IN VITRO CHARACTERIZATION OF TOPICAL SEMISOLID DOSAGE FORMS

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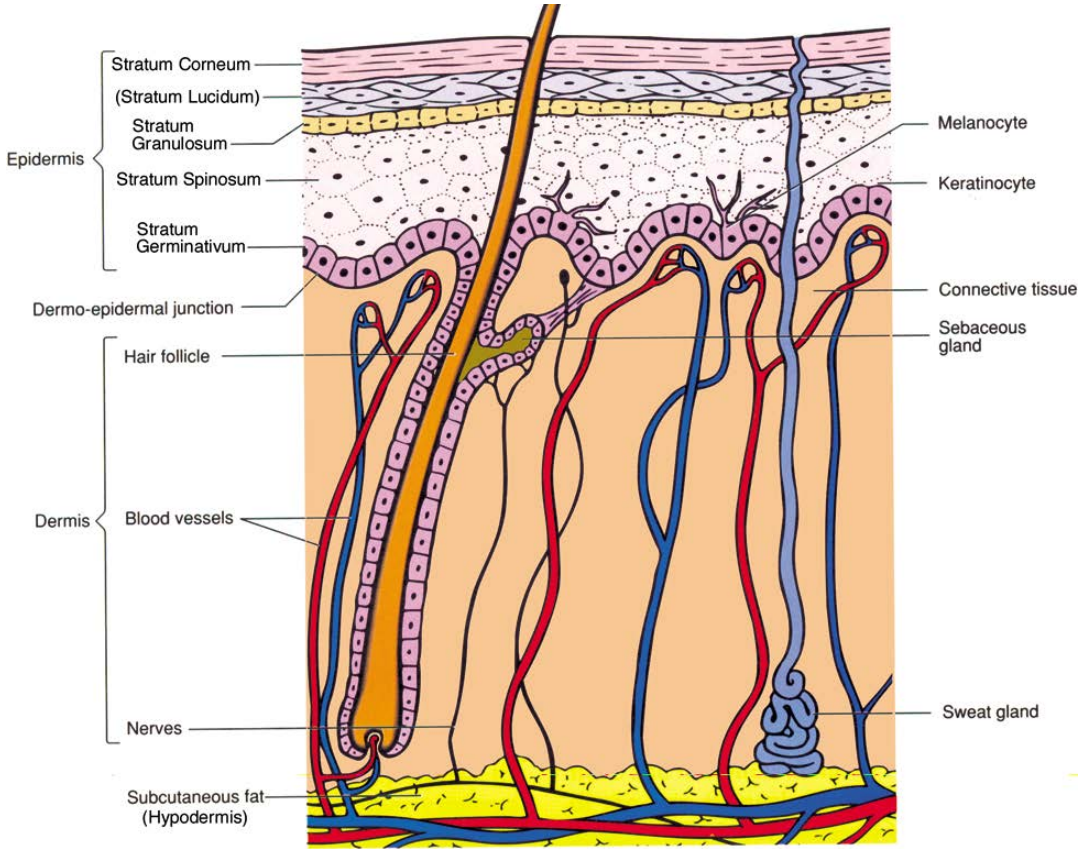
- I do not have any financial interest or conflict of interest with any pharmaceutical companies.

Impact of Product Quality Attributes

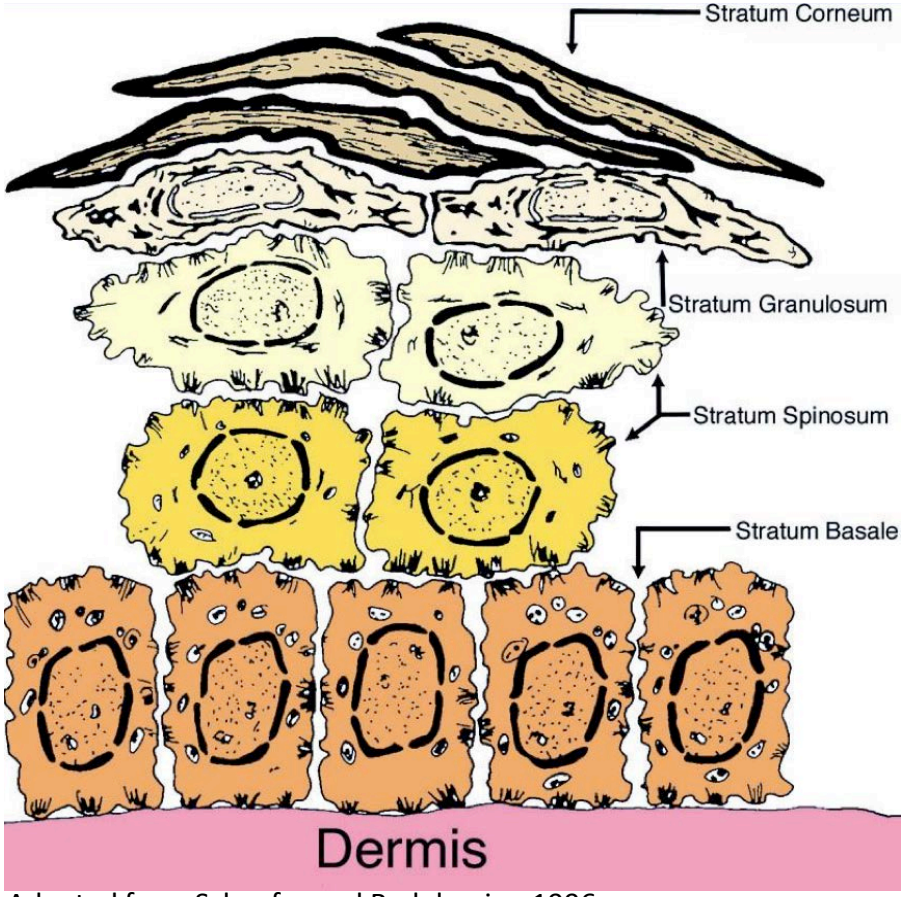
- It is widely understood that the formulation of a topical semisolid dosage form matters greatly
- It is now increasingly clear how excipients exert their influence, by modulating the physicochemical and microstructural arrangement of matter in the dosage form
- The resulting physical and structural characteristics of topical dosage forms, and their metamorphic properties on the skin, can directly influence topical bioavailability

Human Skin Structure



Adapted from Cerio and Archer, 1998

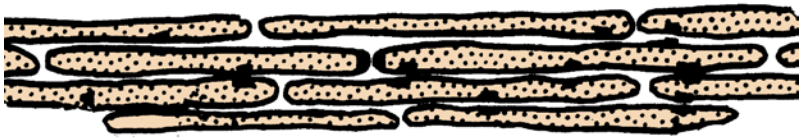
Human Skin Differentiation

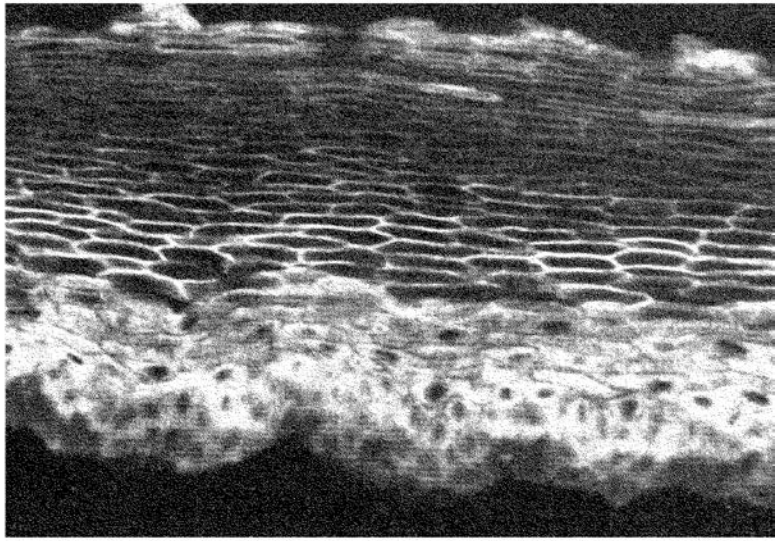


Adapted from Schaefer and Redelmeier, 1996

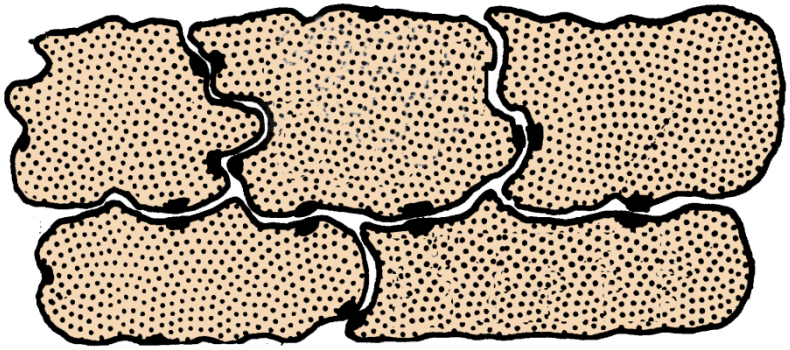
Skin Permeation Pathway

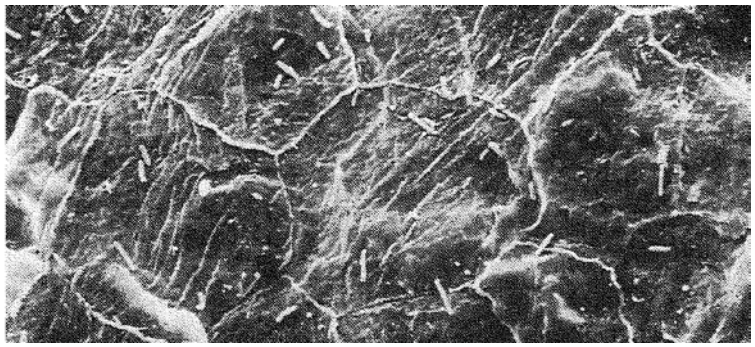
SIDE VIEW





TOP VIEW



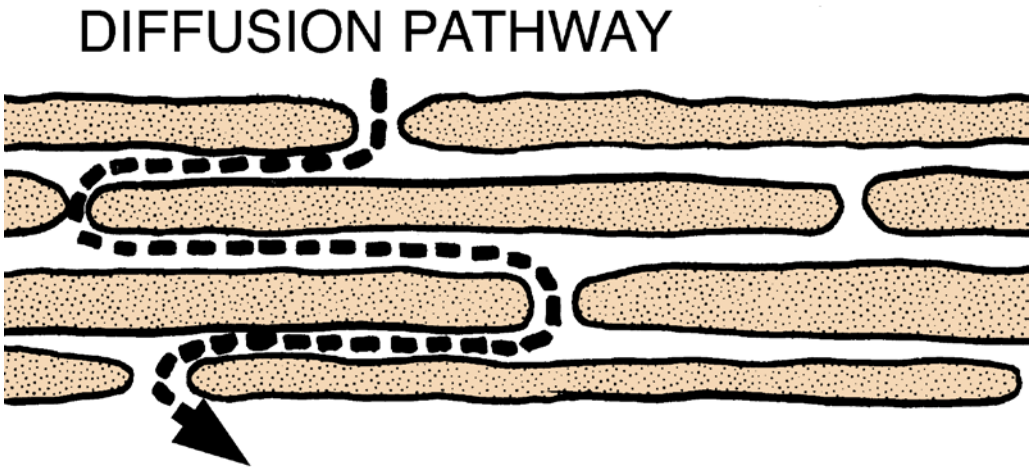


Drawings adapted from Odland, 1971.

Micrograph accompanying “side view” from Christophers and Laurence, 1976.

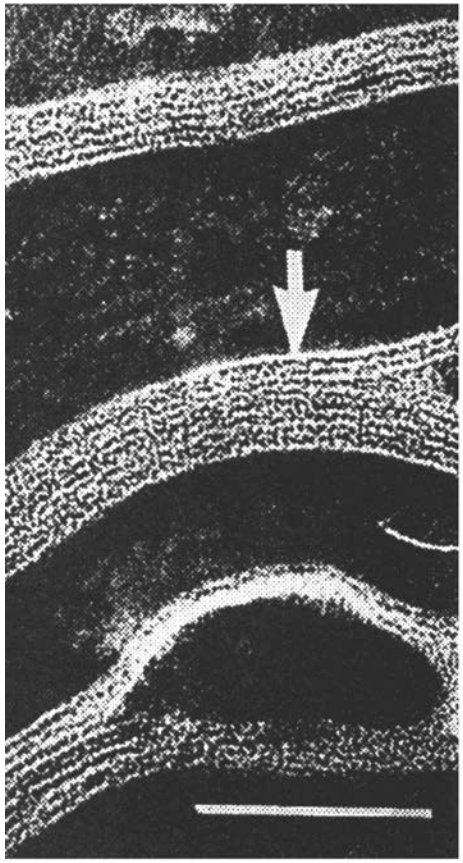
Micrograph accompanying “top view” from Singh and Singh, 1995.

Diffusion of Topical Compounds



Drawing adapted from Odland, 1971.

Micrograph Fartasch et al., 1998.



Diffusion of Topical Compounds

- Katz & Poulsen, 1971 (Fick's Law of Diffusion)

$$J = \frac{P \times D \times \Delta C}{l}$$

- J = Flux (e.g. µg/cm^2/hour)
- C = Concentration
- P = Partition Coefficient
- D = Diffusion Coefficient
- *l* = Length of Travel

Diffusion of Topical Compounds

- Franz & Lehman, 1995 (Finite Dose Equation)

$$J = 2hpDC_0 \sum_{n=1}^{\infty} \frac{\alpha_n e^{-D\alpha_n^2 t}}{\sin \alpha_n l \left[l\left(\alpha_n^2 + h^2\right) + h \right]}$$

- Relevant to clinically applied thin film doses
- Accounts for the thickness of the applied dose as well as dose depletion over time

Impact of Product Quality Attributes

- Product 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

Tests of Product Quality Attributes

- Potential CQAs and Tests:
  - Microscopic Analyses of Microstructure (e.g., Globules)
  - Rheological Analyses (incl. Texture, Tribology, etc.)
  - 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.)
  - Drug Crystalline Habit (Optical Microscopy)
  - Drying Rate (Solvent/Water Activity)
  - Density
  - pH
  - Etc.

IVPT: *In Vitro In Vivo* Correlation

- 92 IVIVC Data Sets (Different Drugs & Formulations)

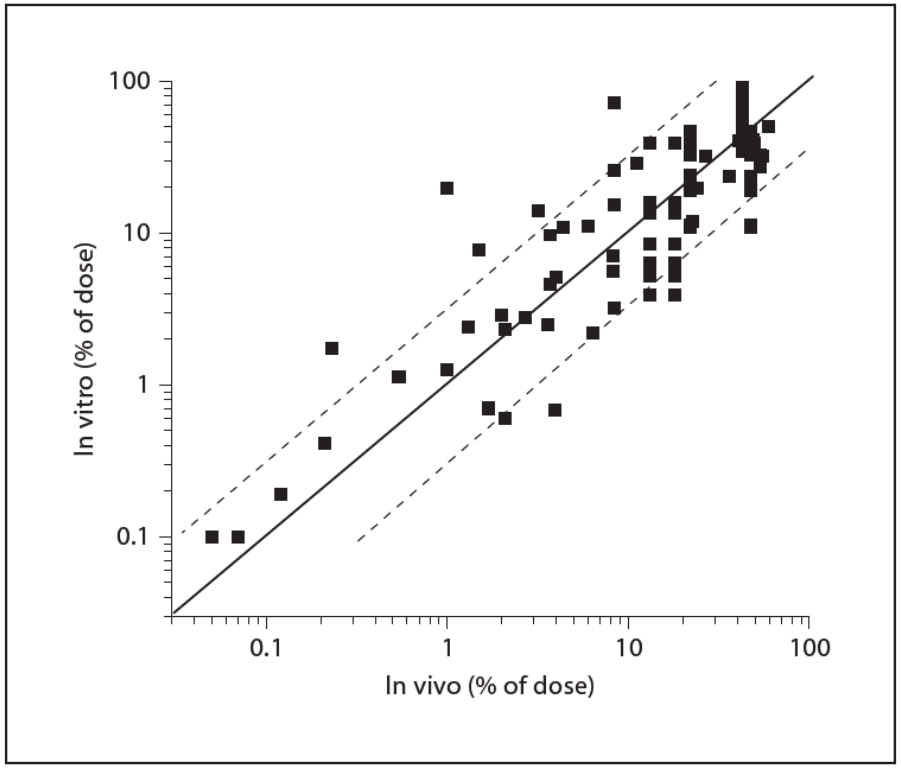


Fig. 1. IVIV ratios of total absorption for all 92 data sets plotted on log-log scale. The IVIV ratios ranged from 0.18 to 19.7, with an overall mean of 1.6. Solid line: ideal 1:1 correlation. Dashed lines: ±3-fold difference from ideal.

Lehman et al. (2011) Percutaneous Absorption in Man: In vitro-in vivo Correlation. Skin Pharmacol Physiol; 24:224–230

IVPT: *In Vitro In Vivo* Correlation

- Subset of 11 **Harmonized** IVIVC Data Sets

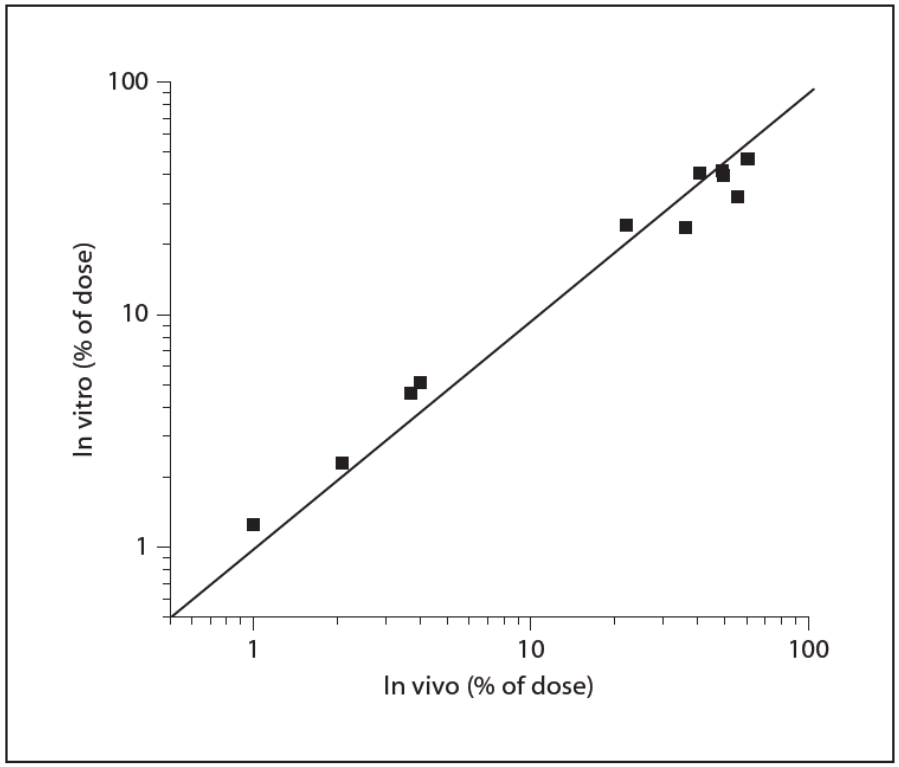


Fig. 2. IVIV ratios of total absorption for 11 fully harmonized data sets plotted on log-log scale. The IVIV ratios ranged from 0.58 to 1.28, with an overall mean of 0.96. Line: ideal 1:1 correlation.

Lehman et al. (2011) Percutaneous Absorption in Man: In vitro-in vivo Correlation. Skin Pharmacol Physiol; 24:224–230

In Vitro Release Test (IVRT)

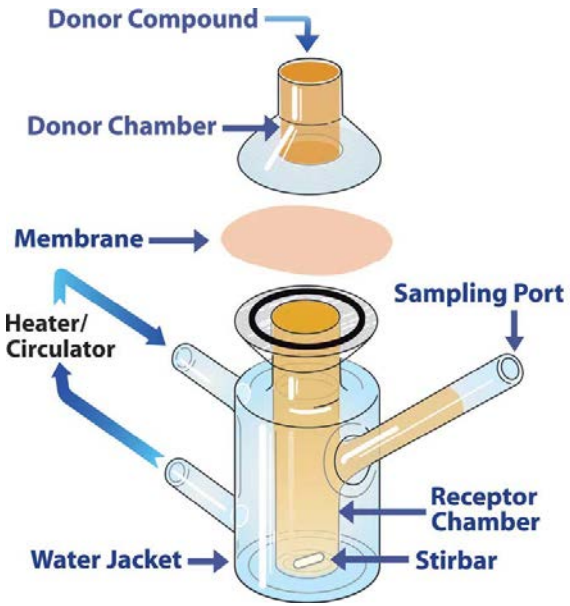
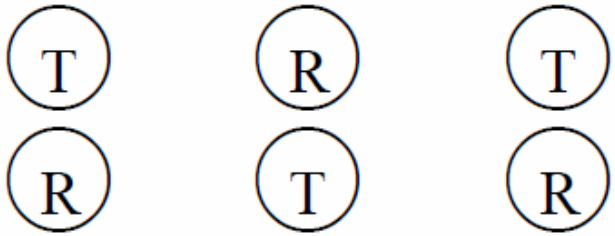
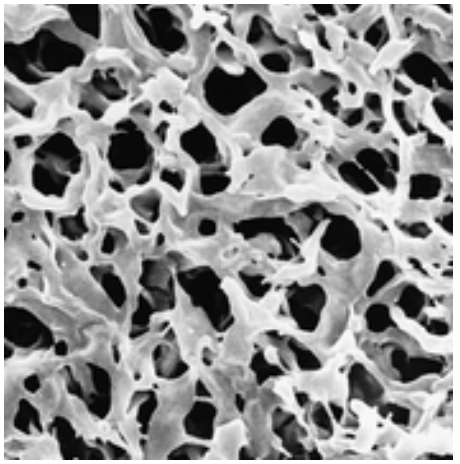
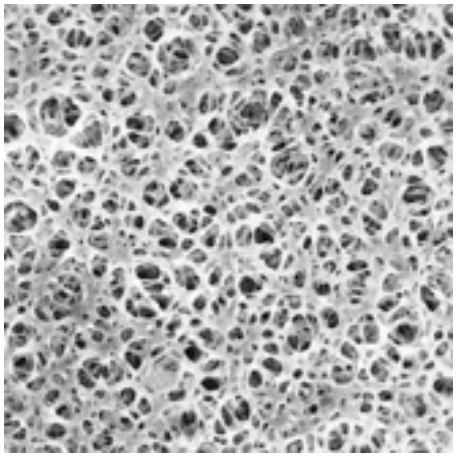


Image courtesy of PermeGear







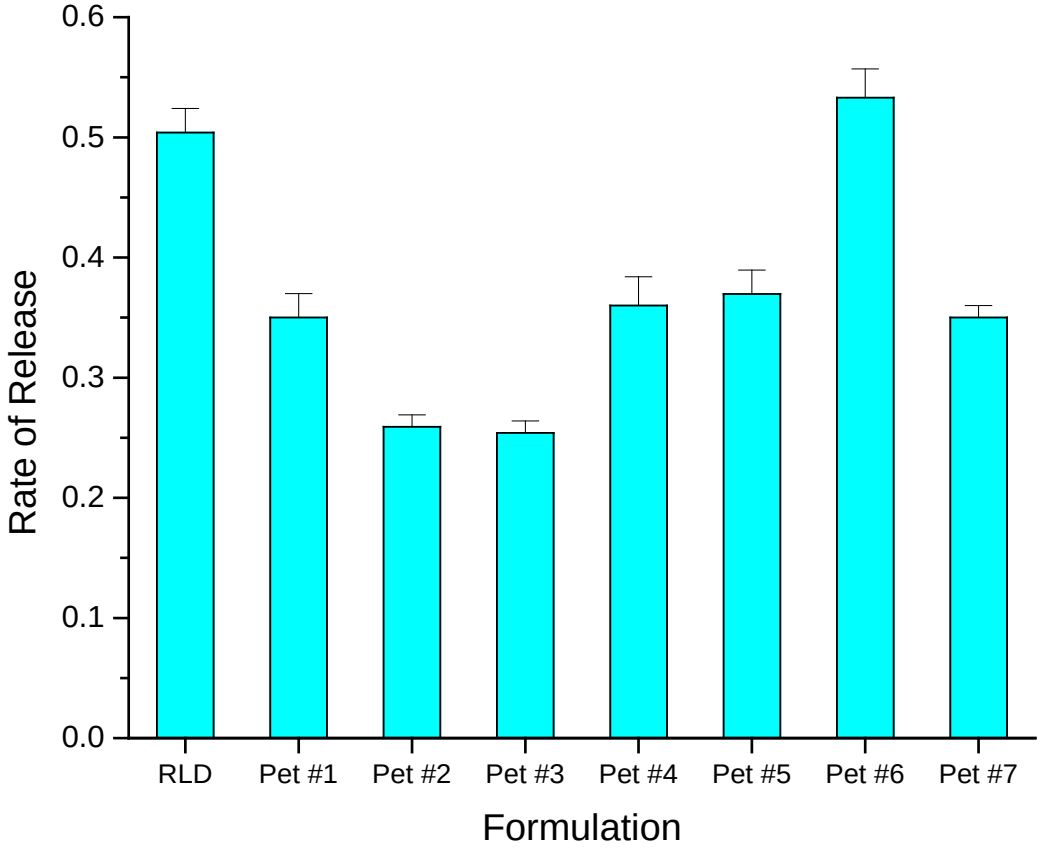
IVPT vs. IVRT

- IVPT (Permeation)
  - **Human Skin**
  - Unoccluded Dose
  - Finite Dose
  - Flux Profile (J_{max}, etc.)
  - Physiological Media
  - pg to ng Range
  - Product stays ‘dry’
  - *IVIV* Correlation
  - Donor Variability

- IVRT (Release)
  - **Synthetic Membrane**
  - Occluded Dose
  - Infinite Dose
  - Release Rate (slope)
  - Alcoholic Media
  - µg to mg Range
  - Product-Media Interface
  - Specific to the Formulation
  - Relative Consistency

Can IVRT Discriminate Microstructure?

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



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

Can IVRT Discriminate Microstructure?

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

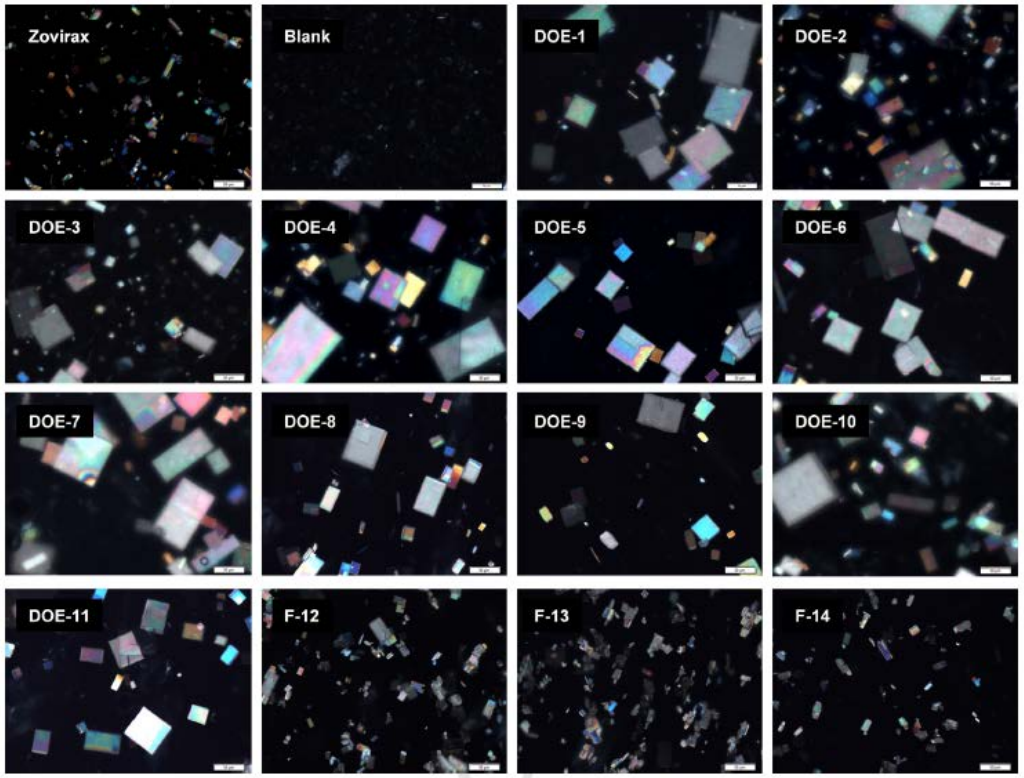


Fig. 3. Polarized light microscopy images of various acyclovir cream formulations (200× magnification, the bar represents 50 μm). At least 10 images were taken for each sample with total of 200–500 particles in order to calculate the size distribution.

Krishnaiah, Y.S.R., et al., Development of performance matrix for generic product equivalence of acyclovir topical creams. Int J Pharmaceut (2014), http://dx.doi.org/10.1016/j.ijpharm.2014.07.034

Q3: Dosage Form Metamorphosis

- Solvent Activity of Q1/Q2 Identical Creams

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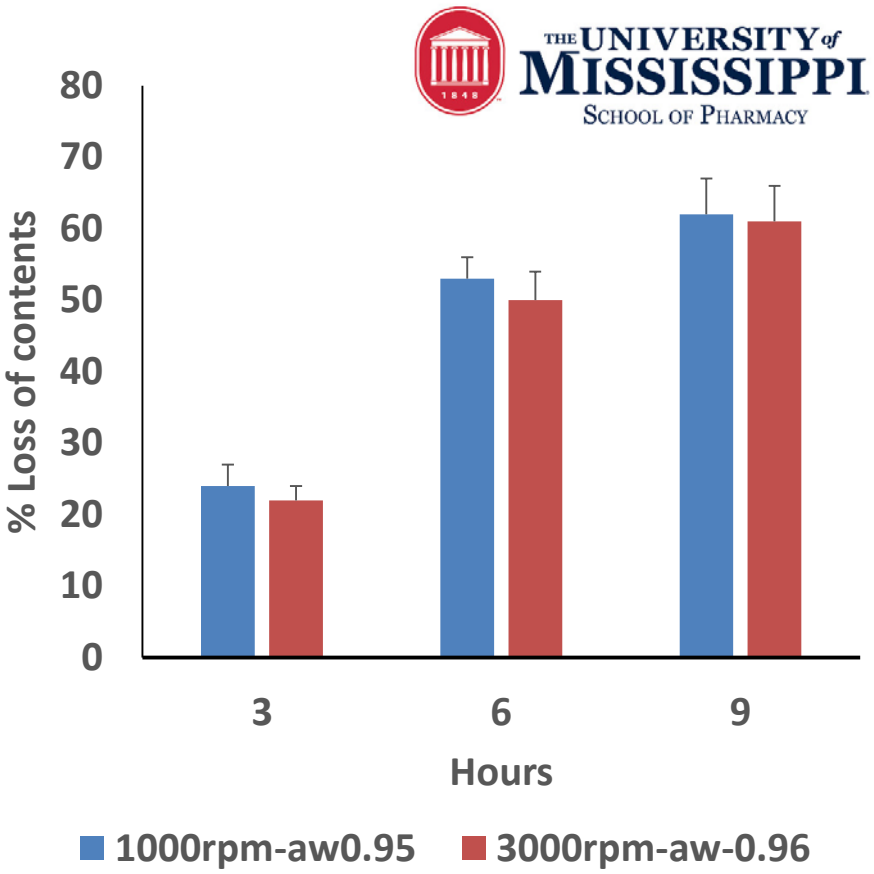
Ingredients	Quantity (%w/w)
Drug	1
Cetostearyl alcohol	7
Cremophor A6	1.5
Cremophor A25	1.5
Mineral Oil	12
Propylene Glycol	8
Water	69
Total	100
Manufacturing Conditions	**Solvent Activity (a_w)**
1000 RPM (20 min)	0.950± 0.004
3000 RPM (20 min)	0.961 ± 0.006



Data provided courtesy of Prof. Narasimha Murthy

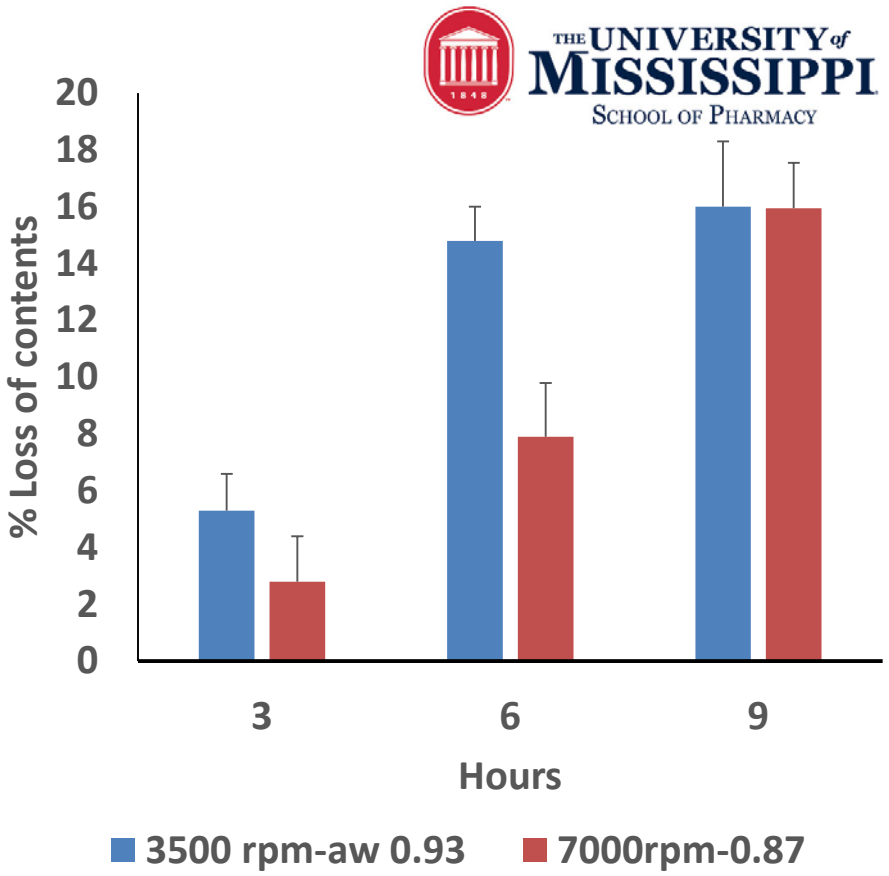
Q3: Dosage Form Metamorphosis

- 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

Q3: Dosage Form Metamorphosis

- Solvent Activity (a_s) = ρ/ρ_0

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- ρ = partial vapor pressure of Solvents in the product
- ρ_0 = vapor pressure of pure Solvent system

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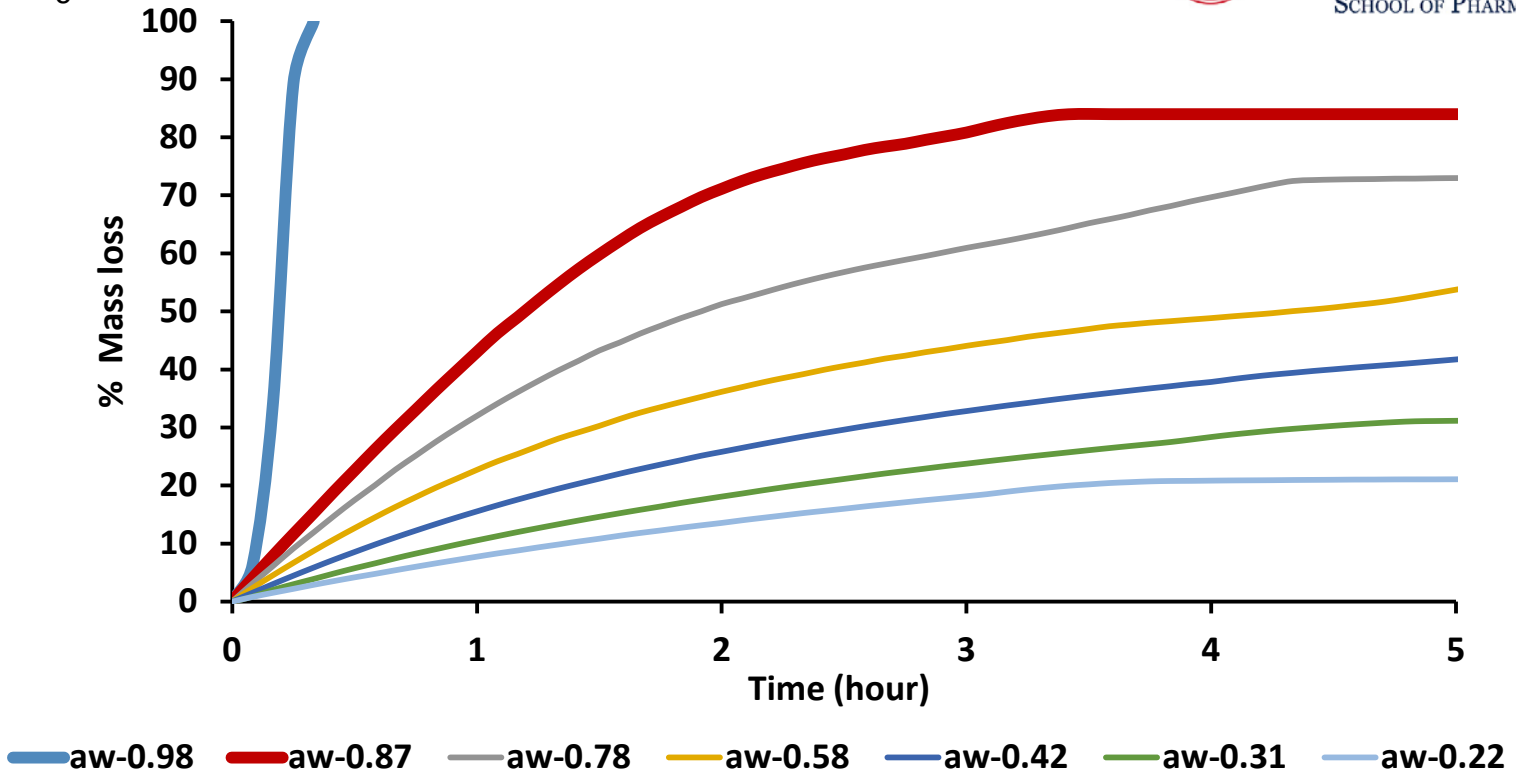

Data provided courtesy of Prof. Narasimha Murthy

Q3: Dosage Form Metamorphosis

- Solvent Activity and Drying Rate

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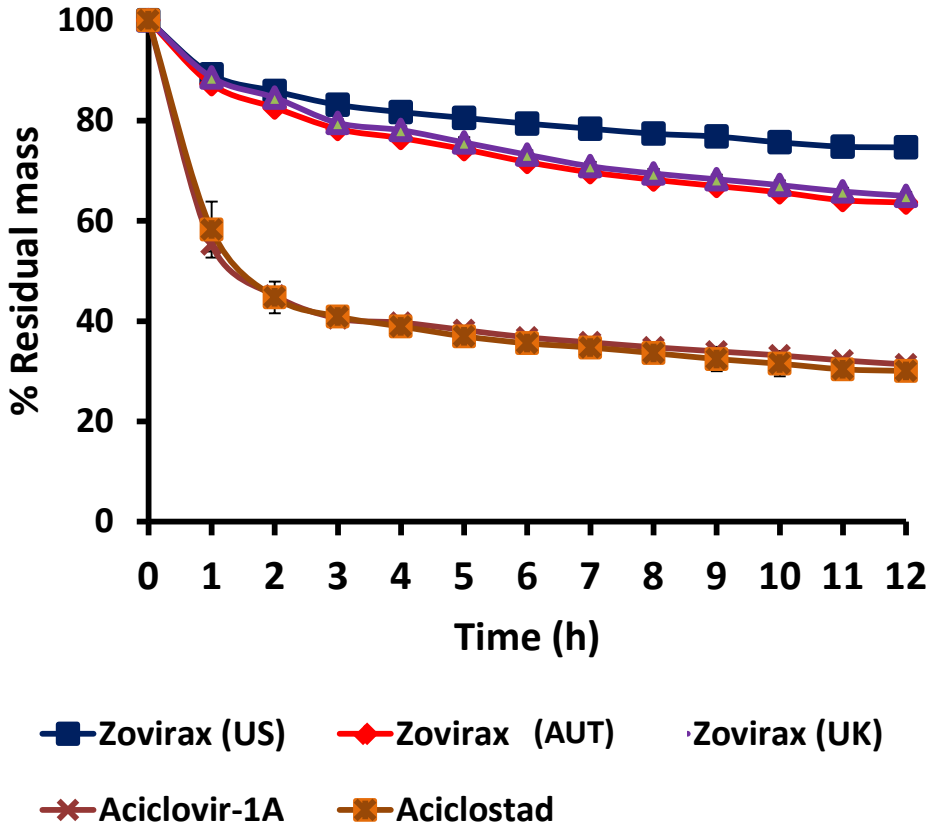

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Product	Solvent Activity (a_w)
Zovirax (US)	0.753 ± 0.002
Zovirax (AUT)	0.735 ± 0.000
Zovirax (UK)	0.732± 0.002
Aciclovir 1A	0.948 ± 0.001
Aciclostad	0.948 ± 0.003

Data provided courtesy of Prof. Narasimha Murthy

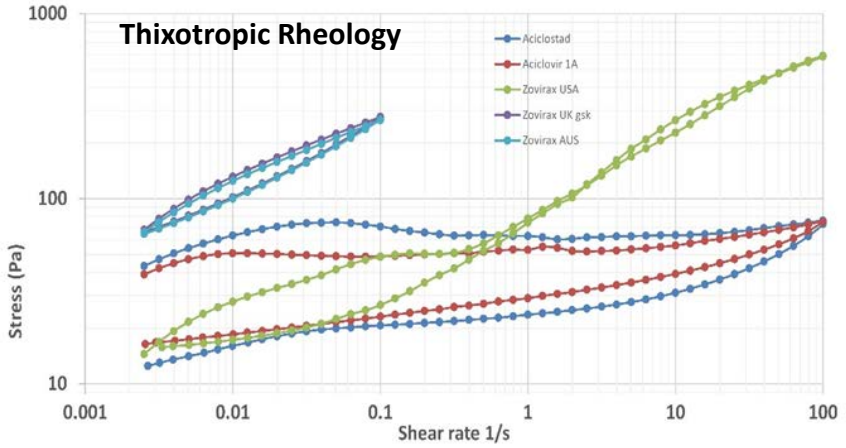
Orthogonal In Vitro Testing Approach

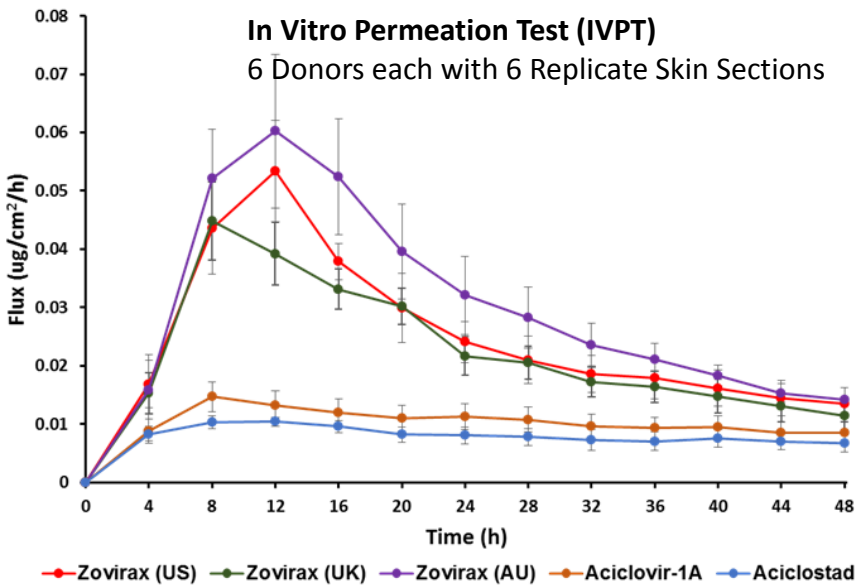
- 5 Pharmaceutically Equivalent Acyclovir Creams

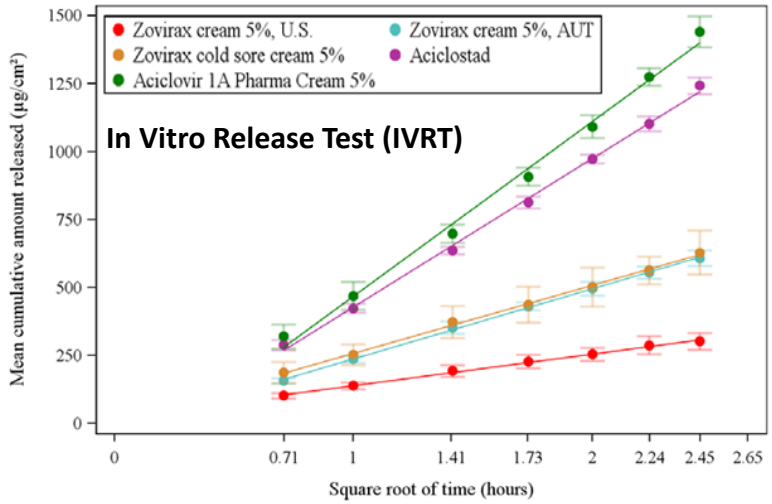
Zovirax (USA)	Zovirax (UK)	Zovirax (Austria)	Aciclostad (Austria)	Aciclovir-1A (Austria)
Water	Water	Purified water	Water	Water
Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol
Mineral oil	Liquid Paraffin	Liquid Paraffin	Liquid Paraffin	Viscous Paraffin
White petrolatum	White soft paraffin	White Vaseline	White Vaseline	White Vaseline
Cetostearyl alcohol	Cetostearyl alcohol	Cetostearyl alcohol	Cetyl alcohol	Cetyl alcohol
SLS	SLS	SLS		
Poloxamer 407	Poloxamer 407	Poloxamer 407		
	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

Orthogonal In Vitro Testing Approach

	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



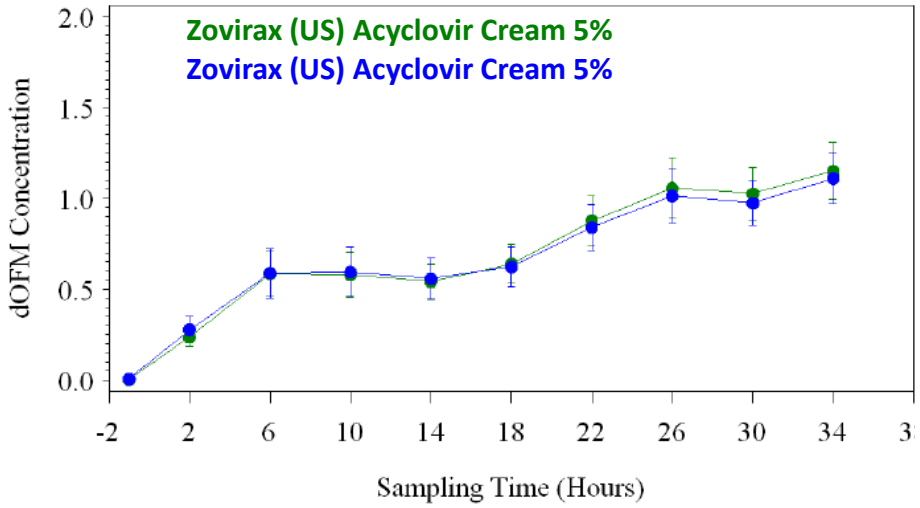


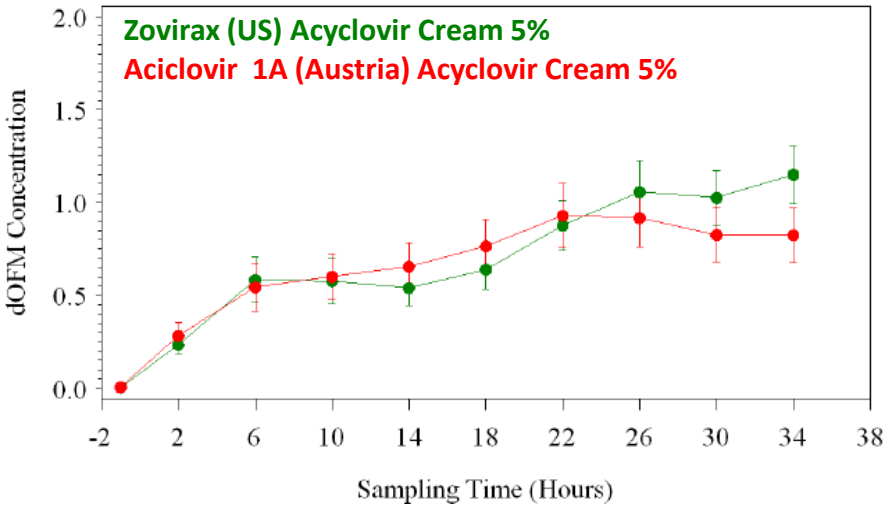


Data provided courtesy of Prof. Narasimha Murthy & Dr. Frank Sinner

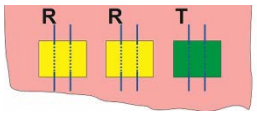
In Vivo Bioavailability/Bioequivalence

- Dermal Pharmacokinetics by dOFM (20 subjects)





Outcome variable	$CI_{90\%}$
log(AUC0-36h)	[-0.148 ; 0.162] or [86.2 % ; 117.5 %]
log(C_{max})	[-0.155 ; 0.190] or [85.7 % ; 120.9%]



Outcome variable	$CI_{90\%}$
log(AUC0-36h)	[-0.369 ; 0.050] or [69.1 % ; 105.2 %]
log(C_{max})	[-0.498 ; 0.022] or [60.8 % ; 102.2%]

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Data provided courtesy of Dr. Frank Sinner

Bodenlenz et al. (2017) Open Flow Microperfusion as a Dermal Pharmacokinetic Approach to Evaluate Topical Bioequivalence. Clin Pharmacokinet. 2017 Jan;56(1):91-98. doi: 10.1007/s40262-016-0442-z (FREE Full Text Article)

Influence of Dispensing Stress on Q3

- Influence of Dose Dispensing on Product Quality

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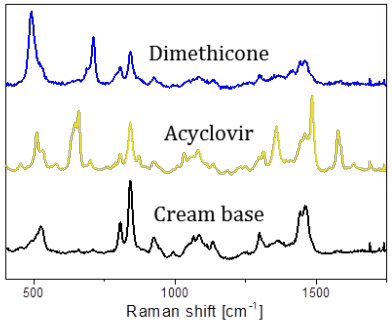

Zovirax® UK
Tube

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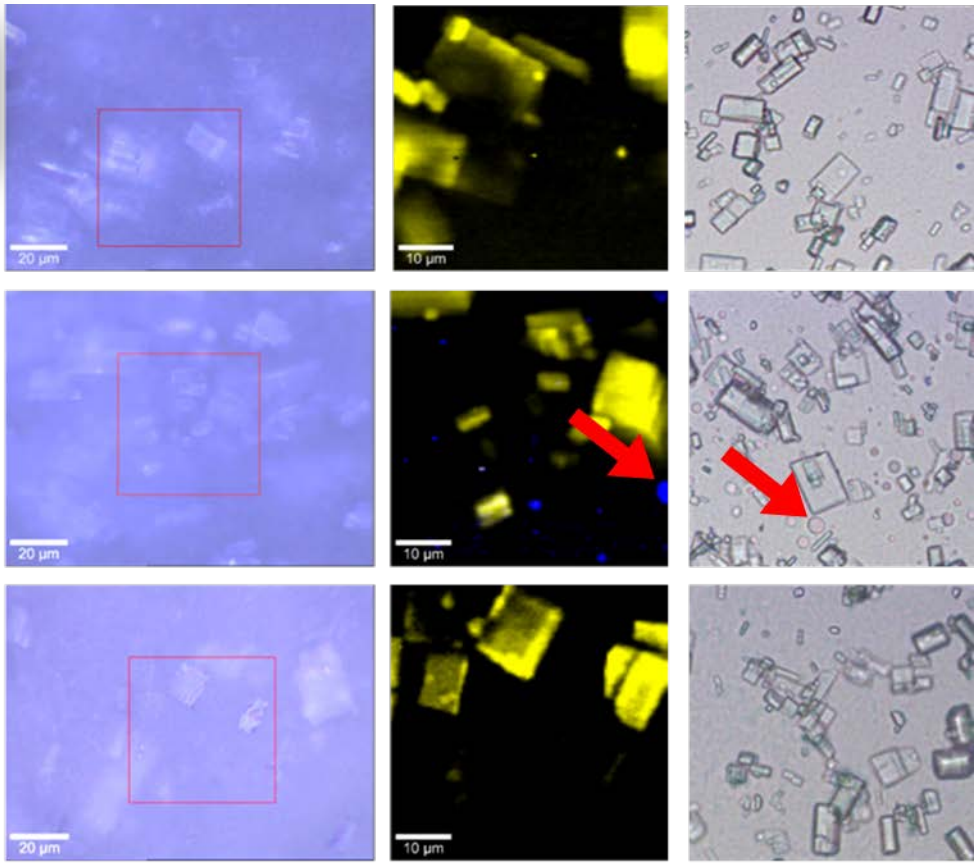
Zovirax® UK
Pump

Zovirax® UK
Pump
(from inside container)



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

Influence of Dispensing Stress on Q3

- Influence of Dose Dispensing on Product Quality

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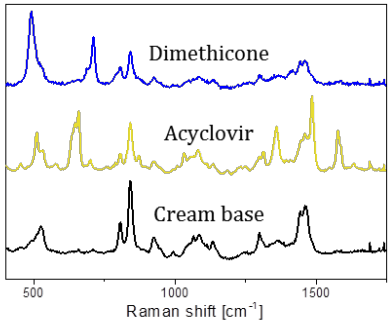

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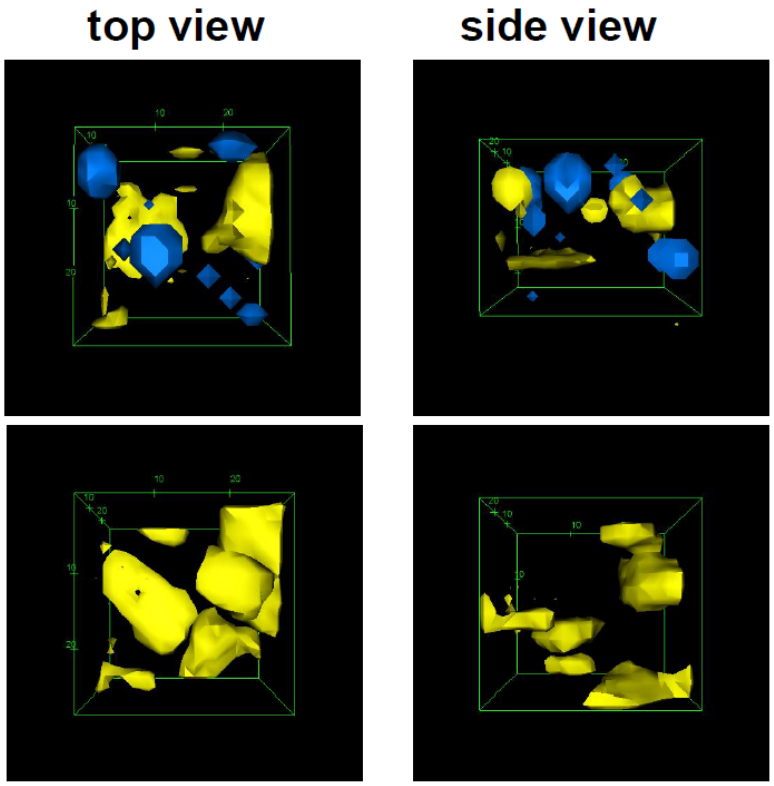
Comparison Zovirax UK pump and tube



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

Influence of Dispensing Stress on Q3

- Influence of Dose Dispensing on Product Quality

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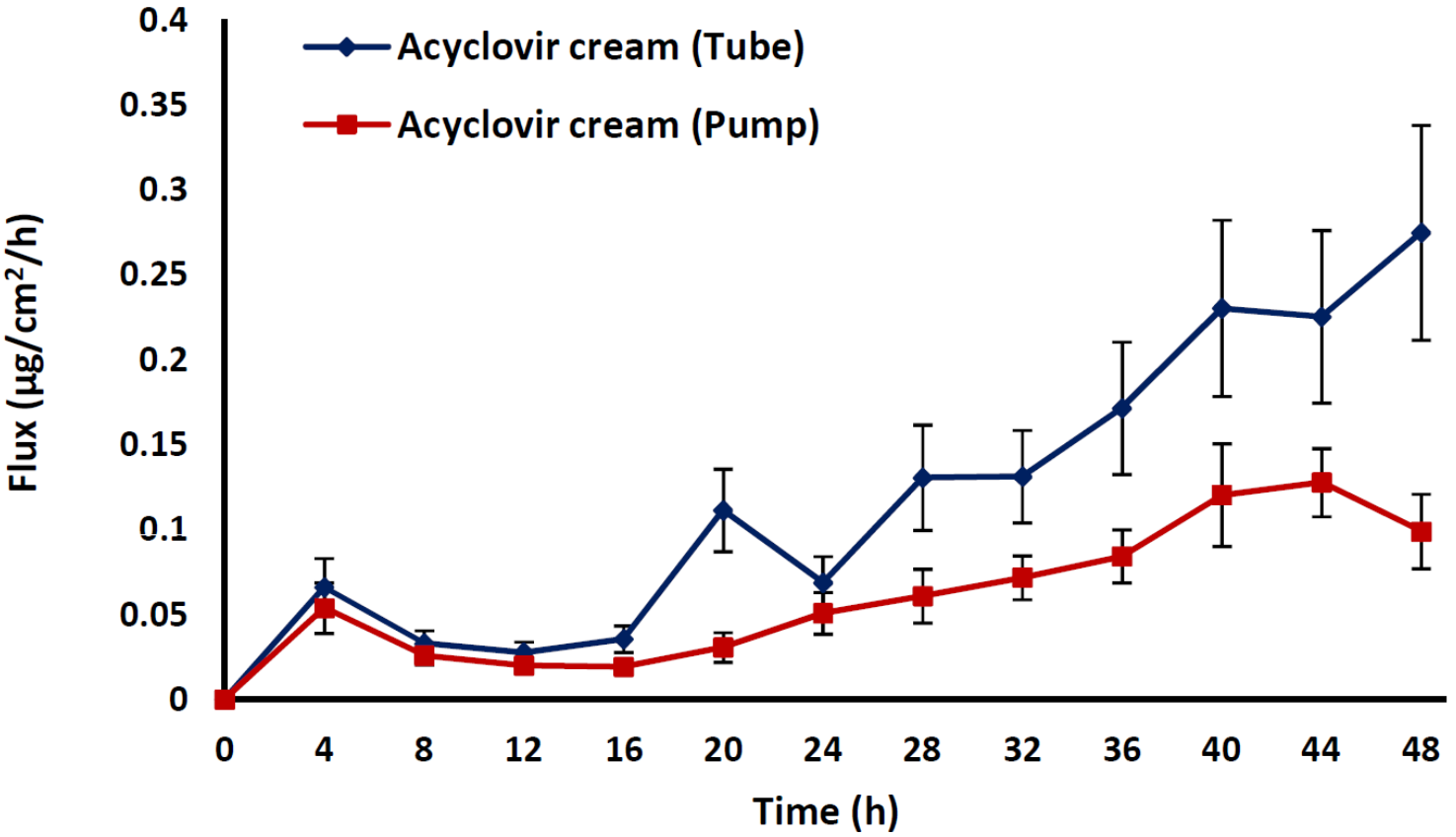

Data provided courtesy of Prof. Michael Roberts

Summary

- All product characterization test methods, both in vitro and in vivo, have limitations
  …but they don't all have the same limitations!
- The collective weight of evidence from orthogonal assessments comparing product quality and performance is more powerful than any single test method.
- The key is to utilize tests that systematically and collectively mitigate the risk of failure modes relevant to the therapeutic performance of the drug product.

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GDUFA Award U01FD00**5226**

- Michael Roberts, PhD

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- Frank Sinner, PhD


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