

Non-Invasive Raman Spectroscopy-Based Bioequivalence Approaches

SBIA 2020: Advancing Innovative Science in Generic Drug Development Workshop

Session 3: Future Directions, Emerging Technology, and Current Thinking on Alternative BE Approaches

Topic 2: Topical Dermatologic Products

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Division of Therapeutic Performance, Office of Research And Standards

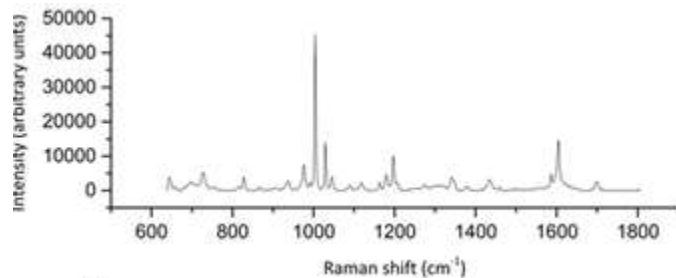
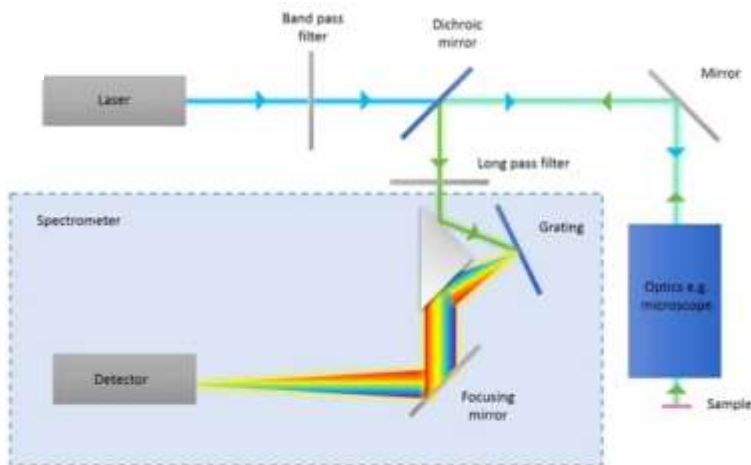
Office of Generic Drugs | CDER | U.S. FDA

September 30, 2020

Learning Objectives

- Understand non-invasive imaging-based techniques
- Utilize imaging-based techniques in generic drug development
 - to understand product microstructure
 - to understand the metamorphosis and drug release
 - for evaluation of (cutaneous) pharmacokinetics

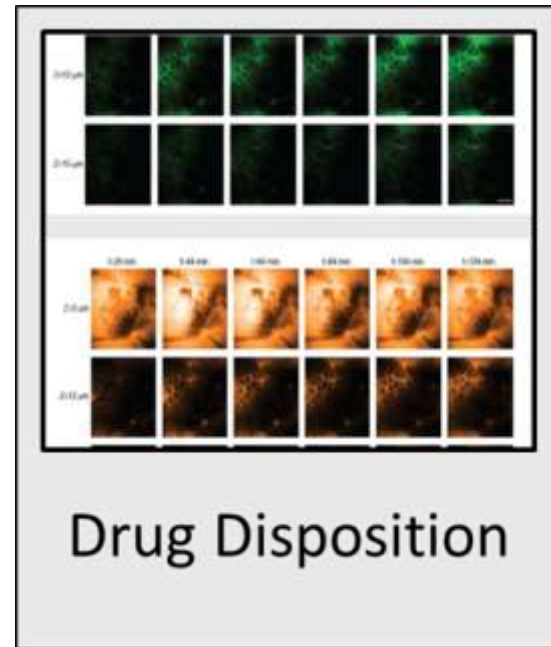
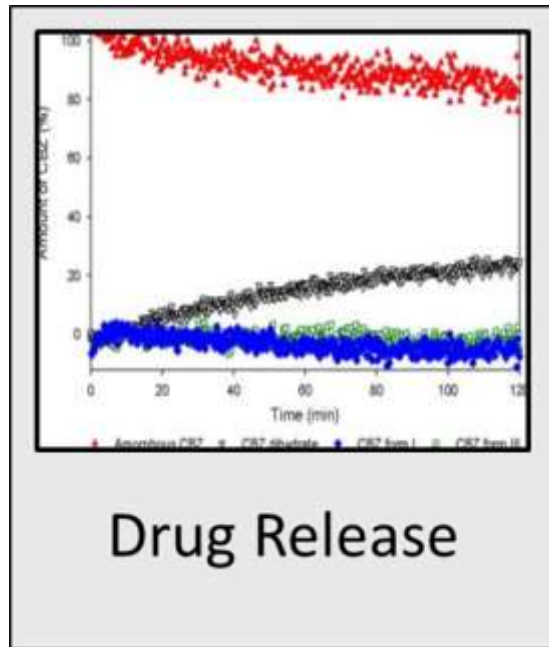
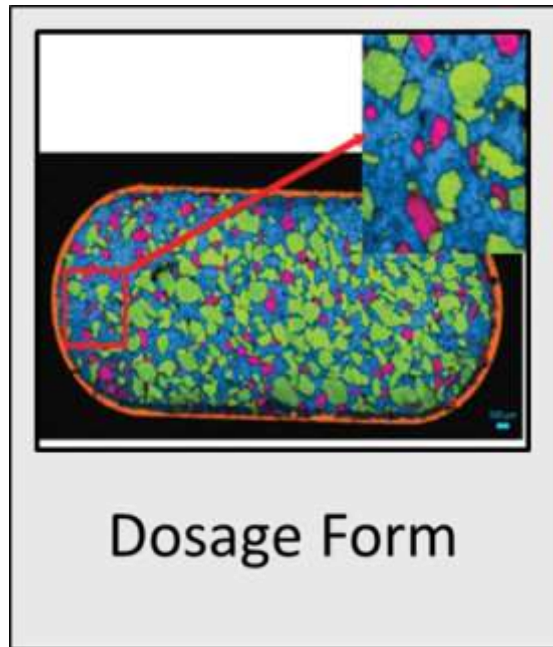
Current Utility of Raman Spectroscopy



Predominantly used during manufacturing and quality control for identification of

- Active ingredient(s)
- Degradation product(s)
- Polymorph/isomorph(s)
- Trace contaminants(s)
- Inactive ingredients including fillers, dyes, coatings

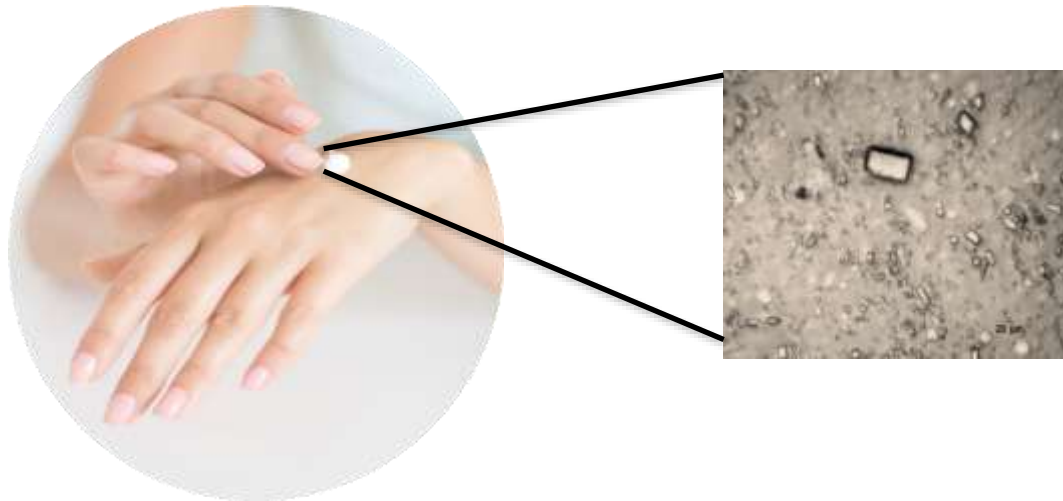
Potential Utility in Dermal Drug Development



https://www.horiba.com/en_en/raman-imaging-and-spectroscopy-recording-spectral-images-profiles/

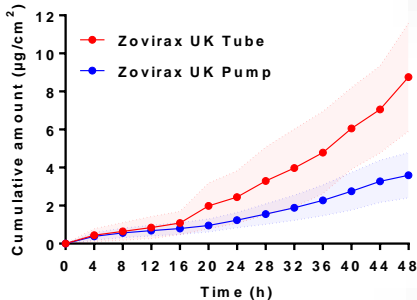
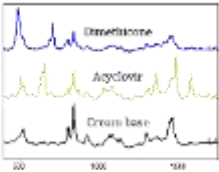
Savolainen M, Kogermann K, Heinz A, et al. **Better understanding of dissolution behaviour of amorphous drugs by in situ solid-state analysis using Raman spectroscopy.** Eur J Pharm Biopharm. 2009;71(1):71-79.

www.fda.gov Saar Brian G. , Contreras-Rojas L. Rodrigo , Xie X. Sunney , and Guy Richard H. **Imaging Drug Delivery to Skin with Stimulated Raman Scattering Microscopy** Molecular Pharmaceutics **2011** 8 (3), 969-975



Understanding the Product Microstructure

Understanding the Product Microstructure

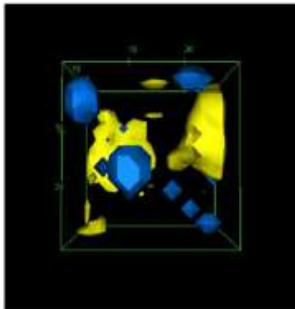


Zovirax® UK
Pump

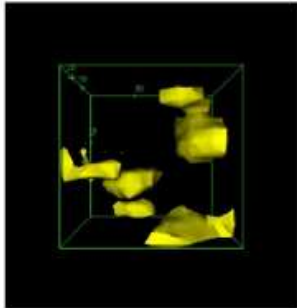
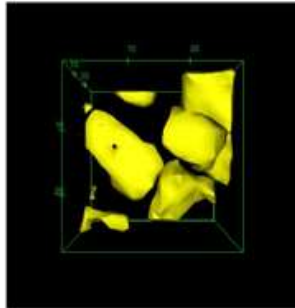
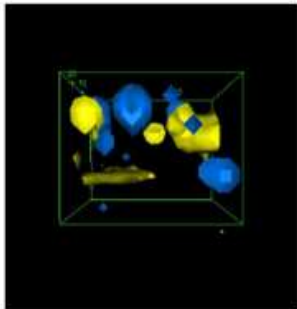


Zovirax® UK
Tube

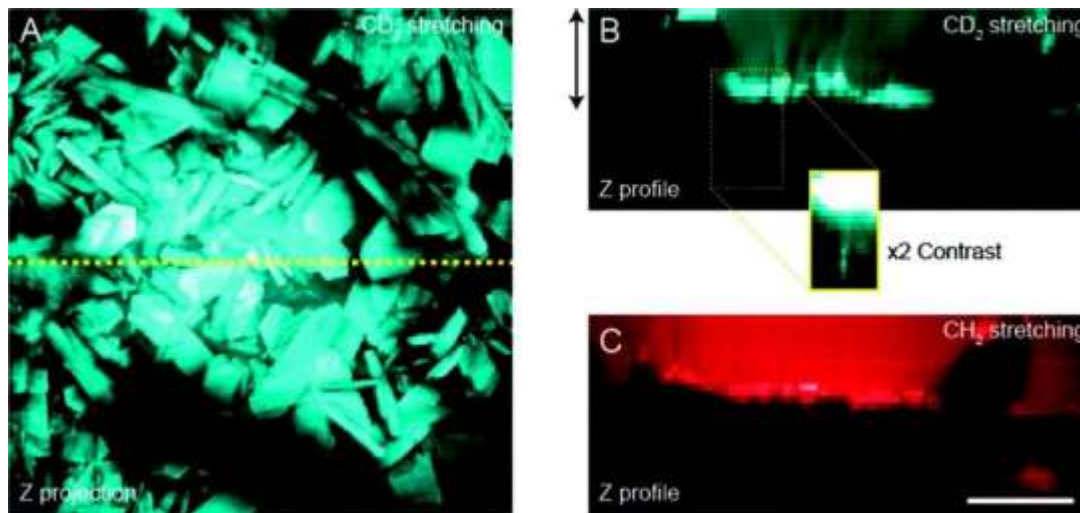
top view

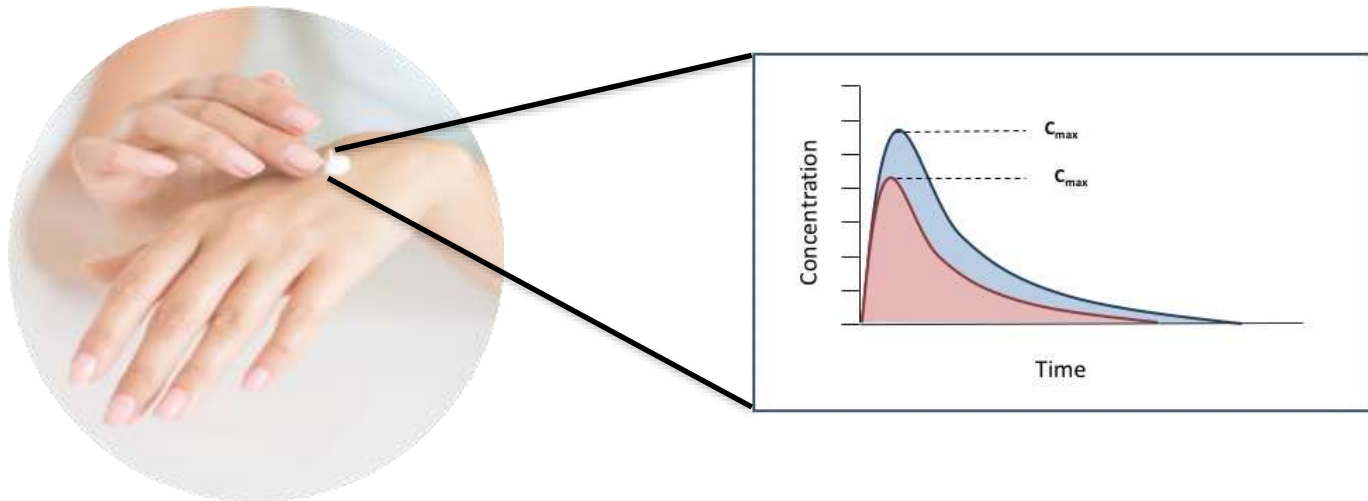


side view



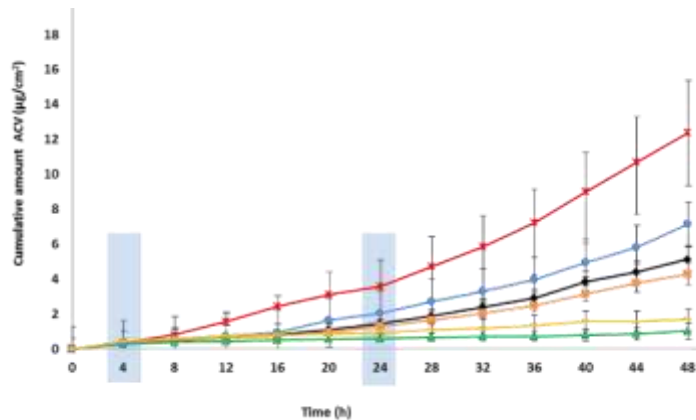
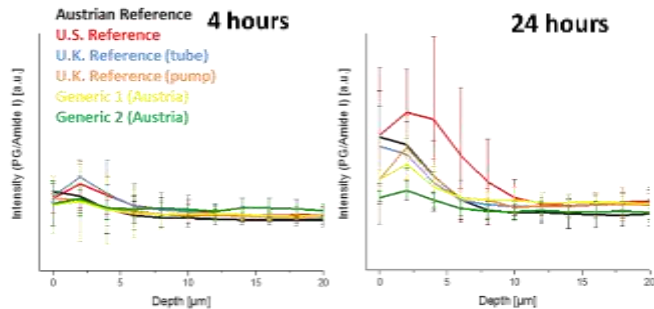
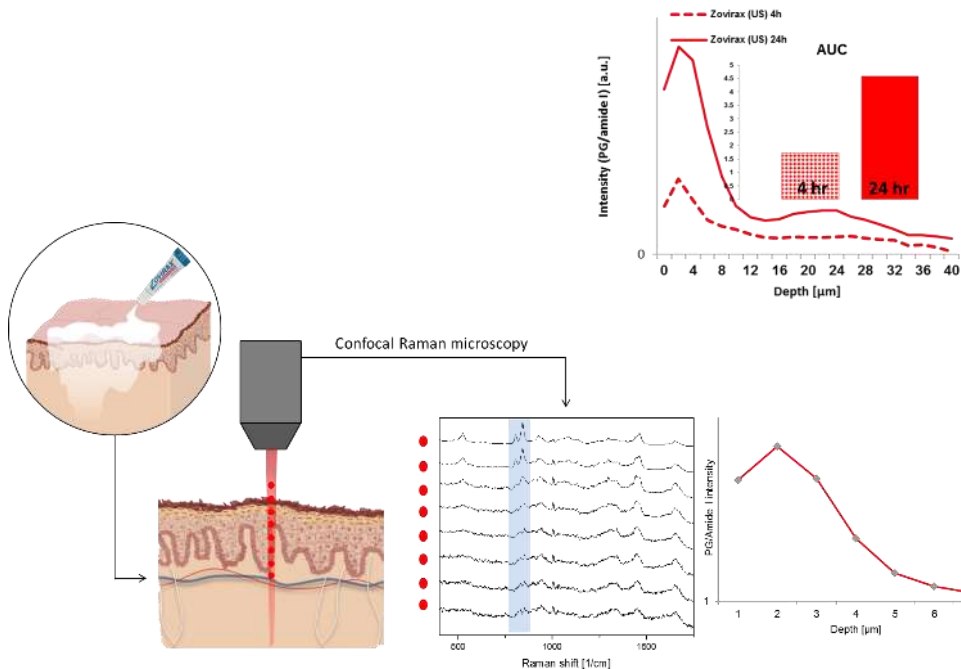
Understanding the Product Metamorphosis





Evaluation of Cutaneous Pharmacokinetics

Evaluation of Cutaneous Pharmacokinetics



Evaluation of Cutaneous Pharmacokinetics



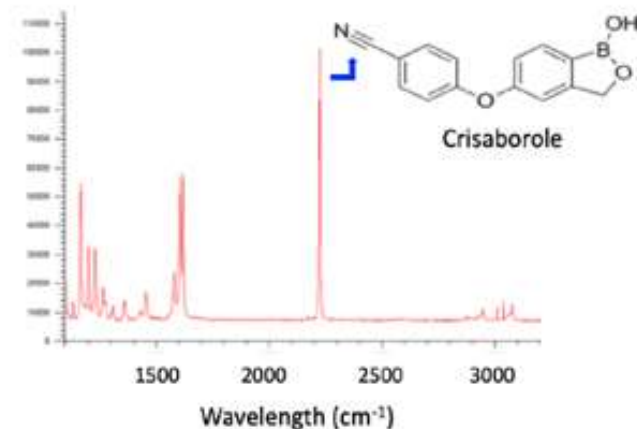
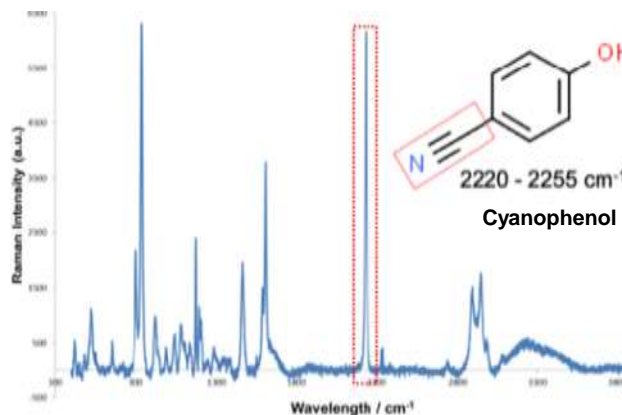
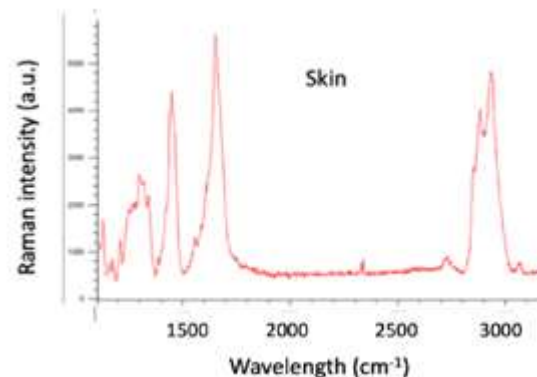
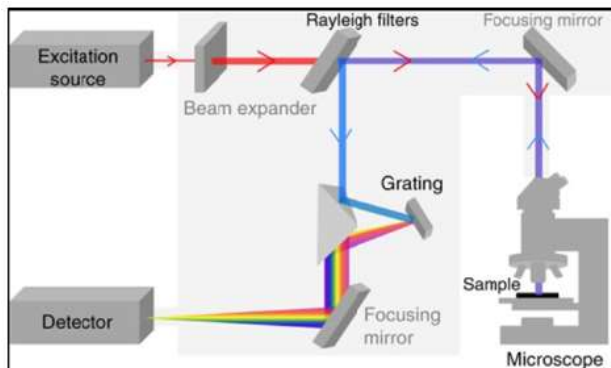
Current Limitations

- *Challenges with detection of molecule in the skin*
- *Challenges related to signal attenuation within the skin*
- *Challenges related to utility of tool as a semi-quantitative evaluation technique*
- *Challenges associated with limited utility, applicable for molecules with strong Raman signal*
- *Challenges related to data collection and data analysis of spectroscopic data*
- *Development of validation strategies for utilization of method in a regulatory setting*

Current Funding

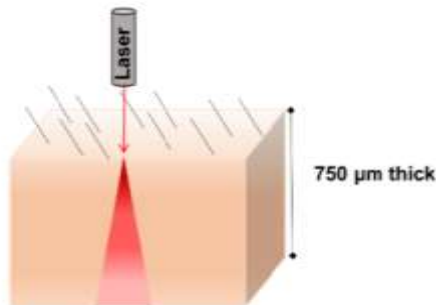
- *1U01FD006533 Bioequivalence of Topical Products: Evaluating the Cutaneous Pharmacokinetics of Topical Drug Products Using Non-Invasive Techniques, [PI Prof. Richard Guy, University of Bath](#)*
- *1U01FD006698 Pharmacokinetic Tomography for the Measurement of Topical Drug Product Bioequivalence, [PI Prof. Conor Evans, Massachusetts General Hospital/ Harvard Medical School](#)*

Detection of a Molecule Within the Skin

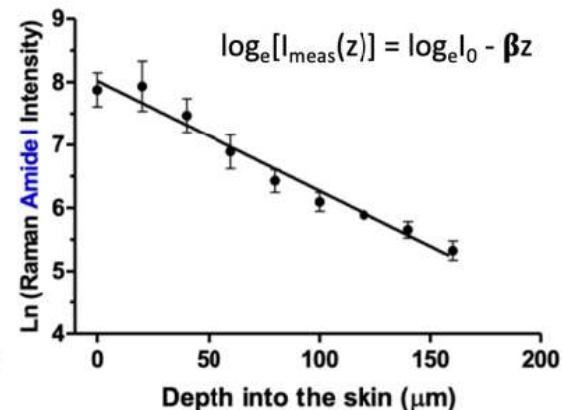
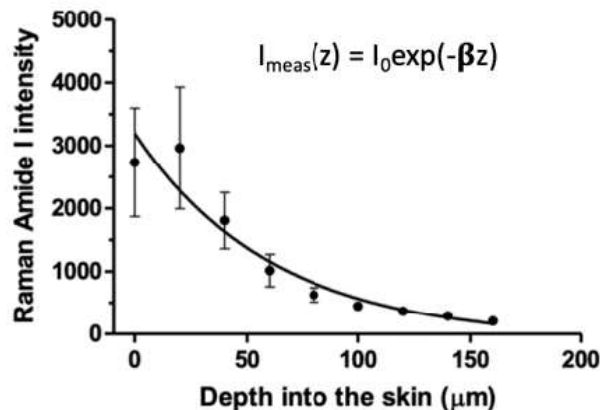
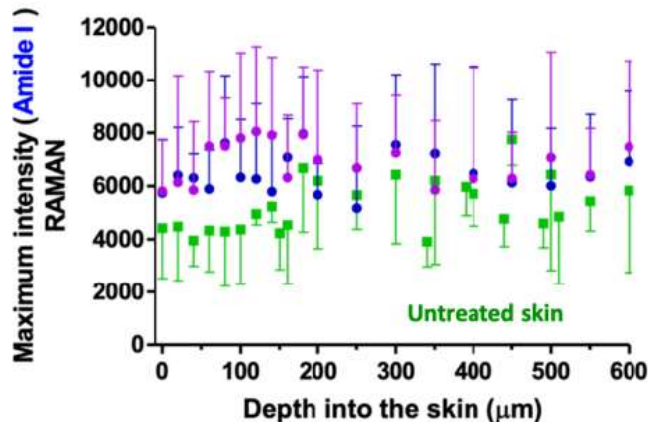
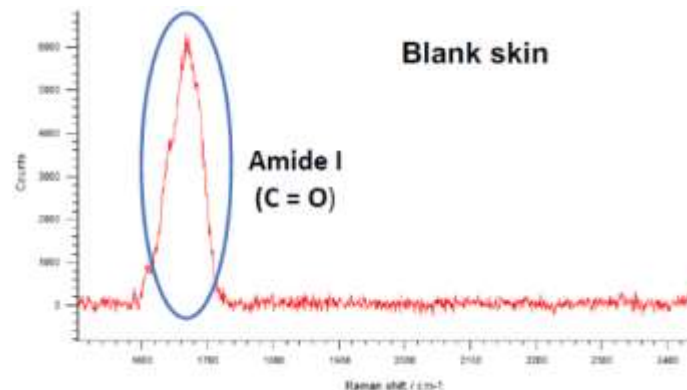


Strategies to Correct for Signal Attenuation

“Top-down” experiments

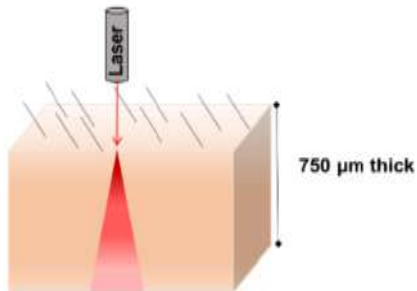


Blank skin

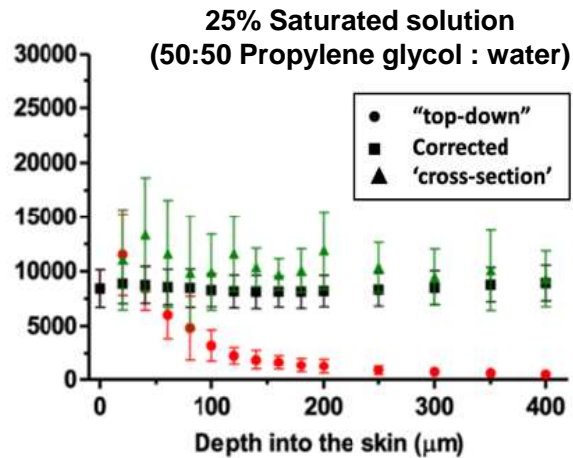
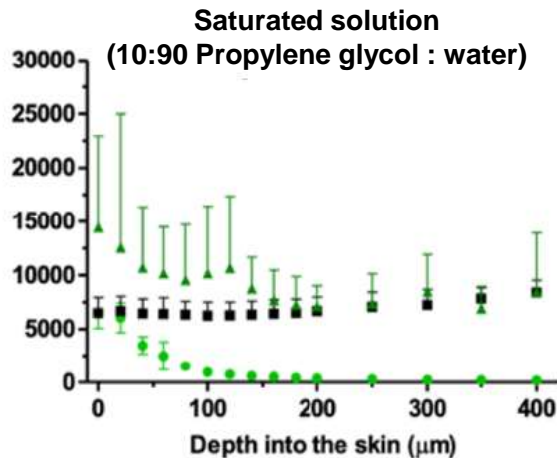
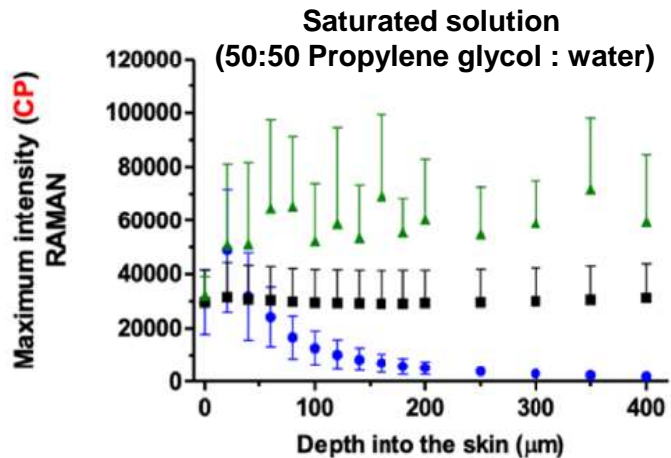
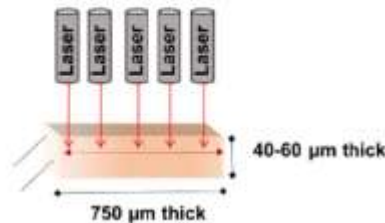


Development of a “Semi-Quantitative” Tool

“Top-down” experiments



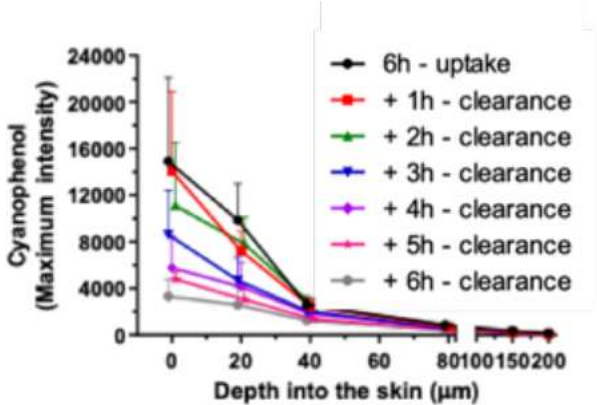
Cross-section experiments



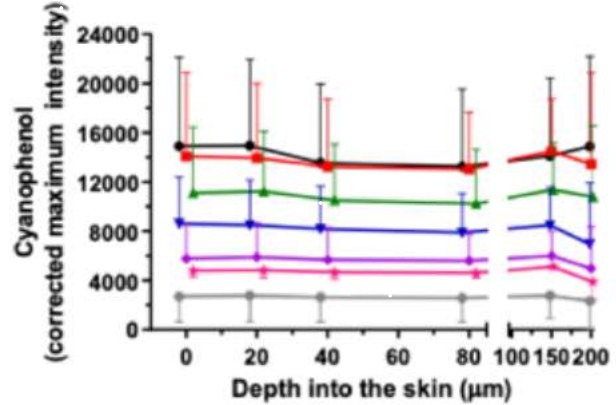
Evaluation of Cutaneous Pharmacokinetics

**Saturated solution
(50:50 Propylene glycol : water)**

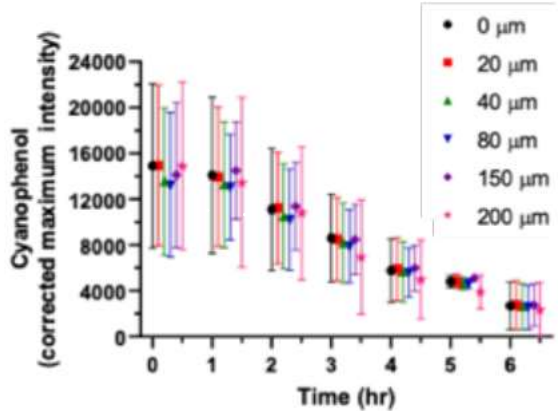
Uncorrected data as function of depth



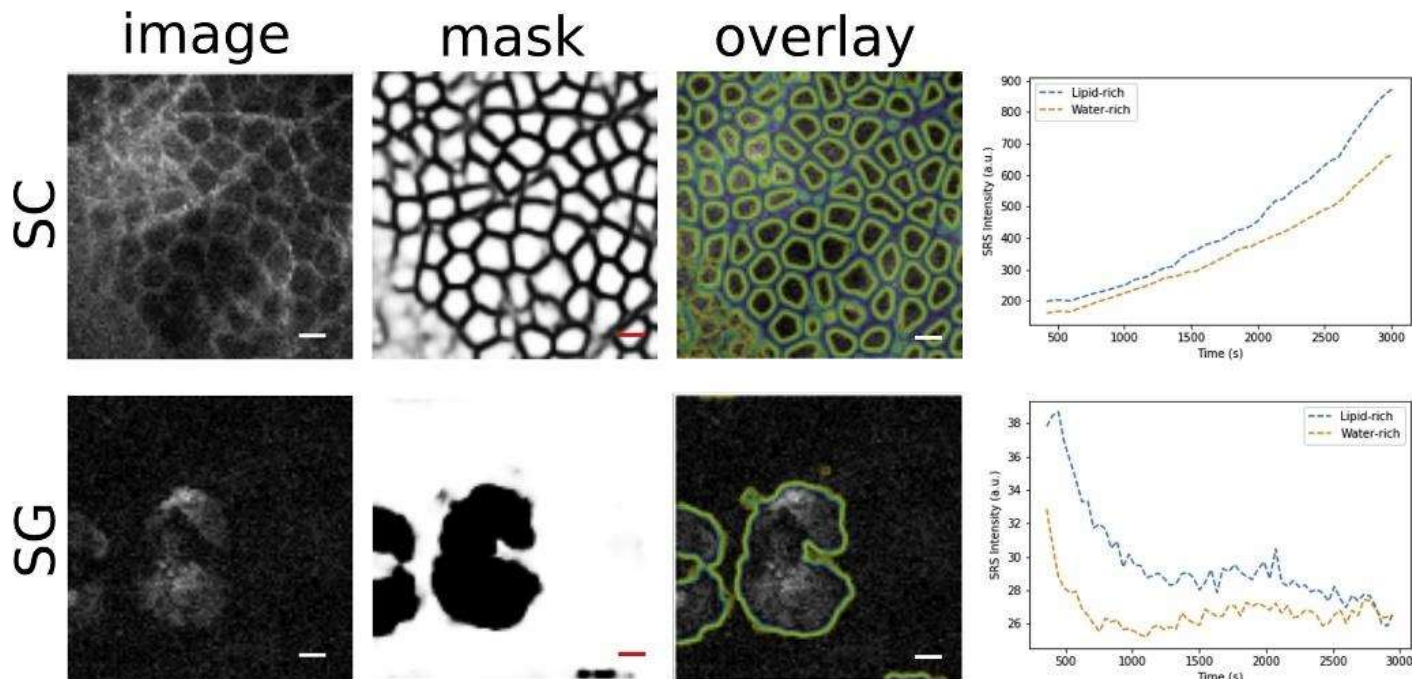
Corrected data as function of depth



Pharmacokinetic profile



Data Collection and Analysis Tools



Summary

- Imaging-based techniques are prevalent within the pharmaceutical industry
- Current literature/data illustrates that it is feasible to use Raman-based techniques for evaluation of drug product microstructure (including metamorphosis), drug release, and cutaneous pharmacokinetics
- Goal of the GDUFA-funded research studies is to develop Raman-based techniques as a “regulatory tool”
 - Identify strategies to enhance the applicability of Raman to a wide range of active ingredients
 - Develop hand-held tools that can be utilized for the evaluation of pharmacokinetics
 - Automate data collection and data analysis tools
 - Develop method validation strategies

Challenge Question

Raman-based imaging techniques can be utilized to monitor :

- A. The changes in the color of the skin
- B. The indication of the drug product
- C. A molecule that generates a Raman signal
- D. The mechanism of action of a drug

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Acknowledgements



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(PI Prof. Richard Guy, University of Bath)
- ***GDUFA Award U01FD006698***
(PI Prof. Conor Evans, Massachusetts General Hospital, Harvard Medical School)

Closing Thought



“Ask the right questions, and nature will open the doors to her secrets”...

Dr. C.V. Raman

The goal over the next few years is to be able to develop and utilize imaging-based strategies to facilitate generic drug development

Thank You

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