A Spreadsheet-Based Method for Simultaneously Estimating the Disposition of Multiple Ingredients Applied to Skin

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ABSTRACT: A spreadsheet-based computer program has been developed to address the problem of simultaneous absorption and evaporation from a multicomponent formulation applied to the skin so that the disposition of each ingredient is tracked. The mass and thickness of the formulation layer (or vehicle) change with time as its components disperse. The presence of each component on the surface of the skin generally affects the activity of the other components at the surface. Thermodynamic activities within the vehicle are governed by either a modified ideal solution model or the UNIversal QUAsiChemical approximation (UNIQUAC) functional group activity coefficient method/UNIQUAC model, at the user's discretion. Program-calculated or experimental solubility limits for the component of greatest interest may be invoked. The predictions of the multicomponent vehicle (MCV) model were compared with human *in vitro* skin permeation data drawn from an earlier report. Absorption of small to moderate doses of vanillylnonamide from a propylene glycol vehicle was predicted significantly better with the MCV model than with simpler models that track only one component. © 2015 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 104:2047–2055, 2015

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INTRODUCTION

A variety of *in silico* dermal absorption models of varying levels of complexity are now available, as recently reviewed by Mitragotri et al.[1] Simple models are often limited to the estimation of steady-state skin permeability coefficients or maximum flux, whereas the more complex ones allow for transient exposures to finite doses of the test compound under various environmental conditions. Although the simpler models may be easily implemented by the user, the more complex ones involving transient diffusion calculations generally cannot. But some of these models are publicly available.[2–4] The model from our research group, which we will call UB/UC (for University of Buffalo/University of Cincinnati),[5] is currently available either as an Excel™ workbook + add-in package[3,6] or as a Java™ program accessible as the Finite Dose Skin Permeation calculator on the NIOSH/CDC website.[4] It is a three-layer effective medium model of the skin in which underlying microscopic transport properties of the tissue are mapped onto a homogeneous slab framework.[3]

The UB/UC model, and others of which we are aware, are limited to tracking the disposition of a single ingredient on the skin. This limitation is acceptable when the other components of an applied formulation are either nonvolatile and nonabsorbing (i.e., immobile) or highly volatile. But it fails when components having intermediate properties [e.g., propylene glycol (PG), glycerol] are present. Furthermore, it does not allow for explicit representation of the dry-down process for an aqueous solution or emulsion, nor does it permit excipients in the formulation to interact with the skin and modify its permeability. The multicomponent vehicle (MCV) extension of the UB/UC model described herein removes these limitations by allowing any component applied to the skin to have intermediate mobility. The disposition of each ingredient is tracked simultaneously, and physicochemical interactions within the vehicle or within the skin are thereby enabled.

The MCV method is exemplified by reanalyzing the results of a previously published human *in vitro* skin permeation study of vanillylnonanamide (VN, a synthetic derivative of capsaicin) delivered from a PG vehicle.[7] The dataset consisted of nine VN doses spanning three orders of magnitude, with a 72-h time course of permeation for each dose. Only the absorption of VN was measured. In the original analysis, a model was found that very well approximated the VN absorption through skin from 0 to 72 h, but only when three parameters were fit to the data. The present analysis utilizes the *a priori* method of calculating transport properties from physical properties and environmental conditions incorporated in the UB/UC model,[3,6] but permits the gradual dissipation of the PG component of the formulation. No adjustable parameters are employed.

THEORY

The UB/UC model,[3,6] modified to accommodate a multicomponent formulation, was used for all calculations. Briefly, the model is a transient, one-dimensional, three-layer diffusion model, which can make predictions for both finite and infinite doses. The stratum corneum (SC) is represented as an effective homogeneous medium based on an underlying microscopic transport model.[8–10] The viable epidermis and dermis are represented as homogenous layers with identical transport

Abbreviations used: DDBST, Dortmund Data Bank Software & Separation Technology GmbH; MCV, multicomponent vehicle; PG, propylene glycol; SC, stratum corneum; UB/UC, University of Buffalo/University of Cincinnati; UNIFAC, UNIQUAC functional group activity coefficient method; UNIQUAC, UNIversal QUAsiChemical approximation; VN, Vanillylnonanamide.

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Table 1. Terminology for Ingredients and Phases in the MCV Model

Formulation	The Composition Applied to Skin
Vehicle	The composition remaining on the skin at any time, $t \geq 0$. At $t = 0$, the terms "vehicle" and "formulation" are synonymous.
Primary component	The ingredient of greatest interest in the formulation, equivalent to the active pharmaceutical agent in a pharmaceutical formulation. It is the only component that is allowed to form a separate phase if present in excess.
Excipient	All other formulation components excluding the primary component.
Solution phase	The fraction of the vehicle containing both the primary component and the excipients.
Excess phase	The fraction of the vehicle containing only the primary component. It exists when the primary component is present in excess of its solubility in the solution phase.

parameters.[11–13] Dermis may be either perfused with blood flow (for *in vivo* simulations) or unperfused (for *in vitro* simulations).

In the MCV model, each ingredient is absorbed and/or evaporates at rates determined by its physical properties and its thermodynamic potential in the vehicle. Component volumes in the vehicle are considered to be additive. The thermodynamic activities of the vehicle components are calculated by one of two methods—ideal solution theory,[14] modified to accept user-entered solubility limits for the component of greatest interest (primary component), and the UNIversal QUAsiChemical approximation (UNIQUAC) functional group activity coefficient method (UNIFAC)/UNIQUAC method.[15] For binary vehicles, a look-up table with interpolation is an easily implemented alternative. This allows the user to enter experimental data or activity coefficients calculated by another method. We choose rational activity coefficients, defined by $a_i = \gamma_i X_i$, and take the standard state of each component to be the pure component in its liquid state at the skin surface temperature (usually taken to be 32°C or 305.15 K). Thus, $a_i = 1$ for a neat liquid at 32°C.

In the ideal solution method, vehicle thermodynamics and component solubility limitations are handled as follows (see Table 1 for terminology): only one saturable component (the primary component) is allowed, and it is furthermore assumed that if this component is present in excess, then a second phase consisting only of this component coexists with the solution phase. This phase is termed the excess phase. Thus, all other components (i.e., the excipients) are miscible. Activity coefficients of all components are assumed to be equal to unity; their thermodynamic activities are therefore equal to their mole fraction in the solution phase, $a_i = X_i$. The solubility of the primary component is calculated using a log linear approximation[16] according to its solubility in each of the other components. If the user does not enter a solubility limit for the primary component in one of the other components, the ideal solubility at the skin surface temperature, T, is employed. Expressed as a mole fraction, this value is $X_i^{sat} = 1$ for liquids, whereas for solids it is equated to the activity of the solid, a_i^{sat}, at the skin surface temperature, T, as estimated from the melting point, T_f, and entropy of fusion, ΔS_f, of the primary component according to Eq. (1) [17,18]:

$$\ln a_i^{sat} = -\frac{\Delta S_f}{RT}(T_f - T) \tag{1}$$

where R is the gas constant ($8.314\,\mathrm{J K^{-1} mol^{-1}}$) and all temperatures are expressed in Kelvin. The value of ΔS_f is calculated from Walden's rule, $\Delta S_f = 56.5\mathrm{j\,K^{-1}\,mol^{-1}}$ for rigid compounds or $\Delta S_f = 56.5 + 2.5(\hat{n} - 5)\,\mathrm{j\,K^{-1}\,mol^{-1}}$ for flexible compounds, where $\hat{n}$ is the number of heteroatoms in the flexible chain.[17]

It is furthermore assumed that the volumes of each component are additive, that is, the partial molar volumes are equal to the molar volumes.[14]

Solubility limitations within the UNIFAC/UNIQUAC method are handled in an analogous manner. Only one saturable component (the primary component) is allowed. Experimental solubility limits for this component in other components may be entered by the user, in which case the log linear approximation is used to estimate its solubility in the mixture. In the absence of this information, the solubility of a solid is equal to the mole fraction $X_i^{sat} = a_i^{sat}/\gamma_i^{sat}$, where a_i^{sat} is calculated from Eq. (1) and γ_i^{sat} is the UNIQUAC activity coefficient at the given composition.[19] The value of X_i^{sat} so calculated is different than that in the ideal solubility method because, in general, $\gamma_i^{sat} \neq 1$.

Component solubilities and thermodynamic activities in the SC are calculated by a simpler approximation, equivalent to that in the UB/UC model.[3,20] First, the SC/water partition coefficients of each component, K_i^{mv}, are calculated,[8] then these values are multiplied by their water solubilities at the skin surface temperature, S_i^w, to yield estimated values of the component solubilities in the SC, C_i^{msat}. This dilute solution approximation is applied separately to each component; the limitations of this approach will be discussed. The activity of each component in the membrane is then calculated as the fraction of saturation (on a mass/volume basis) multiplied by the activity of the pure component, a_i^{sat}; thus

$$a_i^m = \frac{C_i^m}{C_i^{msat}} a_i^{sat} \tag{2}$$

Partitioning at the SC–vehicle interface can now be estimated by equating the activities of each component in the vehicle solution phase and the upper layer of the SC. A full description is given in the Appendix.

Numerical Method

The disposition of each component is tracked in the skin, based on a finite difference approximation to diffusion of noninteracting solutes in dilute solution. This is carried out by alternating the difference equations between species. The resulting system of ordinary differential equations is transformed into a band diagonal matrix having nonzero entries only on the diagonal and one subdiagonal on either side, which is N entries away from the diagonal, N being the number of components. Thus, it is a $(2N-1)$-band matrix. The top sublayer in the SC is maintained in equilibrium with the solution phase of the vehicle. Components are mathematically eliminated from the system as their total mass approaches zero, thereby simplifying the calculation. Further details are as previously described.[20]