W5301

Novel Skin PBPK model in Action: Clindamycin and Tazarotene Modeling Anu Shilpa Krishnatry¹, Valeriu Damian-Iordache¹, Richard Lloyd¹, Jon Lenn², Grace Kang², Setty Hussey², Siladitya Ray Chaudhuri^{3*}, Jessica Spires³, Viera Lukacova³ 1: GlaxoSmithKline, 2:Stiefel, a GSK company, 3: Simulations Plus, Inc.

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 (TCATTM) that allows better understanding of drug penetration through the skin while accounting for the formulation characteristics, evaporation and precipitation effects that influence dermal delivery





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 equation¹, in viable epidermis were calculated using Krestos equation² and in sebum were calculated according to the equation derived from Valiveti et al., data³





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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 plasma⁴ 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 al⁶.



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.

RESULTS



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.

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 Fig.4: Compartm subjects (N= Simulation as shown in 	simulation Time (h nental PK model fit t =8) for 20 mins ⁷ .	rotene dern
Vehicle Database		Viable Epidermis Database
Formulation Solvent Dose (mg) 3.74 Dose Volume (mL) 0.2244 Appl Surface Area (cm^2) 2850 Application time (h) 0 API Diffusivity (cm^2/s) 6.7E-6	Evaporation Emulsion Sublayers Initial VH Thickness (um) 0.78737 Initial VH Conc (mg/mL) 16.667 Initial Dose/ Unit SA (mg/sq cm) 1.312E-3 VH/water Partition Coefficient 4.503E+5	Compound Envisiology Diffusivity (cm ² /s) 1 VE /water Partition Coefficient 0 Percent Bound (%) 9 Metab CL (L/h) 0
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TCAT mod (Fig. 5).	lel of Tazarotene p	Dredicted ex
	40- 	Cp-Tazarotene Gel 🔽 🗆 Cp-Tazarotene
	Concentration (pg/ml)	0 15 20 Simulation Time
Fig.5: Simulated 16) on appli	Plasma concentration of 3.7 mg of	on vs. time p Tazarotene g
CON	CLUSI	ONS
• The TCAT n formulations	nodel within Gast	roPlus is a r
• Its application to be deliver	ons span from can red to the target tis	didate comp ssues in the
REFE	RENC	ES
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odel fit used to characterize systemic drug disposition are presented in Fig.4.



model fit to match observed plasma concentration vs. time profile after 15 ug/kg IV infusion of Tazarotene to healthy mins

ious Tazarotene dermal formulations were carried out using TCAT model set up as described in methods and ble screenshots below.

	🔁 Viable Epidermis	Dermis	Sebum
	Database	Database	Database
lsion Sublayers	Compound Physiology Enzymes Iransporters Sublayer Options	Compound Physiology Enzymes Iransporters Sublayer Options	Compound Physiology Options
m) 0.78737 nL) 16.667	Diffusivity (cm^2/s) 1.522E-6 Permeability (cm/s) 1.665E-4 VE/water Partition Coefficient 0.69993 % Bound to Melanin 0	Systemic Model (Rate of Systemic Uptake): Diffusivity = 1.522E-6 cm^2/s C Ibrahim DE/w Partition Coeff = 0.69993	Diffusivity (cm^2/s) 9.712E-7 Permeability (cm/s) 0.09454 SBM/water Partition Coefficient 1.945E+4 1.945E+4 1.945E+4
m) 1.312E-3	Percent Bound (%) 97 Total Binding = 97	(Kinetic (1st Order)	Percent Bound (%)
	Metab CL (L/h) 0.3438	Permeability = 5.508E-6 cm/s	
ent 4.503E+5	Set Comp Defaults	Set Option Defaults	Set Comp Defaults
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zarotene predicted exposures from both gel and foam formulations of Tazarotene with reasonable accuracy





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

USIONS

thin GastroPlus is a novel model that will enable scientists to simulate the exposures from different topical

from candidate compound and formulation decisions to maximizing the potential for the right amount of drug target tissues in the body.

INCES

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