Overview
FDA's Generic Drug Research
Topical Dermatological Drug Products

Society for Investigative Dermatology Annual Meeting, 2022

FDA Session: Advances in Topical Dosage Form Characterization and Measuring Drug Concentrations in the Skin

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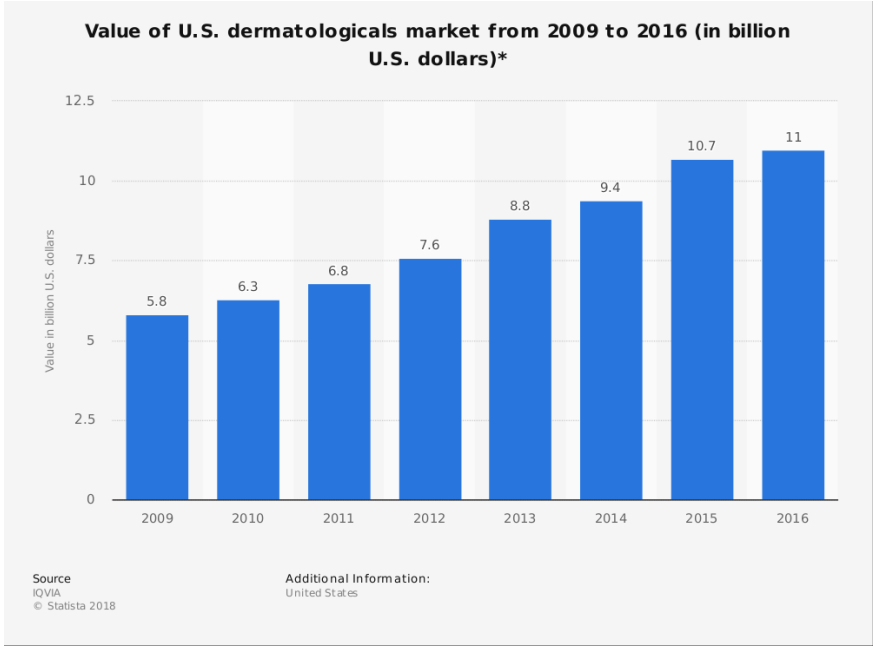
Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Dermatological Drug Products



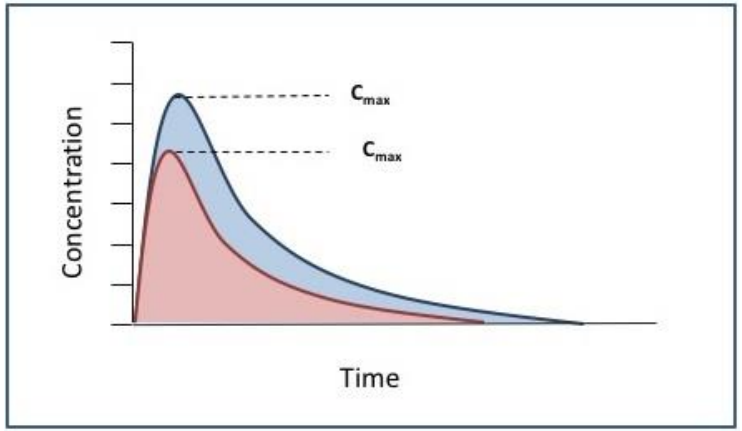
https://brandongaille.com/23-dermatology-industry-statistics-and-trends/
https://www.accessdata.fda.gov/scripts/cder/ob/search_product.cfm

The Promise of Generic Drugs

- Generic drug products use the same active ingredient(s) and can be expected to have the same clinical effect and safety profile when administered under conditions specified in the labeling, as the brand-name (reference) listed drug products
- Generic drug products can be substituted for the reference listed drug products
- ….And they can cost a lot less money

https://www.fda.gov/drugs/generic-drugs/generic-drug-facts

Systemically Acting Drug Products



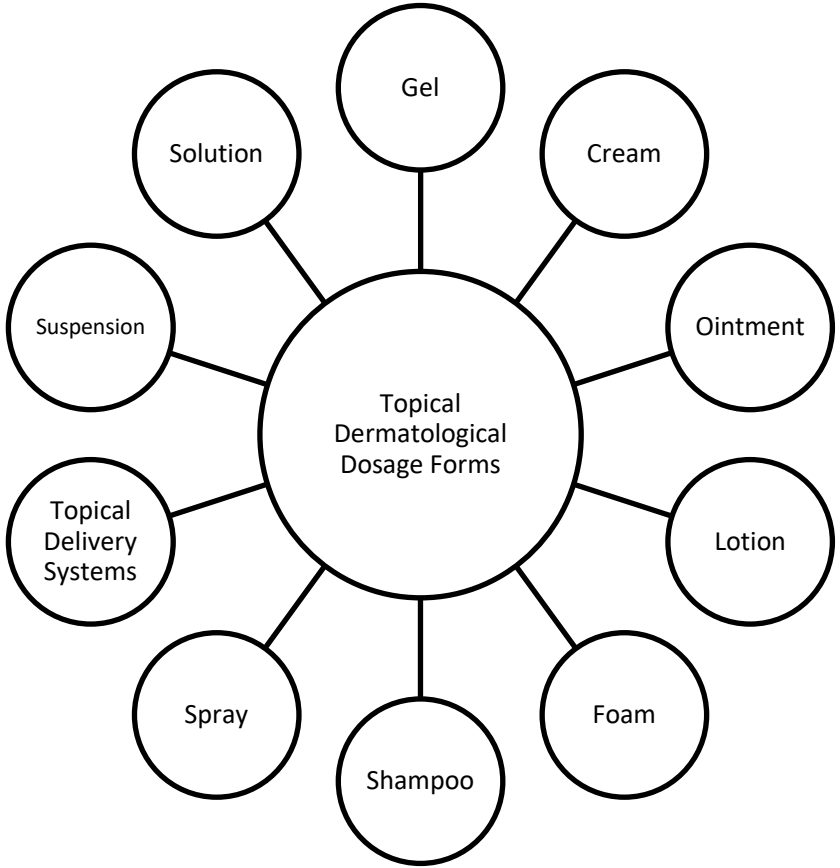
Bioavailability (BA) is assessed, and bioequivalence (BE) is typically established by showing that a generic drug product and the reference drug product are similar in terms of their concentrations over time at the site of action (e.g., in the blood)

https://www.fda.gov/drugs/regulatory-science-action/impact-story-developing-new-ways-evaluate-bioequivalence-topical-drugs

Locally Acting Drug Products

- Dermatological drug products applied to the skin are often indicated for local action
- Approximately 80% of topical dermatological drug products have fewer than three generic competitors; for many products no generics are available at all
- This may have been attributable to the historical barriers to the development of topical dermatological drug products, possibly including
  - Difficulty/issues with comparative clinical endpoint BE studies
  - The complex nature of topical formulations

Complexity of Topical Formulations



https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book

Potential Strategies for Establishing BE

Components and Composition

Prospective Generic Product

"No Difference" in Formulation
(Characterization Based Approach)

- *Characterization of the Physical and Structural Properties **(Q3)***
- ***IVRT** (In Vitro Release Test)*
- ***IVPT** (In Vitro Permeation Test)*
- *In vivo systemic pharmacokinetic **(PK)** studies*
- *In ***silico**-based tools (Modeling and Simulation)*

"Differences" in Formulation
(Currently Under Development)

- *Impact of Formulation Differences on **Thermodynamic** Potential*
- ***Cutaneous PK** Approaches*
  - *Dermal Microdialysis*
  - *Dermal Open Flow Microperfusion*
  - *Raman Spectroscopy-based Tools*
- *Comparative Clinical Endpoint Studies*

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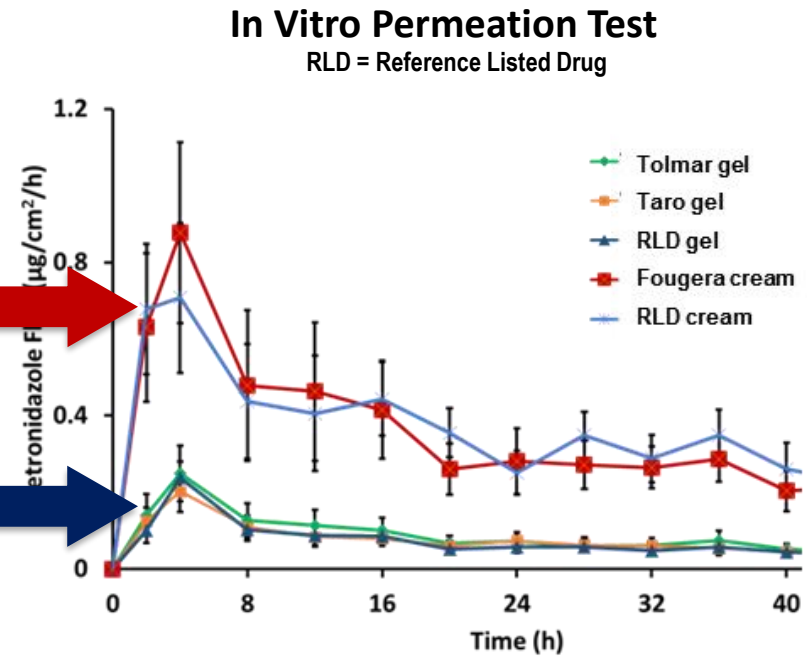
Characterization Based Approach

Quality Attribute	MetroCream® (RLD Cream)	Generic Crear (Fougera)	Metrogel® (RLD Gel)	Generic Gel (Tolmar)	Generic Ge (Taro)
pH	4.8	5.1	5.2	5.0	5.4
Density (g/cc)	1.02	1.02	1.01	1.02	1.02
WOA (g.sec)	57.6	63.9	39.4	43.9	42.0
Particle size (µm)	Active ingre				
Drug in Aq (mg/g)	4.20	2.92	---	---	---
Drug in Oil (mg/g)	2.58	3.94	---	---	---
Solvent Activity	0.977	0.974	0.992	0.994	1.002
Globule size, d_{50} (µm)	2.8	2.2	---	---	---
Drying, T_{30} (min)	17	11.4	5.5	4.7	6.5



Data provided courtesy of Dr. Narasimha Murthy associated with FDA funding for award U01FD005233

Research Portfolio

*Supporting the Development of the **Characterization Based Approaches***

- *1U01FD004947 Bioequivalence of Topical Drug Products: In Vitro-In Vivo Correlations with Audra Stinchcomb at University of Maryland*
- *1U01FD005233 Topical Products and Critical Quality Attributes with Sathyanarayana Murthy at University of Mississippi*
- *1U01FD005226 Characterization of Critical Quality Attributes for Semisolid Topical Drug Products with Michael Roberts at University of South Australia*
- *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*
- *1U01FD006521 Characterization of Key System Parameters of Mechanistic Dermal PBPK Models in Various Skin Diseases and Performance Verification of the Model Using Observed Local and Systemic Concentrations with Sebastian Polak at Simcyp, Ltd.*
- *1U01FD006522 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*
- *1U01FD006526 Assessment of Transdermal Drug Product Quality and Performance Attributes via Enhanced Virtual Bioequivalence Simulations with Jessica Spires at Simulations Plus, Inc*

https://www.fda.gov/media/146749/download#page=122

Potential Strategies for Establishing BE

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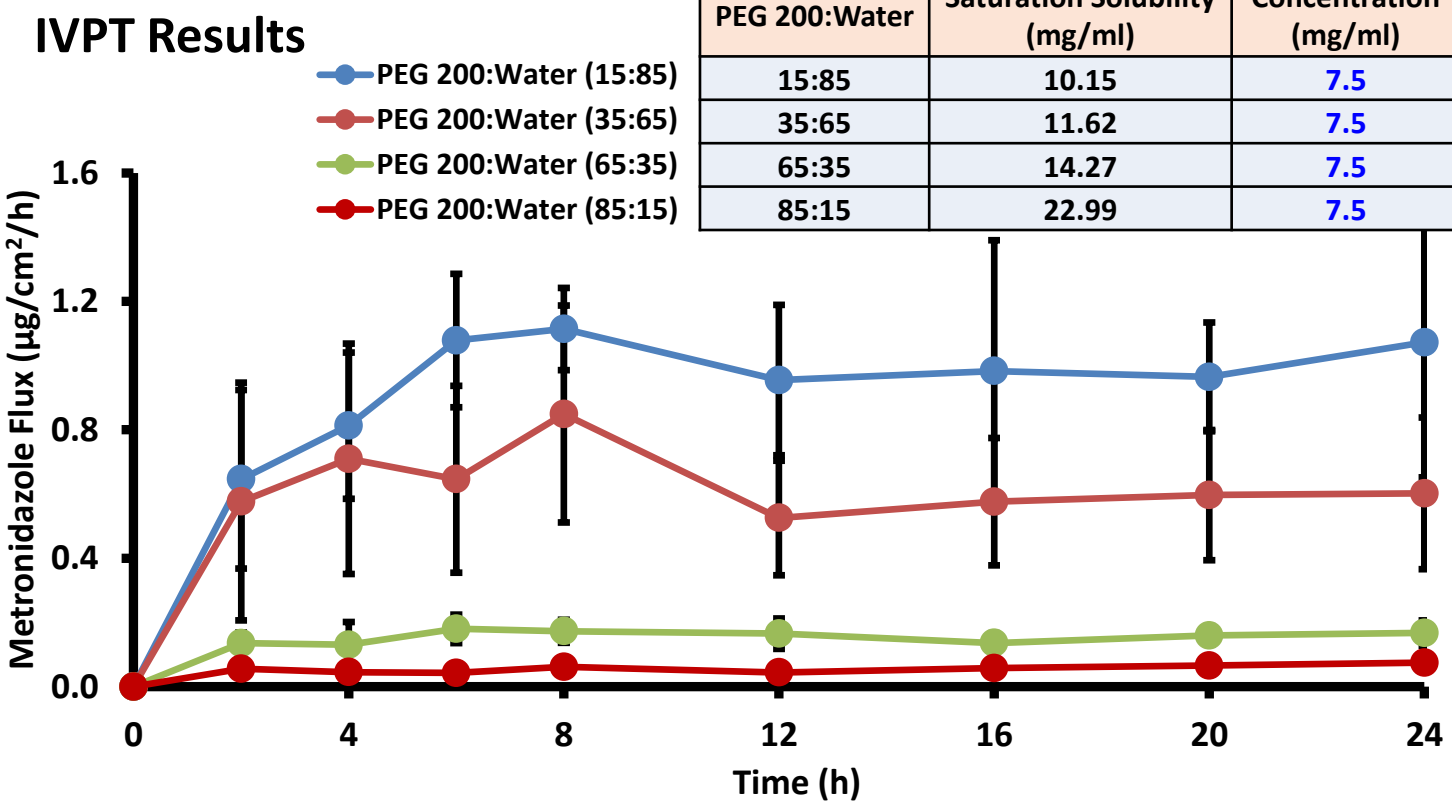
Formulation and Thermodynamics

PEG 200:Water	Saturation Solubility (mg/ml)	Concentration (mg/ml)	α
15:85	10.15	7.5	0.74
35:65	11.62	7.5	0.65
65:35	14.27	7.5	0.53
85:15	22.99	7.5	0.33



Data provided courtesy of Dr. Narasimha Murthy associated with FDA funding for award U01FD0006507

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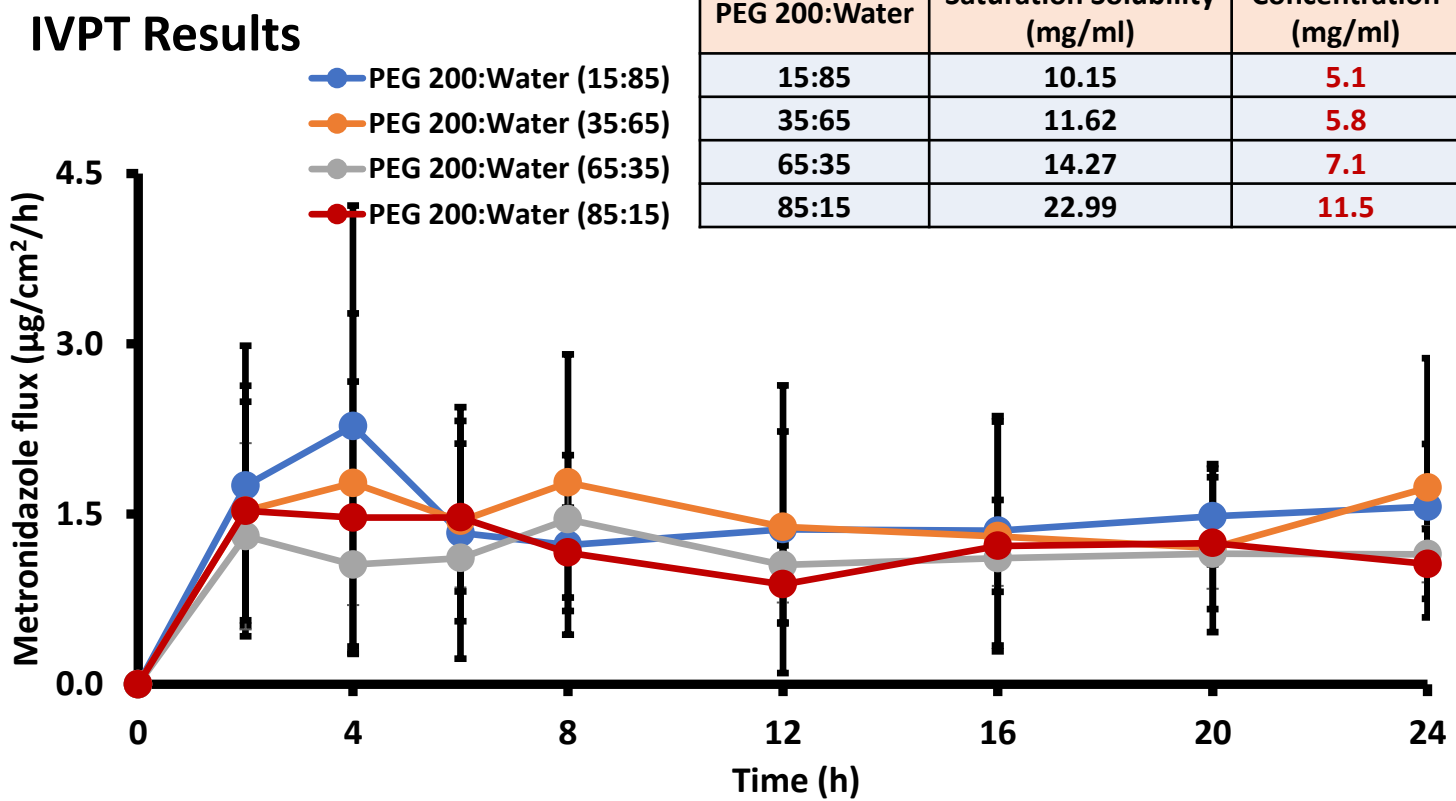


Data provided courtesy of Dr. Narasimha Murthy associated with FDA funding for award U01FD0006507

Cutaneous PK

- Microdialysis (dMD) and Open Flow Microperfusion (dOFM) directly measure the in vivo rate and extent of drug BA at/near the site of action in the skin

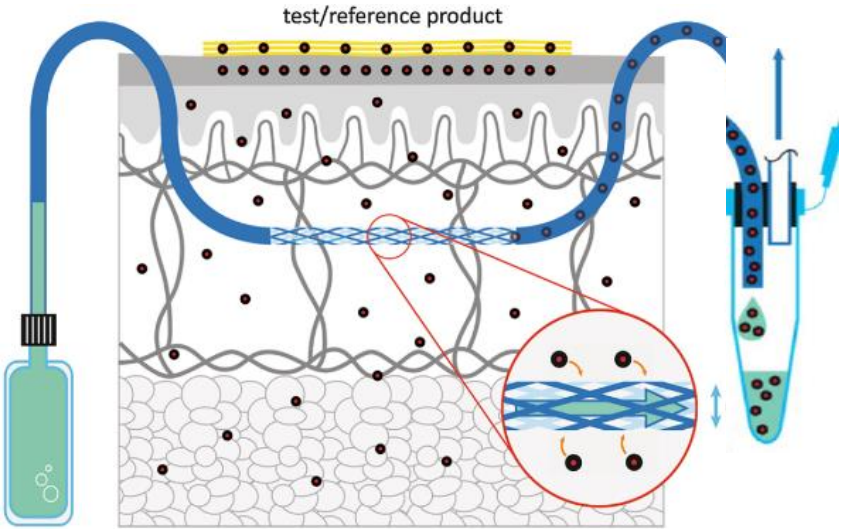
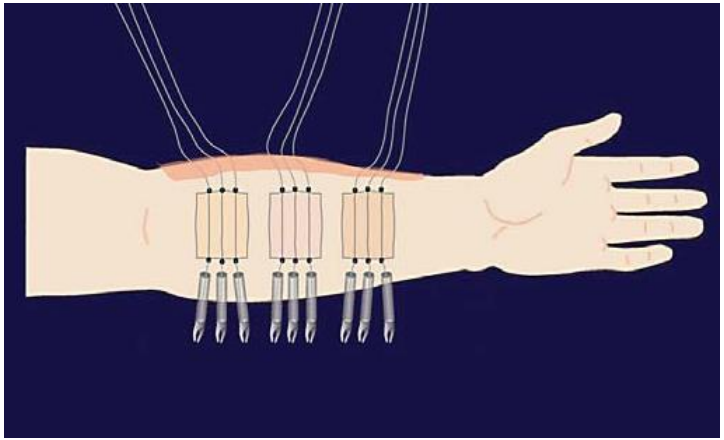


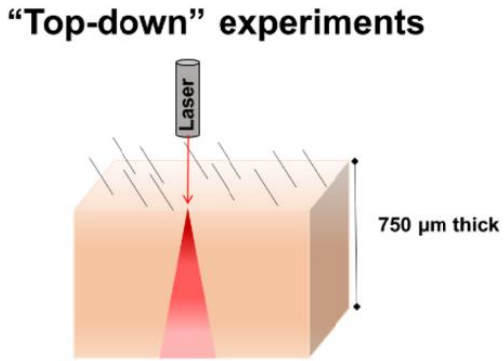
Image provided courtesy of Dr. Frank Sinner, Joanneum Research

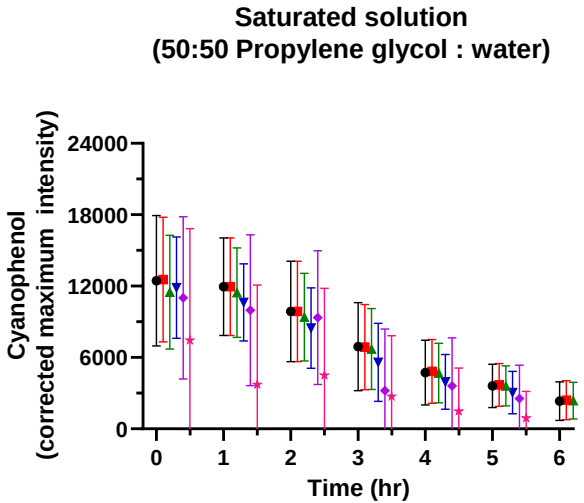


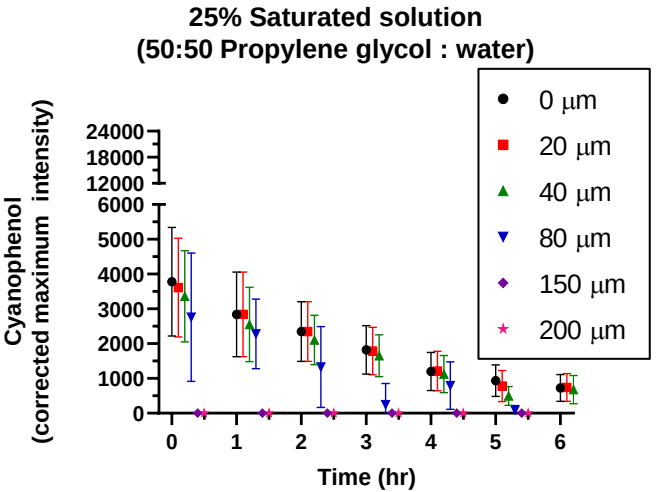
Skin Pharmacol Physiol 2011;24:44–53

Cutaneous PK

- Confocal and Simulated Raman Spectroscopy can directly measure the rate and extent of drug BA at/near the site of action in the skin.







Data provided courtesy of Dr. Richard Guy associated with FDA funding for award U01FD0006533

Research Portfolio

*Supporting the Development of the **Cutting Edge Tools***

- *1U01FD006507 Impact of Formulation Composition on the Structure and Performance Attributes of Topical Products with Sathyanarayana Murthy at University of Mississippi*
- *1U01FD006496 Bioequivalence of Topical Products: Elucidating the Thermodynamic and Functional Characteristics of Compositionally Different Topical Formulations with Michael Roberts at University of South Australia*
- *1U01FD006700 Elucidating Sensorial and Functional Characteristics of Topical Formulations with Yousuf Mohammed at University of Queensland*
- *1U01FD004946 Novel methodologies and IVIVC approaches to assess BE of topical drugs with Frank Sinner at Joanneum Research*
- *1U01FD005861 Development of a Universal Bioequivalence Test Method for Topical Drugs Using dOFM with Frank Sinner at Joanneum Research*
- *1U01FD005862 Benchmark of Dermis Microdialysis to Assess Bioequivalence of Dermatological Topical Products with Grazia Stagni at Long Island University.*
- *1U01FD006930 Elucidating Fundamental Principles of Dermal Pharmacokinetics via Microdialysis with Grazia Stagni at Long Island University*
- *1U01FD006533 Assessing the Skin Pharmacokinetics of Topical Drugs, and the Bio(in)equivalence of Topical Drug Products, Using Non-Invasive Techniques with Richard Guy at University of Bath*
- *U01FD006698 Pharmacokinetic Tomography for the Measurement of Topical Drug Product Bioequivalence with Conor Lee Evans at Massachusetts General Hospital/Harvard Medical School*

https://www.fda.gov/media/146749/download#page=122

Summary

- Topical dermatological drug products are generally complex dosage forms
- Understanding the behavior of a given formulation during evaporation is critical to be able to assess the BA, and assess BE, of the active ingredient from the drug product
- Assessing drug BA at or near the site of action in the skin is challenging
- Goal of the GDUFA regulatory science research program is to facilitate the development of tools that can be utilized to facilitate drug development/ establish BE and thereby enhance the availability of generic topical dermatological drug products

Acknowledgements

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- Sam Raney, PhD
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Research Collaborators

Collaborations within FDA

All of our collaborators within the GDUFA Regulatory Science Research Program

U.S. FOOD & DRUG ADMINISTRATION

Thank You

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