Assessing Formulation Attributes' Impact On Local And Systemic Exposure Of Clindamycin After Topical Application Of Pro-Drug Clindamycin Phosphate Using PBPK Modelling

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Introduction

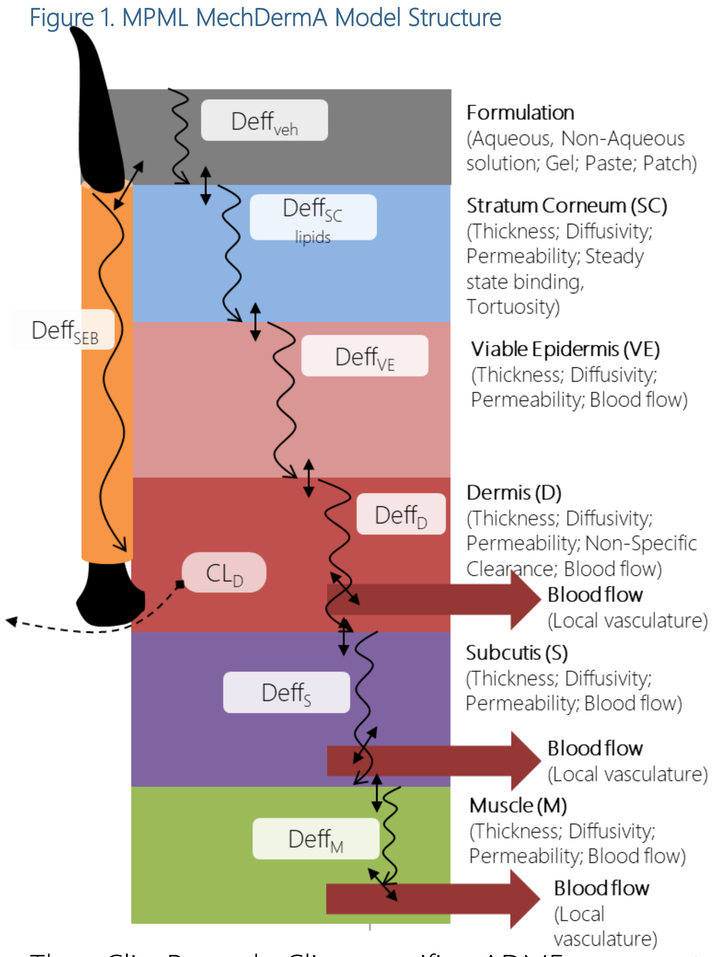
Clindamycin (Clin) is an antibiotic typically given as a prodrug, clindamycin phosphate (Clin-P), which is converted to free base (Clin) and the enzymatic hydrolysis has been suggested as the probable mechanism of conversion [1]. Formulation and excipients attributes affect the absorption and local and systemic exposure of the active ingredient [2].

The aim of this study was to develop a Physiologically Based Pharmacokinetic (PBPK) model describing Clin exposure after topical application of various formulations, with the ultimate aim of using the verified model to run virtual BE clinical studies and perform bioequivalence analysis.

Materials and Methods

Simcyp Simulator V17 with the Multi-Phase Multi-Layer (MPML) Mechanistic Dermal Absorption (MechDermA) (Figure 1) model was used to develop a PBPK model for predicting the drugs disposition in a first step and dermal drug absorption and systemic exposure after topical application in a second step [3,4,5].

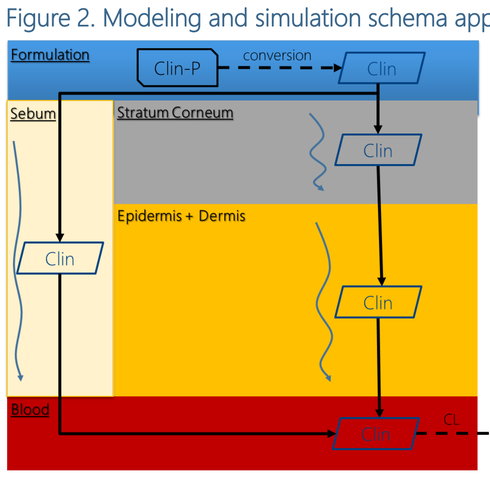
Figure 1. MPML MechDermA Model Structure



The SC is modelled as a brick-and-mortar structure where bricks (corneocytes) are cuboid in shape and embedded within the mortar of intercellular lipid matrix. The corneocyte composes 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.

The Clin-P and Clin specific ADME parameters utilized for the compound files development were derived from the available sources and are presented below (Table 1). Disposition of Clin-P and Clin (after intravenous (IV) administration) and Clin (after dermal (D) application - assuming that hydrolysis occurs at the surface of the skin and the rate of conversion is relatively faster than the rate of absorption; Figure 2) were simulated [ref].

Figure 2. Modeling and simulation schema applied in the current study.



The protein binding, elimination and distribution parameters for Clin-P (parent) and Clin (metabolite) were collated from literature or optimised using clinical observations as shown below.

Dermal formulations included aqueous solution and solution gel (Cleocin-T) and were characterized by viscosity (18 and 5400 cP respectively) and pH of formulation (only gel=5.7) [1].

Table 1. Phys-chem and ADME parameters for clindamycin phosphate and clindamycin.

Compound	Class	Model Mechanism	Parameter	Value (CV%)	Reference
Clin-P	Phys chem	Measured	logP/pKa(s)	0.5/0.9,6.5	[6,7]
	Blood partitioning	Assumed	B/P	0.76	assumed to be equal to Clin
	Plasma protein binding	Predicted	fu	0.75	QSAR predicted
	Distribution	Minimal PBPK	Vss (L/kg)	0.26 (68)	[metaanalysis]
	Elimination	Plasma esterase	$t_{1/2}$ (min)	2.5	optimized
Clin	Phys chem	Measured	logP/pKa(s)	2.16/7.72	[8,9]
	Blood partitioning	Measured	B/P	0.76	[10]
	Plasma protein binding	Measured	fu	0.22	[metaanalysis]
	Distribution	Full PBPK	Vss (L/kg)*	0.992	[metaanalysis]
	Elimination	Total clearance Renal clearance	CLiv (L/h) CL_R (L/h)	23.23 (23) 1	[11]

The MPML MechDermA model was used to describe the clindamycin dermal absorption. All diffusion, partition, and binding parameters were calculated using the build-in QSAR models using based on the literature derived physico-chemical parameters: logP=2.16, pKa for monoprotic base=7.72, MW=424.981 [8,9].

Clinical trials were replicated in the Simulator using the same population size, gender proportion, age range and the site of application when possible. Sensitivity of systemic exposure parameters (AUC and Cmax) towards changes in formulation viscosity and pH was further analysed to get gain insight into the impact of these parameters and also to guide potential new generic formulation development.

Table 2. Partition and diffusion parameters for clindamycin.

Parameter	Value [unit]	Source
$Kp_{sc\_lip:vehicle}$	36.96	predicted – Hansen 2013
$Kp_{sc:ve}$	15.98	predicted – Kretsos 2008
$Kp_{dermis:ve}$	1	assumed
$Kp_{sebum:vehicle}$	432.02	predicted – Valiveti 2008
$Kp_{skin:blood}$	1.93	predicted – Shatkin&Brown 1991
$Kp_{sebum:ve}$	0.085	calculated – $Kp_{lip:vehicle}/Kp_{sebum:vehicle}$
D_{sc_lip}	1.08E-05 [cm^2/h]	predicted – Mitragotri 2003
D_{ve}	0.0018 [cm^2/h]	predicted – Bunge&Cleek 1995
D_{dermis}	0.0018 [cm^2/h]	predicted – Kretsos 2008
D_{sebum}	0.00047 [cm^2/h]	predicted – Johnson 1996
fu sc	0.195	predicted – Polak 2016
$f_{ni,\ corneocytes}$	1	assumed

The clindamycin specific, QSAR predicted parition and diffusion coefficients used as the input parameters are presented in Table 2.

Results

Figure 3A presents the observed (dots) and predicted (lines) Clin-P and Clin concentration after IV dosing of 600 and 1200 mg of Clin-P to 6 individuals [12]. Figure 3B presents the observed (dots) and predicted (lines) Clin concentration after dermal application of clindamycin solution [11] and gel [1].

Figure 3. Results of the simulations after IV (A) and dermal application (B)

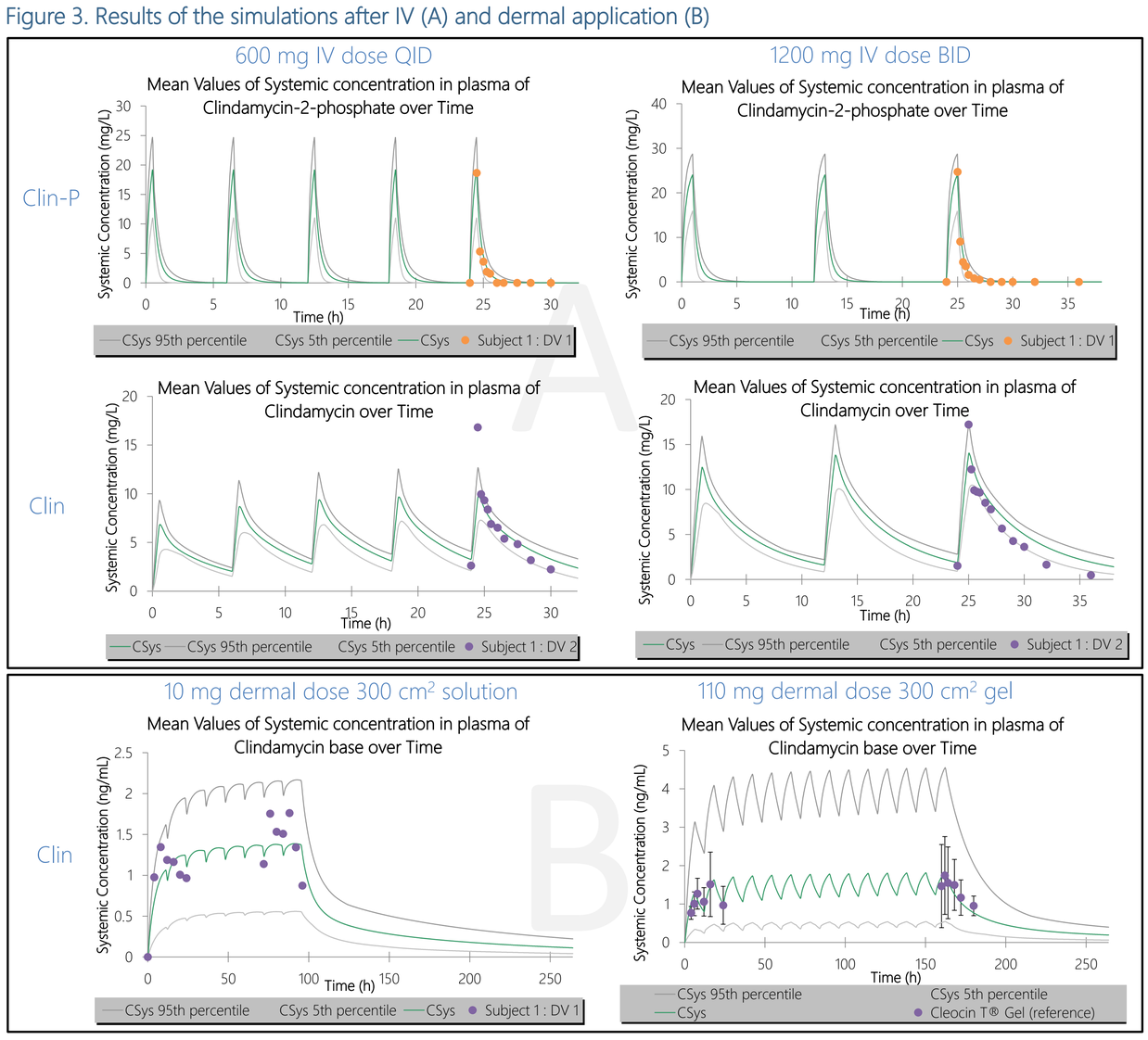
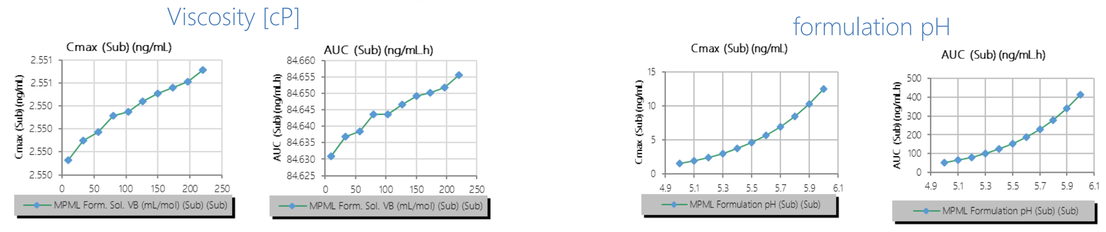


Figure 4 shows the results of model sensitivity analysis of systemic exposure (Cmax and AUC) to gel viscosity and formulation pH.

Figure 4. Results of the model sensitivity analysis for two chosen parameters – formulation pH and viscosity



Discussion and Conclusions

The developed model was able to recover systemic Clin-P (IV) and Clin (IV, D) concentrations and differentiate between the solution and gel topical formulations. The model can also simulate the impact of the formulation pH and other parameters which can become crucial parameters for potential generic products.

References

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