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

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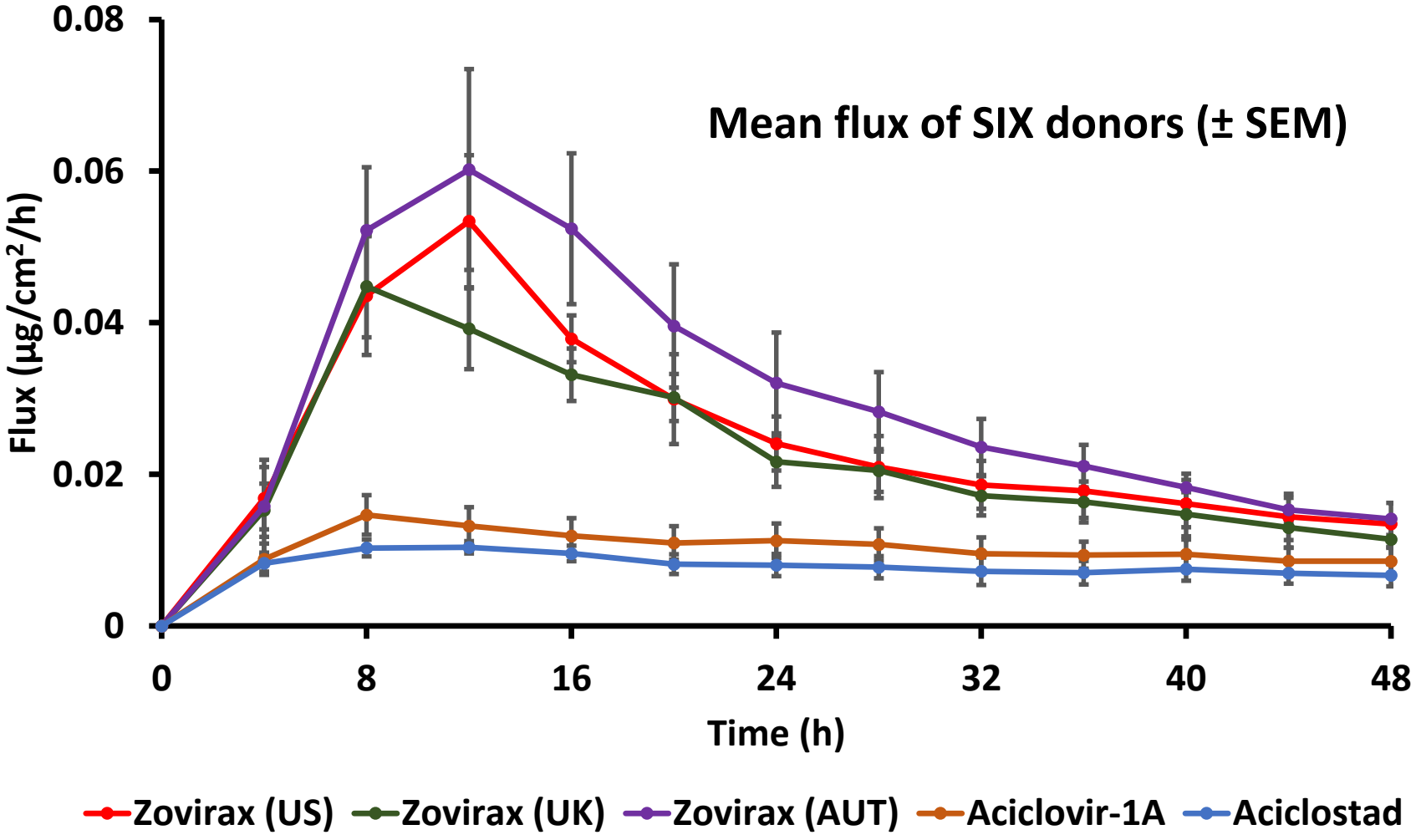
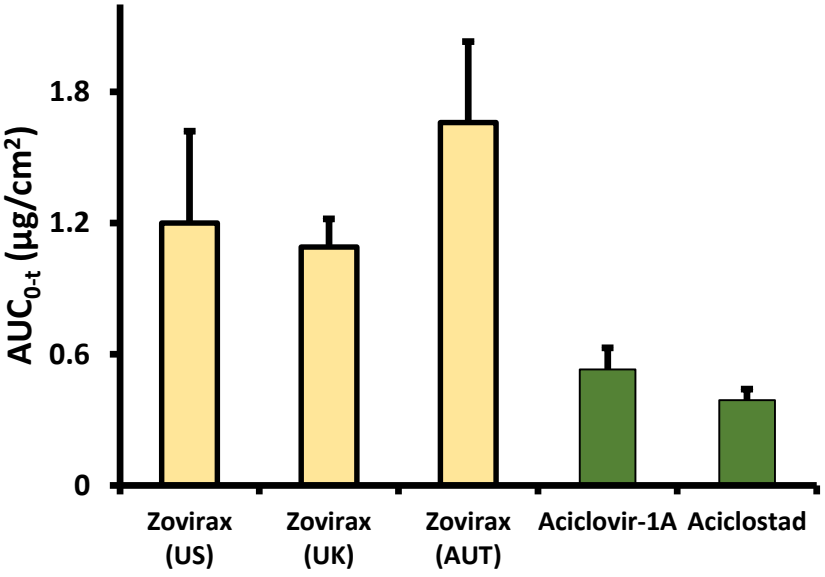
Zovirax (USA)	Zovirax (UK)	Zovirax (Austria)	Aciclostad (Austria)	Aciclovir 1A (Austria)
Mineral oil	Liquid Paraffin	Liquid Paraffin	Liquid Paraffin	Viscous Paraffin
White petrolatum	White soft paraffin	White Vaseline	White Vaseline	White Vaseline
Water	Water	Purified water	Water	Water
Propylene glycol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

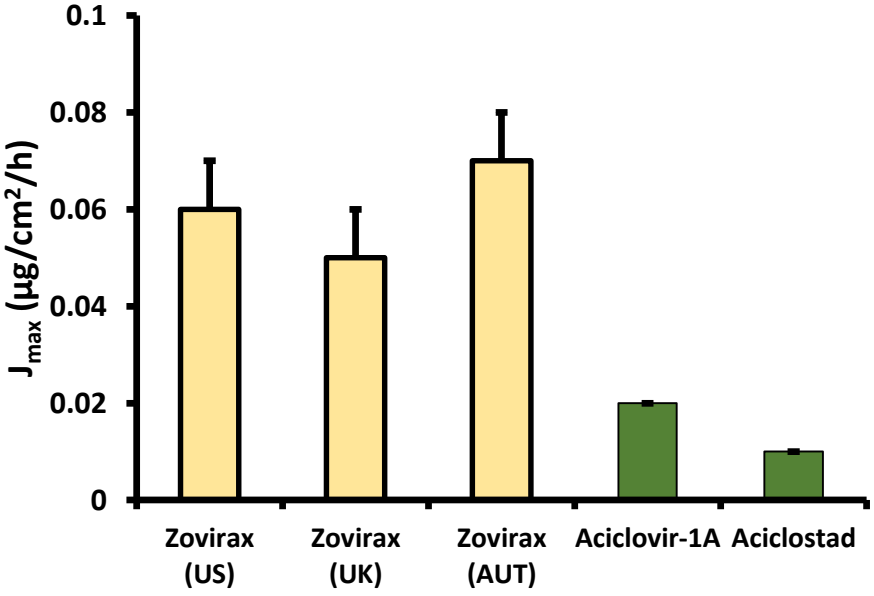
In Vitro Permeation Test



Product	AUC_{0-t} (µg/cm²)	J_{max} (µg/cm²/h)	T_{max} (h)
Zovirax (US)	1.20 ± 0.42	0.06 ± 0.01	10.67 ± 0.85
Zovirax (UK)	1.09 ± 0.13	0.05 ± 0.01	9.33 ± 0.82
Zovirax (AUT)	1.66 ± 0.37	0.07 ± 0.01	10.67 ± 0.82
Aciclovir-1A	0.53 ± 0.10	0.02 ± 0.00	10.0 ± 3.35
Aciclostad	0.39 ± 0.05	0.01 ± 0.00	10.0 ± 1.37



AUC_{0-t} – Acyclovir products



J_{max} – Acyclovir products

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

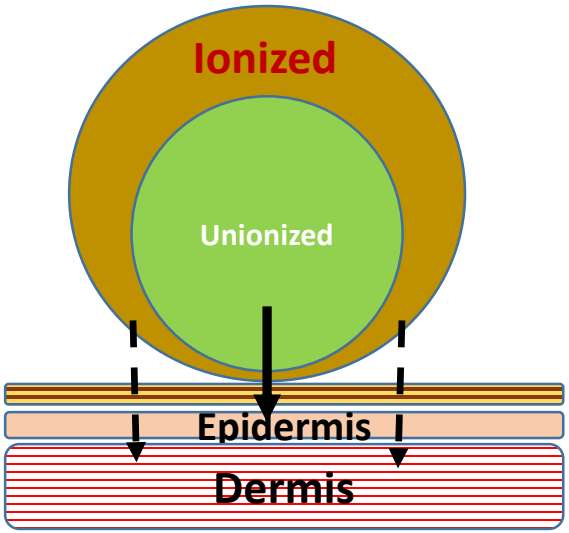
- pH of the formulation
- Dissolved/Undissolved drug
- Particle size
- Polymorphism
- Rheological Studies
- Solvent activity
- Globule size

5% w/w Acyclovir Creams

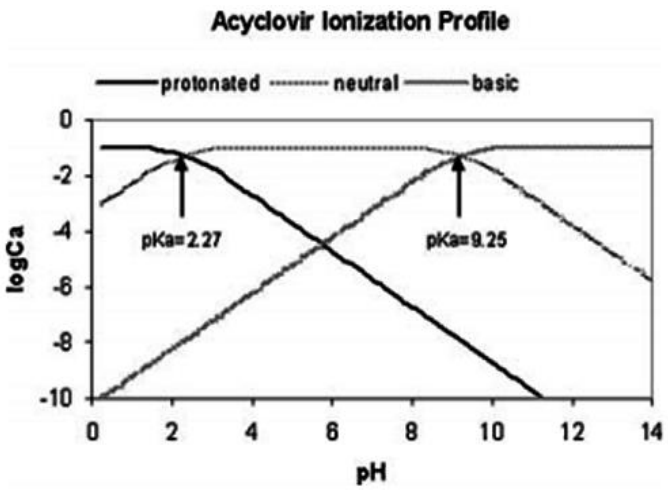
Zovirax (US)
Zovirax (UK)
Zovirax (AUT)
Aciclovir-1A
Aciclostad

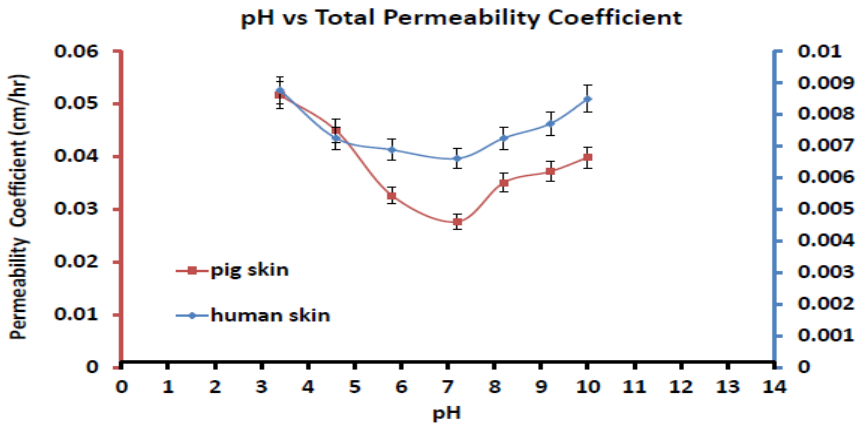
Austria

pH as a Quality Attribute



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





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

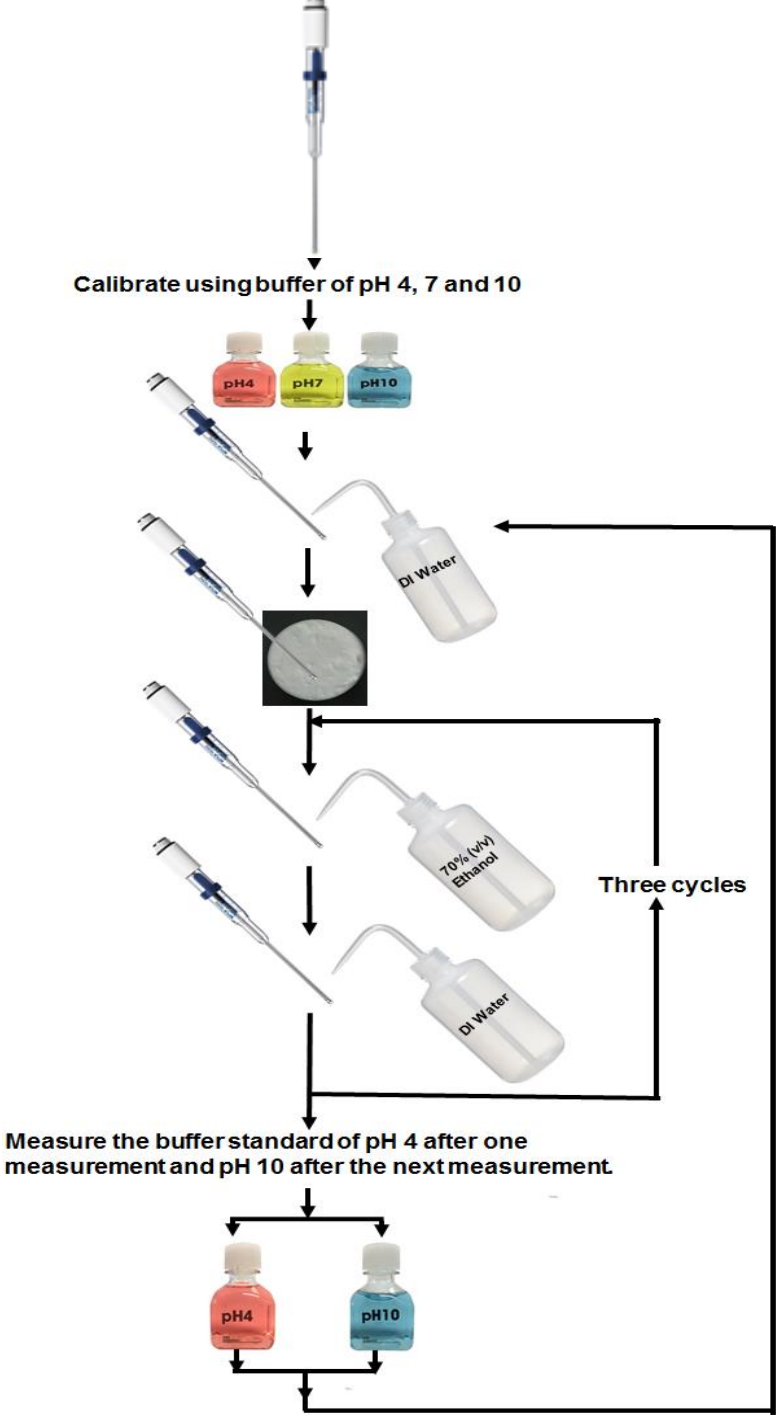
InLab Science

InLab Viscous

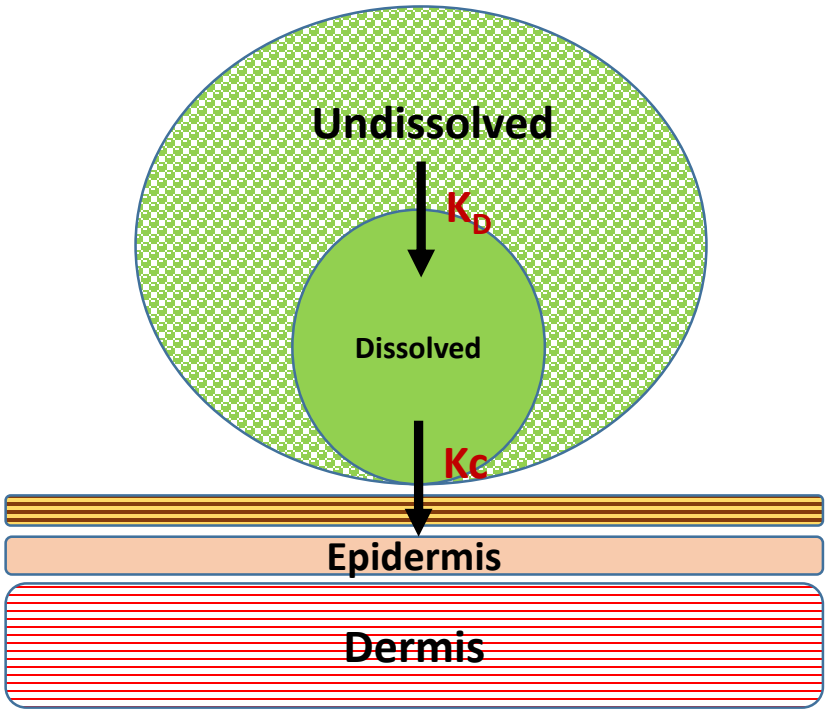
InLab Micro

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.*

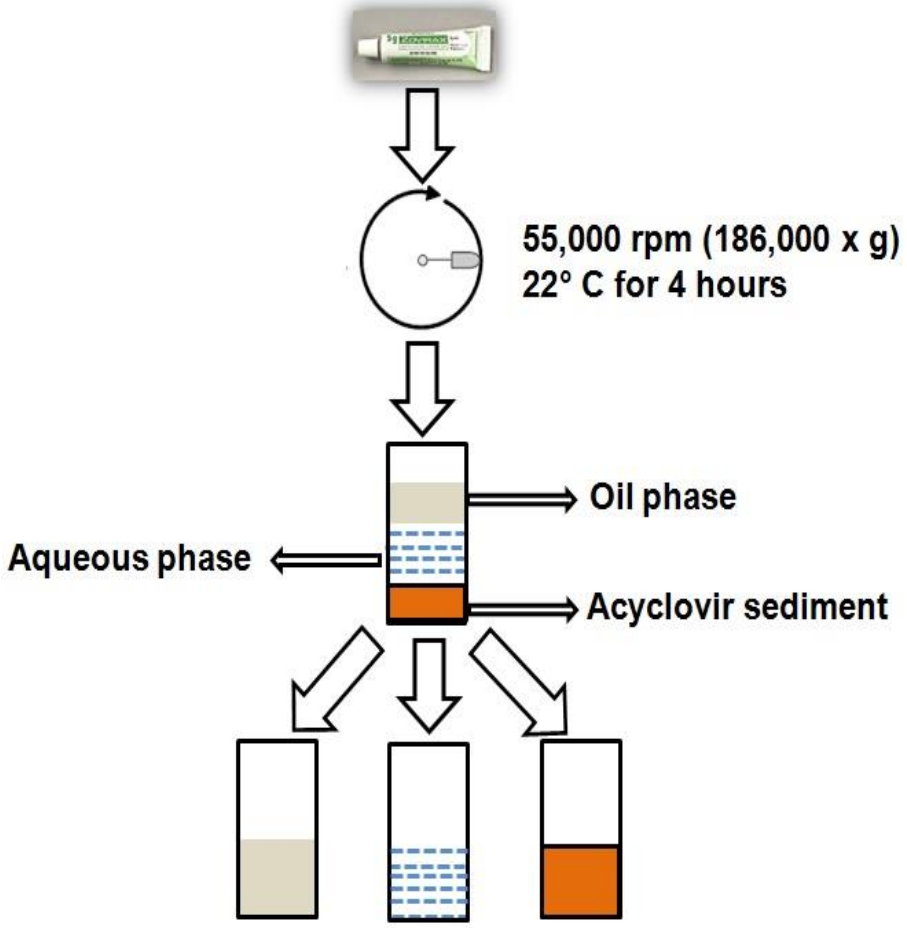


Drug Absorption from Topical Product



$$\frac{\text{Dissolved Drug}}{\text{Undissolved Drug}}$$

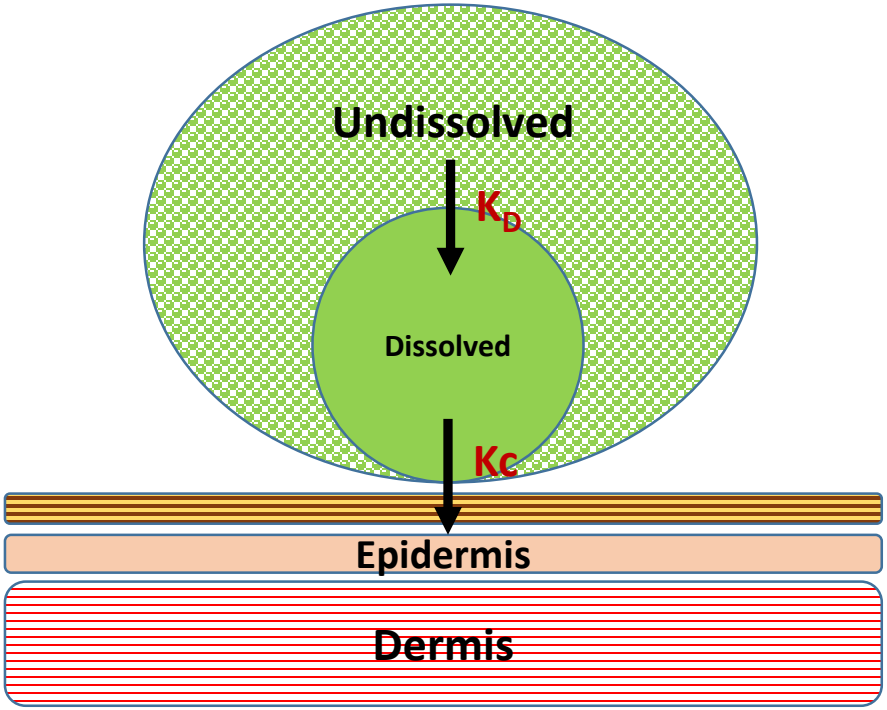
Phase Separation



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	0.3 ± 0.02

Drug Absorption from Topical Product



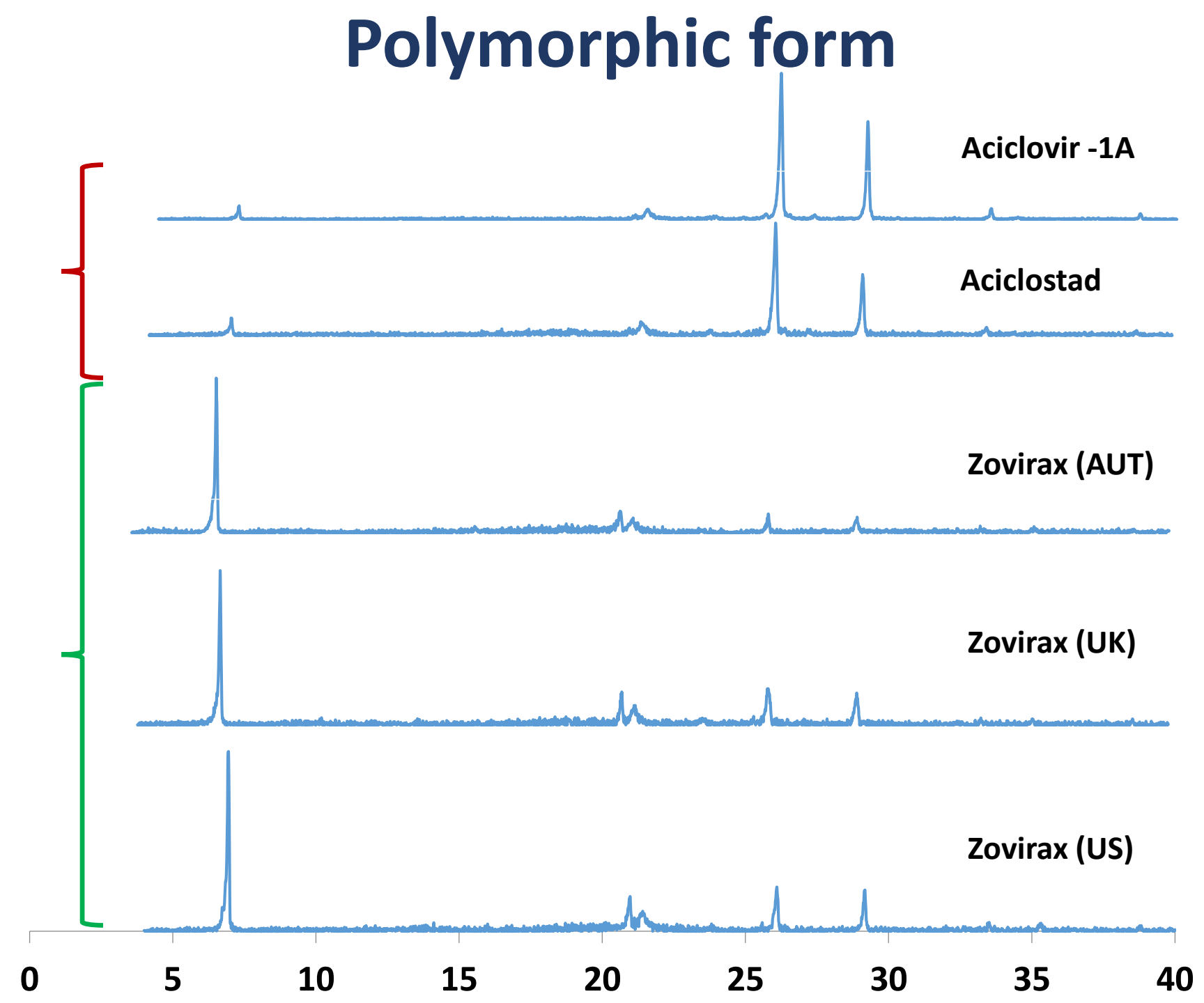
$$K_D \geq K_c$$

Rate of Dissolution of Drug

- Particle Size
- Polymorphic form
- Morphology of particles

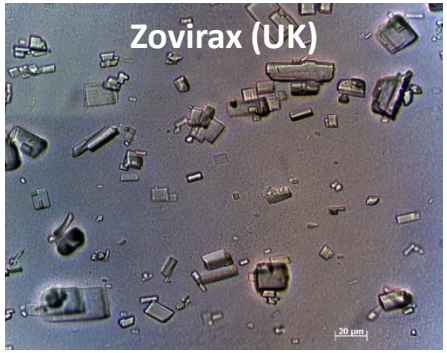
Dose	Total Drug	Dissolved Drug	Undissolved drug
15 mg/cm^2	750 µg/cm^2	18.75 µg/cm^2	731.25 µg/cm^2

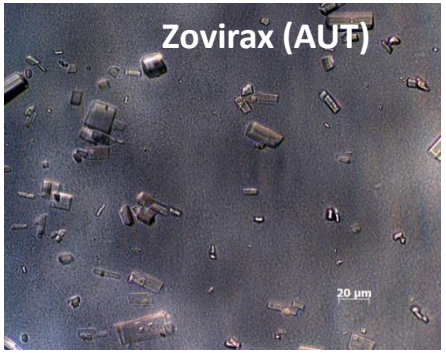
Polymorphic form

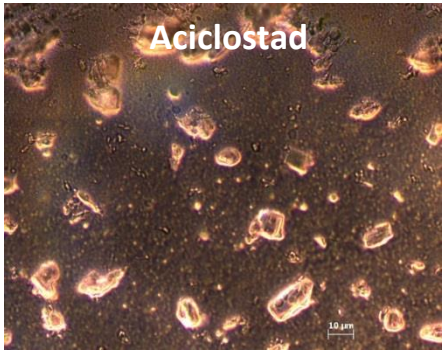


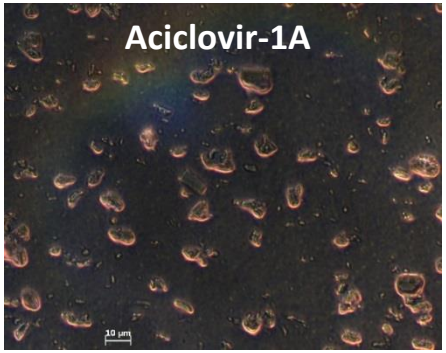
Particle Size and Morphology

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







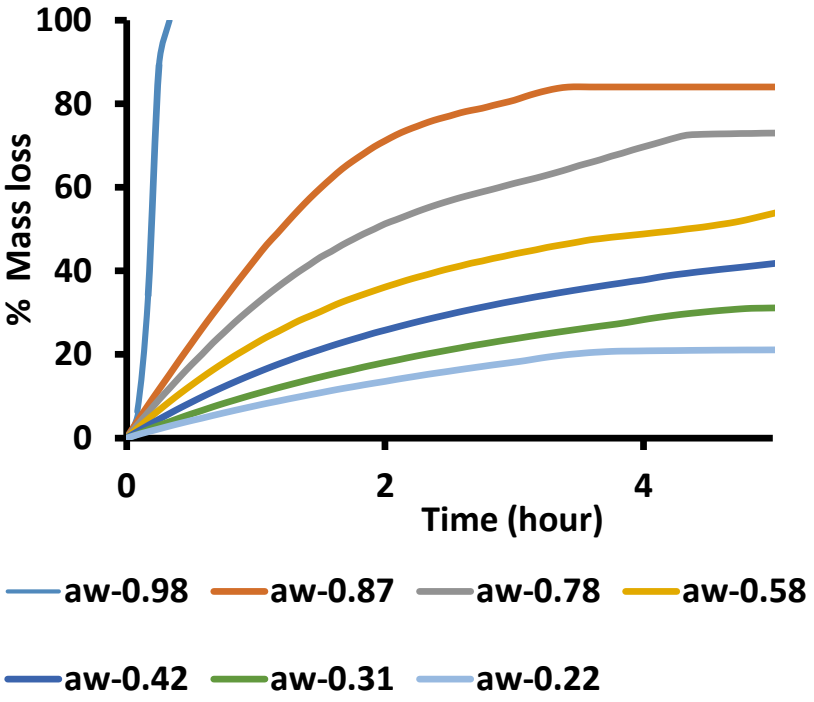


Water Activity (a_w)

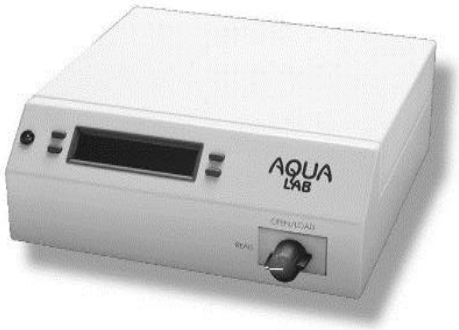
$a_w = \rho/\rho_0$

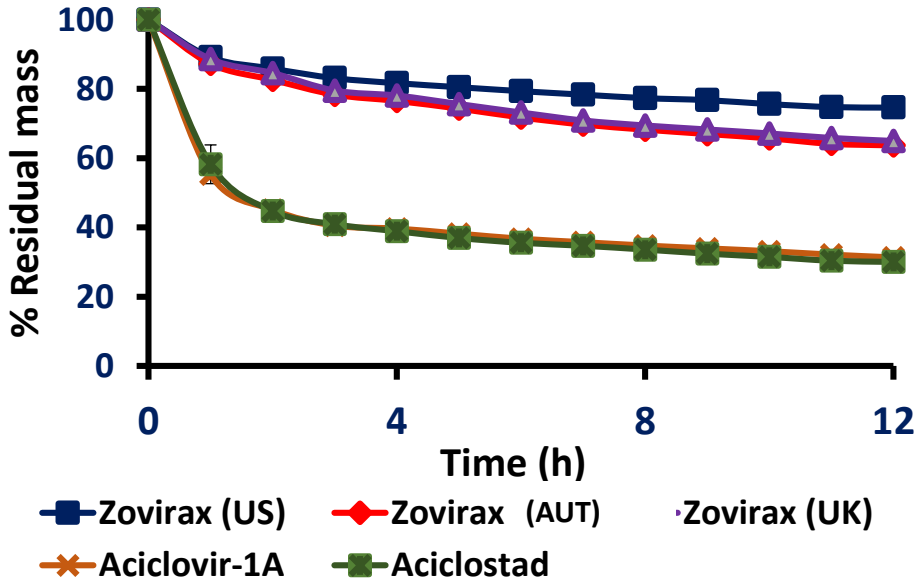
ρ = Partial vapor pressure of water in the product

ρ_0 = vapor pressure of pure water

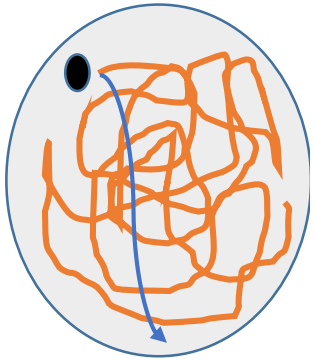


Product	Water Activity (a_w)
Zovirax (US)	0.753 ± 0.002
Zovirax (AUT)	0.735 ± 0.000
Zovirax (UK)	0.732 ± 0.002
Aciclovir–1A	0.948 ± 0.001
Aciclostad	0.948 ± 0.003



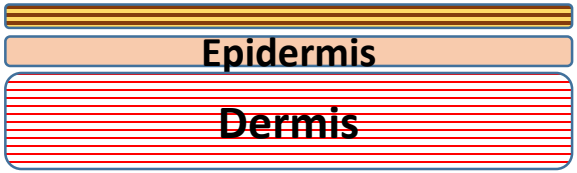


Rheological Studies-Acyclovir Creams



Drug diffusion

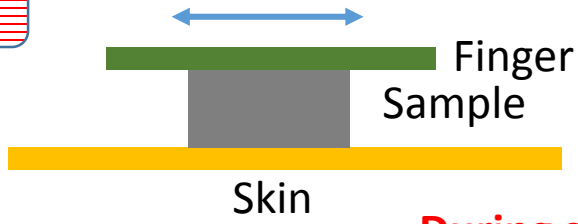
Skin Permeation



Rheology of a formulation is a direct function of microstructure.

Diffusivity inversely scales with the viscosity of the media.

TA Instruments HR2 rheometer with solvent trap



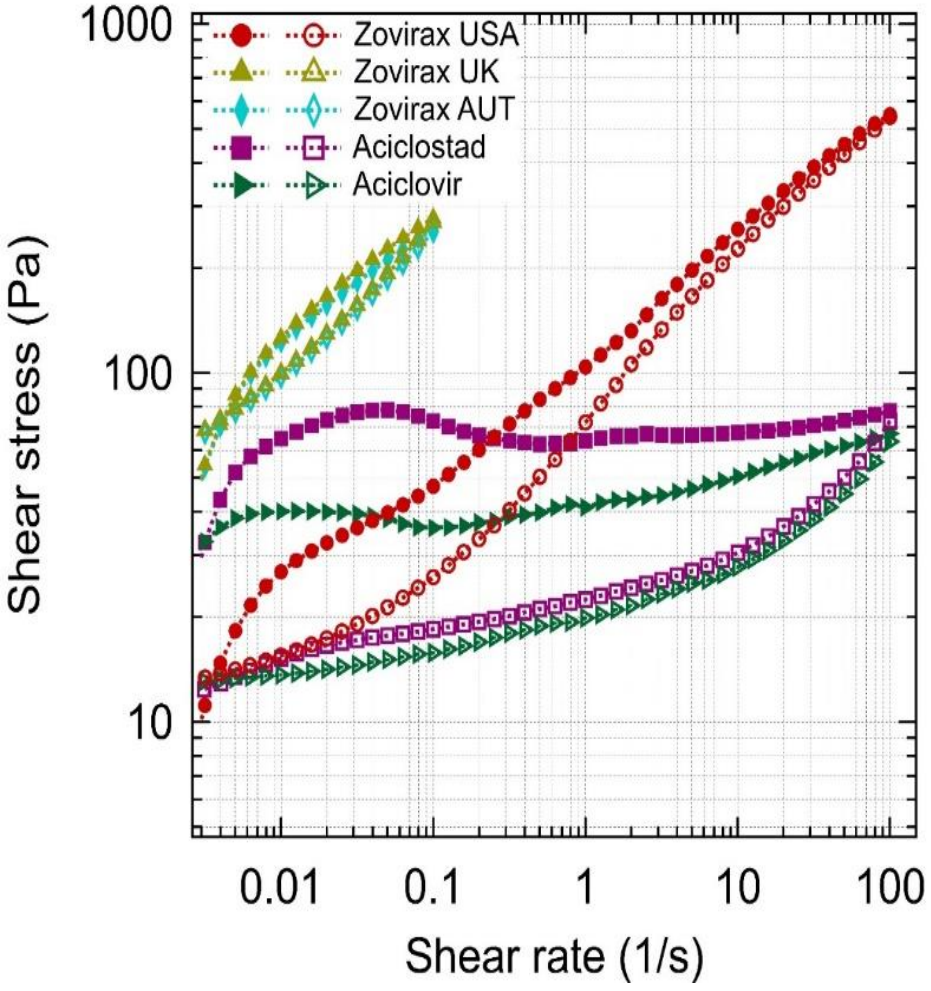
Initial application

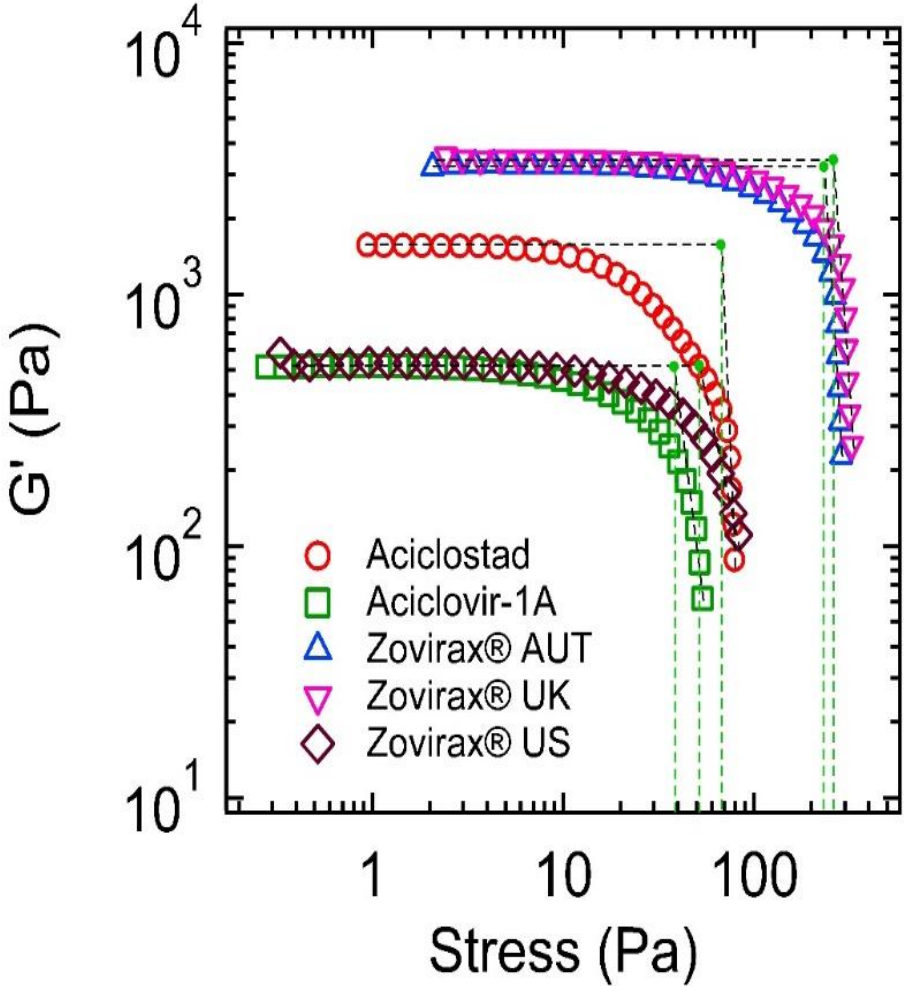
Initial sample thickness (d): 5 mm
Skin area: 1” X 1“
Sample is spread @ 2 cycles/s
Finger tip velocity (V): 0.1 m/s
Estimated Shear rate = V/d = 20 s^{-1}

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 s^{-1}

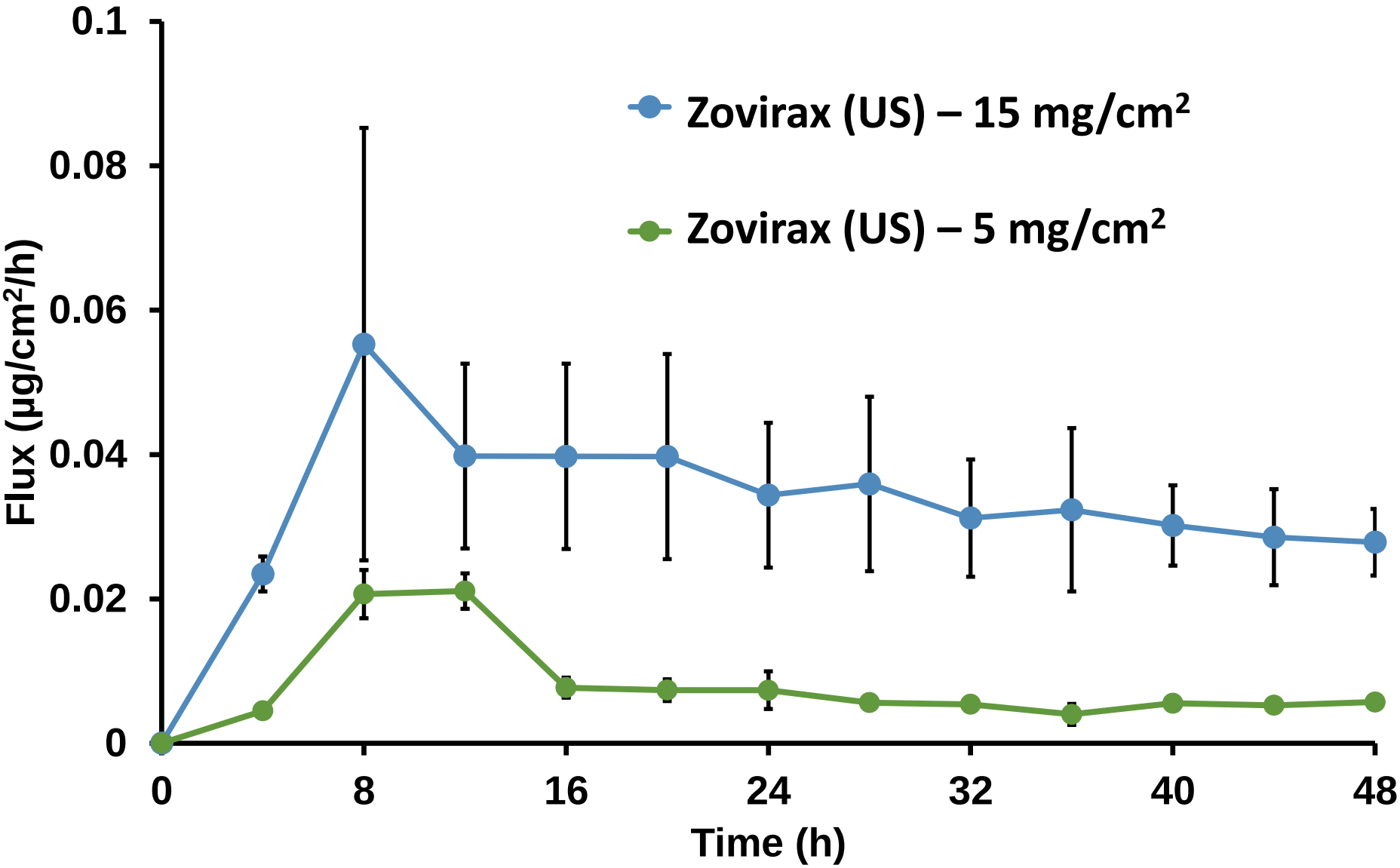
Rheological Studies-Acyclovir Creams



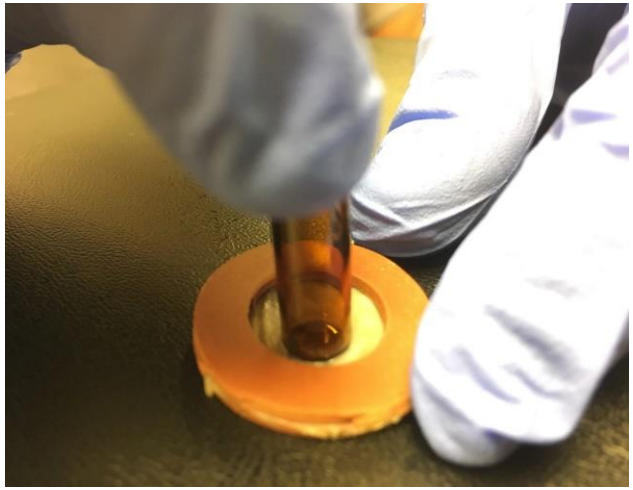


Product	Viscosity, Pa. s			Yield Stress, Pa
	@shear rate: 20 s^{-1}	@ shear rate 3300s^{-1}	@ shear rate: 0.0025 s^{-1}	
Zovirax-USA	17	0.28	8360	50
Zovirax-UK	N/A	N/A	31000	300
Zovirax-AUT	N/A	N/A	30100	300
Aciclostad	3.2	0.06	29300	100
Aciclovir- 1A	2.6	0.06	28100	100
	Dictates the behavior during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

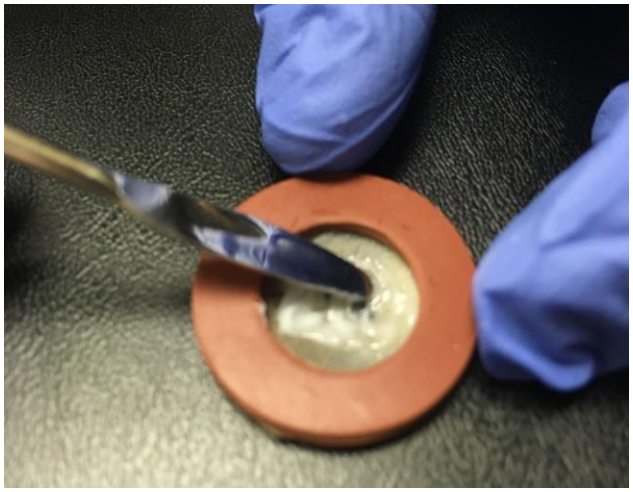
Dose Selection for IVPT



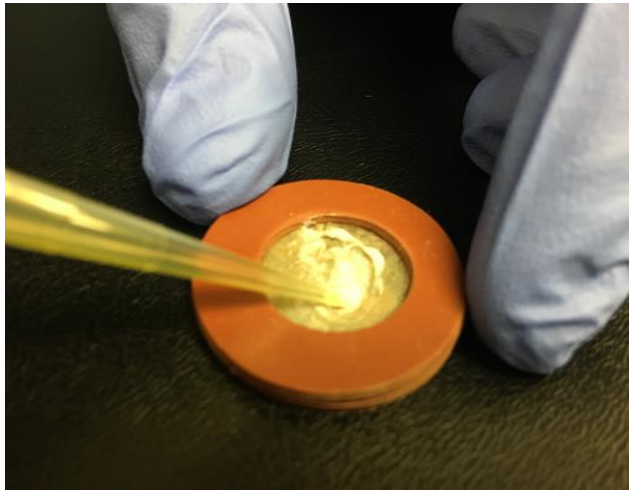
Dose Application Techniques for IVPT



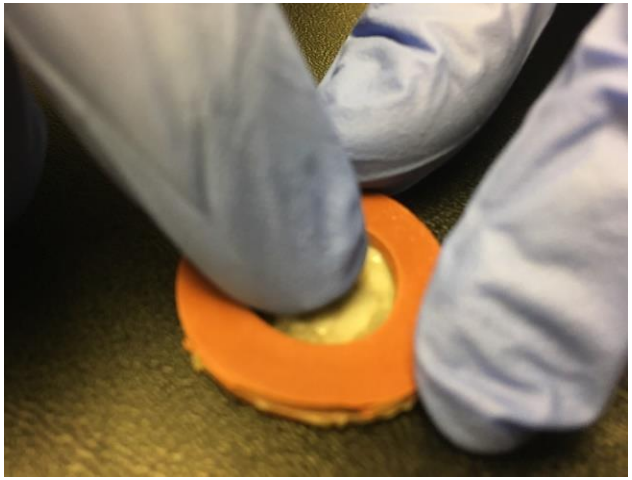
Vial Technique



Spatula Technique

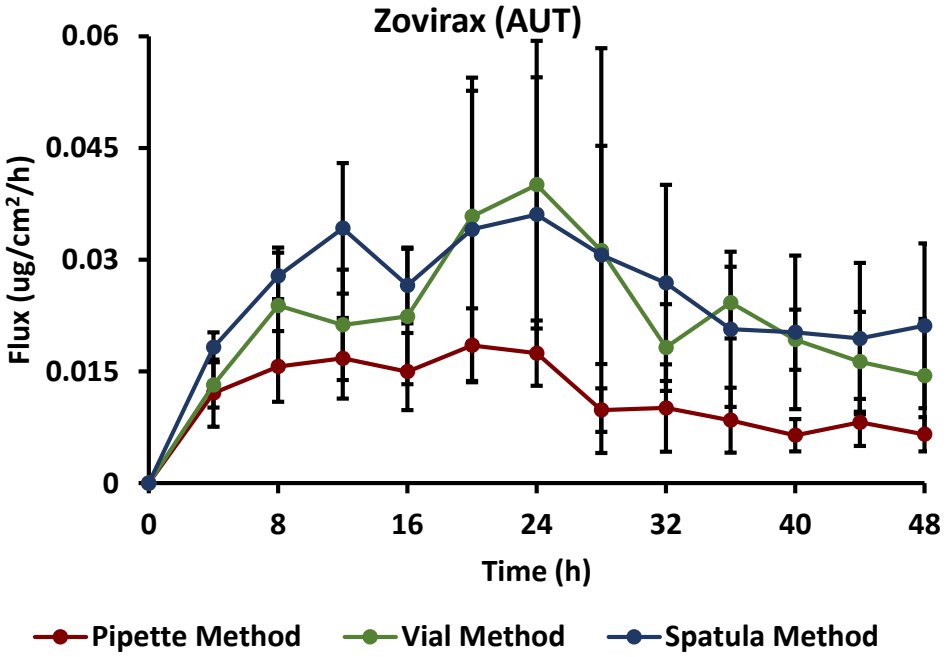


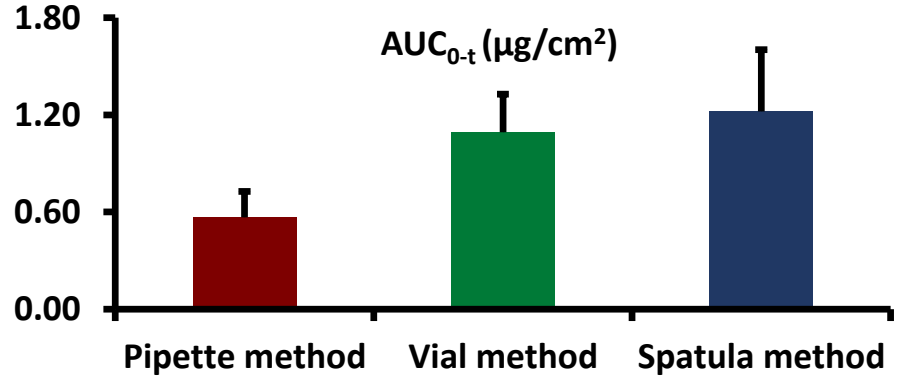
Pipette Technique

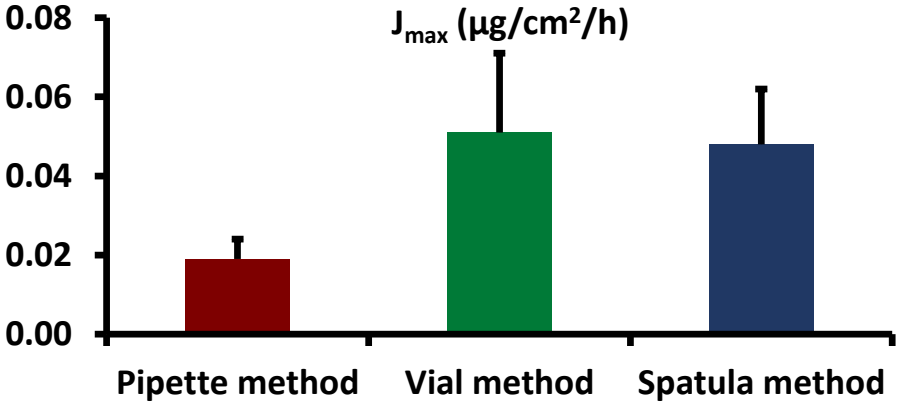


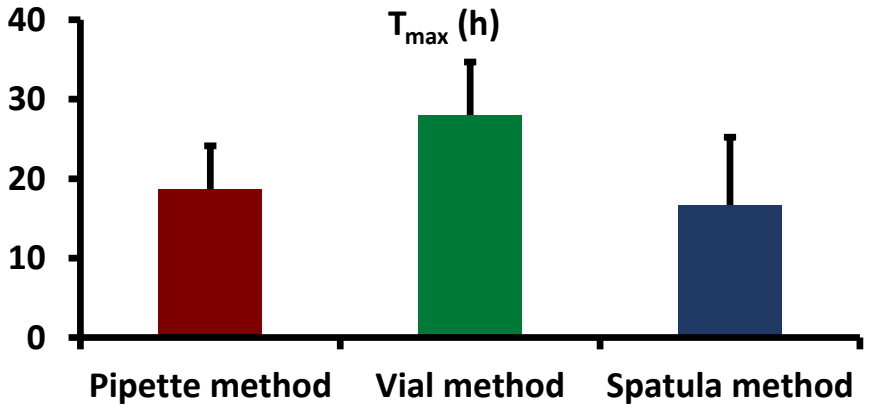
Finger Technique

Method of Application of Acyclovir





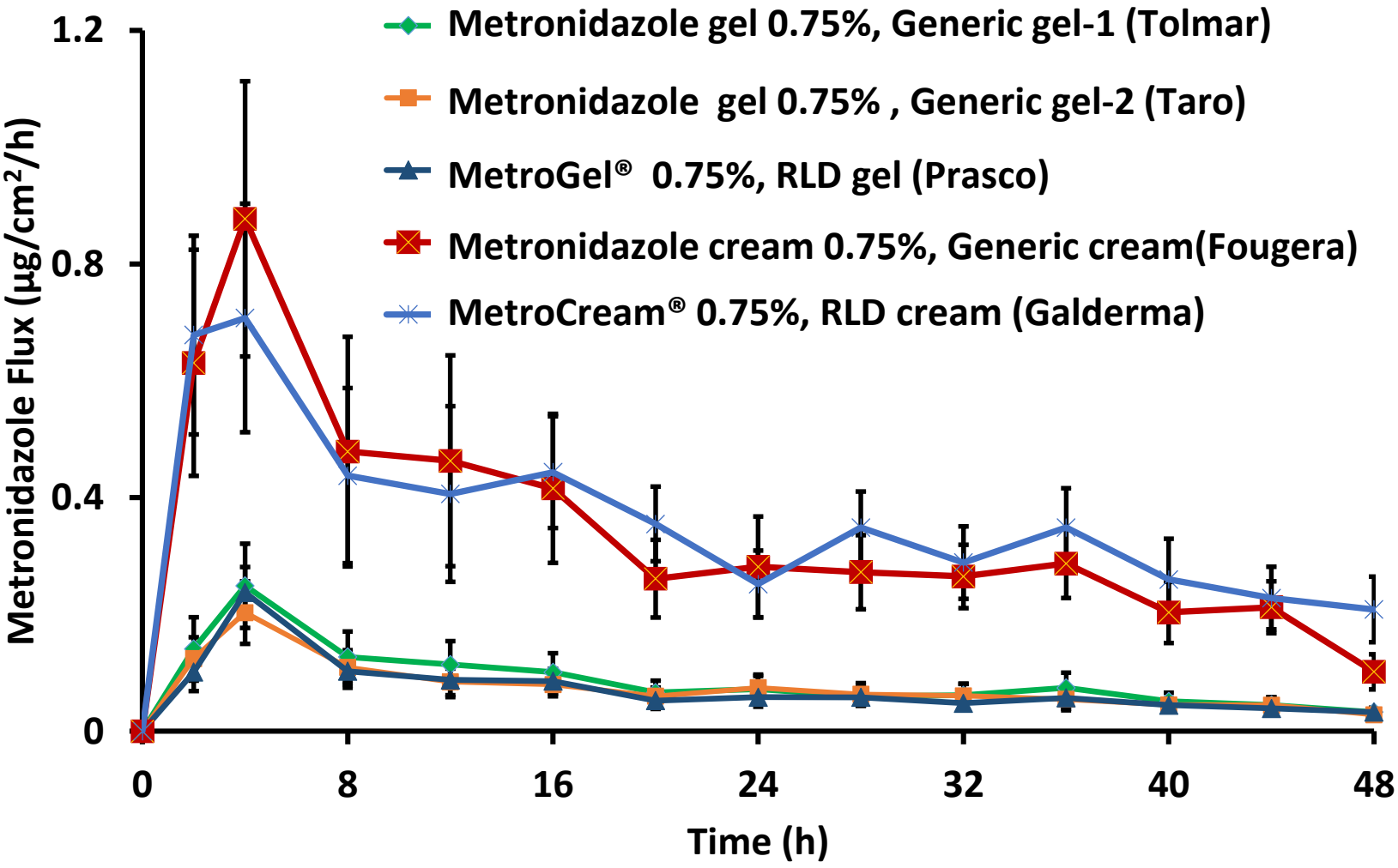




Method	AUC_{0-t} (µg/cm²)	J_{max} (µg/cm²/h)	T_{max} (h)
Pipette method	0.57 ± 0.16	0.02 ± 0.01	18.67 ± 5.47
Vial method	1.09 ± 0.24	0.05 ± 0.02	28.00 ± 6.69
Spatula method	1.22 ± 0.38	0.05 ± 0.01	16.67 ± 8.55

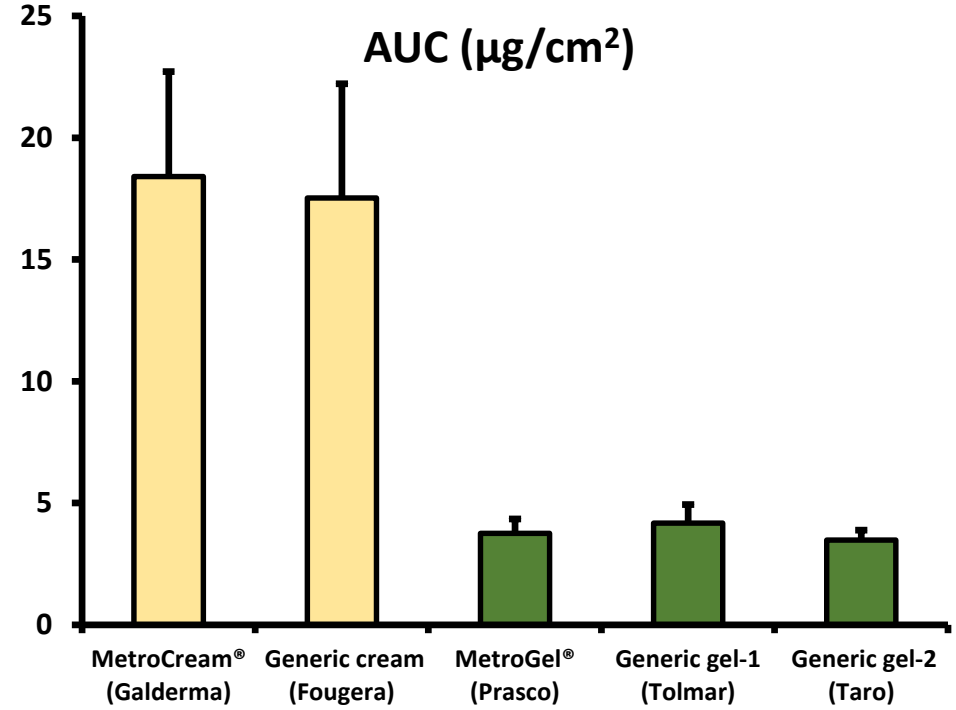
MetroCream® 0.75%, RLD cream (Galderma)	Metronidazole cream 0.75%, Generic cream (Fougera)	MetroGel® 0.75%, RLD gel (Prasco)	Metronidazole gel 0.75%, Generic gel-1 (Tolmar)	Metronidazole gel 0.75%, Generic gel-2 (Taro)
Emulsifying wax	Emulsifying wax	Carbomer 940	Carbopol 980	Carbomer 940
Isopropyl Palmitate	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			

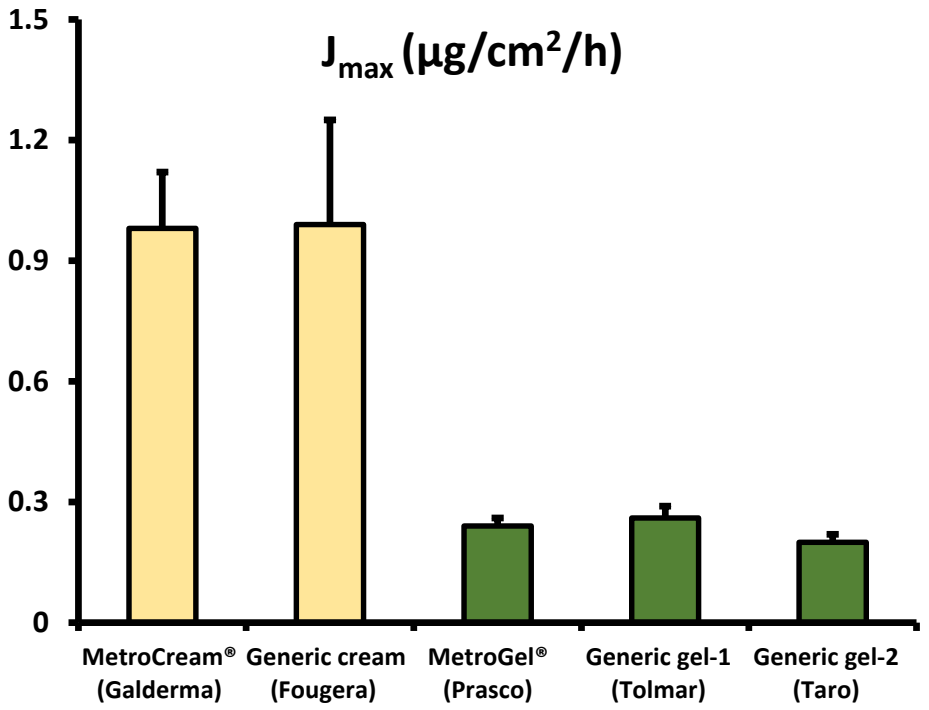
IVPT of Metronidazole Topical Products



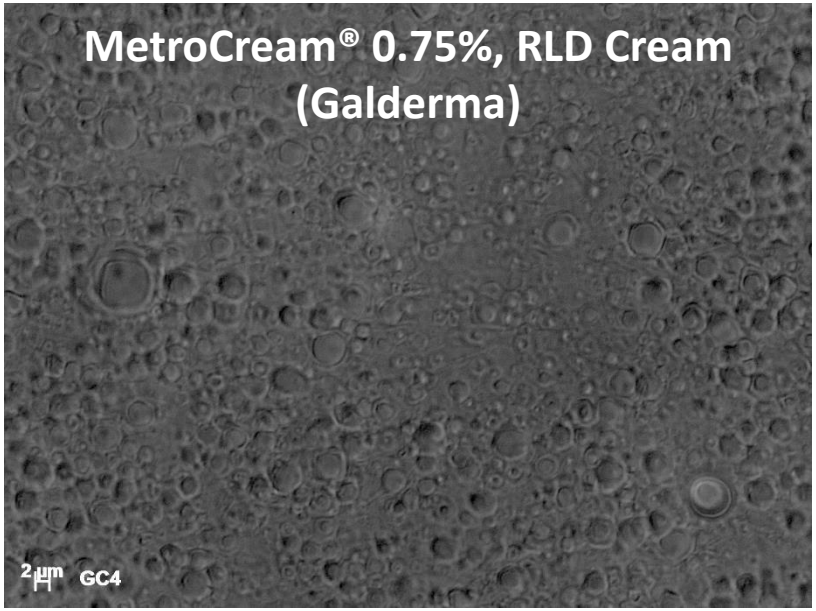
IVPT Results of Metronidazole Products

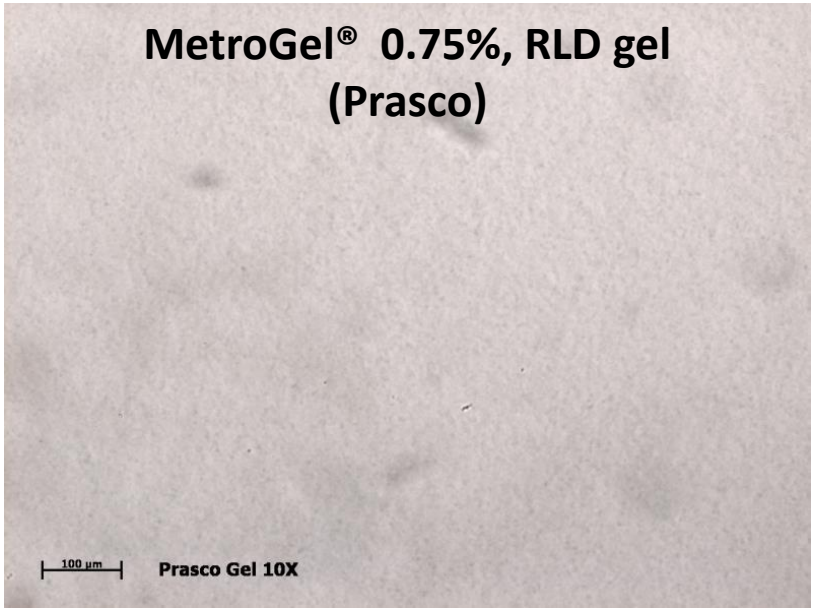
Product	AUC ($\mu g/cm^2$)	J_{max} ($\mu g/cm^2/h$)	T_{max} (h)
MetroCream® (Galderma)	18.41 ± 4.31	0.98 ± 0.14	3.2 ± 0.4
Generic cream (Fougera)	17.53 ± 4.68	0.99 ± 0.26	3.2 ± 0.4
MetroGel® (Prasco)	3.76 ± 0.59	0.24 ± 0.02	4 ± 0
Generic gel-1 (Tolmar)	4.18 ± 0.76	0.26 ± 0.03	3.7 ± 0.5
Generic gel-2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



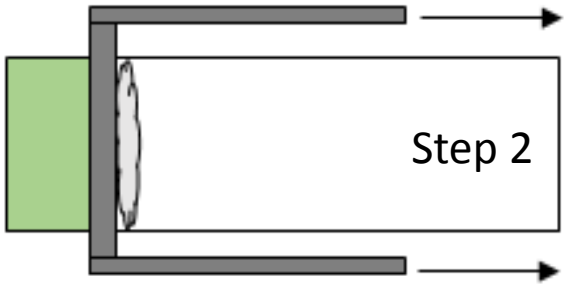


Quality Attribute	MetroCream® 0.75%, RLD cream (Galderma)	Metronidazole cream 0.75%, Generic cream (Fougera)	MetroGel® 0.75%, RLD gel (Prasco)	Metronidazole gel 0.75% , Generic gel - 1 (Tolmar)	Metronidazole gel 0.75% , Generic gel - 2 (Taro)
pH	4.82± 0.01	5.05± 0.05	5.23± 0.01	5.02± 0.01	5.48± 0.01
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	---	---	---	---	---

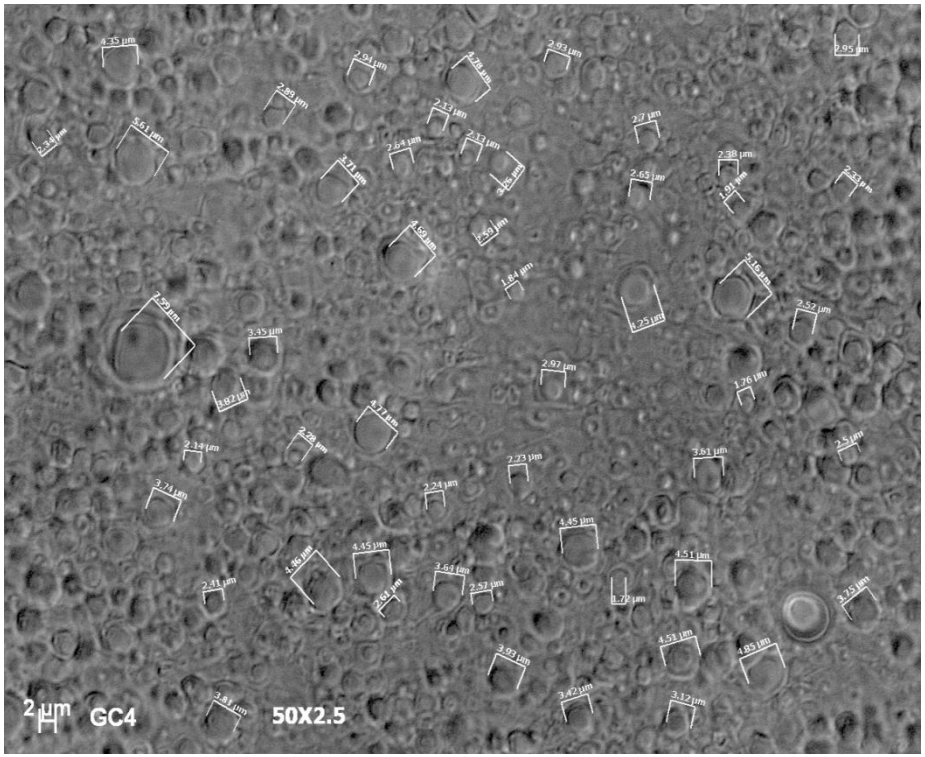




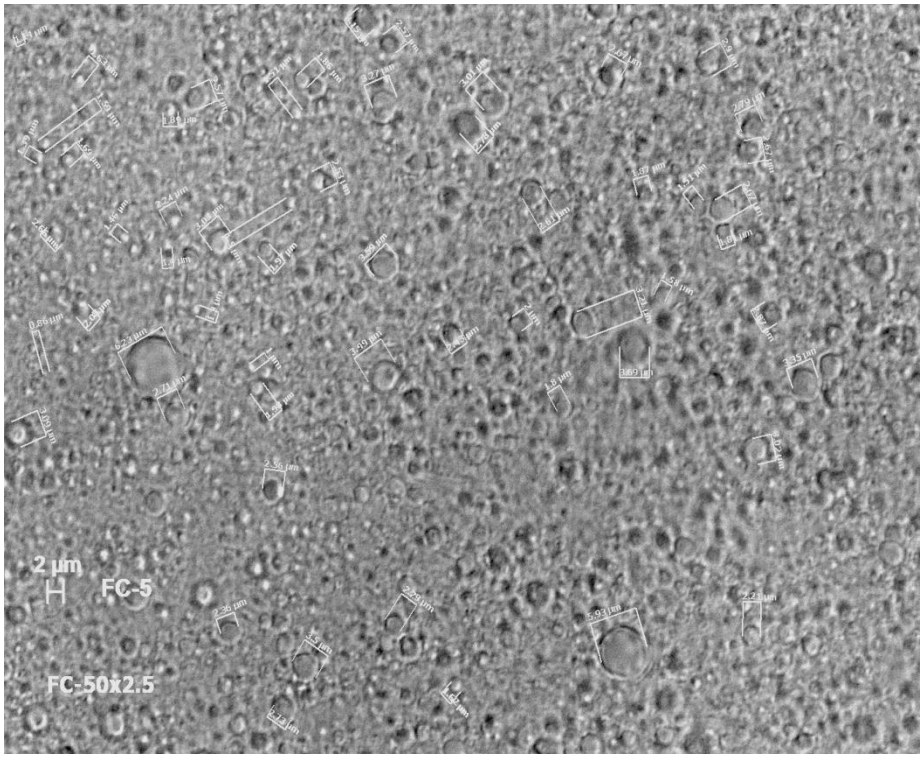
Quality Attribute	MetroCream® 0.75%, RLD cream (Galderma)			Metronidazole cream 0.75%, Generic cream (Fougera)			MetroGel® 0.75%, RLD gel (Prasco)	Metronidazole gel 0.75% , Generic gel - 1 (Tolmar)	Metronidazole gel 0.75% , Generic gel - 2 (Taro)
pH	4.82± 0.01			5.05± 0.05			5.23± 0.01	5.02± 0.01	5.48± 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			



Globule Size Distribution



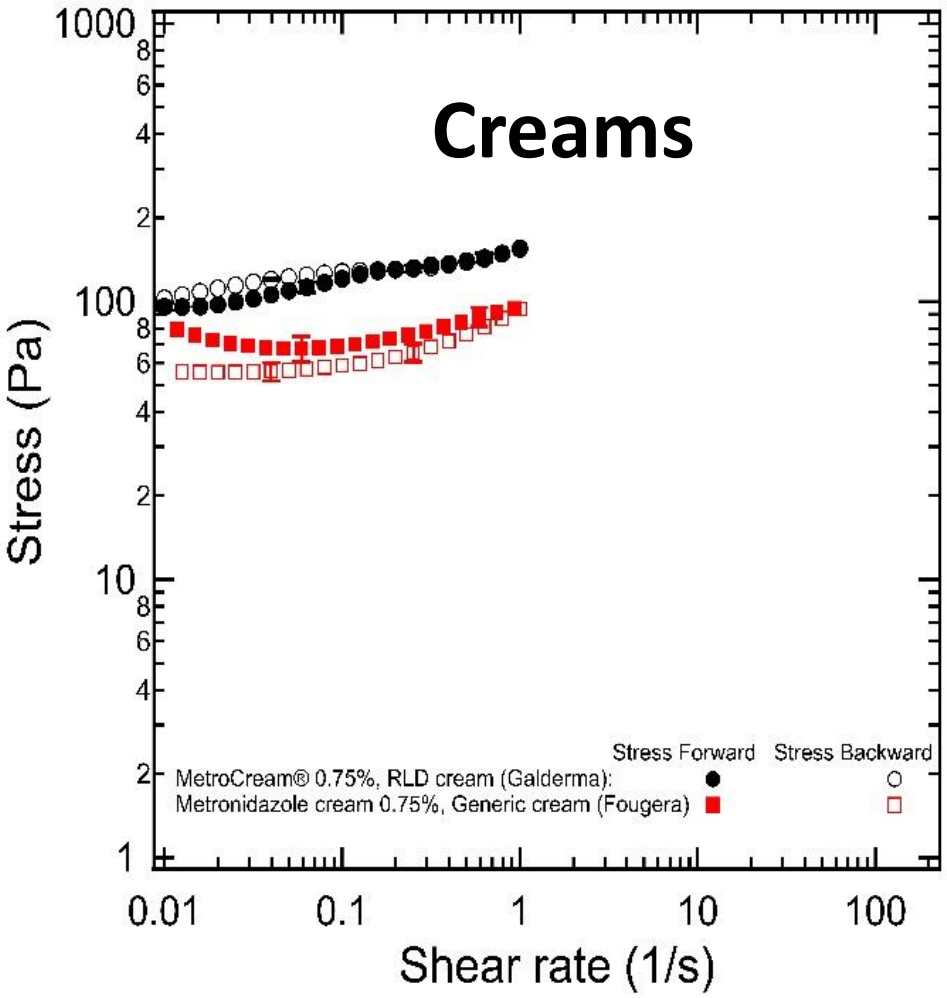
MetroCream® 0.75%, RLD Cream (Galderma)

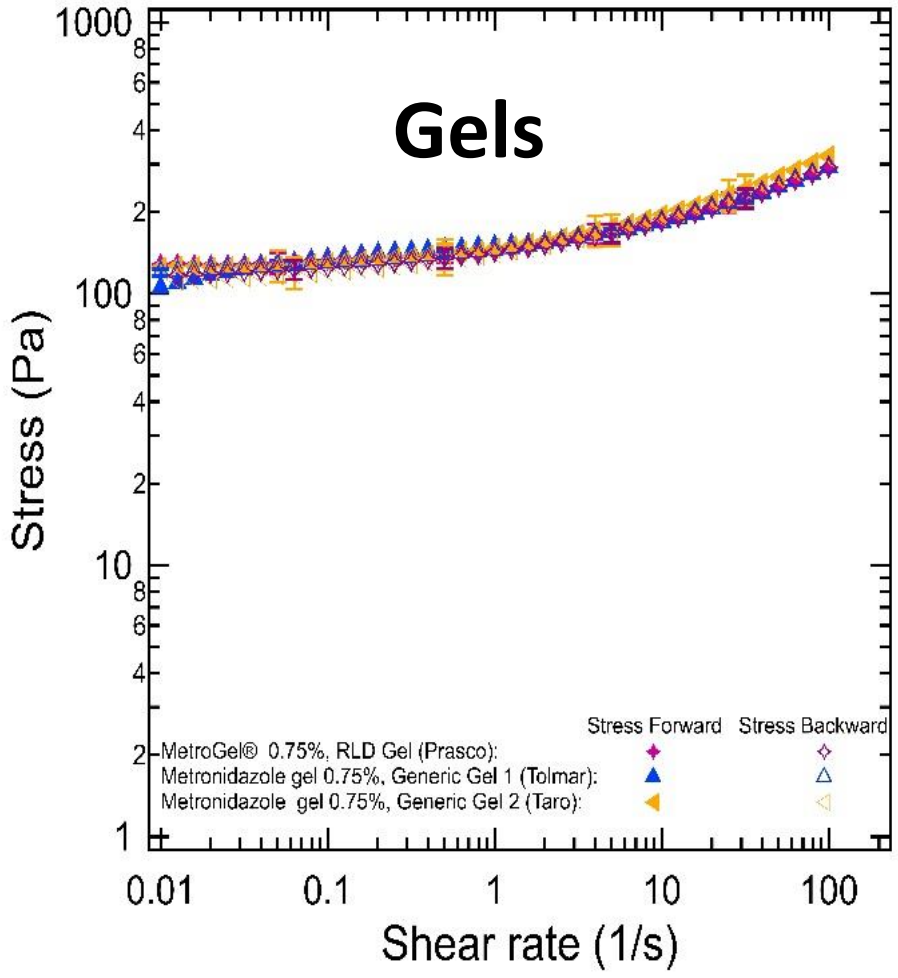


Metronidazole cream 0.75%, Generic cream-1 (Fougera)

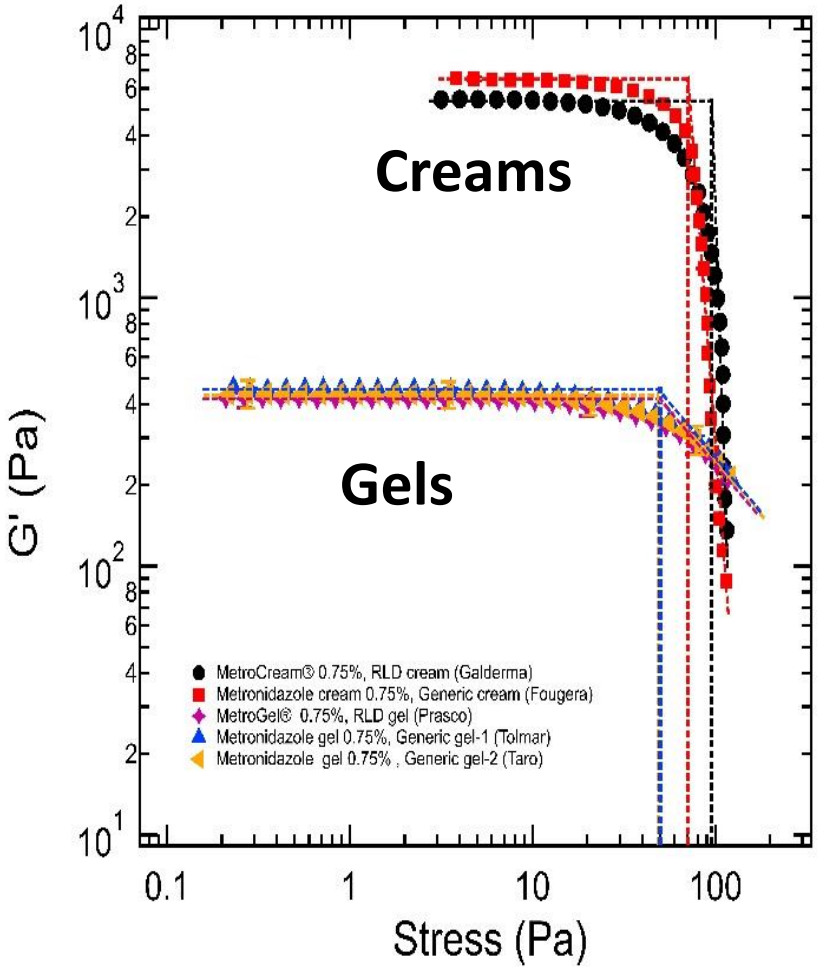
Quality Attribute	MetroCream® 0.75%, RLD cream (Galderma)			Metronidazole cream 0.75%, Generic cream (Fougera)			MetroGel® 0.75%, RLD gel (Prasco)	Metronidazole gel 0.75% , Generic gel - 1 (Tolmar)	Metronidazole gel 0.75% , Generic gel - 2 (Taro)
pH	4.82± 0.01			5.05± 0.05			5.23± 0.01	5.02± 0.01	5.48± 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			---	---	---

Rheological Studies-Metronidazole Products



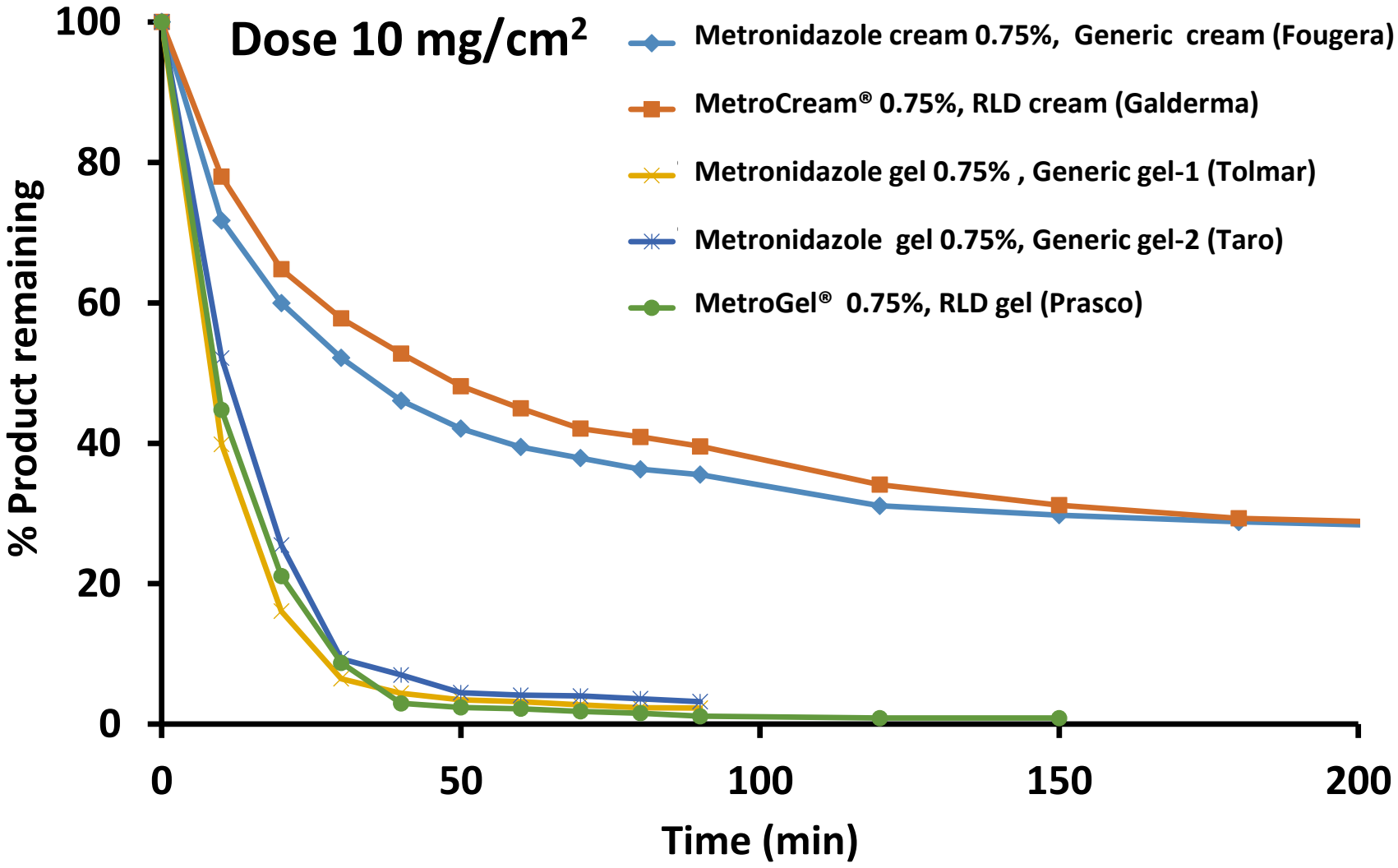


Rheological Studies-Metronidazole Products



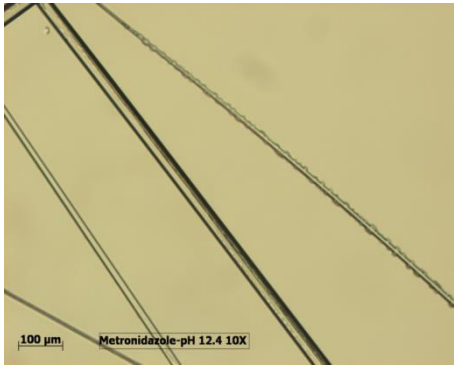
Product	Initial Viscosity (@0.01/S^{-1})	Yield Stress
MetroCream®	9541 ± 284	94 ± 0.00
Generic cream	6830 ± 1166	70 ± 3.00
MetroGel®	12779 ± 1215	50 ± 4.04
Generic gel-1	10534 ± 263	50 ± 0.00
Generic gel-2	12489 ± 1692	49 ± 5.20

Drying Profile of Metronidazole Topical Products

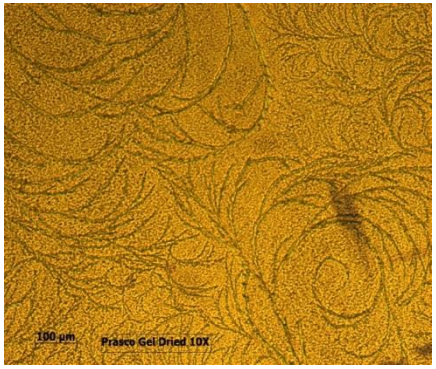


Quality Attribute	MetroCream® 0.75%, RLD cream (Galderma)			Metronidazole cream 0.75%, Generic cream (Fougera)			MetroGel® 0.75%, RLD gel (Prasco)	Metronidazole gel 0.75% , Generic gel - 1 (Tolmar)	Metronidazole gel 0.75% , Generic gel - 2 (Taro)
pH	4.82± 0.01			5.05± 0.05			5.23± 0.01	5.02± 0.01	5.48± 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

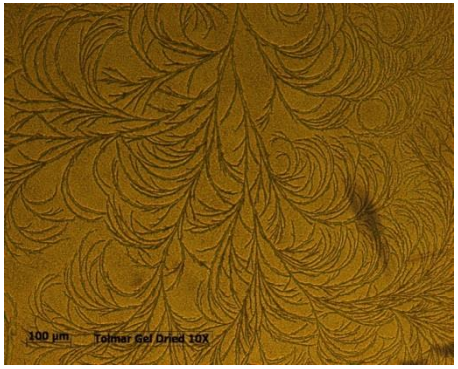
Crystal Pattern in Gels after Drying



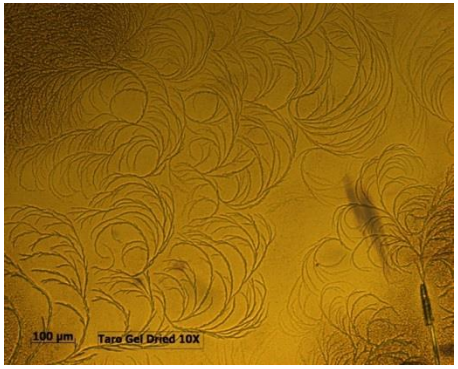
Metronidazole solution



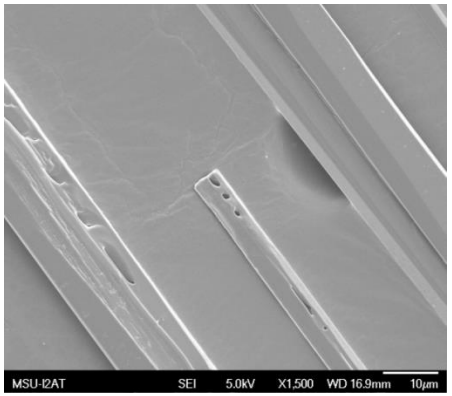
MetroGel® 0.75%, RLD gel (Prasco)



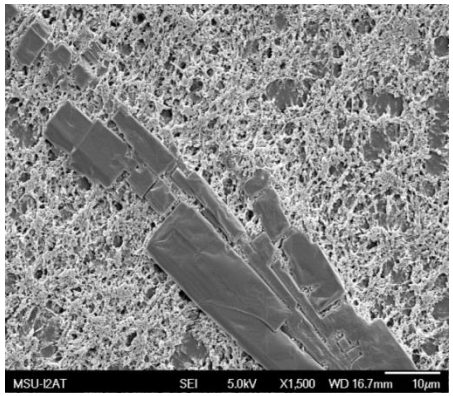
Metronidazole gel 0.75%, Generic gel-1 (Tolmar)



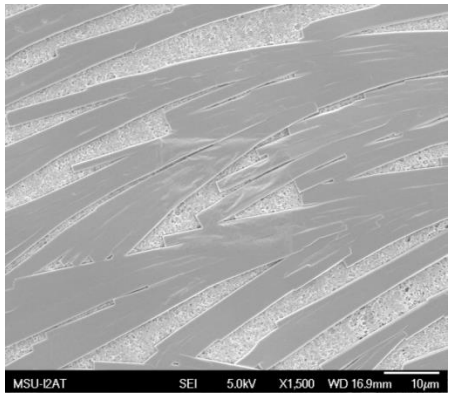
Metronidazole gel 0.75% , Generic gel-2 (Taro)



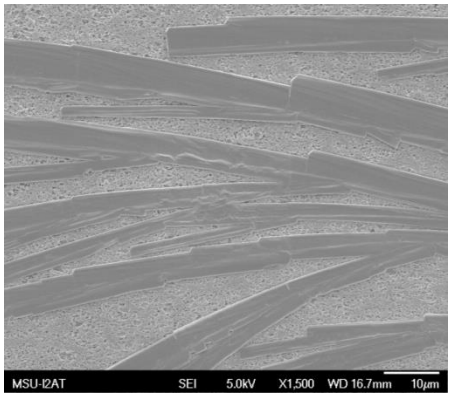
Metronidazole solution



MetroGel® 0.75%, RLD gel (Prasco)

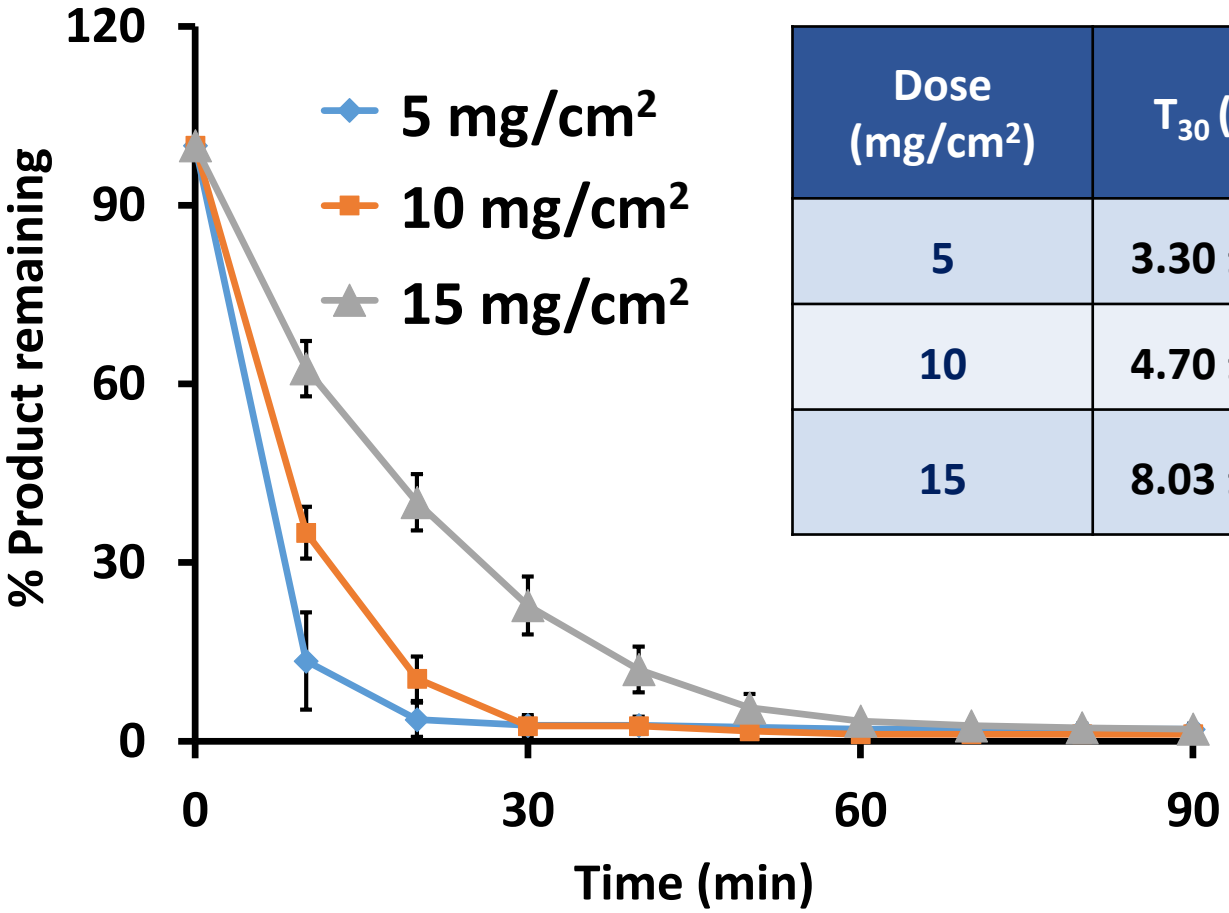


Metronidazole gel 0.75%, Generic gel-1 (Tolmar)



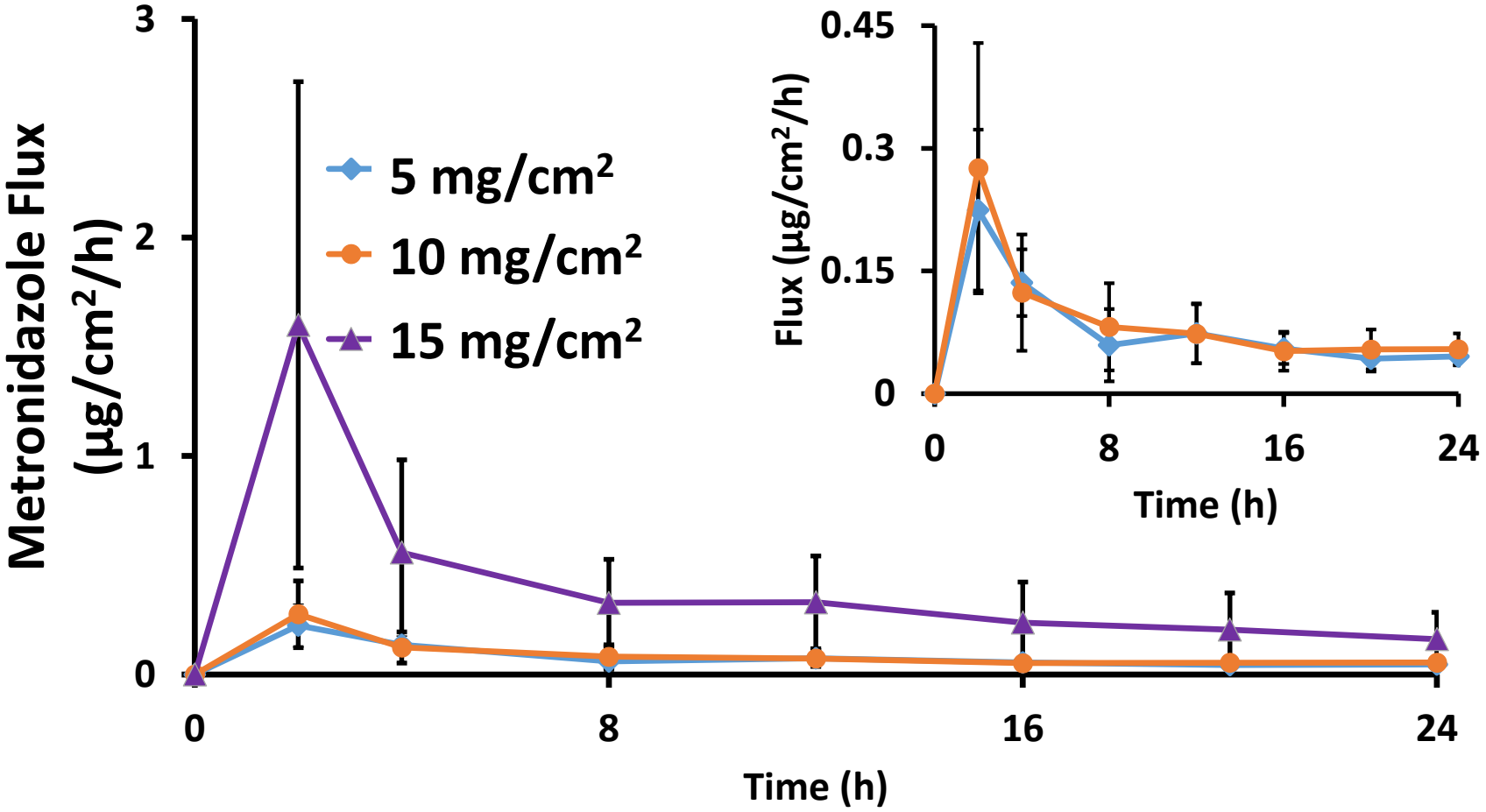
Metronidazole gel 0.75%, Generic gel-2 (Taro)

Drying Rate of Metronidazole Gel 0.75%

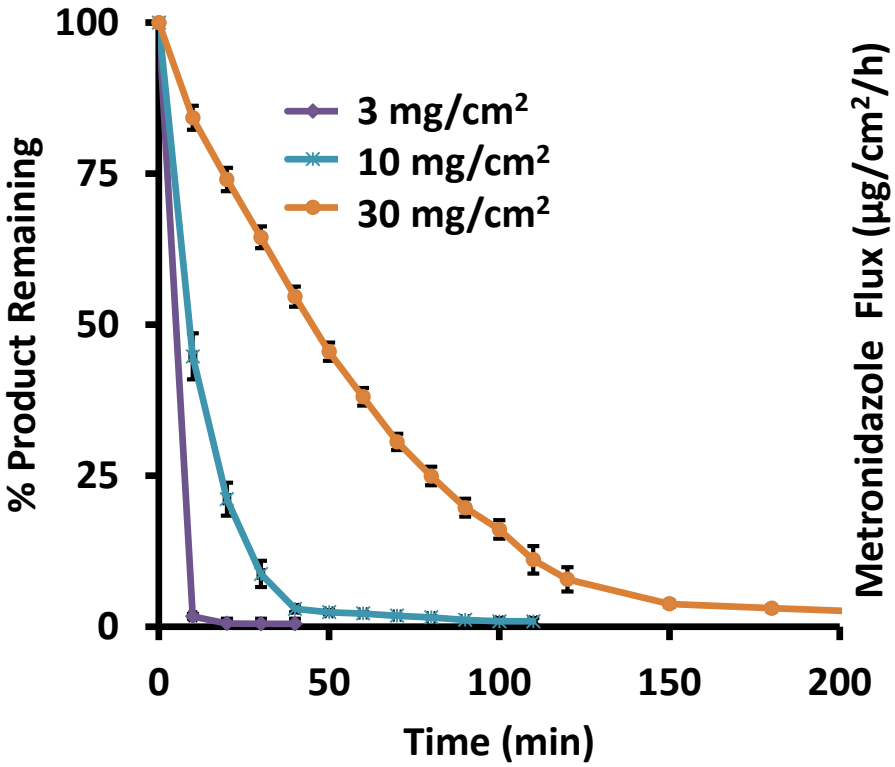


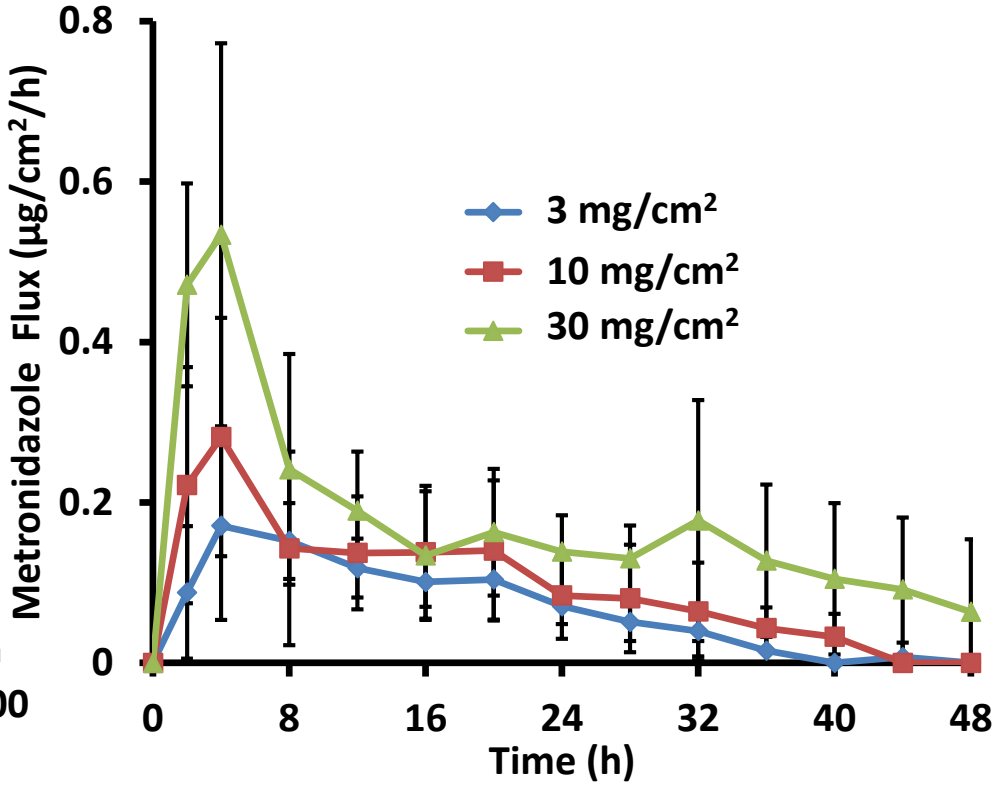
Dose (mg/cm²)	T_{30} (min)	T_{50} (min)
5	3.30 ± 0.26	5.60 ± 0.53
10	4.70 ± 0.26	7.87 ± 0.42
15	8.03 ± 1.07	15.63 ± 2.10

Metronidazole Gel 0.75%
IVPT Dose Comparison



Metronidazole Gel 0.75%
Drying and IVPT Profile

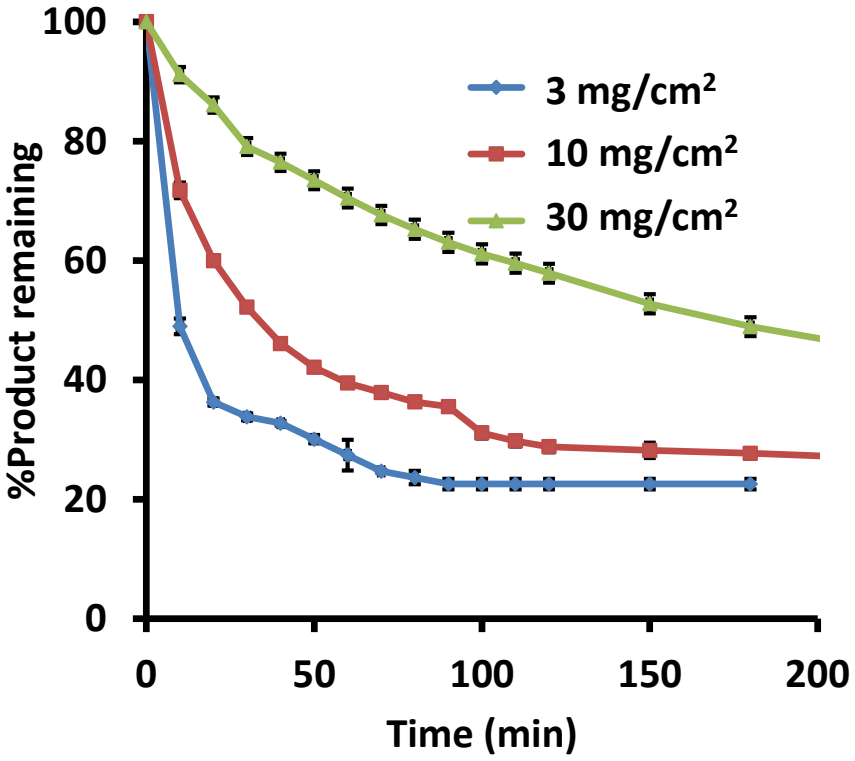


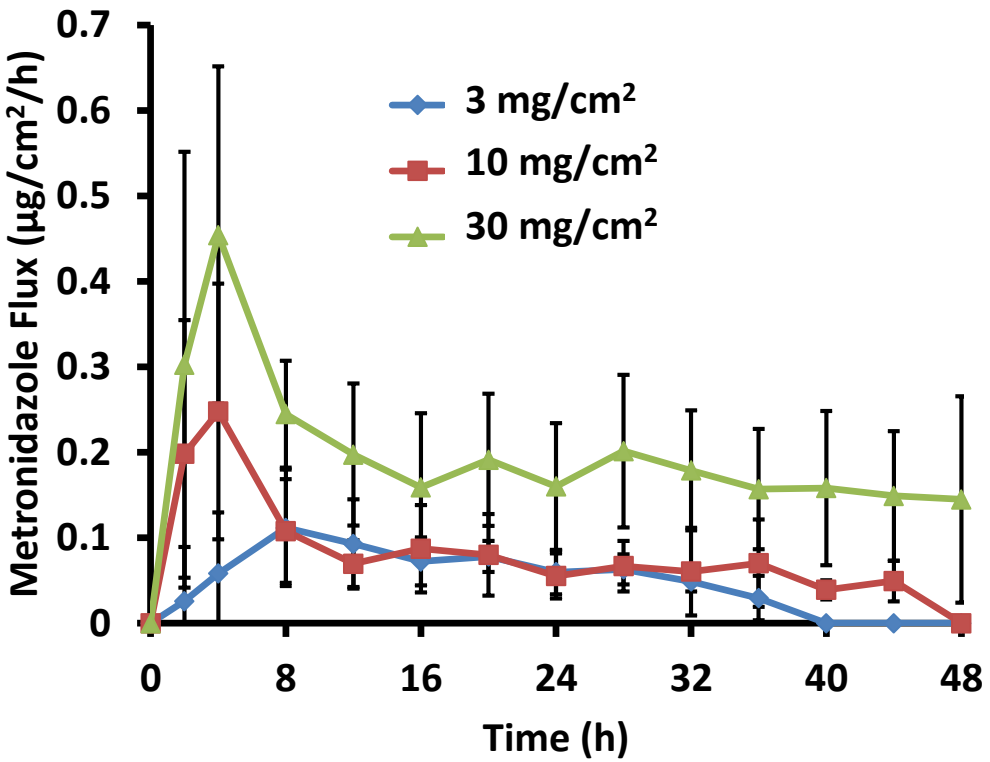


T_{30} (min)		
3 mg/cm²	10 mg/cm²	30 mg/cm²
3.10± 0.00	5.47± 0.45	24.33± 2.02

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





T_{30} (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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