

Topical Semisolid Drug Product Critical Quality Attributes (Q3 Characterization) with Relevance to Topical Bioequivalence

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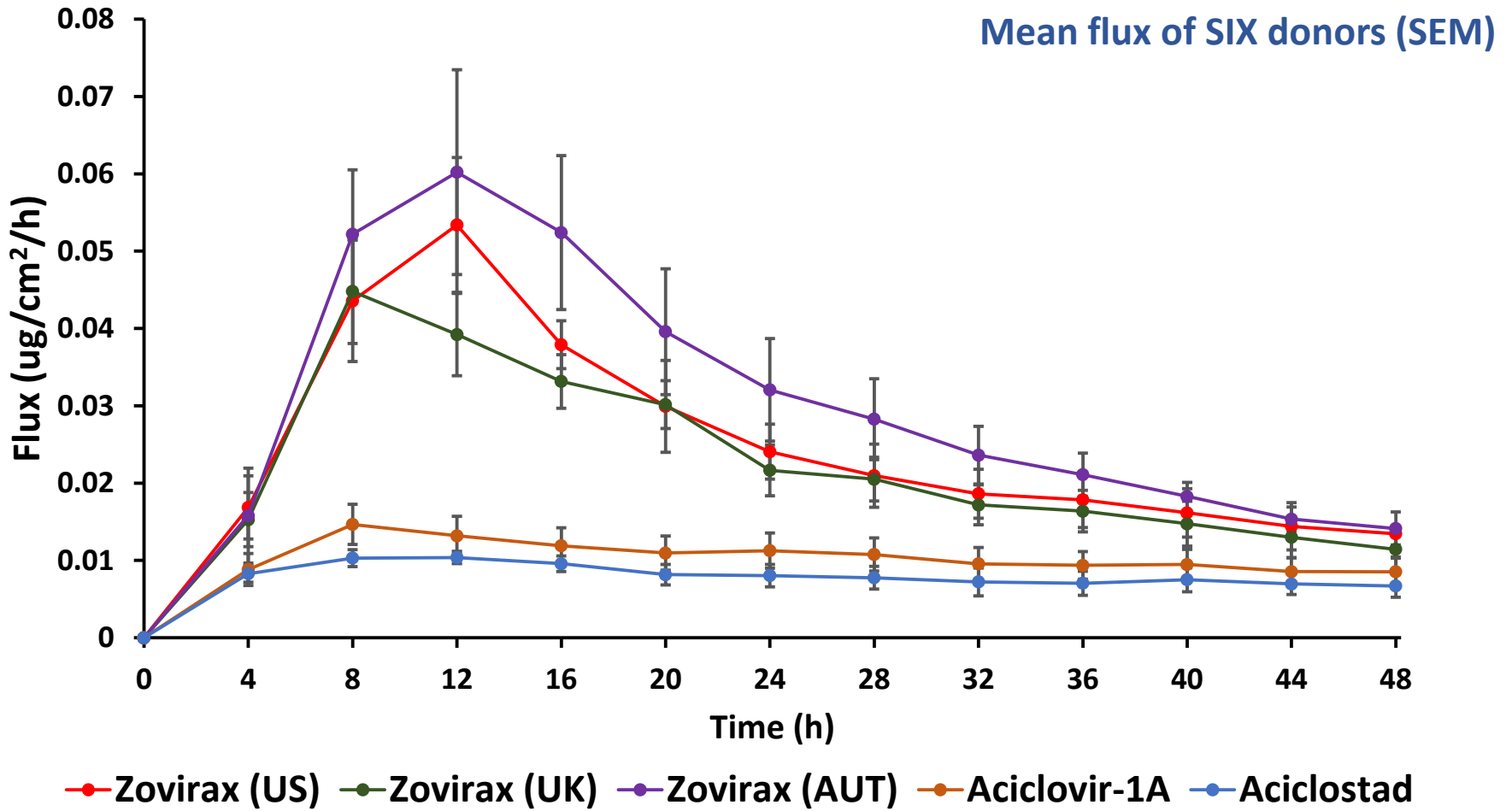
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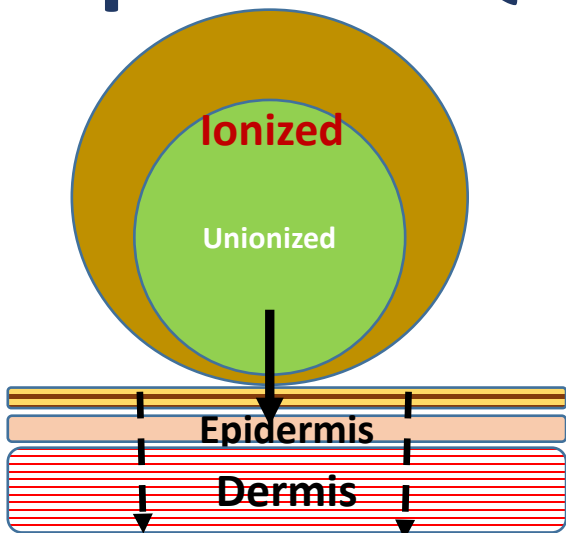
(Rutgers University, 05-24-2016)

Zovirax (USA)	Zovirax (UK)	Zovirax (Austria)	Aciclostad (Austria)	Aciclovir 1A (Austria)
Mineral oil	Liquid Paraffin	Liquid Paraffin	Liquid Paraffin	Viscous Paraffin
White petrolatum	White soft paraffin	White Vaseline	White Vaseline	White Vaseline
Water	Water	Purified water	Water	Water
Propylene glycol	Propylene glycol	Propylene glycol (400 mg/g)	Propylene glycol (150 mg/g)	Propylene glycol (150mg/g)
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

In Vitro Permeation Test



pH as a Quality Attribute



InLab Science



InLab Viscous



InLab Micro

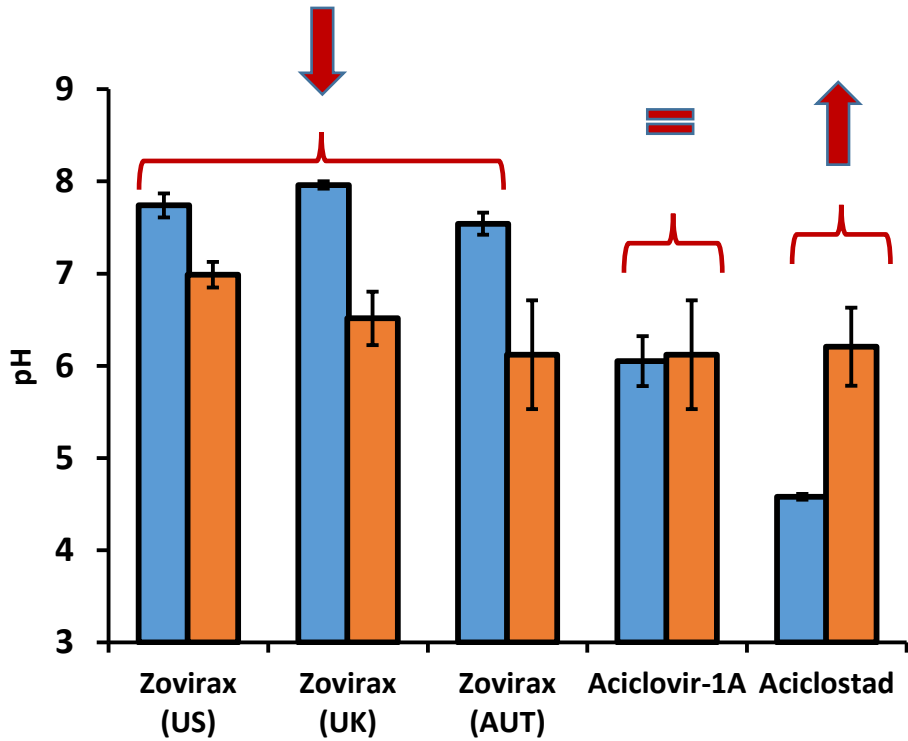
Suggestions

- *Standard buffers of pH 4 and 10 shall be alternated between each measurement.*
- *If it is a cream (o/w) use an electrode with smallest surface area for reproducible readings.*
- *Check the pH of aqueous Phase separated from the Cream.*

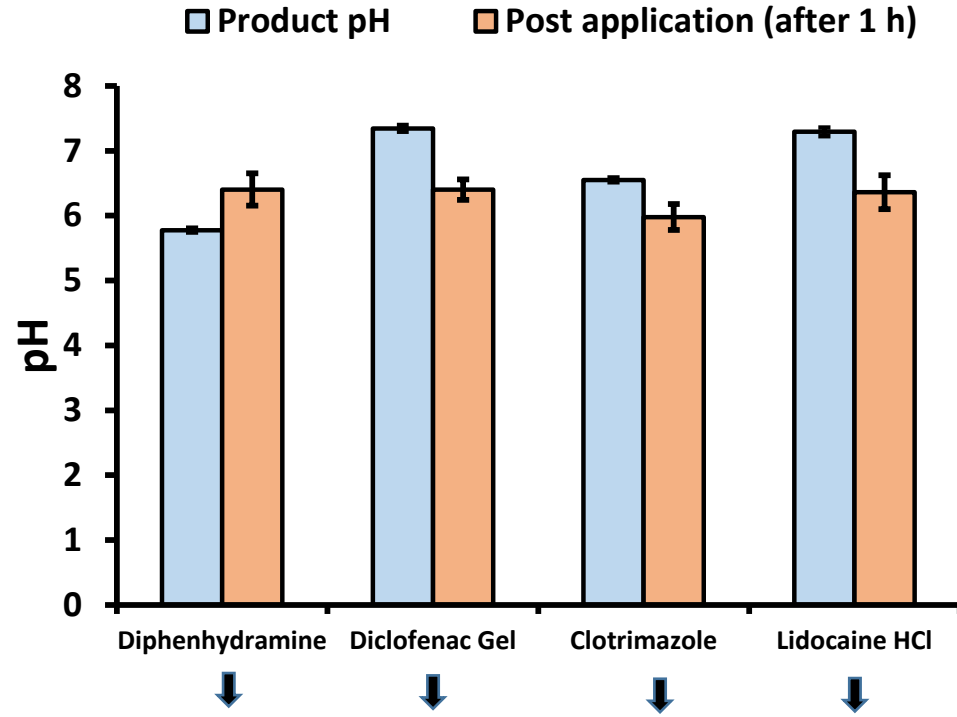
Product	Cream	Aqueous Phase
Zovirax (US)	7.74 ± 0.13	7.94 ± 0.07
Zovirax (Austria)	7.54 ± 0.12	7.80 ± 0.09
Zovirax (UK)	7.96 ± 0.04	8.34 ± 0.02
Aciclovir - 1A	6.05 ± 0.27	6.56 ± 0.11
Aciclostad	4.58 ± 0.03	4.93 ± 0.28

Standard buffers of pH 4 and 10 were alternated between each reading (n=5±SD)

pH could change after application on the skin

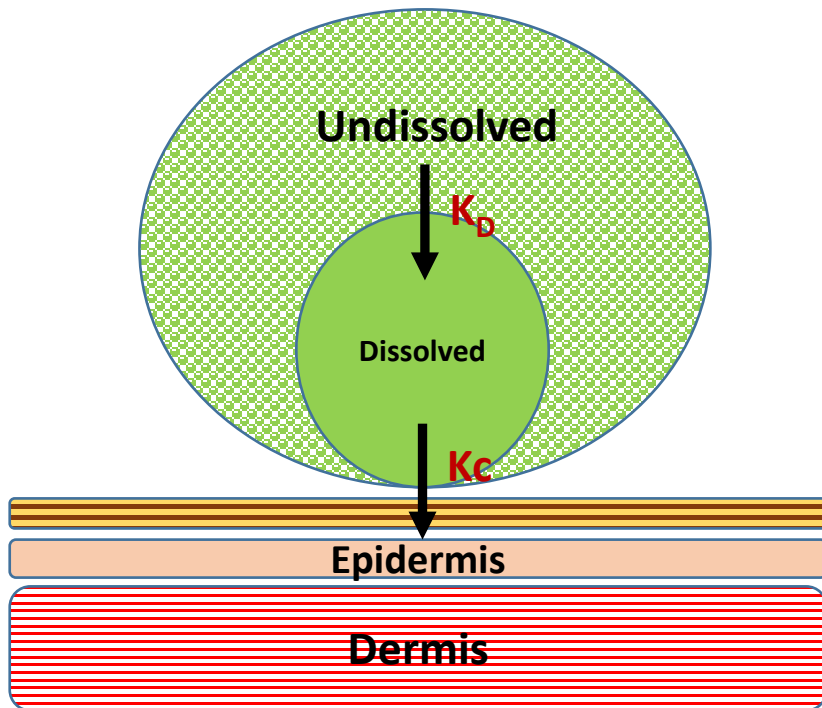


■ Cream pH ■ Post skin application cream pH (after 2 h)



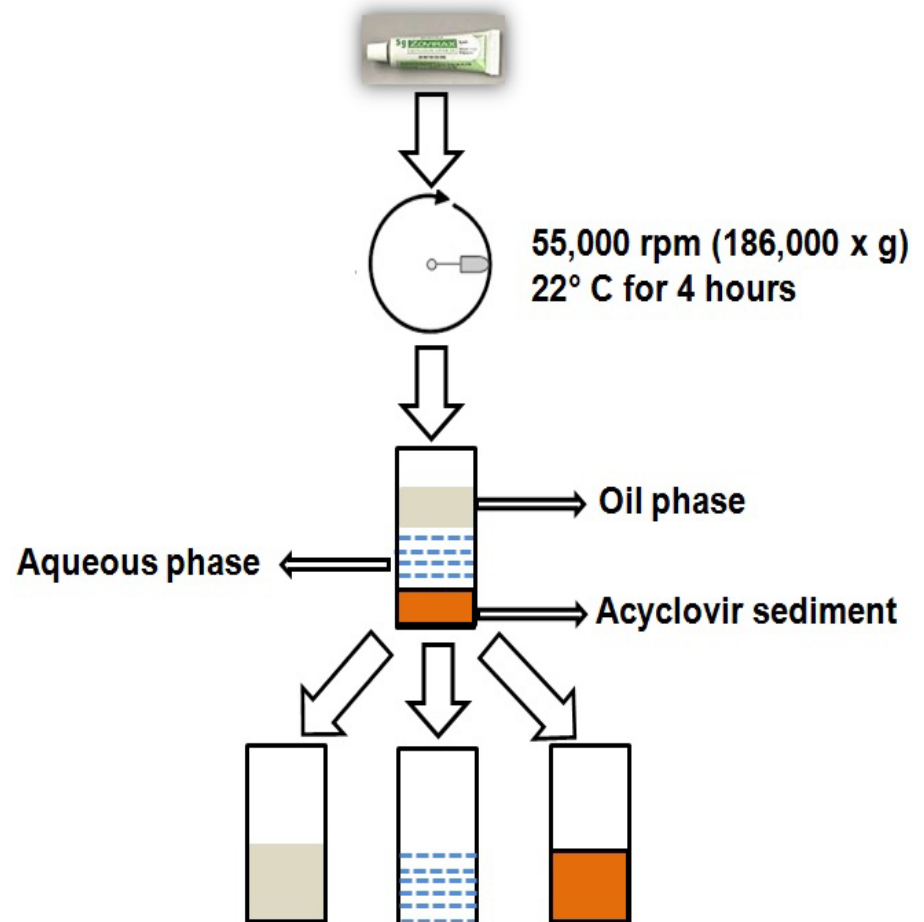
pKa	8.92	4.15	6.62	7.9
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Dissolved/Undissolved drug



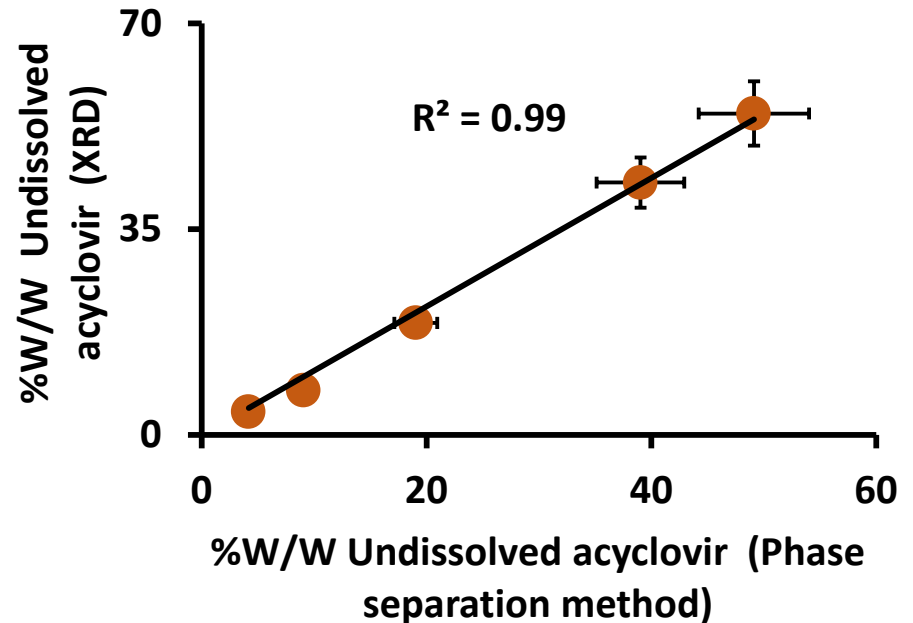
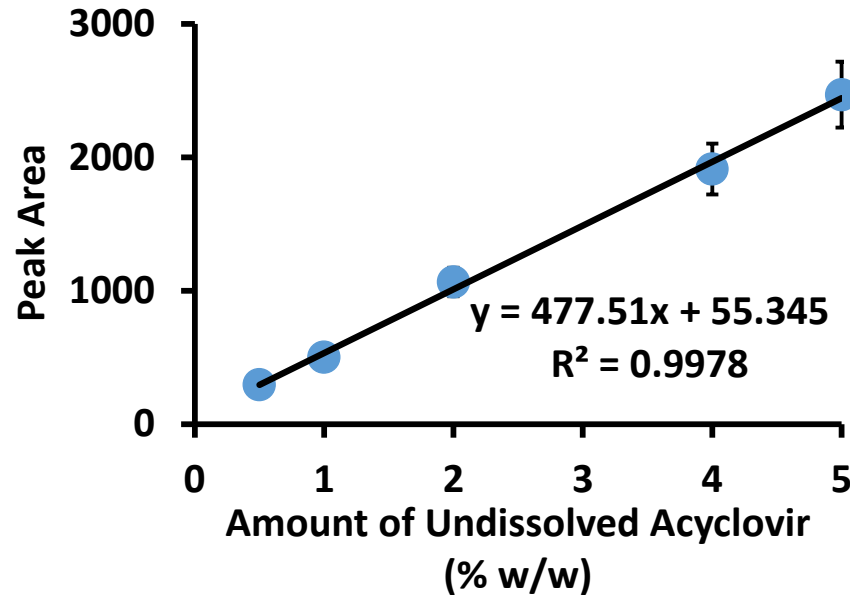
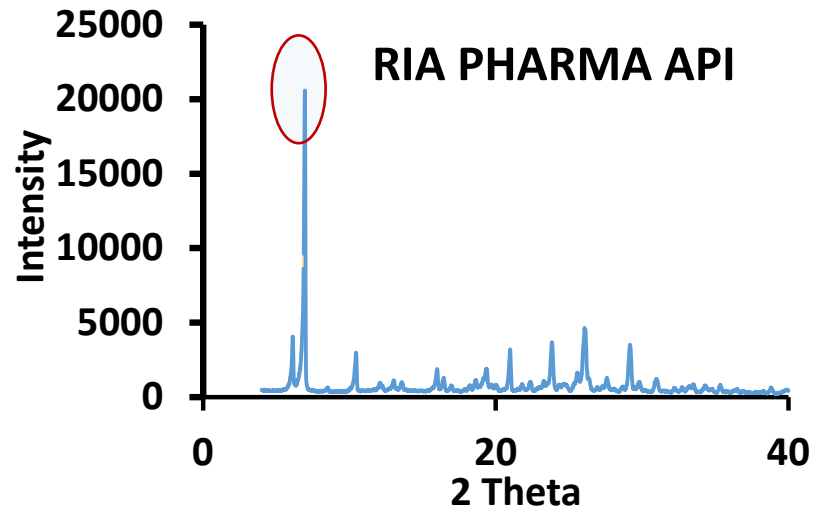
Dissolved Drug
Undissolved Drug

Phase Separation



D/UD – Quantitative XRD

Ingredient	Scale (g/100g)
Cetostearyl Alcohol	12
Cremophor A6	3
Cremophor A25	3
Liquid Paraffin	12
Deionized Water (q.s.)	70



Dissolved/Undissolved drug

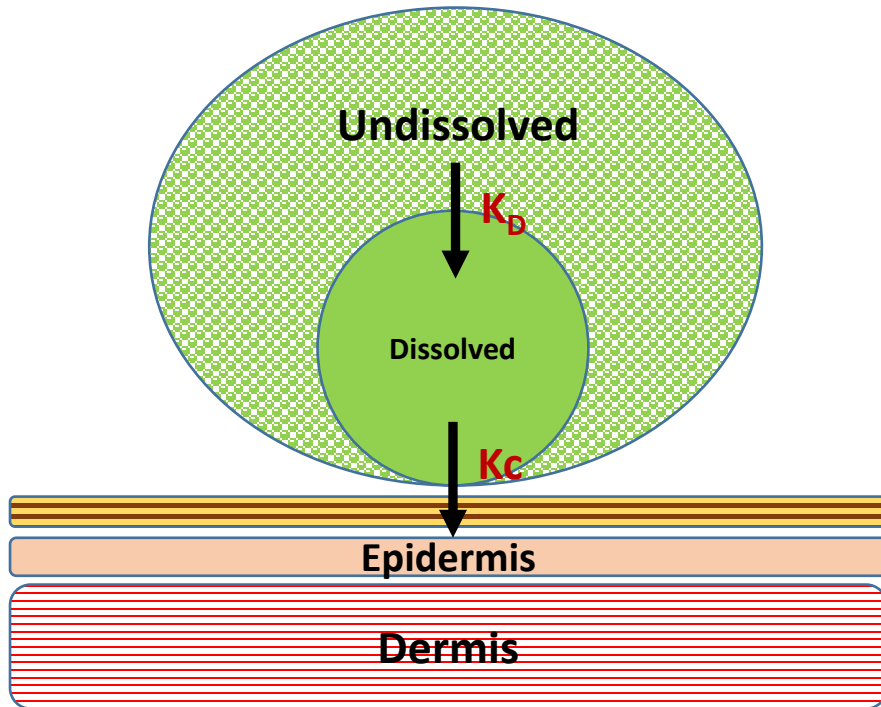
Product	Total dissolved acyclovir in cream (mg/g)	Total undissolved acyclovir in cream (mg)	D/UD	Amount Dissolved in Aqueous Phase (mg/g)
ZOVIRAX (US)	1.354±0.048	48.65±0.05	0.0278	0.492±0.085
ZOVIRAX (AUT)	2.459±0.161	47.57±0.16	0.0517	0.641±0.049
ZOVIRAX (UK)	1.326±0.046	48.67±0.05	0.0272	0.488±0.010
ACICLOVIR -1A	1.436±0.025	48.56±0.02	0.0296	0.255±0.028
ACICLOSTAD	1.339±0.042	48.66±0.04	0.0275	0.365±0.022

Particulate Attributes

$$K_D \geq K_C$$

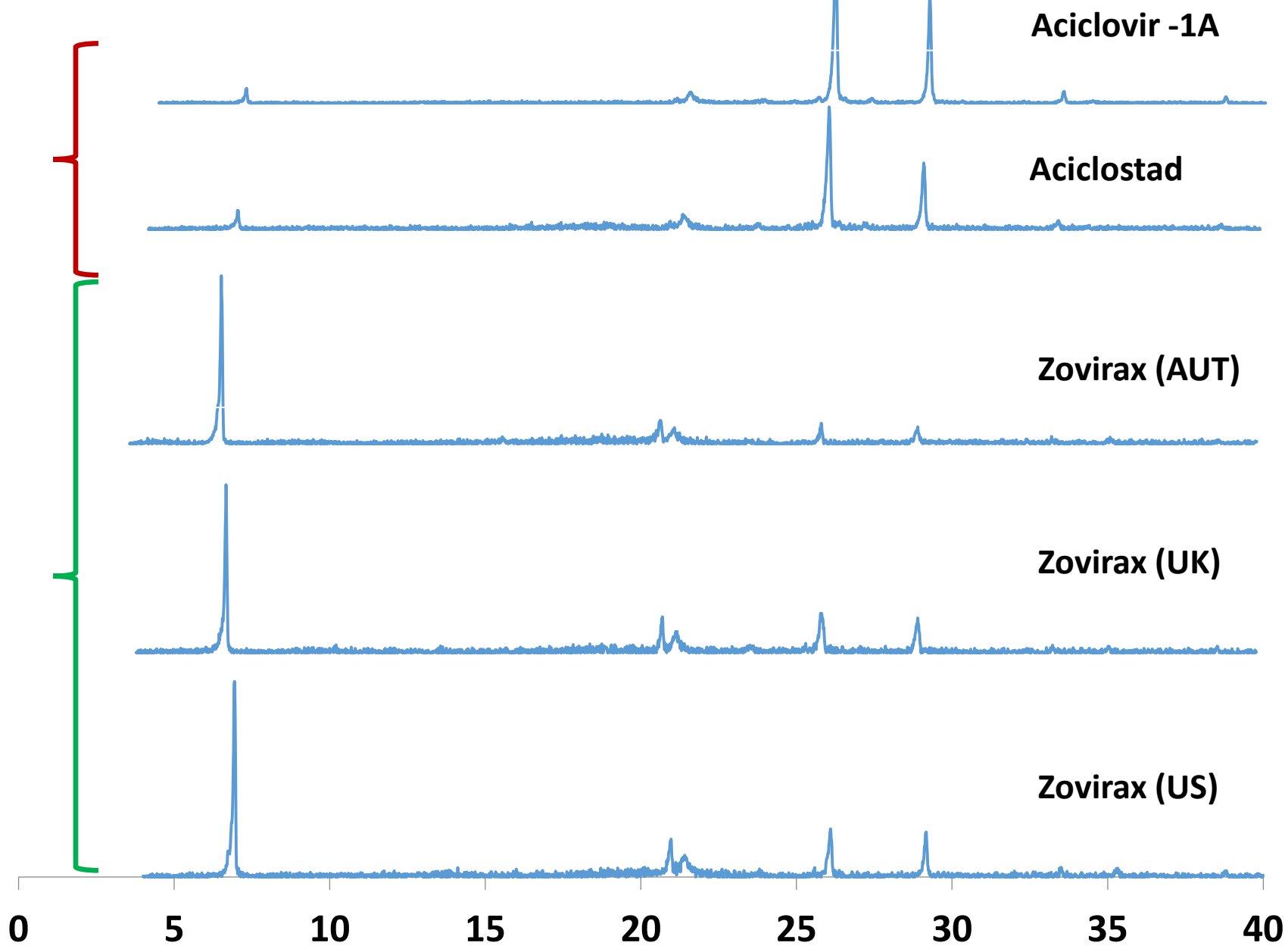
Rate of Dissolution of Drug

- Particle Size
- Polymorphic form
- Morphology of particles



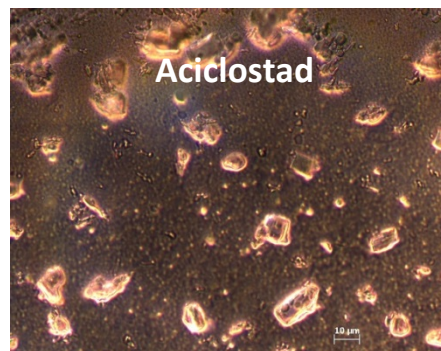
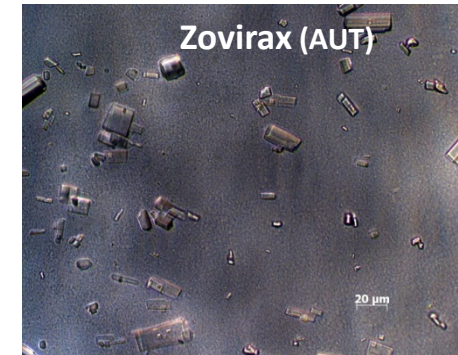
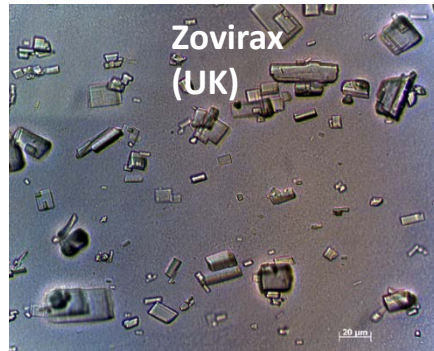
Dose	Total Drug	Dissolved Drug	Undissolved drug
5mg/cm ²	250 ug/cm ²	6.25ug/cm ²	243.75ug/cm ²

Polymorphic form



Particle Size and Morphology

Product	d_{10}	d_{50}	d_{90}
Zovirax (US)	2.07	3.77	19.05
Zovirax (AUT)	1.76	3.43	20.76
Zovirax (UK)	1.36	2.50	24.18
Aciclovir -1A	4.0	5.95	10.94
Aciclostad	3.67	6.75	11.40

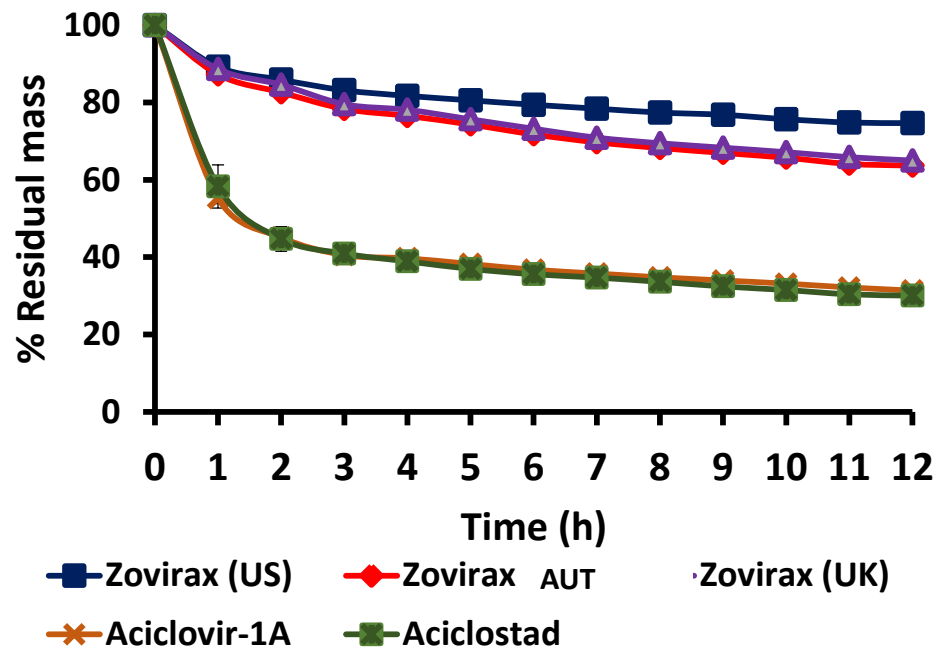
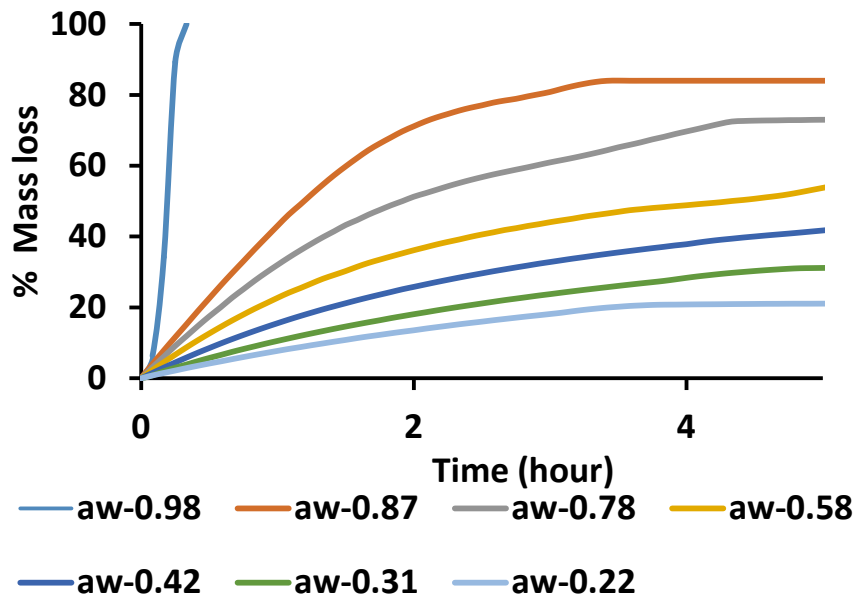


Solvent Activity (a_s)

$$a_s = \rho/\rho_0$$

ρ = partial vapor pressure of Solvents in the product

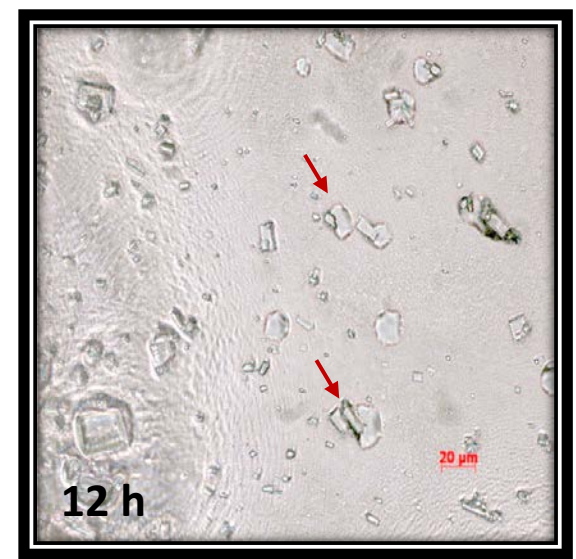
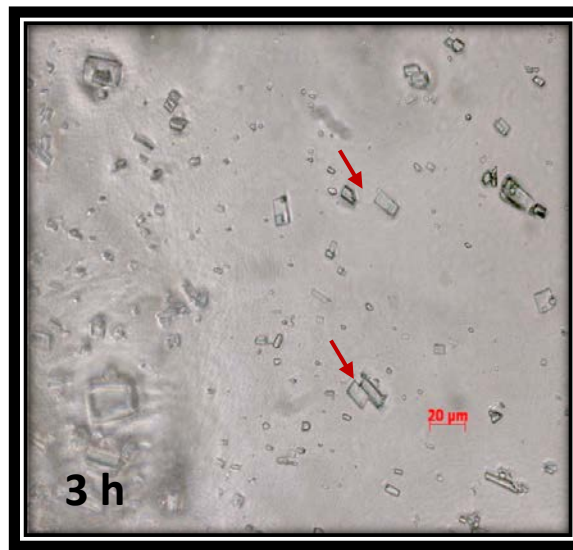
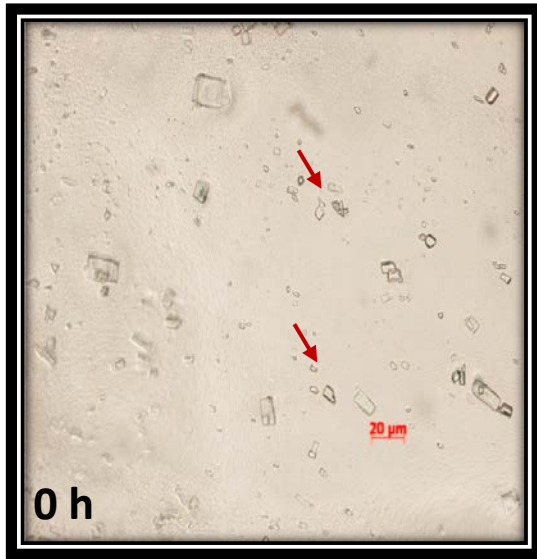
ρ_0 = vapor pressure of pure Solvent system



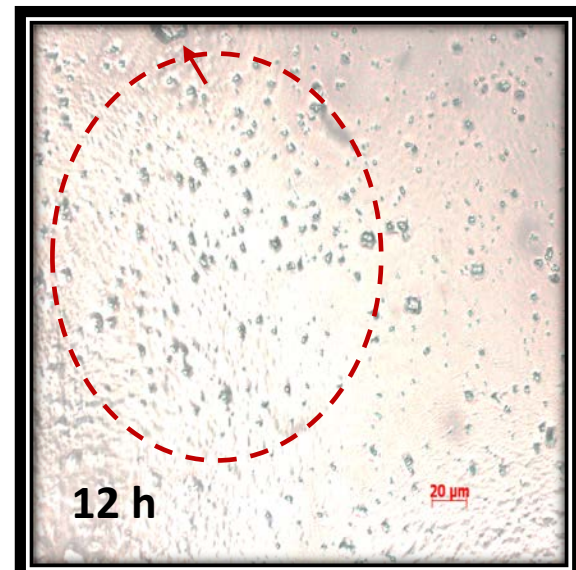
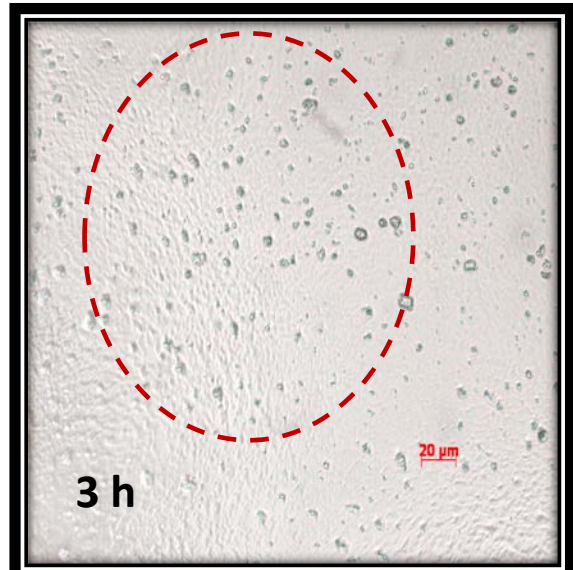
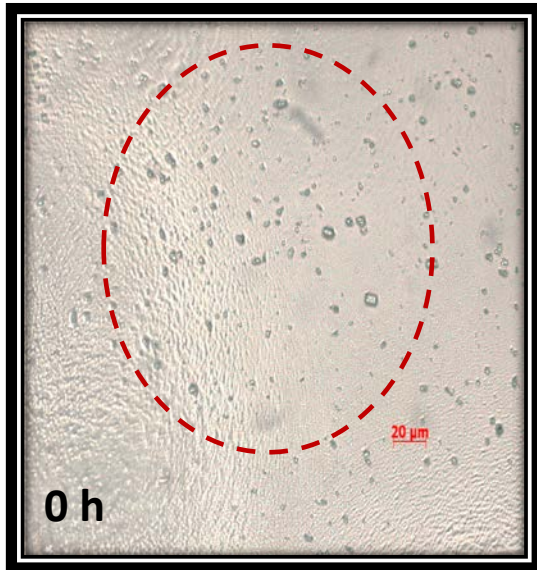
Product	Solvent Activity (a_w)
Zovirax (US)	0.753 ± 0.002
Zovirax (AUT)	0.735 ± 0.000
Zovirax (UK)	0.732 ± 0.002
Aciclovir – 1A	0.948 ± 0.001
Aciclostad	0.948 ± 0.003

Solvent Evaporation and Precipitation of Acyclovir

Zovirax-UK



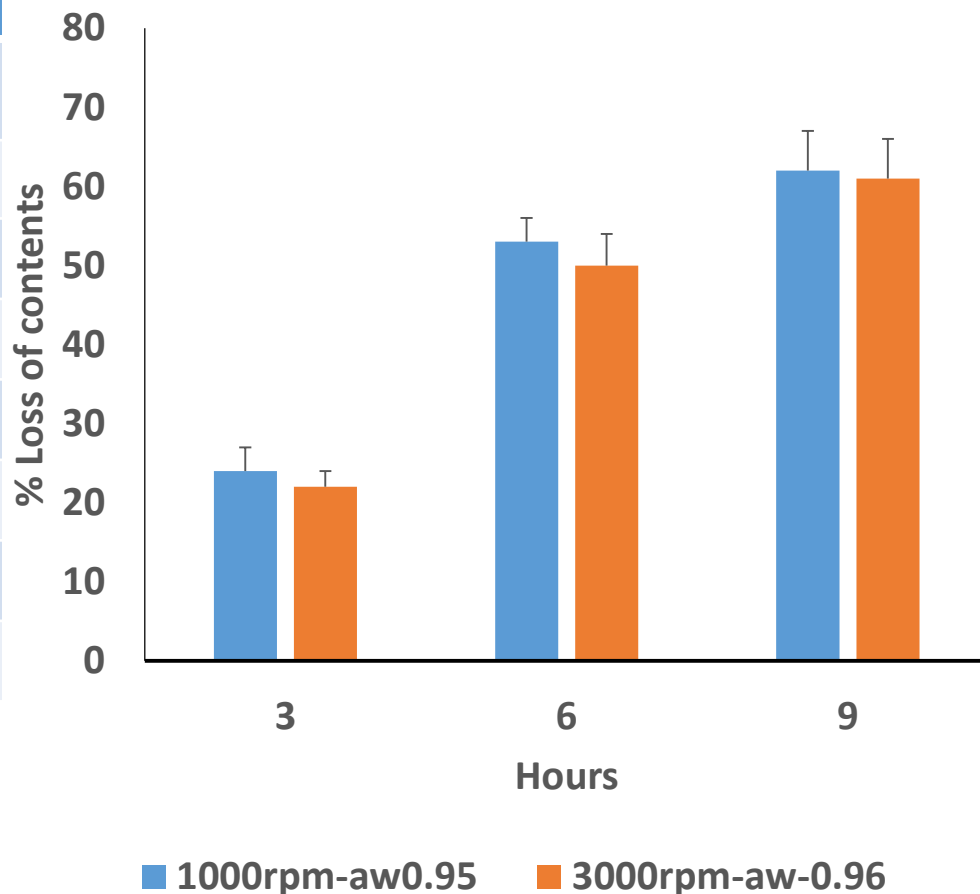
Aciclovir -1A



Solvent activity of Q1 & Q2 identical Creams

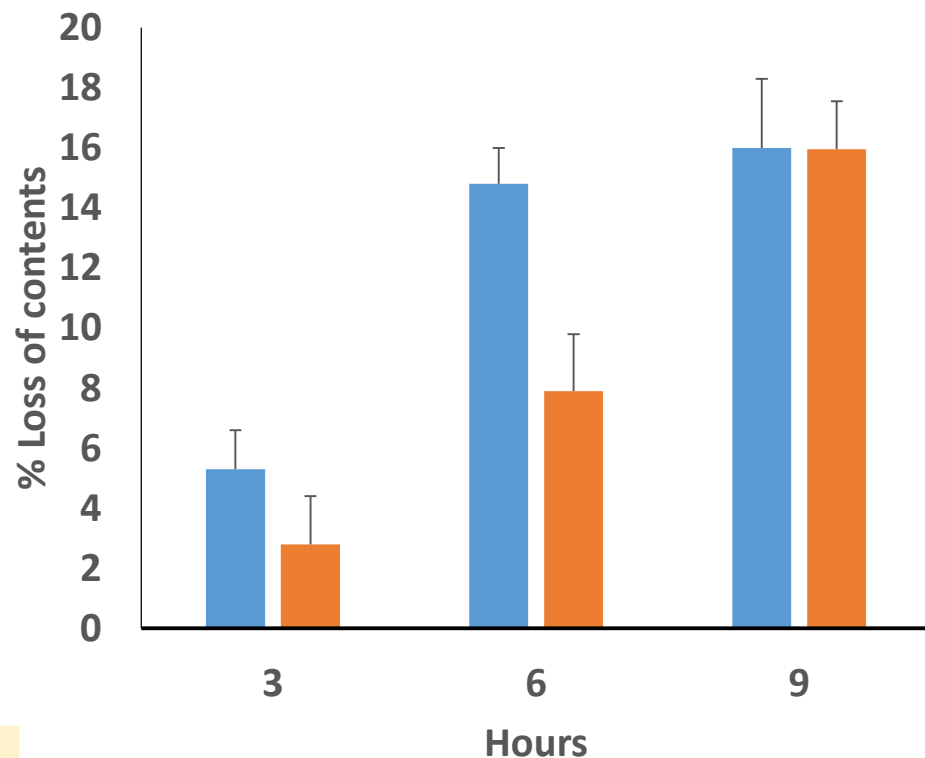
Ingredients (O/W)	Quantity (%)
Drug	1
Cetostearyl alcohol	7
Cremophor A6	1.5
Cremophor A25	1.5
Mineral Oil	12
Propylene Glycol	8
Water	69
Total	100

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



Solvent activity of Q1 & Q2 identical Creams

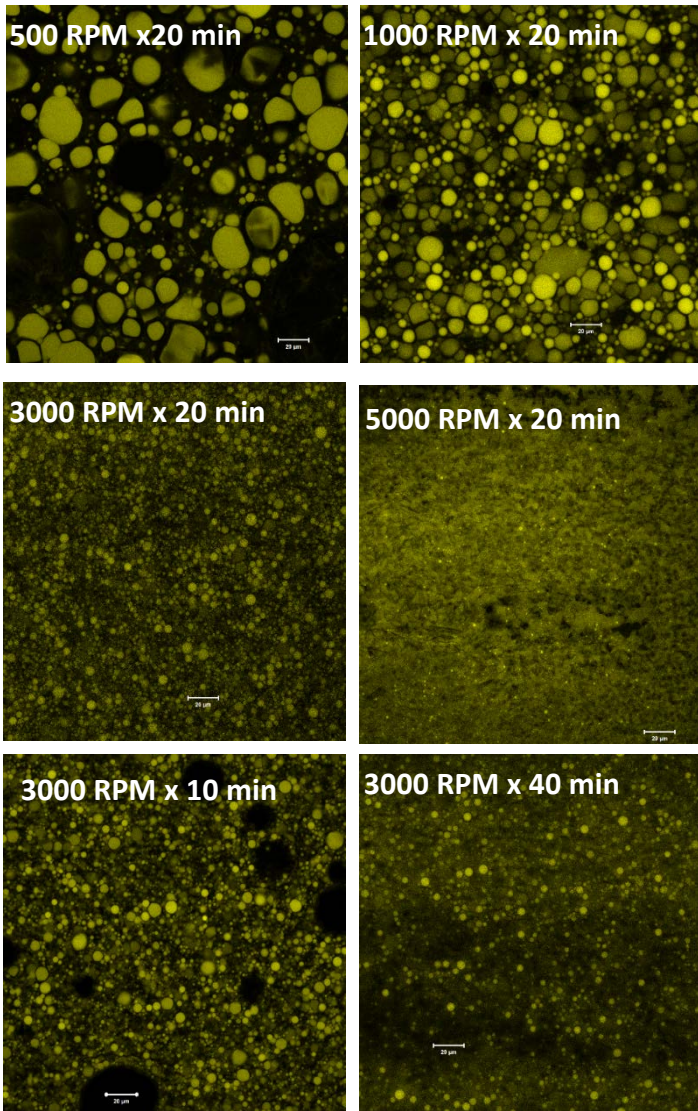
Ingredients (W/O)	Quantity (%)
Cetostearyl Alcohol	12.5
White Wax	12
Mineral Oil	56
Sodium Borate	0.5
Water	19
Total	100



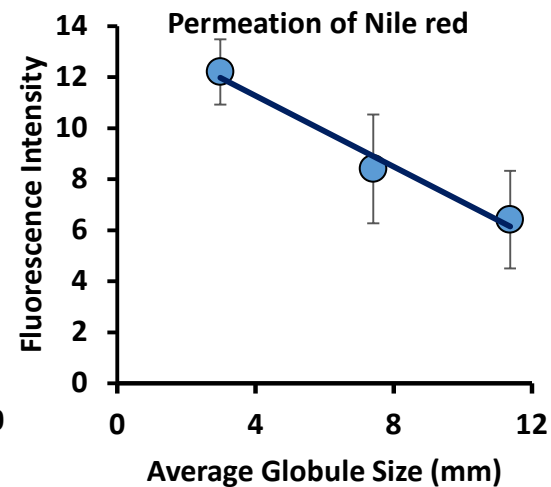
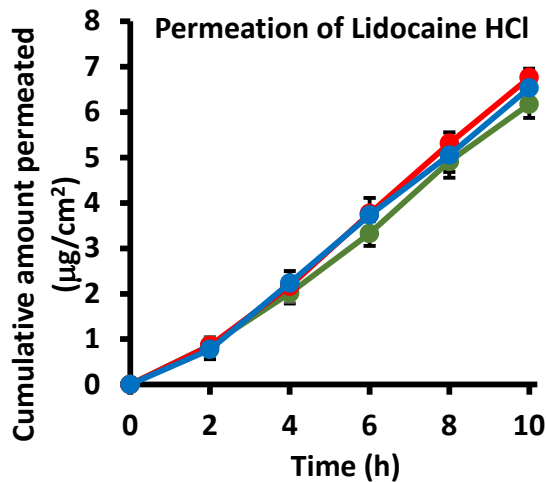
Manufacturing Conditions	Solvent Activity (a_w)
3500 RPM (15 min)	0.931 ± 0.002
7000 RPM (45 min)	0.875 ± 0.006

■ 3500 rpm-aw 0.93 ■ 7000rpm-0.87

Globule size

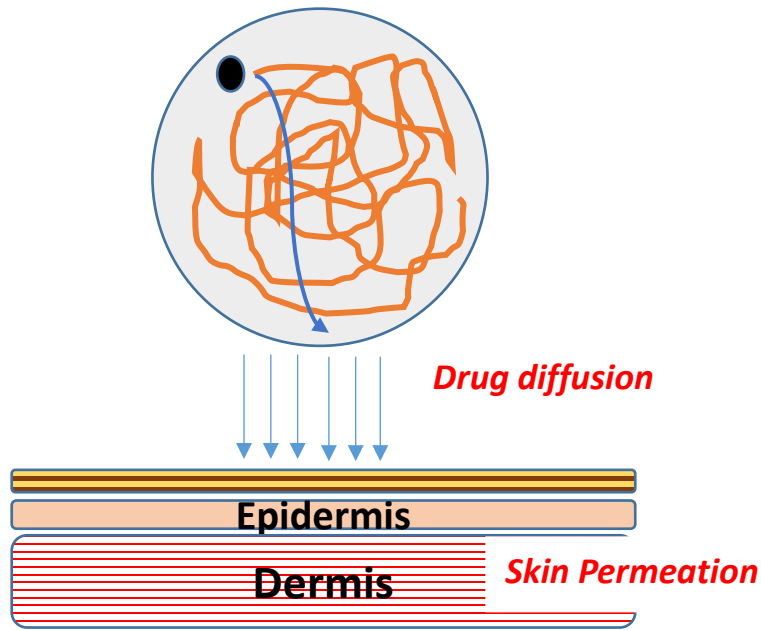


Formulation Code	Variable	Globule Size (um)
F1	500 rpm x 20 min	11.37 ±7.03
F2	1000 rpm x 20 min	7.41 ±2.19
F3	3000 rpm x 20 min	2.98 ±1.25
F4	5000 rpm x 20 min	1.71±0.41
F5	3000 rpm x 10 min	4.30±1.33
F6	3000 rpm x 40 min	4.36±0.88
F7	3000 rpm x 20 min Ambient cooling	4.25±0.99



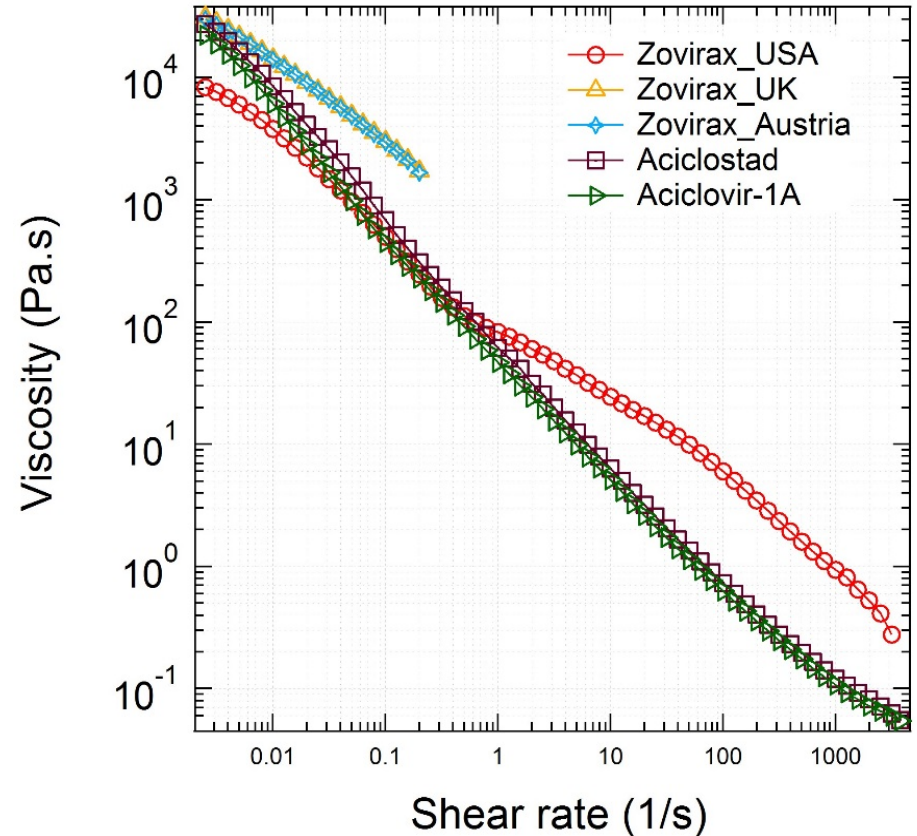
● 1000 RPM ● 3000 RPM ● 5000 RPM

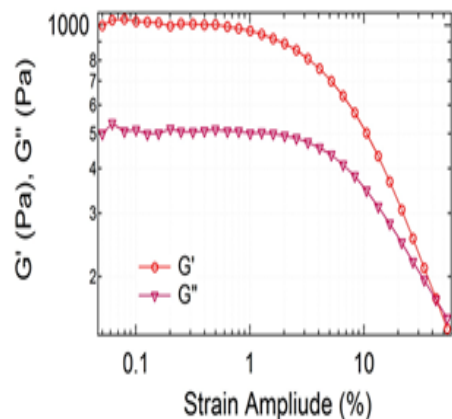
Rheological Studies



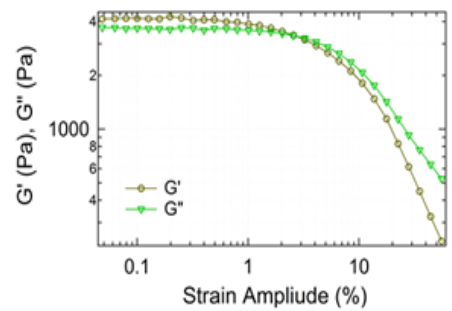
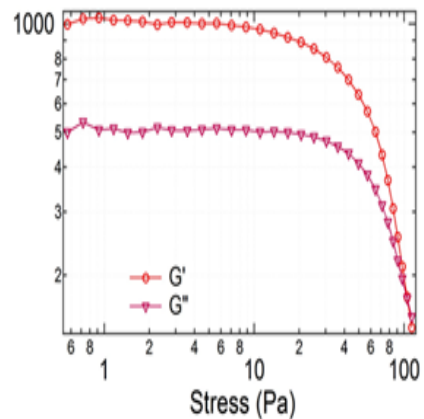
Rheology of a formulation is a direct function of microstructure.

Diffusivity inversely scales with the viscosity of the media.

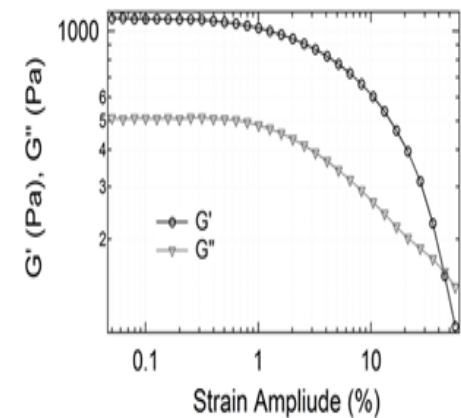
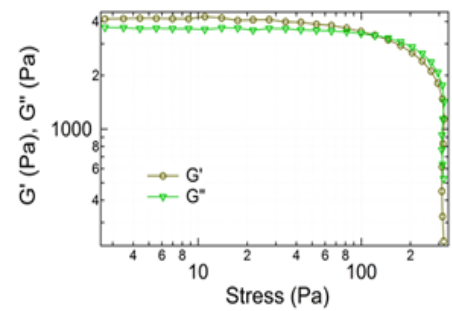




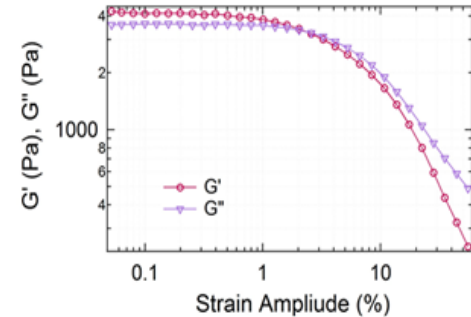
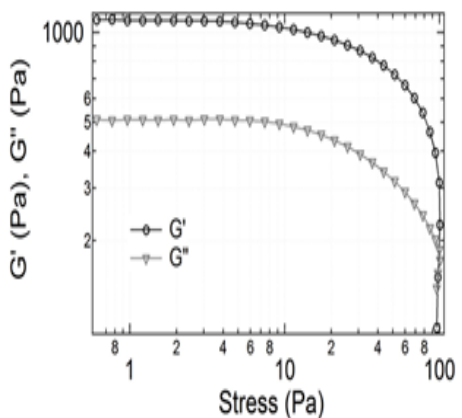
Storage (G') and Loss (G'') moduli as a function of strain (a) and stress (b) for Zovirax-USA.



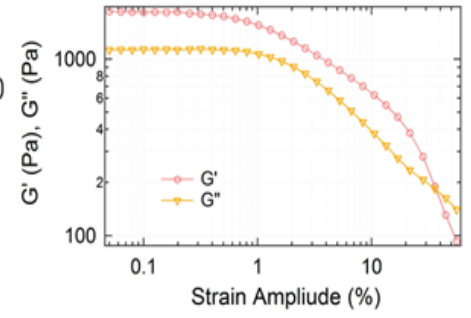
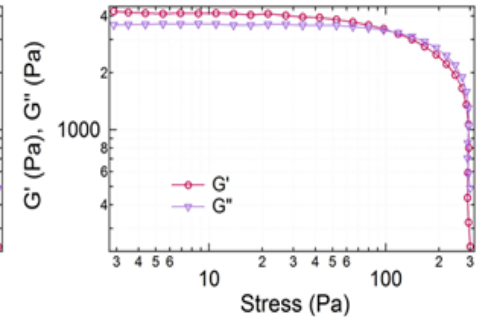
Storage (G') and Loss (G'') moduli as a function of strain (a) and stress (b) for Zovirax-UK.



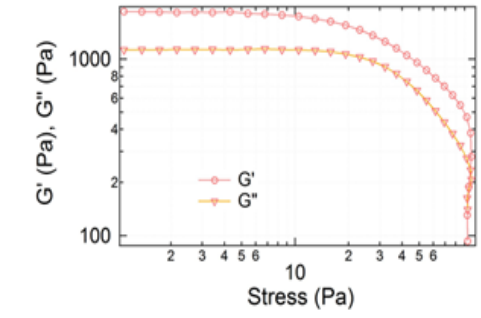
Storage (G') and Loss (G'') moduli as a function of strain (a) and stress (b) for Aciclovir



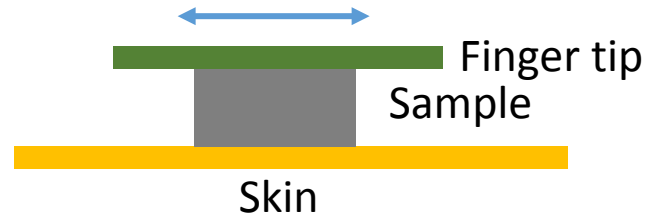
Storage (G') and Loss (G'') moduli as a function of strain (a) and stress (b) for Zovirax-Austria



Storage (G') and Loss (G'') moduli as a function of strain (a) and stress (b) for Aciclostad



Shear Rate Estimation



Initial application

Initial sample thickness (d): 5 mm

Skin area: 1" X 1"

Sample is spread @ 2 cycles/s

Finger tip velocity (V): 0.1 m/s

Estimated Shear rate = $V/d = 20 \text{ s}^{-1}$

During spreading

Sample thickness (d): 30 micrometers

Skin area: 1" X 1"

Sample is spread @ 2 cycles/s

Finger tip velocity (V): 0.1 m/s

Estimated Shear rate = $V/d = 3333 \text{ s}^{-1}$

Product	Viscosity, Pa. s			Yield Stress, Pa
	@ shear rate: 20 s^{-1}	@ shear rate: 3300 s^{-1}	@ shear rate: 0.0025 s^{-1}	
Zovirax-USA	17	0.28	8360	50
Zovirax-UK	N/A	N/A	31000	300
Zovirax-Austria	N/A	N/A	30100	300
Aciclostad	3.2	0.06	29300	100
Aciclovir- 1A	2.6	0.06	28100	100

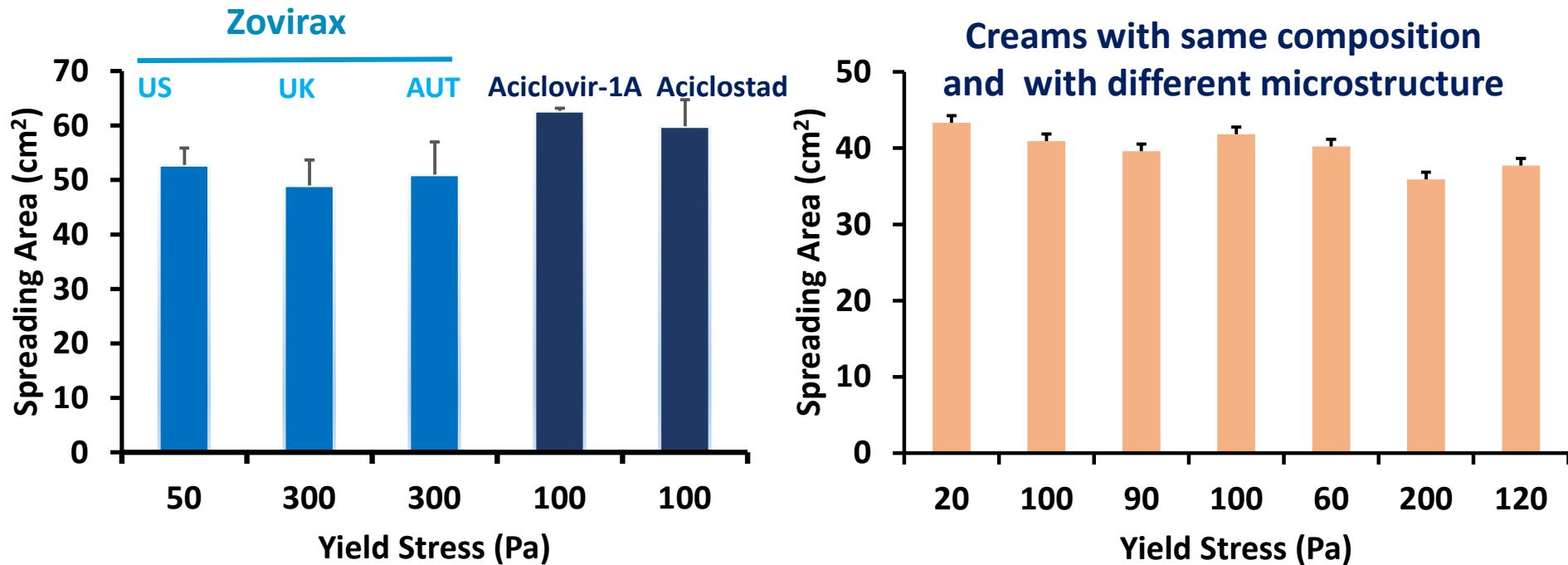
Dictates the behavior during the initial application

Dictates the behavior during spreading the sample on the skin

Dictates at rest condition, i.e., diffusion of drug through thin film

Clinical relevance of Rheological factors

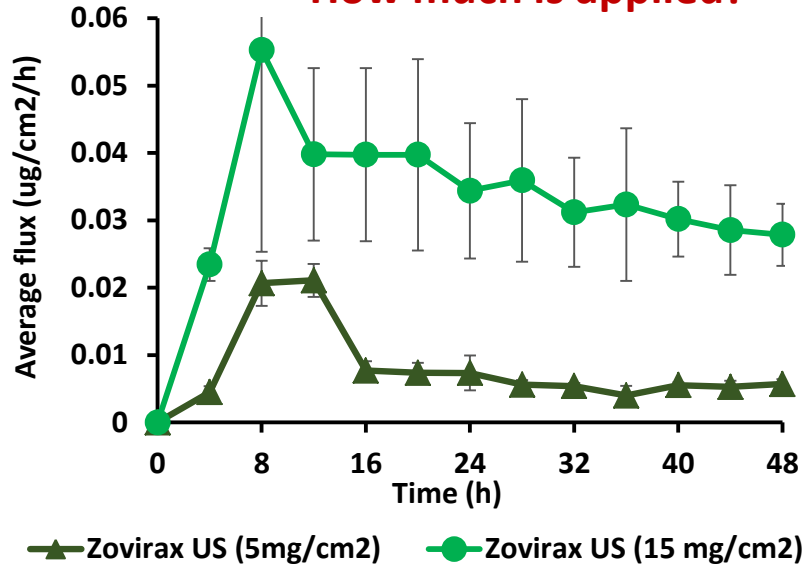
- Rheology of the sample would influence the area of application which in turn could affect the permeation profile.



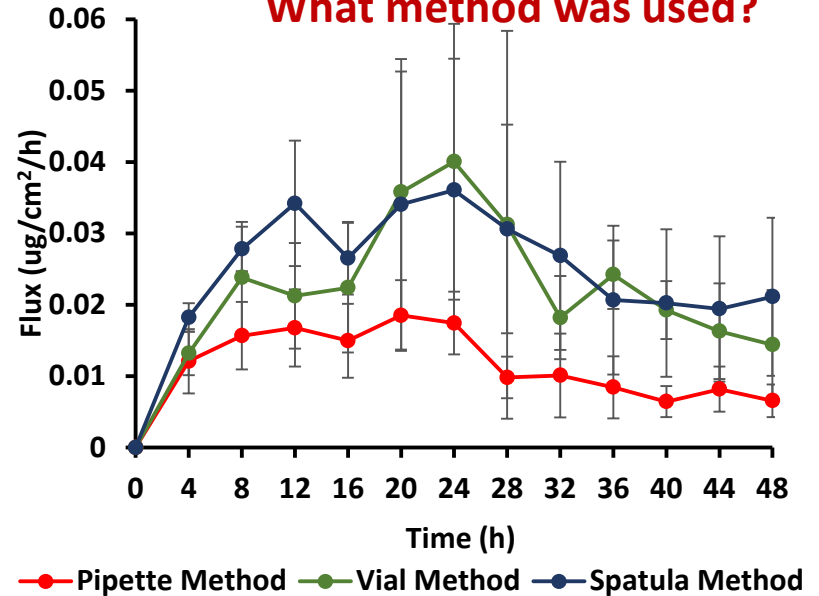
Area of formulation application by three individuals on six volunteers. (Each data Mean $n=3 \pm \text{SEM}$)

In vitro Permeation Testing

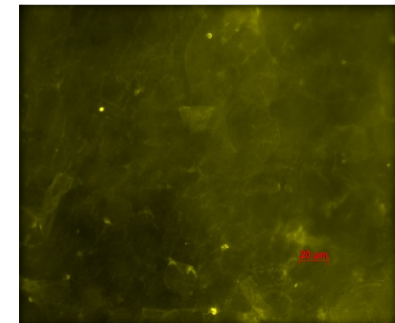
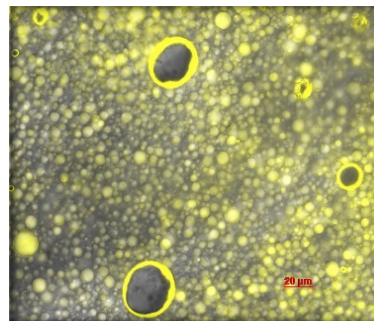
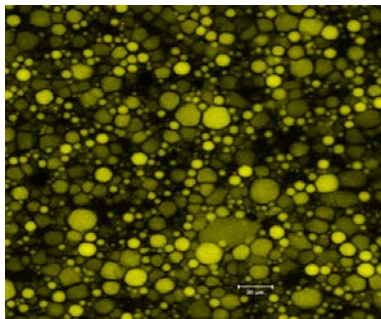
How much is applied?



What method was used?



How intensely was it applied?



Gentle application → Rubbing → Intense Rubbing

Conclusions

- The microstructural differences in topical products could influence the performance of products. However, the relative contribution of individual quality attribute would differ from one to another.
- There is an urgent need to identify and develop a toolkit to characterize the microstructural differences in topical products.
- IVPT is a great tool to determine the performance of the products. While comparing multiple products, the emphasis should be to follow exact same protocol for all products.
- Preferable to run multiple donors (cadavers) and replicates. For each donor, all products be run simultaneously.

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