Understanding the Complexity of Topical (Dermatological) Semisolids

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

High Quality Drug Products

- What does "quality" mean for a drug product?

Fitness for Purpose

*"The totality of **features and characteristics of a product…** that bear on its ability to satisfy stated or implied needs"*

- International Organization for Standardization (ISO)

Control of Failure Modes

*"Good pharmaceutical quality represents **an acceptably low risk of failing** to achieve the desired clinical attributes."*

- Dr. Janet Woodcock, Director, FDA CDER

Woodcock, J. (2004) *The concept of pharmaceutical quality*. Am Pharm Review 7(6):10-15

What is a "Complex" Drug Product

- Complex Drug Products are defined[1] as those with:
  - **Complex active ingredients**
    - peptides, polymeric compounds, complex mixtures of APIs, etc.
  - **Complex formulations**
    - liposomes, colloids
  - **Complex routes of delivery**
    - locally acting drugs
  - **Complex dosage forms**
    - transdermals, metered dose inhalers, extended release injectables, etc.
  - **Complex drug-device combination products**
    - auto injectors, metered dose inhalers
  - **Other products where there is complexity or uncertainty concerning the approval pathway**

[1] Source: *GDUFA II Commitment Letter* accessible on www.fda.gov at https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf

Why are Topical Products "Complex"

- Topical products can be "complex" in multiple ways
  - **Complex formulation:**
    - e.g., a foam, gel, cream, etc.
  - **Complex route of delivery:**
    - e.g., locally acting
  - **Complex dosage form:**
    - e.g., a topical patch
  - **Complex drug-device combination products:**
    - e.g., a topical solution in a metered dose pump

Components in a Topical Formulation

- **An Active Ingredient**
  - Directly responsible for therapeutic effect, frequently via activity in a molecular mechanism associated with the disease state.
- **An Inactive Ingredient (Excipient)**
  - Theoretically inert with respect to the disease state
  - Facilitates the formulation of the active ingredient in a dosage form appropriate for dose administration

Excipients Impact Product Performance

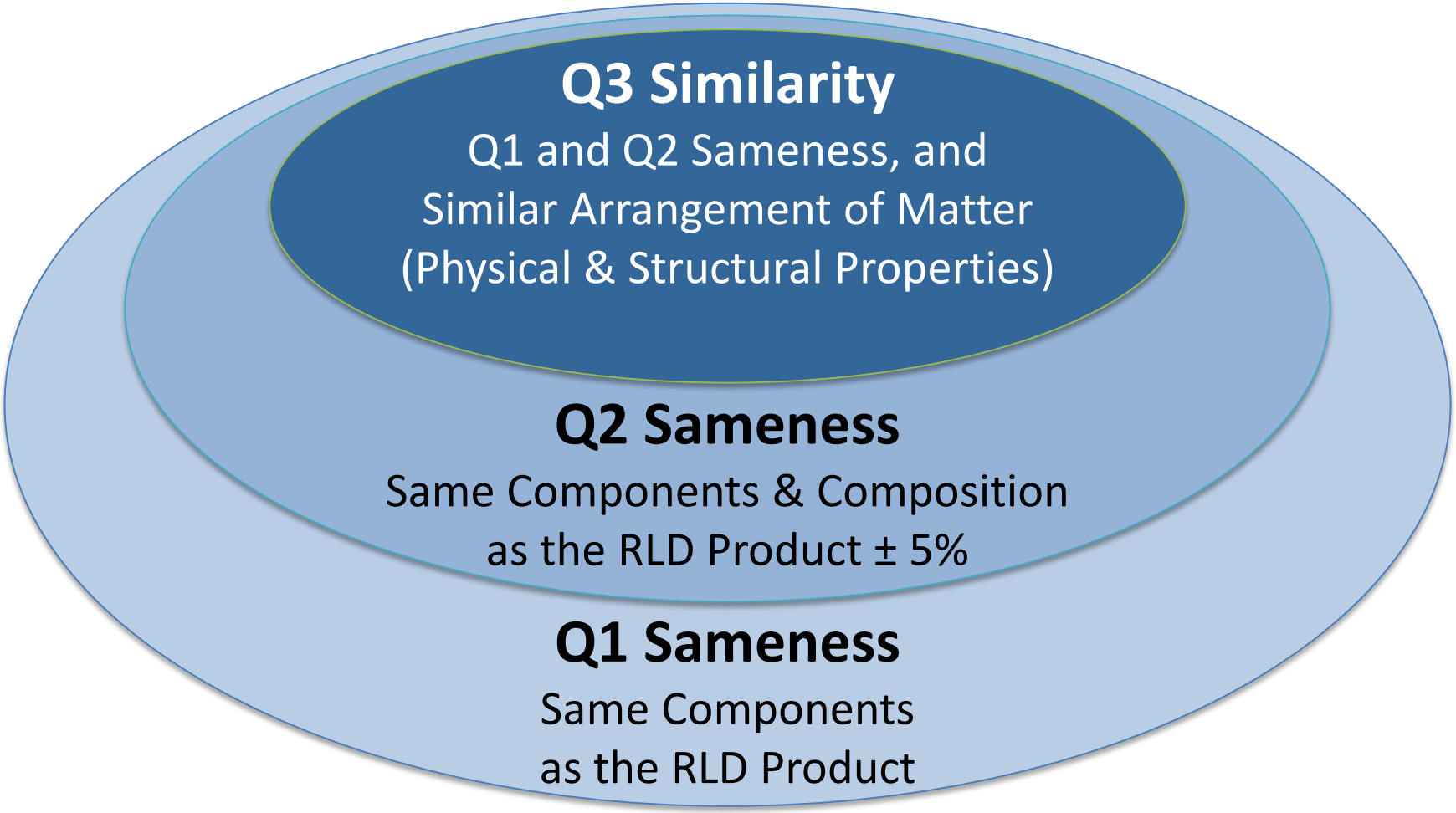
- Excipient quality and composition can affect:
  - The phase states and the arrangement of matter
  - Drug diffusion within the dosage form
  - Drug partitioning from the dosage form into the SC
  - Alteration of skin structure and chemistry
  - Drug diffusion within the skin itself
  - Drug delivery & bioavailability at the target site
  - Skin (de)hydration, irritation or damage
  - Metamorphosis of the dosage form on the skin

Failure Modes for BA/BE

- Consider how failure modes for BA/BE arise from quality attributes
- Consider how the risk of failure modes can be mitigated once the associated quality attributes are designed into the product and controlled within a well-characterized design space
- Consider which qualities to characterize, what measurement techniques to use, and how to correlate results with product performance

Topical Formulation Quality Concepts

- What are Q1, Q2, and Q3?



Q1/Q2 (Composition) Sameness

- Mitigates the risk of known failure modes related to:
  - Irritation and sensitization
  - Formulation interaction with diseased skin
  - Vehicle contribution to efficacy (Placebo effect)
  - Stability, solubility, etc. of the drug

Dosage Form Metamorphosis

- Solvent Activity of Q1/Q2 Identical Creams

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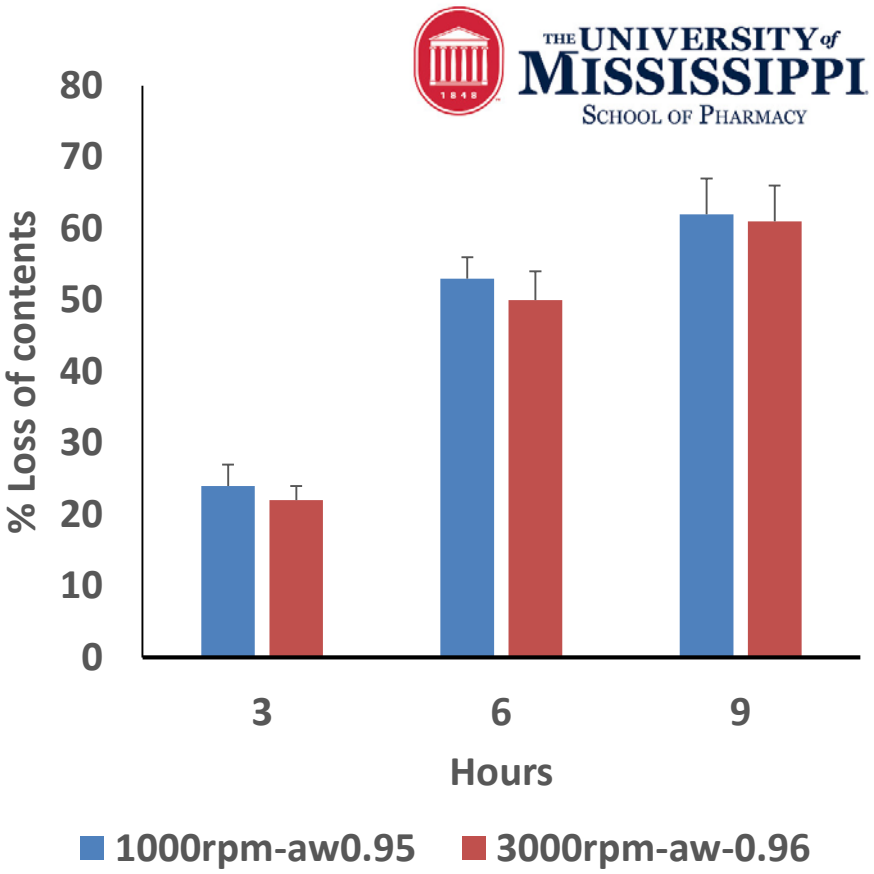
Ingredients	Quantity (%w/w)
Drug	1
Cetostearyl alcohol	7
Cremophor A6	1.5
Cremophor A25	1.5
Mineral Oil	12
Propylene Glycol	8
Water	69
Total	100

Manufacturing Conditions	Solvent Activity (a_w)
1000 RPM (20 min)	0.950± 0.004
3000 RPM (20 min)	0.961 ± 0.006



Data provided courtesy of Prof. Narasimha Murthy

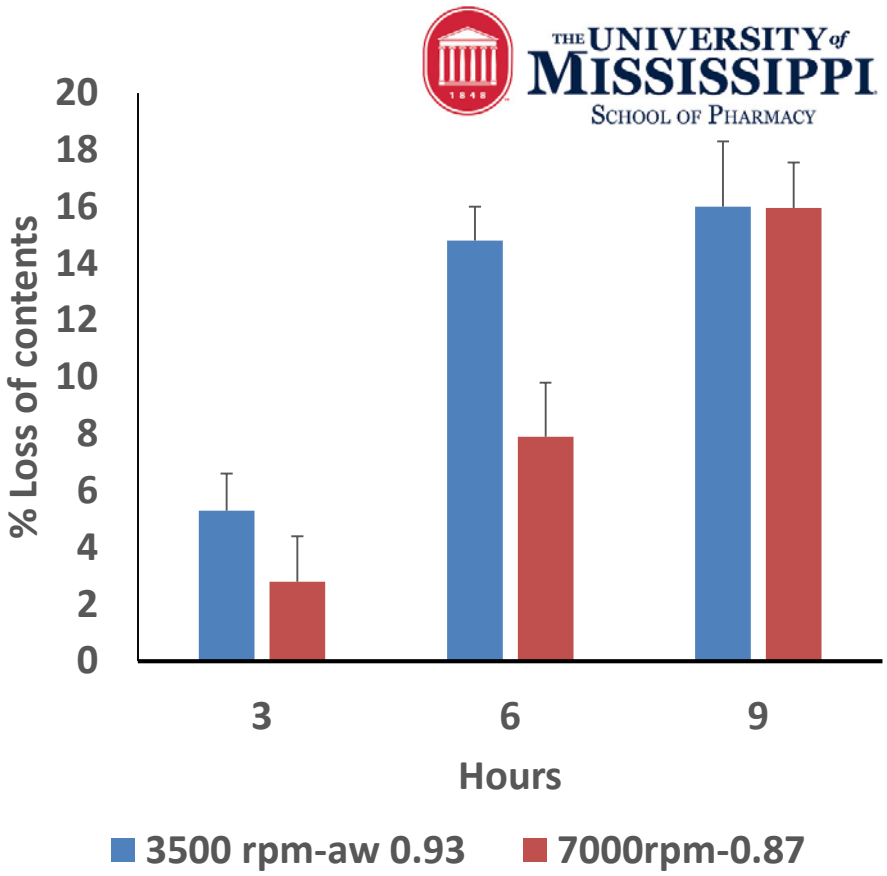
Dosage Form Metamorphosis

- Solvent Activity of Q1/Q2 Identical Creams

Prof. Narasimha Murthy FDA Award U01-FD005223

Ingredients	Quantity (%w/w)
Cetostearyl Alcohol	12.5
White Wax	12
Mineral Oil	56
Sodium Borate	0.5
Water	19
Total	100

Manufacturing Conditions	Solvent Activity (a_w)
3500 RPM (15 min)	**0.931 ± 0.002**
7000 RPM (45 min)	**0.875 ± 0.006**



Data provided courtesy of Prof. Narasimha Murthy

Dosage Form Metamorphosis

- Solvent Activity and Drying Rate

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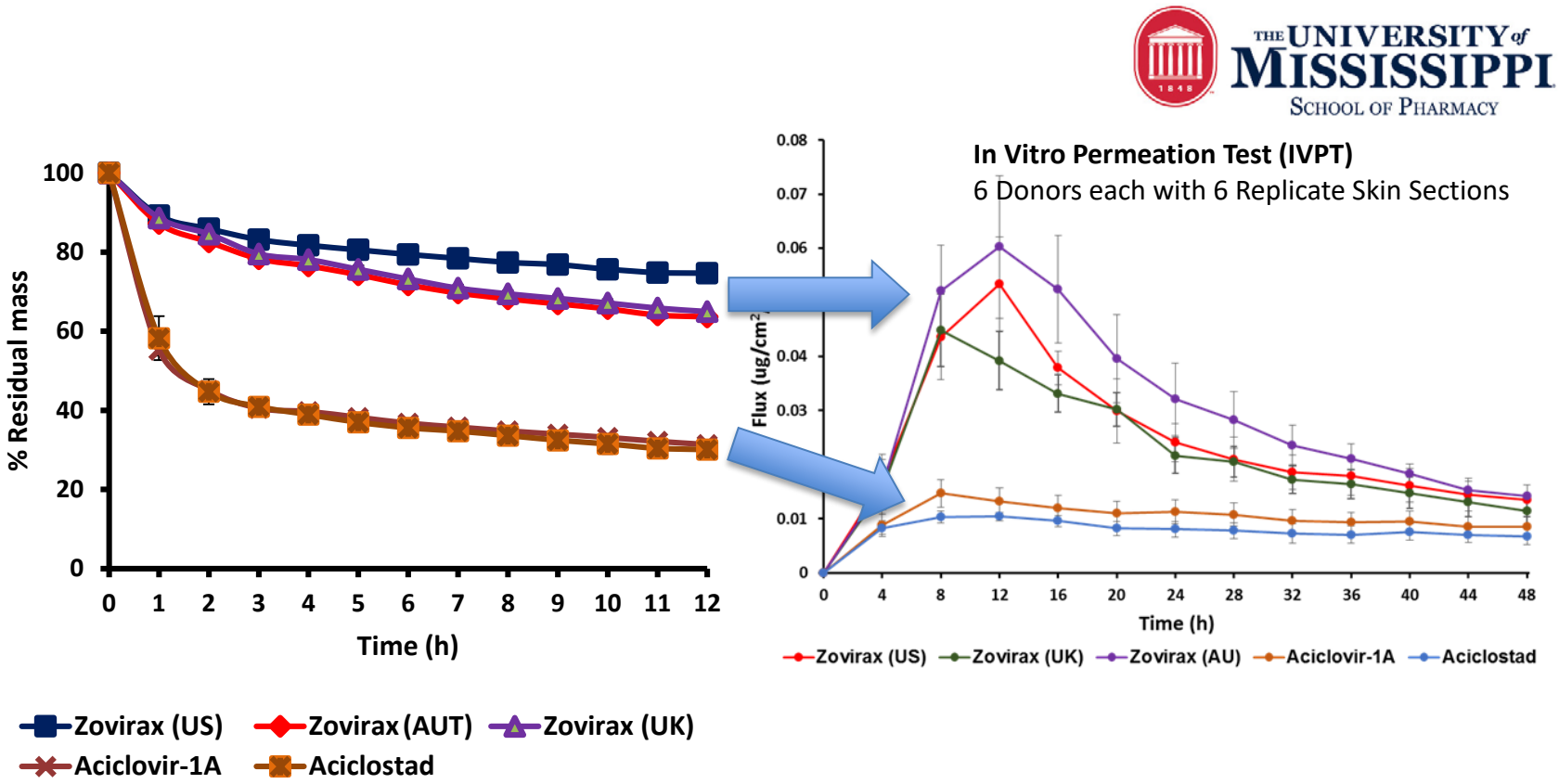

Data provided courtesy of Prof. Narasimha Murthy

Influence of Dispensing Stress on Q3

- Influence of Dose Dispensing on Product Quality

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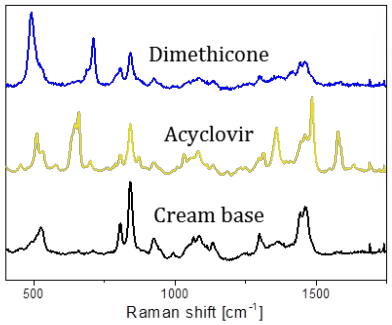


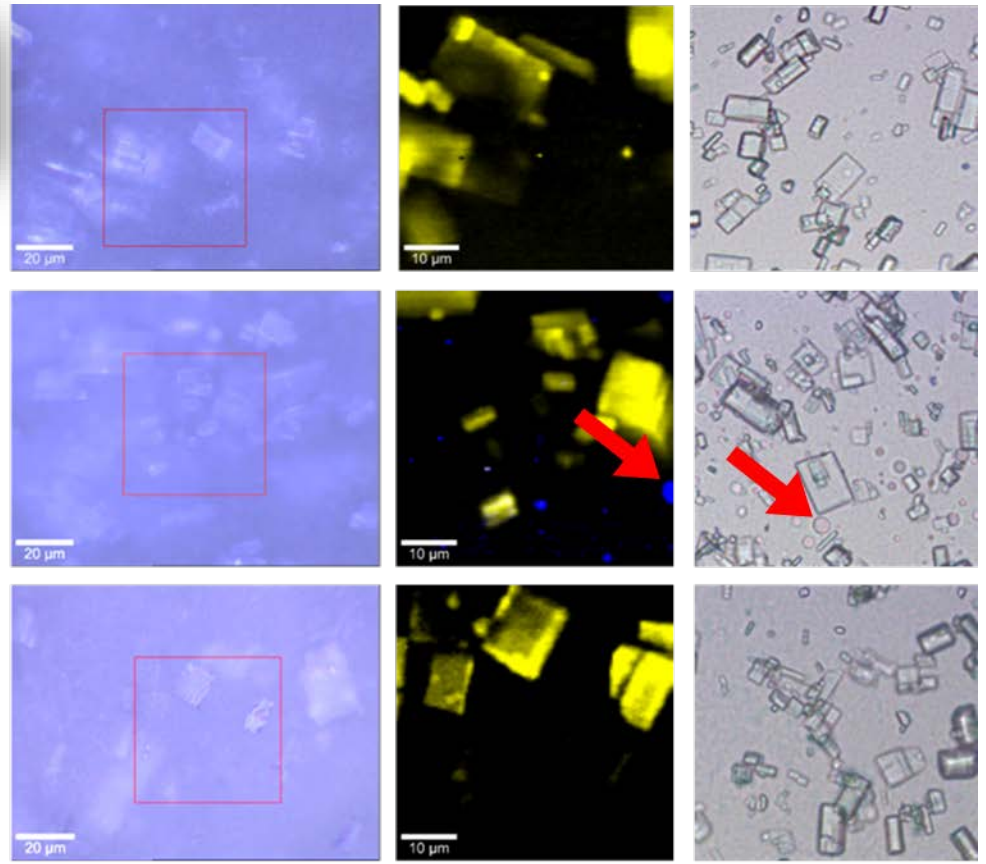
Zovirax® UK
Tube

University of South Australia

UNIVERSITÄT DES SAARLANDES

Zovirax® UK
Pump

Zovirax® UK
Pump
(from inside container)



Data provided courtesy of Prof. Michael Roberts & Prof. Maike Windbergs

Influence of Dispensing Stress on Q3

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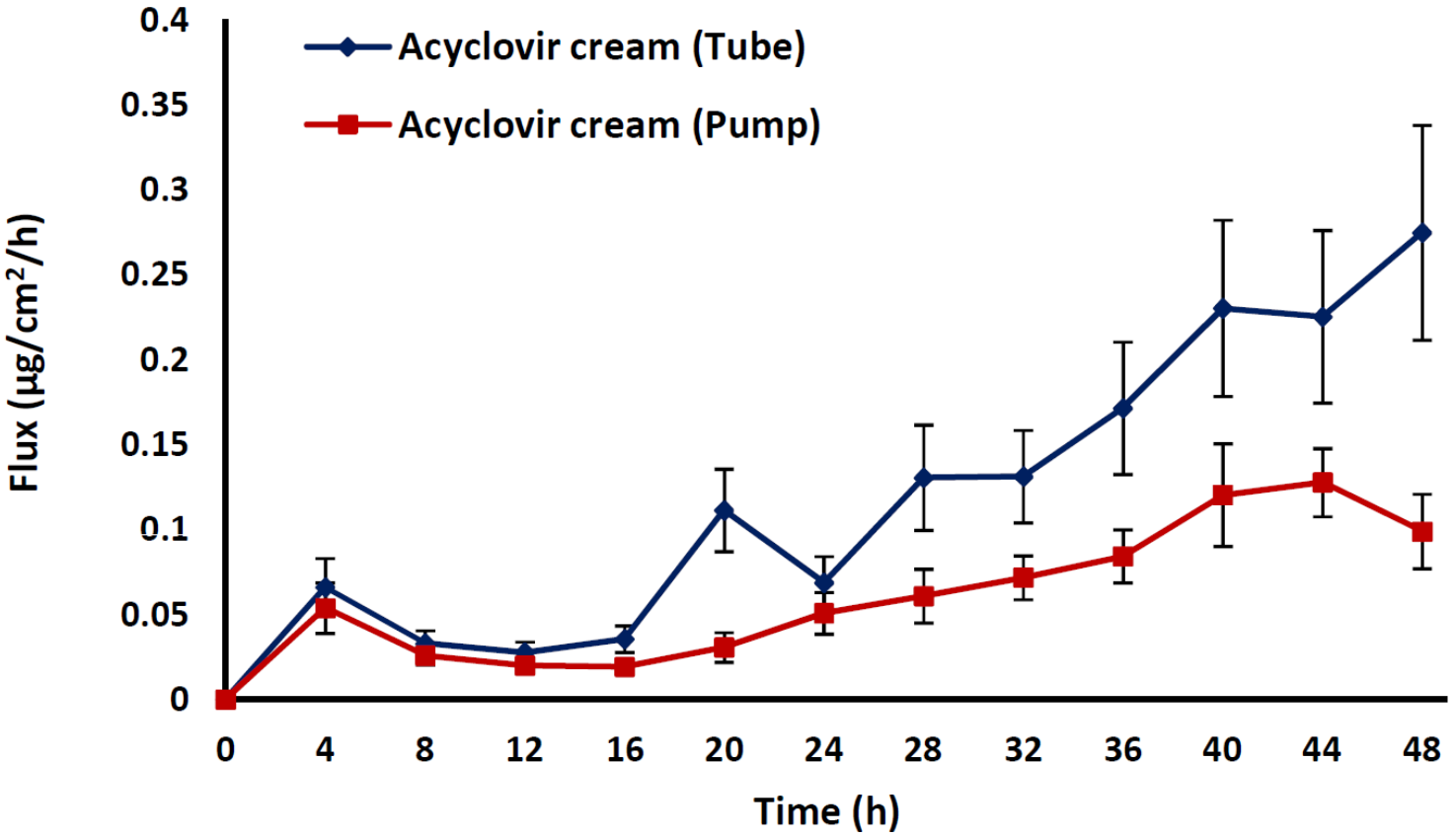
University of South Australia



Data provided courtesy of Prof. Michael Roberts

Tests for Physical & Structural Similarity

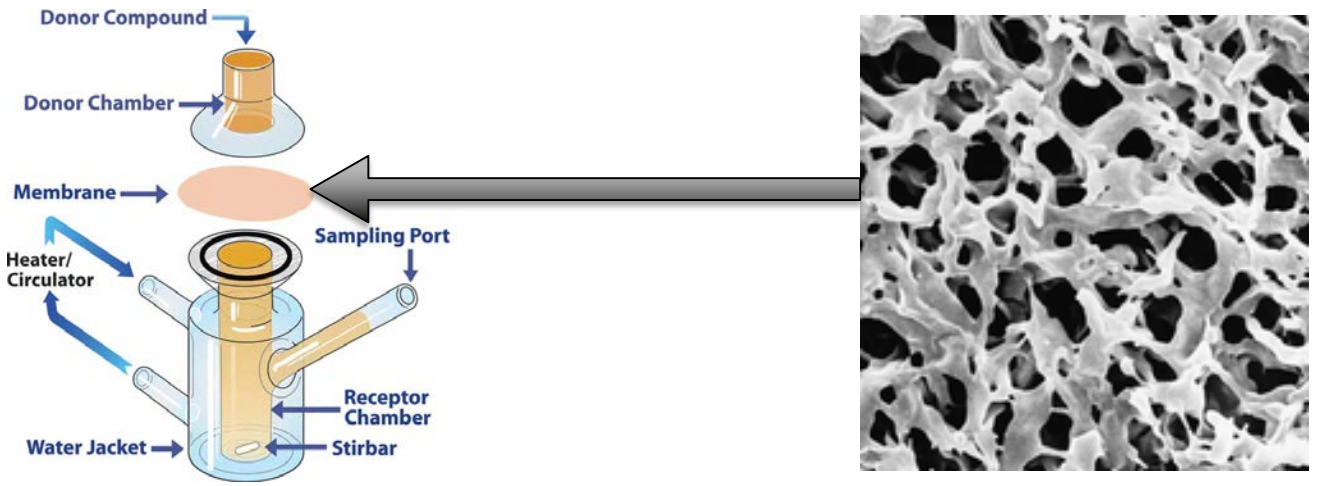
- Microscopic Analyses of Microstructure
- Dissolved vs.Undissolved Amounts of the Drug
- Concentration of Drug in the Continuous Phase
- Size Distribution of Globules/Particles
- Drug Polymorphic State (Raman, XRD, etc.)
- Solvent/Water Activity (Drying Rate)
- Specific Gravity
- pH
- Etc.

Q3 (Physical and Structural) Similarity

- Mitigates the risk of potential failure modes related to:
  - Differences in Q1/Q2 sameness (± 5% tolerances)
  - Differences in pH that may irritate diseased skin
  - Differences in the polymorphic form of the drug
  - Differences in rheology that alter the spreadability, retention, surface area of contact
  - Differences in entrapped air and amount per dose
  - Differences in diffusion and partitioning, etc.
  - Differences in metamorphosis and drying rates

In Vitro Release Testing (IVRT)

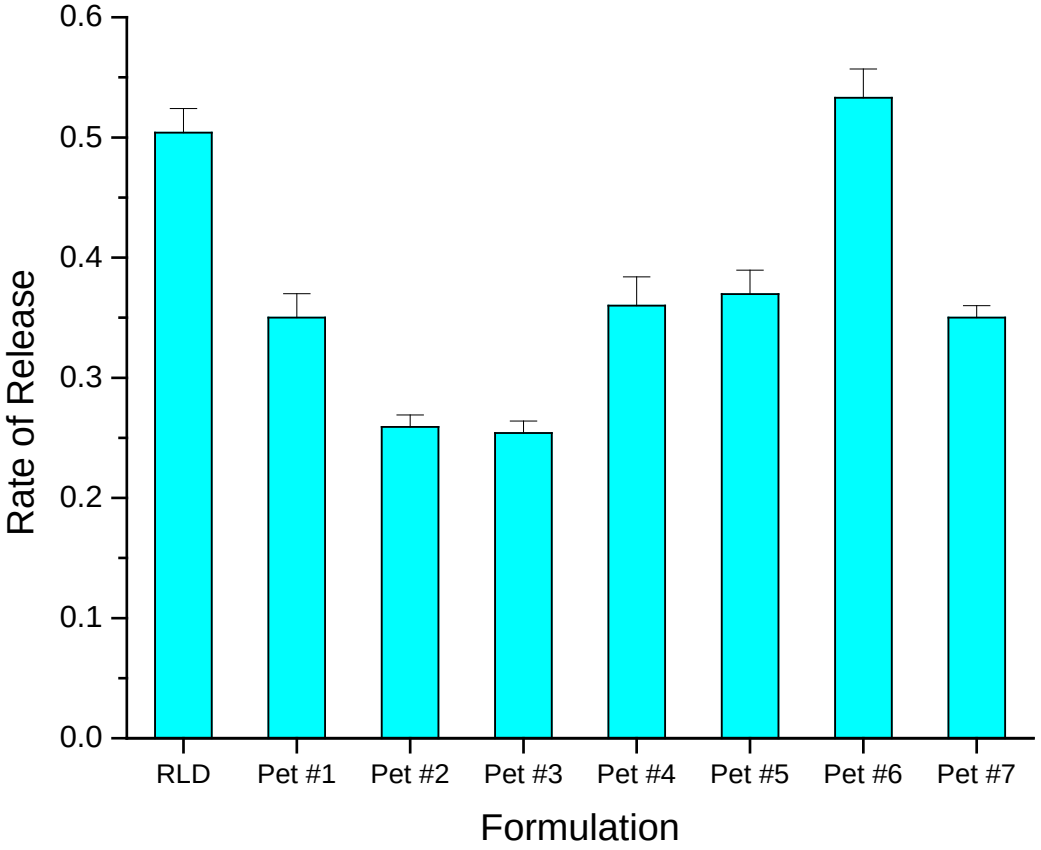
- IVRT is a compendial method with established statistical analyses which can be sensitive and discriminating (but no IVIVC is expected)



- IVRT can mitigate the risk of unknown failure modes related to differences that may not be identified by the quality tests

IVRT ***Can*** Discriminate Some Things

- IVRT **did discriminate** 8 formulations made with Petrolatum, USP from different sources



Data provided courtesy of Paul A. Lehman and Dr. Thomas J. Franz

IVRT ***May not*** Discriminate Some Things

- IVRT **did not discriminate** 14 formulations with substantial variations in particle size

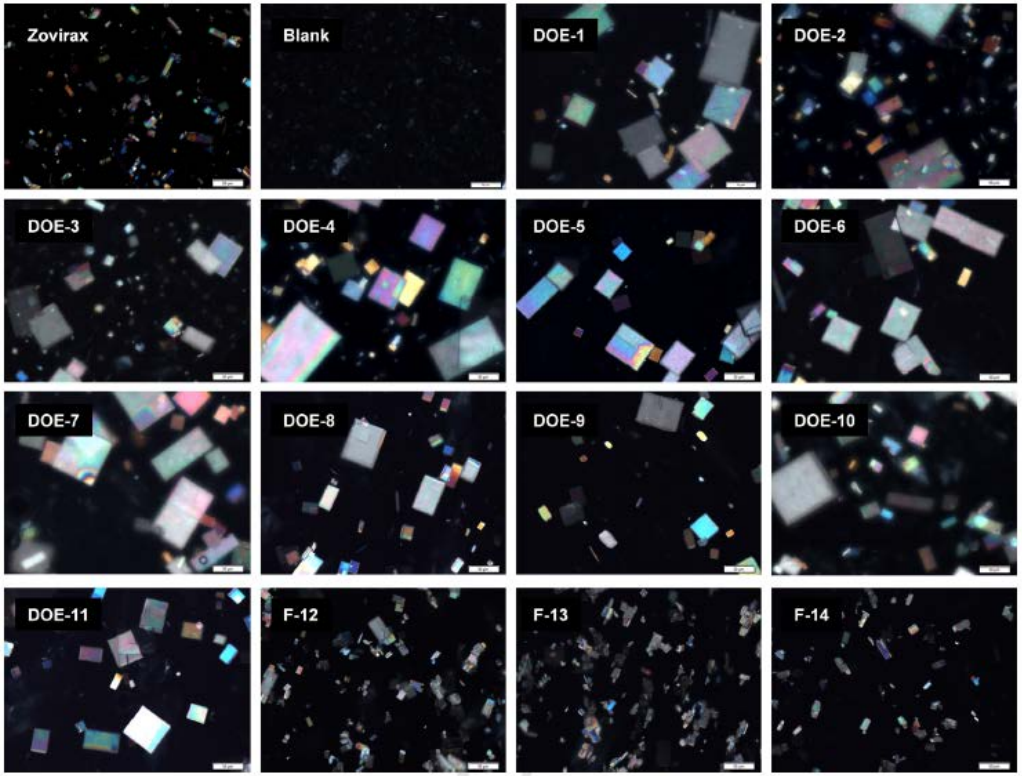
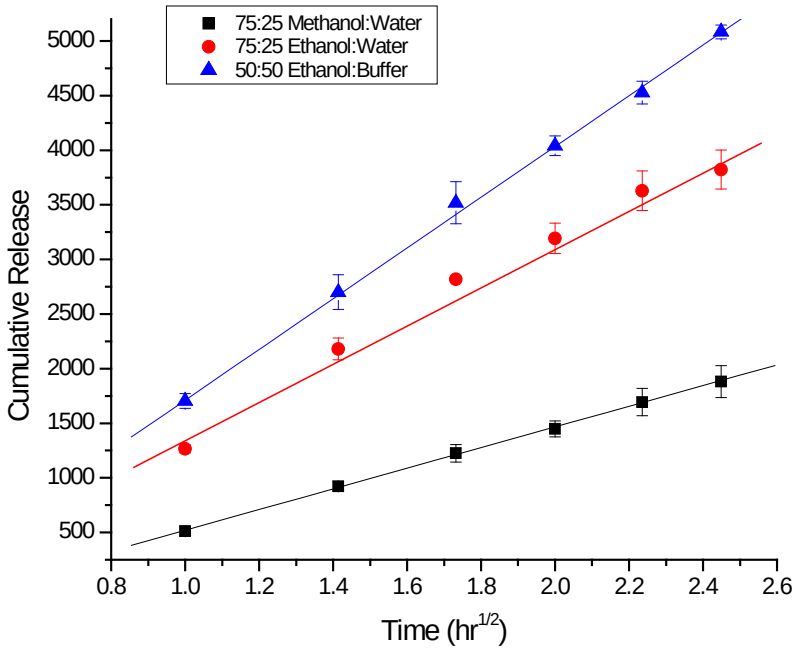


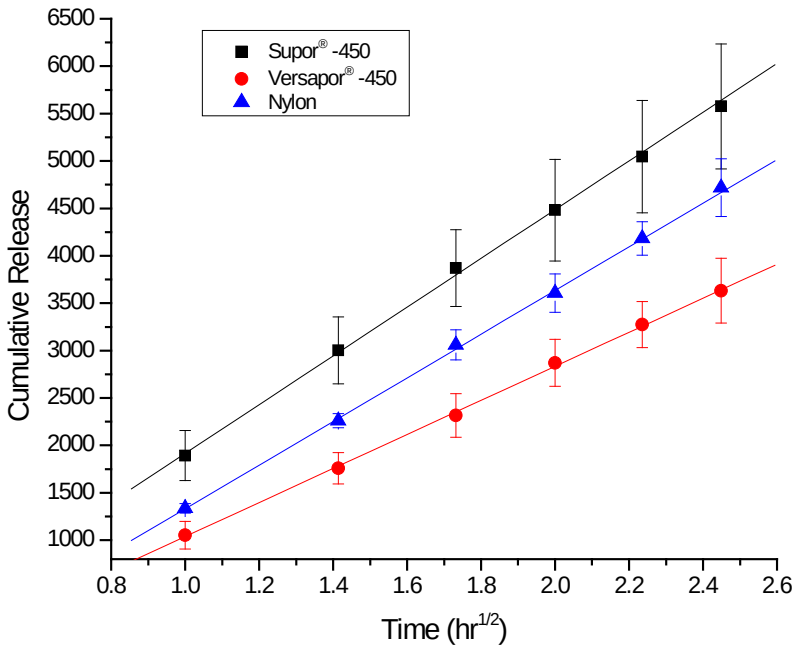
Fig 3. Polarized light microscopy images of various acyclovir cream formulations (200× magnification, the bar represents 50 μm). At least 10 images were taken for each sample with total of 200–500 particles in order to calculate the size distribution.

Figure Source: Krishnaiah, Y.S.R., et al., Development of performance matrix for generic product equivalence of acyclovir topical creams. Int J Pharmaceut 475 (2014):110-22

IVRT Release Rate is not Biorelevant

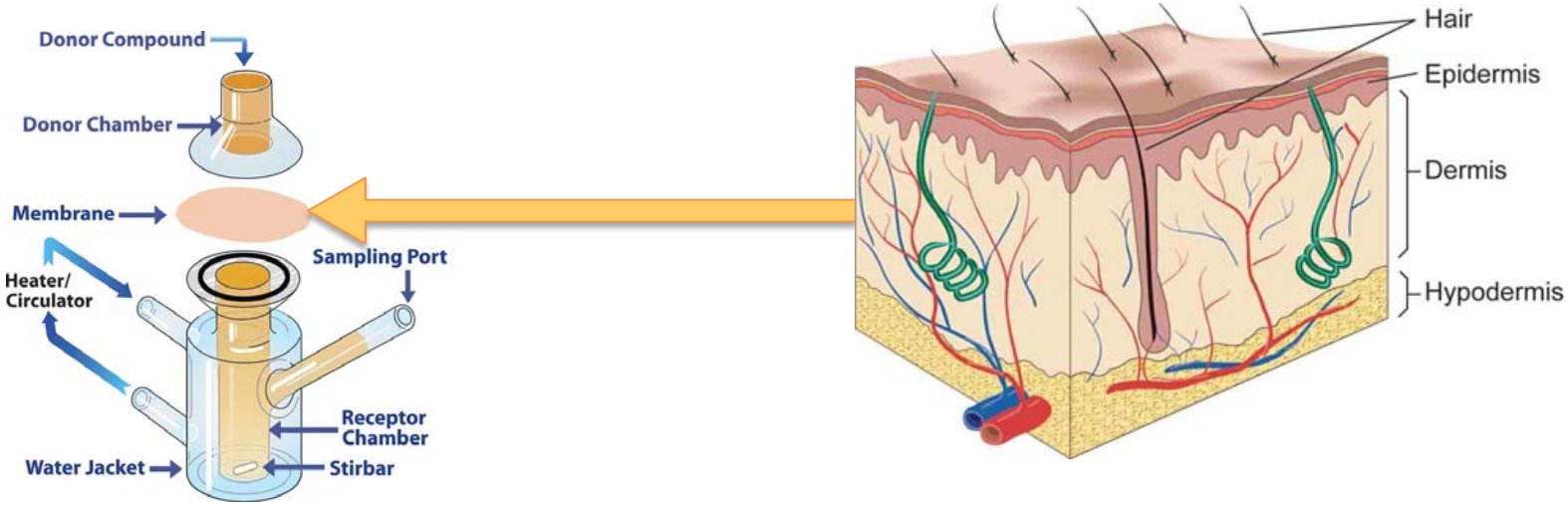
- The release rate measured by an IVRT is **arbitrary**
  - It can be modulated by IVRT method parameters like the choice of receptor solution or membrane





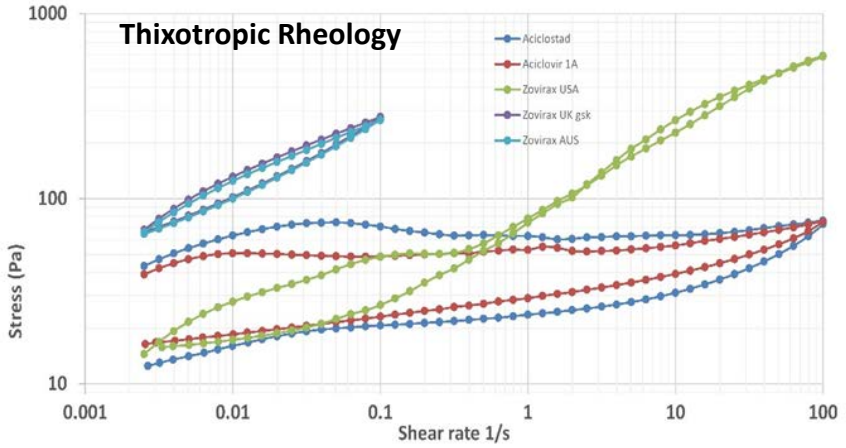
In Vitro Permeation Test (IVPT)

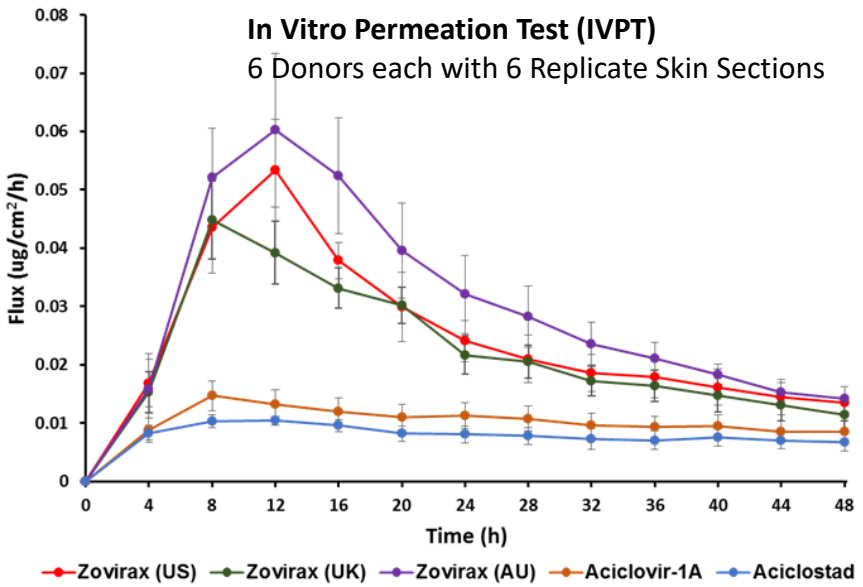
- IVPT can be a sensitive, discriminating indicator of relative bioavailability, and it can exhibit IVIVC

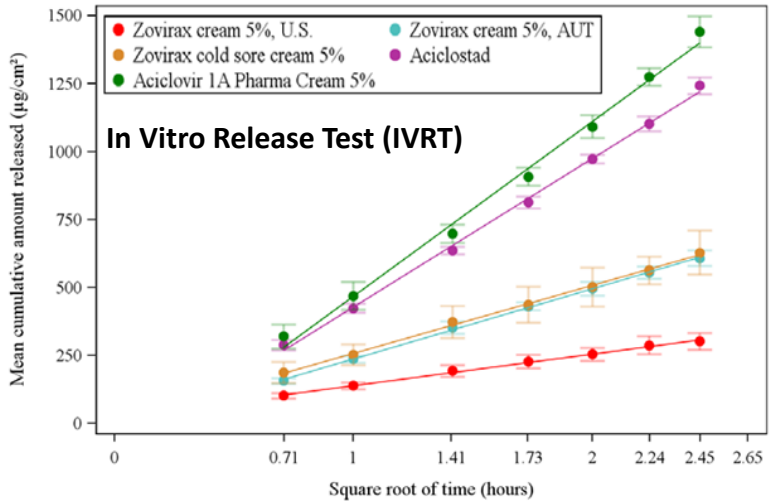


Correlation of Quality and Performance

	Zovirax (USA)	Zovirax (UK)	Zovirax (Austria)	Aciclostad (Austria)	Aciclovir-1A (Austria)
	Water	Water	Purified water	Water	Water
	Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol
	Mineral oil	Liquid Paraffin	Liquid Paraffin	Liquid Paraffin	Viscous Paraffin
	White petrolatum	White soft paraffin	White Vaseline	White Vaseline	White Vaseline
	Cetostearyl alcohol	Cetostearyl alcohol	Cetostearyl alcohol	Cetyl alcohol	Cetyl alcohol
	SLS	SLS	SLS	[redacted]	[redacted]
	Poloxamer 407	Poloxamer 407	Poloxamer 407		
	[redacted]	Dimethicone 20	Dimethicone 20	Dimethicone	Dimethicone
		Arlacel 165	Glyceryl Mono Stearate	Glyceryl Mono Stearate	Glyceryl Mono Stearate
		Arlacel 165	Polyoxyethylene stearate	Macrogol stearate	Polyoxyethylene stearate
Density (g/cc)	1.02	1.02	1.02	1.02	1.01
Content Uniformity (%)	97.9 ± 0.7	99.6 ± 1.4	100 ± 2.2	99.7 ± 1.7	98.3 ± 2.6
Polymorphic Form	2,3 hydrate	2,3 hydrate	2,3 hydrate	2,3 hydrate	2,3 hydrate
Crystilline Habit	Rectangular	Rectangular	Rectangular	Ovoid	Ovoid
Particle size (d50) (µm)	3.8	2.5	3.4	6.8	6
pH	7.74	7.96	7.54	4.58	6.05
Work of Adhesion	59	81	60	17	18
Drug in Aq (mg/g)	0.49	0.64	0.49	0.37	0.26
Drying Rate (T-30%)	>12h	~8h	~7h	<1h	<1h
Water Activity	0.75	0.73	0.74	0.95	0.95



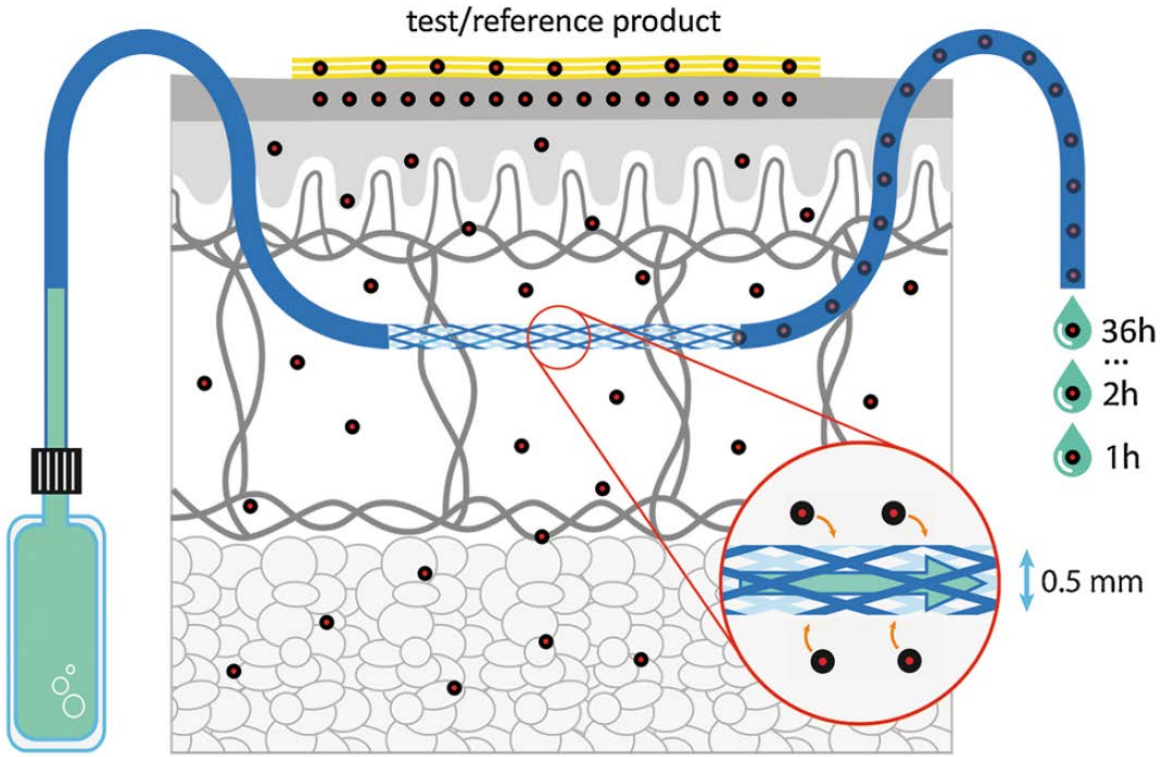


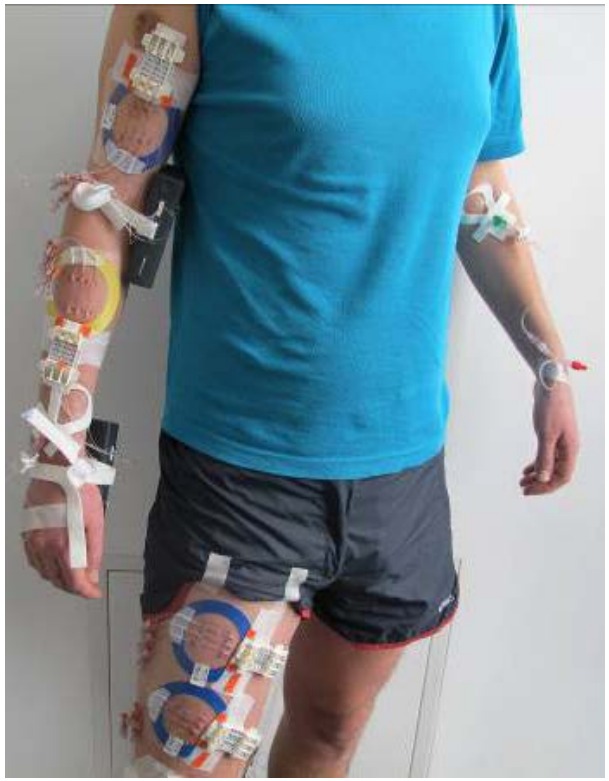


Data provided courtesy of Prof. Narasimha Murthy & Dr. Frank Sinner

In Vivo Cutaneous Pharmacokinetics

- Dermal Open Flow Microperfusion (dOFM)





Images courtesy of Joanneum Research

Patient Access to Topical Generics

- The vast majority (approximately 80%) of topical dermatological drug products have fewer than three generic competitors, and in many cases, have no approved generics at all.
- This may have been attributable to the historical barriers to the development of topical dermatological drug products
  - Comparative clinical endpoint bioequivalence (BE) studies
  - The complex nature of topical formulations
  - The relatively smaller market capitalization for some products

Developing Rational BE Standards

- **A <u>Modular</u> Framework for In Vitro BE Evaluation**
  - **Q1/Q2** sameness of inactive ingredient components and quantitative composition
  - **Q3 (Physical & Structural Characterization)** as relevant to the nature of the product
  - **IVRT** (In Vitro Release Test) for moderately complex products
  - **IVPT** (In Vitro Permeation Test) or another bio-relevant assay for more complex drug products
- **A <u>Scalable</u> Framework for BE Evaluation**
  - **In Vivo** systemic PK studies may be appropriate
  - **In Silico** computational modeling may be useful

Conclusions

- Topical dermatological semisolids are complex drug products
- As the complexity of a formulation, dosage form, drug product, site of action and/or the mechanism of action increases so do the potential failure modes for BA/BE
- With a sufficient product and process understanding, relevant complexities can be identified and addressed systematically for the drug product

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