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Integration of physicochemical product characteristics within a mechanistic dermal PBPK model to support virtual bioequivalence evaluation of topical drug products: A case study with acyclovir topical creams

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PURPOSE

A novel in vitro cutaneous pharmacokinetics (PK)-based approach to establish bioequivalence (BE) could be considered when a topical product demonstrates qualitative and quantitative sameness, as well as physical, chemical and structural similarity to the reference product [1,2]. In other situations, where differences exist between the test and reference product formulations, physiologically-based pharmacokinetic (PBPK) modelling may have the potential to predict whether specific physicochemical or structural formulation differences affect the relative bioavailability, to identify potential critical quality attributes (CQA), and/or justify clinically relevant product specifications [3]. The success of PBPK models rely strongly upon the quality and reliability of the input parameters. Here we leveraged *in vitro* information on product characterization to parameterize a dermal PBPK model, i.e., compare the predicted PK between Reference (R) and Test (T) topical acyclovir cream, 5% products (R = ZOVIRAX® (USA) and T = ACICLOSTAD® (Austria))[4].

METHOD(S)

A PBPK model was built using the Multi-Phase Multi-Layer Mechanistic Dermal Absorption (MPML-MechDermA) module [Fig 1] implemented within the Simcyp Simulator® using physicochemical parameters of acyclovir and *in vitro* formulation characterization of the two aforementioned products [3] [Table 1]. Diffusion and partition parameters for dermal absorption were predicted using the inbuilt Quantitative Structural Activity Relationship (QSAR) models in the Simcyp Simulator V17 (development build). The impact of particle size, dissolved fraction, pH, and viscosity were accounted for by using the 'emulsion with particles' model to simulate the absorption from the two 'cream' formulations. The model accounts for drug distribution in three phases in the formulation - dispersed (oil), continuous (aqueous) and solid (particles); and simultaneously models the dissolution, diffusion and partition of drugs through the polymeric matrices of each cream. The effect of vehicle evaporation of a key excipient, propylene glycol (PG) was also studied. The amount of PG was reported to be either high or low for the R and T creams, respectively. Assuming that the effect of PG would be negligible at the low amount, the excipient effect was applied only to model the R product. The stratum corneum (SC) lipid:vehicle partition coefficient ($K_{sc,lip:v}$) of the R product was enhanced 10-fold as per the maximum effect of PG reported on acyclovir $K_{sc,lip:v}$ from an independent study [4]. The model predictions were compared with the relevant *in vitro* permeation test (IVPT) results for the R and T products in terms of the maximum acyclovir flux (Jmax) and total amount permeated [5, 6].

Table 1. Formulation parameters revised based on Murthy 2015 [5]

Formulation Parameters	ZOVIRAX US	ACICLOSTAD
pH	7.74	4.58
Drug Solubility (mg/mL)*	0.492	0.365
Particle Size (d50) um	5.06	6.75
Viscosity (Pa.S @ 0.0025 s^{-1} shear)	8360	29300
Drying Rate (h^{-1})	0.02	0.07
Oil phase/Continuous Phase Ratio	1.76	2.67
Solid fraction^	0.973	0.987

* measurement was in mg/g but converted using density 1g/mL;^Solid fractions were 0.973 at the start for both formulations but was increased for ACICLOSTAD to account for greater precipitation due to a higher vehicle evaporation rate to match the amount permeated at 48h for T from IVPT study.

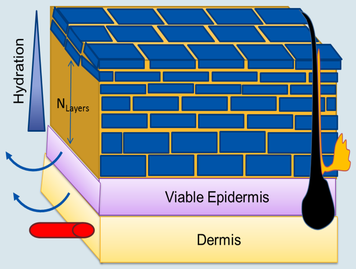

Figure 1. MPML-MechDermA model of Simcyp Simulator

RESULT(S)

The major difference in formulation properties between the R and T creams was hypothesized to be the relative amount of PG, and rate and extent of vehicle evaporation leading to precipitation. Based upon our simulations, both of these properties had a significant impact on the topical bioavailability. The total mass of acyclovir permeated through the skin estimated by the PBPK model and estimated flux over time profiles for both the R and T formulations overlaid with experimentally measured data are provided in Figs 2, 3 and 4. The PBPK model suggested that the two products exhibit significant differences in bioavailability which is in agreement with the independent IVPT studies performed with these two products.

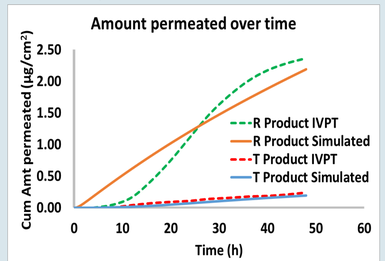

Figure 2. Cumulative amount permeated over time plots

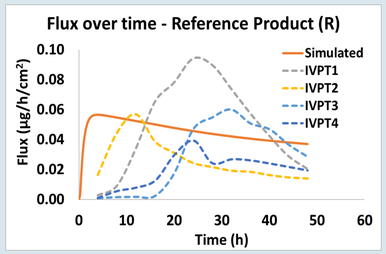

Figure 3. Permeation flux over time for the R Cream

IVPT1 – Data from Murthy 2015 [5] and IVPT2-4 are from Stinchcomb 2015 [6]

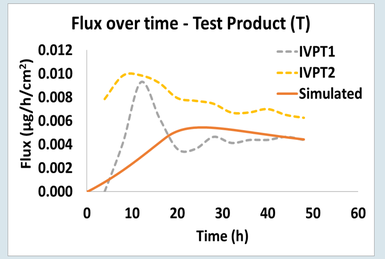

Figure 4. Permeation flux over time for the T Cream

Key Findings

1. PBPK modeling allows to translate the *in vitro* product characterization to *in vivo* situations in terms of local and/or systemic PK and identify impact of formulation differences on exposure
2. We assumed static maximal and minimal effect of PG on R and T formulations throughout the simulation period which lead to good prediction of steady state flux (establishes importance of excipient) but over- and under- estimates initial transient permeation flux for R and T products, respectively [Figs 2 -4].
3. More mechanistic dynamic modelling of excipient is needed in future as to mimic realistic time-varying impact of excipient rather than static effect from time zero onwards.
4. Kinetic modelling of super-saturation and precipitation is desirable to accurately model the formulations with significant vehicle evaporation leading to structural changes to the formulation.

The CQAs for these creams were identified by sensitivity analysis using the PBPK model. While viscosity (not shown) and pH [Fig 5A] were predicted to have little to no impact on bioavailability (as evaluated by the area under the plasma drug concentration time curve (AUC)) in the ranges evaluated, the $K_{sc,lip:v}$ had the most significant impact on exposure (AUC) of the R product [Fig. 5B]. PG directly influences the $K_{sc,lip:v}$ of acyclovir [4] hence amount of PG would be critical for product performance by enhancing the bioavailability of acyclovir substantially, which agrees well with experimental results reported for multiple acyclovir cream, 5% products with 40% vs. 15% PG [7]. Also a significant difference between IVPT results can be seen, e.g., Figs. 3&4 for the same formulation due to skin donor or sample preparation (fresh or frozen and thawed), experimental and application conditions, e.g., with pipette displacement (IVPT3) or inverted HPLC column with rubbing (IVPT4) [6].

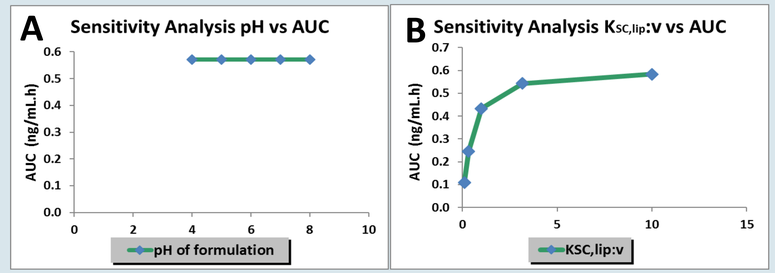

Figure 5. Sensitivity analysis of pH and $K_{sc,lip:v}$ parameters to study their impact on systemic exposure (AUC) of R product

CONCLUSION(S)

Incorporation of in vitro formulation characteristics into PBPK model development to improve topical bioavailability predictions may have a utility in identifying potential CQAs. Moreover a PBPK platform might bridge the translational gap of in vitro topical product characterization and in vivo product performance by connecting the dermal absorption model to a full body disposition model and simulating systemic and local concentrations. Further evaluation of this expanded modeling approach using drugs with various physiochemical characteristics and different formulations is warranted to support the development of virtual BE assessments.

References:

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DISCLAIMER

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The Simcyp Simulator is freely available, following completion of the training workshop, to approved members of academic institutions and non-for-profit organizations for research and teaching purposes.

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