LRI-B13
Development of an *in silico* model of dermal absorption
Executive Summary

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The objectives of the LRI-B13 project were to (1) explain and (2) reliably predict chemical bioavailability from dermal exposure for a broad range of chemical classes and formulations. A goal was to conduct bioavailability and/or exposure assessments directly from molecular structure as well as in a higher tier where some experimental data is fed into the framework.

The work was conducted in the context of three broad aims: (1) To examine the permeation pathways in human stratum corneum (SC) from a molecular perspective and to integrate this knowledge into a dynamic computational model at the continuum level; (2) To develop a thermodynamically-based dynamic multicomponent vehicle (formulation) module to characterize formulation space; and (3) To combine the developments from Aims 1 and 2 into a multi-scale quantitative mechanistic model that enables the user to reliably predict chemical bioavailability from dermal exposure for a broad range of chemical classes and exposure scenarios. Work proceeded in parallel at two academic institutions (UC and UW) working with three industrial partners (P&G, Unilever and BASF).

Aim 1. Atomistic molecular dynamics (MD) calculations on model SC lipid bilayers conducted at UW under full and low hydration confirmed that hydrophilic pores through SC lipid lamellae do not form spontaneously under either hydration condition. It was found that selected additive molecules significantly lower the barrier to pore formation; however spontaneous pore formation is still unlikely. The perpendicular and previously unexplored lateral pathways through the SC lipid lamella were explored in detail [1]. Lipid segregation was observed in fully hydrated bilayers with cholesterol-rich regions having higher permeability to water and other small solutes relative to cholesterol-depleted regions. Hydration of the bilayers was minimal under low hydration conditions; when low amounts of water were placed between the lipid bilayers dewetting occurred and water pools were found to develop between the headgroups in apposing lipid bilayers. These pools were disconnected and did not lead to facile intercellular transport pathways for water or other hydrophilic permeants. The results suggest that water permeation across hydrated SC bilayers occurs transcellularly, with the transbilayer part of the route consisting of alternating steps of transverse permeation across cholesterol-rich regions and lateral diffusion within the hydrophobic core of the bilayers.

The UC group completed an analysis of uptake and desorption of hydrophilic solutes in isolated human SC. The results were used to parameterize the transcellular component of the SC polar pathway eventually added to the working computational model of SC transport and discussed under Aim 3. However, contributions from other research groups firmly established the importance also of a transfollicular pathway in contributing to polar compound transport across the SC.

Aim 2. Initial efforts at UC were directed at expanding the single component, UB/UC diffusion model existing at the outset of the project to include multiple components diffusing and/or evaporating simultaneously from a single phase formulation applied to skin. The framework was quickly expanded to allow a single component – the component of greatest interest– to coexist as a second phase in equilibrium with the solution. This extended the range of applicability to suspensions or emulsions which become saturated with a topical drug or skin benefit agent (the "active" agent) as the formulation dries down on the skin. Thermodynamic activities of each component in the vehicle were calculated according to one of two thermodynamic models, ideal solution or UNIFAC/UNIQUAC. The computational model has been published [2].

Within each model solubility of the active can be entered as an experimental value or it can be estimated from a model-based calculation, yielding a total of four possible combinations for handling the active ingredient. Solubility of the active agent is a key determinate of absorption. The developed model incorporates component interactions in the vehicle, but does not estimate these interactions in the skin. Each component is assumed to diffuse independently once it has entered the SC. Consequently, skin permeation enhancement by formulation components or combinations thereof is not described.

Aim 3. The task for Aim 3 was to combine the developments from Aims 1 and 2 into a multi-scale quantitative mechanistic model incorporating learnings from both areas, MD studies of permeation pathways through the SC and thermodynamic models of multicomponent diffusion from complex formulations. This work proved to be difficult, and much of it was accomplished after the B13 project funding period had expired. Nevertheless significant progress has been made. Work in this area continues as of this writing under separate funding and the direction of Drs. Jaworska and Kasting.

The model eventually recommended by the UC group consists of an SC polar pathway comprised of both transcellular and follicular components. The steady-state properties of this model have been published [3] and an Excel™ workbook embodying the steady-state model is available from the UC group.

References

1. Del Regno A and Notman R. Permeation pathways through lateral domains in model membranes of skin lipids. *Phys Chem Chem Phys* **20**:2162-2174 (2018).
2. Miller MA and Kasting GB. A spreadsheet-based method for simultaneously estimating the disposition of multiple ingredients applied to skin. *J Pharm Sci* **104**:2047-2055 (2015).
3. Kasting GB, Miller MA, LaCount TD and Jaworska J. A composite model for the transport of hydrophilic and lipophilic compounds across the skin. *J Pharm Sci* **108**:337-349 (2019).