Development of the dermal absorption model for the ketoprofen local and systemic exposure prediction

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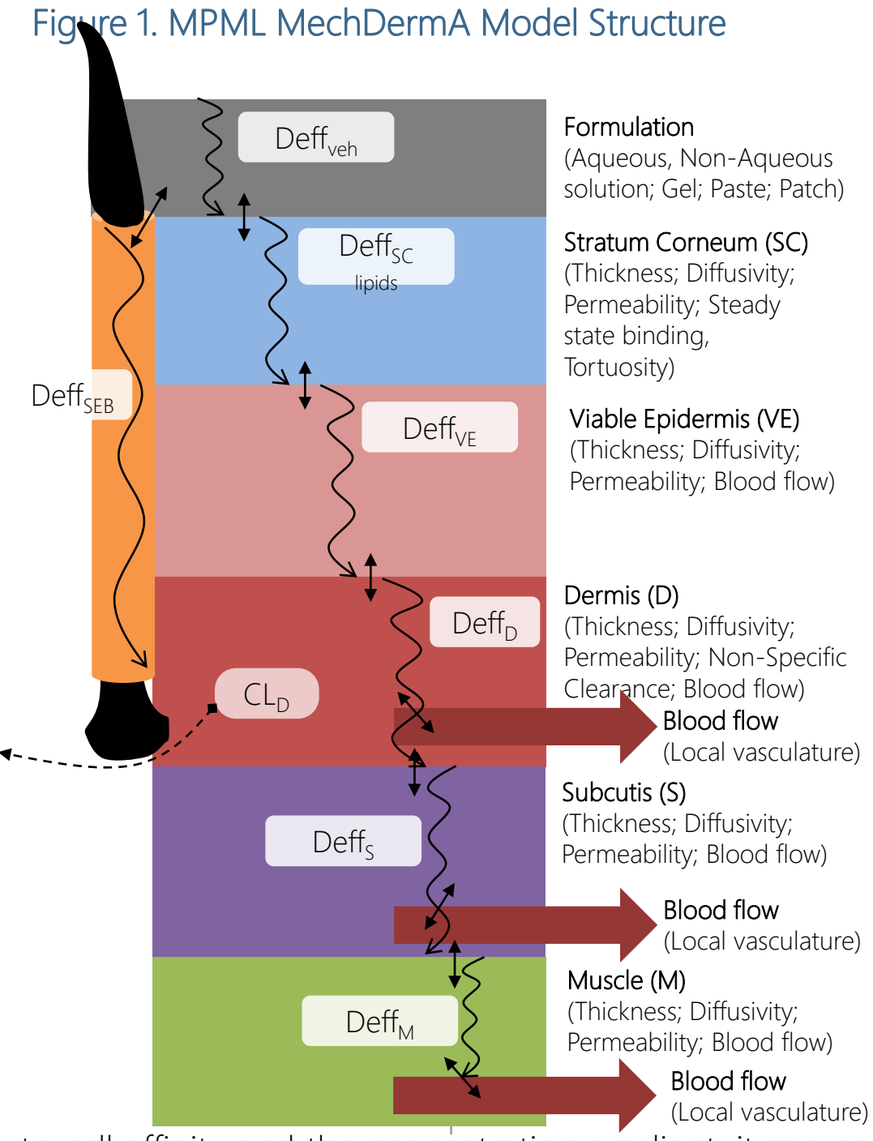
Introduction

Ketoprofen is a nonsteroidal anti-inflammatory agent (NSAIA) with analgesic and antipyretic properties. Topically applied drug is formulated in the form of patches, gels, or solutions. The main aim of the project was to develop physiologically-based pharmacokinetic (PBPK) model allowing for the quantitative assessment of the local (muscle) and systemic exposure after topical application of ketoprofen. Additionally the developed model have been verified against the literature derived clinical data.

Materials and Methods

Simcyp Simulator V17 with the MPML MechDermA model was used for the ketoprofen dermal disposition [1].

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 a water and protein core encapsulated within a lipid envelope. The model can simulate partitioning and absorption through a hair follicular (HF) pathway depending on the drug's affinity to sebum and its molecular size. While the drug diffuses through the intercellular lipid matrix, depending on the drug to cell affinity and the concentration gradient, it can permeate into or out of the cells. Blood flow to dermis was modelled as a function of cardiac output, body weight and body surface area as per the Simcyp PBPK model framework.

Simcyp simulator V17 was used in the study. ADME parameters utilized for the compound file development were derived from the available sources and are presented below (Table 1).

Table 1. ADME parameters for ketoprofen.

Group	Parameter	Value [unit]	Source
phys-chem	MW	254.285	[2]
	logP	3.12	[3]
	type	monoprotic acid	[2]
	pKa	4.45	[2]
Binding	B/P partition ratio	1.1	[4]
	fuplasma	0.01	[3]
Distribution	Vss	0.132 [L/kg]; CV=17.2%	[5]
Elimination	CLIV	5.16 [L/h]; CV=17.4%	[5]

Clinical study settings (i.e. dose, dosing, numer of individuals, formulation, area of application) were closely mimicked during the simulation studies [5-8].

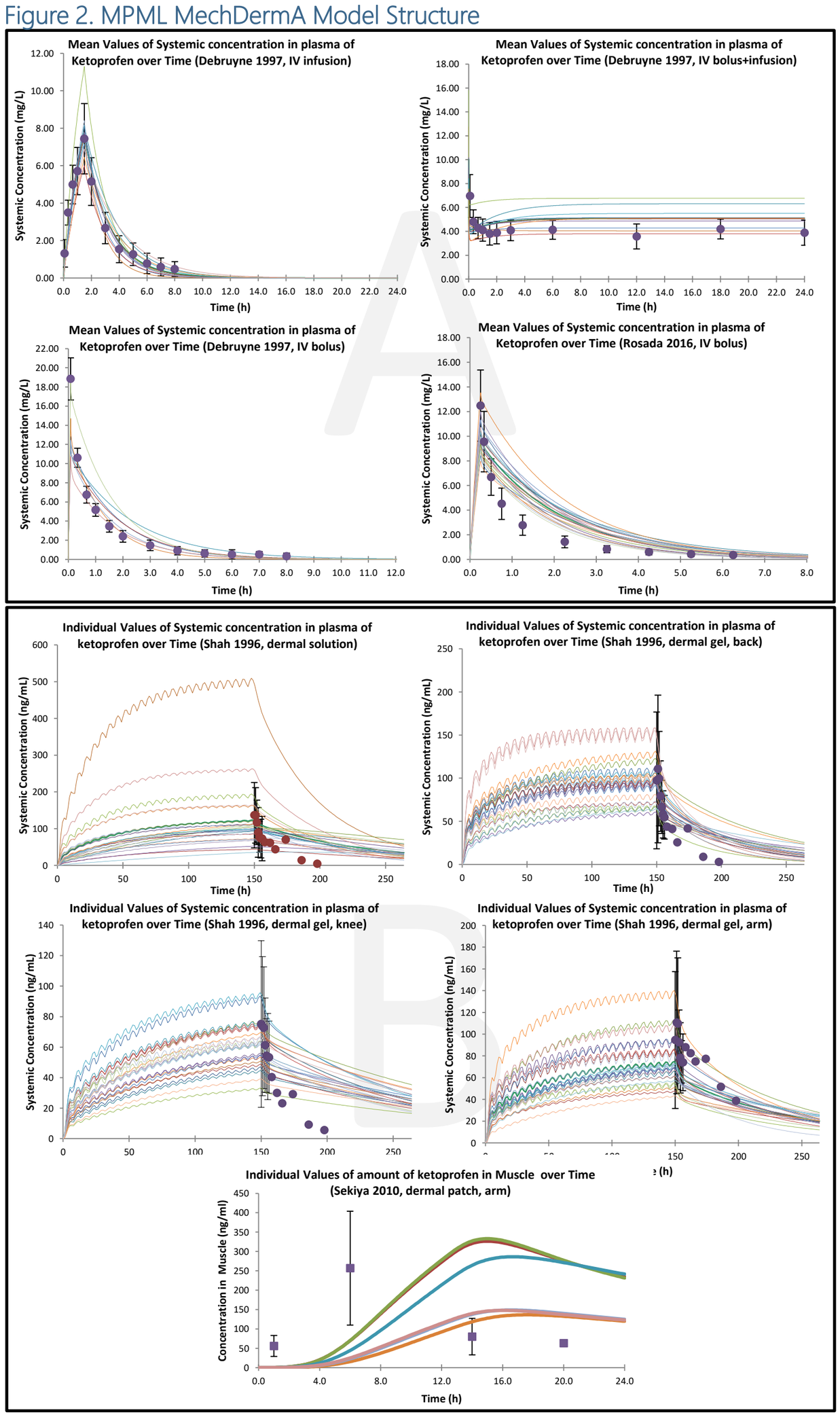
Table 2. Partition and diffusion parameters for ketoprofen.

Parameter	Value [unit]	Source
$Kp_{sc\_lip:vehicle}$	162.5451	predicted – Hansen 2013
$Kp_{sc:ve}$	6.9144	predicted – Kretsos 2008
$Kp_{dermis:ve}$	1	assumed
$Kp_{sebum:vehicle}$	1643.341	predicted – Valiveti 2008
$Kp_{skin:blood}$	2.67544	predicted – Shatkin&Brown 1991
$Kp_{sebum:ve}$	0.0989	calculated – $Kp_{lip:vehicle}/Kp_{sebum:vehicle}$
D_{sc_lip}	3.392E-06 [cm^2/h]	predicted – Mitragotri 2003
D_{ve}	0.000311 [cm^2/h]	predicted – Bunge&Cleek 1995
D_{dermis}	0.000311 [cm^2/h]	predicted – Kretsos 2008
D_{sebum}	0.000653 [cm^2/h]	predicted – Johnson 1996
fu sc	0.0934	predicted – Polak 2016
$f_{ni,\ corneocytes}$	1	assumed

The ketoprofen specific parition and diffision coefficients used as the input parameters are presented in Table 2.

The predicted and observed ketoprofen plasma concentration after single IV dose are presented in Figure 2A and after dermal application in Figure 2B (circles + lines – observed average + SD).

Figure 2. MPML MechDermA Model Structure



Discussion and Conclusions

The developed model was verified against the IV data and was able to recover the systemic and local concentration after dermal application.

1) Martins F, et al. 2017 GRC - Barrier Function of Mammalian Skin, Waterville Valley, NH., 2) https://pubchem.ncbi.nlm.nih.gov/compound/3825; 3) https://www.drugbank.ca/drugs/DB01009; 4) Fura A, et al. Biopharm Drug Dispos. 2008;29(8):455-68.; 5) Debruyne D, et al. Clin Pharmacokinet. 1987;12(3):214-21.; 6) Shah AK, et al. Pharm Res. 1996;13(1):168-72.; 7) Sekiya I, et al. AAPS PharmSciTech. 2010;11(1):154-8.; 8) Rosada M, et al. JMS. 2016; 85(4):254-263.

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