W5301

Novel Skin PBPK model in Action: Clindamycin and Tazarotene Modeling

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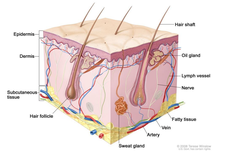
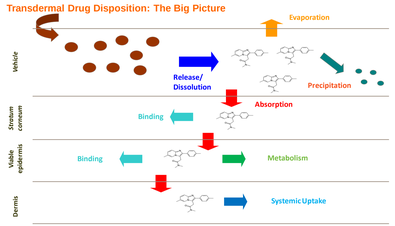
INTRODUCTION

- Skin is the major organ in the human body with a complex barrier that serves as protection from the external environment.
- Predicting dermal and systemic exposures of drug following topical application is especially challenging when considering the impact of formulations.
- Scientists from GlaxoSmithKline, Stiefel (a GSK Company) and Simulations Plus have collaborated to develop a mathematical model, Transdermal Compartmental Absorption & Transit (TCAT™) that allows better understanding of drug penetration through the skin while accounting for the formulation characteristics, evaporation and precipitation effects that influence dermal delivery.

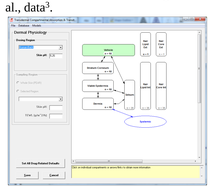


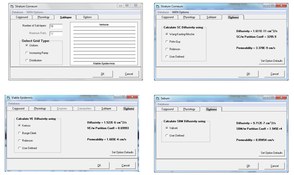
Anatomy of the skin, showing the epidermis, dermis, and subcutaneous tissue (from www.uchospitals.edu)



METHODS

- TCAT model was used to predict systemic exposures upon topical administration of different Clindamycin formulations after single dose (Dalacin T Topical Solution and DUAC gel) and multiple dose (Evoclin foam and Clindagel) administration, as well as two Tazarotene formulations (Tazorac gel and Fabior foam) to evaluate the ability of TCAT model in differentiating the drug exposures from different topical dermal formulations.
- For details on the TCAT model please also visit poster # W5289.
- Compound specific physicochemical parameters were either predicted using ADMET Predictor v6.0 experimental values were used for model building.
- Models describing systemic disposition were calibrated against plasma concentration-time profiles after intravenous administration for each compound.
- The formulation characteristics including type, volatile content, volume, evaporation rate, solubility, application area / region/ time and appropriate skin physiology were accounted for in each case.
- Vehicle /Water partition coefficient and systemic uptake rate was optimized for different formulations.
- Diffusivity and partition coefficients in the Stratum Corneum were calculated using Wang-Kasting Nitsche equation[1] , in viable epidermis were calculated using Krestos equation[2] and in sebum were calculated according to the equation derived from Valiveti et al., data[3].





RESULTS

Clindamycin Modeling

- Pharmacokinetic model fit used to characterize systemic drug disposition are presented in Fig.1. In these studies Clindamycin phosphate was dosed but as the phosphate is quickly converted to Clindamycin in the plasma [4] Clindamycin was modeled .

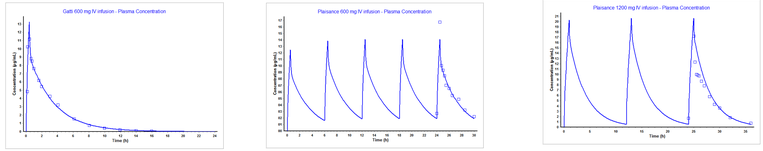
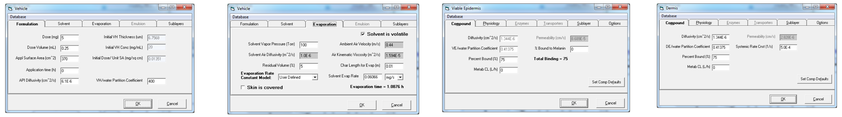


Fig.1: Compartmental PK model fit to match observed plasma concentration vs. time profile after 600 mg IV infusion for 25 mins of Clindamycin phosphate as in Gatti et al.[5]. Model performance was verified by simulating the IV studies (600 mg and 1200mg repeat IV infusions) from Plaisance et al[6] .

- Simulations for various Clindamycin dermal formulations were carried out using TCAT model set up as described in the methods and as shown in example screenshots below.



Clindamycin model was able to appropriately characterize exposure differences with different formulations including a Dalacin T solution, Duac Gel, Clindagel and Evoclin foam (Fig.2). Fig.3 shows Clindamycin concentration in various skin layers after application of Dalacin T solution and a also comparison of amount dissolved in sebum and dermis from different formulations of Clindamycin

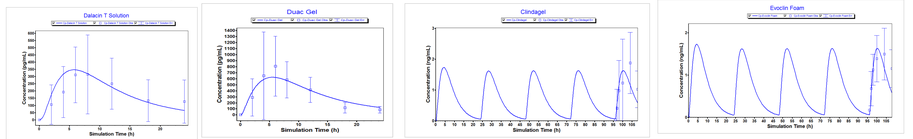


Fig.2: Simulated Plasma concentration vs. time profile (solid line) and observed plasma concentrations (open squares with CV% as the bars, N=12) on application of Dalacin T Solution, Duac Gel, Clindagel and Evoclin foam.

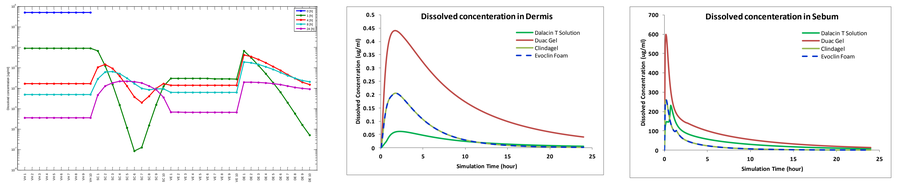


Fig.3: Simulated concentration of (A) Clindamycin in various skin compartments (VH: Vehicle, SC: Startum Corneum; VE: Viable Epidermis and DE: Dermis) at 0, 1, 4, 8, and 24 hours following application of Dalacin T Solution; (B) Dissolved concentration of Clindamycin in dermis and (C) in sebum from different formulations of Clindamycin.

Tazarotene Modeling

- Pharmacokinetic model fit used to characterize systemic drug disposition are presented in Fig.4.

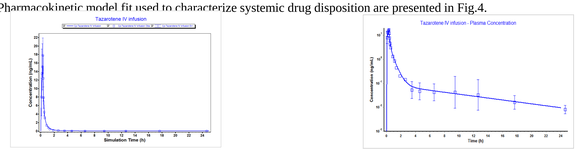
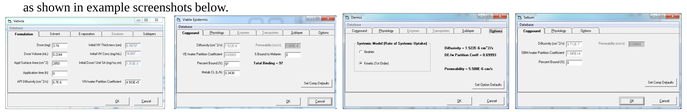


Fig.4: Compartmental PK model fit to match observed plasma concentration vs. time profile after 15 ug/kg IV infusion of Tazarotene to healthy subjects (N=8) for 20 mins[7].

- Simulations for various Tazarotene dermal formulations were carried out using TCAT model set up as described in methods and as shown in example screenshots below.



- TCAT model of Tazarotene predicted exposures from both gel and foam formulations of Tazarotene with reasonable accuracy (Fig. 5).

Fig.5: Simulated Plasma concentration vs. time profile (solid line) and observed plasma concentrations (open squares with CV% as the bars, N=13-16) on application of 3.7 mg of Tazarotene gel or 3.74 mg of Fabior foam to face, neck, upper chest and/or upper back.

CONCLUSIONS

- The TCAT model within GastroPlus is a novel model that will enable scientists to simulate the exposures from different topical formulations.
- Its applications span from candidate compound and formulation decisions to maximizing the potential for the right amount of drug to be delivered to the target tissues in the body.

REFERENCES

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