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PHYSIOLOGICALLY BASED PHARMACOKINETIC SIMULATIONS USING TRANSDERMAL COMPARTMENTAL ABSORPTION AND TRANSIT MODEL (TCAT) FOR RLS-1496 DERMAL PREPARATIONS

Rosario Mollo[1], Ofir Moreno[1], Tarang Vora[2]

1 Rubedo Life Sciences; 2 Simulations Plus, Inc.

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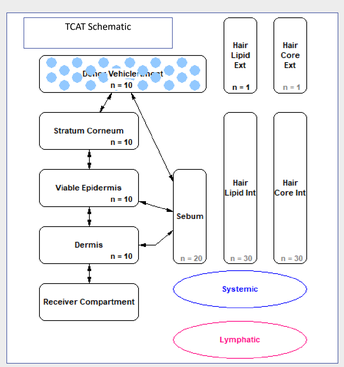
PURPOSE

- RLS-1496 is a senolytic drug formulated as a cream for topical administration and currently in Phase 1 clinical trials for dermatological conditions. A 1% cream strength was determined to be a safe starting dose for first-in-human studies, based on nonclinical toxicology studies.
- In this work, we present the application of PBPK modelling, employing a transdermal compartmental absorption and transit (TCAT) model in GastroPlus®, to support formulation changes and simulate concentrations in the skin compartments resulting from the administration of the 1% cream in a clinical setting.

METHOD(S)

- The TCAT model was developed utilizing in vitro permeation and penetration data (IVPT) from an early development cream formulation CR-16, alongside physicochemical properties of RLS-1496 and formulation-related parameters. Where experimental data were lacking, in silico values obtained from ADMET Predictor were incorporated.
- The cream formulation was treated as an oil-in-water emulsion. The subsequently developed TCAT model, coupled with in silico whole-body clearance estimates, was then employed to simulate RLS-1496 concentrations across various skin layers for the clinical formulation CR-24 (1% w/w).
- Model input parameters, including dispersed phase volume, partition coefficient, and solubility, were systematically evaluated to assess the impact of application time and skin surface area on RLS-1496 levels.



RESULT(S)

- The TCAT model, incorporating the Wang-Kasting-Nitsche (WKN) full hydration model (shown for 1% strength in Figure 1) with dermis fraction bound at 99.9% and 99% for epidermis, reasonably explained the flux observed in the IVPT experiment for prototype CR-16 at 1% w/w (observed 0.491 ng/cm2 and simulated 0.576 ng/cm2, at 24 hours) and 0.1% (observed 0.051 ng/cm2 and simulated 0.056 ng/cm2, at 24 hours).
- In Figure 2, simulated RLS-1496 concentrations for CR-24 1% w/w after a single application of 3g/1500 cm2 over an application period of 3, 12, and 24h were well above the target engagement (TE) concentration of 140 nM in dermis for at least 7 days post-application, regardless of application period. Figure 3 – Figure 4 shows simulated drug concentration over time for the clinical formulation CR-24, in various skin layers.

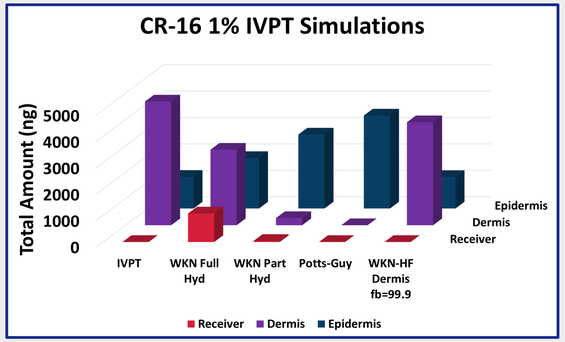


Figure 1: Comparison of the IVPT receiver concentration with simulated RLS-1496 concentrations using different diffusivity models for 1% w/w cream CR-16.

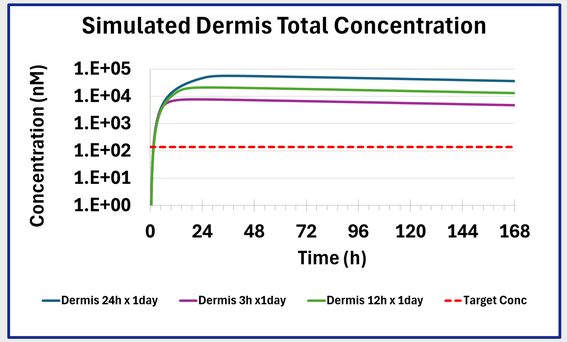


Figure 2: Simulated RLS-1496 dermis concentration for clinical dose 3g of 1% w/w cream CR-24, using whole body clearance for different application times.

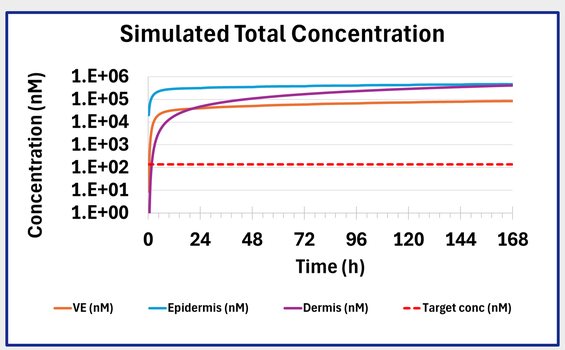


Figure 3: Simulated total RLS-1496 tissue concentrations for 3g of 1% w/w cream CR-24 in the full-thickness dermis skin, for the case of an application period of 24 hours.

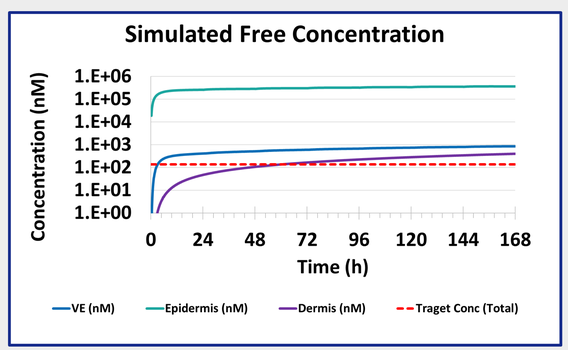


Figure 4: Simulated free RLS-1496 tissue concentrations for 3g of 1% w/w cream CR-24 in the full-thickness dermis skin, for the case of an application period of 24 hours.

CONCLUSION(S)

- Overall, a whole-body PBPK model was developed and showed the best agreement with WKN full hydration and 99.9% fraction bound (fb) in dermis, for simulating the drug delivery of RLS-1496 from topical formulations.
- Based on the parameter sensitivity analysis for RLS-1496 in the TCAT model, for the case of similar extent of fb *in vitro* and *in vivo f*b, it is predicted that in the clinical setting, when 3g of 1% strength CR-24 is applied on a surface area of 1500cm2 of normal healthy skin, the concentration of drug in dermis will be above the expected target engagement (TE) level for RLS-1496 (Figure 2) to provide maximal senolytic response, for at least a week after a single dose.
- In Figure 4, the simulated *free* amount of drug (unbound) reaches, in dermis, the expected TE concentration after approximately 2-3 days of dosing.
- These simulations suggest that in either case, free or total simulated drug in the dermis will reach TE levels in the first week of dosing.

REFERENCE

Predicting Human Dermal Drug Concentrations Using PBPK Modelling and Simulation: Clobetasol Propionate Case Study. AAPS PharmSciTech (2024) 25:39. Van Osdol et al, 2024.

ACKNOWLEDGEMENTS

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Rubedo

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