Towards Virtual Exposure Assessment of Dermally Applied Drugs – PBPK Model of Buprenorphine Transdermal Patches

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Abstract

Dermal drug administration can be a preferred route for the delivery of drugs for local or systemic action, with numerous advantages over oral administration. Physiologically Based Pharmacokinetic (PBPK) models have recently gained significant attention in regulatory submissions to quantitatively predict drug-drug interactions (DDIs) and absorption/bioavailability processes [1, 2]. A PBPK approach has a strong potential to help bridge the gap in clinical knowledge in a situation where clinical studies are either difficult or practically infeasible.

Main objective of the current project was to develop and assess a PBPK model for buprenorphine (BUP) and its metabolite norbuprenorohine (NOR) dermal patches using available physico-chemical, in vitro ADME and formulation specific data for prediction of systemic exposure.

Methods

Prior ADME and formulation specific in vitro data of buprenorphine and its main metabolite norbuprenorphine were collated from publicly available sources. This includes the enzyme specific metabolism information (intrinsic clearances for CYP3A4, CYP2B6, and UGT1A1). The data were used in the Simcyp Simulator (V16) to develop the parent and metabolite compound files. The parent-metabolite model was qualified against published clinical studies using intravenous (bolus and infusion) administration of buprenorphine and the observed plasma concentration of buprenorphine and when available norbuprenorphine. After addition of the formulation (in vitro release rate from the patch, dose, thickness) and application (location and area) specific data the qualified compound files were used to predict the plasma exposure after single and multiple dermal patch application using the Multi-Phase Multi-Layer (MPML) Mechanisitic Dermal absorption model implemented within the Simcyp Simulator (Figure 1).

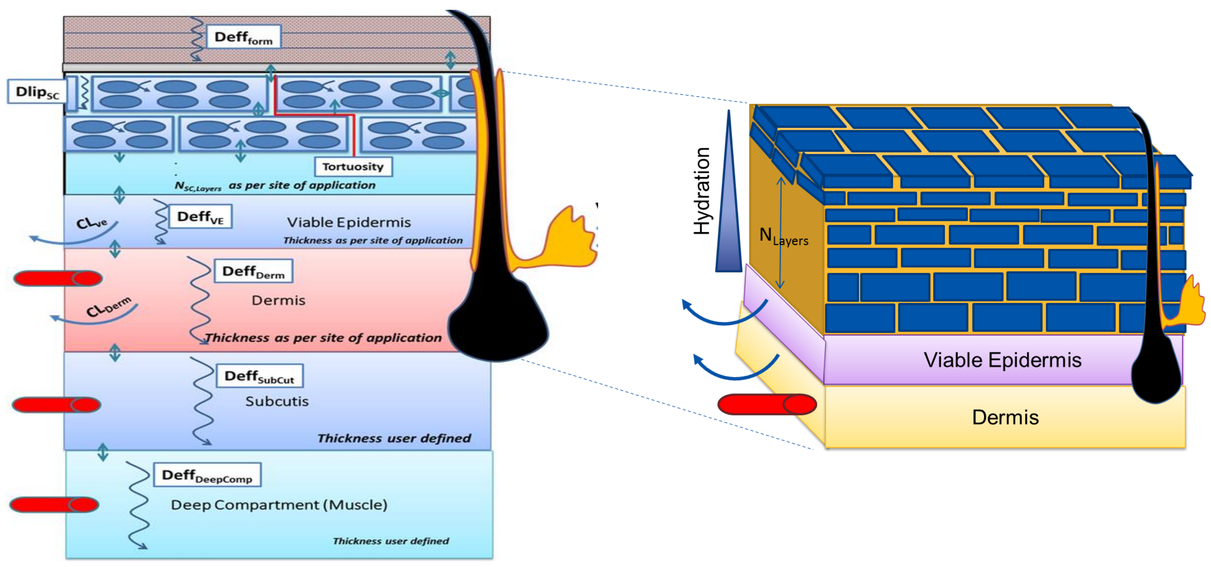

Figure 1. Structure of the MPML-MechDermA model of Simcyp Simulator

Two IV clinical studies were used to validate the developed compound files [1,2]. Norbuprenorohine clearance was assumed to be equal to buprenorohine.

Table 1a, 1b. Buprenorphine ADME / skin permeation parameters.

Group	Parameter	Value [unit]	Source
P-Ch	MW	467.78	https://pubchem.ncbi.nlm.nih.gov/compound/644073
	logP	4.82	https://pubchem.ncbi.nlm.nih.gov/compound/644073
	compound type	ampholyte	021306Orig1s000ChemR https://pubchem.ncbi.nlm.nih.gov/compound/644073
	pKa1 / pKa2	9.62 / 8.31	https://pubchem.ncbi.nlm.nih.gov/compound/644073 Avdeef, A. et al. 1996
B	B/P	1	Launiainen et al. 2013
	fu plasma (predominantly binding to HSA)	0.04	https://www.drugbank.ca/drugs/DB00921 Garrett et al. 1985
D	Vss	13.316 [L/kg]	R&R Method 3 predicted (observed 10.8 L/kg – Huestis et al. 2013)*
E	CLint / CL_R	CYP3A4 = 472 [µl/min/mg] CYP2B6 = 1.2 [µl/min/mg] UGT1A1 = 342 [µl/min/mg] CL_R = 0.535 [L/h]	retrograde calculator assumed from the renally cleared drugs fraction

Group	Parameter	Value [unit]	Source (QSAR model)
A	$Kp_{sc\_lip:vehicle}$	1	assumed (formulation specific - patch)
	$Kp_{sc:ve}$	1	assumed (formulation specific - patch)
	$Kp_{dermis:ve}$	1	assumed (formulation specific - patch)
	$Kp_{sebum:vehicle}$	17506.85	predicted – Valiveti et al. 2008
	$Kp_{skin:blood}$	2.853	predicted – Shatkin&Brown 1991
	D_{sc_lip}	1.08E-05 [cm^2/s]	predicted – Mitragotri et al. 2003
	D_{ve}	0.001182 [cm^2/s]	predicted –Bunge&Cleek
	D_{dermis}	0.001182 [cm^2/s]	predicted –Kretsos et al. 2008
	D_{sebum}	0.00045 [cm^2/s]	predicted – Johnson et al. 1996
	fu sc	0.115	predicted – Polak et al. 2016
	$f_{ni,\ corn}$	1	assumed

Results

For intravenous administration of buprenorphine, visual checks indicated that the model adequately predicted the buprenorphine and norbuprenorphine concentrations (Figure 1A and 1B – Bai and Kuhlman study respectively).

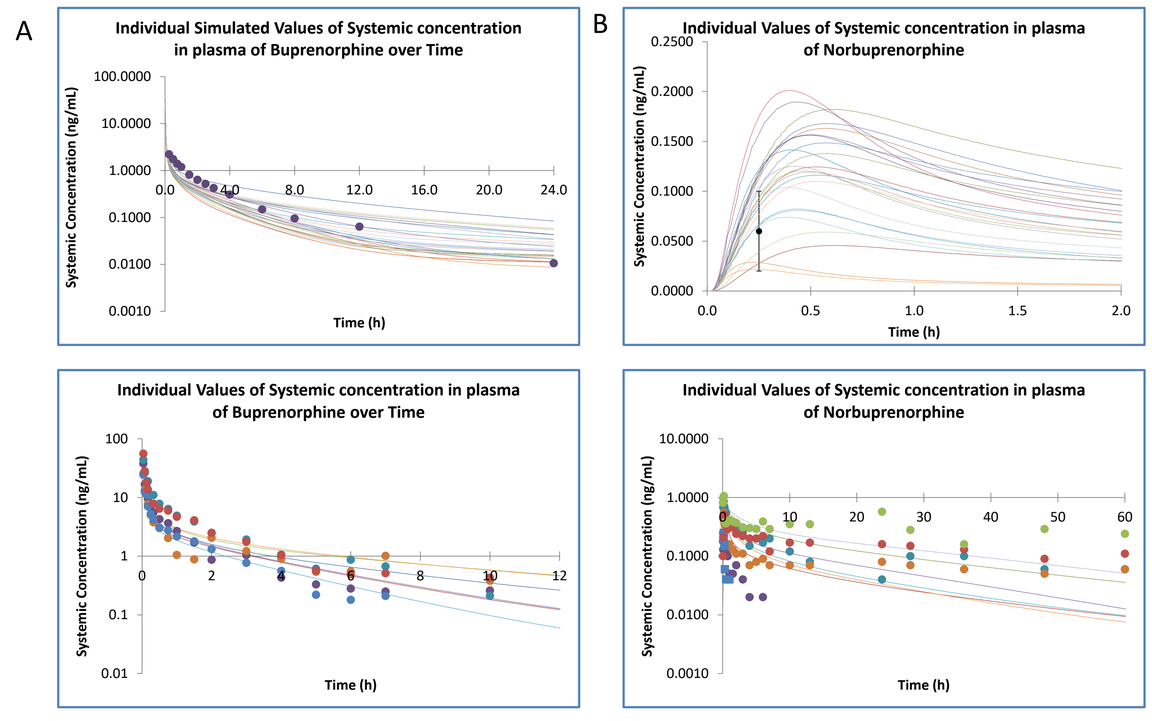

Figure 1. BUP and NOR predicted plasma exposure after IV dose (bolus and infusion).

For topical administration of buprenorphine, visual checks indicated that the model adequately predicted the buprenorphine and norbuprenorphine concentrations (Figure 2A and 2B – Kapil 2012 [3] and Kapil 2013 [4] study respectively).

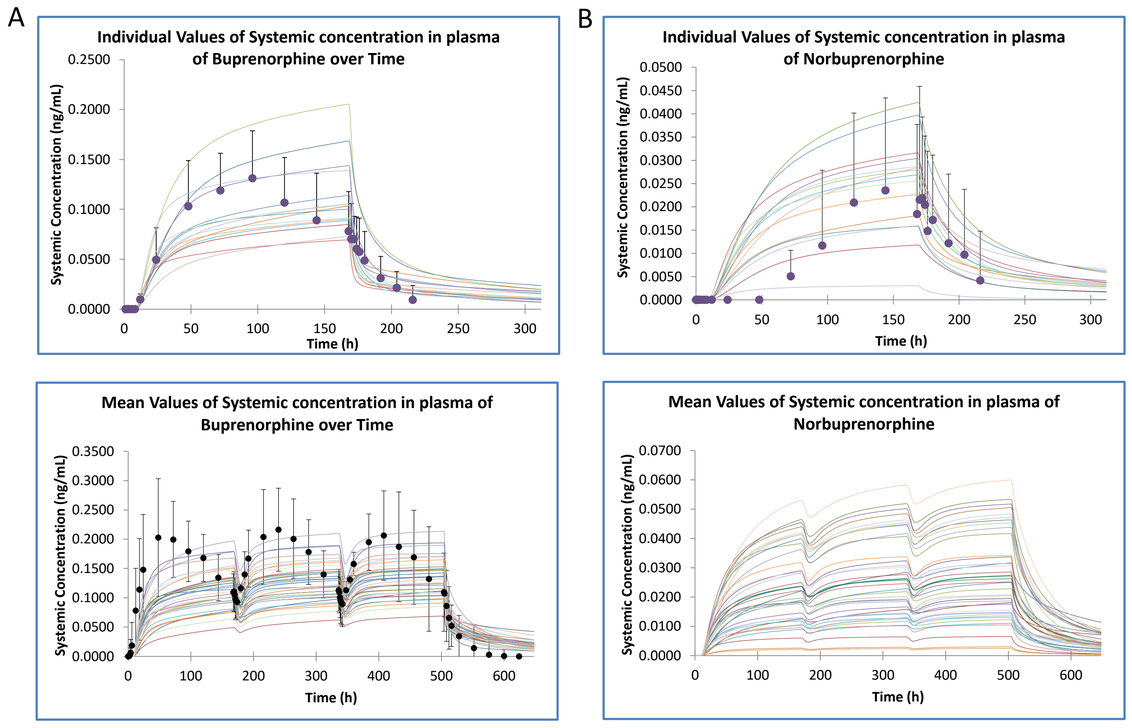

Figure 2. BUP and NOR predicted plasma exposure after topical dose (single and multiple).

Conclusions

Verified PBPK models can be used for virtual assessment of various clinical scenarios including long-term use or misuse and overdose. The ability to simulate and analyse individual profiles for different populations makes such models potentially useful for assessing exposure and safety aspects of dermal formulations, in particular, the in silico based cardiac safety assessment.

Acknowledgement

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References

[1] Bai 2016 PMID: 26804639, [2] Kuhlman 1996 PMID: 8889672, [3] Kapil 2012 PMID: 22845044, [4] Kapil 2013 PMID: 23026548

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