

Characterizing Failure Modes and Critical Quality (Q3) Attributes of Semi-Solid Topical Drug Products

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Some of the characterizations that we generally consider for topical products include

- pH of the formulation
- Dissolved/Undissolved drug
- Particle size
- Polymorphism
- Rheological Studies
- Water or Solvent activity
- Globule size

Model Topical Cream Products

5%w/w Acyclovir Creams

Zovirax (US)

Zovirax(UK)

Zovirax (AUT)

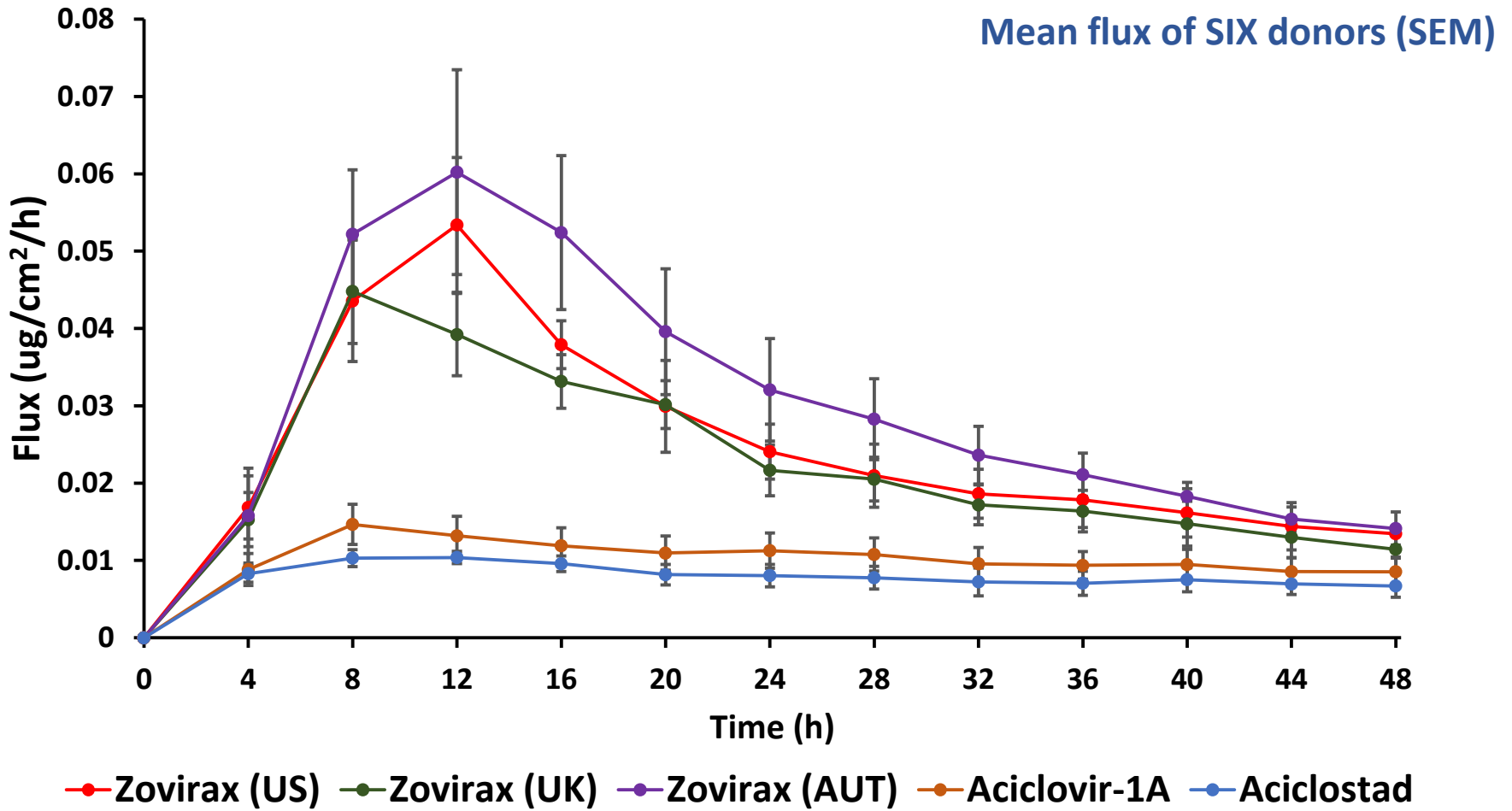
Aciclovir- 1A

Aciclostad

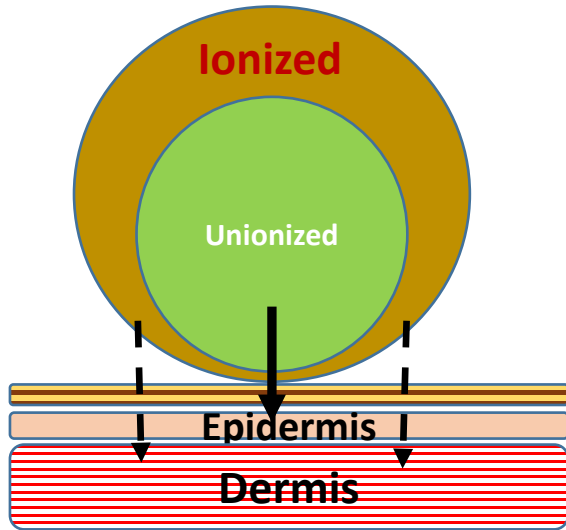
Austria

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

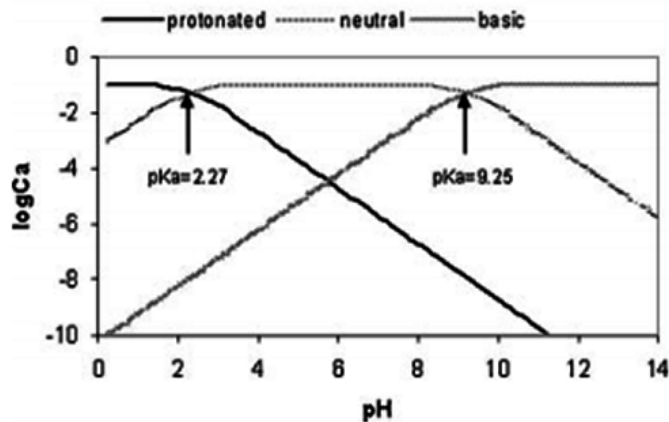


InLab Micro

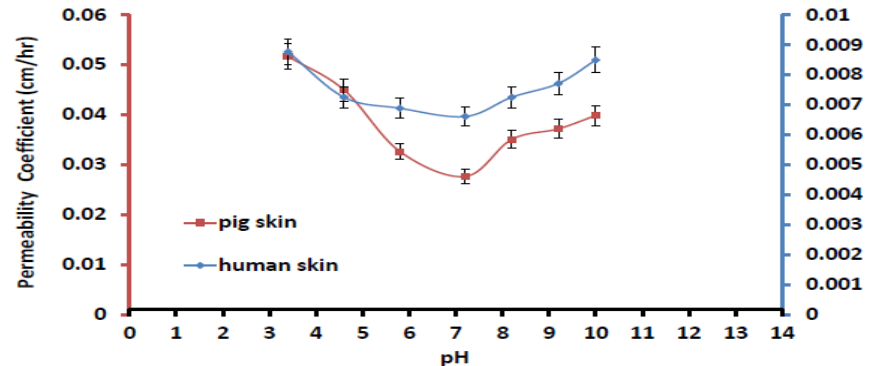
Suggestions

- 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.

Acyclovir Ionization Profile



pH vs Total Permeability Coefficient

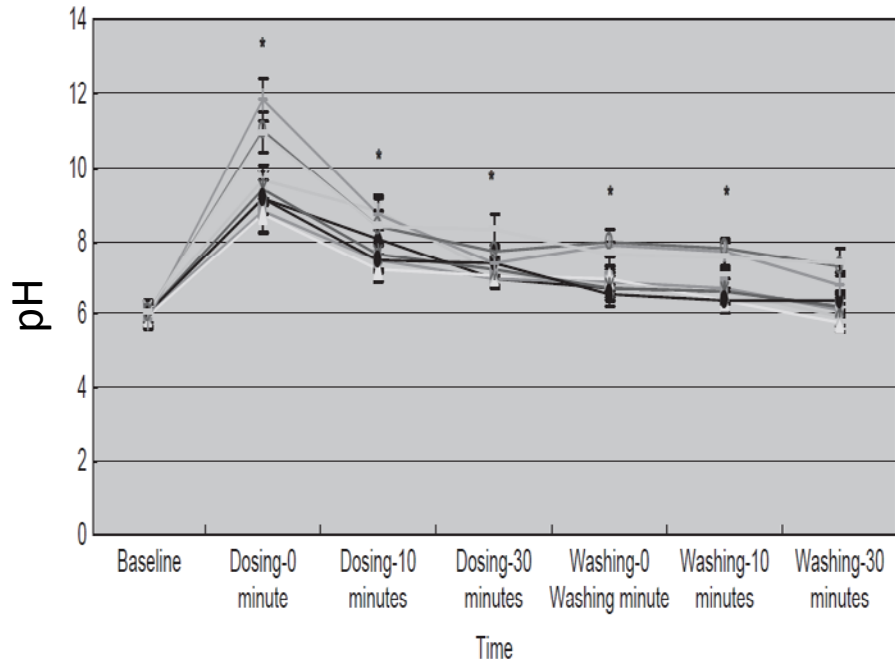


Shukla et al, *In vivo* quantification of acyclovir exposure in the dermis following iontophoresis of semisolid formulations. J Pharm Sci 2009; 98:917-25

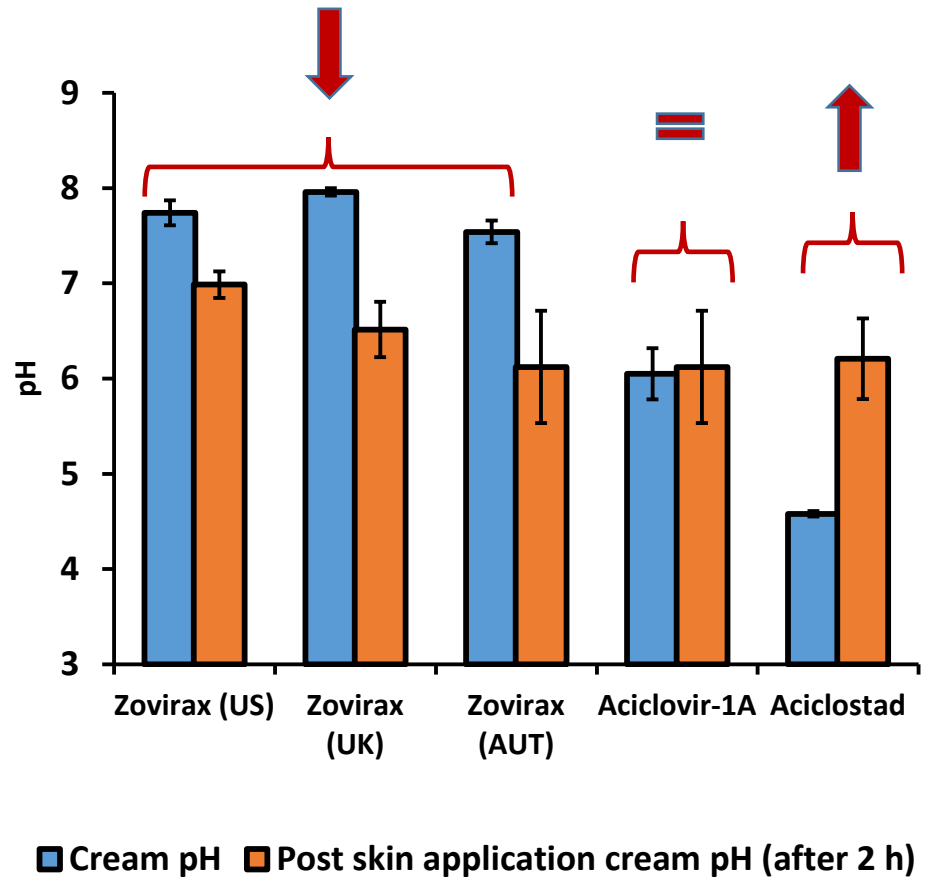
Lingamaneni V, Patel SB. Effect of different pH on permeability of acyclovir through pig skin and human cadaver skin. AAPS Annual meeting and Exposition; November 2-6, 2014; San Diego, Poster W5078

Potential Failure Mode (pH)

Buffer Capacity of skin

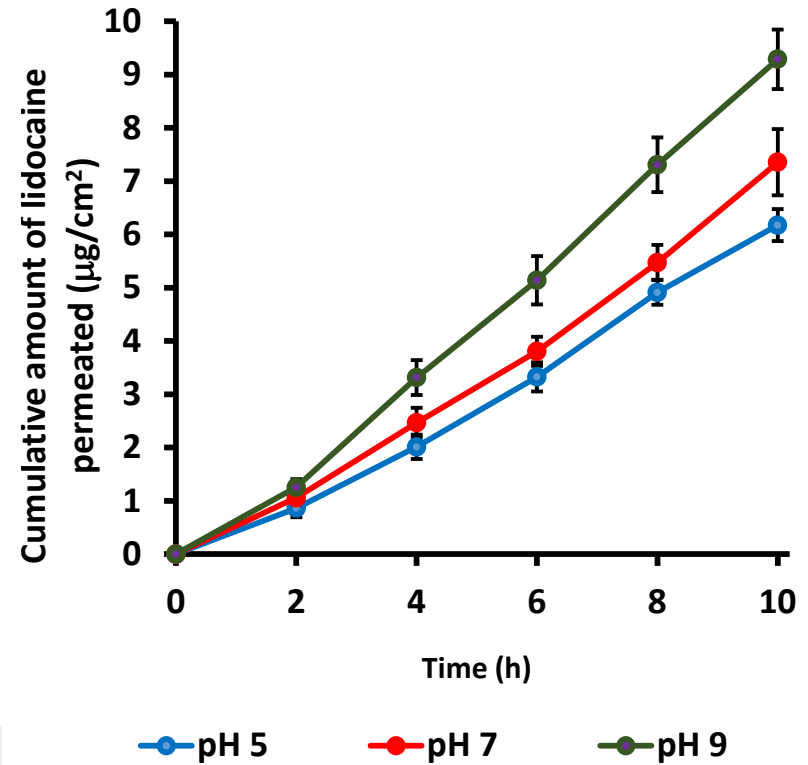
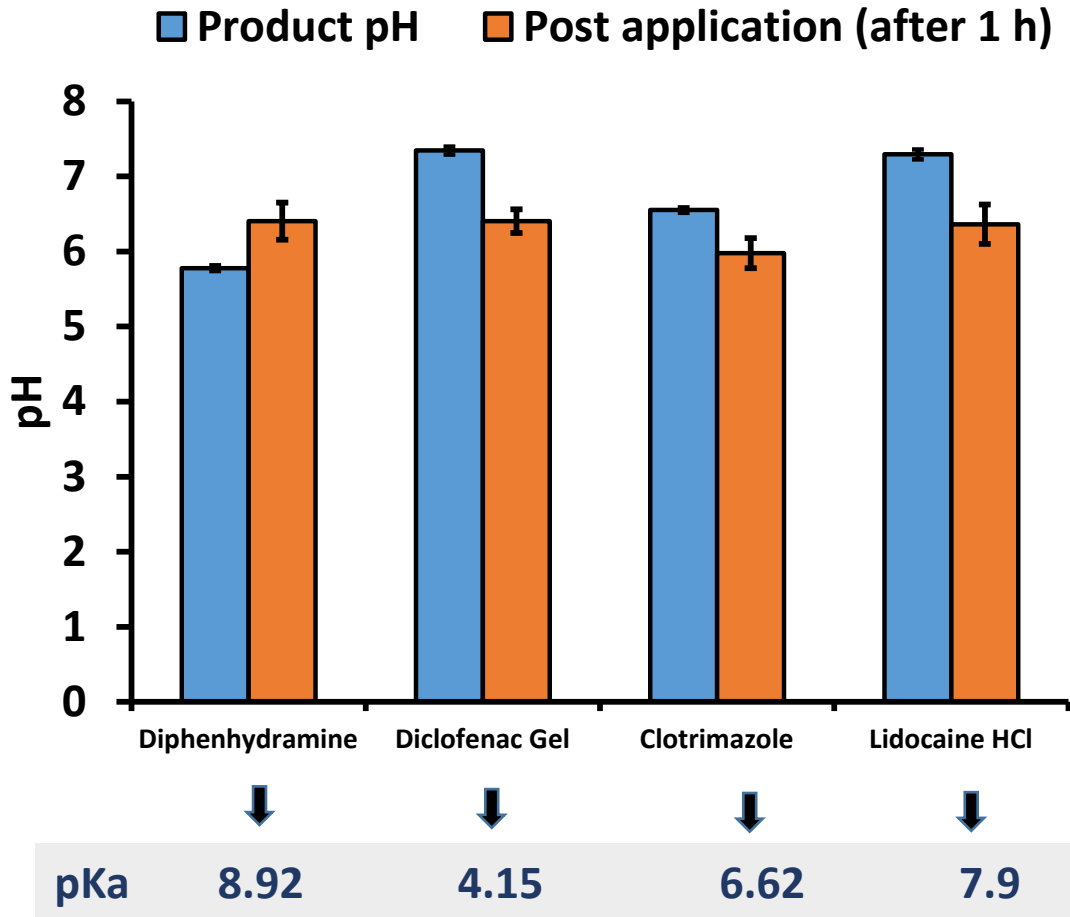


Post application pH of formulation

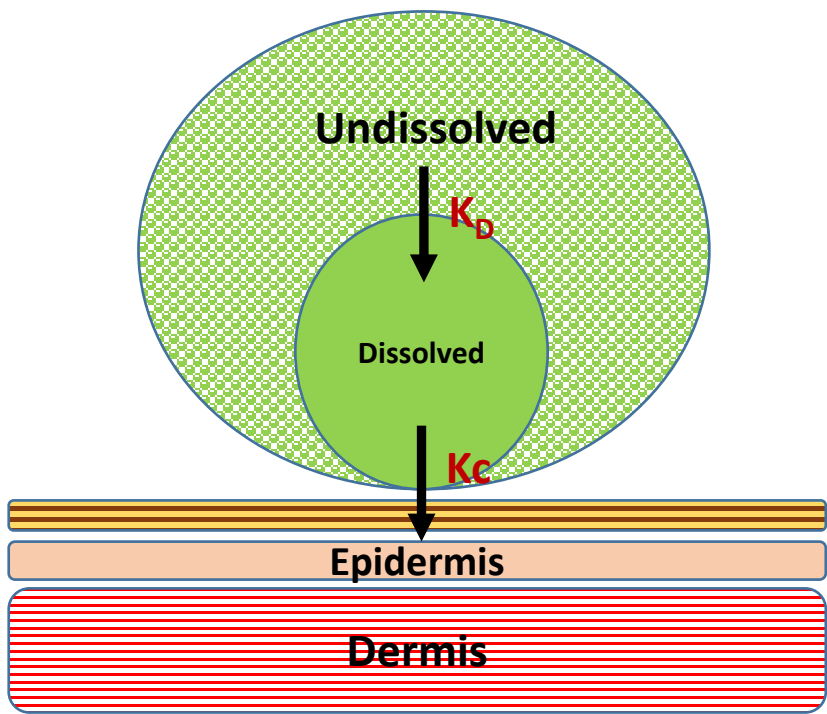


■ Cream pH ■ Post skin application cream pH (after 2 h)

Potential Failure Mode (pH)

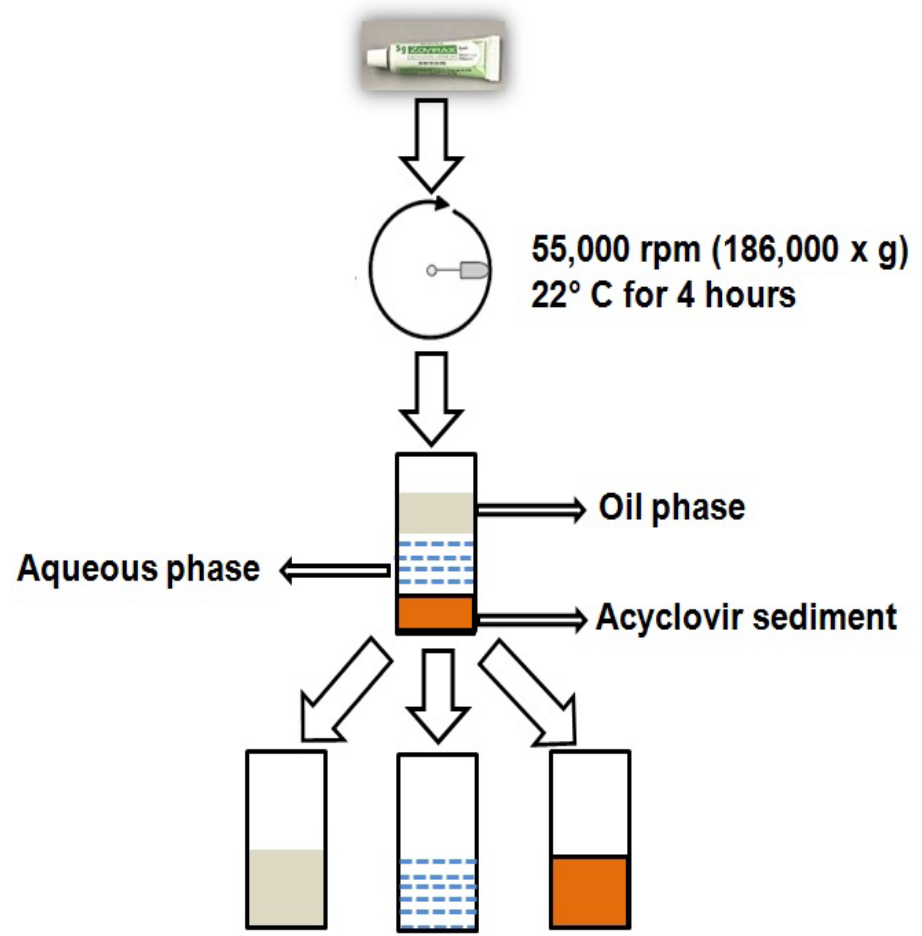


Drug Absorption from Topical Product



Dissolved Drug
Undissolved Drug

Phase Separation



Dissolved/Undissolved drug

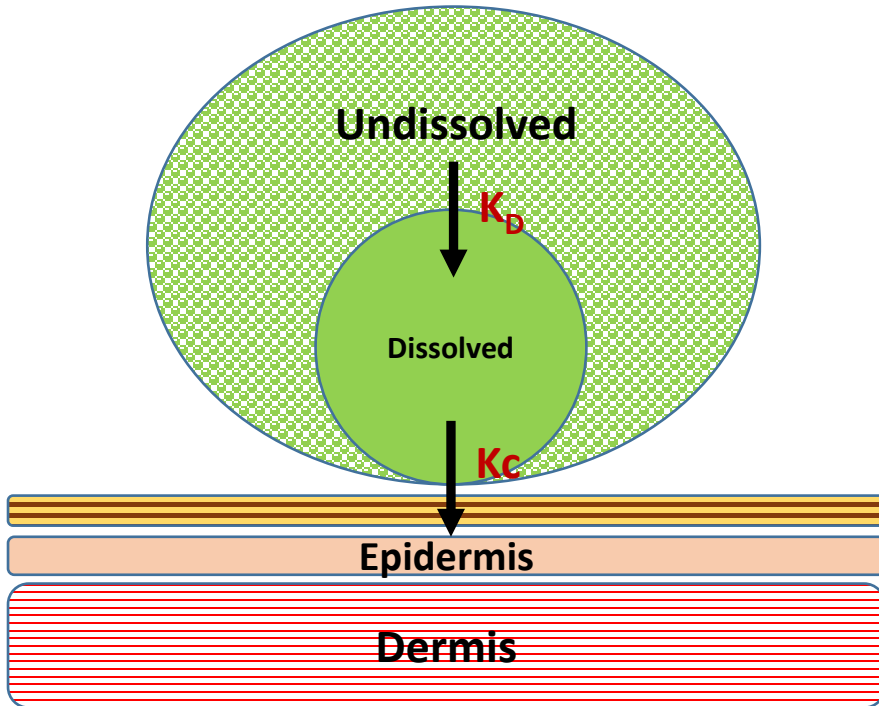
Product	Total dissolved acyclovir in cream (mg/g)	Total undissolved acyclovir in cream (mg)	D/UD	Amount Dissolved in Aqueous Phase (mg/g)
ZOVIRAX (US)	1.354±0.048	48.65±0.05	0.0278	0.492±0.085
ZOVIRAX (AUT)	2.459±0.161	47.57±0.16	0.0517	0.641±0.049
ZOVIRAX (UK)	1.326±0.046	48.67±0.05	0.0272	0.488±0.010
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

Drug Absorption from Topical Product

$$K_D \geq K_c$$

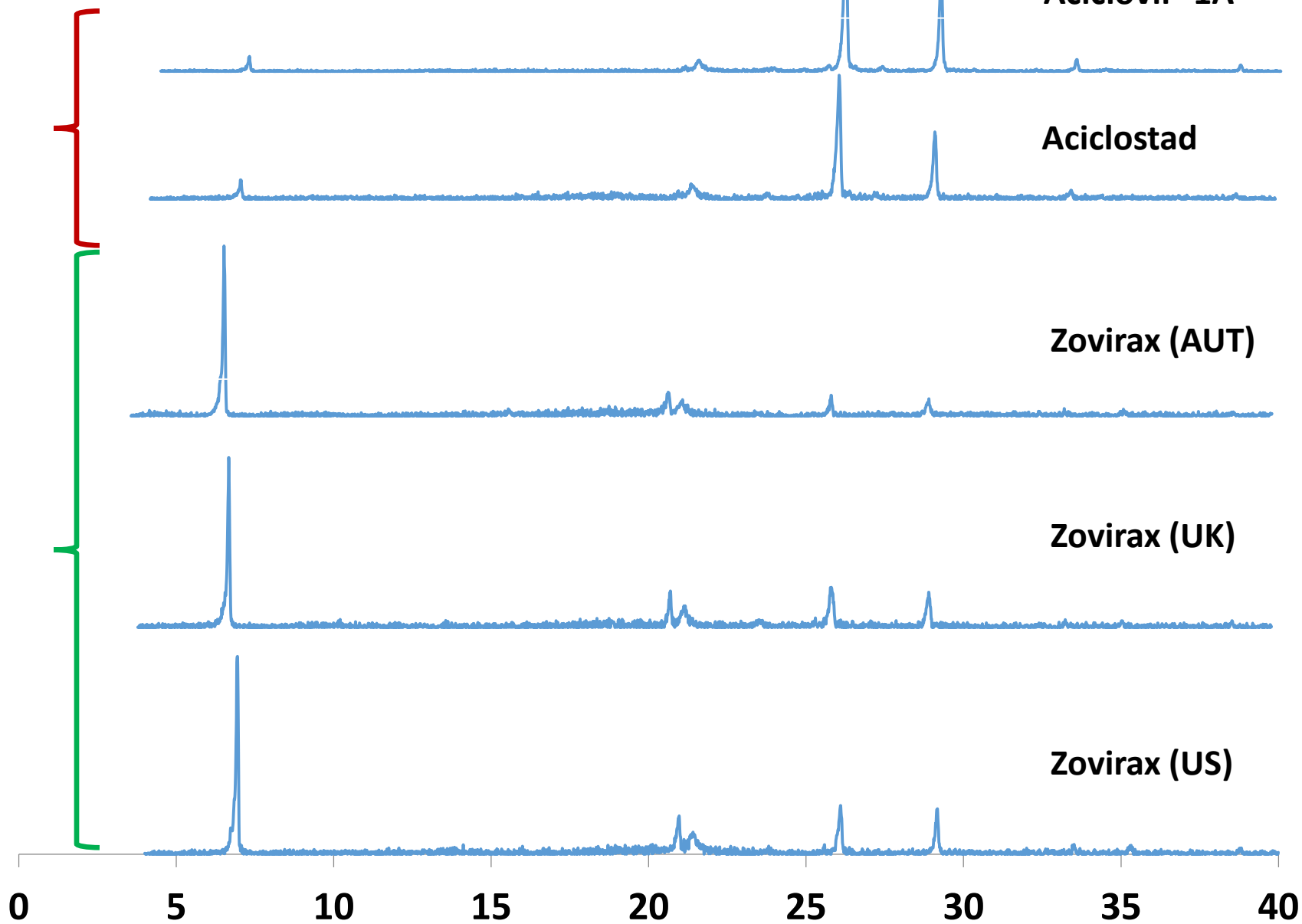
Rate of Dissolution of Drug

- Particle Size
- Polymorphic form
- Morphology of particles



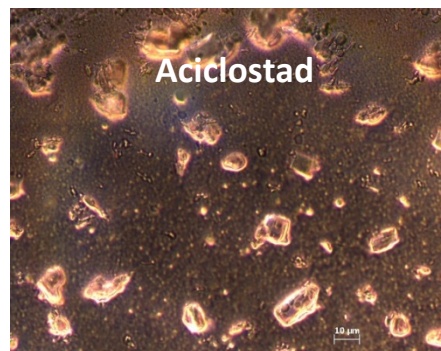
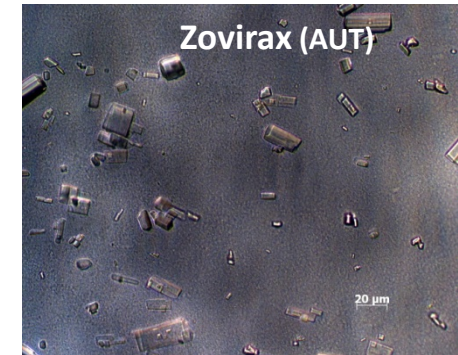
Dose	Total Drug	Dissolved Drug	Undissolved drug
5mg/cm ²	250 ug/cm ²	6.25ug/cm ²	243.75ug/cm ²

Polymorphic form



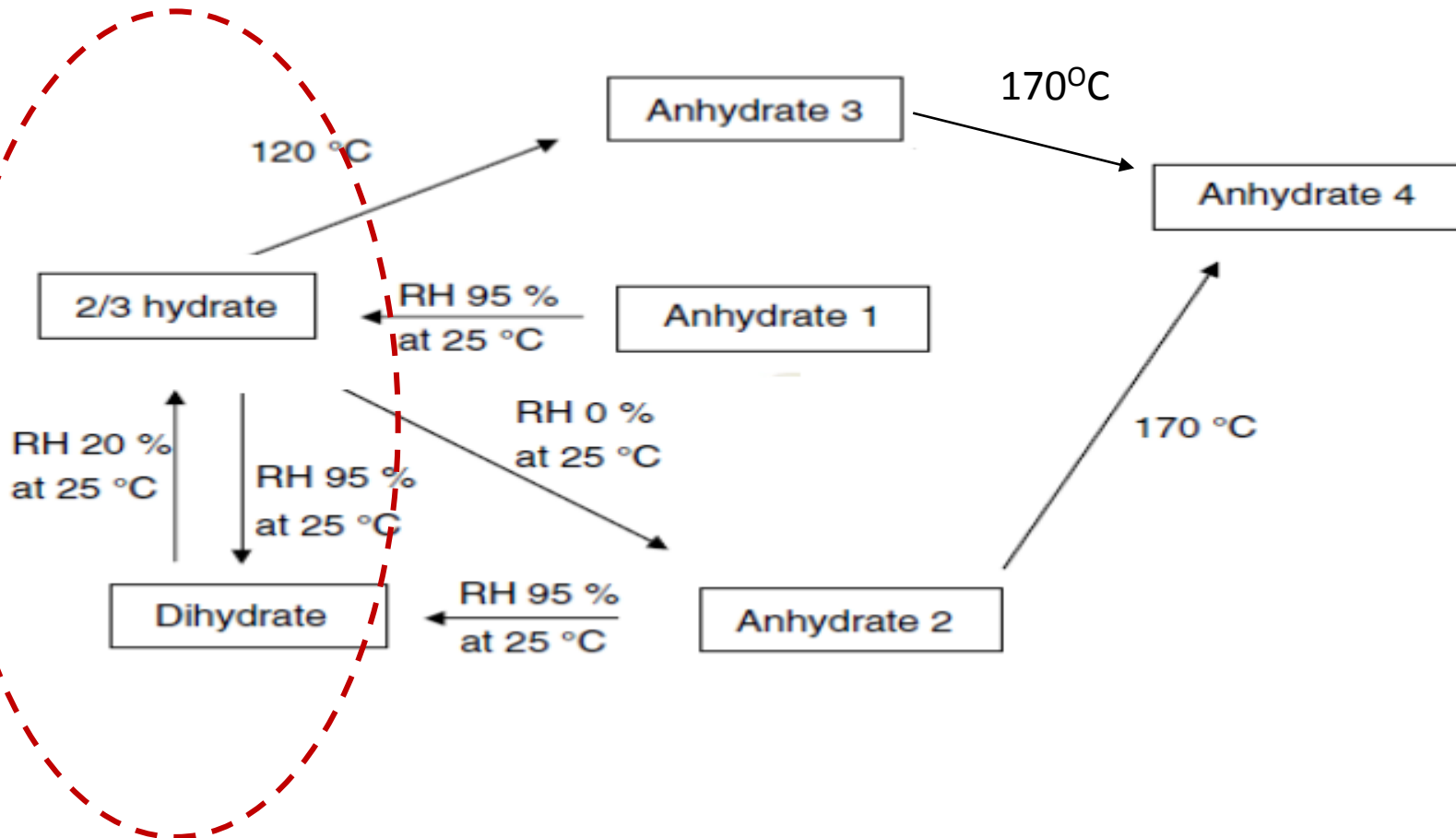
Particle Size and Morphology

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



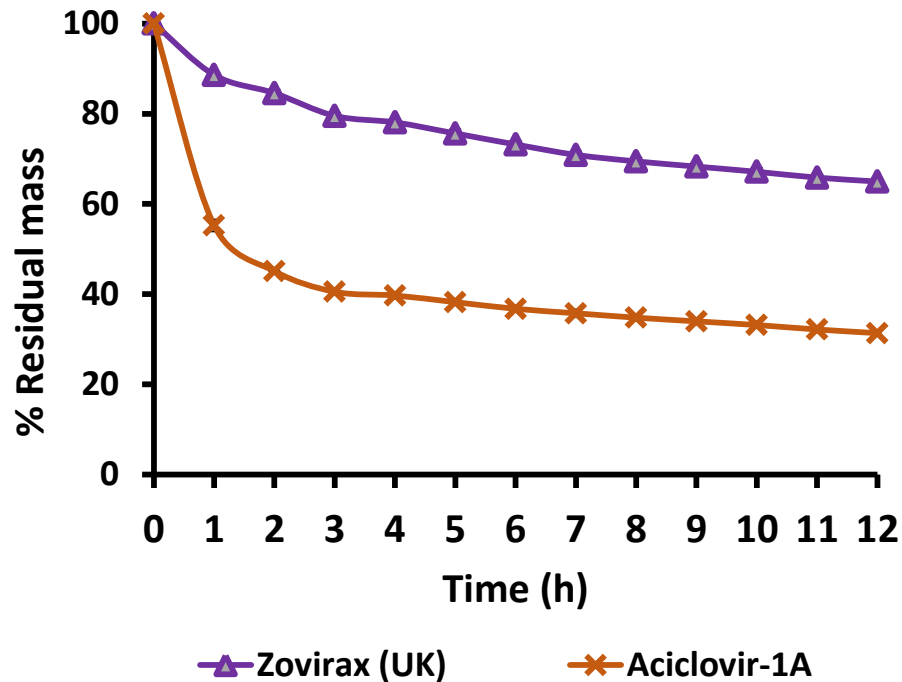
Potential Failure Modes (Polymorphic form)

- Transformation of one polymorphic form to other post application



Potential Failure Modes (D/UD)

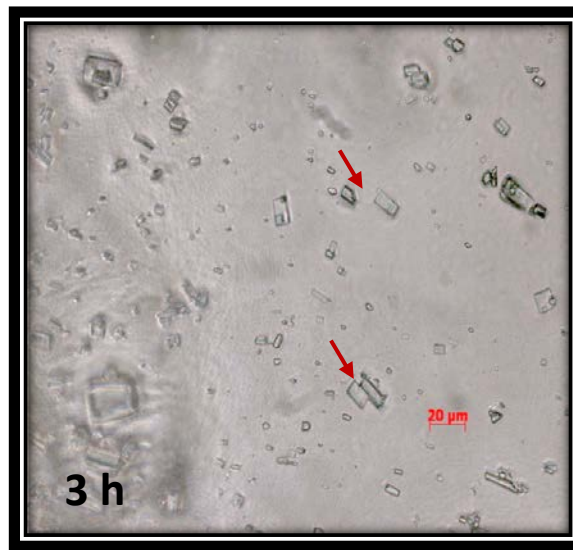
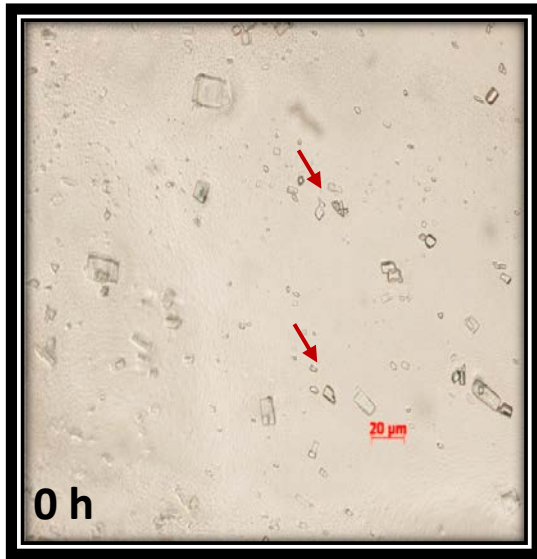
- Change in Solubility depending on pH change in the formulation.



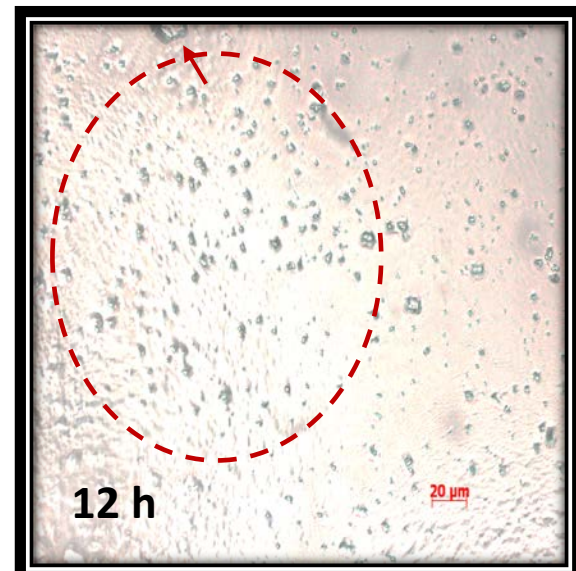
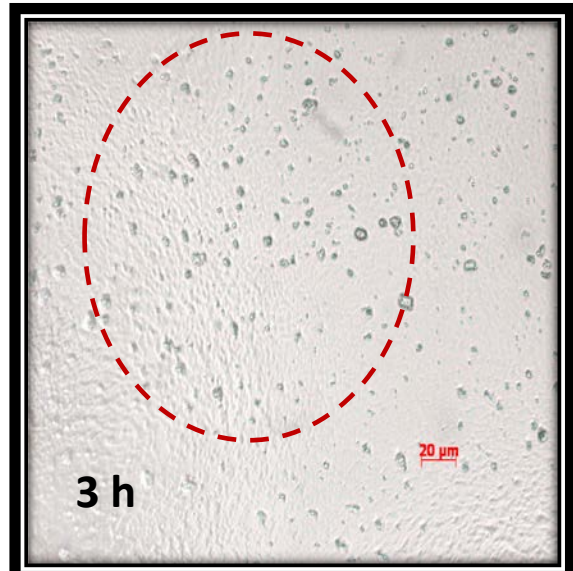
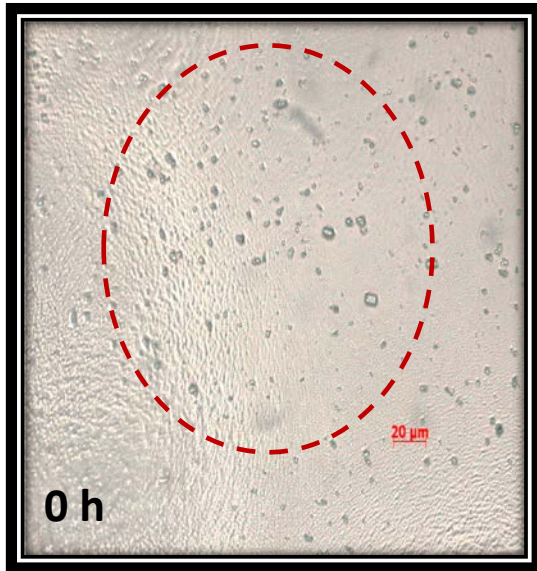
- Solvent Evaporation leading to shift in the ratio of D/UD drug.

Solvent Evaporation and Precipitation of Acyclovir

Zovirax-UK



Aciclovir -1A

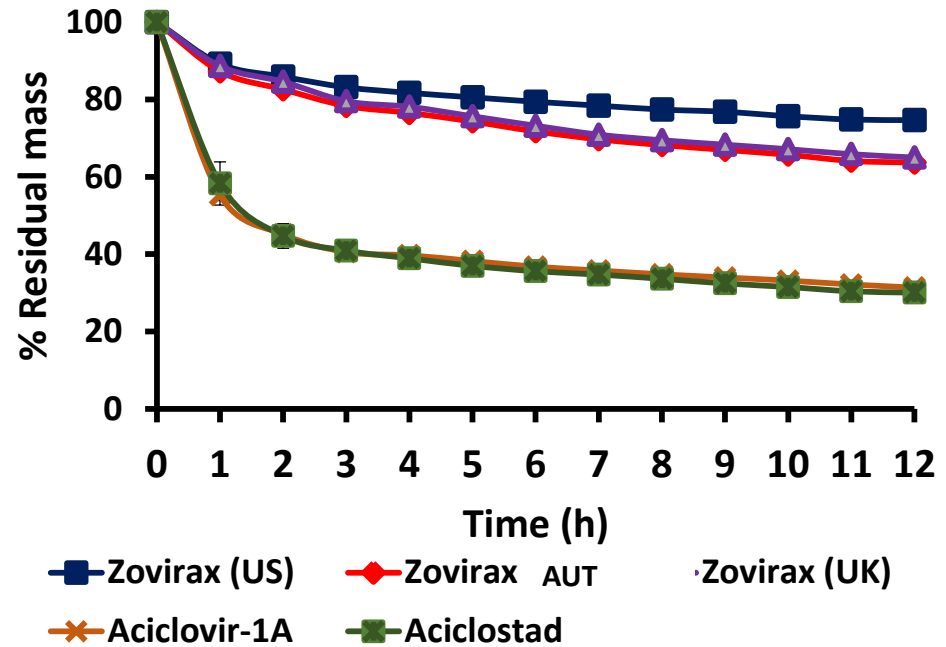
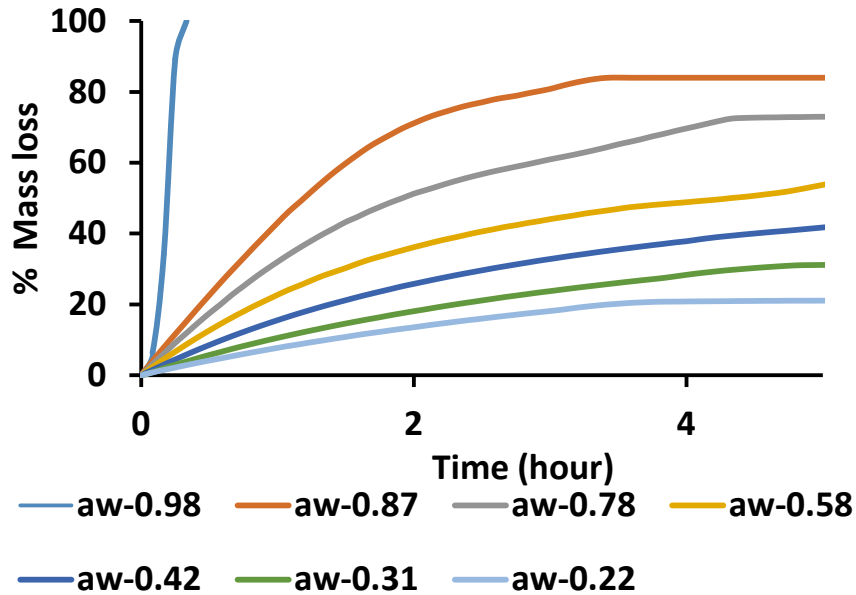


Solvent Activity (a_w)

$$a_w = \rho / \rho_0$$

ρ = partial vapor pressure of Solvents in the product

ρ_0 = vapor pressure of pure Solvent system

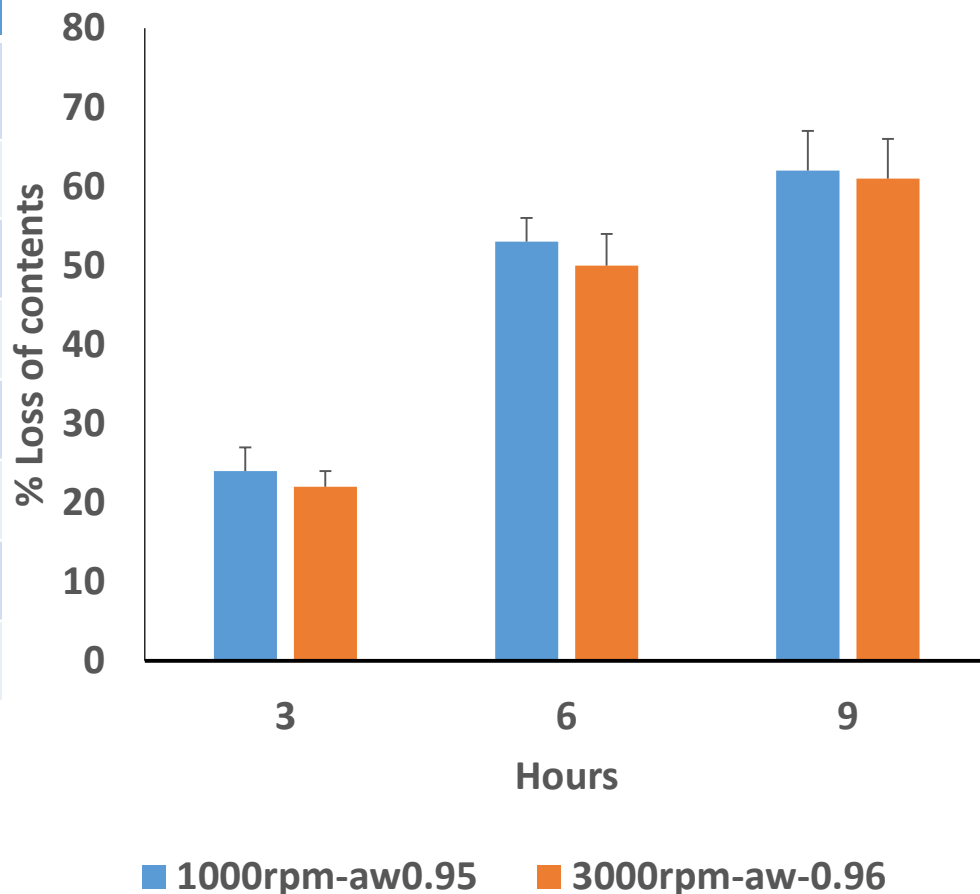


Product	Solvent Activity (a_w)
Zovirax (US)	0.753 ± 0.002
Zovirax (AUT)	0.735 ± 0.000
Zovirax (UK)	0.732 ± 0.002
Aciclovir – 1A	0.948 ± 0.001
Aciclostad	0.948 ± 0.003

Solvent activity of Q1 & Q2 similar Creams

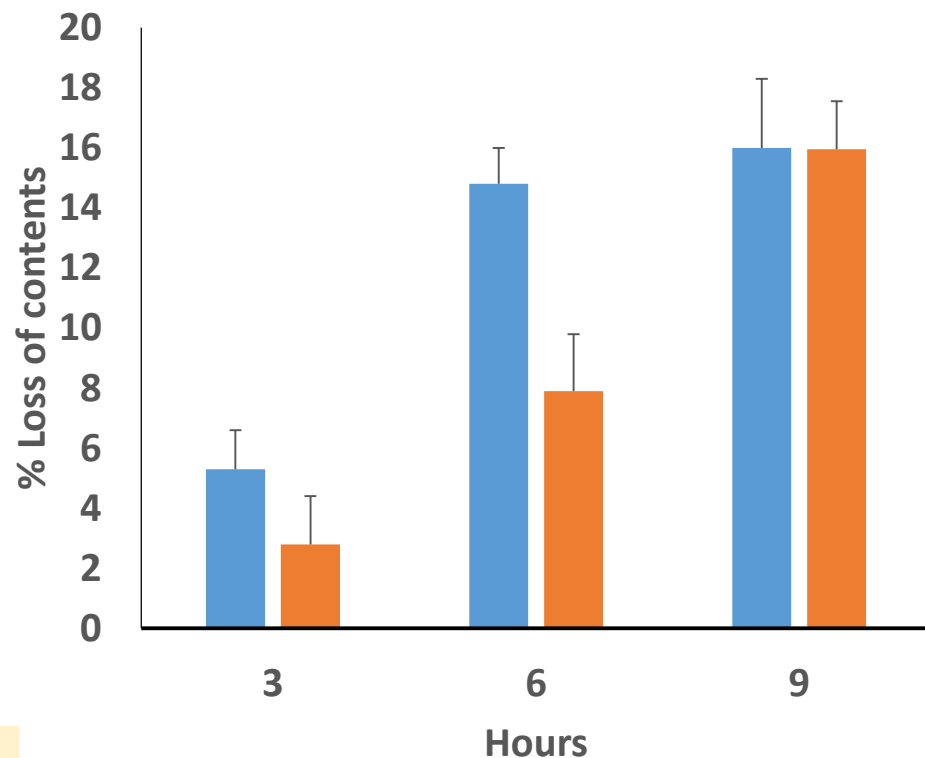
Ingredients (O/W)	Quantity (%)
Drug	1
Cetostearyl alcohol	7
Cremophor A6	1.5
Cremophor A25	1.5
Mineral Oil	12
Propylene Glycol	8
Water	69
Total	100

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 similar Creams

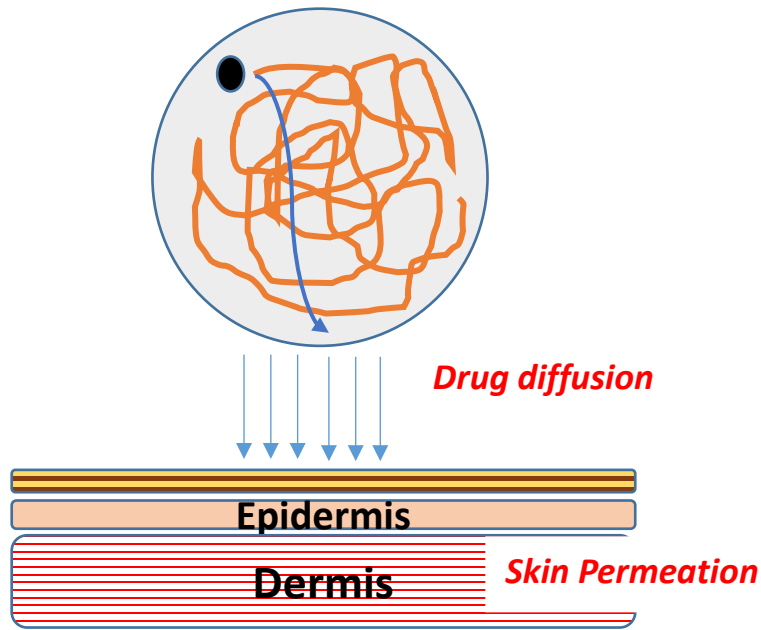
Ingredients (W/O)	Quantity (%)
Cetostearyl Alcohol	12.5
White Wax	12
Mineral Oil	56
Sodium Borate	0.5
Water	19
Total	100



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

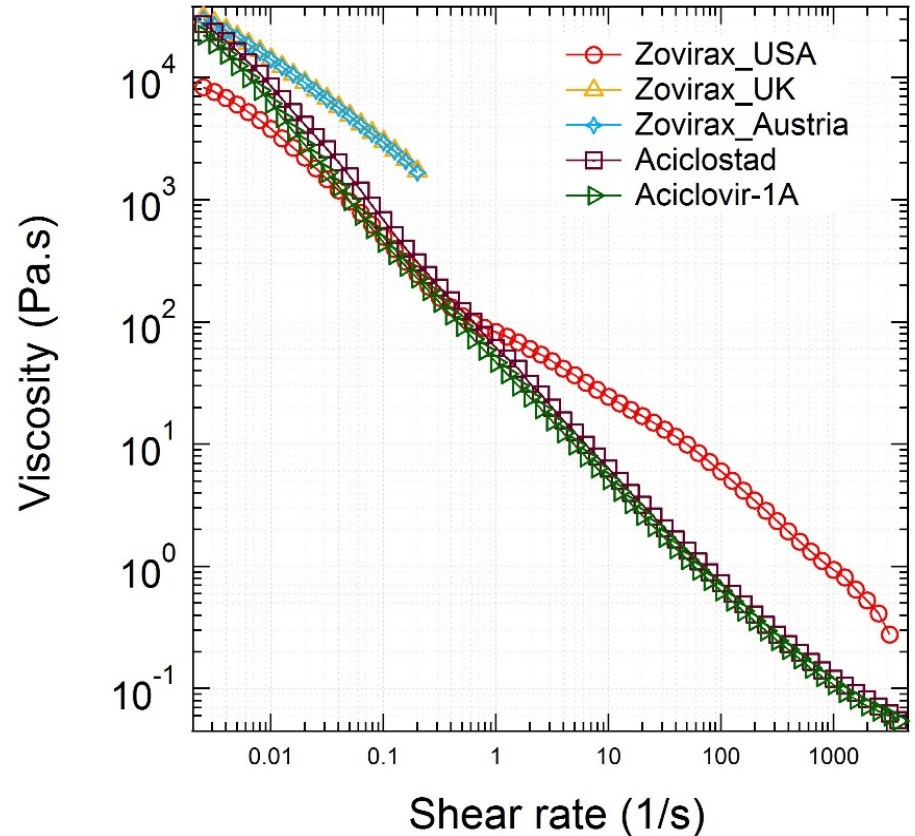
■ 3500 rpm-aw 0.93 ■ 7000rpm-0.87

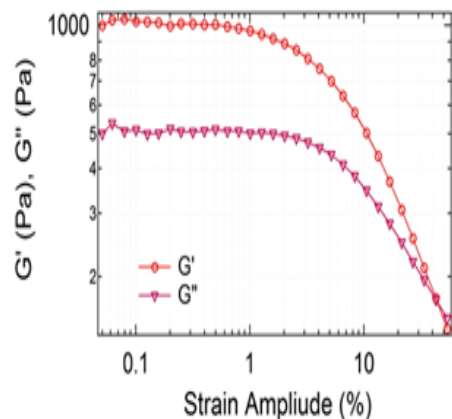
Rheological Studies



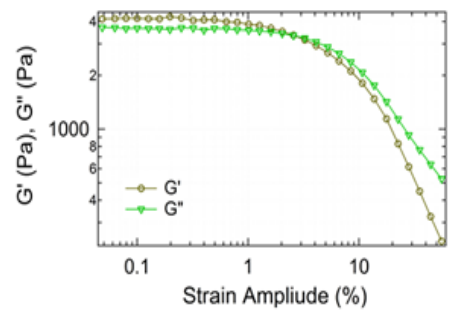
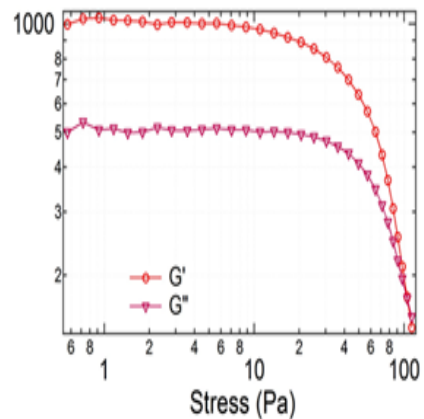
Rheology of a formulation is a direct function of microstructure.

Diffusivity inversely scales with the viscosity of the media.

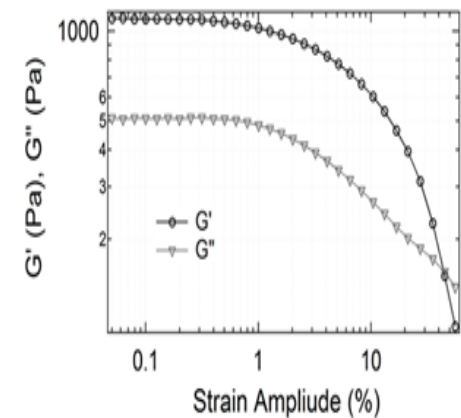
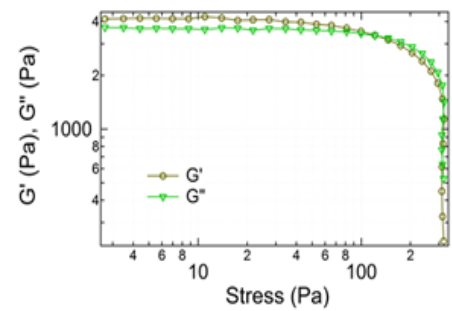




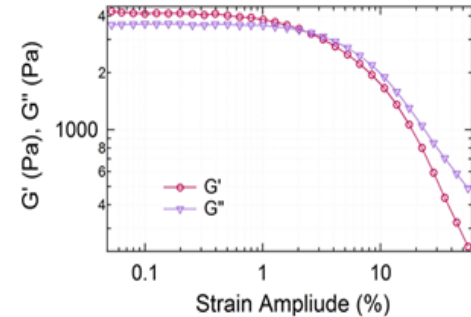
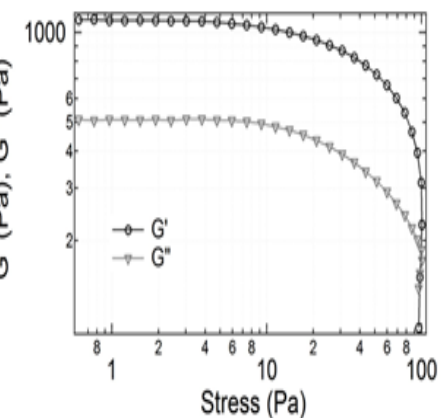
Storage (G') and Loss (G'') moduli as a function of strain (a) and stress (b) for Zovirax-USA.



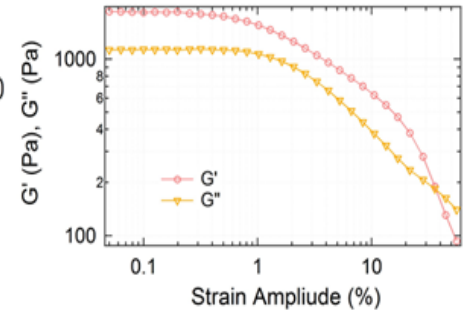
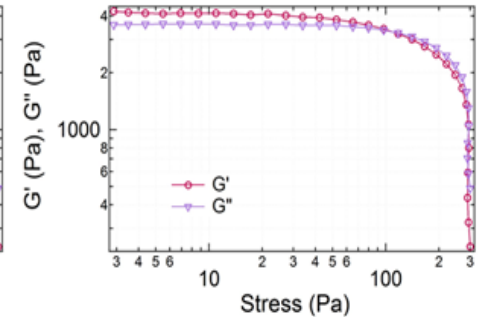
Storage (G') and Loss (G'') moduli as a function of strain (a) and stress (b) for Zovirax-UK.



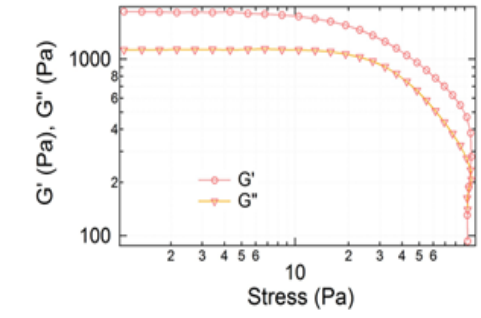
Storage (G') and Loss (G'') moduli as a function of strain (a) and stress (b) for Aciclovir



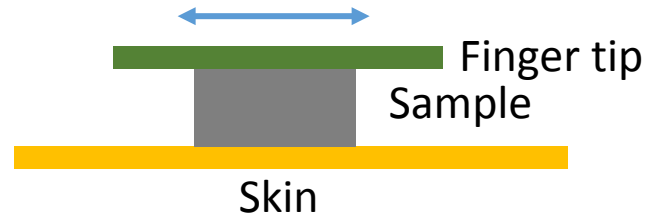
Storage (G') and Loss (G'') moduli as a function of strain (a) and stress (b) for Zovirax-Austria



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

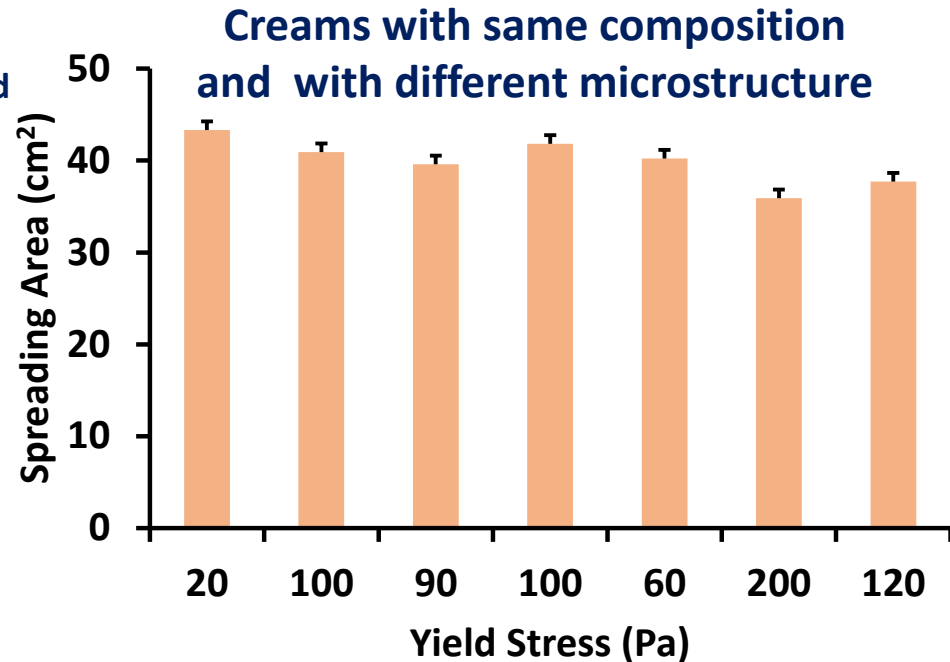
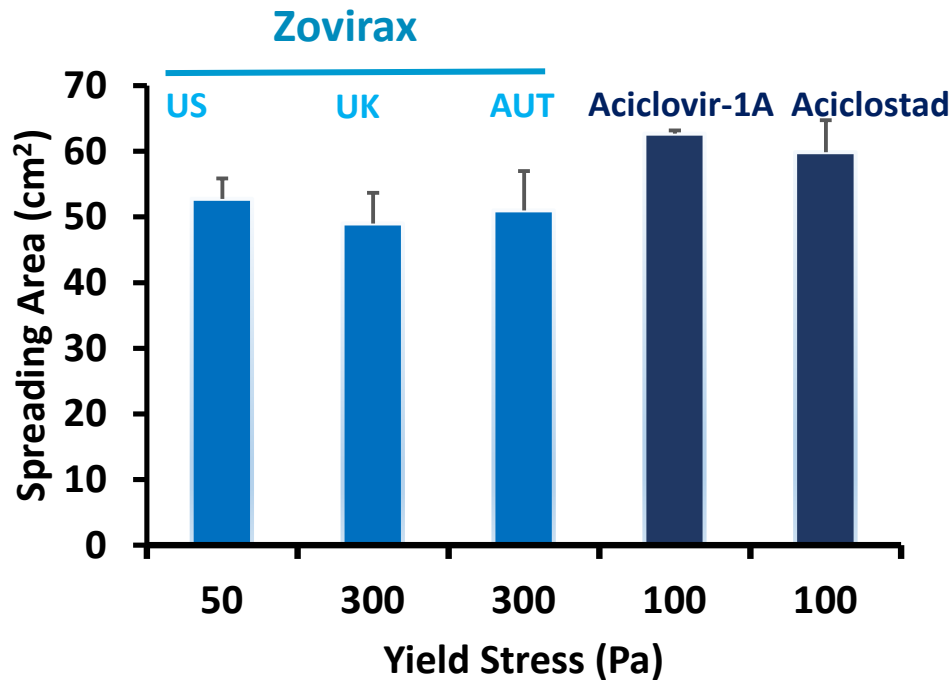
Dictates the behavior during the initial application

Dictates the behavior during spreading the sample on the skin

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

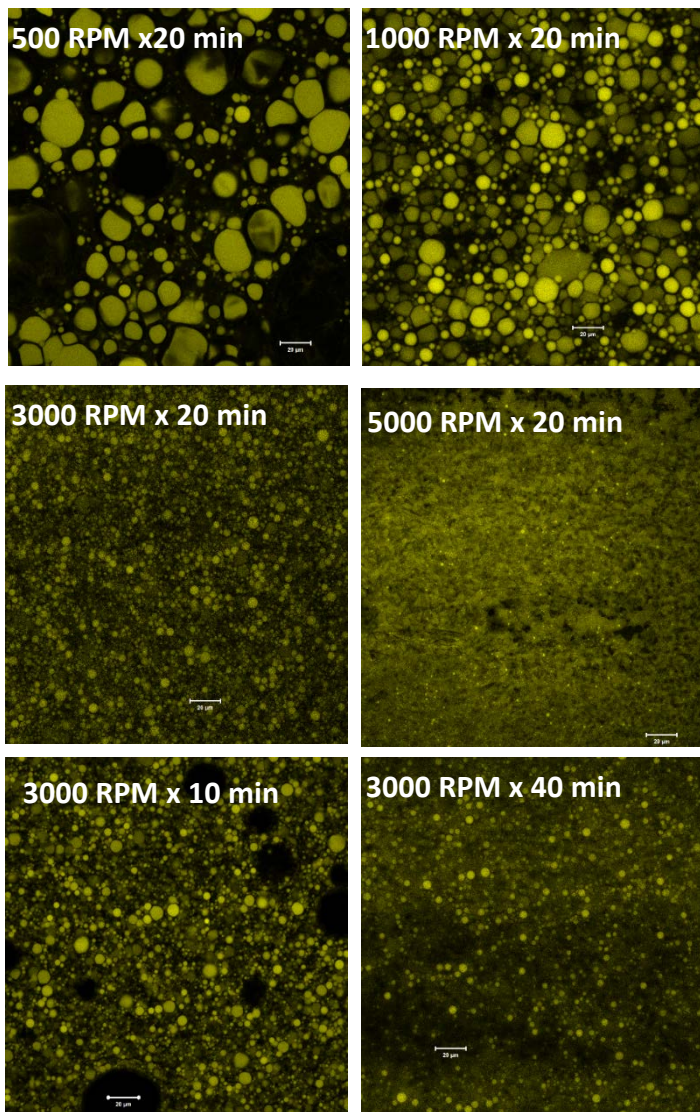
Potential Failure Modes (Rheology)

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

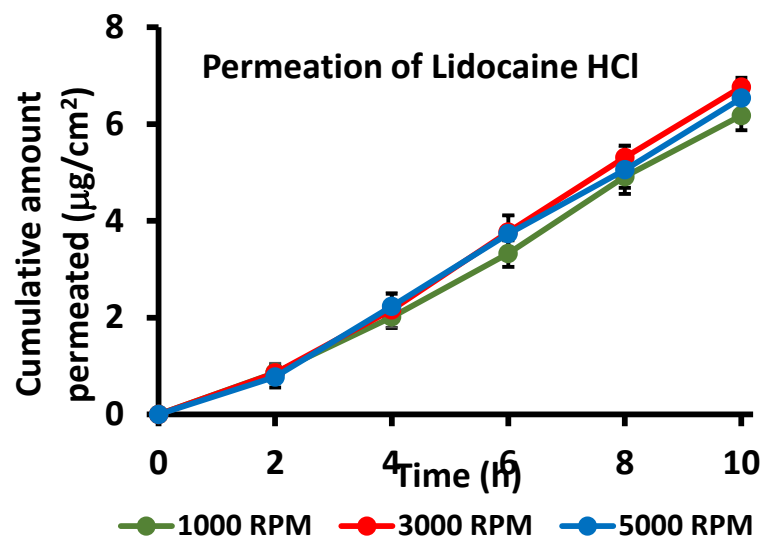


Area of formulation application by three individuals on six volunteers. (Each data Mean $n=3 \pm \text{SEM}$)

Globule size

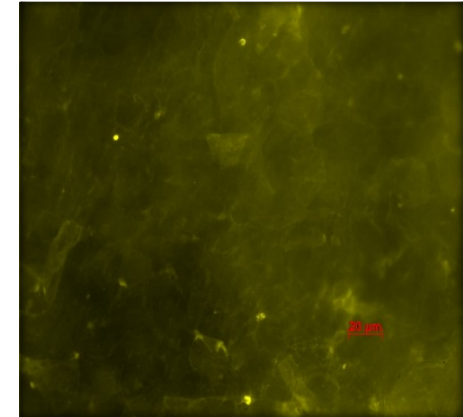
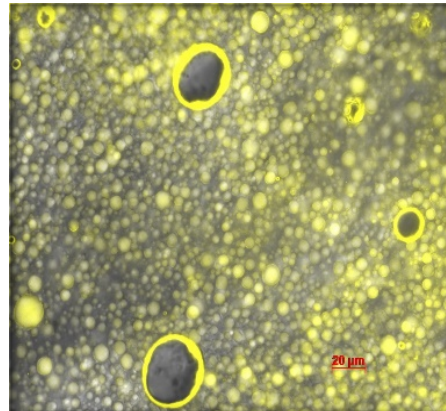
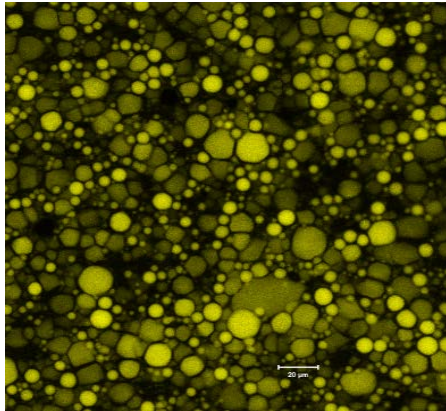


Formulation Code	Variable	Globule Size (um)
F1	500 rpm x 20 min	11.37 ±7.03
F2	1000 rpm x 20 min	7.41 ±2.19
F3	3000 rpm x 20 min	2.98 ±1.25
F4	5000 rpm x 20 min	1.71±0.41
F5	3000 rpm x 10 min	4.30±1.33
F6	3000 rpm x 40 min	4.36±0.88
F7	3000 rpm x 20 min Ambient cooling	4.25±0.99



Potential Failure Mode

Custom made o/w cream with Nile red on the skin



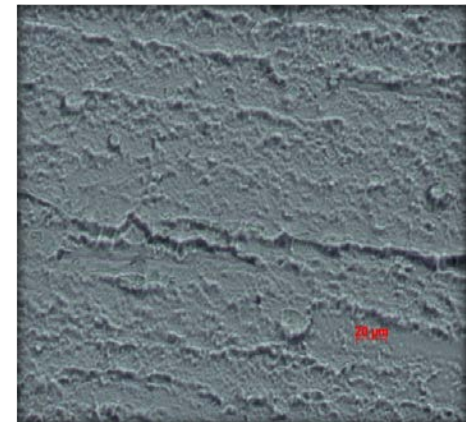
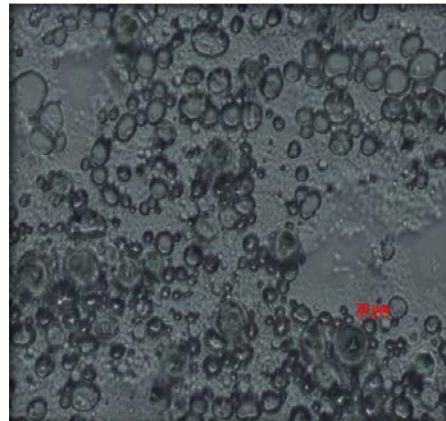
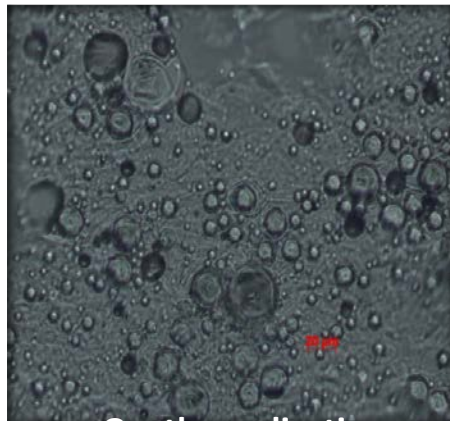
Gentle application



Rubbing



Intense Rubbing



Benadryl cream on glass slide

Conclusions

- There is an urgent need to identify and develop a toolkit to characterize the potential failure modes in topical products.
- It is important to consider potential failure modes while imparting certain quality attribute to the product during developmental stages.

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- Abhijeet Maurya (Grad. Student)
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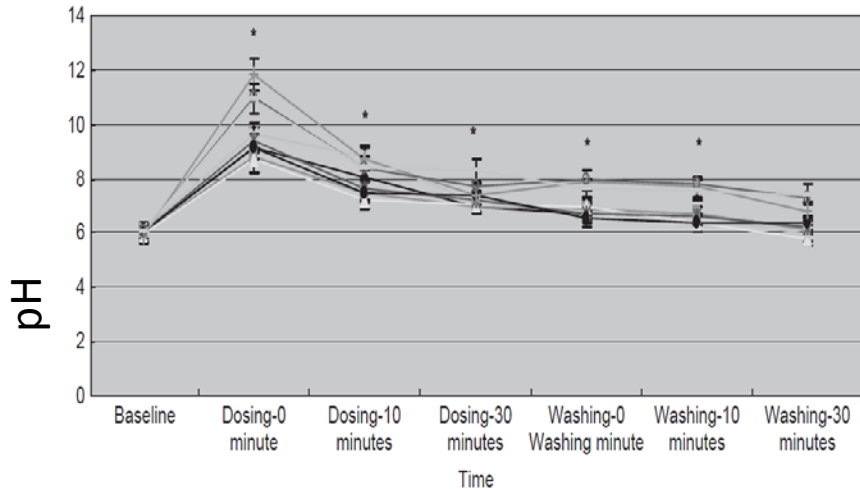
Dr. Darby Kozak

Grant Support-USFDA 1U01FD005223-01

CQA	Zovirax (US)	Zovirax (UK)	Zovirax (AUT)	Aciclovir-1A	Aciclostad
pH	7.74	7.96	7.54	6.05	4.58
D/UD	0.0278	0.0272	0.0517	0.0296	0.0275
Drug in Aq (mg/g)	0.492	0.488	0.641	0.255	0.365
Particle size (d50)	5.06	2.50	3.43	5.95	6.75
Polymorphic form	2,3 hydrate	2,3 hydrate	2,3 hydrate	2,3 hydrate	2,3 hydrate
Morphology	Rectangular	Rectangular	Rectangular	Ovoid	Ovoid
Density (g/cc)	1.0170	1.0202	1.0233	1.0100	1.0155
Rheology (viscosity, Pa. s)	8360	31000	30100	28100	29300
Water activity	0.753	0.732	0.735	0.948	0.948
Drying (T-30%)	>12h	7h	8h	<1h	<1h
Propylene glycol	High	High	High	Low	Low

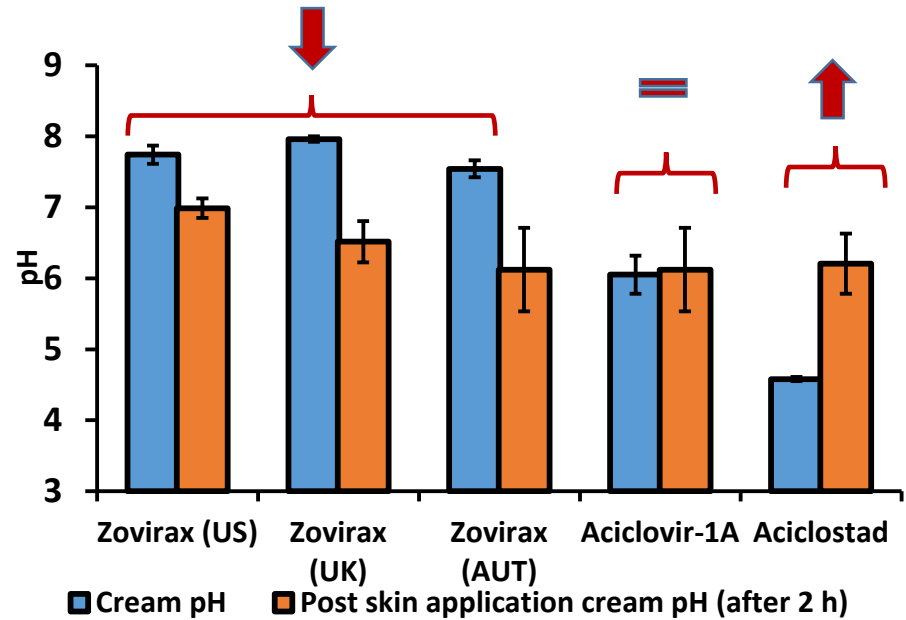
Potential Failure Mode (pH)

Buffer Capacity of skin



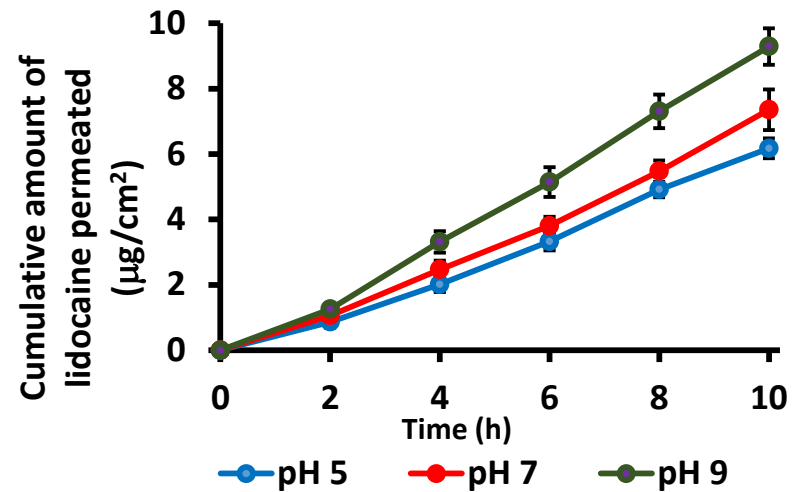
Zheng et al, Buffering capacity of human skin layers: *in vitro*. Skin Research and Technology, 2012, 18: 114-9

Post application pH of formulation



Microenvironment of the disease skin

Factor	Components
Sebum secretion, Stratum Corneum lipid maturation	Source of free fatty acids
Sweat secretion	Source of amino acids, lactic acid, protons
Filaggrin formation and/or degradation	Source of amino acids and urocanic acid

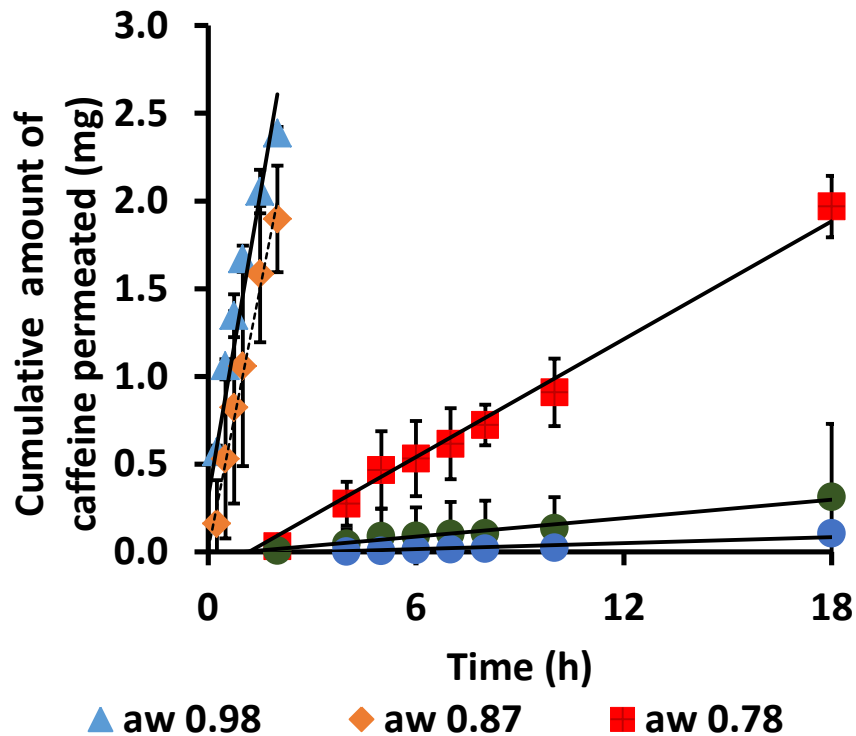


Water Activity (a_w)

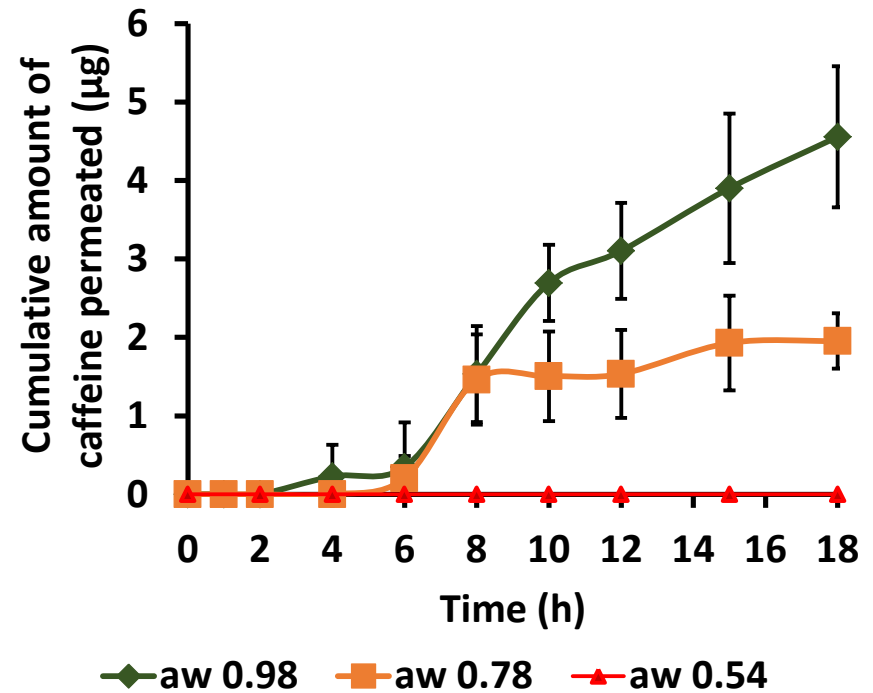
$$a_w = \rho / \rho_0$$

ρ = partial vapor pressure of water in the product

ρ_0 = vapor pressure of pure water



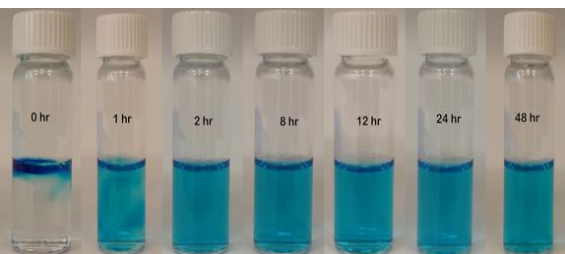
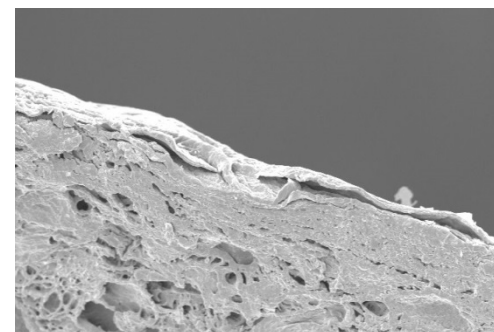
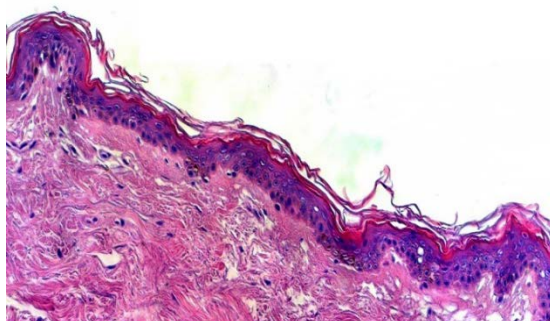
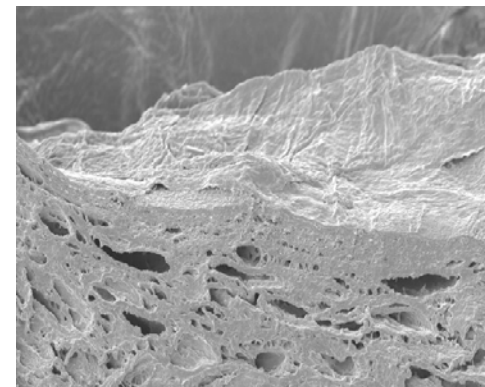
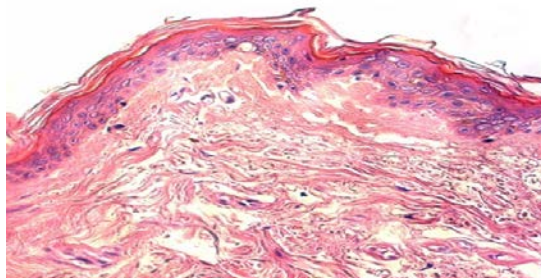
Effect of water activity on caffeine permeation across cuprophan membrane (n=6)



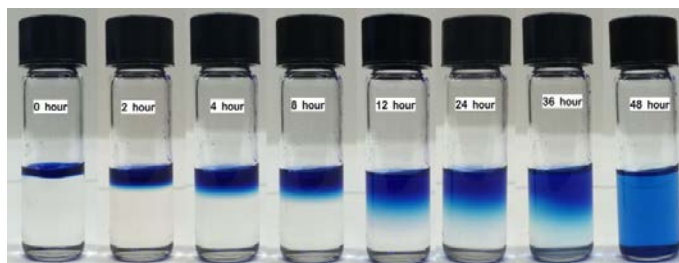
Effect of water activity on caffeine permeation across porcine epidermis (finite dose condition) (n=5)

Mechanistic Studies

Pre-treatment Mode	Apparent water content (% w/w of tissue)
Baseline	37.77 ± 6.44
$a_w = 0.98$	50.28 ± 2.32
$a_w = 0.78$	22.85 ± 4.77
$a_w = 0.54$	17.40 ± 7.89



Time lapse observation of solute (methylene blue) diffusion in a_w 0.98 vehicle.

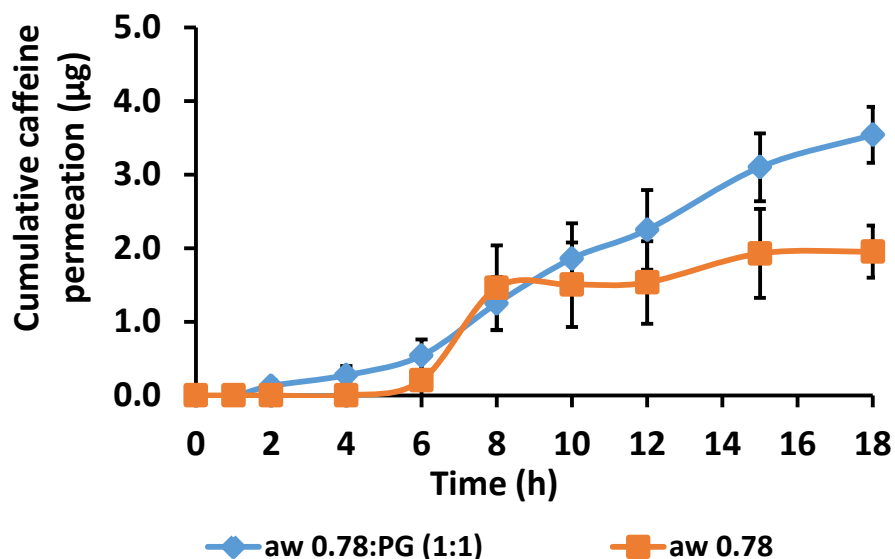
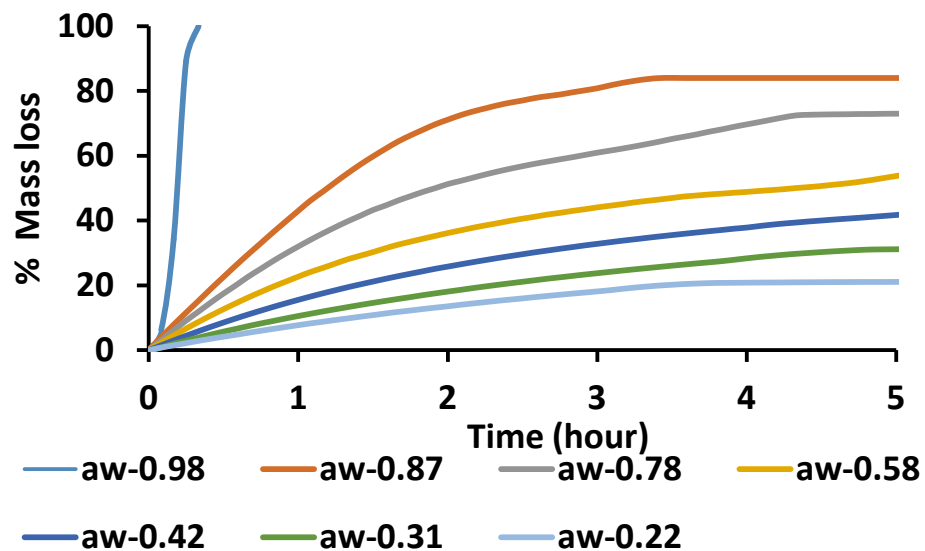


Time lapse observation of solute (methylene blue) diffusion in a_w 0.46 vehicle.-3.6 cPoise

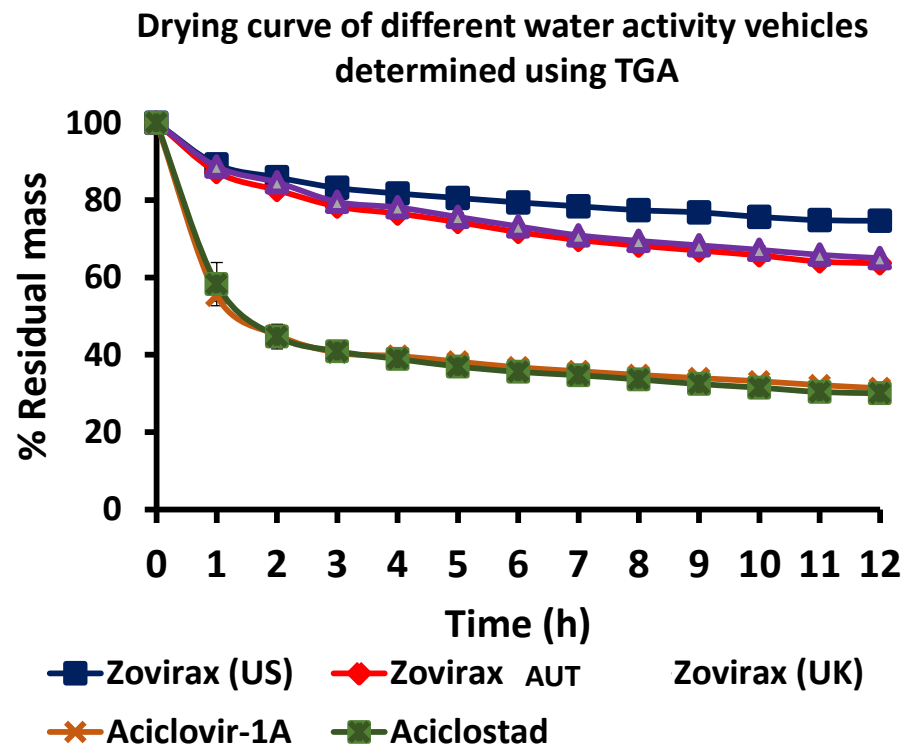


Time lapse observation of solute (methylene blue) diffusion in a_w 0.948 vehicle.-3.6 cPoise)

Product	Water 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



Effect of propylene glycol on caffeine permeation from aw 0.0.652 across porcine epidermis aw 0.78 (n=6)



Water activity of Q1 & Q2 similar creams

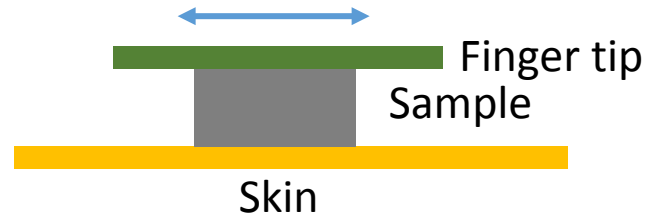
Ingredients (O/W)	Quantity (%)
Drug	1
Cetostearyl alcohol	7
Cremophor A6	1.5
Cremophor A25	1.5
Mineral Oil	12
Propylene Glycol	8
Water	69
Total	100

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

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

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

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

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

Dictates the
behavior during the
initial application

Dictates the behavior
during spreading the
sample on the skin

Solvent activity of Q1 & Q2 similar 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

Ingredients (W/O)	Quantity (%)
Cetostearyl Alcohol	12.5
White Wax	12
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Manufacturing Conditions	Water Activity (a_w)
3500 RPM (15 min)	0.931 ± 0.002
7000 RPM (45 min)	0.875 ± 0.006

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

