

Use of imaging techniques in dermal drug development

Preclinical Development- Chemical (Rapid Fire)
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Biography and Contact Information

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Imaging in Dermal Drug Development



Visualization can facilitate drug development by enhancing our understanding of key features:

1. Changes in skin morphology due to age or disease states
2. Availability of the API/ excipients in the different layers of the skin
3. The dosage form

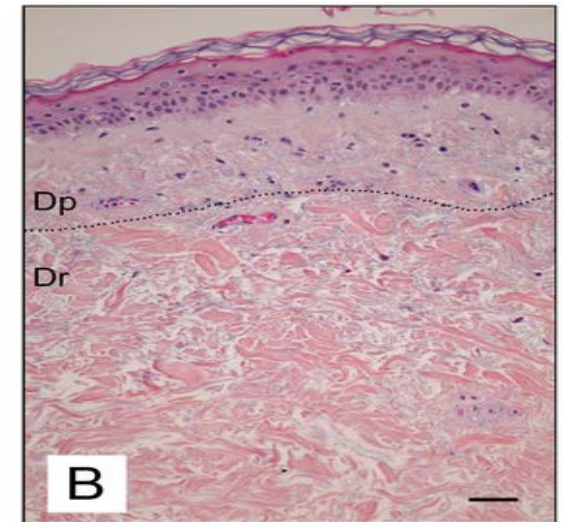
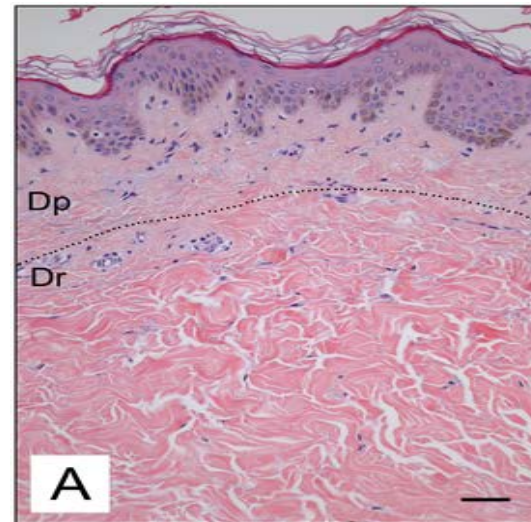
Active pharmaceutical ingredient (API)

1. Changes in skin morphology (with age)

Understanding the morphological differences in skin (e.g., changes in the structure of the skin with age) can facilitate drug development



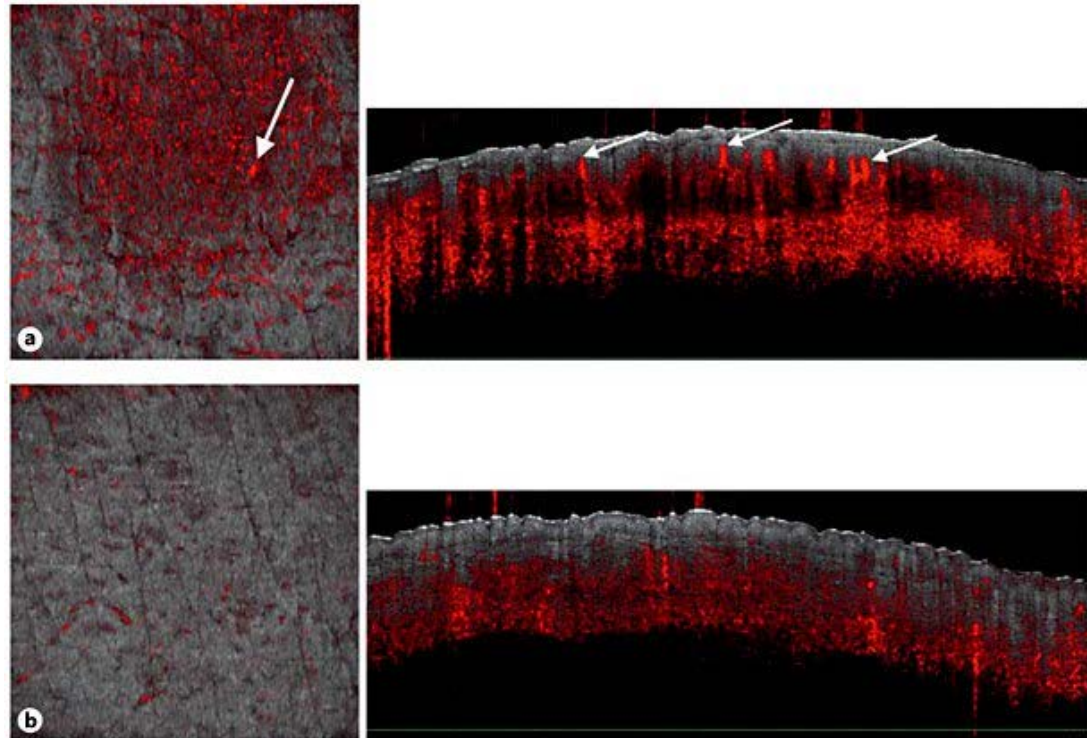
Dermato-endocrinology 4:3, 308–319; July–December 2012; © 2012 Landes Bioscience



Mine S, Fortunel NO, Pagon H, Asselineau D, **Aging Alters Functionally Human Dermal Papillary Fibroblasts but Not Reticular Fibroblasts: A New View of Skin Morphogenesis and Aging.** PLOS ONE 3(12): e4066.

1. Changes in skin morphology (with disease)

Understanding the morphological differences in skin (e.g., changes in the structure of the skin with disease states) can facilitate drug development



Optical Coherence Tomography

(a) Healthy (adjacent) skin

(b) Psoriatic skin- Despite marked morphological differences (thickened and bright stratum corneum, acanthosis), the number of blood vessels is increased in psoriasis. Especially in the upper stratum papillare, loops of dilated capillaries are present (arrows)

Ulrich M, Themstrup L, de Carvalho N, Manfredi M, Grana C, Ciardo S, Kästle R, Holmes J, Whitehead R, Jemec G, B, E, Pellacani G, Welzel J: **Dynamic Optical Coherence Tomography in Dermatology**. *Dermatology* 2016;232:298-311

2. Permeation of API (Fluorescence Microscopy)

Visualization using microscopic techniques can enhance our understanding of drug distribution locally in the skin following treatment

Fluorescence microscopy images

Ex vivo human facial skin

- Control
- 1% BPX-01 (a topical acne gel)
- 4% BPX-01 at 24 hours

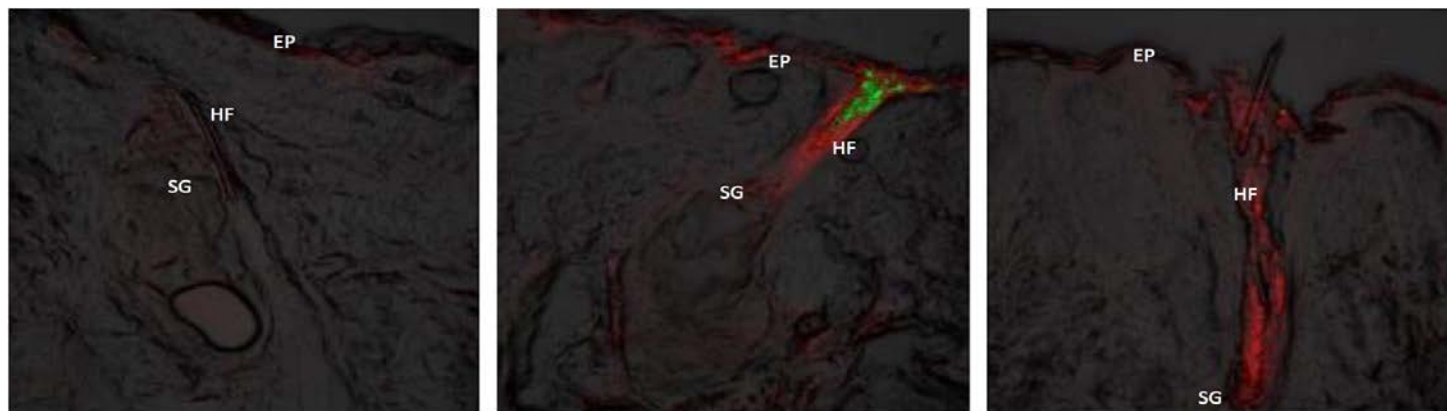
Minocycline fluorescence in red



Two-photon fluorescence microscopy

Ex vivo human facial skin

- Control (endogenous fluorescence in the absence of minocycline in epidermis (EP), hair follicle (HF), and sebaceous gland (SG))
- 1% BPX-01
- 4% BPX-01 at 4 hours

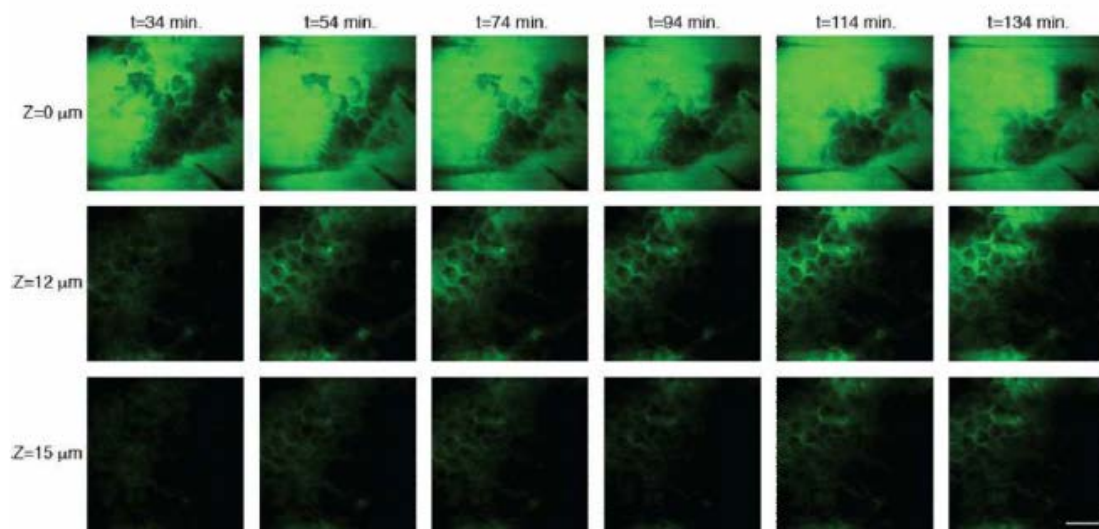


Evans Conor L. , Chan Kin F. , Prow Tarl and Osseiran Sam, **Visualizing and quantifying drug uptake in skin**, Biomedical Optics & Medical Imaging

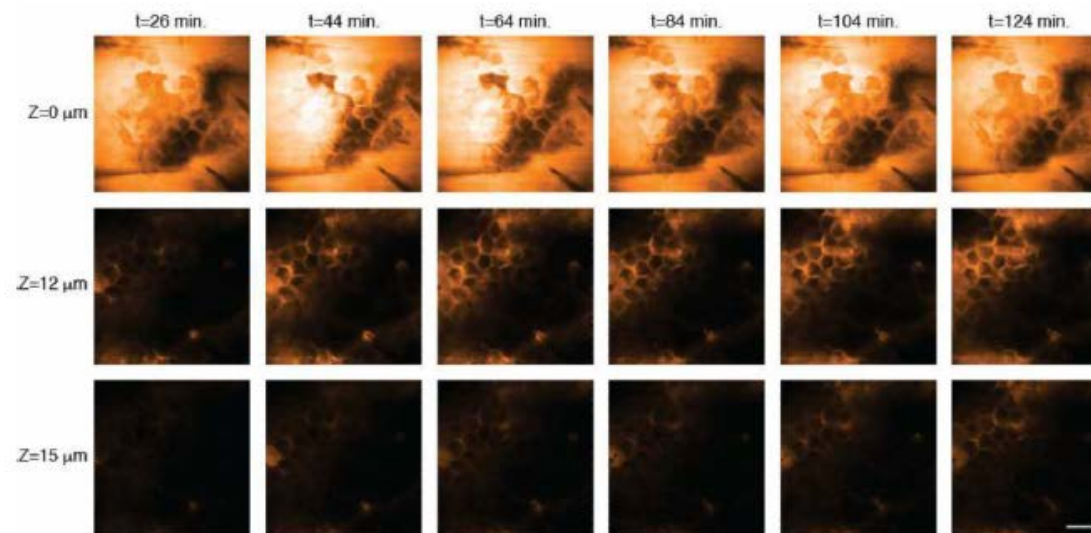
2. Permeation of API/Excipients (Raman Spectroscopy)

Visualization using different spectroscopic techniques can enhance our understanding of drug and excipient distribution locally in the skin following treatment

Ketoprofen (deuterated)



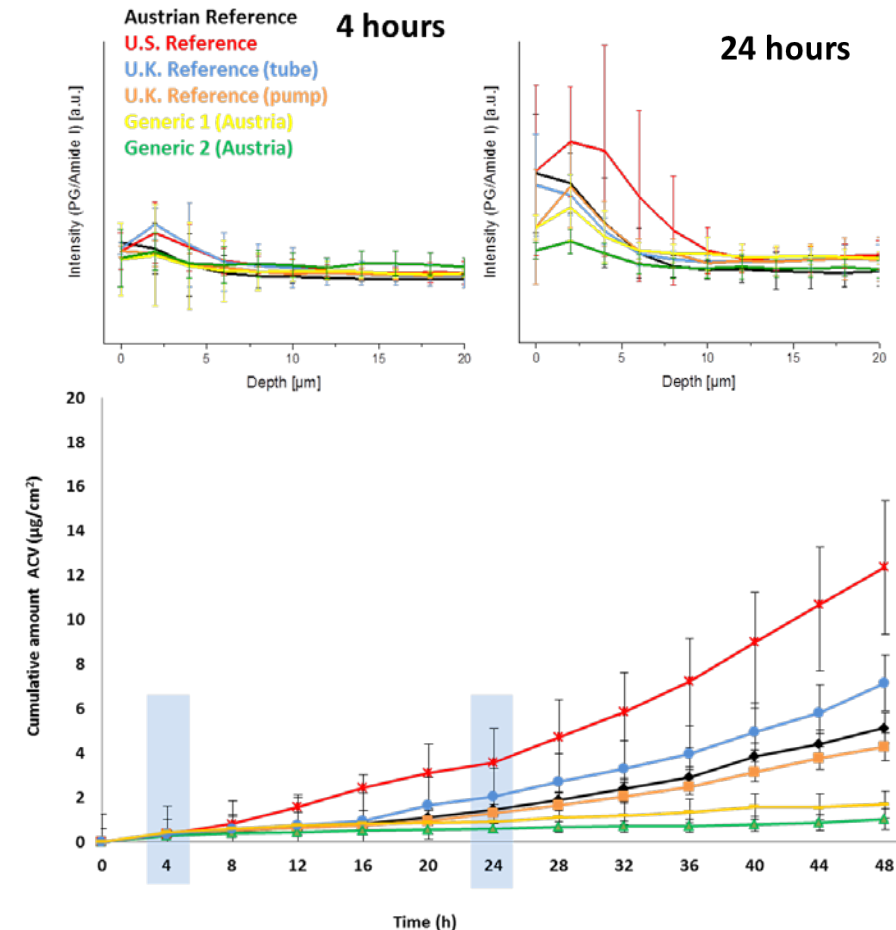
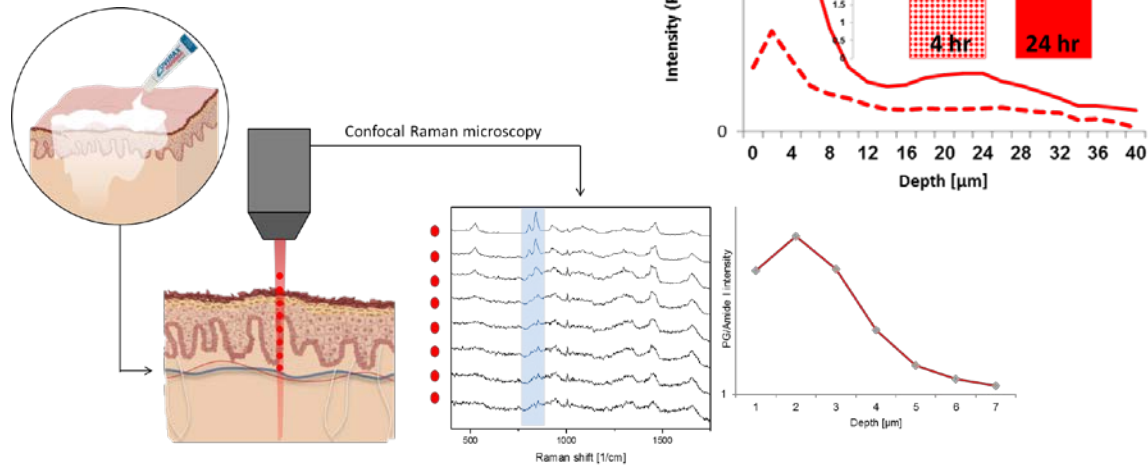
Propylene Glycol (deuterated)



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

2. Permeation of API/ Excipients (Raman Spectroscopy)

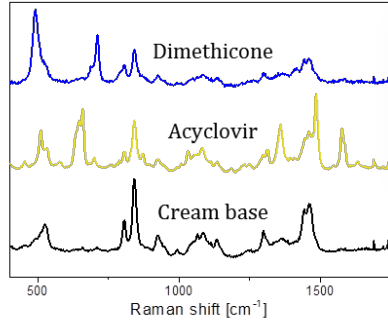
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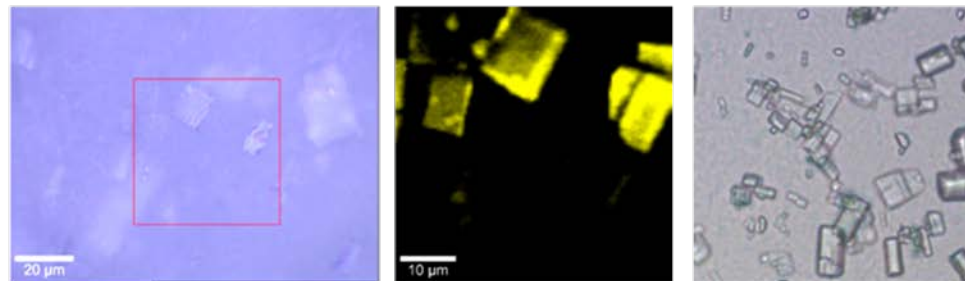
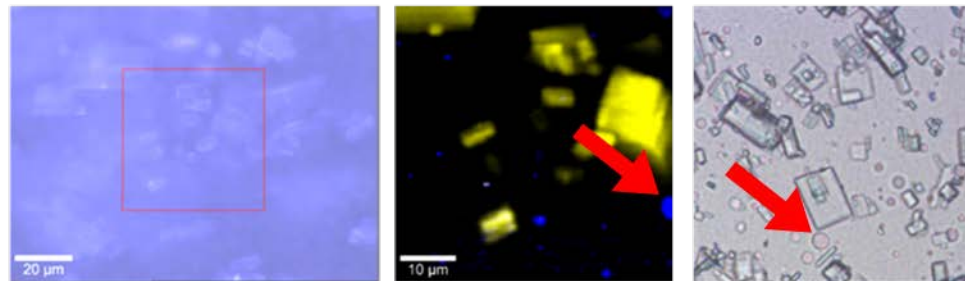
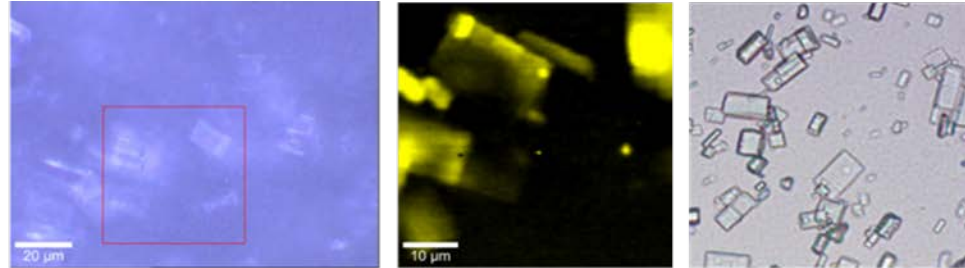
Prof. Michael Roberts FDA Award U01-FD005226

3. The Dosage Form (Raman Spectroscopy)

Spectroscopic techniques can also enhance our understanding of the localization and distribution of the drug within the dosage form



Zovirax[®] UK
Tube



Zovirax[®] UK
Pump

Zovirax[®] UK
Pump
(from inside container)

Prof. Michael Roberts FDA Award U01-FD005226

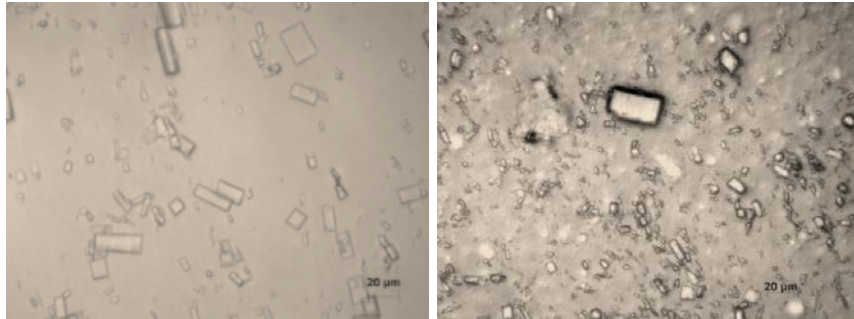
3. The Dosage Form (Optical Microscopy)

Optical microscopy can facilitate our understanding of the drug in the container and following application on the skin

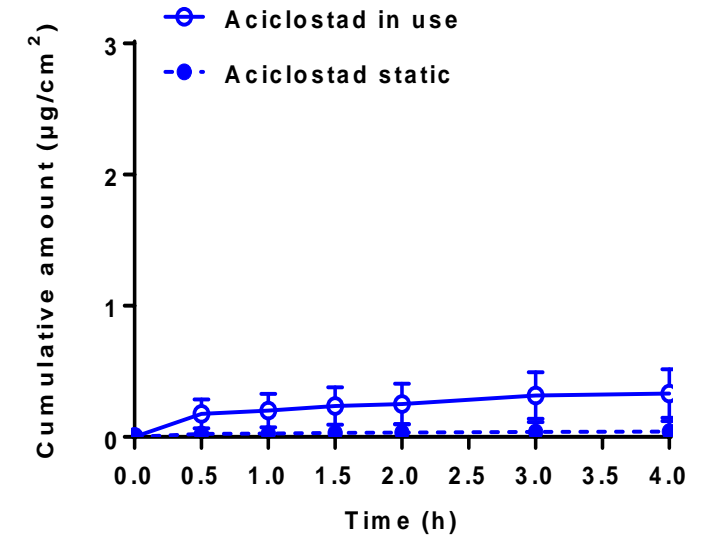
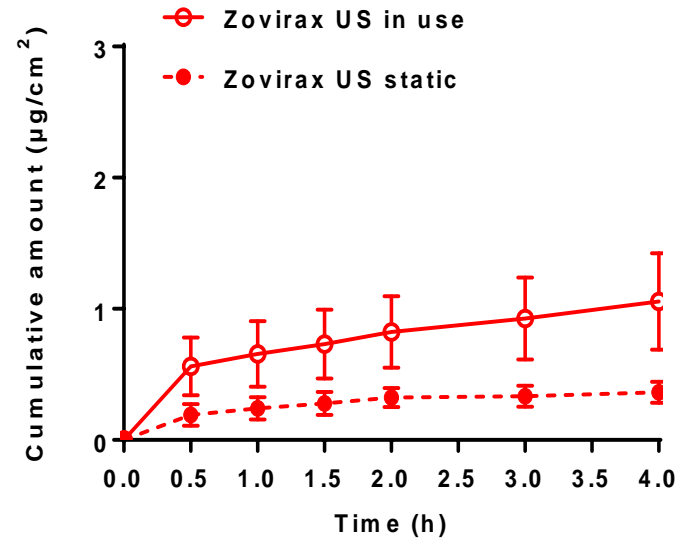
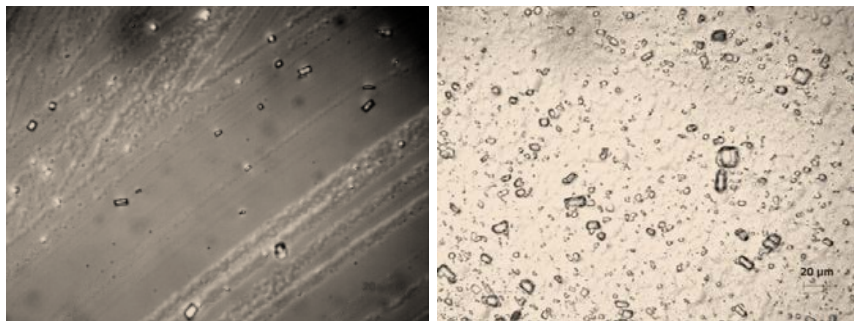
Zovirax US

Aciclostad

Static



In use



Summary

- 'A picture is worth ten thousand words' as stated by **Fred R. Barnard**, of *Printers' Ink*, 10 March 1927.'
- Microscopy and spectroscopy techniques have been used to understand
 - The changes in morphology of diseased skin compared to healthy skin
 - The availability of the API/excipients in the different layers of the skin
 - The dosage form
- Most techniques are qualitative in nature and/or require modifications to the API for detection/quantification
- Challenges exist in routine use of these techniques during drug development

Let us discuss how we can resolve some of these challenges!!!

Acknowledgments

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GDUFA Award U01FD005226

Michael Roberts, PhD

Questions



U.S. FOOD & DRUG
ADMINISTRATION