

TOPICAL SEMISOLID DRUG PRODUCT CRITICAL QUALITY ATTRIBUTES: RELEVANCE OF Q3 ATTRIBUTES TO TOPICAL BIOEQUIVALENCE

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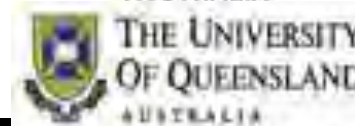
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Goethe University, Frankfurt, Germany

Curtin University, Perth, Australia



TRANSLATIONAL RESEARCH INSTITUTE AUSTRALIA



DIAMANTINA INSTITUTE



Curtin University

Overview of where we started this study

How can we characterise semisolid products?

- Q1, Same components as the reference-listed drug;
- Q2, Same components in same concentration as the reference listed drug;
- Q3, Same arrangement of matter (microstructure) (*often assumed, but not always, with same components in same concentration*)



How do we define their quality?

- Quality should be by design & testing
- However, semisolid dosage forms are complex systems that change in use
- A pharmacokinetic approach for topical products should relate to drug concentrations at the site of action (layers within the epidermis/dermis)
- Measuring epidermal and superficial dermal drug concentrations is presently a challenge
- We therefore use surrogate measures of product performance:
 - *In vivo* methods = microdialysis, dermal perfusion, tape stripping and imaging
 - *In vitro* permeation test (IVPT)
 - *In vitro* testing for product quality attributes by a comprehensive characterisation of Q3

Let us look at testing in terms of the skin morphology & sites of action

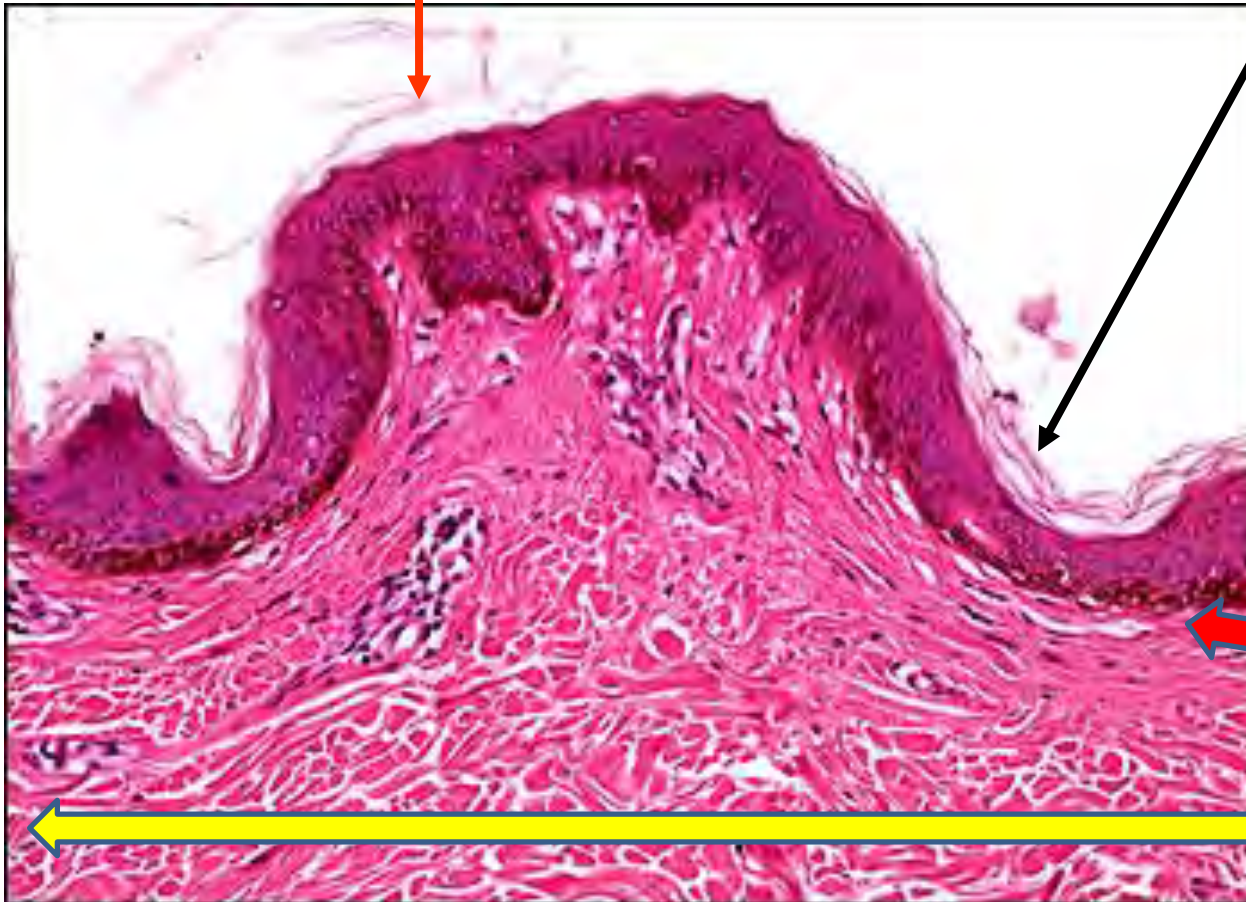
Sampling - stratum corneum stripping is potential method to assess skin permeation

Stratum corneum – main barrier – also potential target site

Various regions in viable epidermis & upper dermis = key target site

Epidermal membrane sampling site

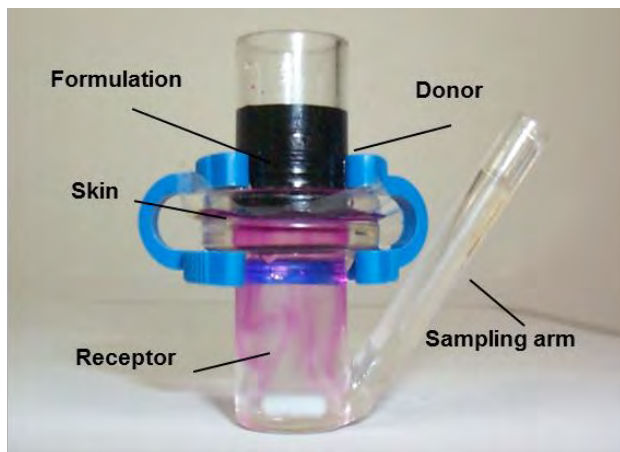
Dermal sampling site for microdialysis and dermal microperfusion (*in vivo*) & *in vitro* dermatomed skin



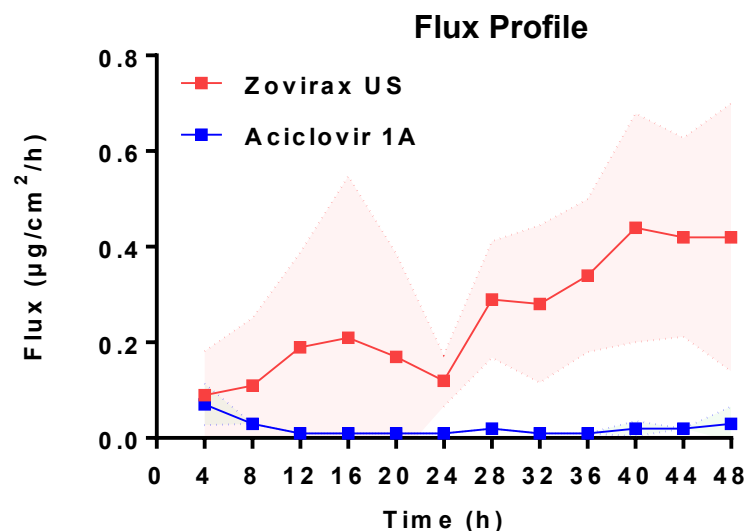
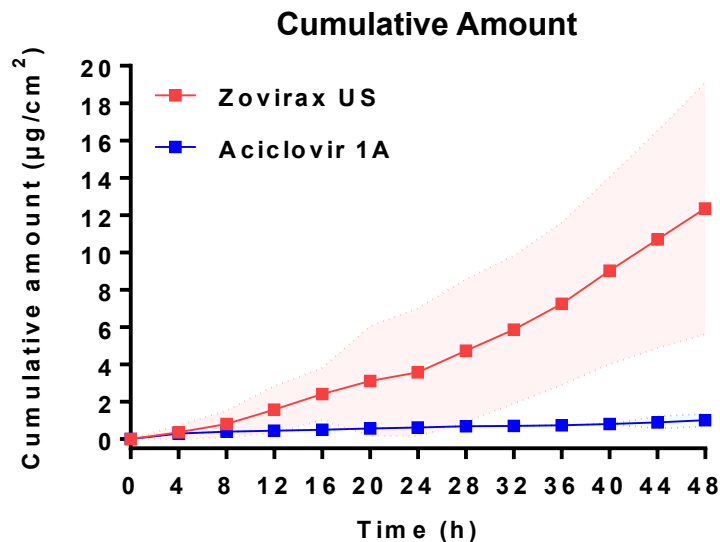
One focus is *In Vitro* Permeation Test (IVPT)

Sandwich stratum corneum, epidermis, dermatomed skin & full thickness skin in a static or flow through Franz diffusion cell

- Long history
- Robust
- Simple
- Precise
- Reproducible



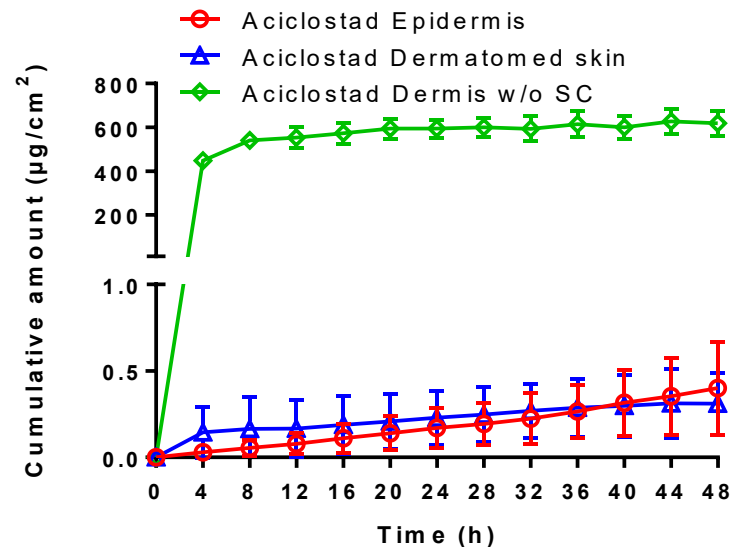
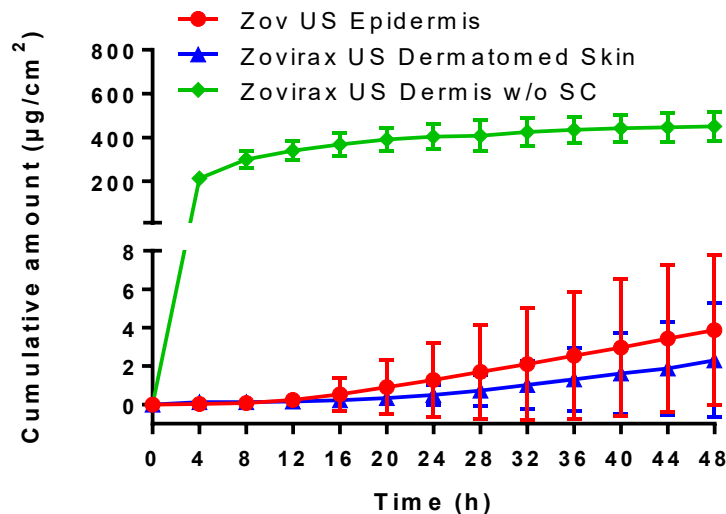
Here, epidermal membranes used for 2 acyclovir products



Data shown as mean \pm 95% Confidence Interval (CI)
Each point is the mean of 9* (3 donors & 3 replicates per skin)

In Vitro Permeation Test (IVPT) Studies

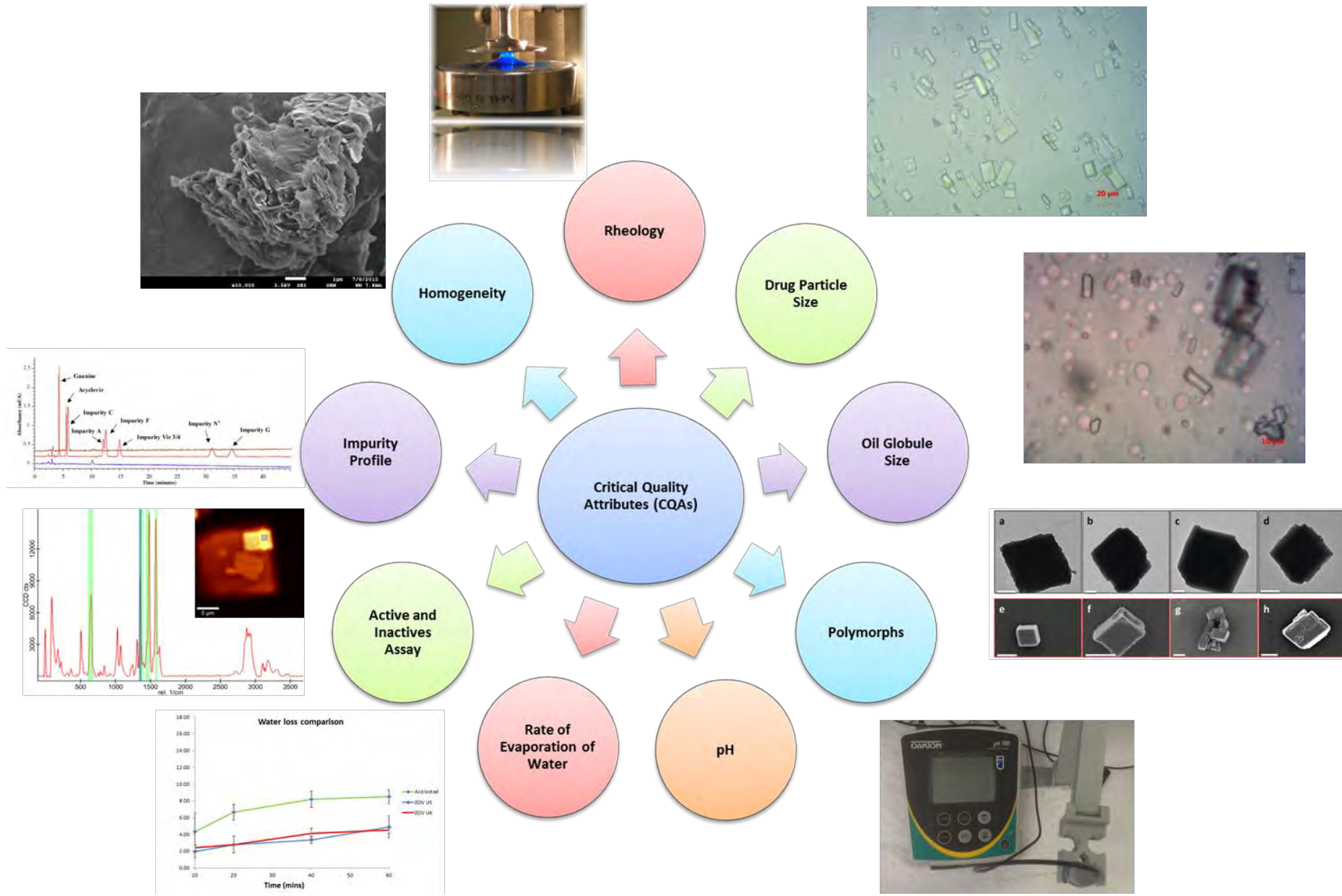
We found similar permeation profiles for 2 acyclovir products using human epidermal membranes & dermatomed skin; dermal membranes are very permeable!



Data shown as mean \pm 95% Confidence Interval (CI)
Each point is the mean of 9* (3 donors & 3 replicates per skin)

- Supports SC being main underlying barrier
- Suggests that either epidermal membranes or dermatomed skin could be used in acyclovir IVPT studies
- Skin barrier integrity is an important control component to get right.

In vitro testing for product quality by an articulated battery of physicochemical tests - potential critical quality attributes, i.e. Q3



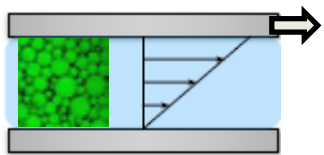
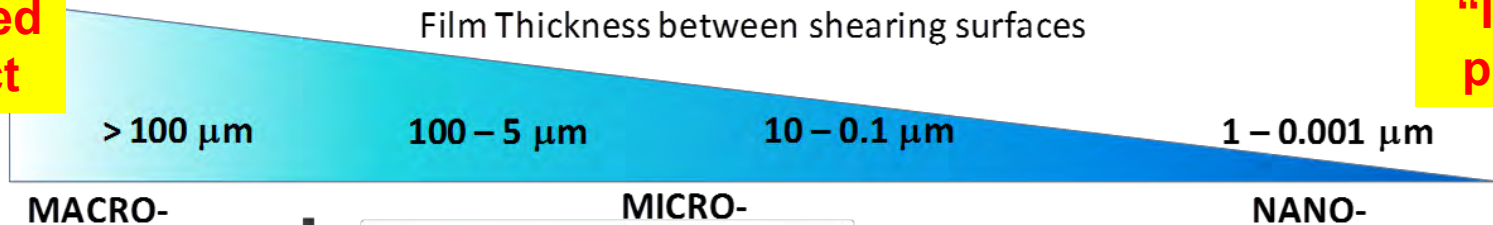
Rheology and tribology as particular critical quality attributes

In-use physics: Multiple scales of deformation

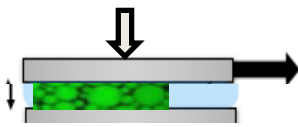
From rheology to tribology – applied to personal care & foods (micro-structured fluids)

Packaged product

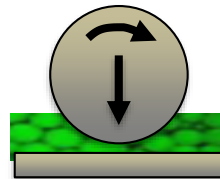
“In-use” product



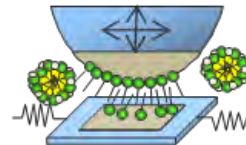
Rheology¹
(fixed gap)



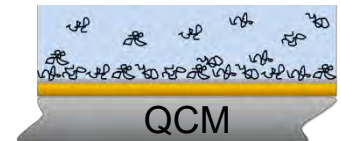
Narrow gap /
GDR² (thin film)



Tribology³
(fixed load)

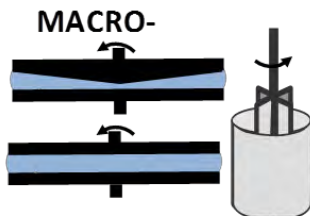


Micro & Nano
Mechanics⁴

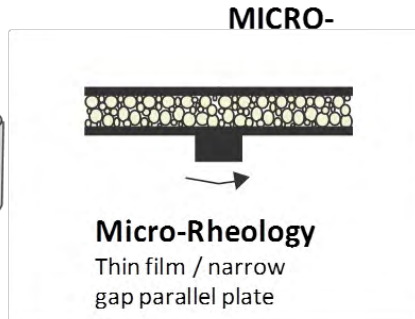


Adsorbed
polymer films⁵

Apparatus



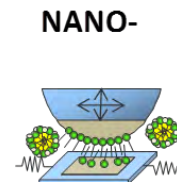
Rheology:
Cone-plate, large gap
parallel plate, Vane-cup,
etc.



Micro-Rheology
Thin film / narrow
gap parallel plate



Soft-Tribology:
Sliding/rolling Ball-Disk
on PDMS substrate



**Nano-rheology,
nano-tribology**
AFM tip/colloid probe

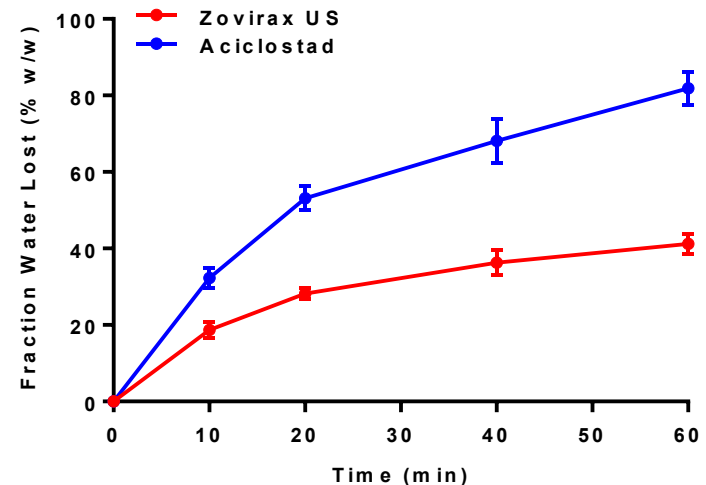
Adaptation of
slide courtesy of
**Prof. Jason
Stokes, UQ**

Let us now return to the Zovirax (US) and Aciclovir 1A products

What are the product differences that cause non-bioequivalence?

- Firstly, they differ in
 - ❖ Q1 (Qualitative – nature of ingredient) and
 - ❖ Q2 (Quantitative - amounts)
- Specific content differences
 - ❖ PG estimated by DSC-TGA data
 - ❖ Water content by Karl Fischer
- Product changes when applied to skin, described as product metamorphosis, may affect acyclovir bioavailability – especially as a result of evaporation
 - Slower evaporation for Zovirax due to presence of PG

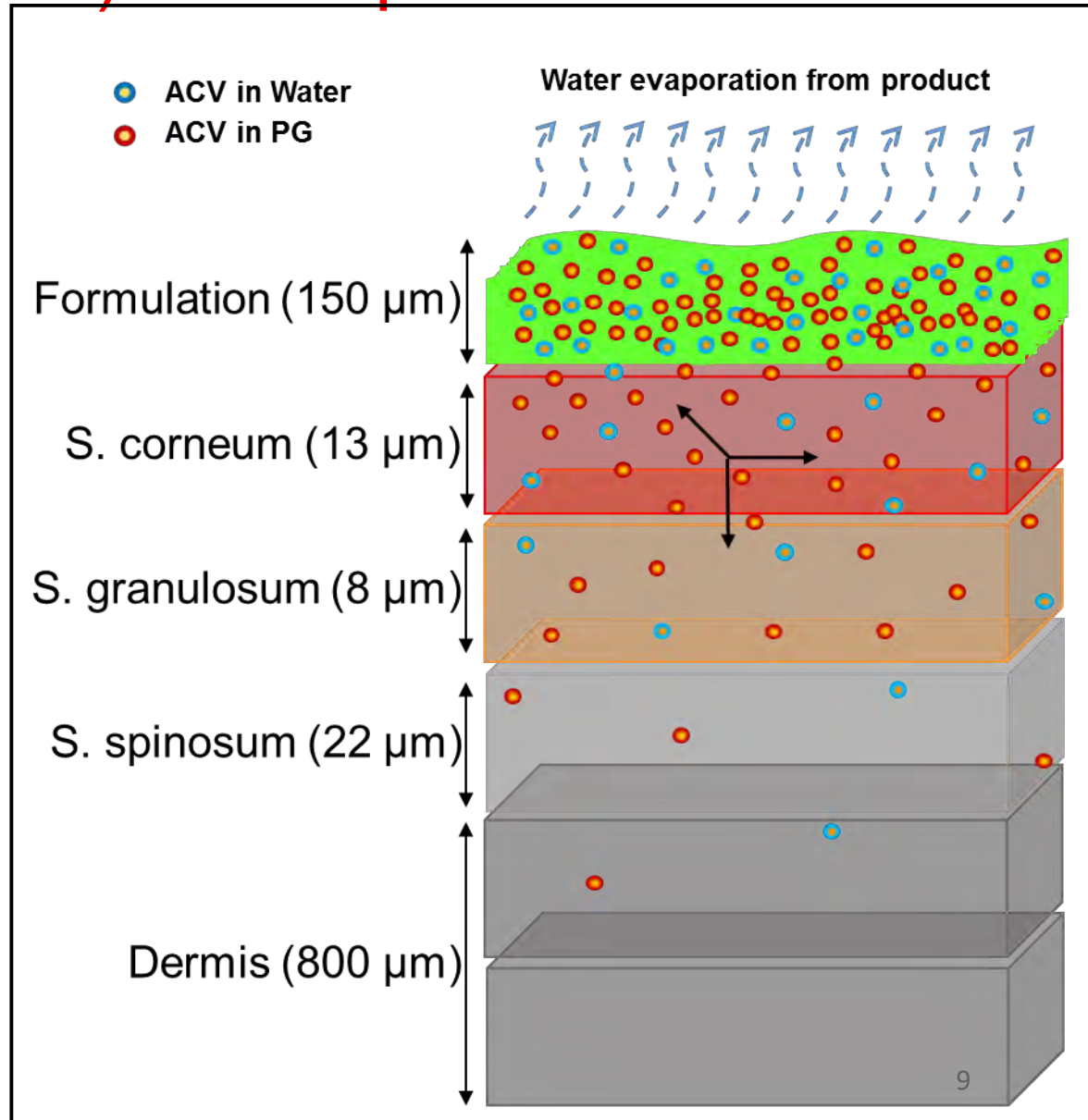
Ingredient Name	Zovirax (U.S.)	Aciclovir 1A Pharma (Austria)
Acyclovir concentration	5% w/w	5% w/w
Propylene glycol (PG)	40% w/w	15% w/w *1
Water Content	≈ 1/3 w/w	≈ 2/3 w/w
Other Ingredients:	Cetostearyl alcohol Mineral oil Poloxamer 407 Sodium lauryl sulfate Water White petrolatum	White Vaseline Viscous paraffin Glycerol monostearate Polyoxyethylene stearate Dimethicone Purified water



*1 Trottet, L., H. Owen, P. Holme, J. Heylings, I. P. Collin, A. P. Breen, M. N. Siyad, R. S. Nandra and A. F. Davis (2005). "Are all aciclovir cream formulations bioequivalent?" *Int J Pharm* 304(1-2): 63-71.

Excipients interact directly with the stratum corneum (SC) can impact on IVPT

- Propylene glycol (PG) and water, known penetration enhancers, are two excipients present in all products
- Our work has also shown that PG and water can carry solutes into the SC & promote their permeation
- Both are likely to promote direct acyclovir uptake into the stratum corneum
- Potentially, product microstructure (Q3) can impact on acyclovir & enhancer bioavailability to the stratum corneum



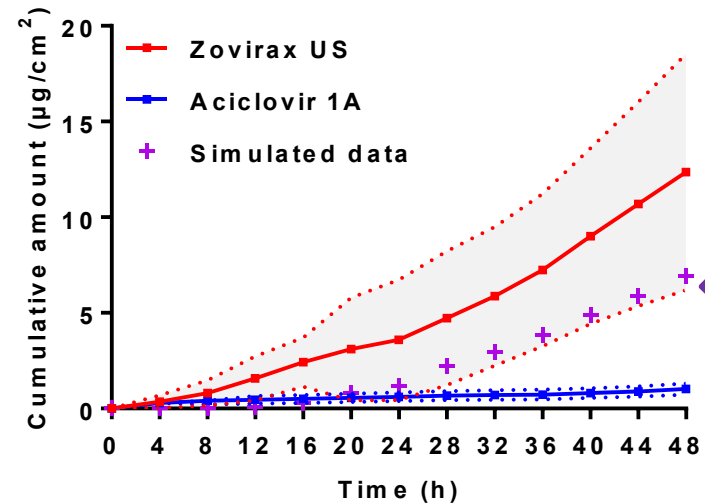
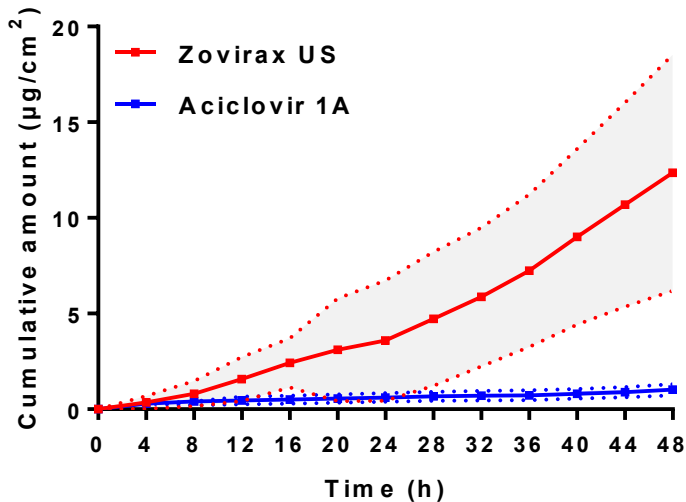
Understanding differences in *IVPT* profiles for acyclovir for 2 products

1. We first consider diffusivity of ACV in SC with no product excipients (PG, water etc.) – SC interactions

Experimental *IVPT* profiles



Can we predict acyclovir permeation theoretically?

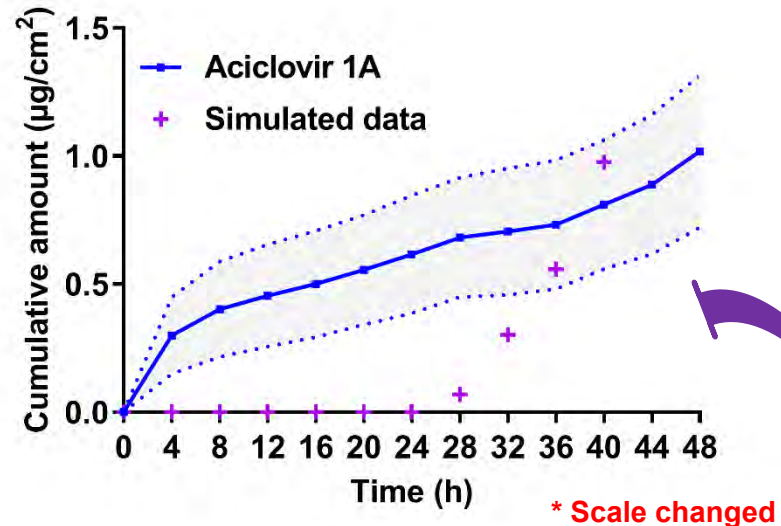
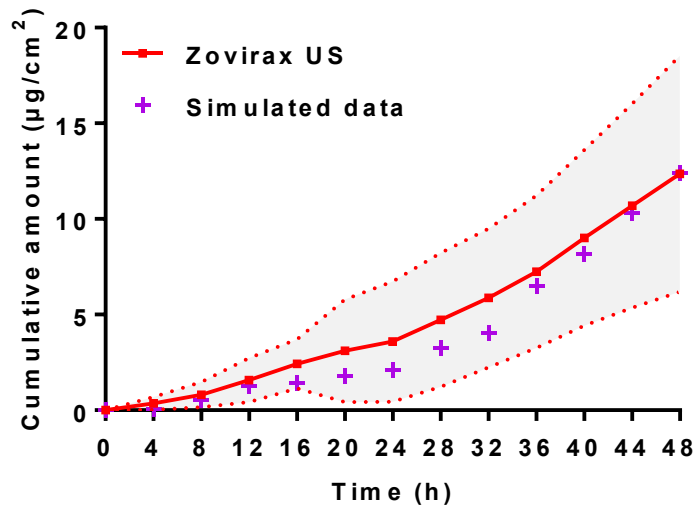


$$K_{ACV,SC} = 0.24; h_{SC} = 13 \mu\text{m};$$
$$D_{ACV,SC} = 2.54 \times 10^{-7} \mu\text{m}^2/\text{s}$$

The predicted profile by simulation is intermediate between the two observed profiles

Understanding differences in *IVPT* profiles for acyclovir for 2 products

2. Now include impact of PG in SC on Acyclovir permeation predictions



- When the effect of PG, a known ingredient in the formulations and a known solubility and penetration enhancer, is taken into account the simulated profile for Zovirax matches with the *IVPT* data.
- However, Aciclovir 1A still does not fit. Is there something more going on?

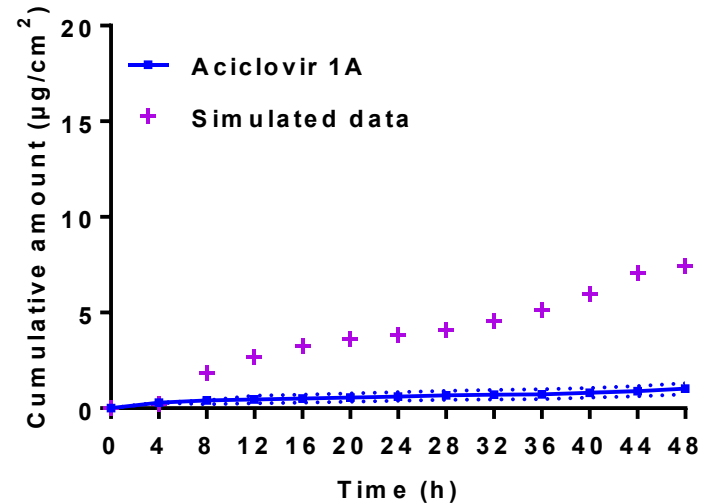
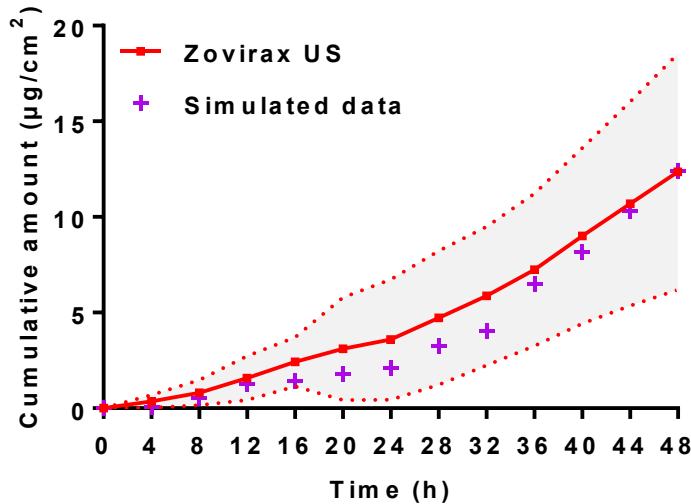
$$K_{PG,SC} = 0.29; h_{SC} = 13 \mu\text{m};$$

$$D_{PG,SC} = 1.03 \times 10^{-4} \mu\text{m}^2/\text{s}$$

$$D^*_{ACV,SC} = D_{ACV,SC} + 0.00003 \times C_{PG,SC}$$

Understanding differences in *IVPT* profiles for acyclovir for 2 products

3. Now including impact of PG and water in SC and water evaporation from the product



- As well as interactions of PG affecting acyclovir diffusion in SC,
- Evaporation of water from product modifies acyclovir availability, and

$$D_{\text{don},\text{H}_2\text{O}} \nabla u_{\text{H}_2\text{O}}(x) \vec{n} = \omega u_{\text{H}_2\text{O}}(x)$$

$$D_{\text{donor},\text{water}} = 6.88 \mu\text{m}^2/\text{s}; \omega = 0.02$$

- Water can modify acyclovir chemical activity and diffusion in SC

$$K_{\text{PG},\text{SC}} = 0.29; h_{\text{SC}} = 13 \mu\text{m};$$

$$D_{\text{PG},\text{SC}} = 1.03 \times 10^{-4} \mu\text{m}^2/\text{s}$$

$$K_{\text{water},\text{SC}} = 0.18; h_{\text{SC}} = 13 \mu\text{m};$$

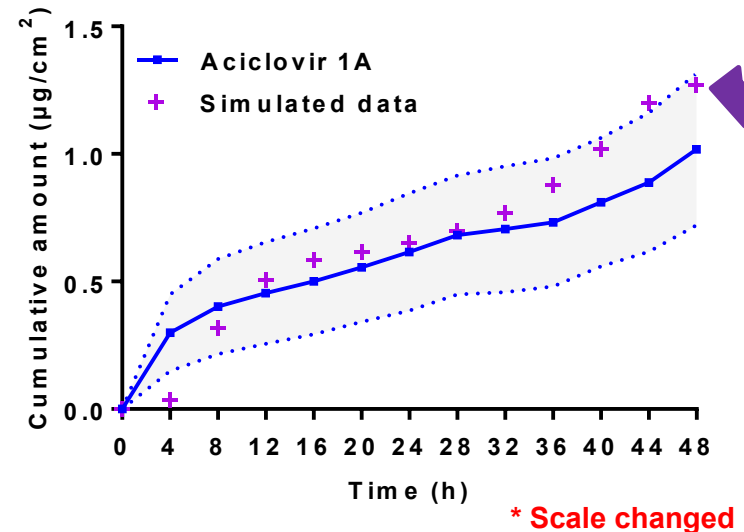
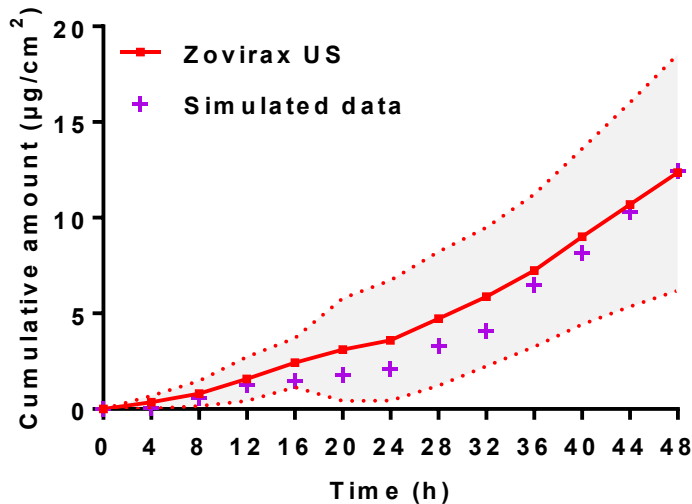
$$D_{\text{water},\text{SC}} = 1.07 \times 10^{-3} \mu\text{m}^2/\text{s}$$

$$D_{\text{ACV},\text{SC}}^* = D_{\text{ACV},\text{SC}} + 0.00003 \times C_{\text{PG},\text{SC}} + 0.000043 \times C_{\text{water},\text{SC}}$$

- Zovirax fits but Aciclovir 1A cannot be fitted.

Understanding differences in *IVPT* profiles for acyclovir for 2 products

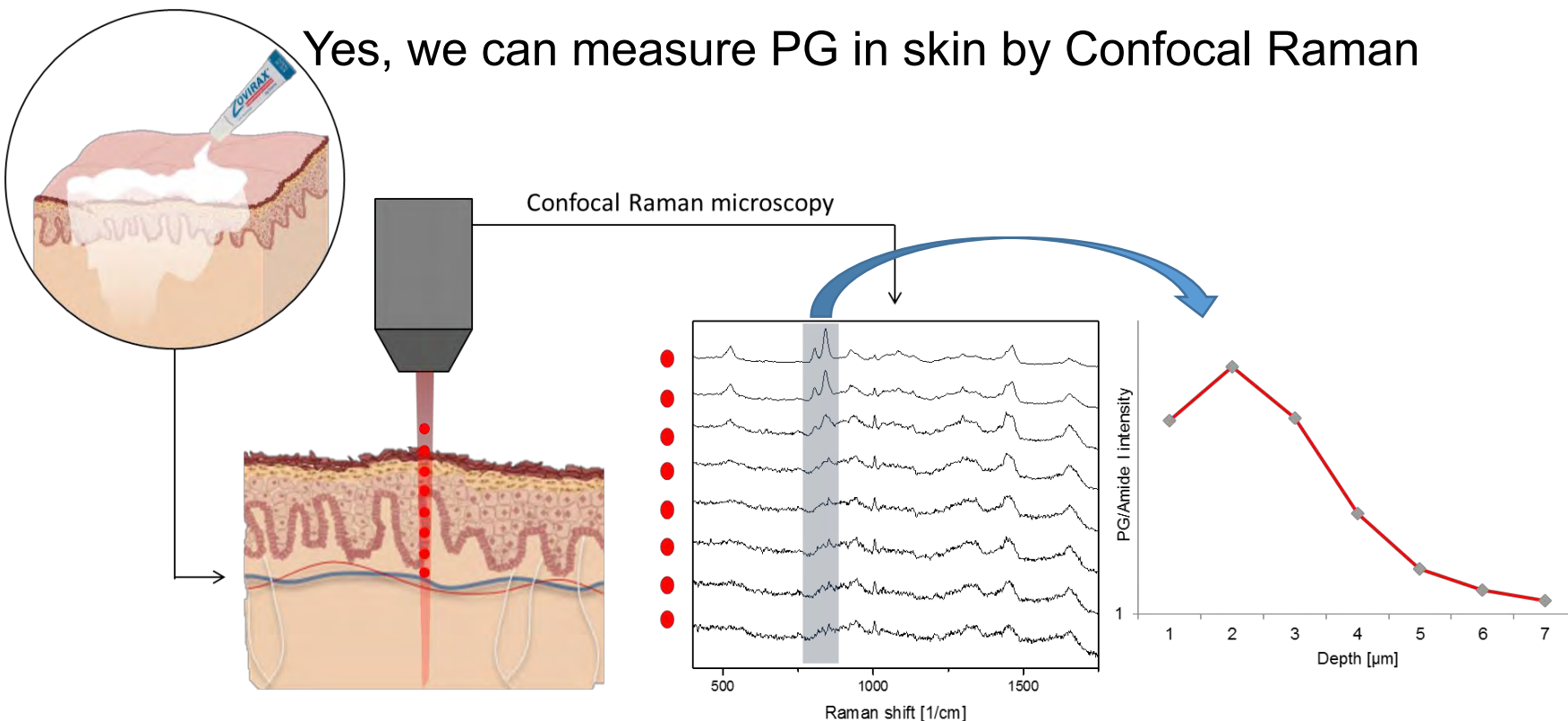
4. Now add the availability of acyclovir in the donor for “in-use” conditions



- Estimated 10% free acyclovir in Zovirax after evaporation (~13.5% before)
- Estimated 1.7% free acyclovir in Aciclovir 1A after evaporation (~14.3% before)
- Now both products fit - emphasises importance of thermodynamic activity!

Can we verify the theoretical predictions experimentally?

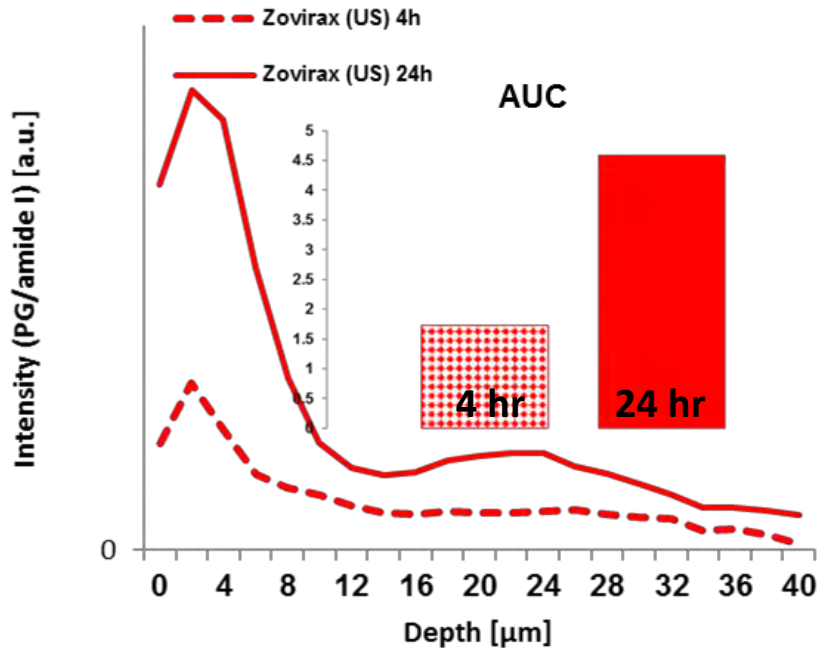
Yes, we can measure PG in skin by Confocal Raman



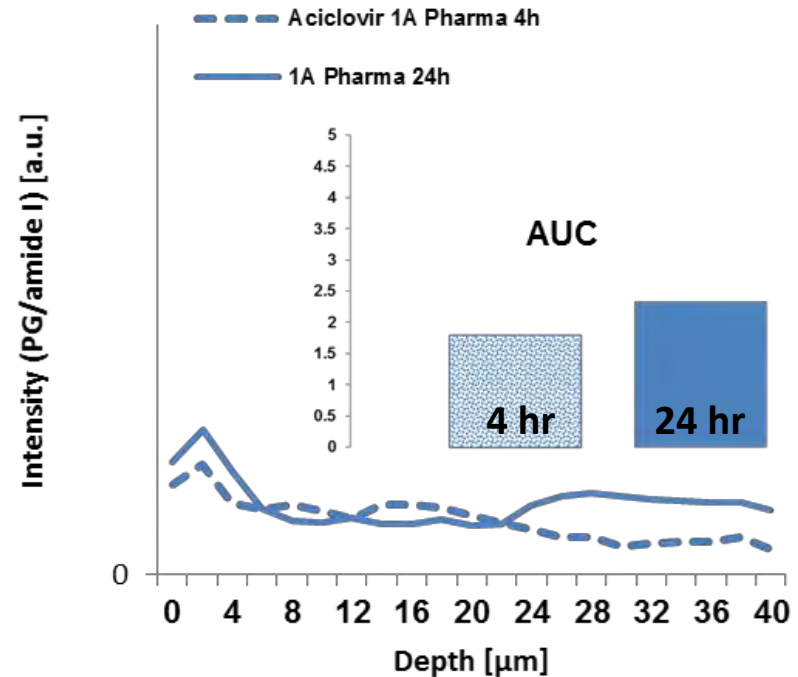
- ❖ After incubation of the sample on the skin, excess cream is removed
- ❖ With the Confocal Raman microscope, vertical line scans are acquired from the skin surface downwards in z-direction
- ❖ In the resulting Raman spectra, a formulation-associated peak (here highlighted is a characteristic peak of PG) is normalized by a skin-derived peak (amide I around 1641 cm⁻¹)
- ❖ The normalized Raman intensity of PG is then plotted against the penetration depth to create a depth profile

We find...

Zovirax (US)



Aciclovir 1A



- Zovirax (US) has 2.5 times the PG content of Aciclovir 1A*
- PG uptake in the SC increases 2.5 fold over time after Zovirax (US) application but not after Aciclovir 1A.

* Trottet, L., H. Owen, P. Holme, J. Heylings, I. P. Collin, A. P. Breen, M. N. Siyad, R. S. Nandra and A. F. Davis (2005). "Are all aciclovir cream formulations bioequivalent?" *Int J Pharm* 304(1-2): 63-71.

Composition of Acyclovir products

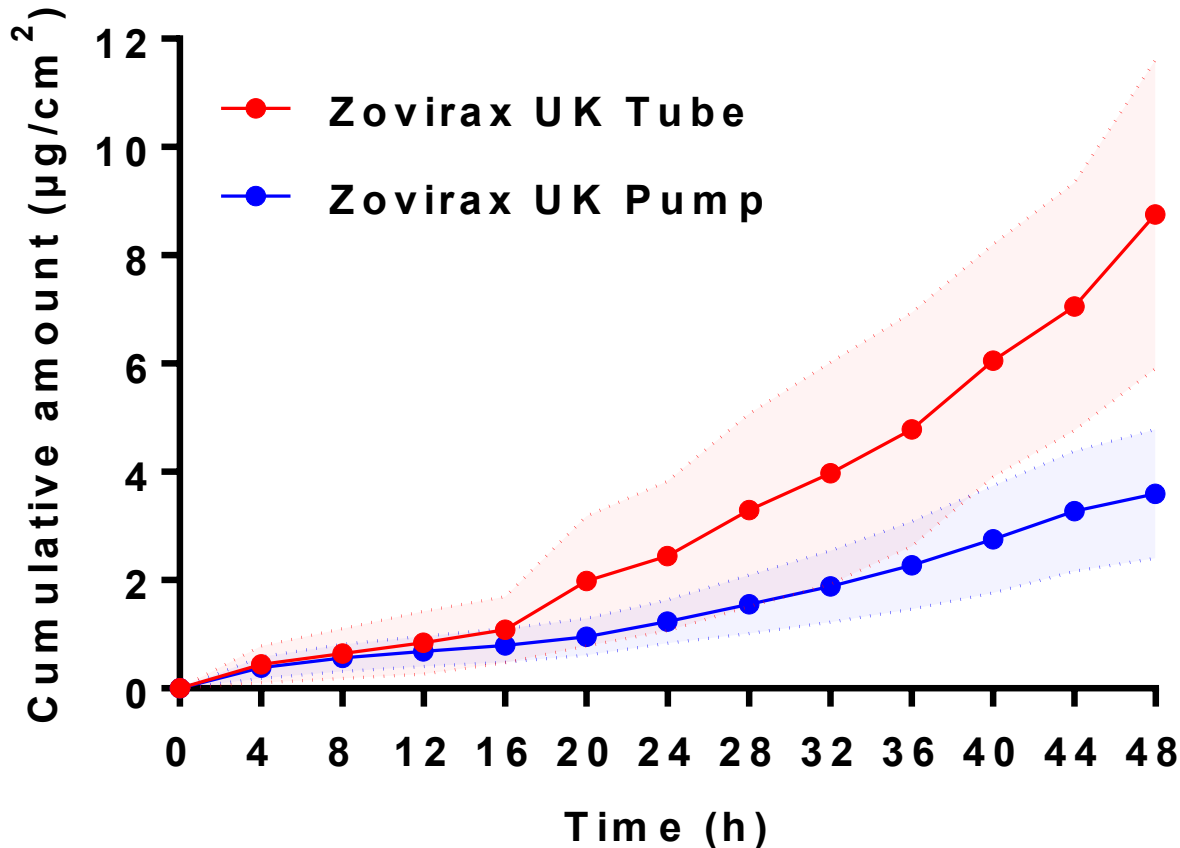
Other excipients also vary & may matter!

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

Q1, Q2 is important. What about Q3?

Need to consider specific case when Q1 and Q2 are the same

- The Q1 and Q2 of acyclovir packaged in a tube and a pump dispenser are the same;
- But their IVPT profiles differ – Why?



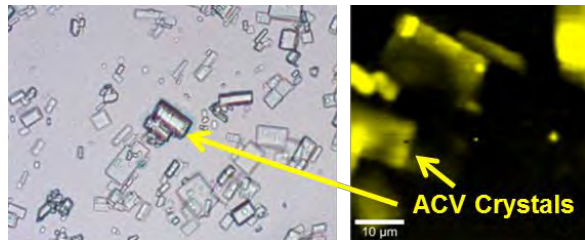
Using confocal Raman & rheology to assess impact of dispensing on Q3 metamorphosis & IVPT

- Confocal Raman suggests that pumping affects the crystal habit for acyclovir and leads to the formation of dimethicone globules
- Rheology suggests that the packaged tube and pump have a similar yield stress but that the product after pumping is higher – due to dimethicone agglomeration?

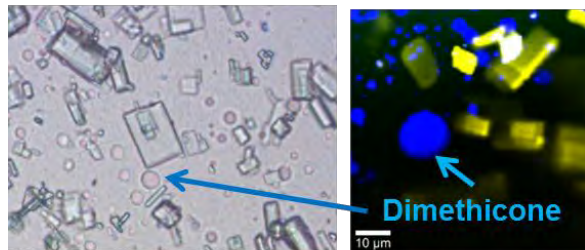
Yield stress
from strain
sweep (Pa)

78 ± 1.3

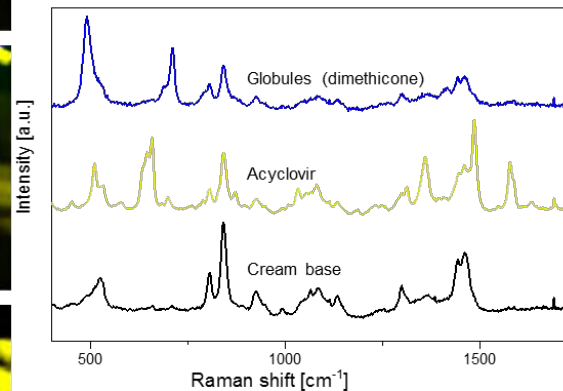
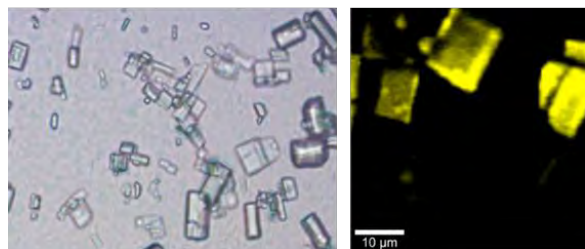
Zovirax UK Tube



Zovirax UK Pump



Zovirax UK Pump
(container opened)



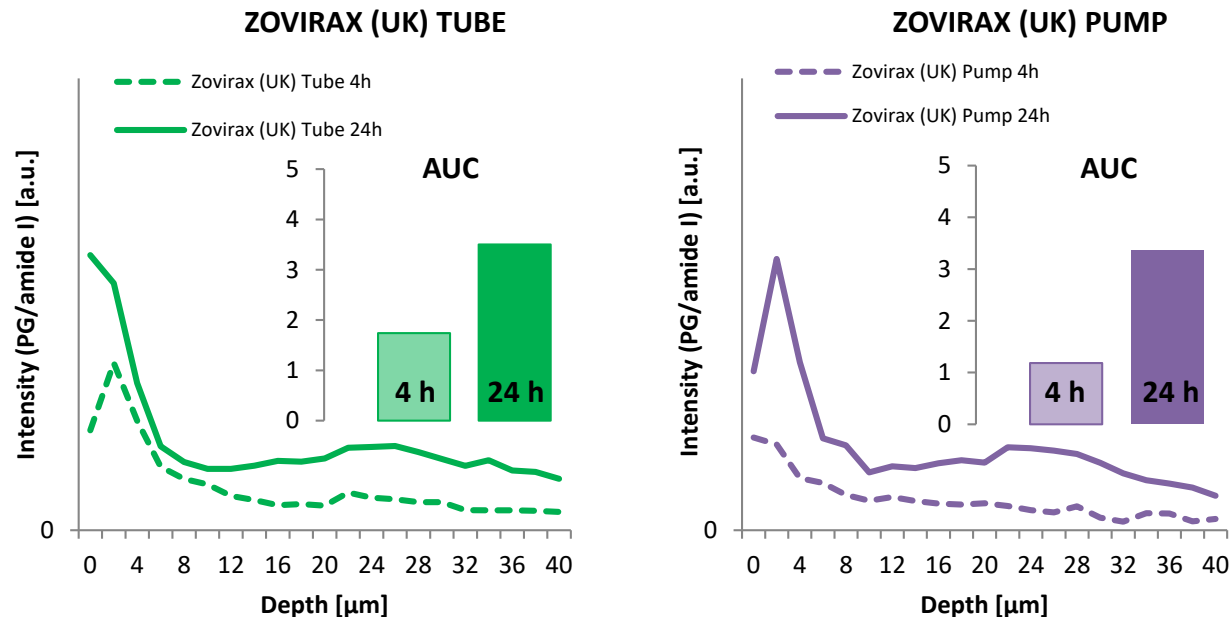
182 ± 0.6

70 ± 10

Correlation of Q3 microstructure with performance (Example I)

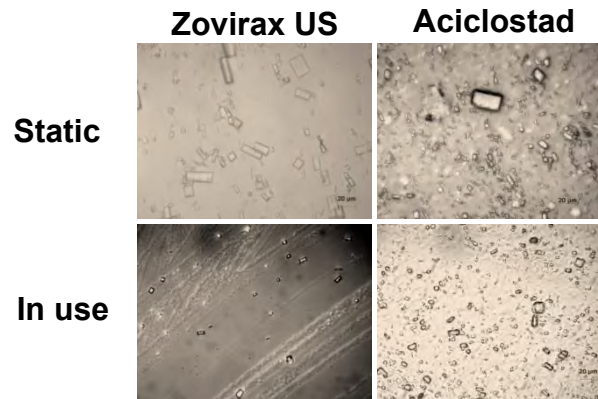
- Reflections on the differences in IVPT permeation flux with the Q3 differences? Impact of pumping on Q3
- Pumping leads to agglomeration of dimethicone (in which ACV is poorly soluble), i.e. a change in product microstructure (Q3)
 - Does the dimethicone agglomeration on the skin surface act as a potential additional barrier to acyclovir permeation?
 - Does this also include affecting the the bioavailability of the enhancer (PG)?

Confocal Raman PG depth profiles

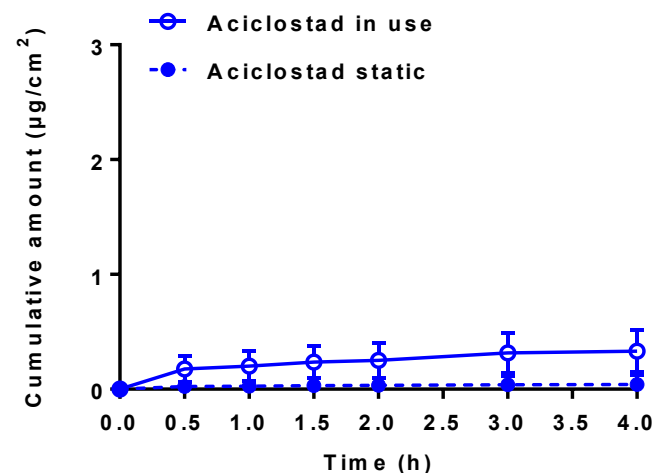
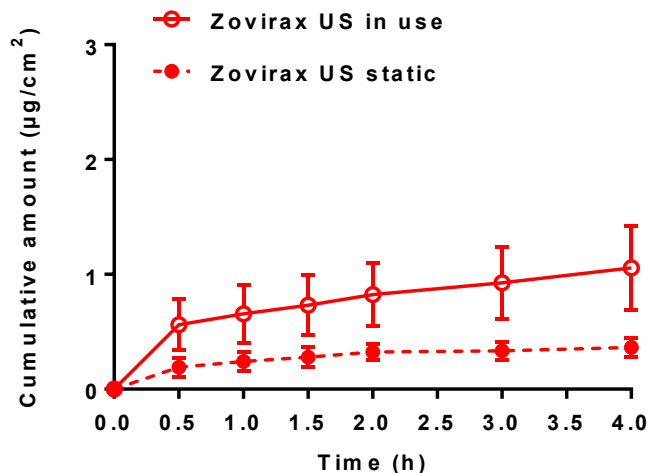


Does how a product is applied to the skin also change the product microstructure (Q3) and resulting IVPT?

- In use (rubbing onto the skin for 30sec) led to a reduction in acyclovir particle size and redistribution of acyclovir in the various phases



The IVPT for both Zovirax and Aciclostad suggests that rubbing enhances permeation and that this effect is more pronounced for the Zovirax product – indeed the ratio for rubbing/static amount permeated for Zovirax is 8-10 times higher than Aciclostad.



Transition – Acyclovir to metronidazole products

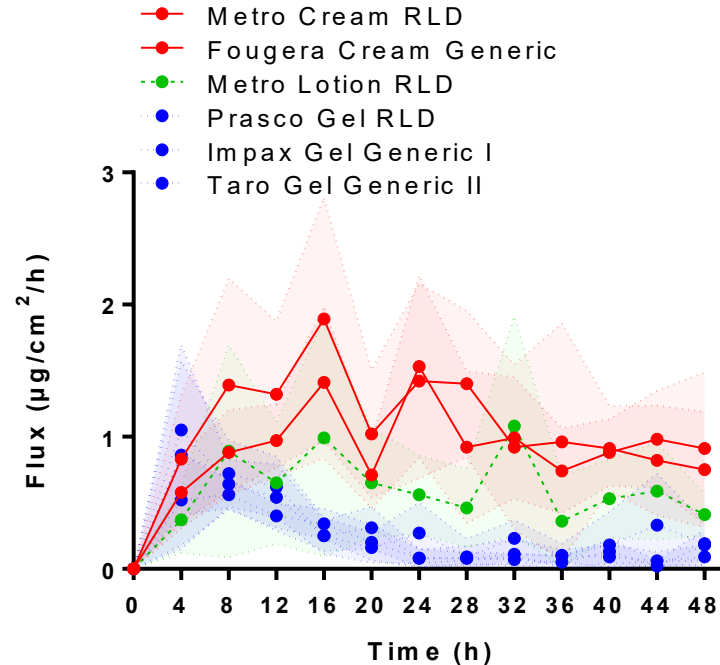
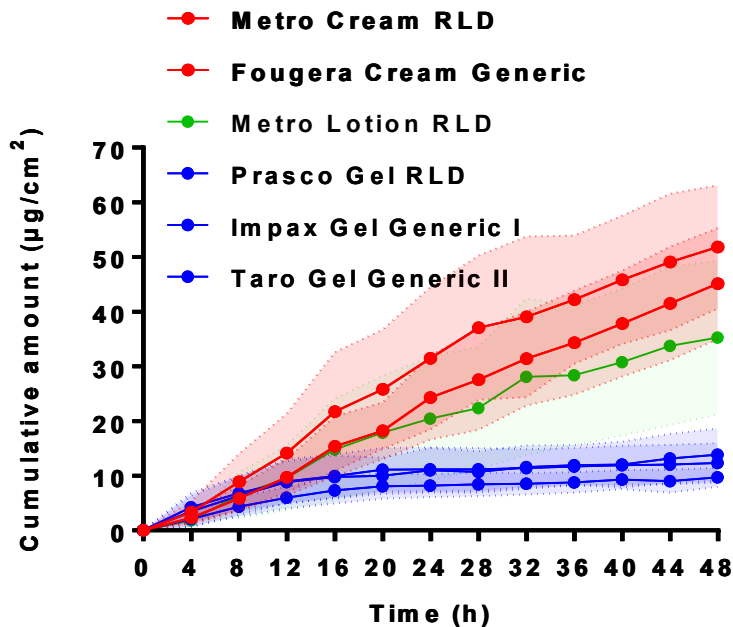
- Acyclovir products have enabled us to understand the impact of variations in:
 - The nature of the excipients (Q1)
 - Product composition (Q2) and
 - Product microstructure (Q3)on acyclovir *IVPT* profiles and, in particular, that significant differences arise in the *IVPT* profiles between the Zovirax group of products and two Austrian “generic” products
- In principle, *IVPT* can be related to *in vivo* microperfusion data in their discrimination between products but we have not shown a consistent *in vitro-in vivo* relationship across the various products as yet
- We have shown that how products are used can have a major impact on *IVPT* outcomes
- Can we show similar findings for the more lipophilic active metronidazole?

Overview of Metronidazole product quality attributes

Test	Creams		Lotion	Gels		
	Metro Cream RLD	Fougera Cream Generic	Metro Lotion RLD	Prasco Gel RLD	Impax Gel Generic 1	Taro Gel Generic 2
pH	5.0 ± 0.3	5.3 ± 0.3	5.1 ± 0.1	4.8 ± 0.1	5.4 ± 0.1	5.2 ± 0.1
Polymorphs	No difference in polymorphic forms					
Crystal Shape/Crystal habit upon drying on Skin	No crystals	Rectangular crystals	Irregular crystals	Rectangular and Branched crystals		
Excipients	Similar as per prescribing information (PI)		Different from cream composition	Similar composition in between them as per PI and different from creams		
Loss of Water	Lower than other products		In between creams and gels	Higher than creams and similar among them		
Globules	Globular structure		Globular structure	No globules appeared		
Microstructure (Without inclusions)	Classic emulsion based microstructure		Classic emulsion based microstructure	Visible polymer matrix		
IVPT						
Cumulative amount 48 hrs (µg/cm ²)	45.1 ± 4.4	51.8 ± 4.9	35.3 ± 6.1	12.3 ± 1.6	9.7 ± 0.8	13.8 ± 2.1
AUC – Flux curve	44.2 ± 5.4	53.0 ± 8.0	29.3 ± 6.5	13.4 ± 2.9	10.2 ± 1.7	15.6 ± 3.7
Jmax (µg/cm ² /h)	1.5 ± 0.3	1.9 ± 0.4	1.1 ± 0.4	0.6 ± 0.1	0.6 ± 0.1	0.9 ± 0.3
Tmax (h)	24	16	32	8	8	4

Q1, Q2 and Q3 variations between product classes - Does this impact on IVPT?

- Q1, Q2 and Q3 could vary between product classes - Is this associated with change in IVPT?



Data shown as mean \pm 95% CI; Each point is the mean of 9* (3 donors & 3 replicates per skin)

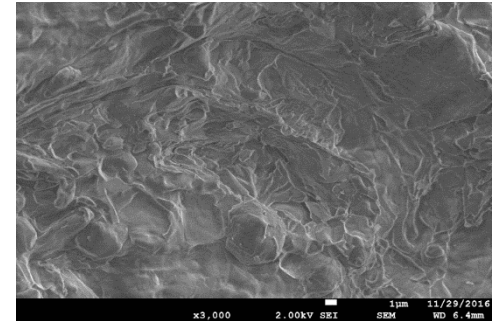
Meaning in parallels?

- IVPT cream \geq lotion $>$ gel and
- Tribology (friction) cream \leq lotion $<$ gel

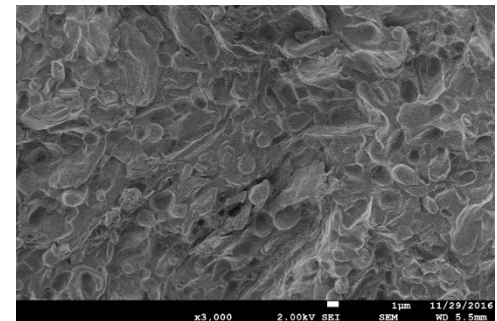
Why are metronidazole gels and creams non-bioequivalent – how do these products differ?

- Q1 (content) and Q2 (amounts)
 - Thermodynamic activity &
 - Enhancer effects
- Microstructure differences
 - ❖ Qualitative and quantitative differences may be present; but here we emphasize – all three different product classes (Creams, Lotions and Gels) have unique structural features
 - ❖ Each product has defined a microstructure and with globules of the internal phase
 - ❖ Emulsion based microstructures could presumably have better solubilisation and hence more available drug
 - ❖ Textural properties and spreading would be different
 - ❖ Evaporation

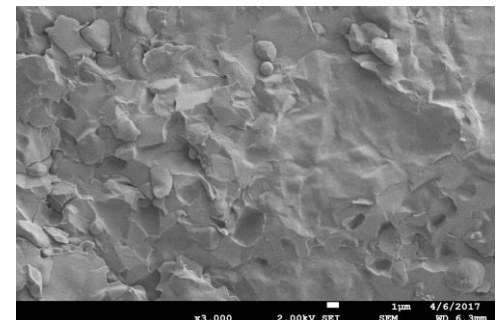
Metronidazole cream 0.75% (RLD)



Metronidazole cream 0.75% (Generic)



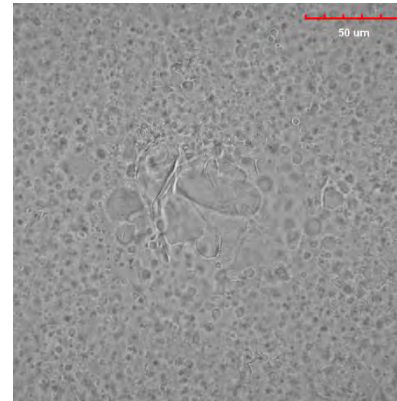
Metronidazole Lotion 0.75% (RLD)



Product drying

- The Gels have a very high water content and therefore evaporate more quickly
- We observed different types of crystals formed after product drying on the skin surface

Cream RLD



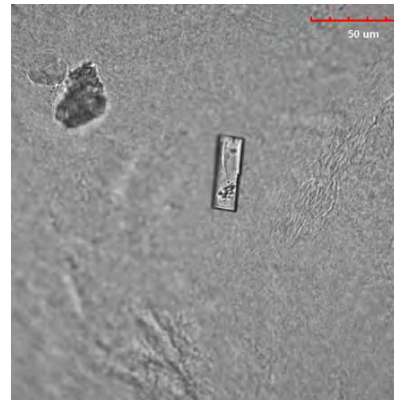
No Crystals

Cream Generic



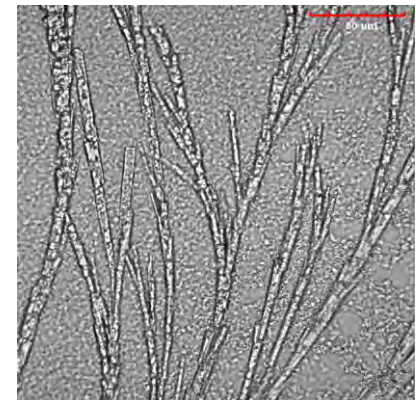
Rectangular Crystals

Lotion RLD

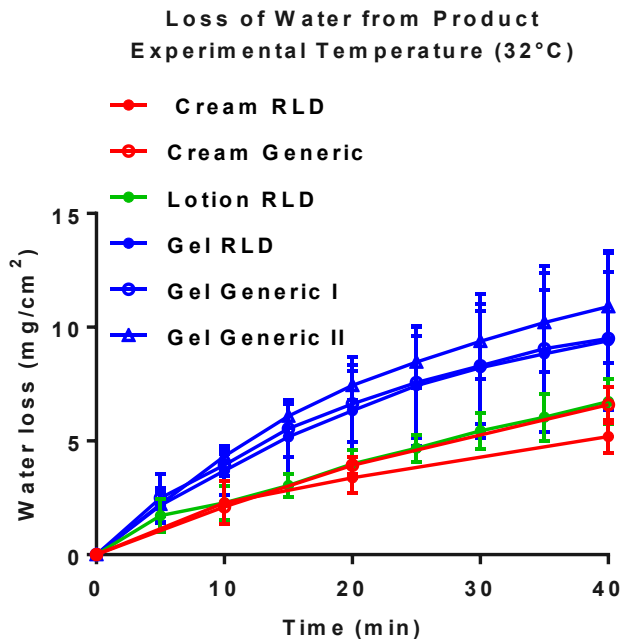


Rectangular Crystals

Gel RLD



Rectangular Crystals forming branched structures



Hence, products may “feel” different after evaporation of products on the skin

Conclusions

- How far have we come?

- ❖ We have developed an elaborate tool box of methods for evaluation of Quality Attributes.
- ❖ Some of these attributes have been found to be critical to product performance
- ❖ We have also developed different product performance testing tools (IVPT) in varied conditions (Skin prep, donor dose, receptor phase, application methods etc.)

- Where to from here?

- ❖ Our goal is to further develop these techniques and test the whole range of semisolid product microstructures with molecules of different physicochemical properties
- ❖ Ultimately, these tools should be able to facilitate a quality and timely generic product approval process

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