# Development and Validation of a Dermal PBPK Model for Prediction of the Hair Follicular Absorption of Caffeine: Application of the Simcyp MPML MechDermA model

**Frederico S Martins[1], Nikunjkumar Patel[1], Masoud Jamei[1] and Sebastian Polak[1,2]**

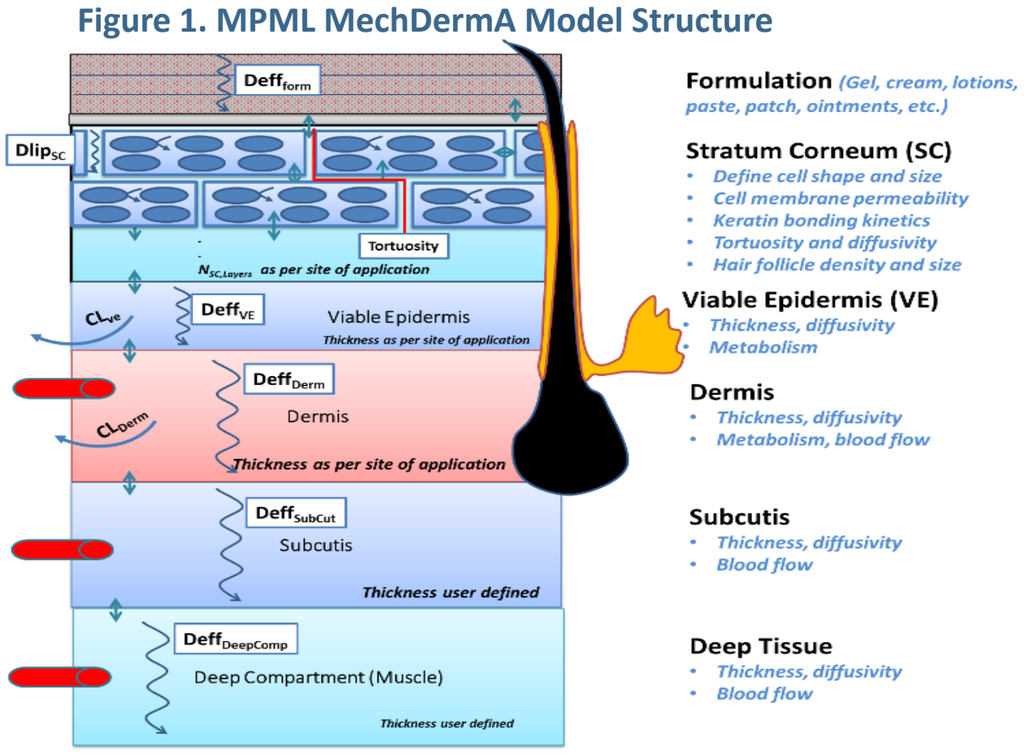
**[1]Simcyp (a Certara company), Sheffield, United Kingdom, [2]Jagiellonian University Medical College, Kraków, Poland**

## Abstract

Dermal drug application can be a route of choice for the delivery of drug for local and systemic action due to numerous advantages over oral administration [1]. Absorption into and through hair follicle is of significant interest for local delivery of drugs and enhancement of transdermal permeation of small hydrophilic drugs which have limited permeation via lipophilic stratum corneum tissue. Recently, it has been shown clinically that hair follicles can significantly contribute to the absorption of topically applied caffeine [2]. Mechanistic physiologically based pharmacokinetics models such as the Mechanistic Dermal Absorption (MechDermA) have a unique advantage in integrating both the drug and formulation characteristics and the underlying skin physiology [3]. Aim of the present work was to demonstrate the application of the Multi-Phase and Multi-Layer (MPML) MechDermA model [Figure 1] in predicting the impact of hair follicular pathway on caffeine absorption.

## Background

**Figure 1. MPML MechDermA Model Structure**




The SC is modelled as brick-and-mortar structure where bricks (corneocytes) are cuboid in shape embedded within the mortar of intercellular lipid matrix. The corneocyte is composed of water and protein core encapsulated within a lipid envelope. Model can simulate partitioning and absorption through hair follicular (HF) pathway depending on affinity for sebum and molecular size. While the drug diffuses through intercellular lipid matrix, depending on the drug to cell affinity and the concentration gradient, it can permeate into or out of the cells. Once inside the cell, the drug can get adsorbed onto the keratin. The adsorption can be modelled as steady state (fuSC) or transient nonlinear adsorption/desorption kinetics (Kon/Koff). The drug present in the lipid matrix can diffuse to the next layer of SC. From the last layer of SC drug can partition into the VE depending on SC:VE partition coefficient. The partition coefficient between VE and dermis was set as 1 (i.e. no difference in affinity). Blood flow to the dermis was modelled as a function of cardiac output, body weight and body surface area as per the Simcyp PBPK model framework. Further longitudinal diffusion into the subcutis and deep tissue was neglected in this work.

## Method

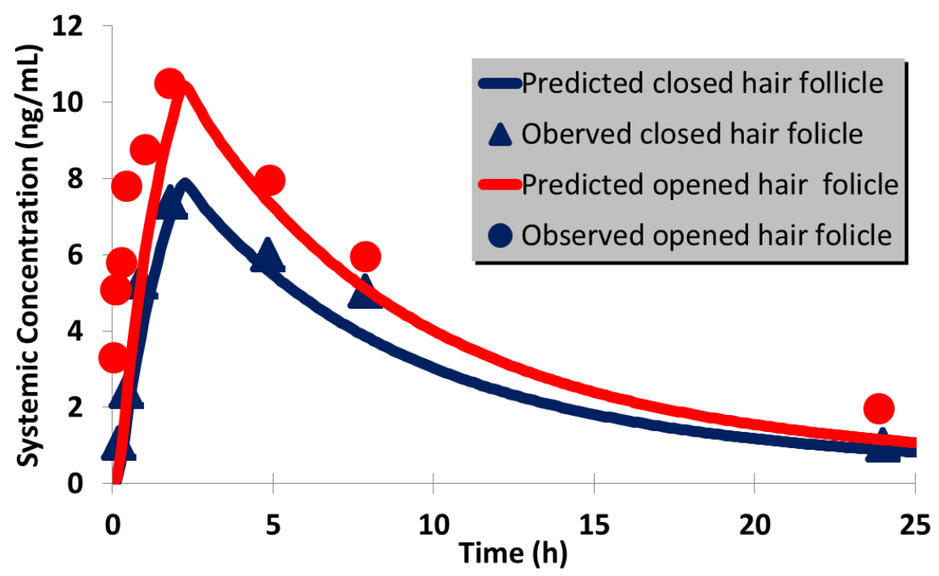
The model performance has been assessed using caffeine as a model drug. Input data included physicochemical were MW=192.19, pKa = 1.05, LogP = -0.07,$fu_{sc}$=0.42, $fni_{skin\ surface}$=0.99, oral plasma clearance $CL_{po}$=5.6 L/h, volume of distribution Vss= 0.45L/kg, and the surface skin pH=5.5. Diffusion and partition coefficients were calculated using QSAR models (se Table 1). Solution ethanol/propylene glycol (3:7) loaded with 2.5 % of caffeine was simulated as per clinical study design and compared with observed clinical plasma drug concentration time profiles [4]. Caffeine has significantly higher affinity for sebum than SC (Table 1). Caffeine solution was applied on 25cm$^2$ of chest to six males Caucasian healthy volunteers. To study the closed hair follicle effect on caffeine absorption in clinic, each hair follicle orifice in the test area was blocked with a micro drop of varnish-wax mixture prior to the caffeine solution being applied, reducing the area of application by 8%. We mimicked the clinical scenario in MPML-MechDermA model of Simcyp V16 using back (trunk) skin physiology. The skin metabolism was neglected.

**Table 1: QSAR prediction of diffusion and partition coefficients of caffeine in solution**

| | Parameter | QSAR prediction | Reference |
|---|---|---|---|
| **Partition Coefficient** | Lipid: vehicle | 1.18 | Hansen 2013 [5] |
| | Sebum: vehicle | 19.39 | Valiveti 2008[6] |
| | VE:SC | 1.44 | Kretsos 2008 [7] |
| | Skin:blood | 0.99 | Shatkin&Brown [8] |
| **Diffusion Coefficient ($cm^2/h$)** | SC lipid | $1.85x10^{-5}$ | Mitragotri 2003[9] |
| | VE | 0.011 | Kretsos 2008[7] |
| | Dermis | 0.011 | Kretsos 2008[7] |
| | Sebum | 0.00081 | Johnson 1996[9] |
| | Formulation | 0.00046 | Scheibel 1954[10] |
| **Keratin binding** | Kon/koff | 82.4 and 0.86 | Seif 2012[11] |

The predicted plasma concentration time profiles with open and closed hair follicles compared with corresponding observed clinical data is shown in Figure 2.

**Figure 2. Comparison of model prediction and clinical observations**




## Discussion

The study results show that the MPML MechDermA model can predict the absorption through the hair follicle reasonably well and the results are encouraging. The kinetic penetration processes are likely to be dependent on the nature of substance and formulation employed such as pH, viscosity, volume, excipients and duration of application. Hence those parameters should be accounted for as accurately as possible for better prediction. The binary solvent (ethanol/propylene glycol) could increase the skin permeation of chemicals by causing variation in the fluidity of the stratum corneum lipids. Frum et al. [5] reported the percentage contribution by follicles decreased with an increase in the lipophilicity of topically applied or exposed compounds. The hair follicles occupy only about 0.1% of the whole skin area, but this can be as high as about 10% for the face around the mouth and scalp [12]. The absorption by HF area contributed 27% of caffeine absorbed. Liu et al 2011 observed higher $T_{max}$ with closed HF, but we could not predict this effect. However the $T_{max}$ is highly variable parameter in dermal drug delivery. Hence, it is not clear if the higher $T_{max}$ was due to HF closure or due to smaller study size leading to difference in the mean $T_{max}$. Further validation of the model using drugs with various physicochemical characteristics and different types of formulations and site of application are warranted to improve confidence in such a modelling strategy.

## References

1. Mohd, F., et al., Contribution of the Hair Follicular Pathway to Total Skin Permeation of Topically Applied and Exposed Chemicals. Pharmaceutics, 2016. 8(4): p. 32.
2. Trauer, S., et al., Development of an in vitro modified skin absorption test for the investigation of the follicular penetration pathway of caffeine. Skin Pharmacol Physiol, 2010. 23(6): p. 320-7.
3. Polak, S., et al., Prediction of concentration-time profile and its inter-individual variability following the dermal drug absorption. J Pharm Sci, 2012. 101(7): p. 2584-95.
4. Liu, X., et al., Hair follicles contribute significantly to penetration through human skin only at times soon after application as a solvent deposited solid in man. British Journal of Clinical Pharmacology, 2011. 72(5): p. 768-774.
5. Hansen et al. 2013. Improved input parameters for diffusion models of skin absorption. *Adv drug deliv rev* 65(2): 251-264.
6. Valiveti et al. 2008 Investigation of drug partition property in artificial sebum." *Int J Pharm* 346(1): 10-16.
7. Kretsos et al. 2008 Partitioning, diffusivity and clearance of skin permeants in mammalian dermis." *Int J Pharm* 346(1): 64-79
9. Mitragotri. 2003 Modeling skin permeability to hydrophilic and hydrophobic solutes based on four permeation pathways." *J Contr Rel* 86(1): 69-92.
10 Scheibel 1954 Correspondence. Liquid Diffusivities. Viscosity of Gases." *Ind & Eng Chem* 46(9): 2007-2008.
11 Seif & Hansen 2012 Measuring the stratum corneum reservoir: desorption kinetics from keratin. *J Pharm Sci* 101: 3718-3728.
12 Frum,Y.;Bonner,M.C.;Eccleston,G.M.;Meidan,V.M.Theinfluenceofdrugpartitioncoefficientonfollicular penetration: In vitro human skin studies. Eur. J. Pharm. Sci. 2007, 30, 280–287.

**Acknowledgement** Funding for the work presented here was made possible, in part, by the Food and Drug Administration through grant 1U01FD005225-01, views expressed here by the authors of the work do not necessarily reflect the official policies of the Food and Drug Administration; nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.