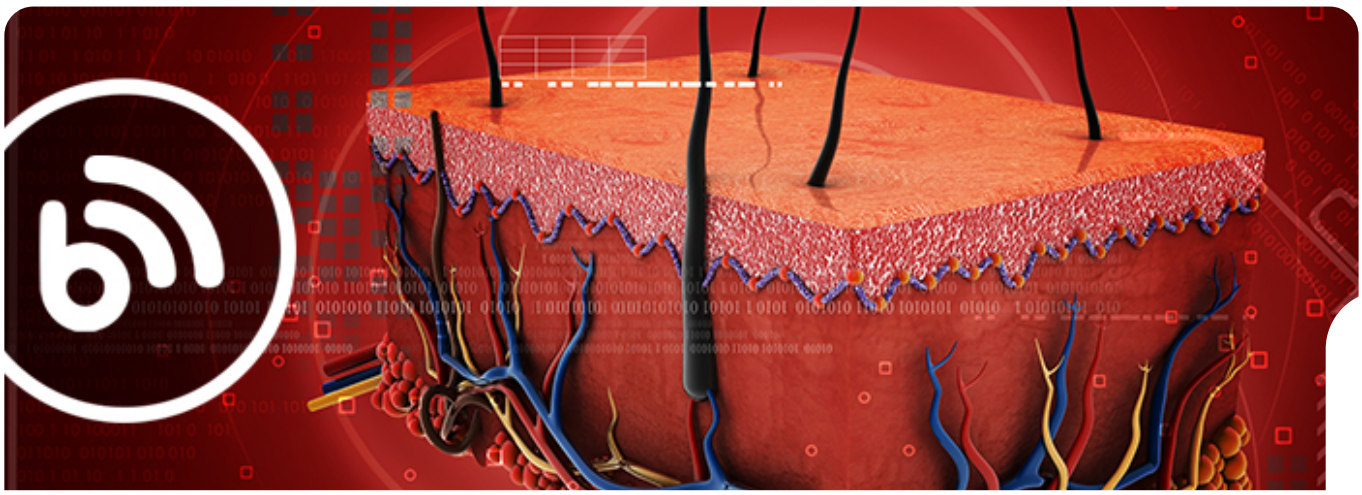


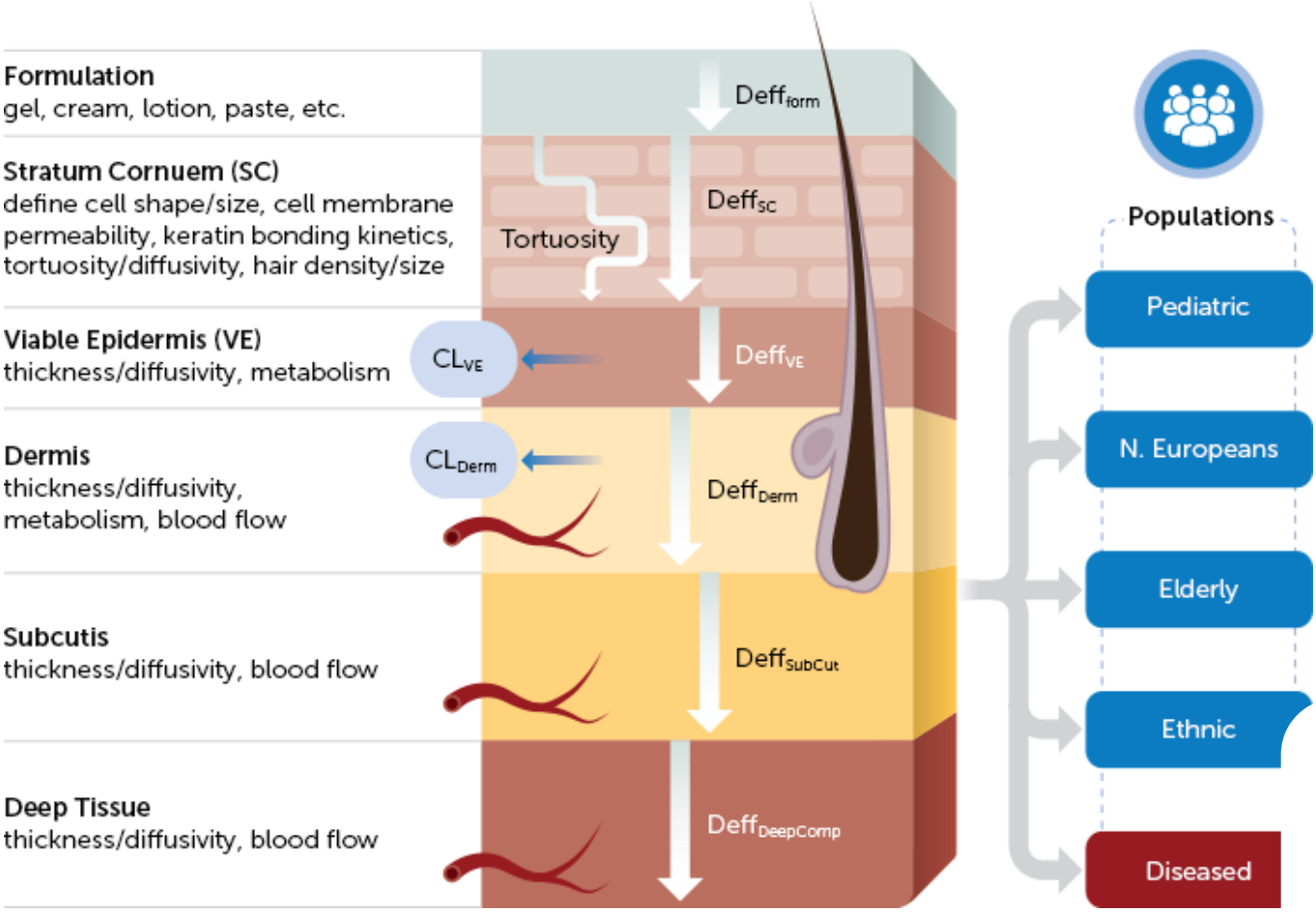
Skin in the Game: Mechanistic Modeling of Dermal Drug Absorption

Posted on March 2, 2018 by Nikunjkumar Patel

The ability to estimate systemic exposure from dermal absorption is essential in developing new dermatological medications or assessing the toxicological liability of commercially-used chemicals. Historically, animal models were used to evaluate dermal drug absorption prior to clinical testing. However, both differences in human and animal physiology as well as ethical concerns over animal testing have spurred the development of *in silico* methods to assess dermal drug absorption. In this blog post, I'll explain some recent updates to the Simcyp Simulator's mechanistic dermal model, and how it can be used to inform development of topical and transdermal drug products.

The Simcyp mechanistic dermal model—structures and parameters

The model describes the anatomy of the skin, the types of dermal formulations that can be modeled (gels, creams, ointments, pastes, and patches), and physiological differences reflective of patients of different ages, ethnicities, and disease states.



Let's briefly discuss what skin anatomical features the model includes. The first compartment is the surface skin where drugs are applied. On the surface of the skin, we account for the number and size of hair follicle the effects of gender and age on them. In addition, the pH of the skin surface is accounted for as some der drug formulations are pH-modifying. Moreover, the pH of the skin's surface determines how much drug is i or un-ionized. By default, un-ionized drugs can traverse lipidic channels in the stratum corneum—the outer layer of the epidermis. Lipophilic drugs are typically absorbed via this tortuous pathway, and that is one of th rate-limiting steps. The model is able to automatically decide whether the drug is absorbed via the intracellular lipidic pathway or the intercellular pathway, depending on the hydrophilicity, lipophilicity, and molecular weight of the compound. Once inside the corneocytes of the stratum corneum, the drug can get absorbed on the keratin which serves as a depot. So even after removal of the formulation from the skin surface, some drugs can still be absorbed from such a depot.

Once the drug passes through the stratum corneum, it crosses the viable epidermis to the dermis and the deeper layers. Within the viable epidermis and dermis, we have provided the ability to consider the metabolism of the drug while it is getting absorbed. The deep compartment is mainly muscle at the moment. But it can be modified to account for any other regions or another sub-dermal layer, for example, synovial fluid. The dermis, subcutis, and deep compartments also have their own blood flows, which are predicted based on cardiac output and body surface area of individual patients. The model also accounts for regional differences in dermis blood flow. For example, the blood flow to facial skin is relatively larger (per 100g of tissue) as compared to skin on the torso.

Accounting for differences in skin physiology between populations

Skin varies drastically between populations. Consider the difference between the smooth, plump, unblemished skin of babies and the thin, wrinkled, mottled skin of the elderly. We tried to account for differences in skin physiology between various subpopulations. The default skin model is for a healthy North European Caucasian population. When possible, we accounted for the effect of gender.

We also incorporated the changes in dermal physiology from birth to adulthood as part of the Simcyp Simulator so the user can model the impact of maturation of various skin physiology parameters with age on the dermal drug absorption. We carried out a detailed meta-analysis of literature from 1960 onwards to derive pediatric skin ontogeny functions and provided them by default in the pediatric population of the Simcyp Simulator. However, if you have additional information, you can modify the default values. In version 17, we also provided skin physiology data for a virtual elderly population, different ethnic groups (East Asian), and a dermal disease population for psoriasis.

It was a huge effort to conduct this meta-analysis to understand skin physiology. We used around 350 clinical studies to derive more than 100 parameters values for the dermal model. Overall, more than 2 person-years was spent understanding, collecting and analyzing the skin physiology data to support this model! This was made possible in part by the multi-year research funding by the US FDA* under the Generic Drug User Fee Amendment (GDUFA) initiative.

Features added in version 17

The Simcyp Simulator version 17 has several new features that have been added to the dermal model. First, support handling of vehicle evaporation. The evaporation of vehicle is important for accurately predicting th absorption of gels and formulations containing alcohol or hydro-alcoholic solutions.

We also added sub-dermis diffusion compartments for subcutis and muscle. Again, this was a huge effort b the dermal model already accounts for eight different anatomical locations on the human body. You can im that the subcutis on the face versus the thigh would be significantly different. Likewise, the subcutis tissue c thigh is significantly different between males and females. The model can also account for gender differenc drug diffusion in the sub-dermis. Similarly, the muscles in different parts of body differ in their thickness, physiology, and physical characteristics. So, we tried to account for this information in the model.

Also, we characterized the dermal drug absorption model for psoriatic skin whereby we accounted for the n and size of cracks on the skin surface, increased blood flow due to inflammation, and hyper-proliferation of skin tissue leading to changes in skin layer thickness, hydration, and pH. Currently, we are conducting performance verification of this dermal disease model, and it should be available soon.

Pediatric skin absorption can be modeled from birth up to adulthood as well. The Pediatric Simulator already accounts for age-related changes in metabolism and distribution processes. Thus, the addition of dermal physiology allows simulation of local as well as systemic exposure levels after topical application of drugs in pediatric populations.

The dermal model for all populations now has connections between pharmacokinetics (PK) and pharmacodynamics (PD). So, users can connect local skin drug concentrations to PD to simulate any response of interest.

We also added geriatric and gender effects on skin physiology in v17. Regarding the effect of ethnicity on skin physiology, it was not possible to differentiate the dermal characteristics between Korean, Japanese, and Chinese populations. So we have a common virtual East Asian population where we combined data for Korean, Japanese, and Chinese skin physiology into one population library.

Moreover, the dermal model now allows users to simulate more complicated virtual trial designs. It now supports running up to four simultaneous drug absorptions for multiple anatomical locations and mixed dosing types (dermal, oral, IV, inhaled, etc.).

Performance verification

Clearly, the updated dermal absorption model is quite detailed and flexible in terms of the populations and drugs that can be simulated. The next question is how predictive is it? To answer this question, we are conducting a thorough performance verification.

The model should support a range of different types of dermal drugs. Thus, we examined compounds that varied in terms of pKa and included neutral, acidic, and alkaline drugs. We also studied compounds that spanned a wide range of lipophilicity. Lastly, we assessed the model's ability to predict absorption for different types of formulations, including transdermal formulations like patches and topical formulations like gels and creams where the target site is local.

In addition, we are trying to predict the systemic exposure resulting from dermal absorption within different populations like pediatrics or psoriasis patients. Lastly, we sought to assess the ability of the model to simulate virtual bioequivalence for two different formulations of the same drug. Thus, the model can be used to detect formulation differences and can inform the bioequivalence assessment of different formulations.

Apart from that, many Simcyp consortium members and academic associates are using the model indepen and feeding back the performance verification of the model.

Most of the above performance verification is complete and has been published or presented at scientific conferences. Our team is also writing a series of manuscripts for publication in peer-reviewed journals.

Case study on impact of site of dermal drug application

In this case study, we used the model to predict the impact of site of drug application. By default, the mode contains dermal physiology information for eight anatomical locations (forehead, cheek, volar forearm, dor forearm, upper arm, back, thigh, and lower leg).

So we used the default skin locations and simulated the systemic PK profiles that resulted from application of rivastigmine patches. The simulated PK profiles were then compared to clinical data. The model recovered the observed exposure reasonably well when the same drug patch was applied to different anatomical locations. Thus, we verified the model's performance not only for the effect of patch, but also for the effect of application to different anatomical locations.

Case study on virtual bioequivalence assessment

The second case study examined if we can recover formulation differences for the same compound. We simulated the systemic exposure of ibuprofen ointment versus cream versus gel. The model captured the differences in systemic exposure that resulted from different topical formulations. You could also use the model to compare two different cream formulations.

Another application for this model is simulating the population variability for dermal drug formulations. This model can help identify individuals whose exposure might lie at the outer extremes and thus may be at high risk for toxicity or lack of efficacy.

Perhaps the most important application of the model is that it allows identifying clinically-relevant, critical product quality attributes. For example, we examined a formulation for a drug and found that its viscosity, but not pH, dramatically affected drug exposure. So for this compound, the viscosity may need to be closely monitored during manufacturing. The model also allows you to understand the impact of physiological parameters, like tortuosity of the stratum corneum, on drug exposure, which can be impacted by the excipients. As part of the v18 Simcyp Simulator, we will support simulating the effect of excipients on skin physiology in turn affecting the absorption of the active drug. This functionality would allow better simulation of virtual bioequivalence as the functional excipient differences can be accounted for.

As you can see, we've made many exciting updates to the dermal model of the Simcyp Simulator. We anticipate that it will help our users gain a better understanding of dermal drug disposition in different patient populations and thus support developing safer and more effective topical and transdermal drugs.

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To learn more about how our research has helped expand the Simcyp Simulator's capabilities, please watch this webinar that I gave with my colleagues, Oliver Hatley and Matthew Harwood.

Archived Webinar:
What's New in the Simcyp Simulator v17?

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Nikunj Patel is a senior research scientist in Certara's modeling and simulations group where he is leading o dermal absorption projects and is a member of the Cardiac Safety Simulator development team. He joined Ce in August 2011 and led the development of the physiologically-based IVIVC (PB-IVIVC) module of the Simcyp Simulator and the Pharmaceutics module of SIVA (Simcyp In Vitro (data) Analysis) platform. Before joining Certara, he spent three years at the life science innovation labs of Tata Consultancy Services as a research scientist, mainly working on pharmacokinetic/pharmacodynamic modeling and QSAR development for various ADMET properties. During his graduate studies, he used computer aided drug design (CADD) and molecular modeling to identify safe and potent novel anti-diabetic ligands.

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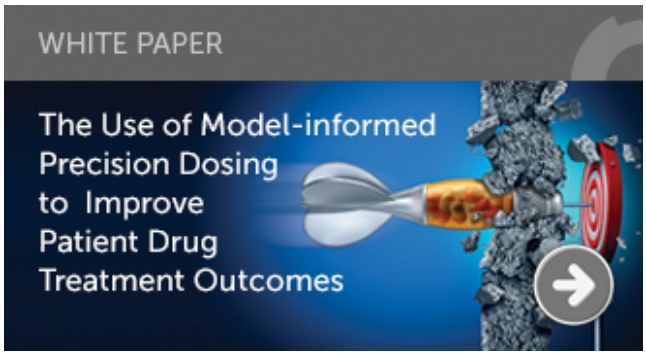

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