

Characterizing the Critical Quality Attributes and *In Vitro* Bioavailability of Acyclovir and Metronidazole Topical Products

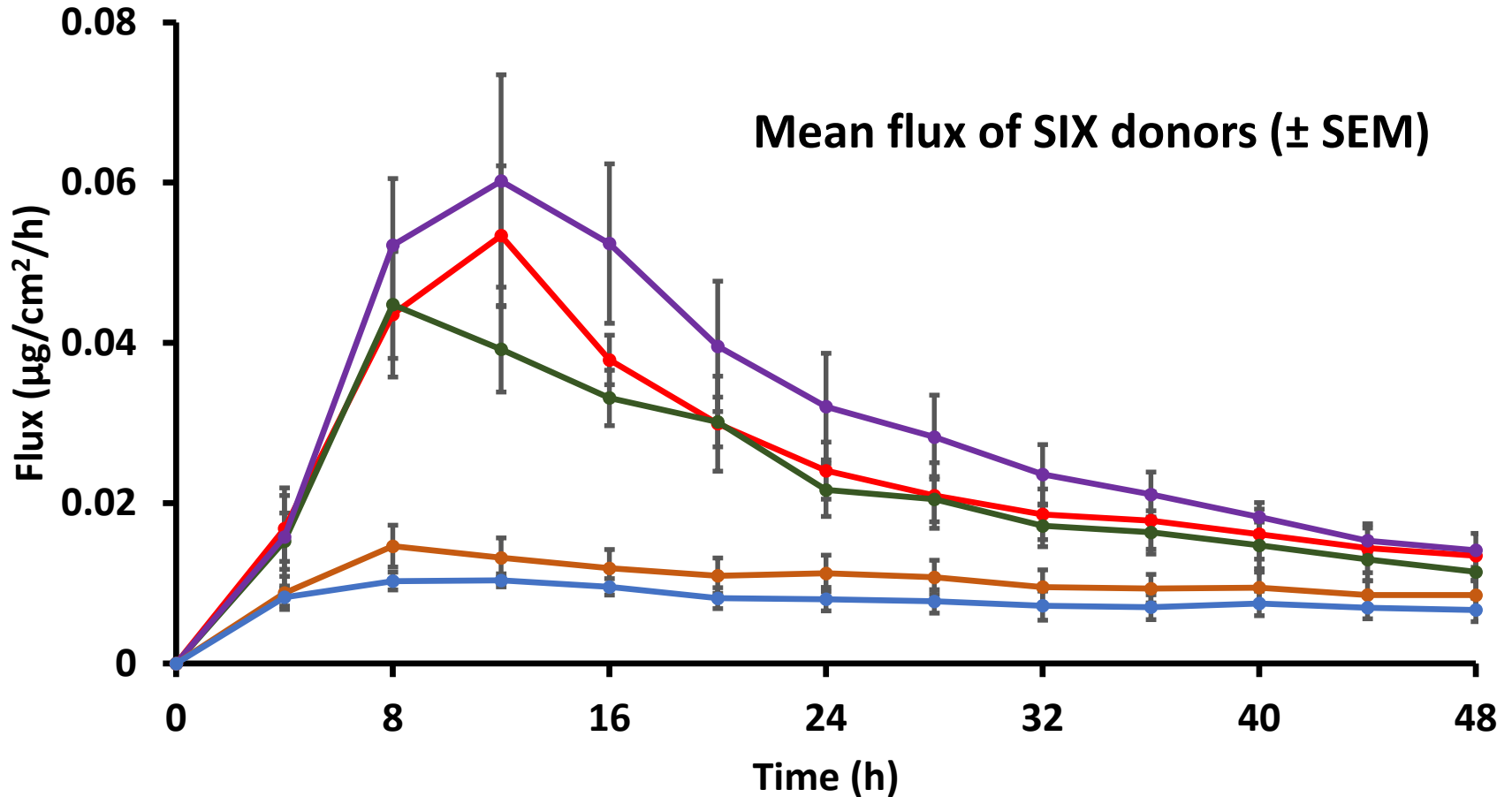
S. Narasimha Murthy Ph.D

Professor of Pharmaceutics and Drug Delivery

The University of Mississippi

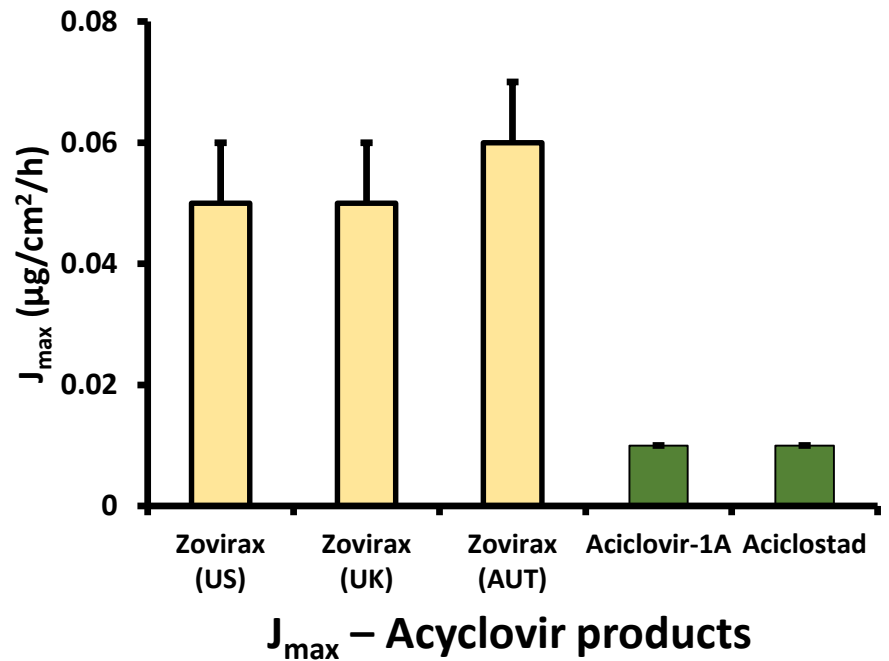
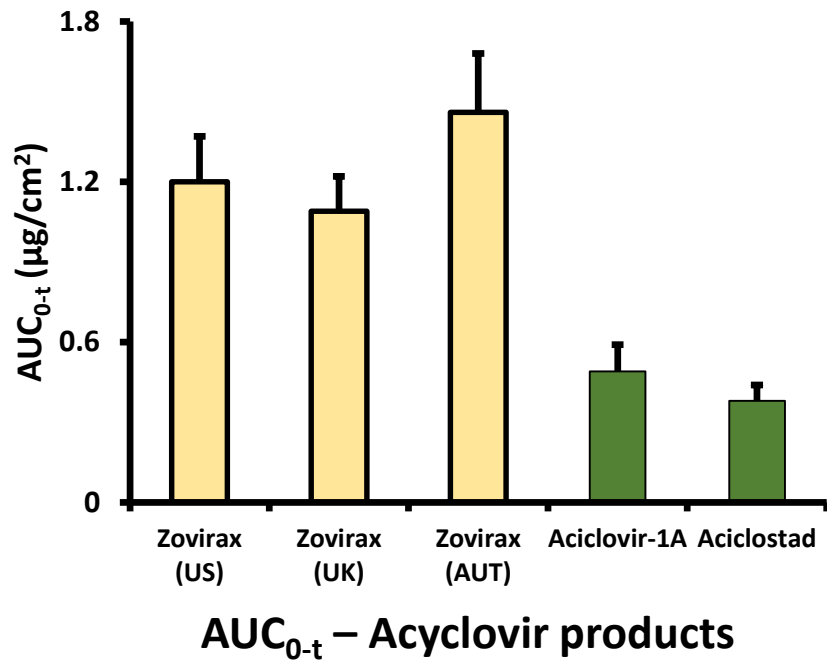
Zovirax (USA)	Zovirax (UK)	Zovirax (Austria)	Aciclostad (Austria)	Aciclovir 1A (Austria)
Mineral oil	Liquid Paraffin	Liquid Paraffin	Liquid Paraffin	Viscous Paraffin
White petrolatum	White soft paraffin	White Vaseline	White Vaseline	White Vaseline
Water	Water	Purified water	Water	Water
Propylene glycol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



—●— Zovirax (US) —●— Zovirax (UK) —●— Zovirax (AUT) —●— Aciclovir-1A —●— Aciclostad

Product	AUC_{0-t} ($\mu\text{g}/\text{cm}^2$)	J_{max} ($\mu\text{g}/\text{cm}^2/\text{h}$)	T_{max} (h)
Zovirax (US)	1.20 ± 0.17	0.05 ± 0.01	10.67 ± 0.84
Zovirax (UK)	1.09 ± 0.13	0.05 ± 0.01	10.67 ± 1.33
Zovirax (AUT)	1.46 ± 0.22	0.06 ± 0.01	10.67 ± 0.84
Aciclovir-1A	0.49 ± 0.10	0.01 ± 0.00	12.0 ± 2.17
Aciclostad	0.38 ± 0.06	0.01 ± 0.00	10.0 ± 1.34



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

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

5% w/w Acyclovir Creams

Zovirax (US)

Zovirax (UK)

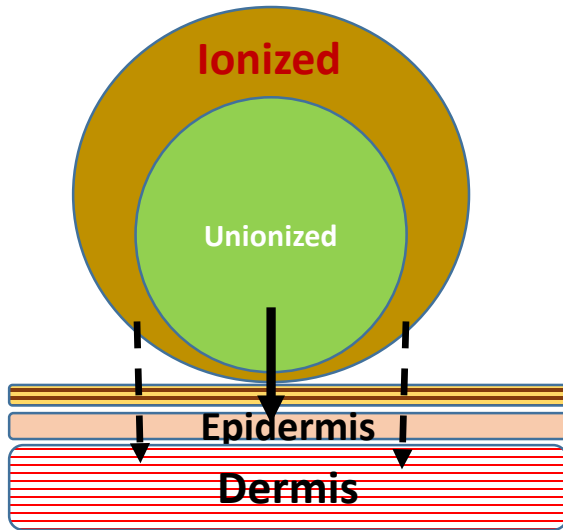
Zovirax (AUT)

Aciclovir-1A

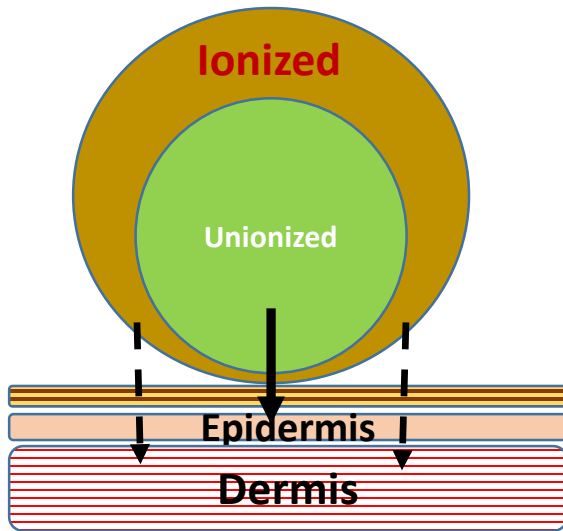
Aciclostad

Austria

pH as a Quality Attribute

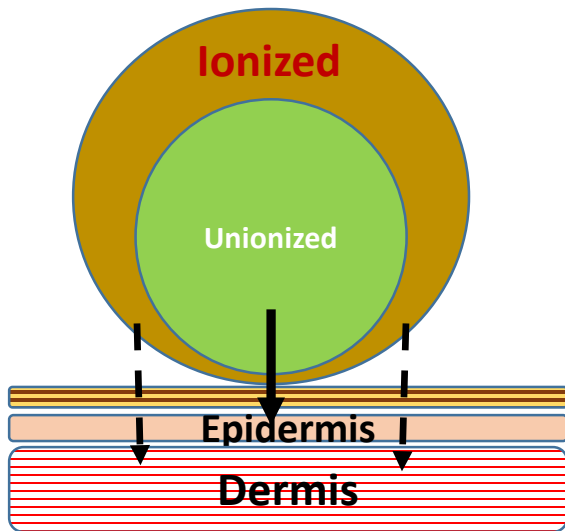


pH as a Quality Attribute



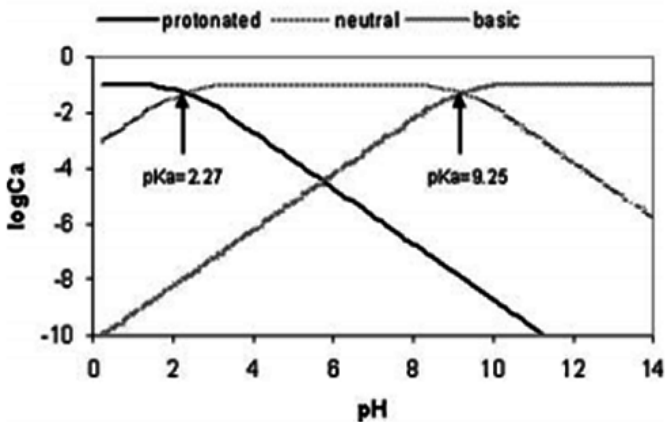
Product	pH
Zovirax (US)	7.74 ± 0.13
Zovirax (UK)	7.96 ± 0.04
Zovirax (AUT)	7.54 ± 0.12
Aciclovir-1A	6.05 ± 0.27
Aciclostad	4.58 ± 0.03

pH as a Quality Attribute

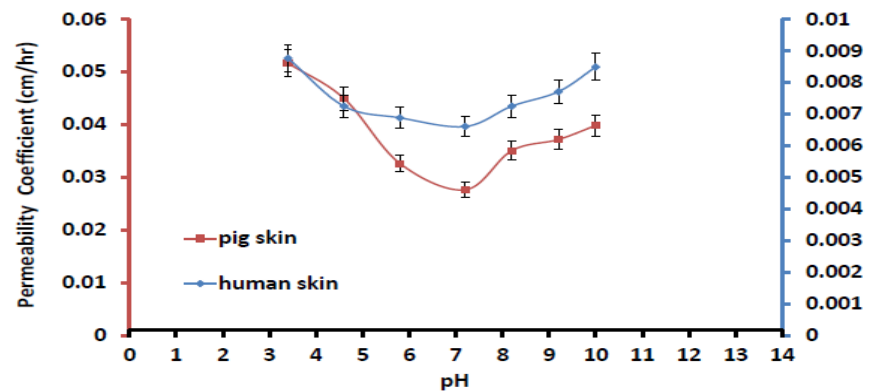


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Zovirax (US)	7.74 ± 0.13
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Zovirax (AUT)	7.54 ± 0.12
Aciclovir-1A	6.05 ± 0.27
Aciclostad	4.58 ± 0.03

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

pH Measurement



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 probe with smallest surface area for reproducible readings.*
- *Check the pH of aqueous Phase separated from the Cream.*

pH Measurement



InLab Science



InLab Viscous



InLab Micro

Suggestions

- *Standard buffers of pH 4 and 10 shall be alternated between each measurement.*
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- *Check the pH of aqueous Phase separated from the Cream.*



pH Measurement



InLab Science



InLab Viscous



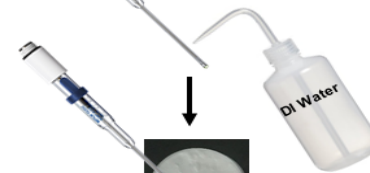
InLab Micro

Suggestions

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



Calibrate using buffer of pH 4, 7 and 10

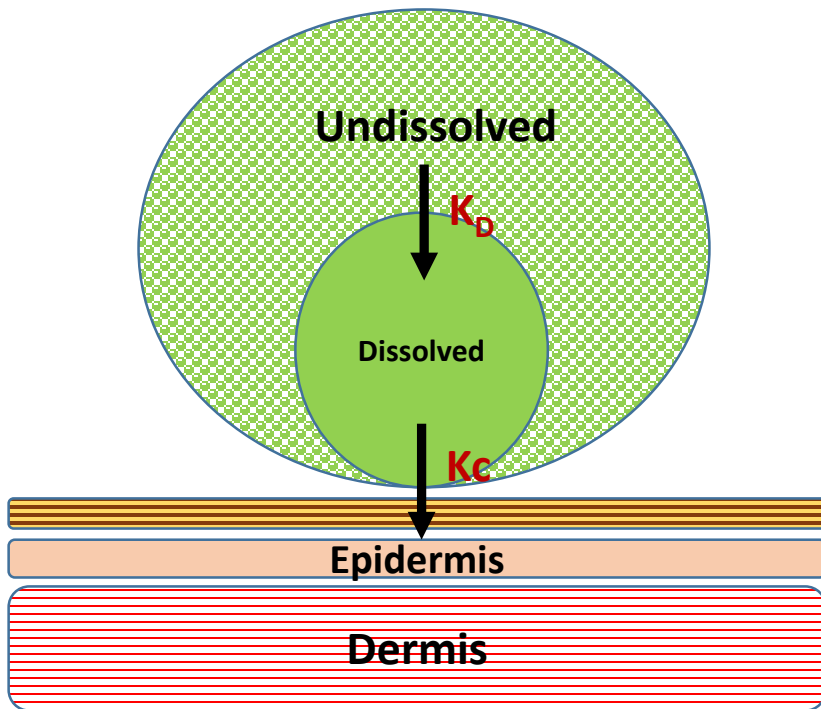


Three cycles

Measure the buffer standard of pH 4 after one measurement and pH 10 after the next measurement.



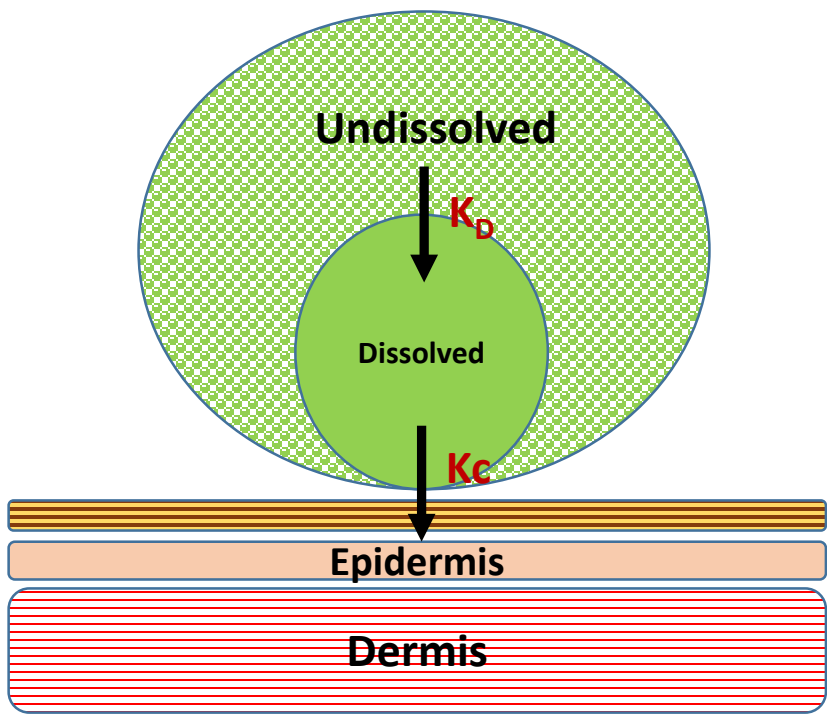
Drug Absorption from Topical Product



Dissolved Drug

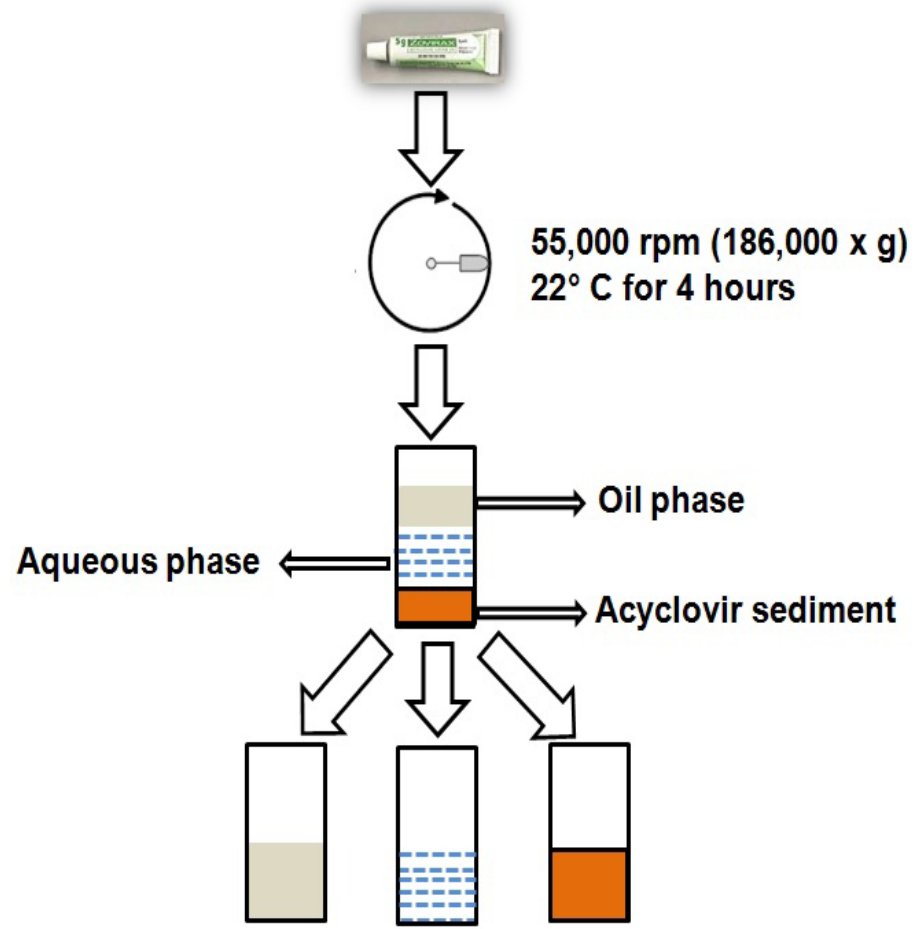
Undissolved Drug

Drug Absorption from Topical Product



Dissolved Drug
Undissolved Drug

Phase Separation



Dissolved/Undissolved drug

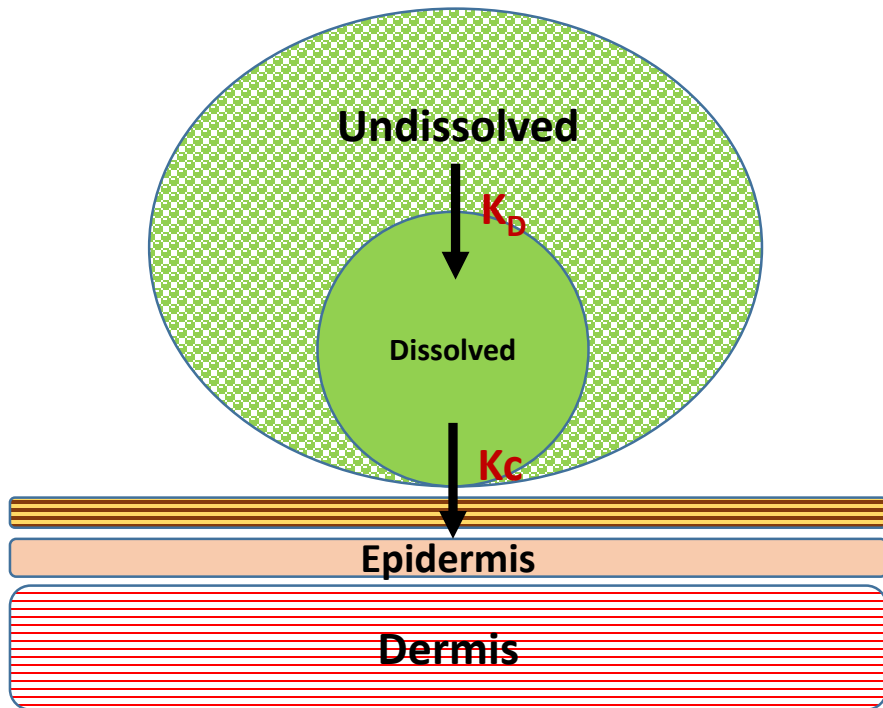
Product	Total dissolved acyclovir in cream (mg/g)	Total undissolved acyclovir in cream (mg/g)	D/UD
ZOVIRAX (US)	1.35 ± 0.05	48.65 ± 0.05	0.028
ZOVIRAX (AUT)	2.46 ± 0.16	47.57 ± 0.16	0.052
ZOVIRAX (UK)	1.33 ± 0.05	48.67 ± 0.05	0.027
ACICLOVIR-1A	1.44 ± 0.03	48.56 ± 0.02	0.030
ACICLOSTAD	1.34 ± 0.04	48.66 ± 0.04	0.028

Dissolved/Undissolved drug

Product	Total dissolved acyclovir in cream (mg/g)	Total undissolved acyclovir in cream (mg/g)	D/UD	Amount Dissolved in Aqueous Phase (mg/g)
ZOVIRAX (US)	1.35 ± 0.05	48.65 ± 0.05	0.028	0.49 ± 0.08
ZOVIRAX (AUT)	2.46 ± 0.16	47.57 ± 0.16	0.052	0.64 ± 0.04
ZOVIRAX (UK)	1.33 ± 0.05	48.67 ± 0.05	0.027	0.49 ± 0.13
ACICLOVIR-1A	1.44 ± 0.03	48.56 ± 0.02	0.030	0.26 ± 0.02
ACICLOSTAD	1.34 ± 0.04	48.66 ± 0.04	0.028	0.30 ± 0.02

Drug Absorption from Topical Product

$$K_D \geq K_C$$



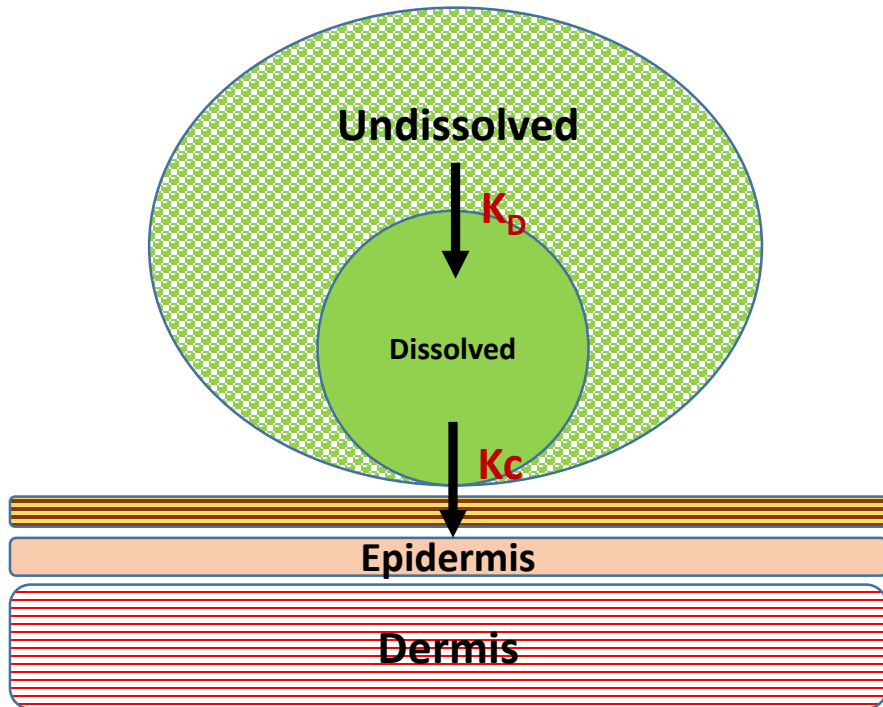
Dose	Total Drug	Dissolved Drug	Undissolved drug
15 mg/cm ²	750 μg/cm ²	18.75 μg/cm ²	731.25 μg/cm ²

Drug Absorption from Topical Product

$$K_D \geq K_C$$

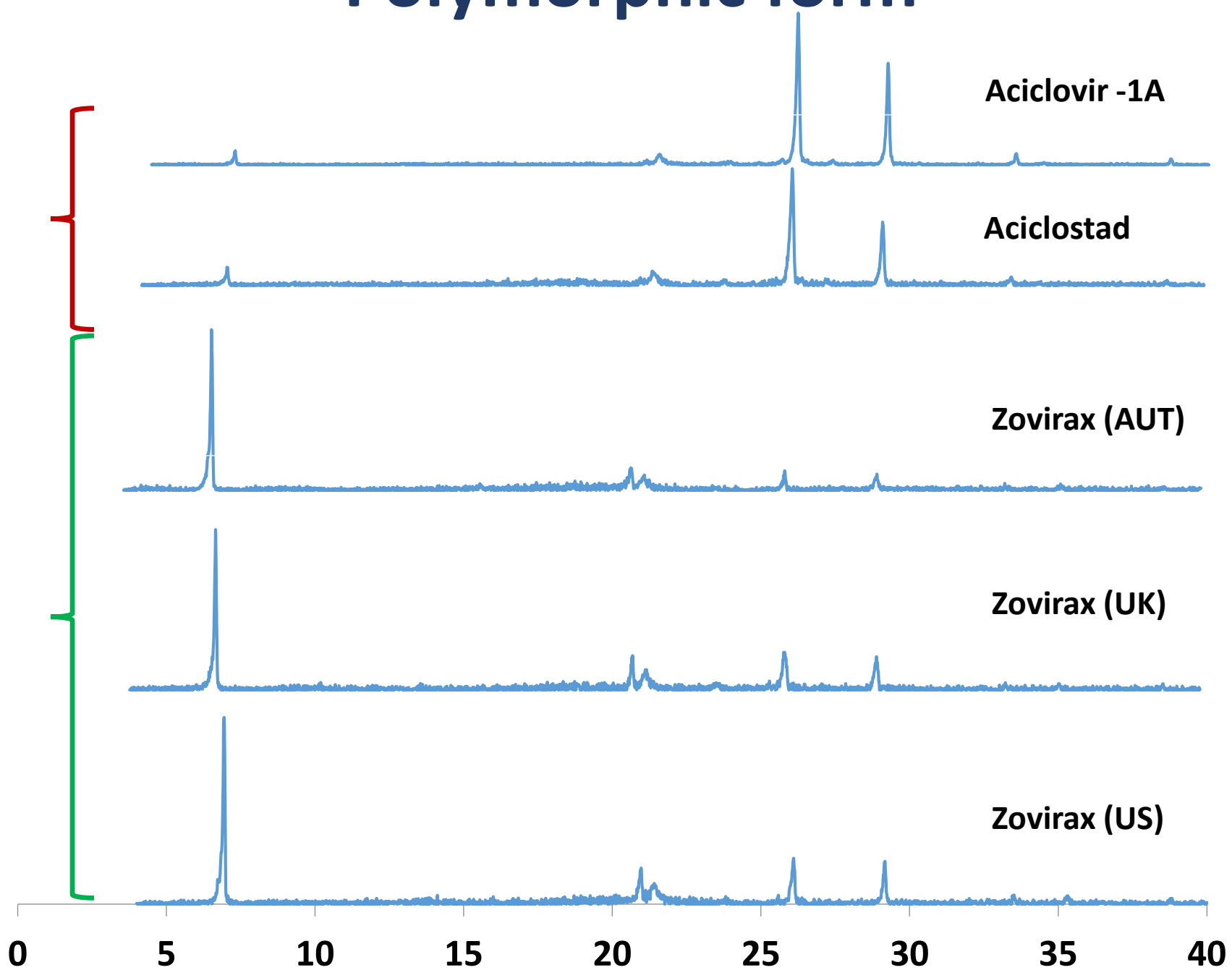
Rate of Dissolution of Drug

- Particle Size
- Polymorphic form
- Morphology of particles



Dose	Total Drug	Dissolved Drug	Undissolved drug
15 mg/cm ²	750 µg/cm ²	18.75 µg/cm ²	731.25 µg/cm ²

Polymorphic form

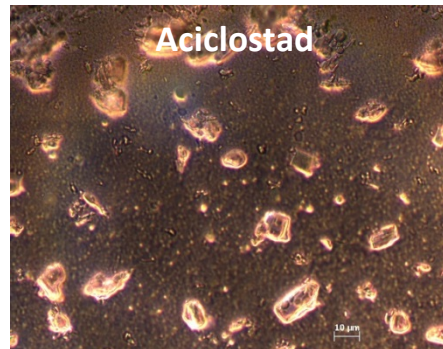
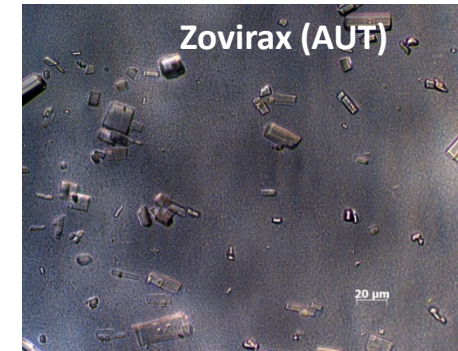
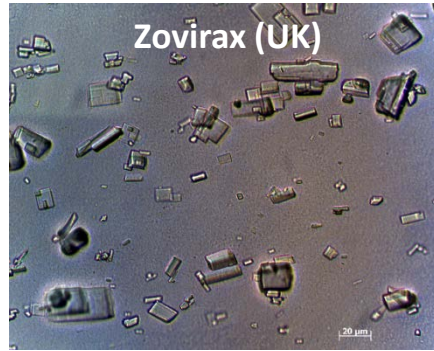


Particle Size and Morphology

Product	d_{10} (μm)	d_{50} (μm)	d_{90} (μm)
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	4.00	5.95	10.94
Aciclostad	3.67	6.75	11.40

Particle Size and Morphology

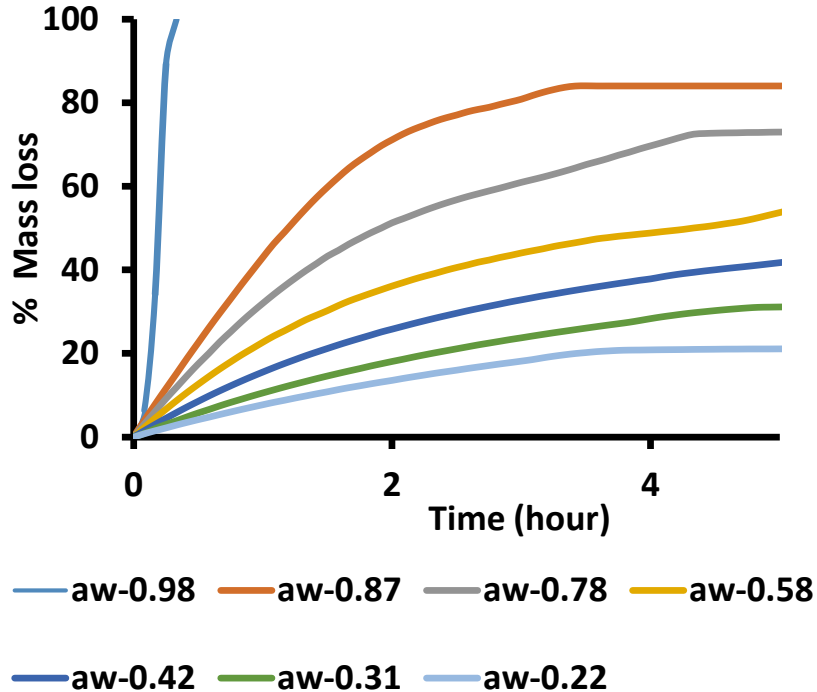
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Zovirax (US)	2.07	3.77	19.05
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Aciclostad	3.67	6.75	11.40



Water Activity (a_w)

$$a_w = \rho / \rho_0$$

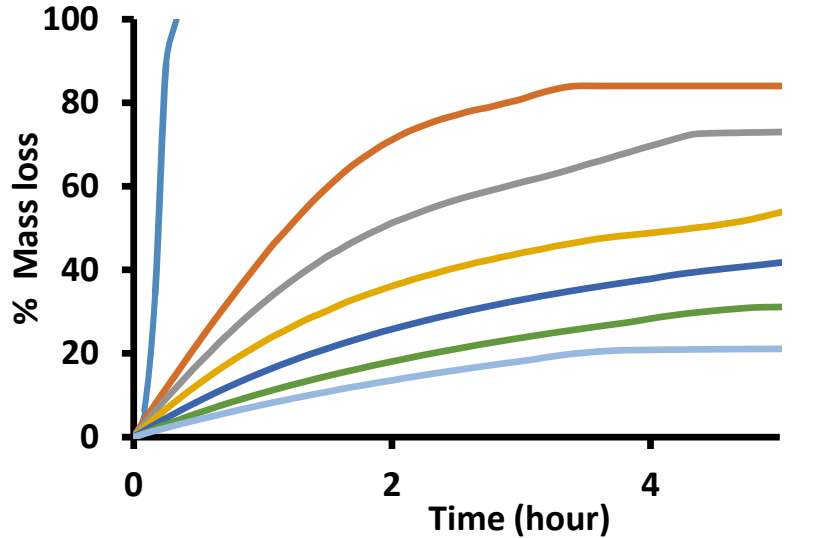
ρ = Partial vapor pressure of water in the product
 ρ_0 = vapor pressure of pure water



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



— aw-0.98 — aw-0.87 — aw-0.78 — aw-0.58

— aw-0.42 — aw-0.31 — aw-0.22

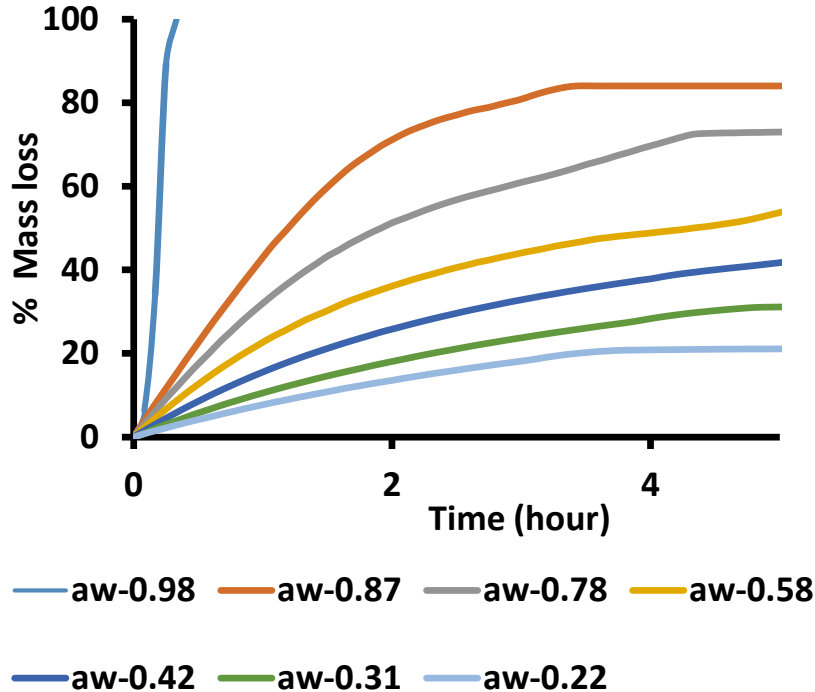
Product	Water Activity (a_w)
Zovirax (US)	0.753 ± 0.002
Zovirax (AUT)	0.735 ± 0.000
Zovirax (UK)	0.732 ± 0.002
Aciclovir-1A	0.948 ± 0.001
Aciclostad	0.948 ± 0.003



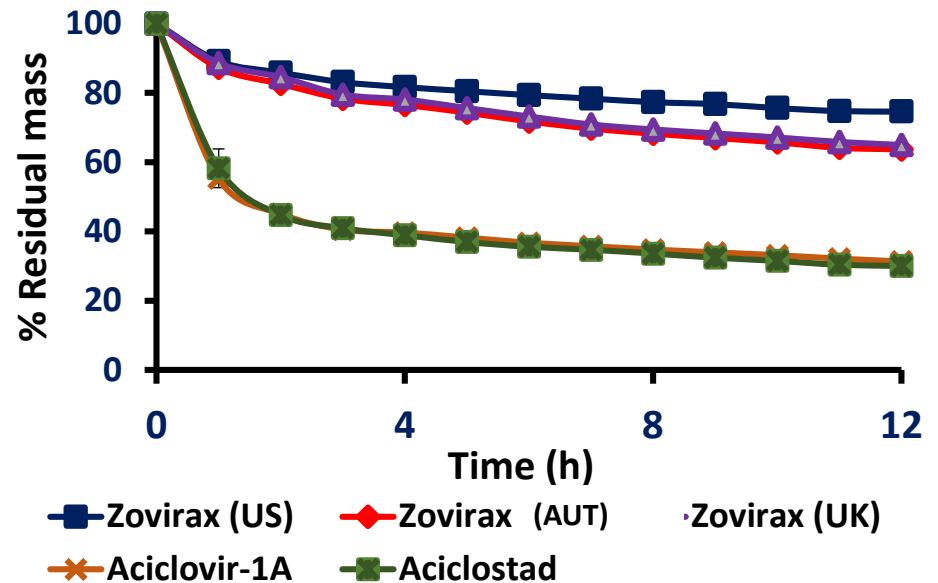
Water Activity (a_w)

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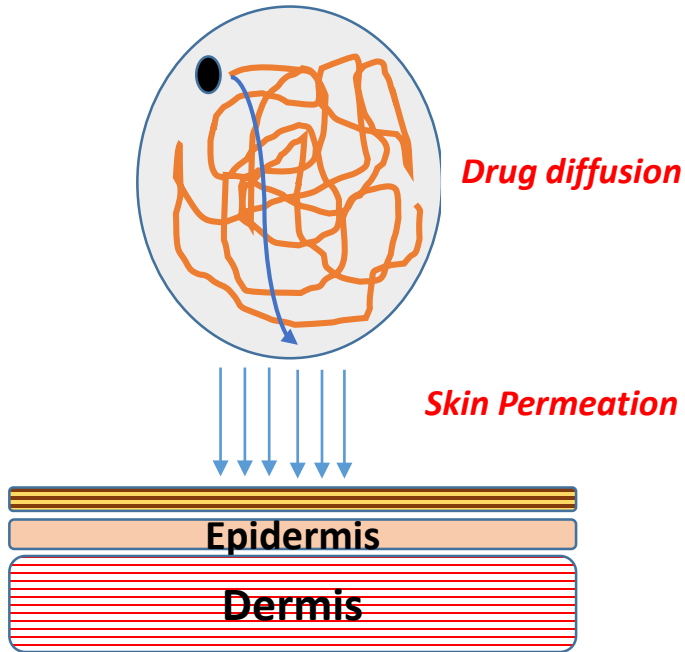
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 ρ_0 = vapor pressure of pure water



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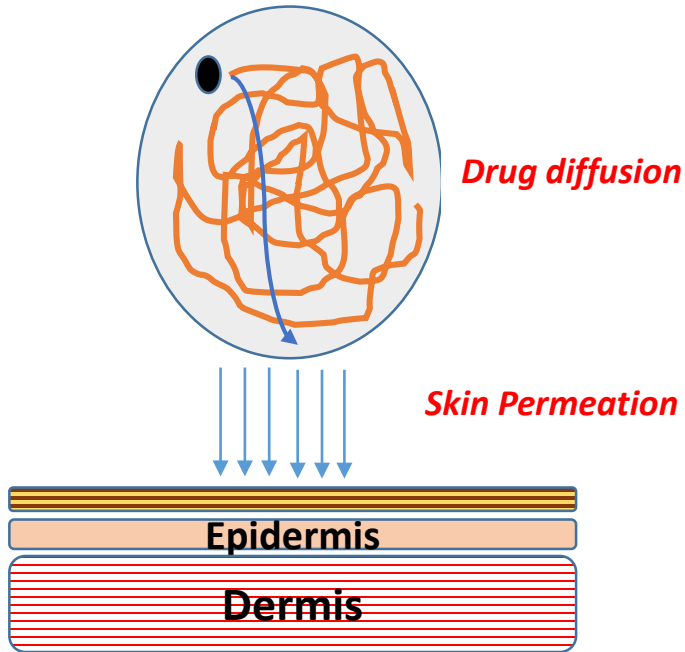
Rheological Studies-Acyclovir Creams



Rheology of a formulation is a direct function of microstructure.

Diffusivity inversely scales with the viscosity of the media.

Rheological Studies-Acyclovir Creams



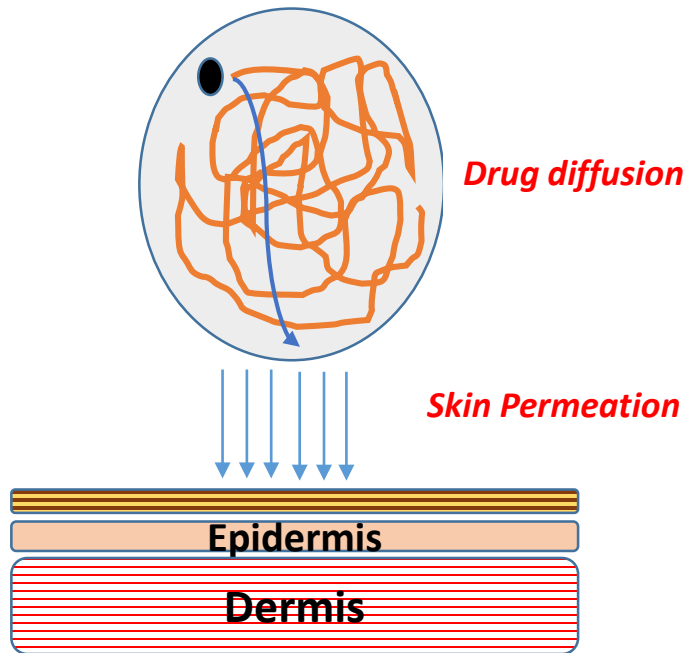
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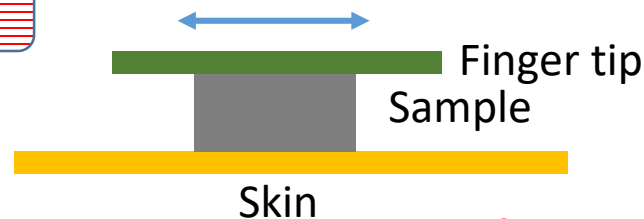
**TA Instruments HR2
rheometer with
solvent trap**

Rheological Studies-Acyclovir Creams



Rheology of a formulation is a direct function of microstructure.

Diffusivity inversely scales with the viscosity of the media.



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

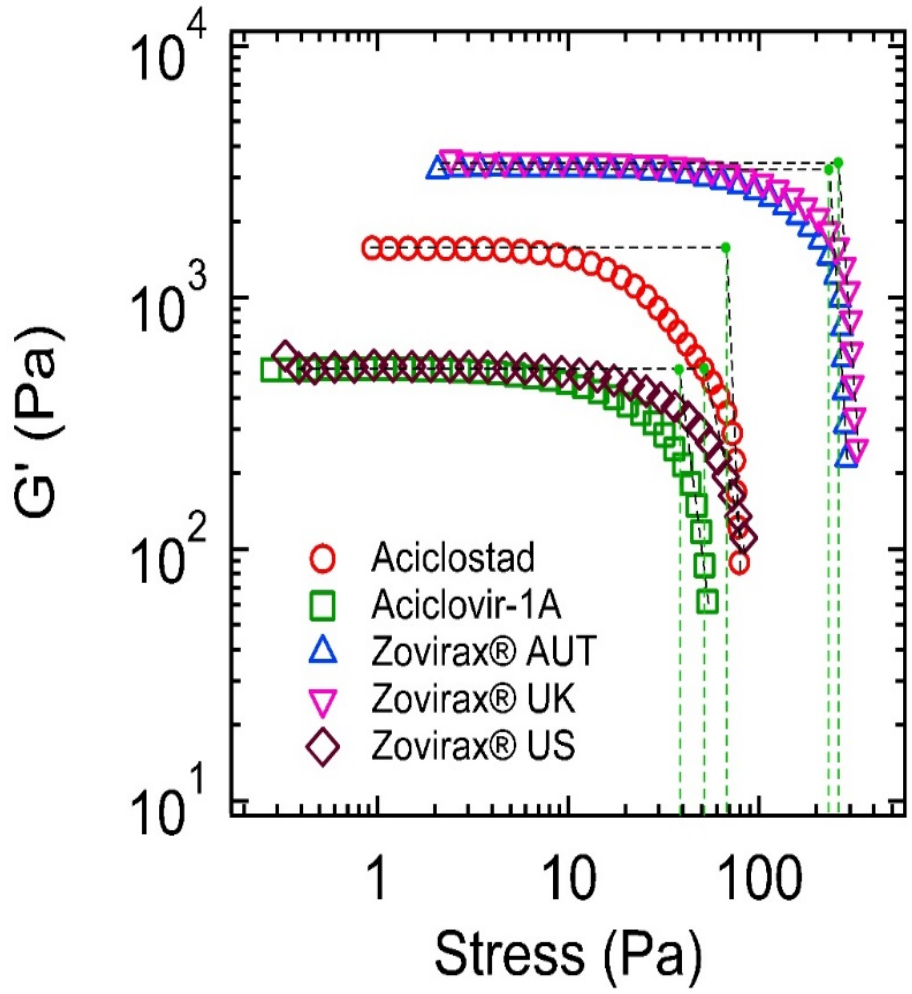
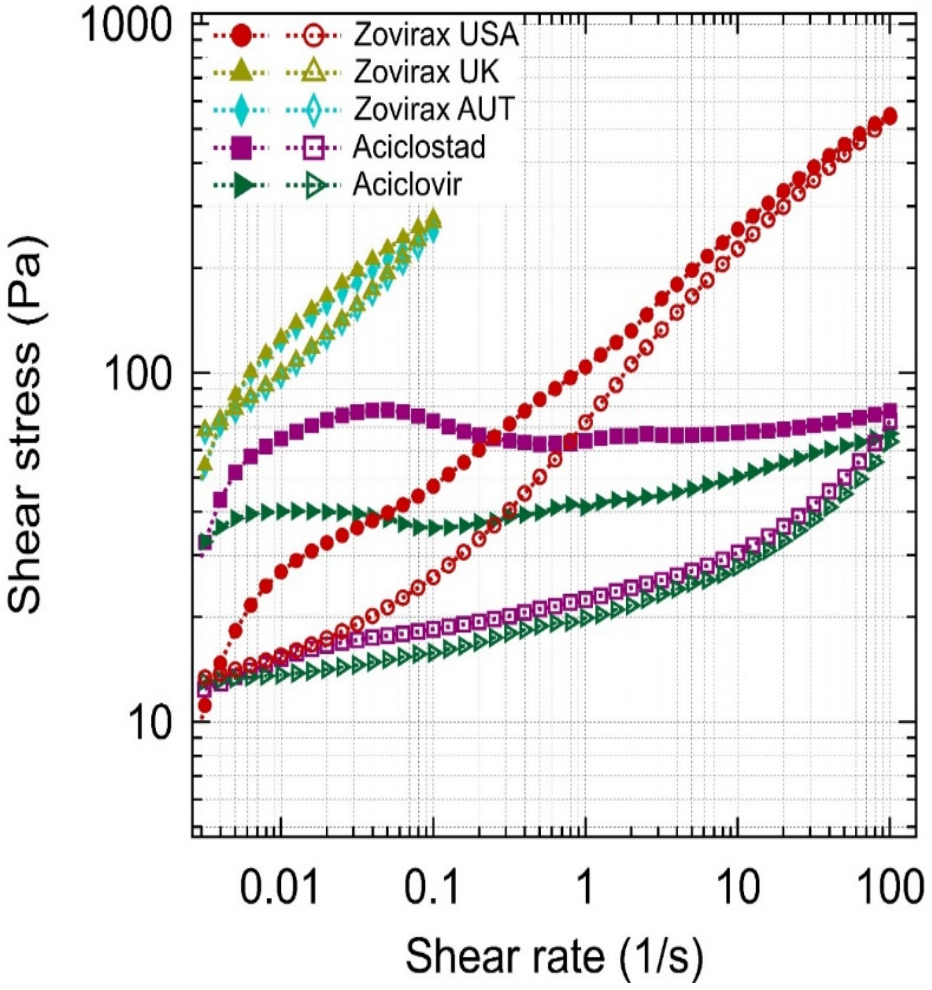
During spreading

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



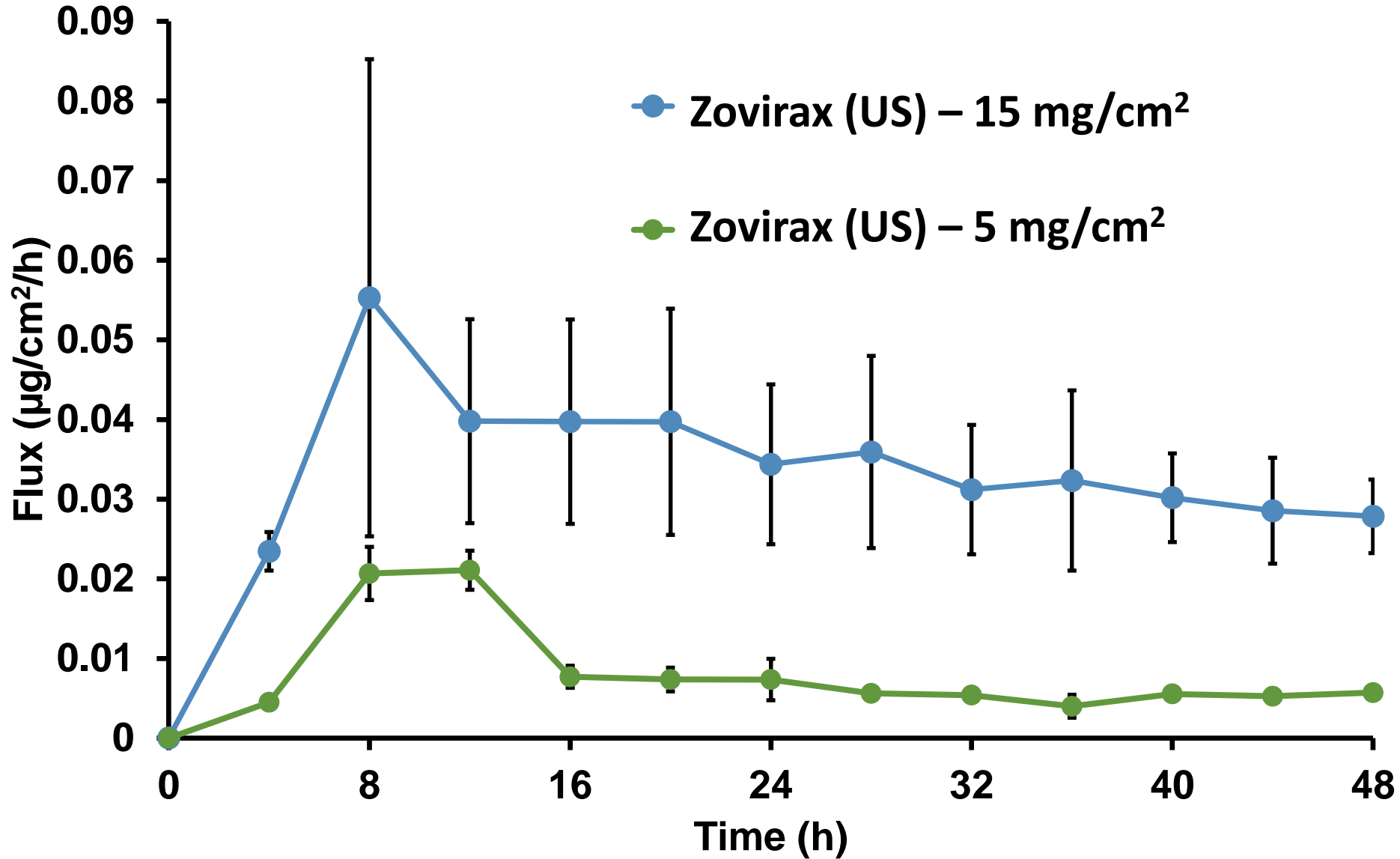
TA Instruments HR2 rheometer with solvent trap

Rheological Studies-Acyclovir Creams

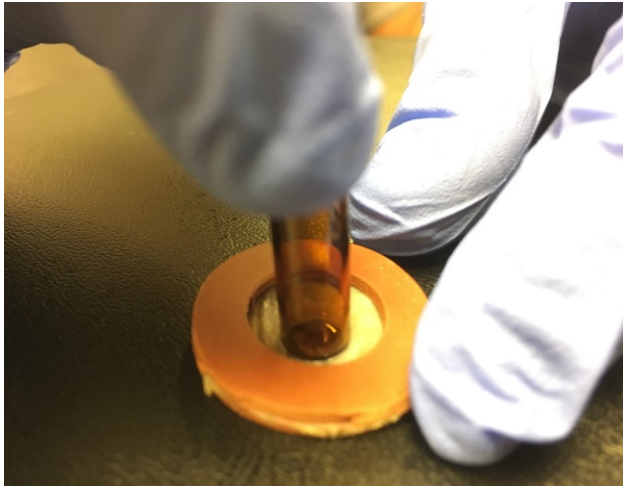


Product	Viscosity, Pa. s			Yield Stress, Pa
	@shear rate: 20 s ⁻¹	@ shear rate 3300s ⁻¹	@ shear rate: 0.0025 s ⁻¹	
Zovirax-USA	17	0.28	8360	50
Zovirax-UK	N/A	N/A	31000	300
Zovirax-AUT	N/A	N/A	30100	300
Aciclostad	3.2	0.06	29300	100
Aciclovir- 1A	2.6	0.06	28100	100
	Dictates the behavior during the initial application	Dictates the behavior during spreading the sample on skin	Dictates at rest condition, i.e., diffusion of drug through thin film	

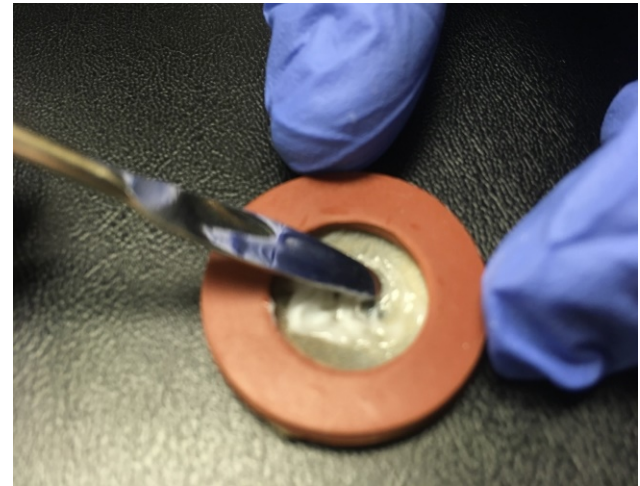
Dose Selection for IVPT



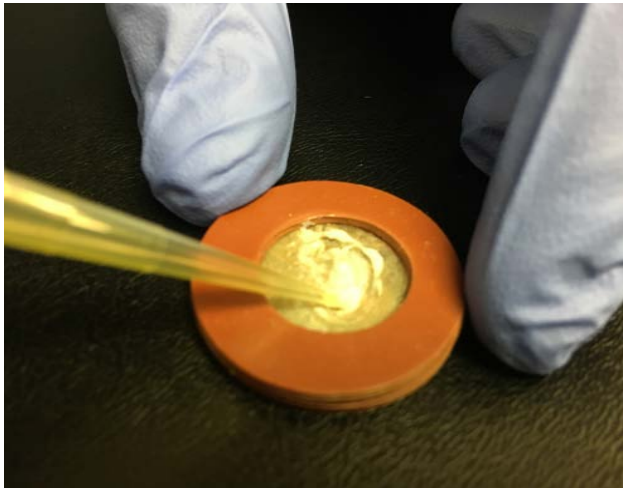
Dose Application Techniques for IVPT



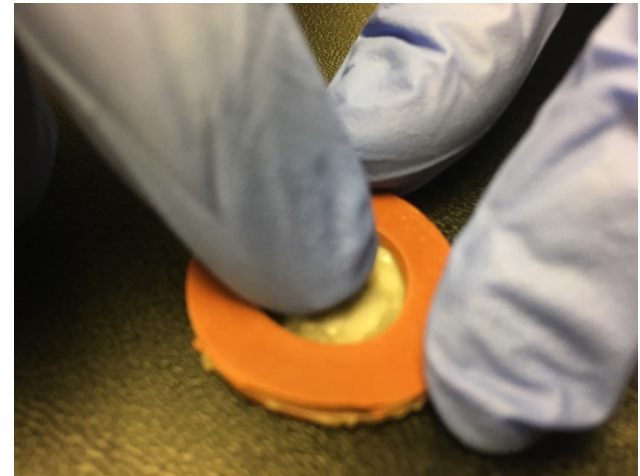
Vial Technique



Spatula Technique

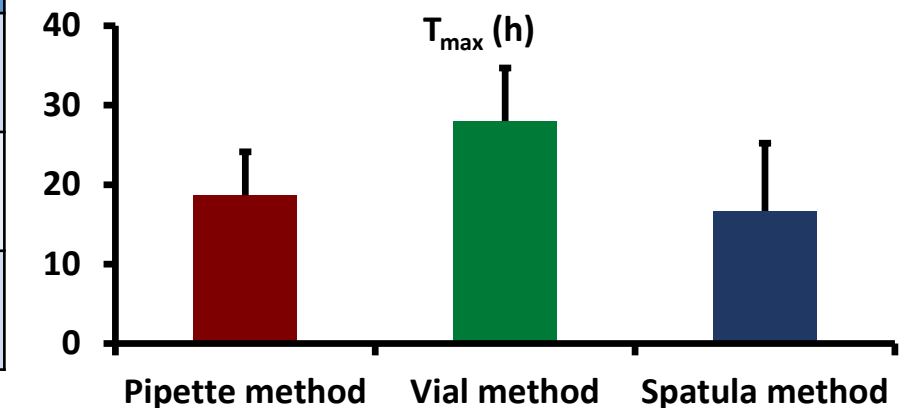
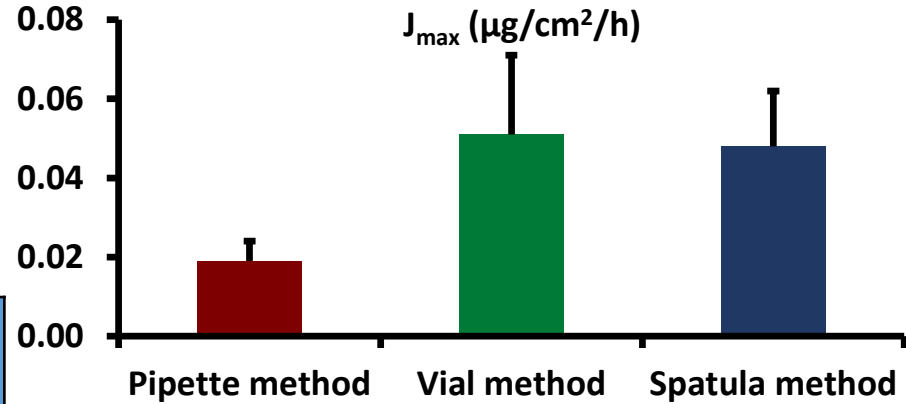
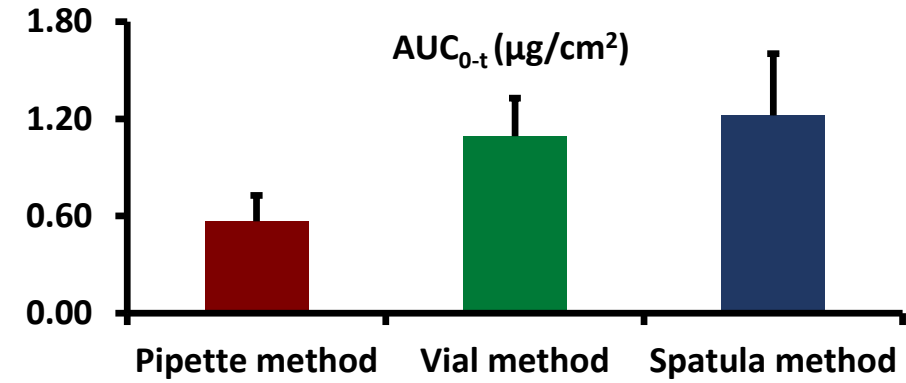
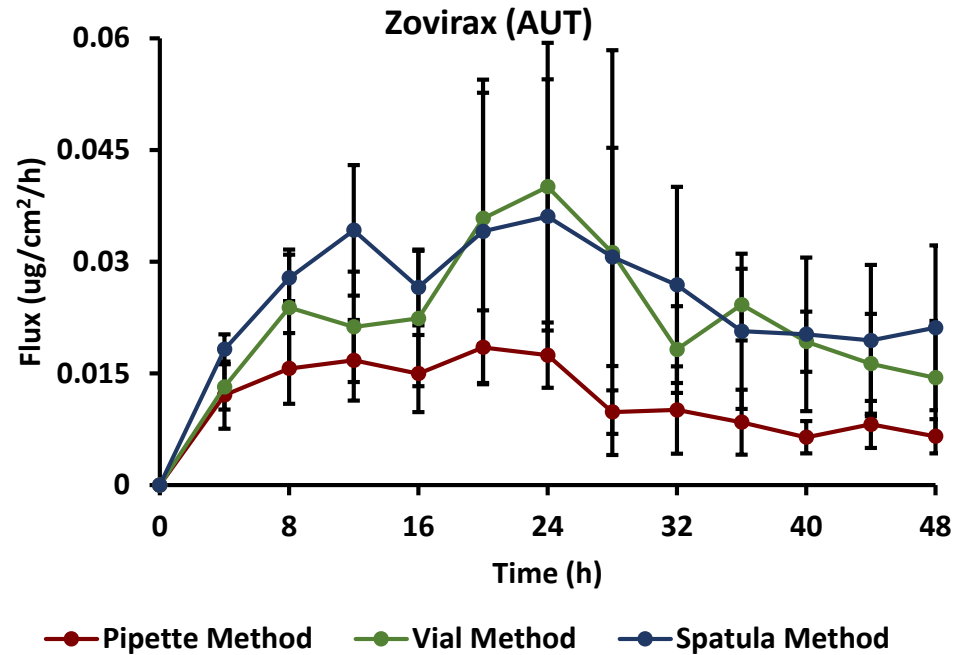


Pipette Technique



Finger Technique

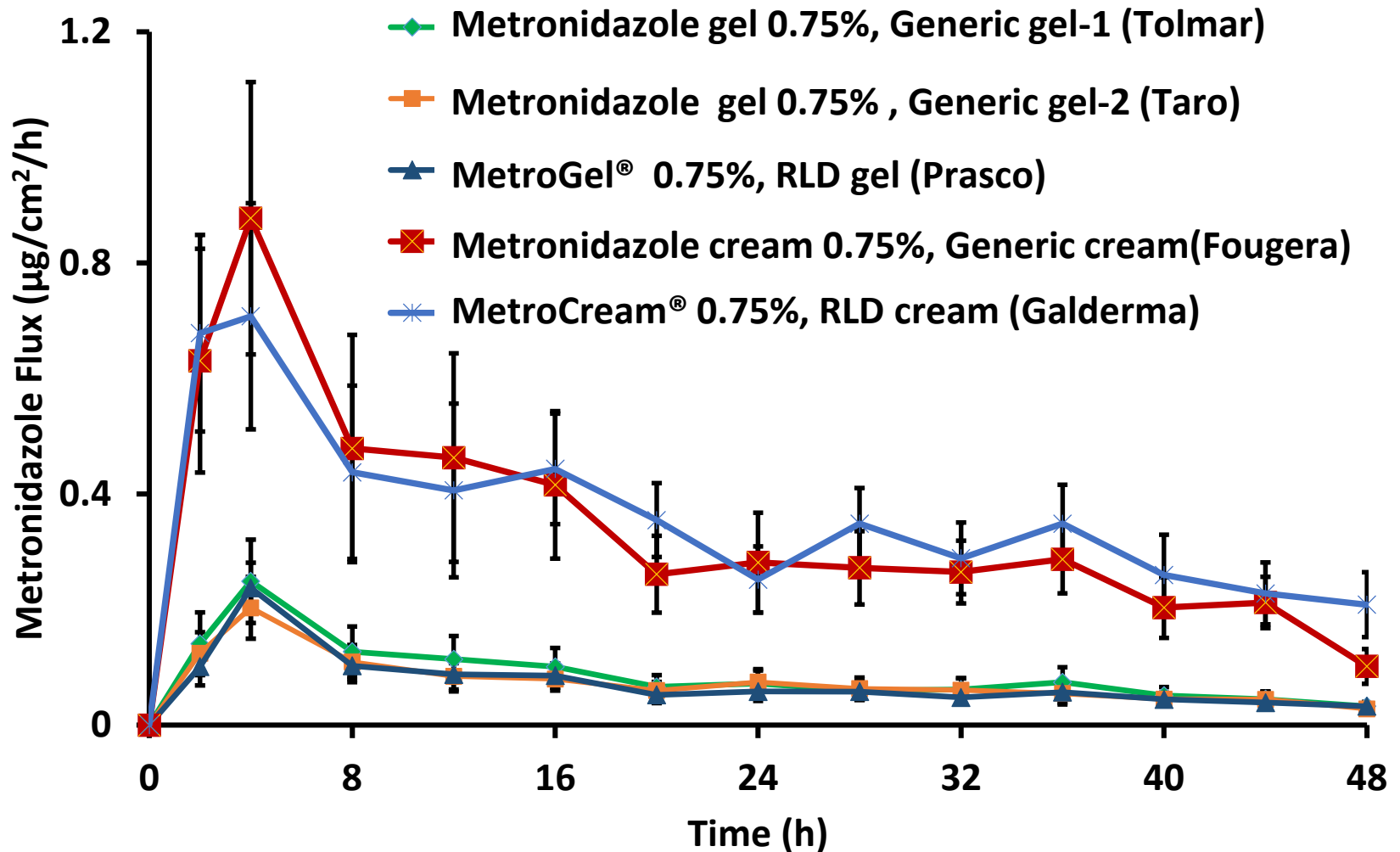
Method of Application of Acyclovir



Method	AUC_{0-t} ($\mu\text{g}/\text{cm}^2$)	J_{max} ($\mu\text{g}/\text{cm}^2/\text{h}$)	T_{max} (h)
Pipette method	0.57 ± 0.16	0.02 ± 0.01	18.67 ± 5.47
Vial method	1.09 ± 0.24	0.05 ± 0.02	28.00 ± 6.69
Spatula method	1.22 ± 0.38	0.05 ± 0.01	16.67 ± 8.55

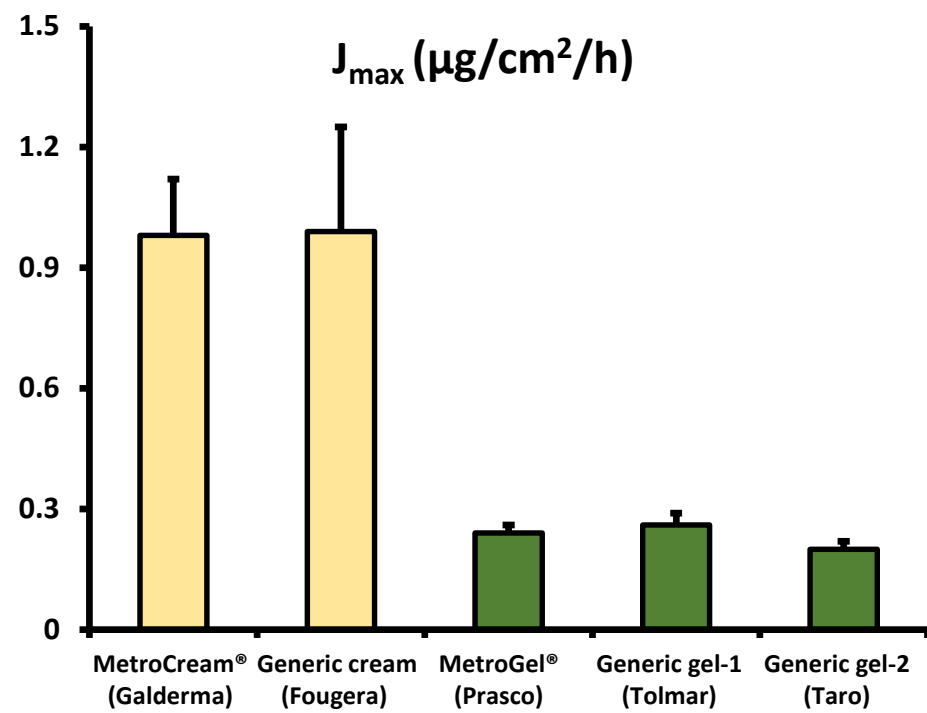
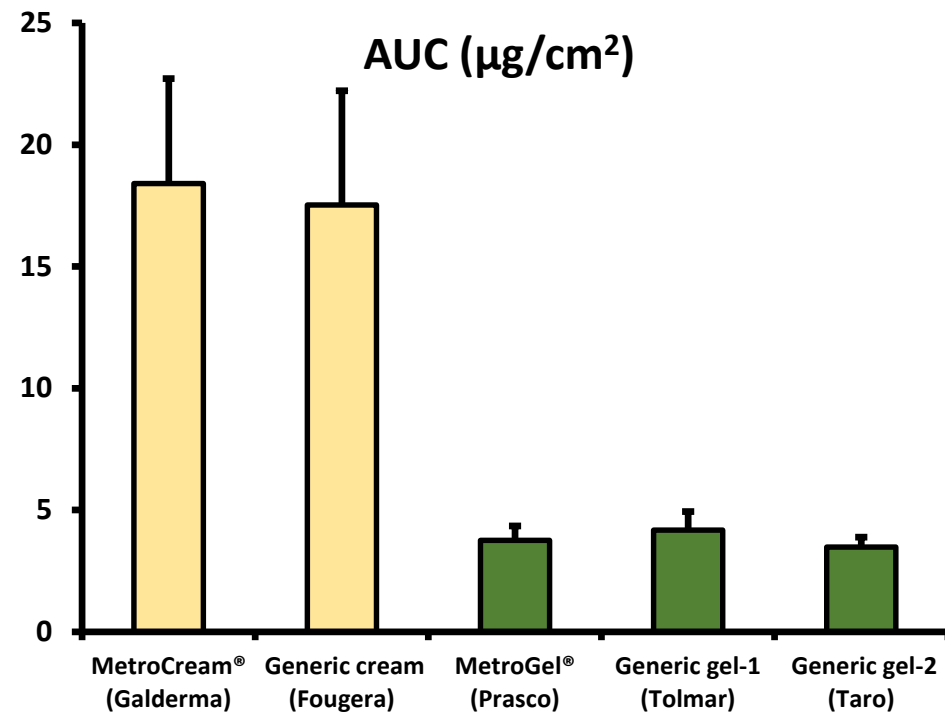
MetroCream[®] 0.75%, RLD cream (Galderma)	Metronidazole cream 0.75%, Generic cream (Fougera)	MetroGel[®] 0.75%, RLD gel (Prasco)	Metronidazole gel 0.75%, Generic gel-1 (Tolmar)	Metronidazole gel 0.75%, Generic gel-2 (Taro)
Emulsifying wax	Emulsifying wax	Carbomer 940	Carbopol 980	Carbomer 940
Isopropyl Palmitate	Isopropyl Palmitate			
Glycerin	Glycerin	Propylene glycol	Propylene glycol	Propylene glycol
Benzyl alcohol	Benzyl alcohol	Methyl paraben	Methyl paraben	Methyl paraben
		Propyl paraben	Propyl paraben	Propyl paraben
Sodium hydroxide/lactic acid	Sodium hydroxide/lactic acid	Sodium hydroxide	Sodium hydroxide	Sodium hydroxide
Purified water	Purified water	Purified water	Purified water	Purified water
		Edetate sodium	Edetate sodium	Edetate sodium
Sorbitol	Sorbitol			

IVPT of Metronidazole Topical Products



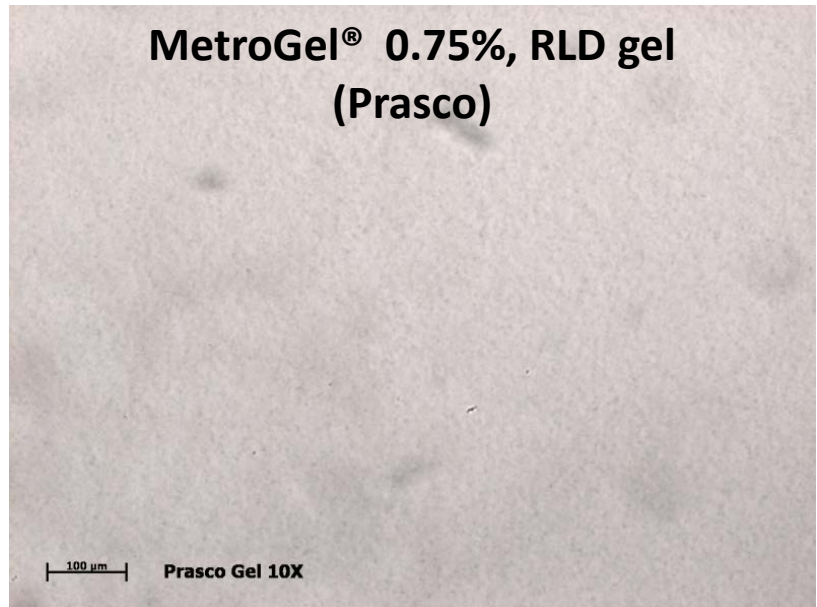
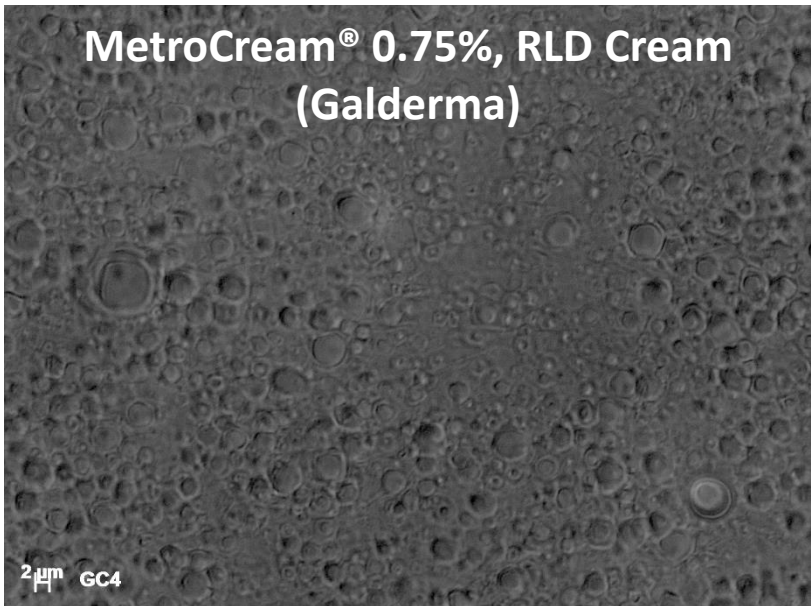
IVPT Results of Metronidazole Products

Product	AUC ($\mu\text{g}/\text{cm}^2$)	J_{max} ($\mu\text{g}/\text{cm}^2/\text{h}$)	T_{max} (h)
MetroCream® (Galderma)	18.41 ± 4.31	0.98 ± 0.14	3.2 ± 0.4
Generic cream (Fougera)	17.53 ± 4.68	0.99 ± 0.26	3.2 ± 0.4
MetroGel® (Prasco)	3.76 ± 0.59	0.24 ± 0.02	4 ± 0
Generic gel-1 (Tolmar)	4.18 ± 0.76	0.26 ± 0.03	3.7 ± 0.5
Generic gel-2 (Taro)	3.48 ± 0.41	0.20 ± 0.0	4 ± 0

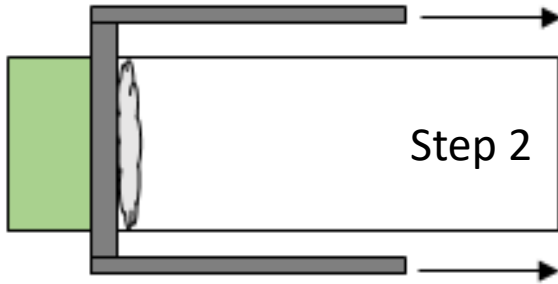


Quality Attribute	MetroCream® 0.75%, RLD cream (Galderma)	Metronidazole cream 0.75%, Generic cream (Fougera)	MetroGel® 0.75%, RLD gel (Prasco)	Metronidazol e gel 0.75% , Generic gel - 1 (Tolmar)	Metronidazol e gel 0.75% , Generic gel - 2 (Taro)
pH	4.82± 0.01	5.05± 0.05	5.23± 0.01	5.02± 0.01	5.48± 0.01
Density (g/cc)	1.0238 ± 0.0004	1.0232 ± 0.0002	1.0104 ± 0.0002	1.0183 ± 0.0007	1.0186 ± 0.0002
WOA (g.sec)	57.61± 0.91	63.95± 0.80	39.38± 0.30	43.93± 0.78	42.03 ± 0.81

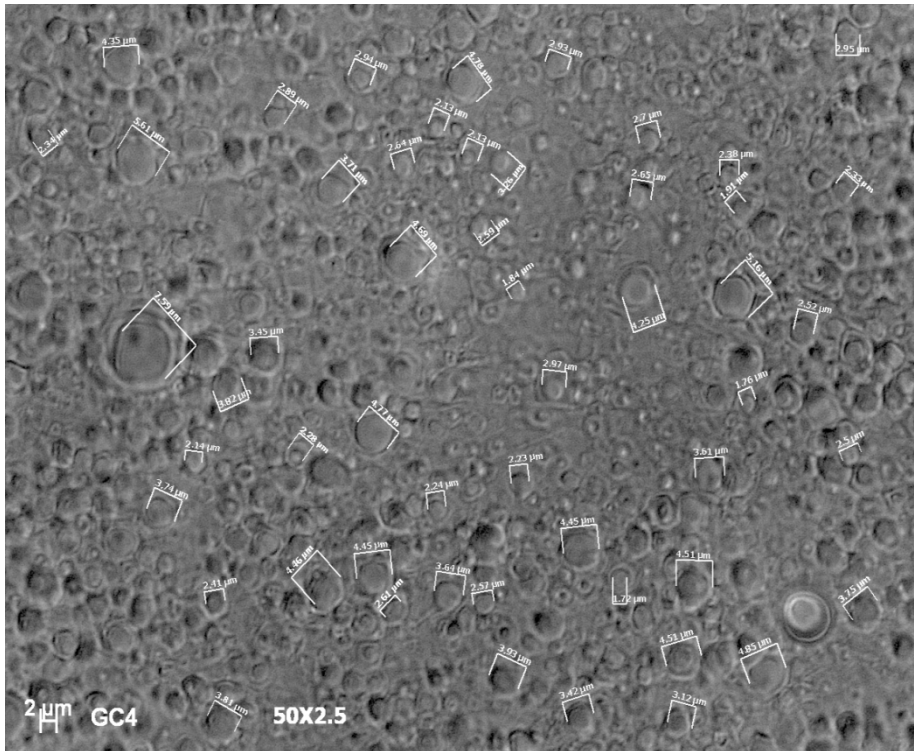
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pH	4.82± 0.01	5.05± 0.05	5.23± 0.01	5.02± 0.01	5.48± 0.01
Density (g/cc)	1.0238 ± 0.0004	1.0232 ± 0.0002	1.0104 ± 0.0002	1.0183 ± 0.0007	1.0186 ± 0.0002
WOA (g.sec)	57.61± 0.91	63.95± 0.80	39.38± 0.30	43.93± 0.78	42.03 ± 0.81
Particle size	---	---	---	---	---



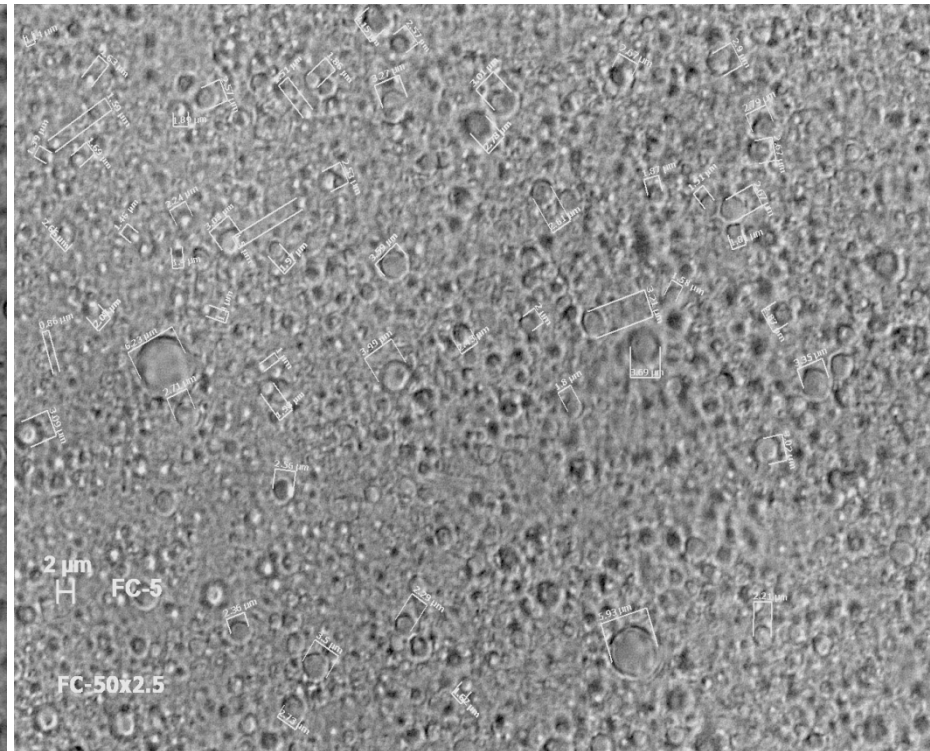
Quality Attribute	MetroCream® 0.75%, RLD cream (Galderma)	Metronidazole cream 0.75%, Generic cream (Fougera)	MetroGel® 0.75%, RLD gel (Prasco)	Metronidazol e gel 0.75% , Generic gel - 1 (Tolmar)	Metronidazol e gel 0.75% , Generic gel - 2 (Taro)	
pH	4.82± 0.01	5.05± 0.05	5.23± 0.01	5.02± 0.01	5.48± 0.01	
Density (g/cc)	1.0238 ± 0.0004	1.0232 ± 0.0002	1.0104 ± 0.0002	1.0183 ± 0.0007	1.0186 ± 0.0002	
WOA (g.sec)	57.61± 0.91	63.95± 0.80	39.38± 0.30	43.93± 0.78	42.03 ± 0.81	
Particle size	---	---	---	---	---	
Globule size, d50 (µm)	d ₁₀	d ₅₀	d ₉₀	d ₁₀	d ₅₀	d ₉₀
	1.88	2.80	4.85	1.38	2.22	3.35



Globule Size Distribution



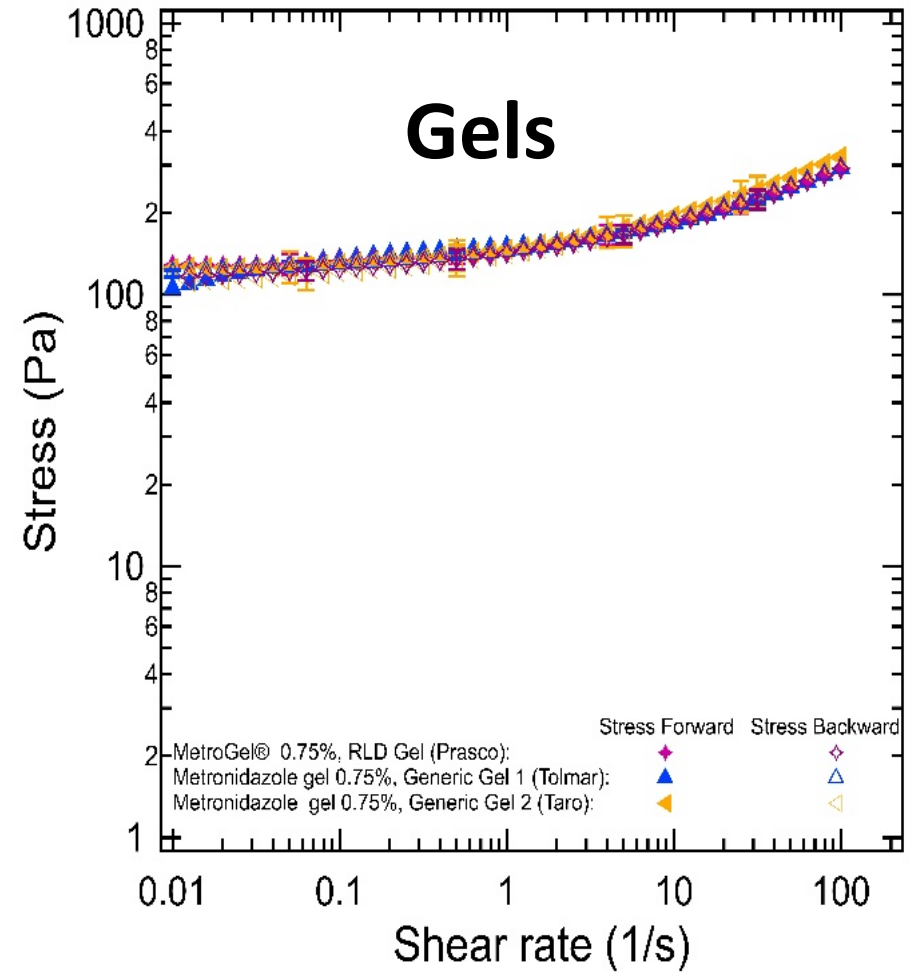
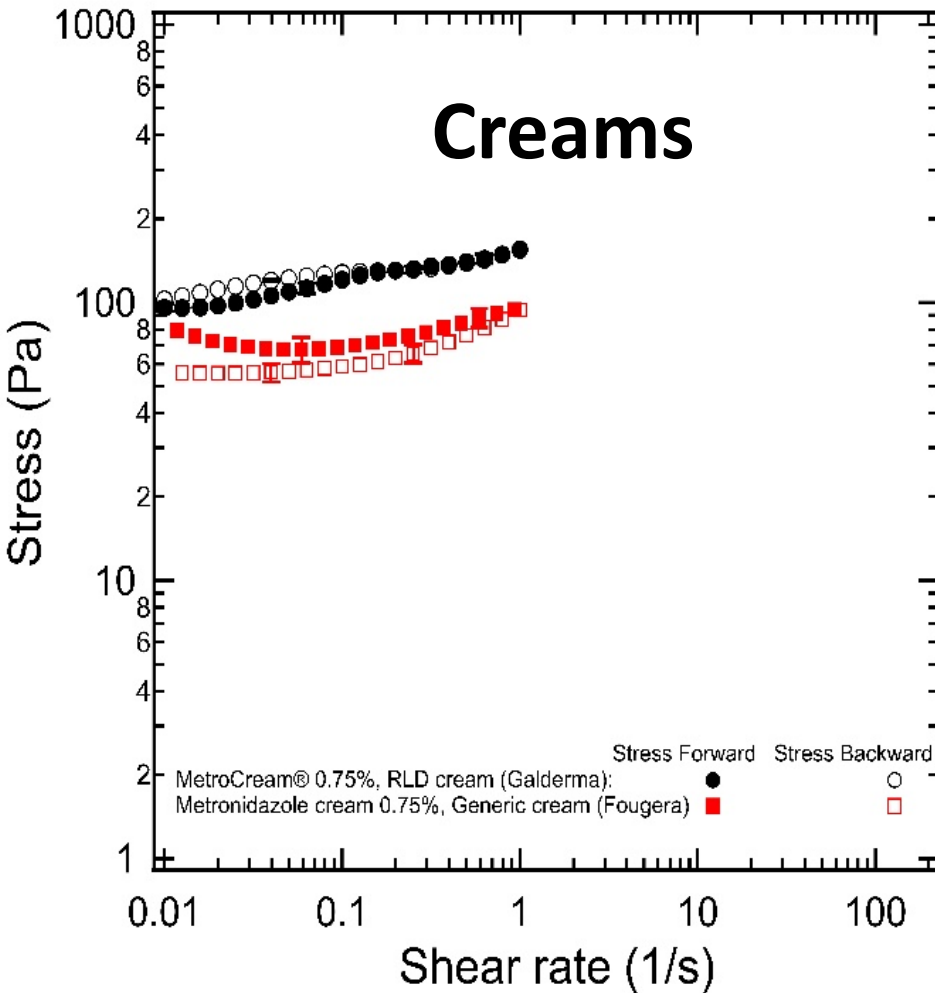
**MetroCream® 0.75%, RLD
Cream (Galderma)**



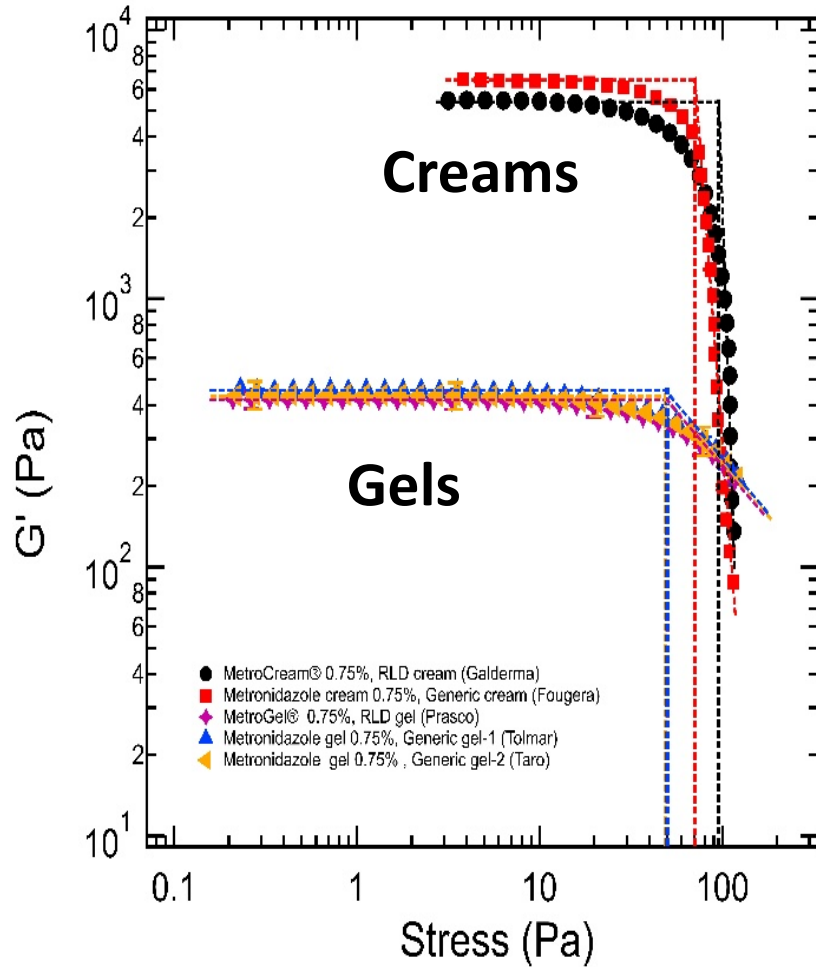
**Metronidazole cream
0.75%, Generic cream-1
(Fougera)**

Quality Attribute	MetroCream® 0.75%, RLD cream (Galderma)			Metronidazole cream 0.75%, Generic cream (Fougera)			MetroGel® 0.75%, RLD gel (Prasco)	Metronidazol e gel 0.75% , Generic gel - 1 (Tolmar)	Metronidazol e gel 0.75% , Generic gel - 2 (Taro)
pH	4.82± 0.01			5.05± 0.05			5.23± 0.01	5.02± 0.01	5.48± 0.01
Density (g/cc)	1.0238 ± 0.0004			1.0232 ± 0.0002			1.0104 ± 0.0002	1.0183 ± 0.0007	1.0186 ± 0.0002
WOA (g.sec)	57.61± 0.91			63.95± 0.80			39.38± 0.30	43.93± 0.78	42.03 ± 0.81
Particle size	---			---			---	---	---
Globule size, d50 (µm)	d ₁₀	d ₅₀	d ₉₀	d ₁₀	d ₅₀	d ₉₀	---	---	---
	1.88	2.80	4.85	1.38	2.22	3.35			
Drug in Aq (mg/g)	4.20± 0.42			2.92± 0.35			---	---	---
Drug in Oil (mg/g)	2.58± 0.11			3.94± 0.18			---	---	---

Rheological Studies-Metronidazole Products



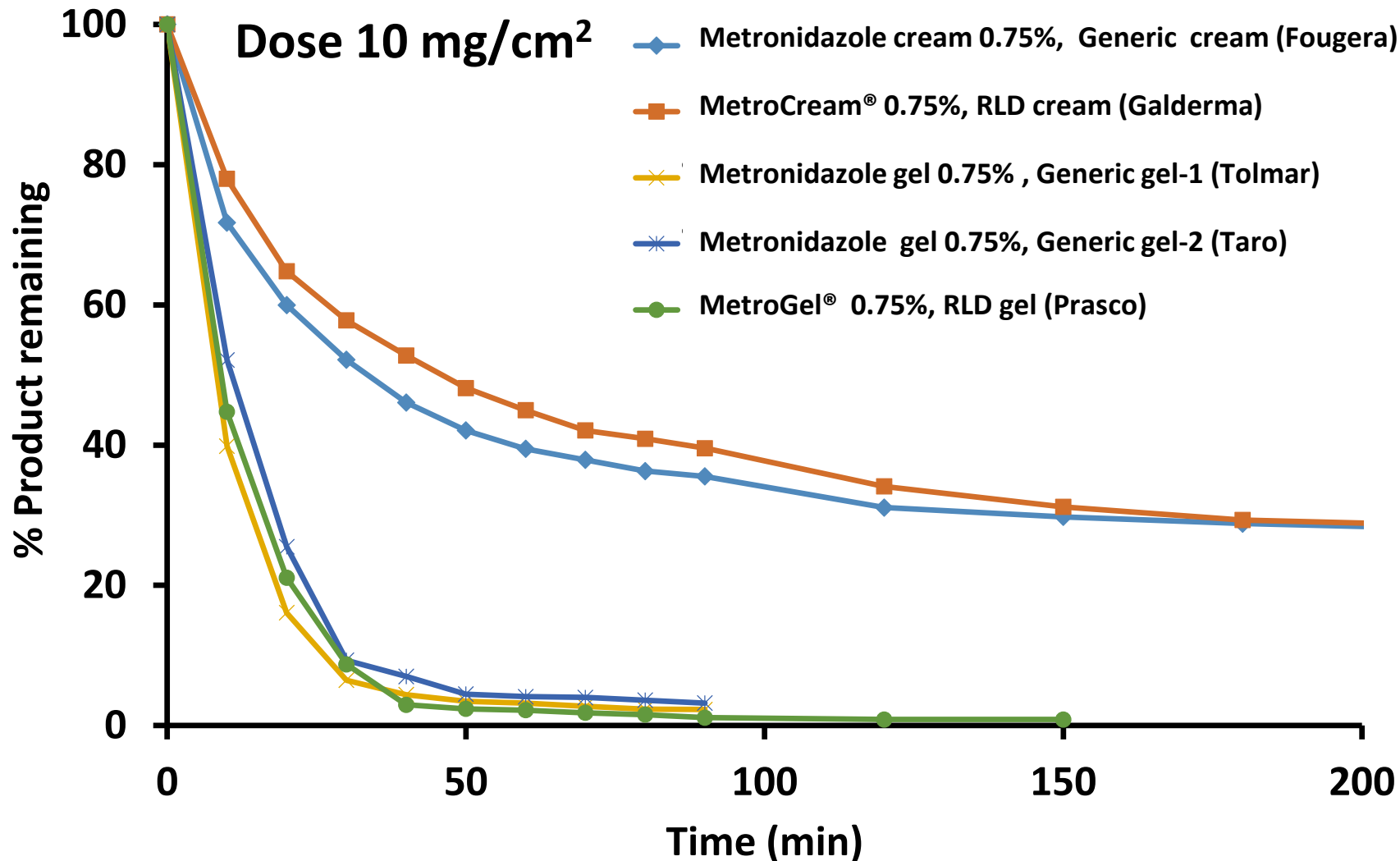
Rheological Studies-Metronidazole Products



Product	Initial Viscosity (@0.01/S ⁻¹)	Yield Stress
MetroCream®	9541 ± 284	94 ± 0.00
Generic cream	6830 ± 1166	70 ± 3.00
MetroGel®	12779 ± 1215	50 ± 4.04
Generic gel-1	10534 ± 263	50 ± 0.00
Generic gel-2	12489 ± 1692	49 ± 5.20

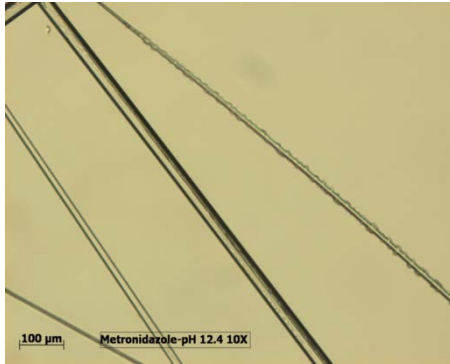
Quality Attribute	MetroCream® 0.75%, RLD cream (Galderma)	Metronidazole cream 0.75%, Generic cream (Fougera)	MetroGel® 0.75%, RLD gel (Prasco)	Metronidazole gel 0.75% , Generic gel - 1 (Tolmar)	Metronidazole gel 0.75% , Generic gel - 2 (Taro)	
pH	4.82± 0.01	5.05± 0.05	5.23± 0.01	5.02± 0.01	5.48± 0.01	
Density (g/cc)	1.0238 ± 0.0004	1.0232 ± 0.0002	1.0104 ± 0.0002	1.0183 ± 0.0007	1.0186 ± 0.0002	
WOA (g.sec)	57.61± 0.91	63.95± 0.80	39.38± 0.30	43.93± 0.78	42.03 ± 0.81	
Particle size	---	---	---	---	---	
Globule size, d50 (µm)	d ₁₀	d ₅₀	d ₉₀	d ₁₀	d ₅₀	d ₉₀
	1.88	2.80	4.85	1.38	2.22	3.35
Drug in Aq (mg/g)	4.20± 0.42	2.92± 0.35	---	---	---	
Drug in Oil (mg/g)	2.58± 0.11	3.94± 0.18	---	---	---	
Water activity	0.977 ± 0.000	0.974 ± 0.002	0.992 ± 0.005	0.994 ± 0.004	1.002 ± 0.008	

Drying Profile of Metronidazole Topical Products

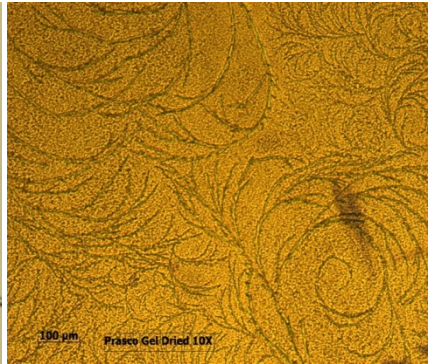


Quality Attribute	MetroCream® 0.75%, RLD cream (Galderma)	Metronidazole cream 0.75%, Generic cream (Fougera)	MetroGel® 0.75%, RLD gel (Prasco)	Metronidazole gel 0.75% , Generic gel - 1 (Tolmar)	Metronidazole gel 0.75% , Generic gel - 2 (Taro)	
pH	4.82± 0.01	5.05± 0.05	5.23± 0.01	5.02± 0.01	5.48± 0.01	
Density (g/cc)	1.0238 ± 0.0004	1.0232 ± 0.0002	1.0104 ± 0.0002	1.0183 ± 0.0007	1.0186 ± 0.0002	
WOA (g.sec)	57.61± 0.91	63.95± 0.80	39.38± 0.30	43.93± 0.78	42.03 ± 0.81	
Particle size	---	---	---	---	---	
Globule size, d50 (µm)	d ₁₀	d ₅₀	d ₉₀	d ₁₀	d ₅₀	d ₉₀
	1.88	2.80	4.85	1.38	2.22	3.35
Drug in Aq (mg/g)	4.20± 0.42	2.92± 0.35	---	---	---	
Drug in Oil (mg/g)	2.58± 0.11	3.94± 0.18	---	---	---	
Water activity	0.977 ± 0.000	0.974 ± 0.002	0.992 ± 0.005	0.994 ± 0.004	1.002 ± 0.008	
Drying, T ₃₀ % (min)	15.67± 0.76	11.40± 1.15	5.45± 0.45	4.70 ± 0.26	6.47± 0.55	

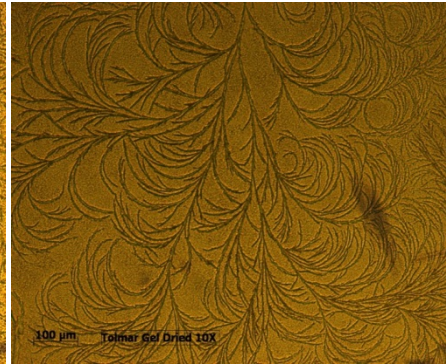
Crystal Pattern in Gels after Drying



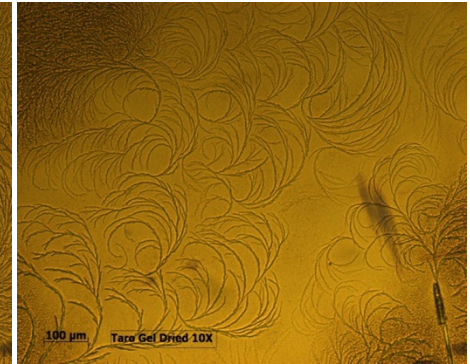
**Metronidazole
solution**



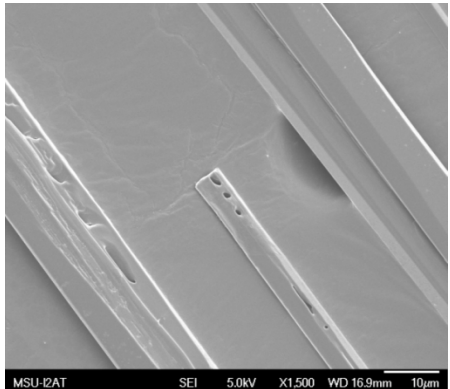
**MetroGel® 0.75%,
RLD gel (Prasco)**



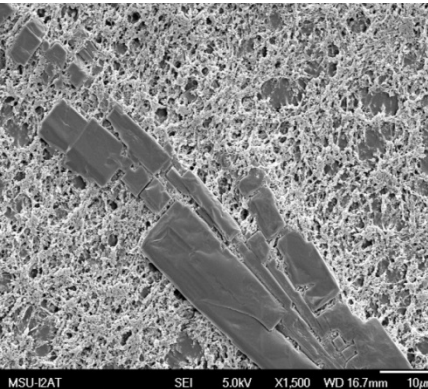
**Metronidazole gel
0.75%, Generic gel-1
(Tolmar)**



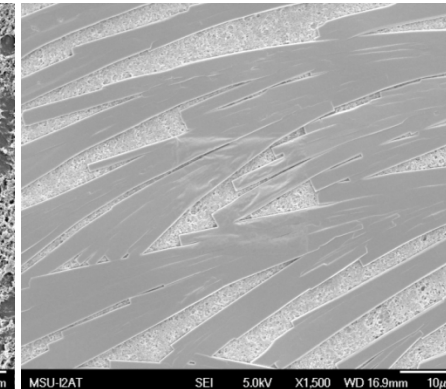
**Metronidazole gel
0.75%, Generic gel-2
(Taro)**



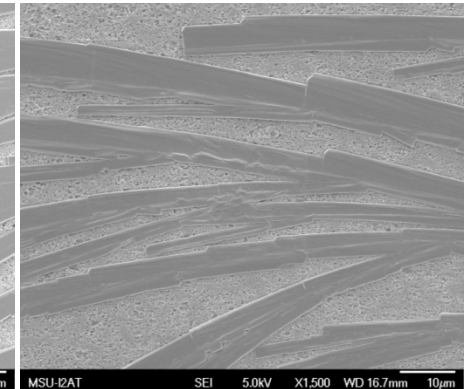
**Metronidazole
solution**



**MetroGel® 0.75%,
RLD gel (Prasco)**

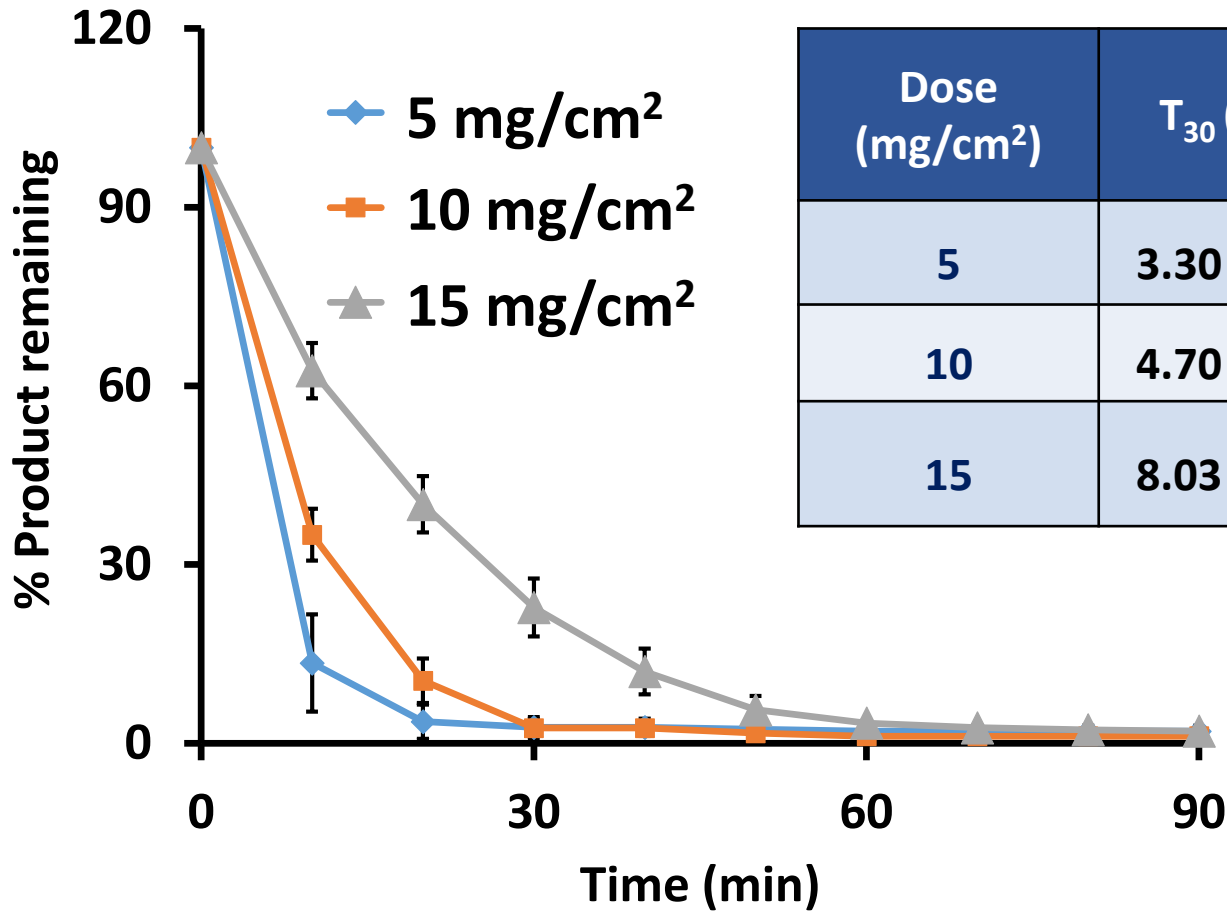


**Metronidazole gel
0.75%, Generic gel-1
(Tolmar)**



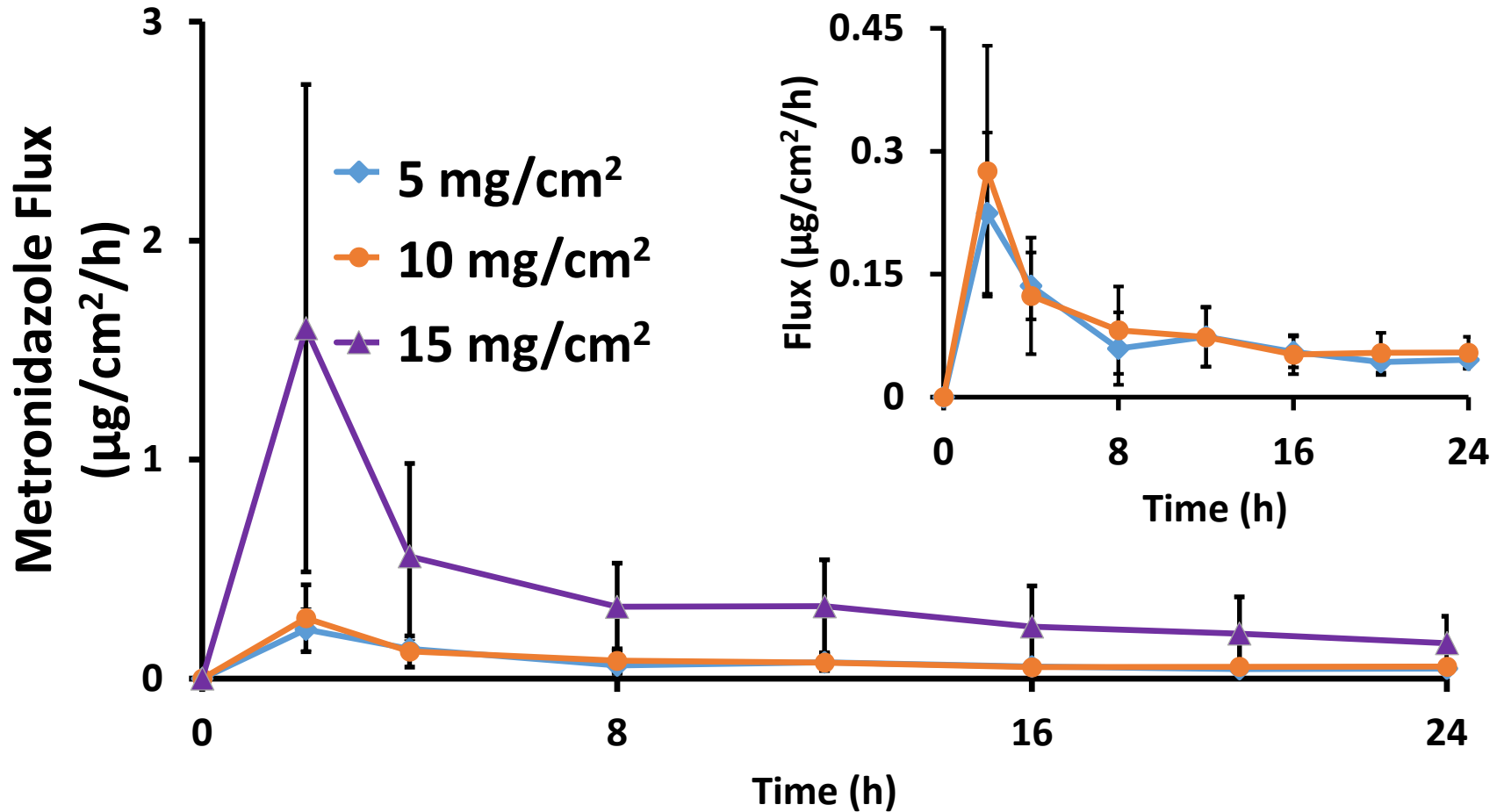
**Metronidazole gel
0.75%, Generic gel-2
(Taro)**

Drying Rate of Metronidazole Gel 0.75%

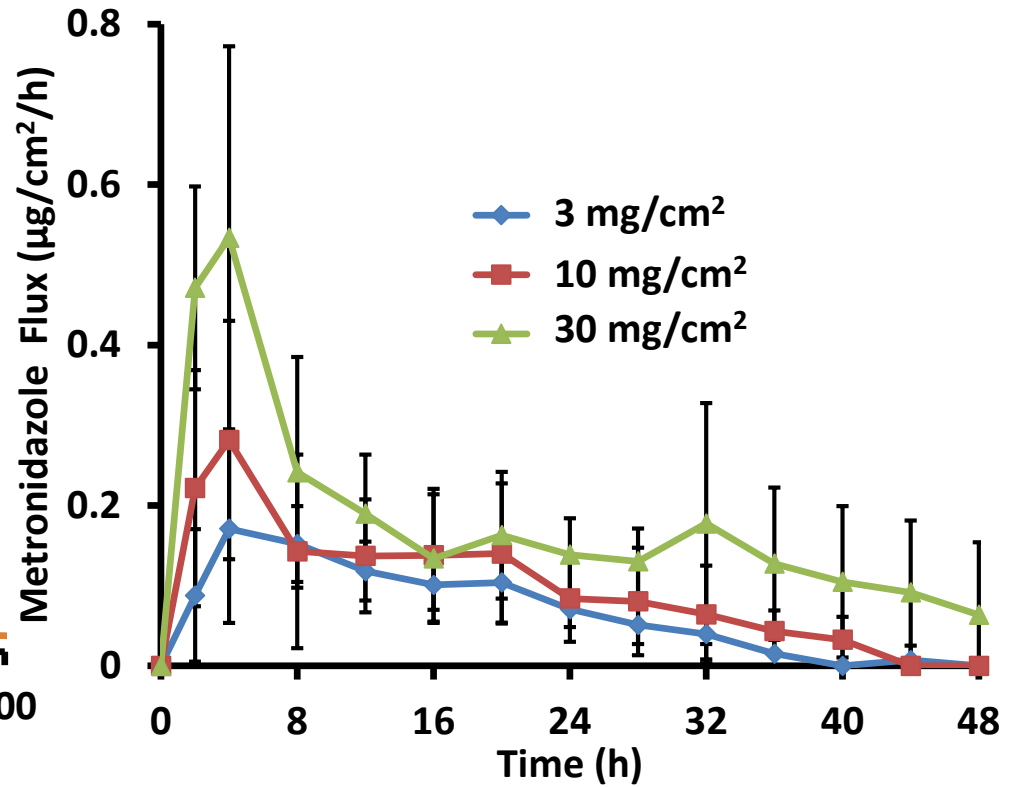
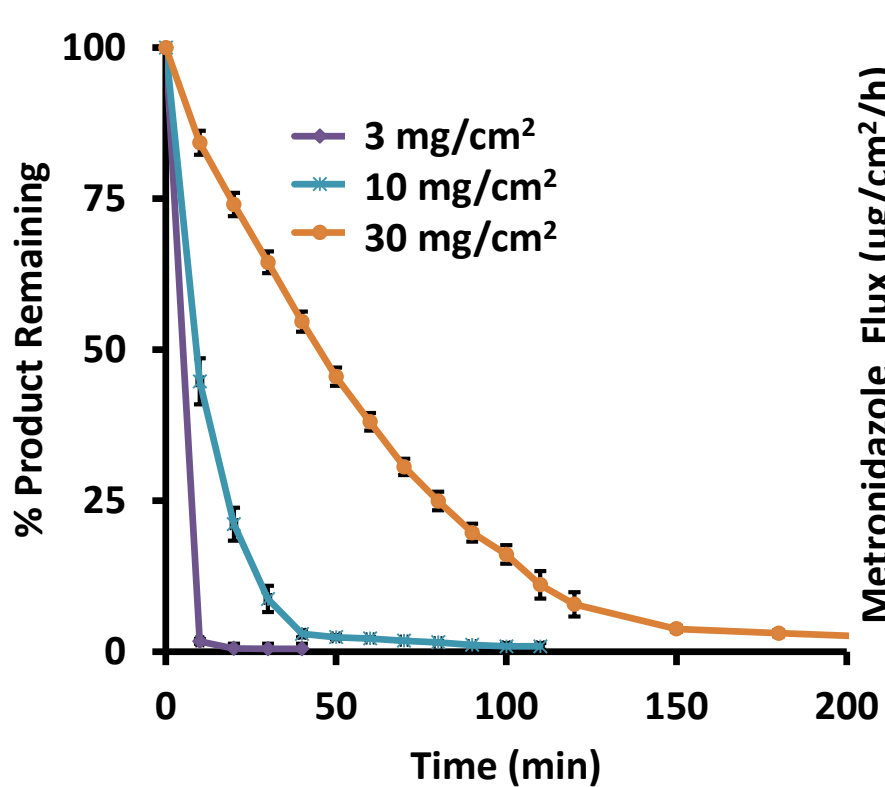


Dose (mg/cm ²)	T ₃₀ (min)	T ₅₀ (min)
5	3.30 ± 0.26	5.60 ± 0.53
10	4.70 ± 0.26	7.87 ± 0.42
15	8.03 ± 1.07	15.63 ± 2.10

Metronidazole Gel 0.75% IVPT Dose Comparison



Metronidazole Gel 0.75% Drying and IVPT Profile



T₃₀ (min)

3 mg/cm²

10 mg/cm²

30 mg/cm²

3.10 ± 0.00

5.47 ± 0.45

24.33 ± 2.02

AUC (µg/cm²/h)

3 mg/cm²

10 mg/cm²

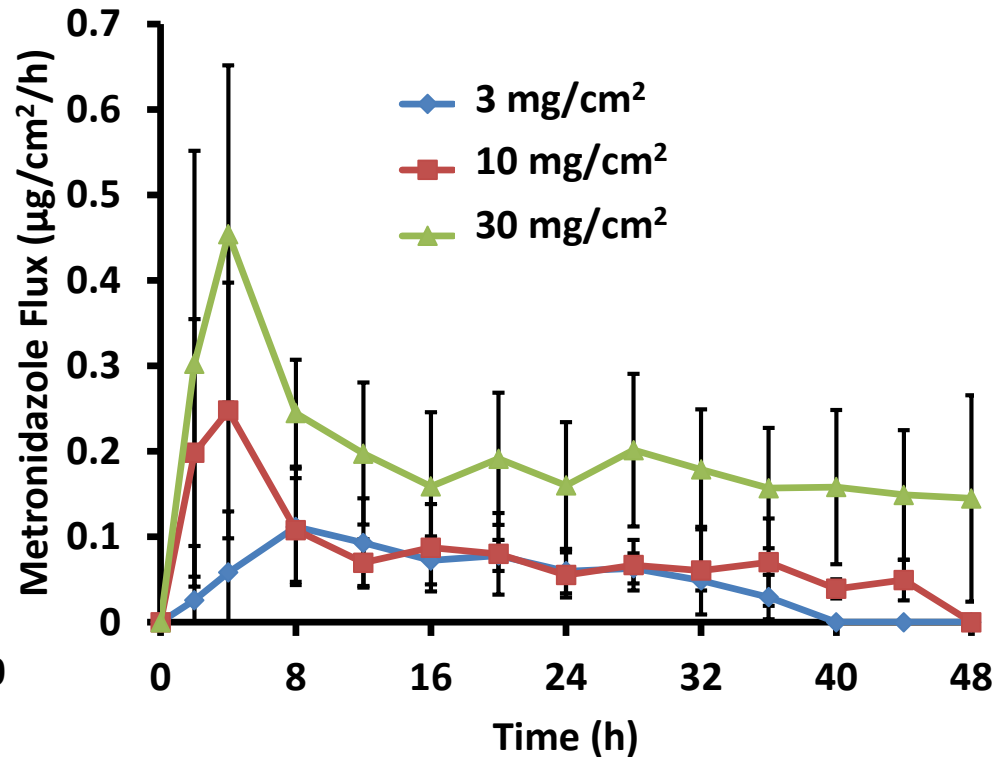
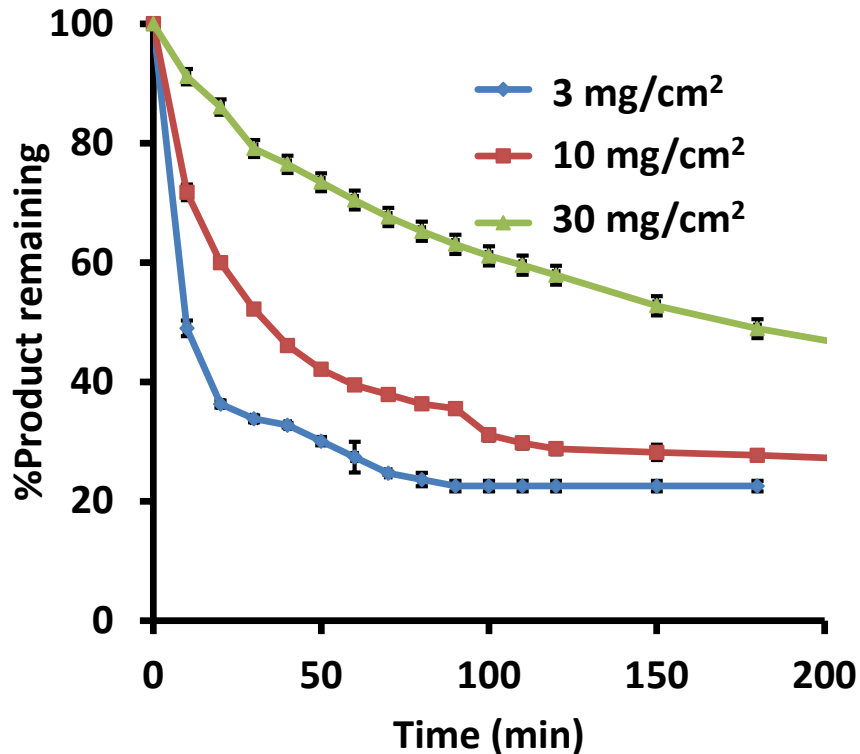
30 mg/cm²

3.32 ± 0.91

4.74 ± 2.19

8.66 ± 3.11

Metronidazole Cream 0.75% Drying and IVPT Profile



T₃₀ (min)

3 mg/cm²

10 mg/cm²

30 mg/cm²

6.00± 0.1

11.40± 1.15

61.67± 5.13

AUC (µg/cm²/h)

3 mg/cm²

10 mg/cm²

30 mg/cm²

2.45±0.69

3.89±1.97

9.45± 3.38

Conclusions

- The microstructural characteristics could significantly influence the formulation performance.
- Post application changes in the formulation plays a major role in determining dermal bioavailability of drugs.
- Development of appropriate tools to characterize the microstructural characteristics of topical dosage forms needs to be developed and validated.
- IVPT is a reliable tool to assess the BA/BE of topical products. A systematic approach would help in a good study design of IVPT.

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