) and (14). Though the approximate formula (12) captures certain geometrical features of the thermodynamic factor curve, the parameters \( K_2 \ldots, K_5 \) of the phenomenological model have no physical meaning (and the same problem generally applies to a majority of empirical fitting equations for sorption isotherm). However, the advantage of accurate fitting of the thermodynamic factor \( \mathcal{F}_T \) allows to recover valuable information about important thermodynamic parameters, like the generalized Fick's law diffusivity \( \mathcal{D}_T \) and the variable Flory–Huggins interaction parameter \( \chi \).

3. Results

3.1. Composite sorption isotherm

By definition of the weight water fraction, we have \( x_w^{\text{SC}} = m_w^{\text{SC}} / (m_w^{\text{SC}} + m_l^{\text{SC}}) \), where \( m_w^{\text{SC}} \) is the mass of water absorbed by SC of the dry mass \( m_d^{\text{SC}} \). According to the assumed composition of SC, we have \( m_d^{\text{SC}} = m_d^{SC} + m_l^{SC} \) and \( m_w^{\text{SC}} = m_w^{\text{SC}} + m_w^{\text{SC}} \), where \( m_w^{\text{SC}} = x_w^{\text{SC}} m_d^{\text{SC}} / (1 - x_w^{\text{SC}}) \) and \( m_w = x_w m_d^{\text{SC}} / (1 - x_w) \). Thus, taking into account the notation \( \omega_c^{\text{SC}} \) and \( \omega_l^{\text{SC}} \) for the mass fractions of the SC phases, we can express the SC weight water ratio \( x_w^{\text{SC}} \) in terms of \( x_w^{\text{SC}} \) and \( x_w^{\text{SC}} \) as follows:

\[
\begin{align*}
\omega_c^{\text{SC}} &= \omega_c^{\text{SC}} / (1 - \omega_c^{\text{SC}}) \\
\omega_l^{\text{SC}} &= \omega_l^{\text{SC}} / (1 - \omega_l^{\text{SC}})
\end{align*}
\]  

Further, in view of Eqs. (8) and (9), formula (15) can be rewritten in terms of the volume fractions as

\[
\psi_{c}^{\text{SC}} = \frac{\omega_c^{\text{SC}} \phi_c^{\text{SC}} (1 - \phi_c^{\text{SC}}) + \omega_l^{\text{SC}} \phi_l^{\text{SC}} (1 - \phi_l^{\text{SC}})}{\omega_c^{\text{SC}} \phi_c^{\text{SC}} (1 - \phi_c^{\text{SC}}) + \omega_l^{\text{SC}} \phi_l^{\text{SC}} (1 - \phi_l^{\text{SC}})}
\]  

It is to emphasize here that formula (16) yields the sorption isotherm for SC \( \psi_{c}^{\text{SC}}(a_w) \), provided we know the individual sorption isotherms \( \psi_c(x_w) \) and \( \psi_l(x_w) \) for isolated corneocytes and extracted lipids. Finally, we note that formulas (15) and (16) can be shown to be in complete accord with the rule of mixtures (Eq. (4)).

3.2. Efficiency of the phenomenological model

To illustrate the fitting performance of the five-parameter phenomenological models (11), (12), and (13), we compare it with the following five-parameter sorption isotherm suggested by Park (38):

\[
\psi_a = \frac{K_1 \phi_a}{1 + K_1 \phi_a} + K_2 a_w + K_3 (a_w) K_5^{\psi_a}.
\]  

Here, \( K_1, \ldots, K_5 \) are empirical parameters, and \( (a_w) K_5^{\psi_a} \) is the \( K_5 \)-th power

of \( a_w \), that is, \( (a_w) K_5 = a_w a_w \cdots a_w \) when \( K_5 \) is a natural number, and \( (a_w) K_5^{\psi_a} = \exp \{ K_5 \ln (a_w) \} \) in the general case.

It is important to note that the five-parameter model (Eq. (7)) of D'Arcy and Watt (31) differs from Eq. (17) by the last term, which now can be rewritten in the form \( K_5 \ln (a_w) \), and thus, the condition \( K_5 \leq 1 \) is needed for the D'Arcy–Watt to work in the whole range \( a_w \in (0,1) \). It can be shown that both last terms in the mentioned fitting models describe sorption isotherm curves of type III, but the Park model is found to be more robust in the least-square fitting. We also note that in the case under consideration the Hinz five-parameter fitting model (Eq. (6)) also shows a worse fitting performance than the Park five-parameter fitting model (Eq. (17)).

The quality of the fitting performance will be estimated using the following error measures (39,40):

\[
\text{MAPE} = \frac{100}{N} \sum_{i=1}^{N} \frac{|\psi_{fit}^i - \psi_{exp}^i|}{\psi_{exp}^i} \\
\text{HYBRID}_p = \frac{100}{N - p} \sum_{i=p+1}^{N} (\psi_{fit}^i - \psi_{exp}^i)^2
\]  

where, \( N \) is the number of data entries, \( \psi_{exp}^i \) and \( \psi_{fit}^i \) are the experimental and calculated values of a quantity \( \psi \), and \( p \) is the number of the employed fitting parameters.

The accuracy results of Park's model (Eq. (17)) and our models (11), (12), and (13) in fitting the sorption isotherms presented in Fig. 1a are listed in Table 1. It is to note here that the negative value \(-0.024 \times 10^4 \) exhibited by the Park model in the case of lipids is due to its negative predictions in the interval \( a_w \in (0,0.25) \). Thus, from Table 1, it is readily seen that in the case under consideration the five-parameter phenomenological models (11), (12), and (13) outperforms the five-parameter Park model (Eq. (17)). We note that the two models under comparison yield the following \( R^2 \) values for stratum corneum \( 9.999 \times 10^3 \) and \( 9.999 \times 10^3 \), for corneocytes \( 9.994 \times 10^3 \) and \( 9.997 \times 10^3 \), and for lipids \( 9.983 \times 10^3 \) and \( 9.996 \times 10^3 \), also supporting the conclusion that the new phenomenological model fits better than Park's model. However, since the square of the correlation coefficient is traditionally defined only for linear regression (41), we did not include these results in Table 1.

The graphical results of fitting the phenomenological model (Eq. (11)) to the sorption isotherms presented in Fig. 1a are shown in Figs. 2–4. Observing that Fig. 3a includes results for the thermodynamic correction factor based on the five- and three-parameter models (12) and (14), interestingly, the corresponding sorption isotherms are indistinguishable (see Fig. 3b). The evaluated model coefficients are listed in Table 2.

When regarding the issue of potential uncertainties in the composite sorption isotherm of SC, which is based on the experimental sorption isotherms of its two main phases (corneocytes and lipids), we would like to highlight the following aspects. The composite model utilizes not only the individual sorption isotherms \( \phi_c(x_w) \) and \( \phi_l(x_w) \), but also the lipid mass fraction \( \omega_c^{\text{SC}} \) (as the mass fraction of corneocytes is given by \( \omega_c^{\text{SC}} = 1 - \omega_c^{\text{SC}} \)), and therefore, uncertainties associated with these data may influence both the model fits and the interpretation of the results. In the example of a single set of three sorption isotherms considered above, the SC isotherm has served as a verification of the accuracy of the composite sorption isotherm. From Fig. 4b it is seen that the experimental errors and other uncertainties are very small in the range of water activities \( a_w \) starting from 0.3. The discrepancy between curves 1 and 2 observed in Fig. 4 for the intact SC might be explained by non-equilibrium effects due to a “delayed” hydration of the SC lipids and corneocytes in the glassy states and the protective envelop formed by lipids. An undeniable advantage of the developed approach is that the uncertainty associated with the goodness of fit is substantially reduced compared to the models of Hinz, D'Arcy and Watt, and Park.
3.3. Sensitivity analysis of the composite SC sorption isotherm model

Fig. 5a shows the variation of the composite sorption isotherm (Eq. (16)) in response to the discrete variation of the lipids mass fraction \( \omega_d^l = 0.15, 0.20, 0.25, 0.30, 0.35 \). It is readily seen that all curves cross at a single point, which corresponds to the point of intersection of the sorption isotherm of lipids and the sorption isotherm of corneocytes in Fig. 1a.

It is of practical interest to evaluate the following sensitivity measure [42]:

\[
S_{ld} = \frac{\partial \phi^w_{SC}}{\partial \omega_d^l}
\]  

(19)

The dimensionless coefficient \( S_{ld} \) characterizes the sensitivity of the predicted water volume fraction \( \phi^w_{SC} \) to small changes of the composition variable \( \omega_d^l \).

Fig. 5b shows the variation of the sensitivity measure \( S_{ld} \) as a function of the weight water fraction for the same discrete set of the lipids mass fraction on dry basis \( \omega_d^l \). It is important to observe that to maintain the SC in a stable condition by stabilizing the short lamellar structure in the intercellular lipid matrix, it was proposed [43] that the water content in human SC should be regulated to be at 20–30 wt%. Fig. 6b shows that the sensitivity coefficient \( S_{ld} \) is positive in this interval, and thus, an increase in the lipids mass fraction \( \omega_d^l \) will result in a slight increase of the water volume fraction in SC.

Table 1

Comparison of the phenomenological fitting models (11), (12), and (13) with the Park model (Eq. (17)) for the cases of stratum corneum and its phases.

<table>
<thead>
<tr>
<th>Biopolymer</th>
<th>( \rho_d^l, \text{g/cm}^3 )</th>
<th>Park's model</th>
<th>New model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>MAPE,%</td>
<td>HYBRID,%</td>
</tr>
<tr>
<td>Stratum corneum</td>
<td>1.26</td>
<td>4.25</td>
<td>0.012</td>
</tr>
<tr>
<td>Extracted lipids</td>
<td>1.0</td>
<td>284.5</td>
<td>0.625</td>
</tr>
<tr>
<td>Isolated corneocytes</td>
<td>1.4</td>
<td>1.64</td>
<td>3.40 \times 10^{-3}</td>
</tr>
</tbody>
</table>

Fig. 2. a) Fitting of the thermodynamic correction factor for isolated corneocytes; b) fitting of the sorption isotherm.

Fig. 3. a) Fitting of the thermodynamic correction factor for extracted lipids (curves 1 and 2 correspond to the five- and three-parameter models); b) fitting of the sorption isotherm (both curves are indistinguishable).

Fig. 5a illustrates the contribution to the composite sorption isotherm of stratum corneum originated from its phases for the mass fractions \( \omega_d^c = 0.73 \) and \( \omega_d^l = 0.27 \). The densities of dry corneocytes and lipids are taken to be \( \rho_d^c = 1.4 \text{ g/cm}^3 \) and \( \rho_d^l = 1.0 \text{ g/cm}^3 \), respectively, so that formula (8) yields \( \rho_d^{SC} = 1.264 \text{ g/cm}^3 \). It should be emphasized that in terms of the water mass fraction \( r_w \), the composite isotherm has the simplest expression (Eq. (4)), which is in the form of additive rule of...
mixtures. The good agreement between the experimental sorption isotherm for SC and the composite isotherm yields a plausible conclusion that the corneocytes–lipids mechanical interaction during unconstrained swelling of the SC membrane in the in vitro laboratory experiment is negligible, since the composite sorption isotherm (Eq. (16)) is based on the rule of mixtures for the individual phase sorption isotherms.

It is also of practical interest to consider the effect of the SC composition on the variation of the sorption isotherm. Since \( \omega_d + \omega_d^l = 1 \), the composite sorption isotherm (Eq. (15)) can be regarded as a parameterized function \( x_w^{SC} \) of the lipids friction \( \omega_d^l \). In this way, we may introduce the following percentage measure of the isotherm variance due to the lipids content change: \( (x_w^{SC}(\omega_d^l) - x_w^{SC}(\omega_d^l_0))/x_w^{SC}(\omega_d^l_0) \times 100\% \). Here, \( \omega_d^l_0 \) is a certain fixed value of the lipids mass fraction. Fig. 6b shows the behavior of the relative variance against the variation of the water mass content 100\% \( x_w^{SC}(\omega_d^l) \) for \( \omega_d^l = 0.25 \). We recall [44] that the normal water content in SC is about 30\%. Hence, as it follows from Fig. 6b, the increase of the lipids mass fraction on dry basis \( \omega_d^l \) above \( \omega_d^l_0 \) implies the increase of the water content, as \( x_w^{SC}(\omega_d^l) > x_w^{SC}(\omega_d^l_0) \) in the range of water content under consideration (corresponding to the normal conditions).

It is of interest to observe that formula (19) can be represented as

\[
S_d^l = \frac{\partial}{\partial \ln \omega_d^l} \left( \ln x_w^{SC} \right) / \partial (\ln \omega_d^l),
\]

that is in the same form as that of the thermodynamic correction factor (Eq. (10)). Thus, the reciprocal of the thermodynamic factor, i.e., the quantity \( 1/F_T \), can be interpreted as the sensitivity of the water concentration \( C_w \) to the water activity \( a_w \).

4. Discussion and conclusions

It is to emphasize that the proposed phenomenological model is a conceptually new fitting model, as it provides fitting of the sorption isotherm via approximating the thermodynamic correction factor. Namely, the difference between the isotherms of different types becomes more pronounced, when the thermodynamic correction factor \( F_T \) is considered as a function of the water activity \( a_w \). At the same time, the choice of approximations for the functional dependence \( F_T(a_w) \) is more evident based on the revealed features of the \( F_T \)-curve.

In contrast to the existing empirical models of sorption isotherm, the generality of the proposed phenomenological model (Eq. (11)) is
Observe that the sorption isotherm is measured in quasi-static sorption/desorption process and assumes that the system reaches its thermodynamic equilibrium. At the same time, the thermodynamic correction factor $\mathcal{F}_T$, being solely determined by the sorption isotherm, relates two diffusion coefficients $D$ and $D_T$ that describe the non-equilibrium diffusion process. As it was pointed out [22], the explanation for this paradox can be suggested in the framework of "local equilibrium" concept [46,47] that allows considering systems with nonuniform distribution of components.

It should be noted that our conclusions are drawn from the analysis of only one example of SC isotherm taken from the literature. However, to the authors’ knowledge, the paper [26] by Silva et al. is the only publication to date that presents sorption data set not only for stratum corneum, but also those for both its main phases (corneocytes and lipids). Also, it is to note that the available set of sorption data was obtained for porcine stratum corneum, and thus, further experimental studies are needed to validate the drawn conclusions for human stratum corneum.

The majority of experimental studies on water sorption equilibrium in biological materials like foods are made using the gravimetric static procedure employing different relative humidifies corresponding to saturated salt solutions that results in 6–8 experimental points. If such a limited data were fitted using polynomial approximations, then the so-called low dimensional instability problem would arise with increasing the number of fitting parameters. The non-linear regression analysis faces the same problem, and thus the number of data points, $N$, should be always greater than the number of fitting parameters. In the case of the phenomenological fitting model due to the specific construction of the approximation of the thermodynamic correction factor $\mathcal{F}_T$, the fitting expression for the sorption isotherm accounts for both limit behaviors as $a_w \rightarrow 0$ and $a_w \rightarrow 1$. At the same time, it should be stressed that the proposed fitting procedure does not require numerical differentiation for evaluating the values of $\mathcal{F}_T$. This is especially important as the error of numerical differentiation increases with decreasing the number of data points. Finally, we note that a more accurate modeling of sorption isotherms implies a general need of obtaining better resolution sorption data using more advanced techniques (e.g., sorption calorimetry, HS QCM-D [48]).

To conclude, a novel phenomenological model has been introduced for modeling sorption isotherms by accounting for characteristic features in the variation of the thermodynamic correction factor. In comparison to the empirical models with the same same degree of freedom (five fitting parameters), the phenomenological model shows a high flexibility and fitting performance. Based on the previously published sorption isotherm data for stratum corneum and its two main phases, the validity of the composite sorption isotherm has been established, and explicit analytical expressions are derived for the composite isotherm in terms of the water contents and volume fractions.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This research was carried out in the Biobarriers profile and was funded by the Knowledge foundation (KK-Stiftelsen). JE and VK thank the Gustaf Th Ohlsson Foundation for financial support.

Author contributions statement

V.K. and J.E. conceptualized the research design. I.A. worked on model derivation and drafted the manuscript. J.E. and V.K. edited the
References