FY2018 GDUFA Science and Research Report: Topical Dermatological Drug Products

This section contains only new information from FY2018. For background scientific information and outcomes from previous years on this research topic, please refer to:

- FY2015 GDUFA Science and Research Report: Topical Dermatological Drug Products
- FY2016 GDUFA Science and Research Report: Topical Dermatological Drug Products

Introduction

The goals of our research program in topical dermatological drug products are to explore and develop new in vitro (laboratory), in silico (computational modeling) and in vivo (human subject studies) approaches, which may be used to establish bioequivalence (BE) for topical products. The ultimate intent is to develop more efficient regulatory standards that generic drug applicants could use to demonstrate BE for prospective generic topical products. The expectation is that generic topical products could be efficiently developed and approved using the new approaches, thereby improving patient access to topical drug products.

Research

To achieve this goal, and to explore the general applicability of these new approaches with which to evaluate topical BE, the GDUFA research during FY2018 encompassed multiple different topical drugs and dosage forms. The results of this research elucidated how the qualitative (Q1) and quantitative (Q2) composition, as well as the physical and structural arrangement of matter in the dosage form (Q3), control the rate and extent to which topical drugs become available at the site of action. These results were confirmed in vitro and in vivo using novel approaches to evaluate the cutaneous pharmacokinetics (PK) of topical drugs. A technique known as an In Vitro Permeation Test (IVPT) was used to evaluate the cutaneous PK of metronidazole, lidocaine, and prilocaine, each from cream and gel products. The same metronidazole, lidocaine, and prilocaine cream and gel products were also evaluated in vivo, using dermal microdialysis (dMD) and/or dermal open flow microperfusion (dOFM) probes inserted into the skin. In addition, the cutaneous PK of lidocaine from a topical delivery system (patch) was also evaluated both, in vitro and in vivo.

Parallel, complementary in vitro research performed independently at the University of Mississippi and the University of South Australia characterized the physical and structural (Q3) properties of metronidazole, lidocaine, and prilocaine cream and gel products, and correlated these results with IVPT studies using the same products. The IVPT studies with these products were also performed at the University of Maryland (Baltimore). The metronidazole cream and gel products were also evaluated in vivo using dMD at Long Island University (Brooklyn), and the lidocaine and prilocaine cream and gel products were evaluated in vivo using dOFM at Joanneum Research (Austria).
Collectively, the results of the research with different drugs and drug products, using Q1, Q2 and Q3 characterization techniques, in vitro methodologies (e.g., IVPT), and in vivo techniques (dMD and dOFM), all performed in parallel by independent research groups, consistently demonstrated that products which are Q1 and Q2 the same, and Q3 similar, when compared to a reference listed drug (RLD) product, deliver topical drugs at the same rate and to the same extent as the RLD product. This work also consistently demonstrated that IVPT studies (Figure 1) are a sensitive and discriminating approach by which to evaluate the cutaneous PK of topical drugs. Of particular importance, this research illustrated the generalizability of the principles that influence BE for various topical drug products and supported the development of additional product-specific guidances which include an in vitro option by which to demonstrate BE.

The excised human skin that is used in IVPT experiments as the rate-controlling membrane to the permeation of compounds applied on the skin is an important factor for obtaining meaningful, biorelevant permeation data that has the potential to correlate with and be predictive of in vivo product performance. Yet, while IVPT studies have the benefit of providing biorelevant information, the inherent variability of these biological skin samples may limit the utility of IVPT studies as routine quality control tests. By contrast, synthetic membranes made of materials like cellulose acetate and polyethersulfone, which are utilized for in vitro release test (IVRT) experiments, have the advantage that they are generally consistent and provide reproducible results, making them potentially suitable as quality control tests. However, unlike IVPT studies with excised human skin, IVRT studies with synthetic membranes are not expected to correlate with or be predictive of in vivo product performance.

To develop an in vitro test that could be precise and reproducible as well as being biologically meaningful (biorelevant), we explored using genetically consistent, cultured (lab-grown) three-dimensional human skin membranes in an IVPT study. To evaluate the relative variability of the cultured skin compared to that of natural, excised human skin (prepared as either heat-separated epidermis (HSE) or dermatomed skin), each type of membrane was mounted in the same type of diffusion cell apparatus, and used to characterize the cutaneous PK of testosterone (as a model compound). The influence of different diffusion cell apparatus on the consistency of the permeation data was also assessed.

The results indicated that lab-cultured human skin preparations were typically less variable but more permeable than excised human (cadaver) skin preparations. Although cultured human skin preparations may provide lower sample-to-sample variability compared to excised human (cadaver) skin, the compromised barrier function of cultured skin (to testosterone permeation) currently appears to limit its usefulness for IVPT studies. Nonetheless, this is a promising area of research and development as a method that could potentially be biorelevant and may be suitable to monitor the quality and performance of topical or transdermal formulations over their shelf life or for certain scale-up and post-approval changes (SUPAC).

Additional research is in progress as part of a contract with QPS, LLC, using physical and structural (Q3) characterization studies, In Vitro Release Test (IVRT) studies, and IVPT studies that are intended to evaluate the comparability of AT-rated topical ointments. Also, in silico (computational modeling and simulation) research in progress is currently verifying the predictions of physiologically-based PK models by comparison with empirical datasets, including those described above. Additional internal FDA research related to the optimization of diffusion cell designs and the comparability of different types of skin membranes and diffusion devices for IVPT studies is currently in progress.
Figure 2: A schematic illustration of an IVPT study showing how sections of excised human skin from multiple donors are each mounted on diffusion cells in vitro and dosed with either the Test or the Reference topical drug product. The topical drug permeates through the skin into the solution in the receptor chamber, which is sampled at progressive time points to characterize the cutaneous PK of the drug. The diffusion cell shown in this diagram is a vertical (Franz) diffusion cell, although other types can be used. The cutaneous PK of lidocaine is shown in the inset PK profile, based upon six replicate skin sections from a single donor dosed with either the Reference (EMLA®) lidocaine/prilocaine cream, 2.5%;2.5% or a Test product, which is a generic version of EMLA® for which BE was originally established based upon a comparative clinical endpoint BE study.

Research Projects and Collaborations

New Grants and Contracts

- New Grant (U01FD006533) Bioequivalence of Topical Products: Evaluating the Cutaneous Pharmacokinetics of Topical Drug Products Using Non-Invasive Techniques with Richard Guy at University of Bath
- New Grant (U01FD006521) Characterize Skin Physiology Parameters Utilized in Dermal Physiologically-Based Pharmacokinetic Model Development Across Different Skin Disease States with Sebastian Polak at Simcyp, Ltd.
- New Grant (U01FD006507) Bioequivalence of Topical Products: Elucidating the Thermodynamic and Functional Characteristics of Compositionally Different Topical Formulations with Sathyanarayana Murthy at University of Mississippi
• New Grant (U01FD006496) Bioequivalence of Topical Products: Elucidating the Thermodynamic and Functional Characteristics of Compositionally Different Topical Formulations with Michael Roberts at University of South Australia
• New Grant (U01FD006526) Formulation Drug Product Quality Attributes in Dermal Physiologically-Based Pharmacokinetic Models for Topical Dermatological Drug Products and Transdermal Delivery Systems with Jessica Spires at Simulations Plus, Inc.
• New Grant (U01FD006522) Formulation Drug Product Quality Attributes in Dermal Physiologically-Based Pharmacokinetic Models for Topical Dermatological Drug Products and Transdermal Delivery Systems with Michael Roberts at University of Queensland

Continuing Grants and Contracts
• Active Grant (U01FD004947) Bioequivalence of Topical Drug Products: In Vitro - In Vivo Correlations with Audra L Stinchcomb at University of Maryland
• Active Grant (U01FD005226) Characterization of Critical Quality Attributes for Semisolid Topical Drug Products with Michael Roberts at University of South Australia
• Active Grant (U01FD005233) Topical Products and Critical Quality Attributes with Sathyanarayana Murthy at University of Mississippi
• Active Contract (HHSF223201610125C) Assessment of the In Vitro Percutaneous Absorption, In Vitro Rate of Release, and Physicochemical Properties of Selected Commercially Available AT Rated Ointment Formulations with Shanna Geigle at QPS, LLC
• Active Grant (U01FD005862) Benchmark of Dermis Microdialysis to Assess Bioequivalence of Dermatological Topical Products with Grazia Stagni at Long Island University
• Active Grant (U01FD005861) Development of a Universal Bioequivalence Test Method for Topical Drugs Using dOFM with Frank Sinner at Joanneum Research
• Active Grant (U01FD005232) Physiologically Based Biopharmaceutics and Pharmacokinetics of Drug Products for Dermal Absorption in Humans with Michael Roberts at University of South Australia
• Active Grant (1U01FD005225) Development and Validation of Dermal PBPK Modeling Platform Toward Virtual Bioequivalence Assessment Considering Population Variability with Sebastian Polak at Simcyp, Ltd.

Active FDA Research
• Snowflakes in Transdermal Systems: Influence of Drug Crystallization on Drug Permeation and Quality of TDS
• Performance comparison of permeation membranes and devices used in modern in vitro skin permeation test (IVPT) studies
• Computational Fluid Dynamics (CFD) Analysis of Spreadability of Topical Formulations
• Verification of IVRT method for AT-rated topical ointments

Outcomes

Product-Specific Guidances
• Revised Draft Guidance for Tacrolimus Topical Ointment (0.03%). FDA Guidance Posting. Sept. 13, 2018. Link to Posting.

Publications

Presentations


**Posters**


• Patel, N. and Polar, S. *Development of the Dermal Absorption Model for the Ketoprofen Local and Systemic Exposure Prediction.* June 20, 2018.


• Tiffner, K., Bodenlenz, M., Schimek, D., Reisenegger, P., Rantou, E., Raml, R., Raney, S., and Sinner, F. *Bioequivalence of Topical Products in Excised Human Skin Assessed with Dermal Open Flow Microperfusion (dOFM)*. Poster Presentation at Perspective in Percutaneous Penetration. La Grande Motte, France, Apr. 3, 2018.
