Development and application of a dermal PBPK modeling for ethinyl estradiol-containing transdermal delivery systems to predict exposure for different application sites

Eleftheria Tsakalozou, Khondoker Alam, Andrew Babiskin, Lanyan (Lucy) Fang, and Liang Zhao
Division of Quantitative Methods and Modeling, Office of Research and Standards, Office of Generic Drugs,
Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD 20993, USA.

INTRODUCTION

Contraceptive transdermal delivery systems (TDS), such as ORTHO EVRA® TDS [ethinyl estradiol (EE) and norelgestromin] Transdermal Extended Release Film, 0.035 mg/24 hours; 0.15mg/24 hours (NDA 021180), prevent pregnancy by suppressing gonadotropins.

Per the current product-specific guidance (PSG) (1) for the EE and norelgestromin extended-release transdermal film, an in vivo BE study with pharmacokinetic (PK) endpoints is recommended to demonstrate bioequivalence (BE) between a generic (Test) TDS and its respective Reference Standard (RS) by applying the products at the same anatomical site on all female healthy subjects who are candidates for hormonal contraception. The PSG does not specify the anatomical site (i.e., the abdomen or the back) for applying this product. The PSG recommends additional comparative adhesion and skin irritation and sensitization studies for this TDS product.

The products studied were: ORTHO EVRA® TDS which is the Reference Listed Drug (RLD) in the Orange Book (2), XULANE® TDS (ANDA 200910) which is designated as the RS in Orange Book because RLD is discontinued, and a generic (Test) TDS.

OBJECTIVES

- Develop and validate dermal physiologically-based pharmacokinetic (PBPK) models to describe EE skin absorption following application of the ORTHO EVRA®, XULANE® and the Test TDSs.
- Use the validated models for the RS and Test products to predict the EE systemic exposure for these two TDSs when applied on the back of virtual healthy subjects.
- Demonstrate how the dermal PBPK model can be used to inform decision-making throughout the product lifecycle for both new and generic drugs such as during drug development, regulatory assessment, and post-approval changes.

METHODS

The Multi-Layer Multi-Phase Mechanistic Dermal Absorption (MPML MechDermA) model and the in vitro permeation testing (IVPT) model in the Simcyp® Simulator v21 were used to predict EE skin permeation by accounting for the interplay between product quality attributes and skin physiology. EE systemic disposition was informed by fitting the model to intravenous PK data of EE (3). Literature sources and application submission data were used to assess the ability of the model to predict IVPT data (not shown) and systemic EE exposure following the application of the ORTHO EVRA® TDS in healthy subjects (4-7). Skin permeation model parameters were optimized against observed plasma PK profiles, and model performance was assessed using independent datasets. Systemic EE exposure data collected for the abdomen were utilized to validate dermal PBPK models developed for the RS and the Test products (8). EE released from all three TDSs studied here was modeled empirically.

Assumptions: 1. TDS releases the API at the same rate regardless of the application site, which is consistent with the current knowledge of TDS function. Therefore, differences in PK exposure following TDS application at different anatomical sites would be due to the differences in skin physiology. 2. Parameters contributing to variability include study-to-study variability, differences in skin physiology at various anatomical sites and differences in drug distribution and elimination between subjects. 3. Potential impact of adhesion on the drug product performance is beyond the scope of this work and was not considered.

Dermal PBPK model for ORTHO EVRA® TDS predicted ~~well~~ EE systemic exposure well following application on the abdomen and back in female healthy subjects.

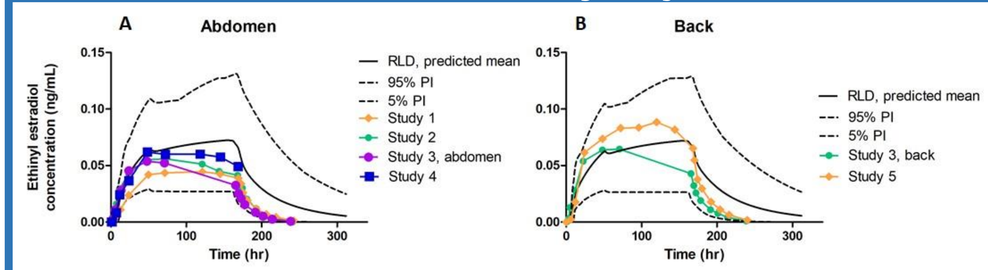

Fig. 1: Observed (solid points) versus predicted (black solid line is mean and black dashed lines are 5% and 95% prediction intervals) PK profiles of EE following single application of the ORTHO EVRA® TDS on the abdomen (A) and the back (B) of healthy, female, virtual subjects (n=79, TDS application time: 7 days). Observed data were from refs 4-7. RLD: Reference Listed Drug, PI: Prediction Interval.

Validated dermal PBPK models predicted EE systemic exposure following application of the RS and a generic on the back of virtual female subjects.

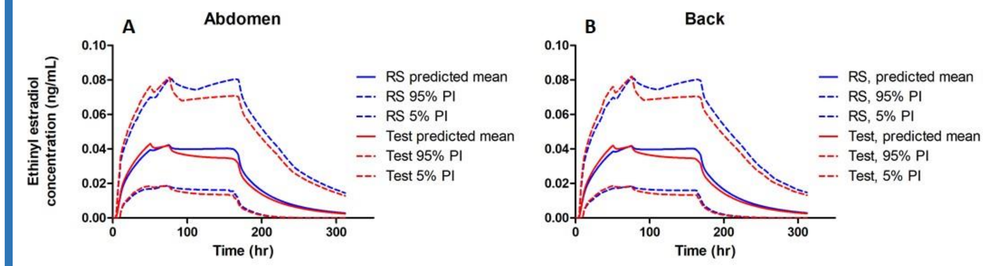

Fig. 2: Predicted (solid line is mean and dashed lines are 5% and 95% prediction intervals) PK profiles of EE following single application of the RS and the Test drug product on the abdomen (A) and the back (B) of healthy, female, virtual subjects (n=79, TDS application time: 7 days). RS: Reference Standard, PI: Prediction Interval.

CONCLUSIONS

Consistent with an in vivo study for the RLD (5), (9), the developed dermal PBPK model predicted comparable systemic EE disposition following TDS application between the back and abdomen suggesting that the TDS application site does not impact systemic EE exposure.

The validated EE dermal PBPK models for the RS and Test products were successfully used to compare EE exposure resulting from application on an application site other than the one where bioequivalence was assessed in vivo between the two products. This work demonstrates that dermal PBPK modelling can be used as a quantitative tool and provide supportive evidence for BE demonstration throughout the lifecycle of a TDS development. Similar modeling approach may be followed for norelgestromin.

RESULTS

Observed data were described reasonably well by the dermal PBPK model developed for the ORTHO EVRA® TDS.

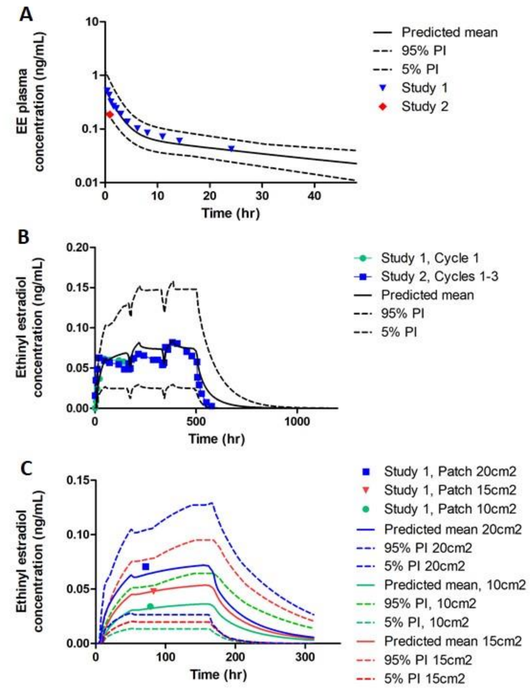

Fig. 3: Mean (95%CI) predicted plasma EE following (A) administration of intravenous EE, (B) multiple applications and (C) single application for varying TDS surface areas of the ORTHO EVRA® TDS in healthy, female, virtual volunteers. Observed data were from ref 4-7. Study number across different panels does not refer to the same study. PI: Prediction Interval. Panels B and C are considered external model validation.

Disclaimer

Views expressed in this poster are those of the authors and do not necessarily reflect the official policies of the Department of Health and Human Services; nor does any mention of trade names, commercial practices, or organizations imply endorsement by the United States Government.

References:
(1) Draft Product-Specific Guidance on Ethinyl Estradiol; Norelgestromin, Recommended May 2009; Revised Jul 2009, Oct 2016, Oct 2018, Nov 2019, https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_021180.pdf

(2) The Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm

(3) Back DJ, Grimmer SF, Rogers S, Stevenson PJ, Orme ML. Comparative Pharmacokinetics of Levonorgestrel and Ethinyloestradiol Following Intravenous, Oral and Vaginal Administration. Contraception. 1987 Oct;36(4):471-9.

(4) 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 .

(5) Abrams LS, Skee DM, Natarajan J, Wong FA, Anderson GD. Pharmacokinetics of a Contraceptive Patch (Evra/Ortho Evra) Containing Norelgestromin and Ethinyloestradiol at Four Application Sites. Br J Clin Pharmacol. 2002 Feb;53(2):141-6.

(6) Abrams LS, Skee DM, Natarajan J, Wong FA, Lasseter KC. Multiple-dose Pharmacokinetics of a Contraceptive Patch in Healthy Women Participants. Contraception. 2001 Nov;64(5):287-94.

(7) Ezuruike U, Humphries H, Dickins M, Neuhoff S, Gardner I, Rowland Yeo K. Risk-Benefit Assessment of Ethinyl estradiol Using a Physiologically Based Pharmacokinetic Modeling Approach. Clin Pharmacol Ther. 2018 Dec;104(6):1229-1239.

(8) ANDA 200910 Approval Package, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/200910Orig1s000.pdf .

(9) Labeling for ORTHO EVRA®, (norelgestromin/ethinyl estradiol transdermal system), https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021180s048lbl.pdf.