M2106

Does Vehicle Evaporation Affect Drug Distribution within Different Phases of Topically-Applied Emulsion? A Modeling Case Study with Clindamycin Phosphate Lotion

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PURPOSE

Topical lotion products are known to contain a high proportion of the aqueous phase and are expected to undergo vehicle evaporation upon application on the skin. Cleocin T® (clindamycin phosphate) topical lotion, EQ 1% base, is an emulsion-based lotion that contains the ester form of the drug (clindamycin phosphate) as the active pharmaceutical ingredient. Following topical application of the lotion, clindamycin phosphate is expected to be hydrolyzed to clindamycin base by esterases/phosphatases on the skin surface and within the skin.[1] The current study has utilized physiologically-based pharmacokinetic (PBPK) modeling and simulation approaches to assess the impact of vehicle evaporation on the distribution of clindamycin phosphate and clindamycin base in the dispersed and continuous phases of the formulation post skin application and the subsequent skin permeation of clindamycin phosphate and clindamycin base.

METHOD(S)

The Multi-Layer Multi-Phase Mechanistic Dermal Absorption (MPML-MechDermA) model available in the Simcyp Simulator Version 19 (Certara UK Limited) was used to develop mechanistic dermal PBPK models for both clindamycin phosphate and clindamycin base. Product quality attributes of the clindamycin phosphate lotion such as pH, viscosity, and oil globule size along with information on the vehicle evaporation profile and the volume fraction of the dispersed phase were incorporated into the developed PBPK models. To match with the clinical study design,[2] simulations were carried out in Simcyp using the following study design: study population: healthy subjects (5 trials x 5 subjects); skin application site: back; area of application: 1700 cm^2; and application dose: 4 mL clindamycin phosphate lotion (eq. 40 mg of clindamycin base). Different vehicle evaporation scenarios were explored.

RESULT(S)

As clindamycin base is the only moiety that is reported in the systemic circulation following topical application of the clindamycin phosphate lotion, the dermal PBPK model of clindamycin base was verified using the systemic PK profile of clindamycin base obtained following topical administration of clindamycin phosphate lotion.[2] The simulated PK profile of clindamycin base predicted the in vivo PK data of clindamycin base reasonably well, i.e., trough concentrations of clindamycin base from Days 1 to 6 and the shape of the full PK profile for Day 7 of product application. Under the assumption of no vehicle evaporation, simulations with the developed dermal PBPK models of clindamycin phosphate and clindamycin base suggested that about 7.5% of total dose would remain in the oil phase at equilibrium condition as clindamycin phosphate and clindamycin base. However, vehicle evaporation appeared to enhance the accumulation of drug into oil globules from ~7.5% to ~40% of the total applied dose post skin application. Additionally, vehicle evaporation increased skin permeation of clindamycin base by >4.5-fold, compared to when there was no vehicle evaporation. Sensitivity analysis on oil globule size suggested that larger emulsion globules may increase the delivery of drug into skin layers such as the stratum corneum (SC), the viable epidermis (VE), and the dermis as well as increase drug's entry into the systemic circulation.

CONCLUSION(S)

Dermal PBPK models for clindamycin base and clindamycin phosphate formulated in a topical lotion were developed to describe skin permeation for these moieties by accounting for their physicochemical properties as well as drug product quality attributes for the lotion. Model validation was performed leveraging available data of clindamycin base systemic exposure. Simulations with the dermal PBPK models for clindamycin phosphate and clindamycin base suggested that as the vehicle undergoes evaporation, the drug may redistribute between the different phases of the emulsion. Accumulation in the oil globules over time and the size of the oil globules have been shown to impact the local and systemic availability of the clindamycin base via simulation. This work highlights the utility of dermal PBPK modeling and simulation approaches in describing drug distribution following the evaporation of vehicle on skin surface for topical emulsion to assess the potential impact of vehicle evaporation on skin permeation.

REFERENCE

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Utility of Clindamycin Lotion Dermal PBPK Model in Describing the Drug Distribution in Different Phases of the Emulsion And in Skin Permeation Following the Evaporation of Vehicle Following Application on the Skin Surface

Presumed distribution of clindamycin phosphate in clindamycin phosphate lotion

Clindamycin phosphate lotion is an emulsion-based formulation that contains the ester form of the drug (clindamycin phosphate) as the active pharmaceutical ingredient (API).

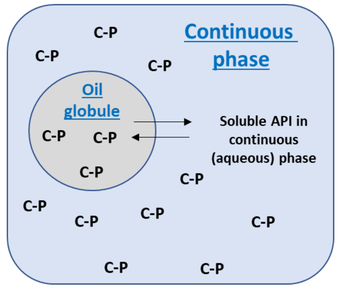


Figure 1: Schematic representation of presumed distribution profile in clindamycin phosphate lotion. Clindamycin phosphate is represented by "C-P".

Model assumptions

- Following topical application of the lotion, clindamycin phosphate is expected to be hydrolyzed to clindamycin base by esterases/ phosphatases on the skin surface and within the skin.[1] Due to inability of the current modeling platform to account for enzymatic conversion on skin surface and within skin layers, two separate dermal PBPK models of clindamycin phosphate and clindamycin base were developed, assuming that either clindamycin phosphate or clindamycin base, respectively exist in the formulation at all time.
- Per the model structure, API partitioning to the stratum corneum can take place from the formulation continuous phase, and not the globules.

Verification of Dermal PBPK Model of Clindamycin Base

As clindamycin base is the only moiety that is reported[2] in the systemic circulation following topical application of the clindamycin phosphate topical lotion, the dermal PBPK model of clindamycin base was verified against reported plasma concentration of clindamycin base obtained following multidose (every 12 hours) topical applications of clindamycin phosphate lotion for 7 days.

Product quality attributes of the clindamycin phosphate lotion such as pH, viscosity, oil globule size, volume fraction of dispersed phase and experimentally determined vehicle evaporation profile were incorporated into the developed PBPK models. The 'Depth Resolved Dermis Model' under MPML-MechDermA model with Simcyp Simulator Version 19 was used to develop dermal PBPK models.

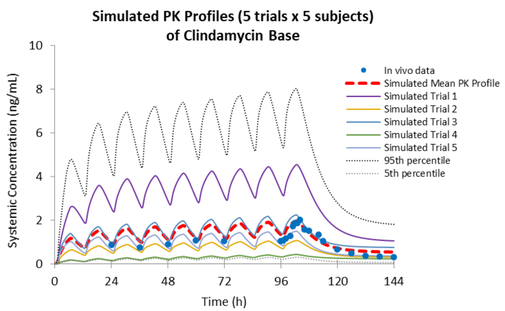


Figure 2: Simulated PK profiles of clindamycin base following multiple (every 12 hours) topical applications of clindamycin phosphate lotion for 7 days.

Predicted distribution dynamics of clindamycin phosphate and clindamycin base between oil and aqueous phases with and without vehicle evaporation

At zero time (i.e., prior application to the skin), about 7.5% of drug (either clindamycin phosphate or clindamycin base) remain distributed in oil phase. If there is no vehicle evaporation, distribution of drug in oil and aqueous phases remains almost unchanged. The percent of dose permeated in skin is also very low (Figure 3 A-B). However, vehicle evaporation appeared to promote the accumulation of drug into the oil globules from ~7.5% to ~40% of the total applied dose post skin application (Figure 3 C-D). Additionally, vehicle evaporation increased skin permeation of clindamycin base by >4.5-fold, compared to the scenario when no vehicle evaporation was assumed (Figure 3D).

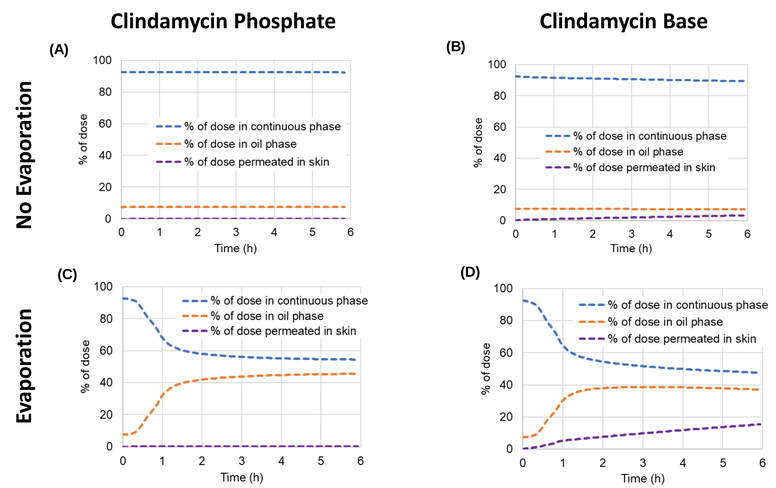
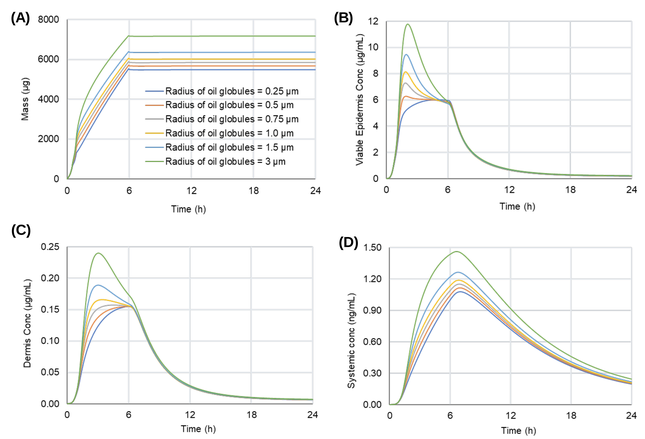


Figure 3: Simulated distribution dynamics of clindamycin phosphate and clindamycin base between oil and water phases till the end of application duration, i.e., 6 hours. Distribution of clindamycin phosphate **(A)** and clindamycin base **(B)** in absence of vehicle evaporation. Distribution of clindamycin phosphate **(C)** and clindamycin base **(D)** in presence of vehicle evaporation.

Sensitivity analysis to assess the impact of oil globule size on skin permeation of clindamycin base



Sensitivity analysis on oil globule size suggested that larger emulsion globules may increase the delivery of drug into skin layers such as the SC, the VE, and the dermis as well as an increase systemic exposure. Model assumption: partitioning of clindamycin base to the skin may only take place from the aqueous phase.

Figure 4: Sensitivity analysis on the globule radius (µm) of the emulsion oil phase to evaluate the effect of globule radius on the exposure of clindamycin base in SC (A) VE (B), dermis (C) and systemic circulation (D).