Predicting diclofenac systemic and synovial fluid concentrations after dermal application using the Multi-Phase Multi-Layer MechDermA PBPK model

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Background

Topical formulations of diclofenac are developed for local application, aimed at targeted delivery to the site of action (soft tissue/joint). The rationale for this approach is to minimize systemic concentrations of diclofenac and thereby minimize the risk of the systemic side-effects. There is general consensus that following topical application, plasma concentrations of diclofenac are significantly lower than following oral or intramuscular administration [10]. However, this does not appear to be the case for local tissue concentrations. Some authors reported that following topical application to the knees, diclofenac distributes preferentially to the target site and the concentrations measured in synovial fluid and synovial tissue were up to 20 times that of the measured values in plasma [11].

The objective of the current study was to assess the prediction performance of the recently developed Multi-Phase Multi-Layer (MPML) Mechanistic Dermal Absorption (MechDermA) model for predicting systemic and local drug concentrations. The ultimate goal is to develop a flexible framework for the topically applied drugs. Diclofenac in various gel formulations was used as a model compound due to availability of wide range of clinical data.

Methods

The MPML MechDermA model is incorporated within a whole-body physiologically based pharmacokinetics (PBPK) model. Within this model, the stratum corneum (SC) is modelled as a brick-and-mortar structure with cuboid bricks representing the corneocytes immersed in the lipidic matrix [1]. The model determines the number of corneocytes that can be accommodated in the skin surface area where the formulation is applied, accounting for the tight packing mosaic arrangement of cells with intercellular lipid thickness. The model considers water, protein and the lipid fractions. This structure allows simulation of complex diffusion through the SC for drugs with different physicochemical properties as well as different formulations, namely gels, emulsions, patches, suspensions, and pastes [2]. The MPML-MechDermA model can also simulate partitioning and absorption through the hair follicular pathway. The tortuosity parameter was taken from the experimentally reported value for in vivo human skin [3]. Blood flow to the dermis was modelled as a function of cardiac output, body weight and body surface area as per the Simcyp Simulator (V16).

The Simcyp default diclofenac compound file was used and the skin disposition parameters (partition, diffusion and binding coefficients) were calculated using the built-in QSAR models. The Single Adjusting Compartment (SAC) was used to mimic the synovial fluid tissue. Drug transfer between systemic compartment and synovial fluid was described by fitting the first order rate constants k_{in} and k_{out} [h^{-1}]. There was no direct transdermal diclofenac transport to synovial fluid [Figure 1]. Clinical data from 6 different studies, 2 different formulations, namely emulsion gel and solution gel of diclofenac, 4 different locations (back, thigh, arm, and knee), a range of application areas (100 - 1200 cm^2), multiple dosing scenarios (2-4 times a day), single and multiple dosing in various populations for different genders and age distribution were used. All clinical data were derived from the available literature reports [4-9]. Plasma and, whenever available, synovial fluid concentration were the endpoints for comparison.

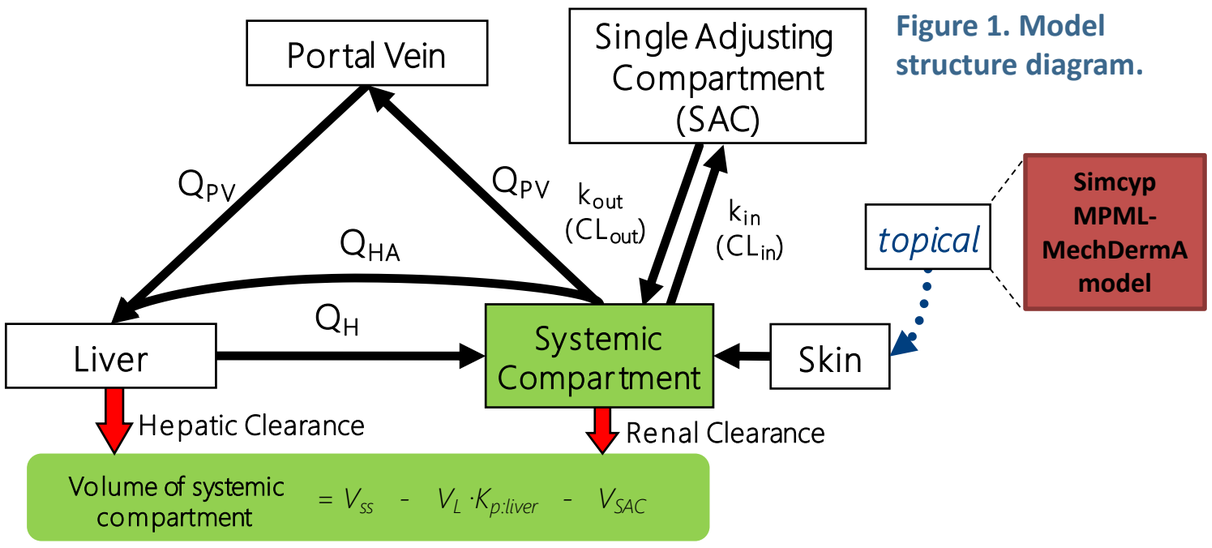


Figure 1. Model structure diagram.

Results``

Table 1 presents simulation results and their comparison against the observed concentrations for various, defined in the original work, time points.

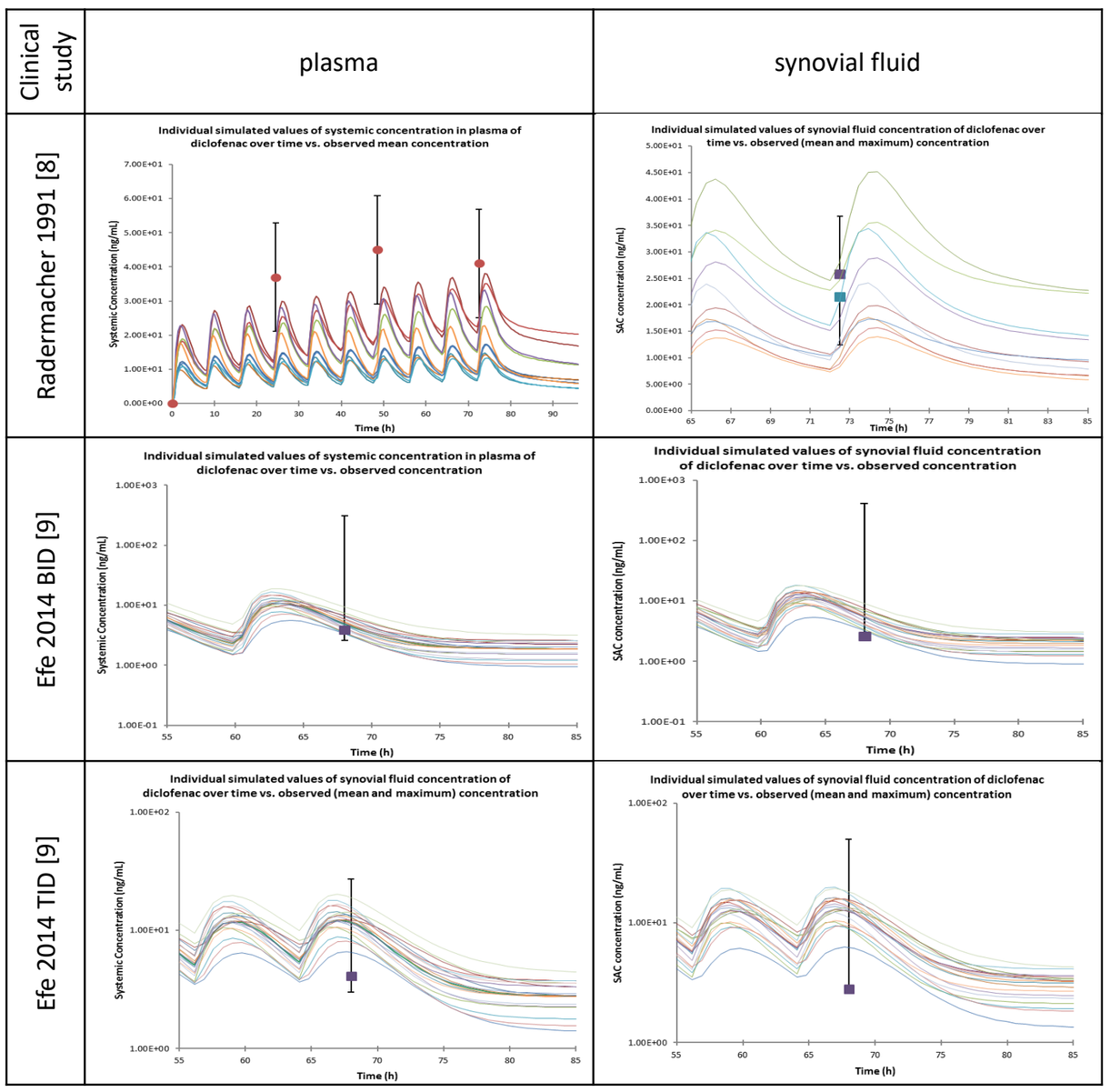
Table 1. Comparison of the clinically observed and simulated plasma (A) and local (B) concentrations after topical application of various diclofenac formulations.

A. Clinical study	Plasma concentration (mean or median*) [ng/ml]			
	observed	SD or range	predicted	SD or range
Brunner 2005 [4]	4.9*	3.8	8.37	4.3
Kienzler 2010 knee [5]	9.7	5.3	9.35	3.5
Kienzler 2010 knee+hand [5]	33.6	19.9	32.5	10.5
Dehghanyar 2004 [6]	8.5	3.6	12.0	3.3
Sioufi 1994 [7]	12.9	8.1	15.1	7.6
Radermacher 1991 [8]	41.0	15.8	23.4	9.0
Efe 2014 BID [9]	3.9*	1.3-302.2	4.5*	3.1-8.8
Efe 2014 TID [9]	4.1*	1.1-23.0	11.5*	6.4-18.2

B. Clinical study	Synovial fluid concentration (mean or median*) [ng/ml]			
	observed	SD or range	predicted	SD or range
Radermacher 1991 [8]	23.7	8.9	15.2	6.5
Efe 2014 BID [9]	2.6*	0.4-408.5	5.0*	3.0-8.4
Efe 2014 TID [9]	2.8*	0.2-47.1	12.1*	6.1-17.5

Concentration-time profiles comparing plasma and synovial fluid are presented in Figure 2.

Figure 2. Individual simulated plasma and synovial fluid concentrations vs mean observed values.



The mechanistic MPML-MechDermA model of the skin absorption accounts for the drug, formulation, physiology and environmental parameters. The presented results show the model capability to successfully simulate various clinical scenarios accounting for formulation effects. It is also capable of providing acceptable level of the observed variability, which was significant across reported clinical studies.

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