Development of a dermal PBPK modeling for an ethinyl estradiol-containing transdermal delivery system

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INTRODUCTION

Contraceptive transdermal delivery systems (TDS), such as ORTHO EVRA® TDS [ethinyl estradiol (EE) and norelgestromin], prevent pregnancy by suppressing gonadotropins.

OBJECTIVES

- Develop a dermal physiologically-based pharmacokinetic (PBPK) model to describe EE skin absorption following TDS application.
- Demonstrate how the dermal PBPK model can be used to inform decision-making throughout product lifecycle for both new and generic drugs such as during drug development, regulatory assessment, and post-approval changes.

METHOD

The Multi-Layer Multi-Phase Mechanistic Dermal Absorption (MPML MechDermA) model in Simcyp® Simulator v19 (Certara, Sheffield, UK) was used to predict EE skin permeation by accounting for the interplay between product quality attributes and skin physiology. EE systemic disposition was informed from intravenous data[1,2]. Literature sources were used to model the abdomen application site as it is not offered in the platform. To that end and due to its overall resemblance to the abdomen, the anatomical site back was modified as described in Table 1. EE released from the TDS was modeled empirically. Skin permeation model parameters [partition coefficient from the stratum corneum (SC) to the viable epidermis (VE), diffusion coefficient in VE and dermis] were optimized against EE plasma PK profiles[2,7], and model performance was assessed using independent datasets[2,8,9]. Sensitivity analysis was employed to identify formulation attributes with the potential to impact in vivo systemic EE exposure.

Table 1: Model parameter values informing the abdomen anatomical site developed in the MPML MechDermA model.

Parameter	Value (CV%) males/females	Source
SC, skin surface pH	5.29 (10%)/5.98 (10%)	Bailey et al.,2012[3]
VE, thickness (µm)	99.8 (50%)	Wei et al.,2017[4]
Dermis, thickness (µm)	2284 (50.1%)	Wei et al.,2017[4]
Subcutis, thickness (mm)	6.8 (30%)	Lancerotto et al.,2011[5]
Muscle, thickness (µm)	8 (30%)/4 (30%)	Tahan et al.,2016[6]

EE systemic disposition predicted following application of the TDS on the abdomen of healthy, female volunteers

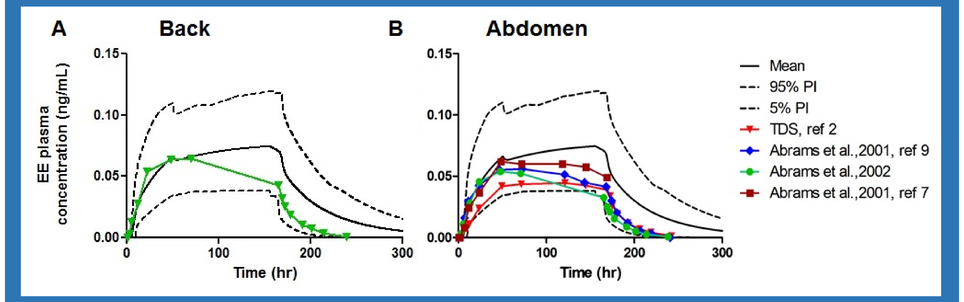

Fig. 1: Observed (solid points) versus predicted (black solid line is mean and black dashed lines are 5% and 95% prediction intervals) PK profiles of EE following single application of the TDS on the back (A) or the abdomen (B) of healthy, female, virtual volunteers. PI: Prediction Interval.

EE release profile, TDS size and EE loaded amount are predicted to impact EE systemic exposure proportionally

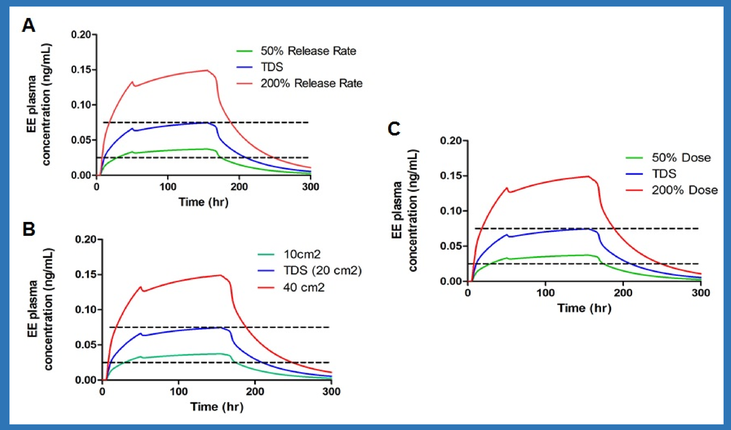

Fig. 2: Mean predicted plasma EE concentration versus time profiles following 0.5- and 2-fold increase (50% and 200% Release Rate, respectively) in the EE release profile compared to the TDS (A), following various TDS sizes (10cm^2, 20cm^2 and 40cm^2) (B) and following 0.5- and 2-fold increase (50% and 200% Dose, respectively) in the EE loaded amounts (C). Simulations were generated leveraging the dermal PBPK model for the TDS applied on the back of healthy, female, virtual volunteers. Dashed lines represent the targeted steady state concentration of EE (25-75 pg/mL)[2].

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RESULTS

Observed data were described reasonably well by the dermal PBPK model.

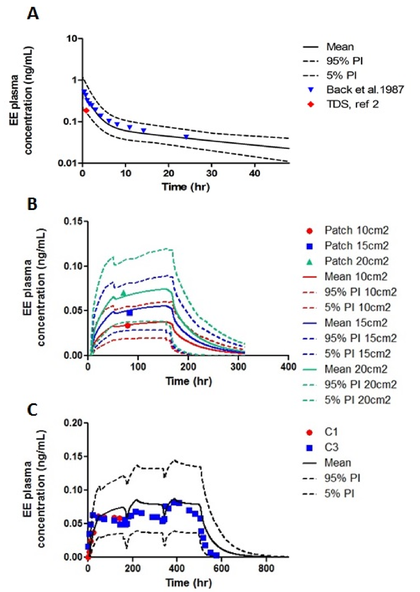

Fig. 3: Mean (5%/95% PI) predicted plasma EE following administration of intravenous administration (A) and single (B) and multiple (C) applications of the TDS on healthy, female, virtual volunteers. Observed data were from ref 1 and 2 (A), from ref 2 (B) and from ref 7 (C). C1: Cycle 1 of treatment, C3: Cycle 3 of treatment, PI: Prediction Interval.

CONCLUSIONS

- The dermal PBPK model described skin and systemic EE disposition following TDS application at the back and abdomen.
- The validated EE dermal PBPK model was used to assess the impact of changes in EE release rate, TDS size and EE loaded amounts on the EE systemic exposure and drug product performance.
- Similar modeling approach may be followed for norelgestromin.

References:
(1) Back et al. Contraception. 1987 Oct;36(4):471-9. (2) ORTHO EVRA® TDS (NDA 021180), Clinical Pharmacology and Biopharmaceutics Review, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/021-180_Ortho%20EVRA_biopharmr.pdf, (3) Bailey et al. Lasers Surg Med. 2012 Feb;44(2):131-42. (4) Wei et al. Sci Rep. 2017 Nov 21;7(1):15885. (5) Lancerotto et al. Surg Radiol Anat. 2011 Dec;33(10):835-42. (6) Tahan et al. J Physiol Anthropol. 2016 Aug 23;35(1):17. (7) Abrams et al. Contraception. 2001 Nov;64(5):287-94. (8) Abrams et al. Br J Clin Pharmacol 2002 Feb;53(2):141-6. (9) Abrams et al. J Clin Pharmacol. 2001 Dec;41(12):1301-9.