

Microstructural Characterization and In Vitro Permeation Testing of Topical Products

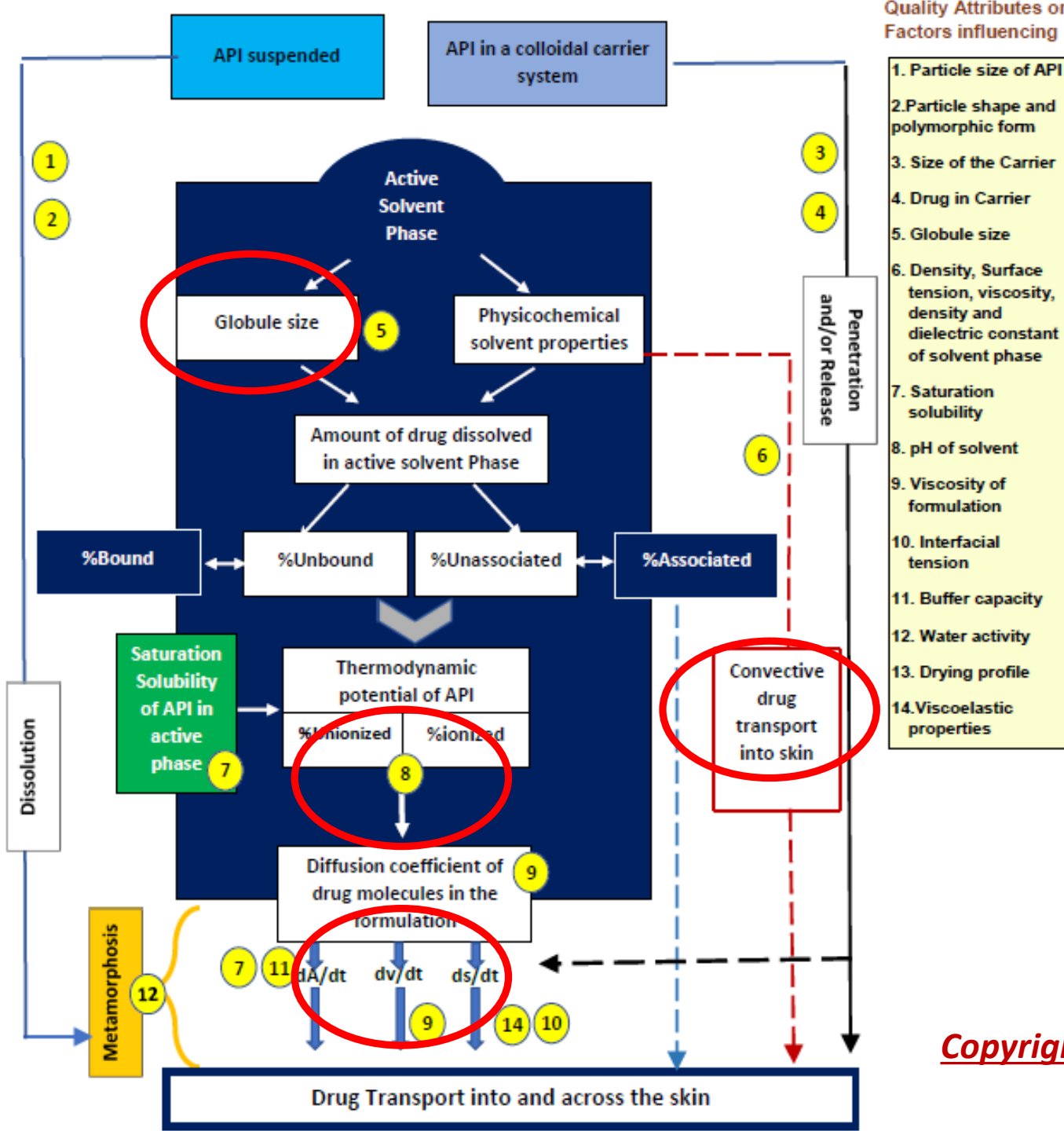
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Some of the characterizations that we generally consider for topical products include

- **pH and Buffer Capacity**
- **Molecular Association of API**
- **Globule size**
- **Water Activity**
- **Phase Distribution of drug**

pH change could impact the drug permeation

Product	pKa	% Unionized	
		Initial	After one hour
Clotrimazole	6.6	43.1% (pH 6.5)	7.1% (pH 5.5)
Lidocaine	7.9	20.1% (pH 7.3)	2.5%(pH 6.3)

Measurement of Buffer Capacity of Topical Products

Products	Initial pH	Buffer Capacity _{24h} (moles/pH)
RLD-Cream	4.82 ± 0.01	(4.1 ± 0.2) × 10 ⁻⁴
Generic Cream	5.05 ± 0.05	(2.0 ± 0.4) × 10 ⁻⁴

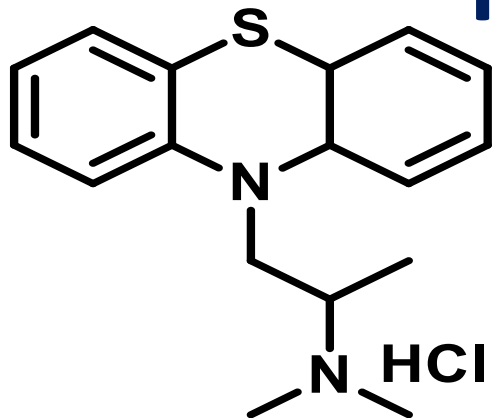


P>0.05



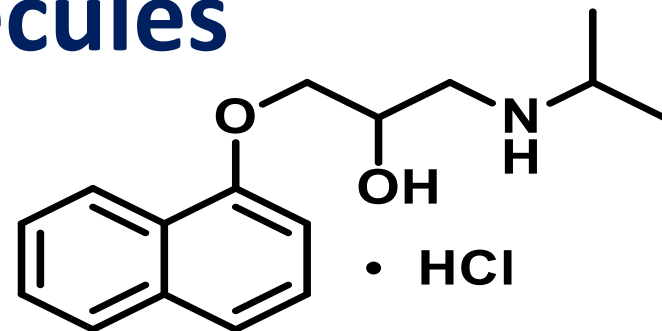
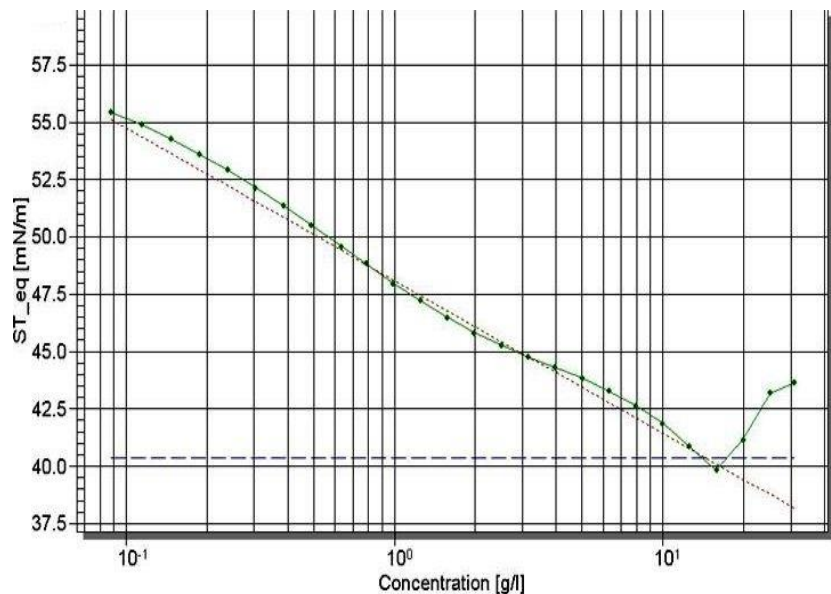
P*<0.05

Molecular Association of Surfactant like Drug Molecules



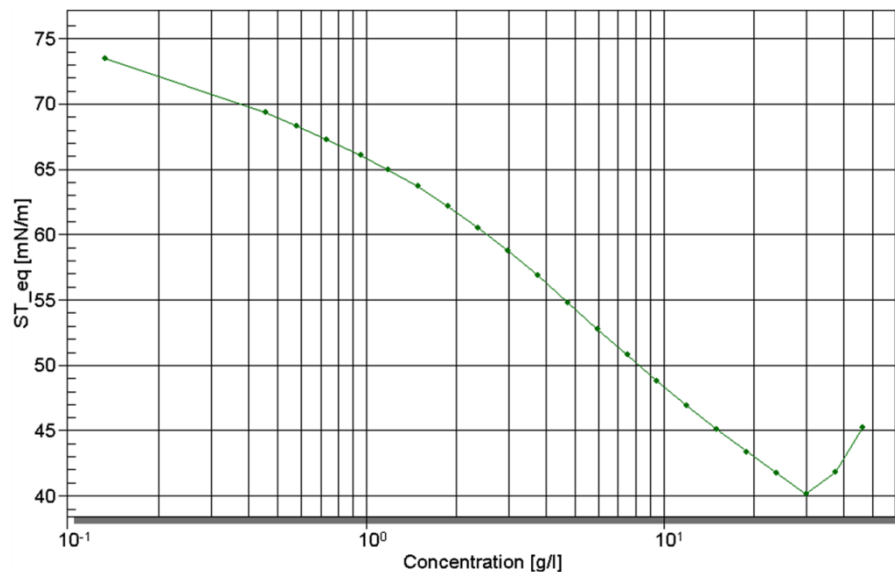
Promethazine hydrochloride structure

CMC = 49.2 mM

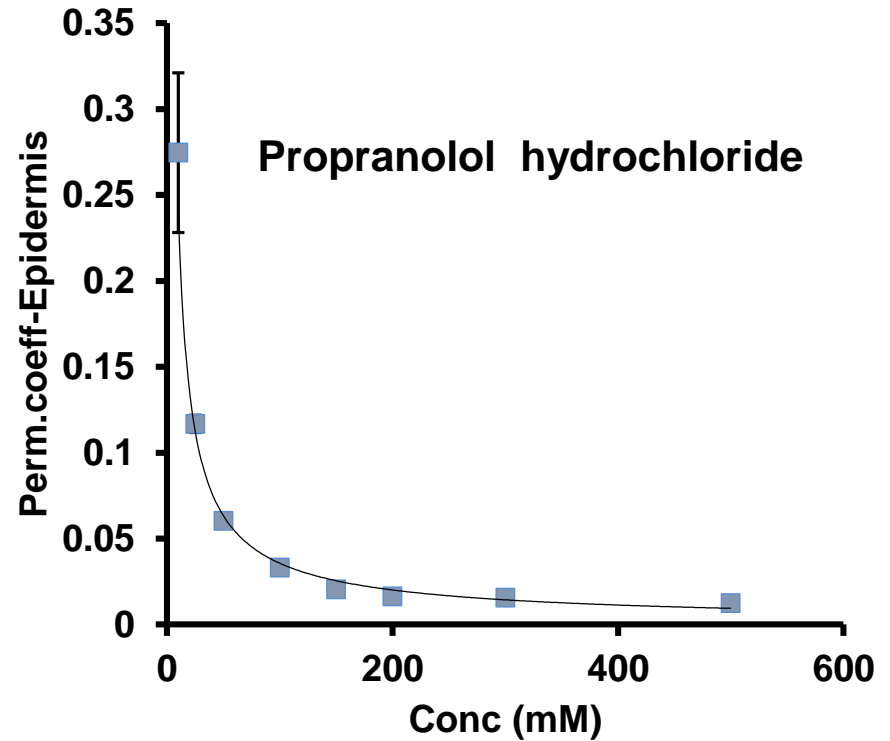
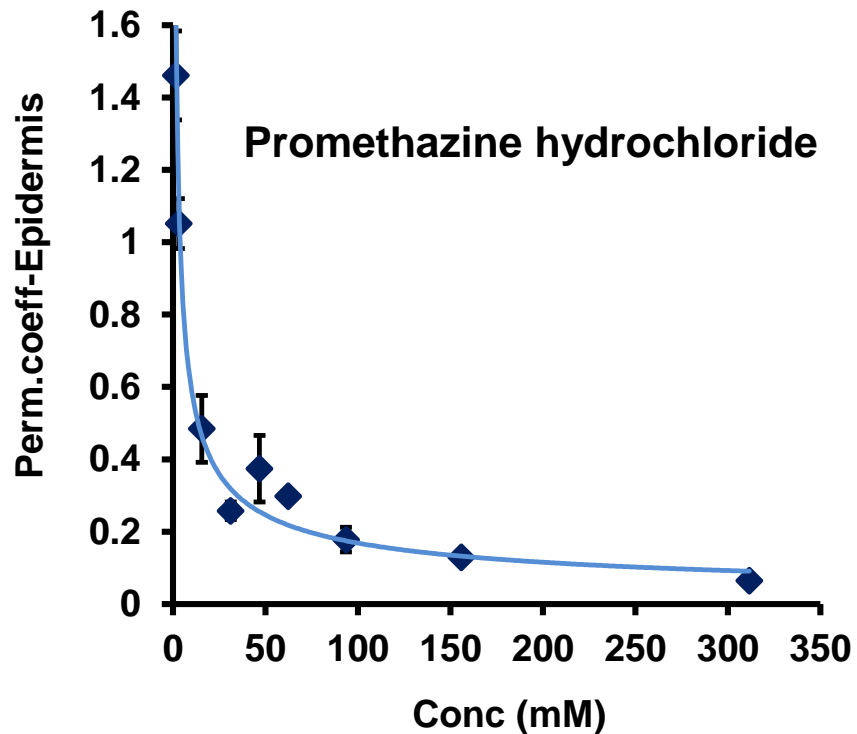


Propranolol hydrochloride structure

CMC = 98.4 mM



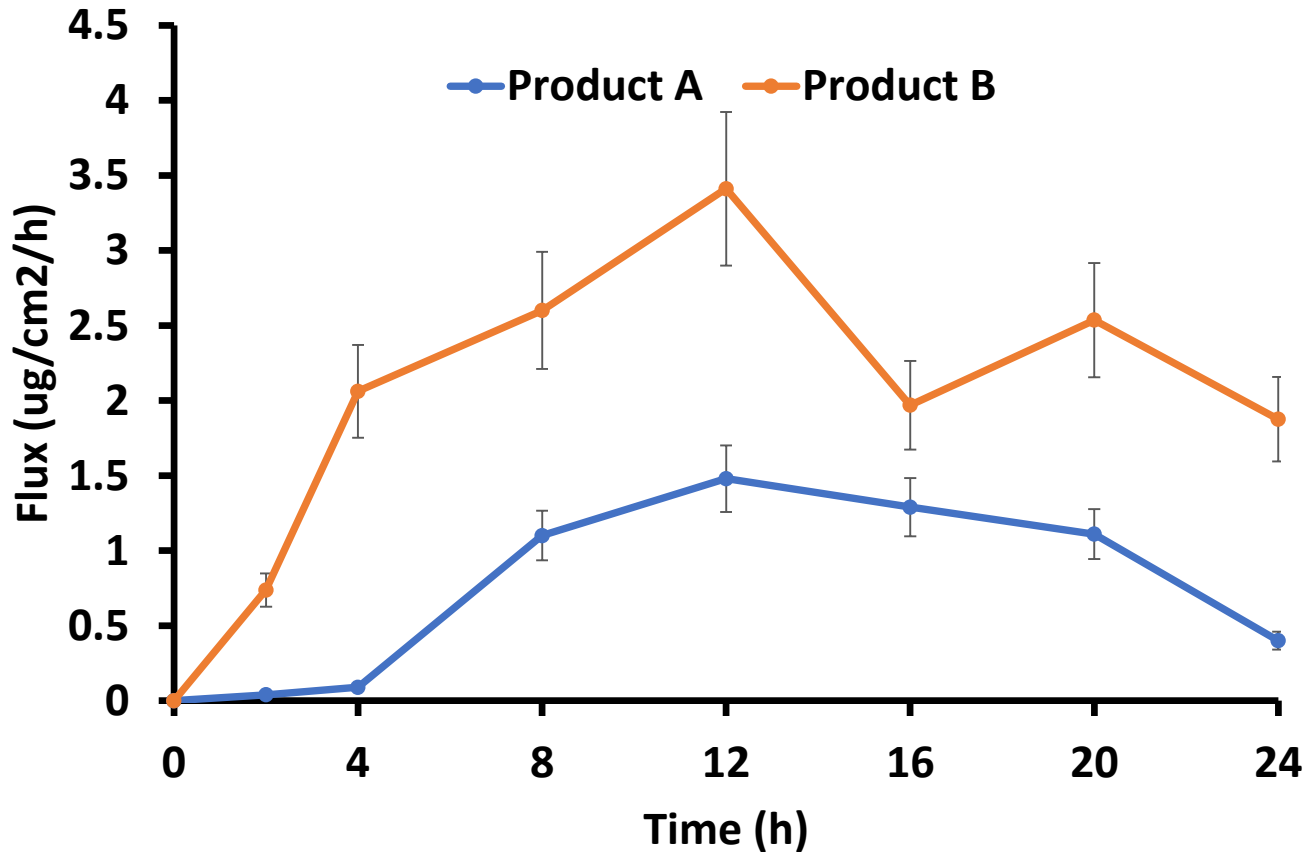
Permeability Coefficient Changes with Concentration



Permeation profile of Promethazine from Gels

Product A: API dissolved in Water (50 mg/ml)+ HPMC HV 4%

Product B: 2% HPMC in water +API dissolved in water+2% HPMC

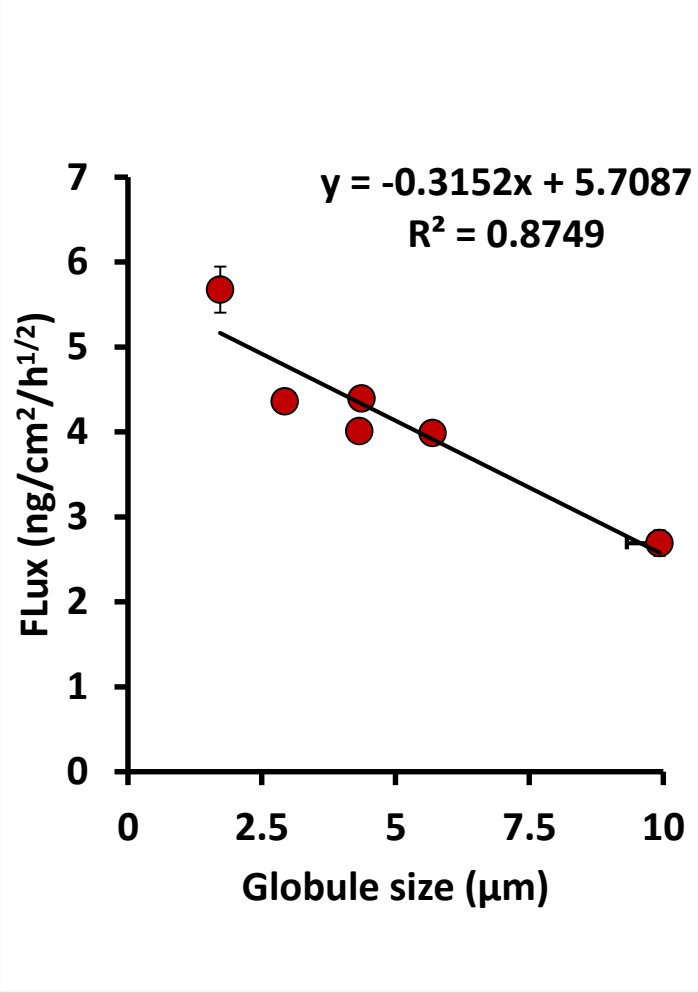
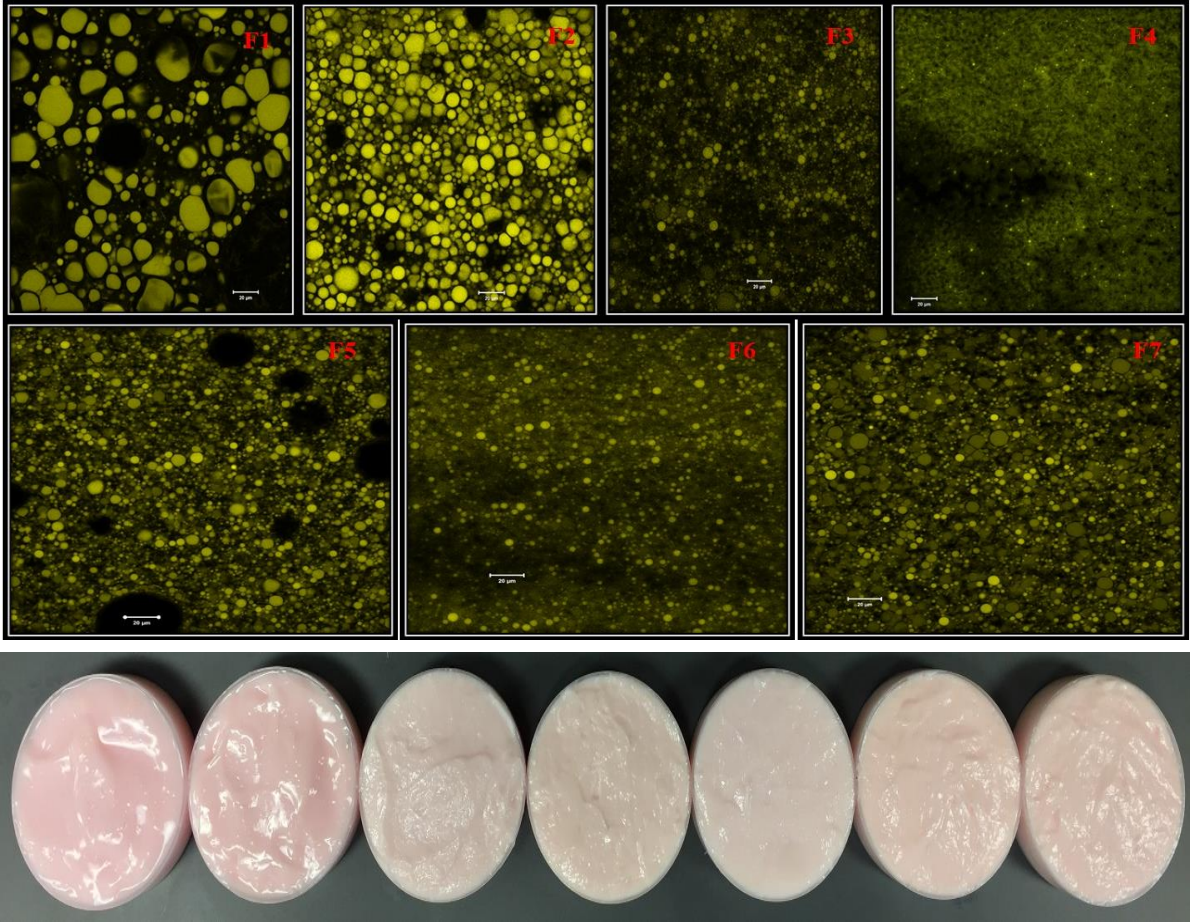


O/W Creams with Identical Composition and Different Globule size

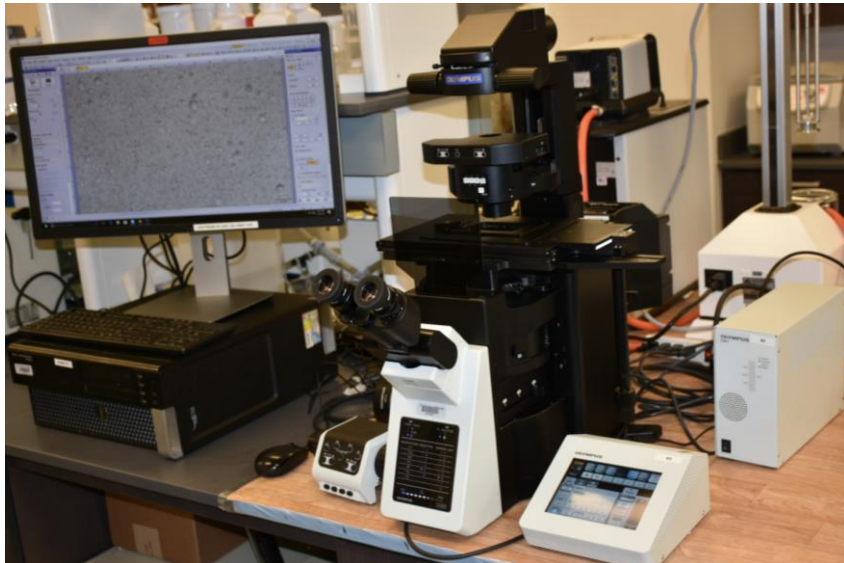
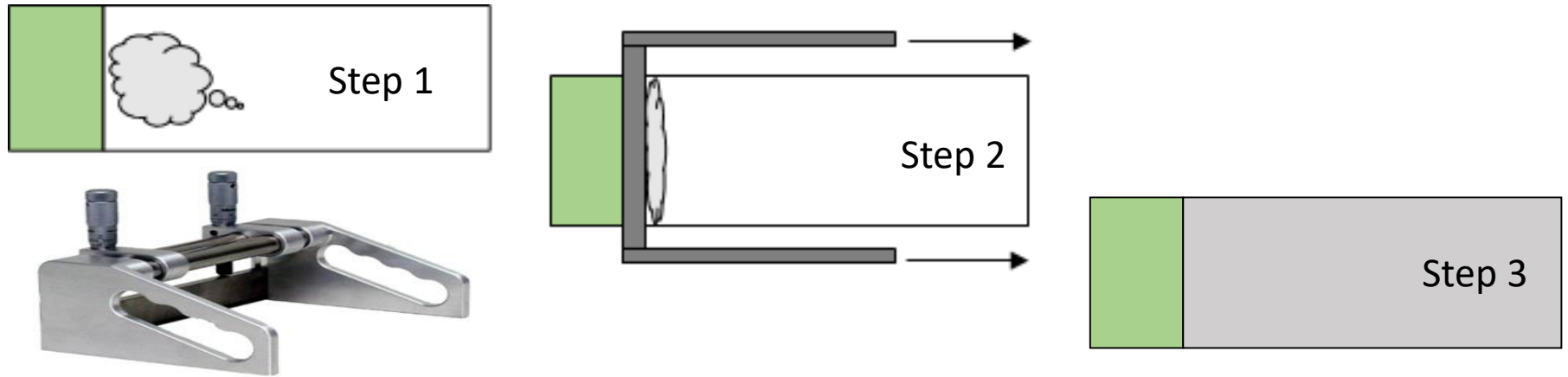
Ingredients (O/W)	Quantity (%)
Cetostearyl alcohol	7
Cremophor A6	1.5
Cremophor A25	1.5
Mineral Oil	12
Propylene Glycol	8
Water	70

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

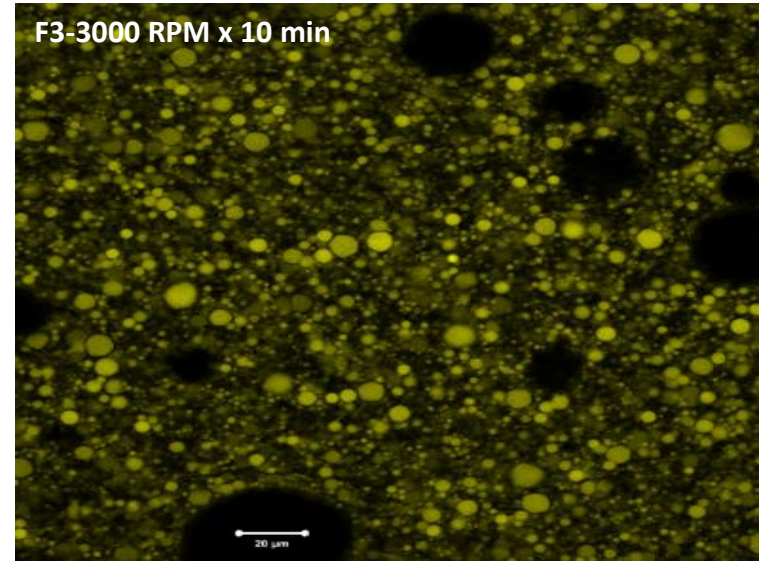
Appearance due to Globule Size Differences



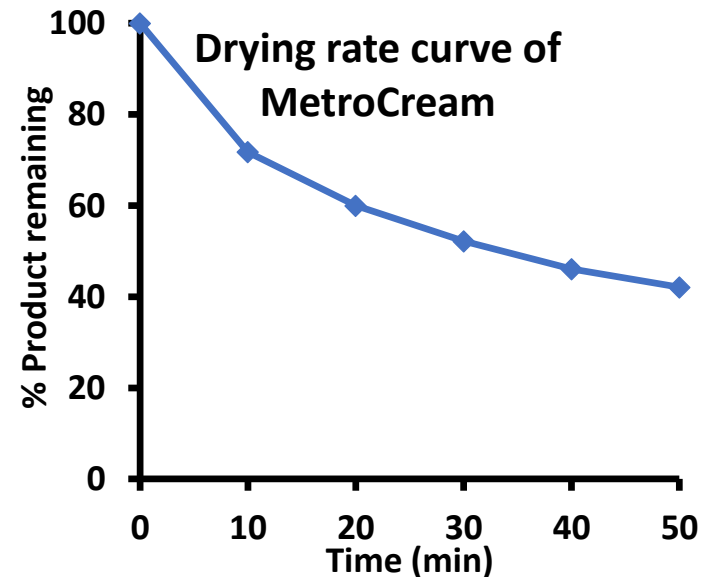
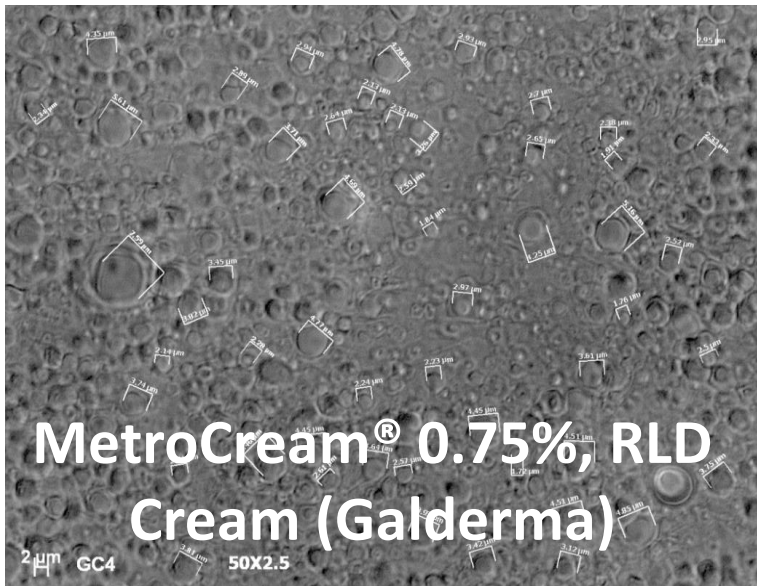
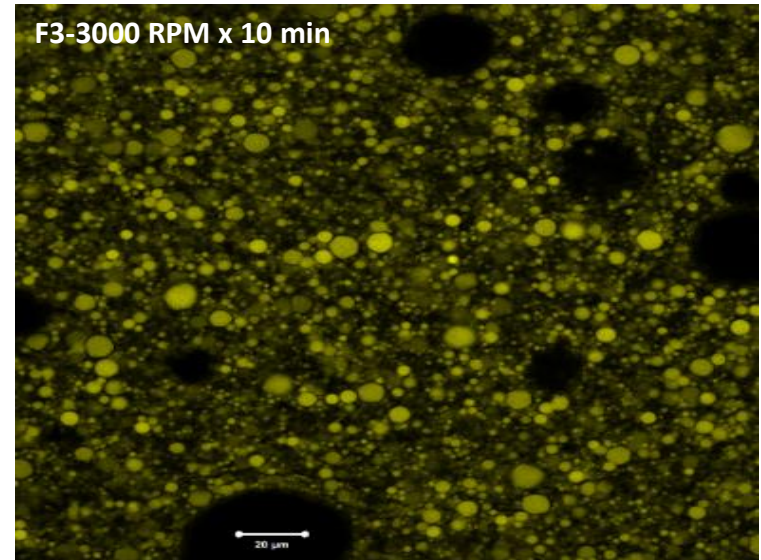
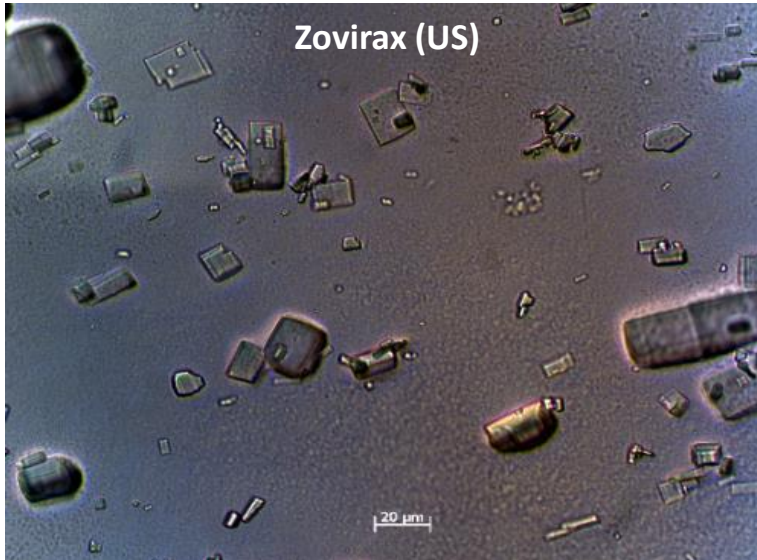
Microscopy-Globule size



Microscopy-Globule size



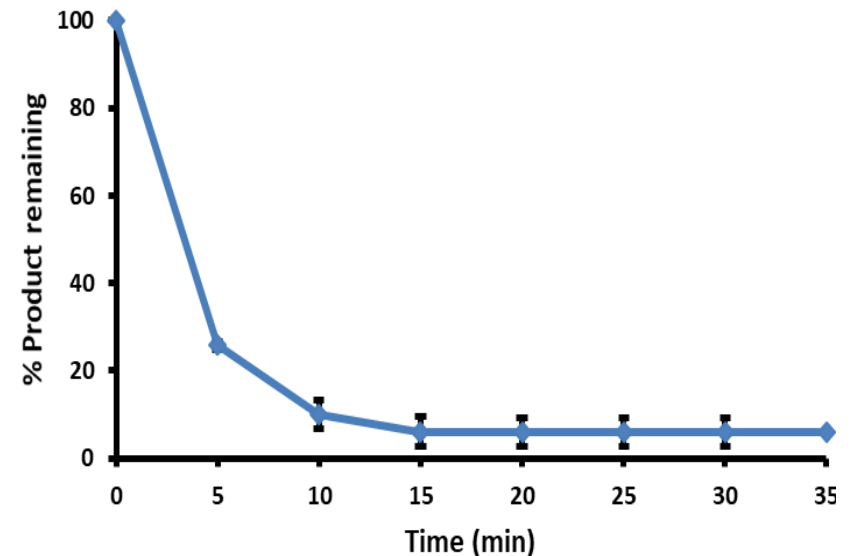
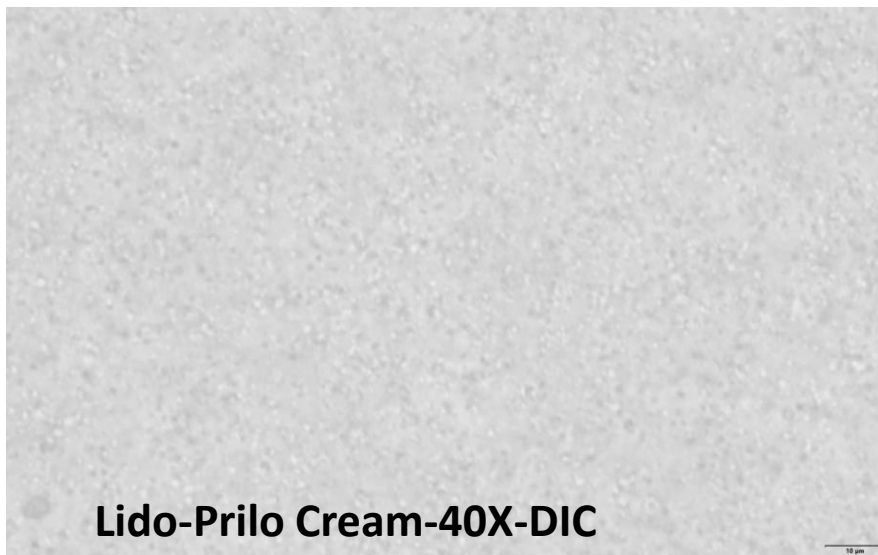
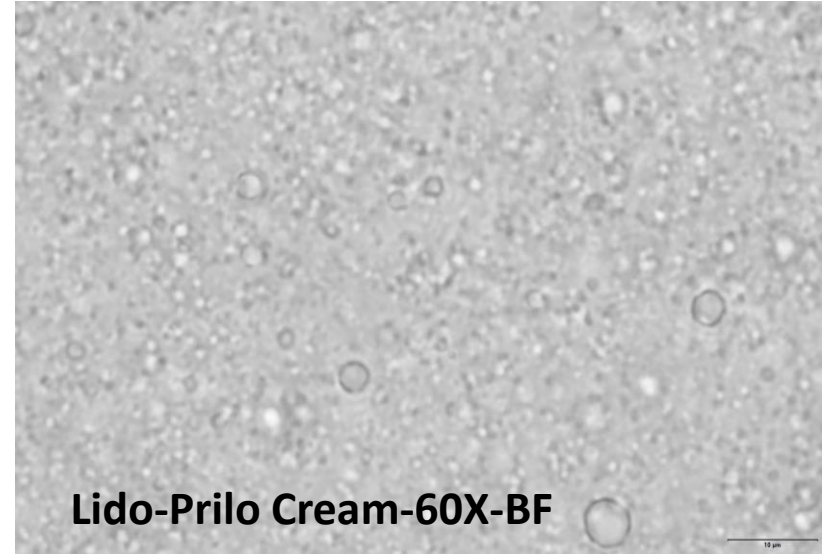
Microscopy-Globule size



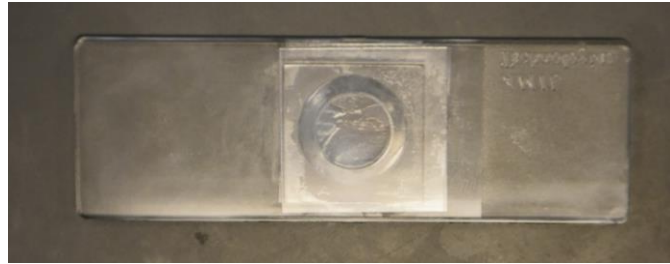
Microscopy-Globule size



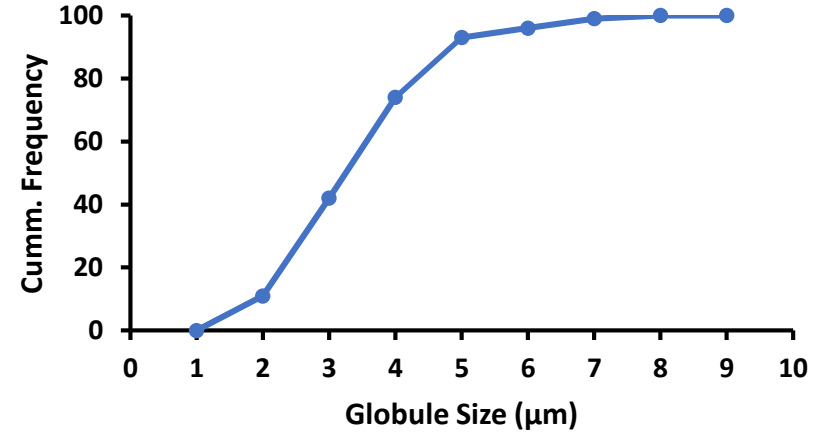
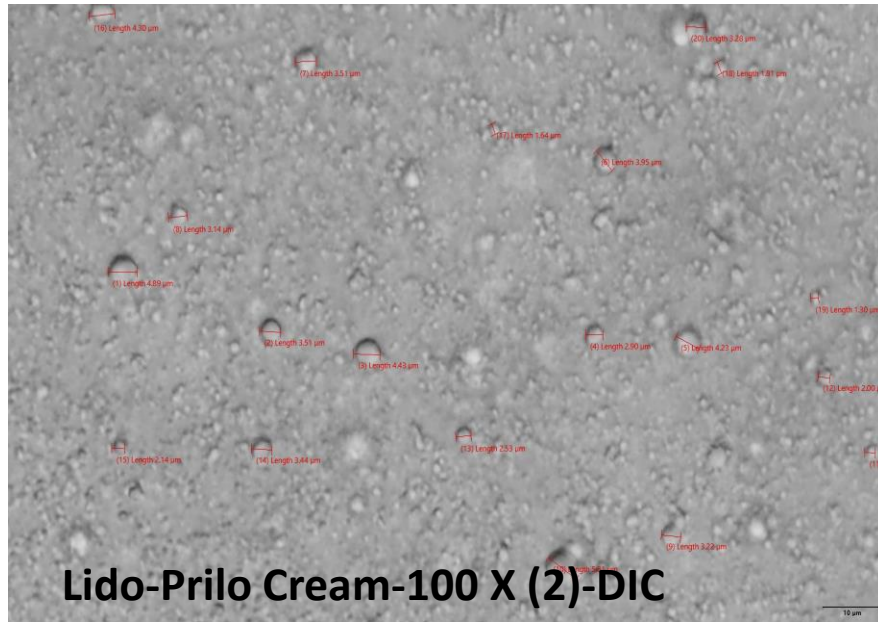
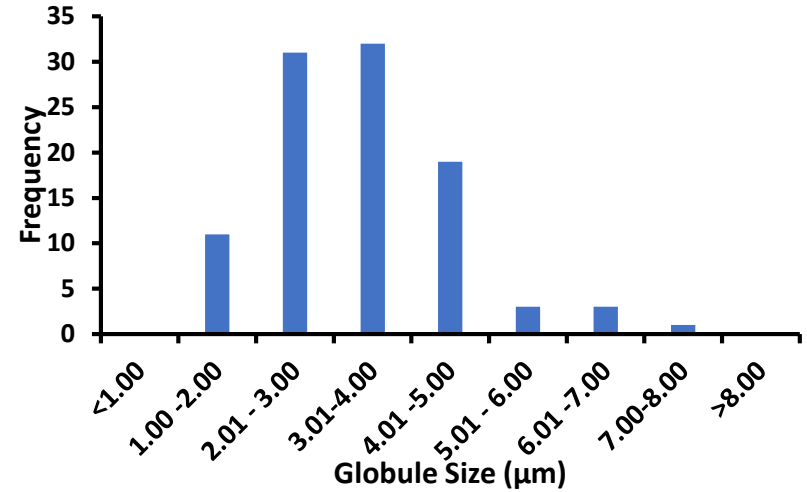
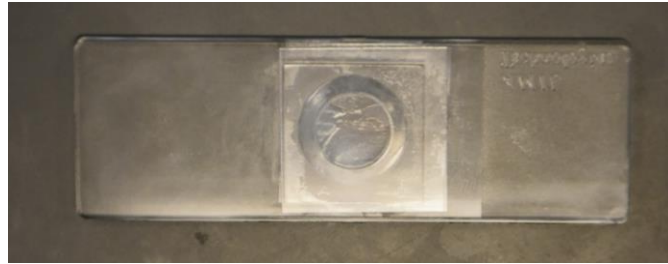
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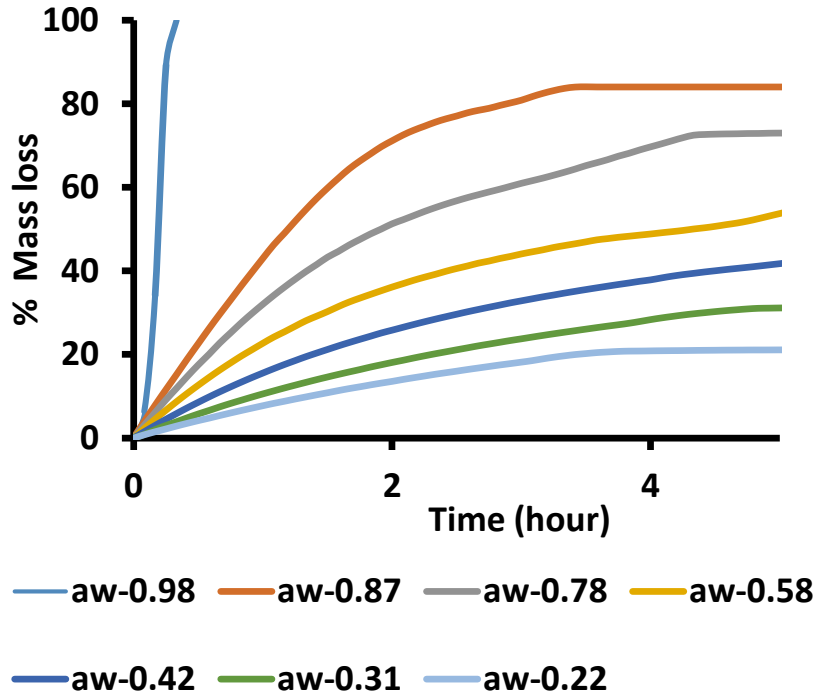


d10 (µm)	1.90
d50 (µm)	3.25
d90 (µm)	4.85

Water Activity (a_w)

$$a_w = \rho / \rho_0$$

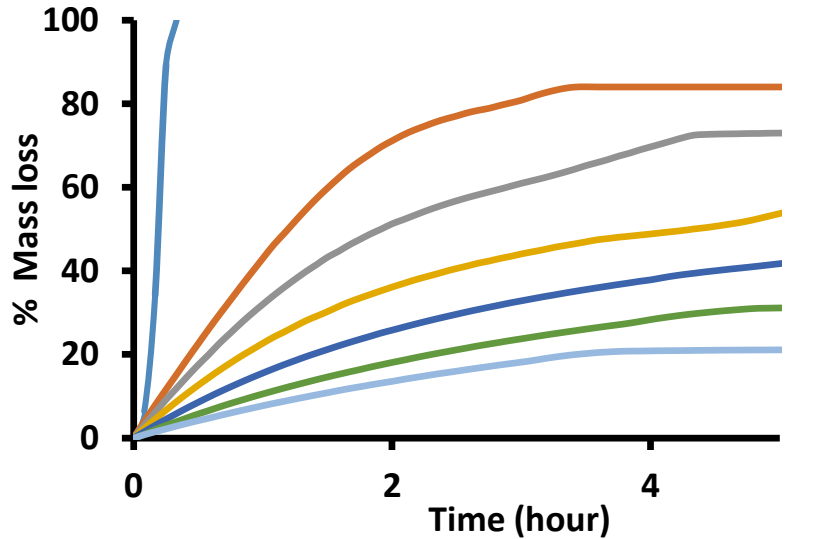
ρ = Partial vapor pressure of water in the product
 ρ_0 = vapor pressure of pure water



Water Activity (a_w)

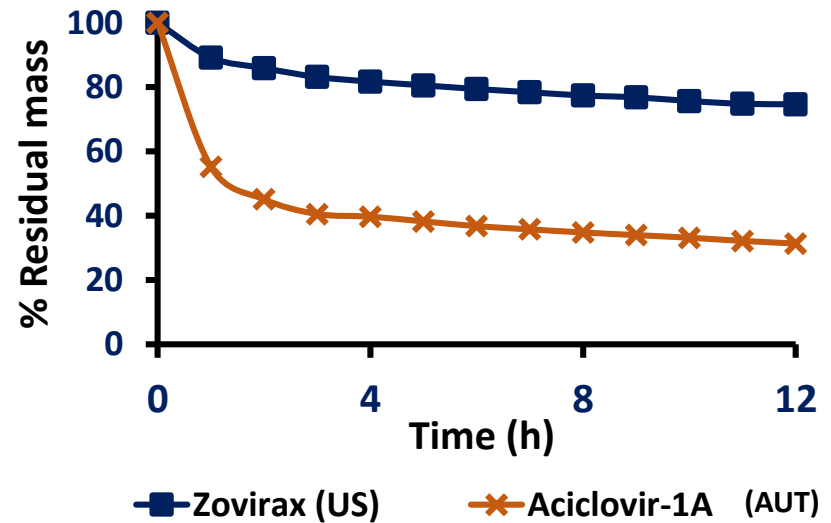
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— aw-0.98 — aw-0.87 — aw-0.78 — aw-0.58
— aw-0.42 — aw-0.31 — aw-0.22

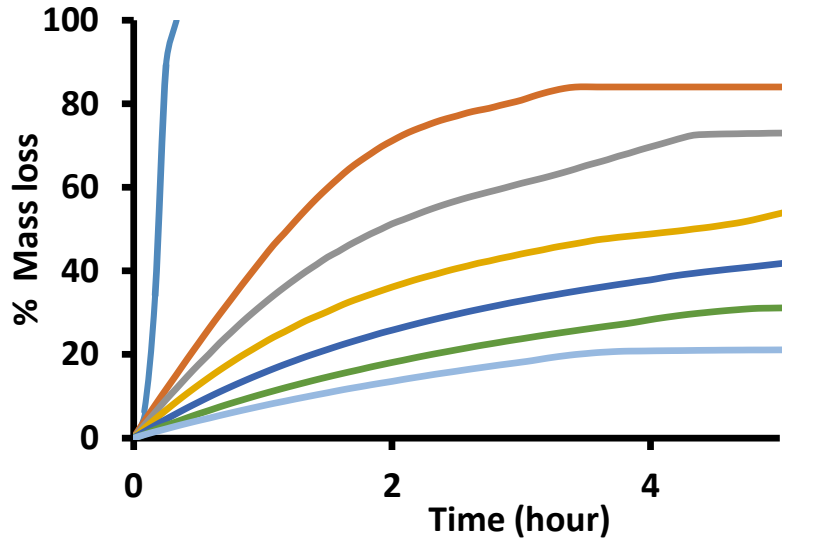
Zovirax (UK)	0.732 ± 0.002
Aciclovir-1A	0.948 ± 0.001



Water Activity (a_w)

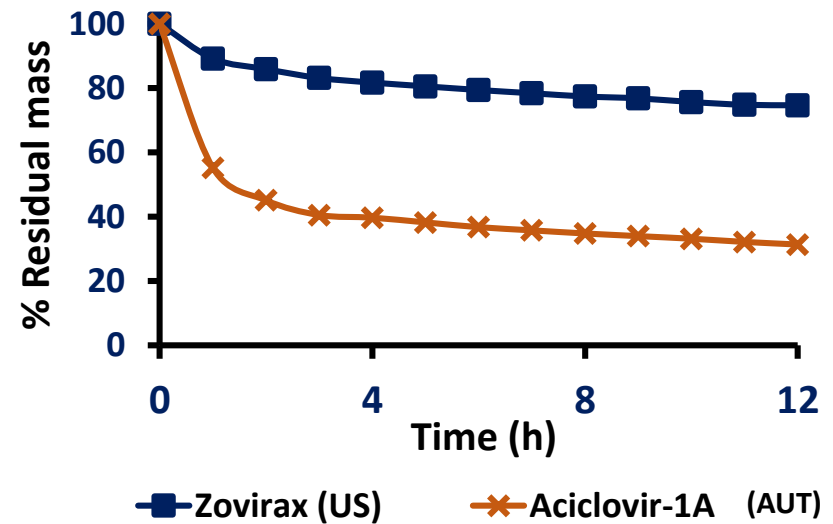
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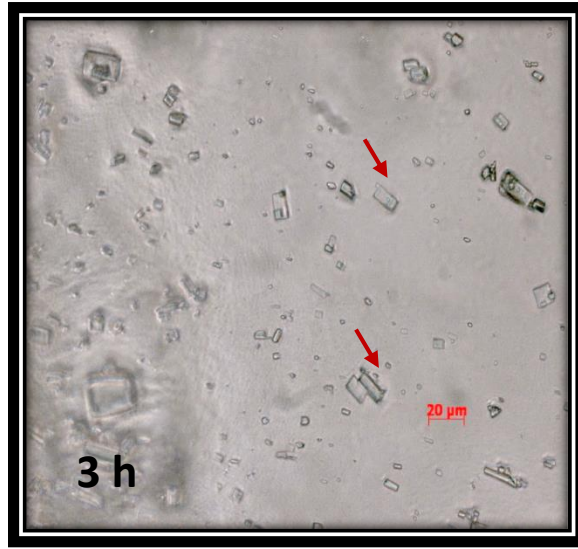
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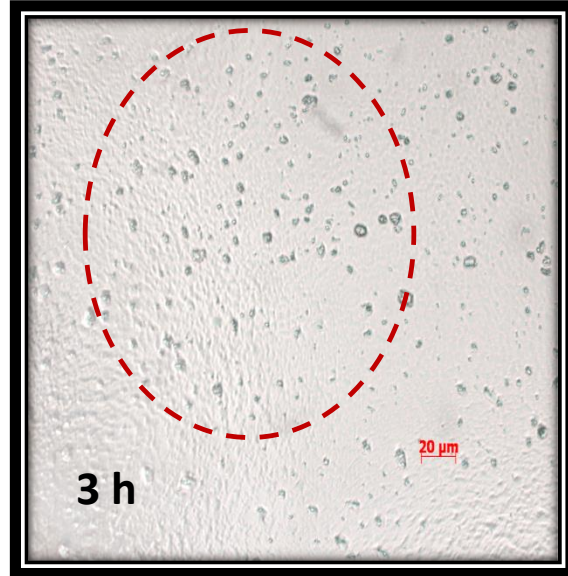
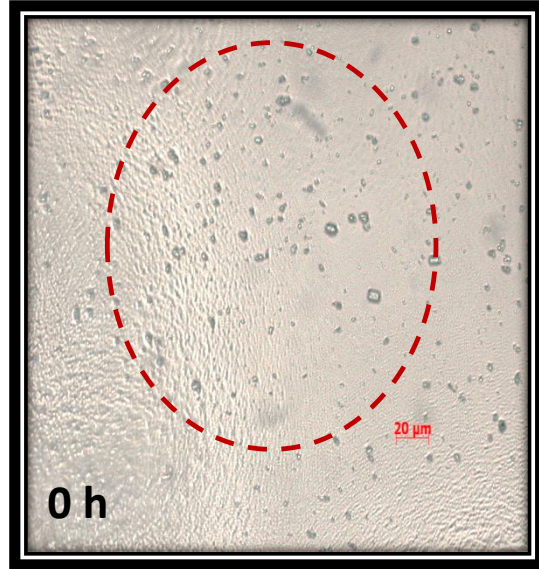
Dose	Total Drug	Dissolved Drug	Undissolved drug
5 mg/cm^2	$250 \text{ } \mu\text{g/cm}^2$	$6.25 \text{ } \mu\text{g/cm}^2$	$243.75 \text{ } \mu\text{g/cm}^2$

Solvent Evaporation and Precipitation of Acyclovir

Zovirax-UK



Aciclovir -1A



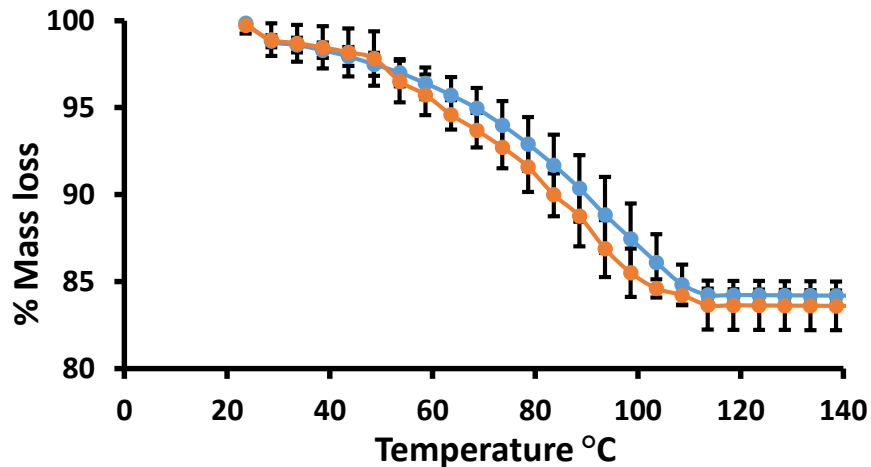
Water activity of Q1 & Q2 identical Creams

Ingredients (W/O)	Quantity (%)
Cetostearyl Alcohol	12.5
White Wax	12
Mineral Oil	59
Sodium Borate	0.5
Water	16

Water activity of Q1 & Q2 identical Creams

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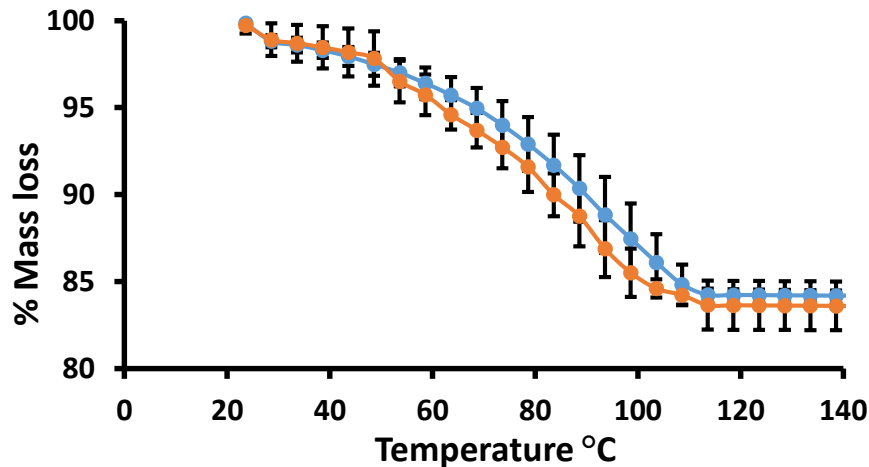
Formulation Code	Loss on Drying(%)	Water Content(%)
F1 (3000rpm-15 min)	84.32 ± 1.15	~16%
F2 (7000rpm-45 min)	83.75 ± 1.39	



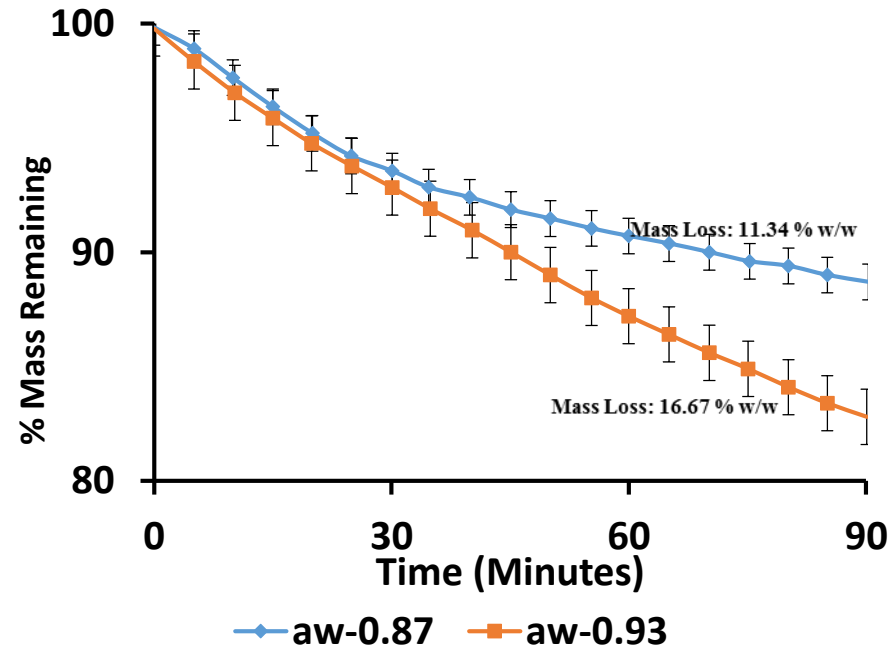
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Formulation Code	Loss on Drying(%)	Water Content(%)
F1 (3000rpm-15 min)	84.32 ± 1.15	~16%
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Formulation Code	Water Activity (aw)	% Mass loss at 90min
F1	0.93	16.67%
F2	0.87	11.34%



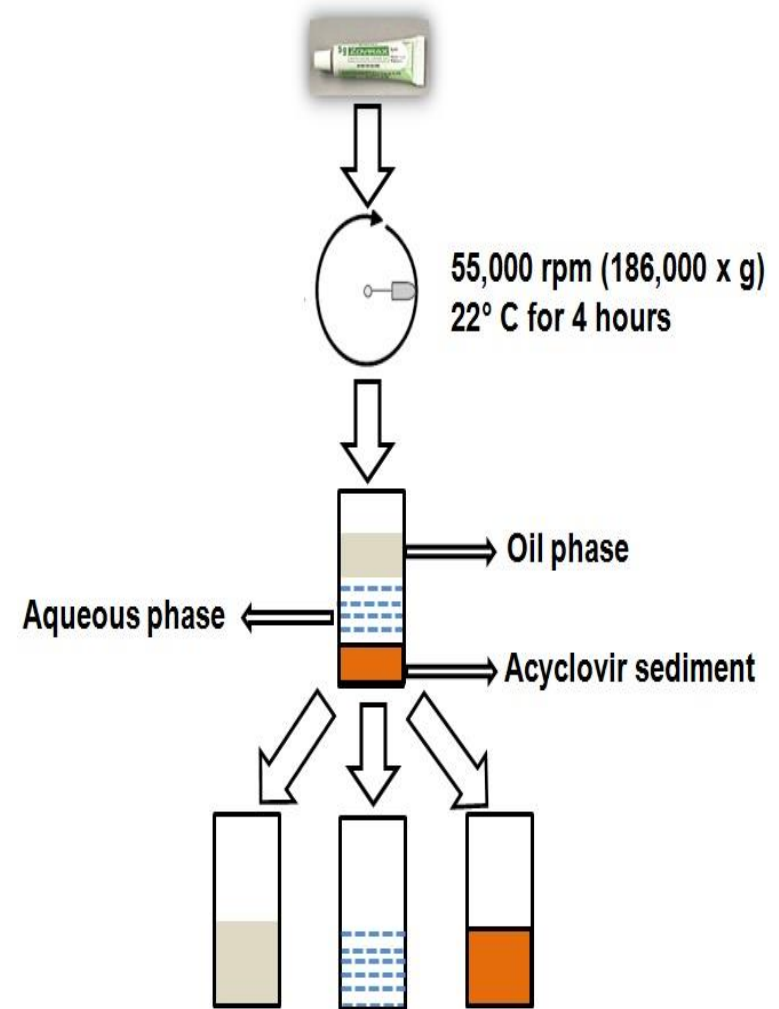
Determination of drying rate of model w/o type cream formulation using thermogravimetry at 32°C.

Phase Distribution of Drug

Product	Total dissolved acyclovir in cream (mg/g)	Total undissolved acyclovir in cream (mg/g)	Amount Dissolved in Aqueous Phase (mg/g)
ZOVIRAX (US)	1.35 ± 0.05	48.65 ± 0.05	0.49 ± 0.08
ACICLOVIR -1A	1.44 ± 0.03	48.56 ± 0.02	0.26 ± 0.02

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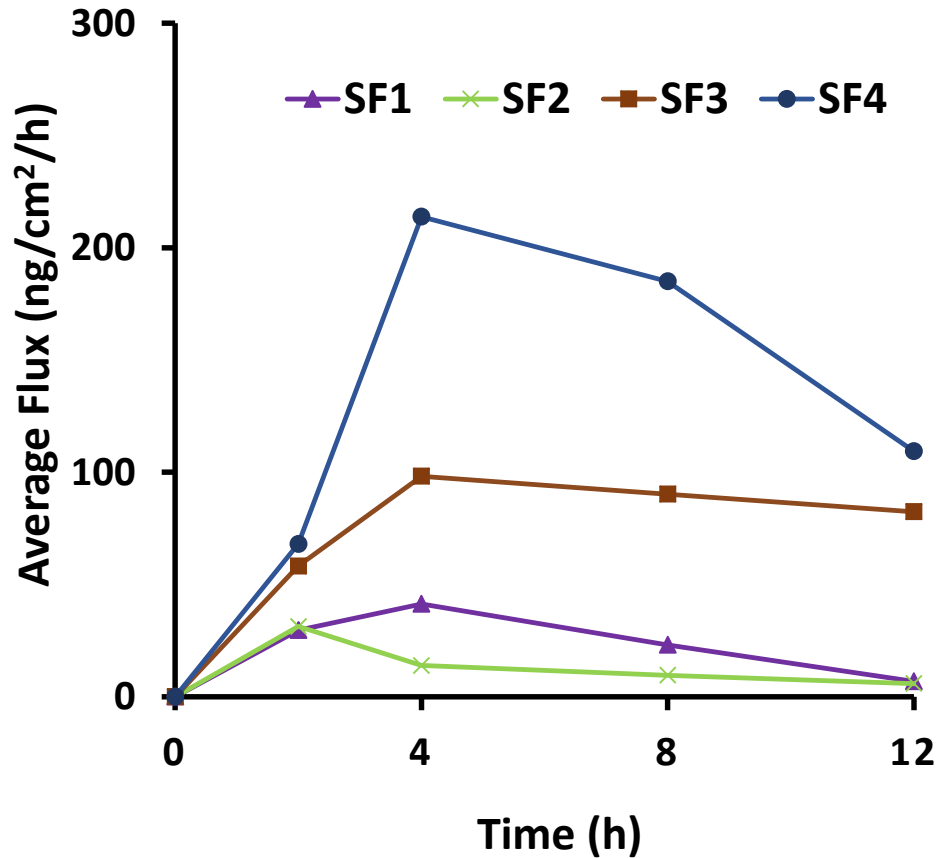
Cream Formulations

Ingredients	SF1 (% w/w)	SF2 (% w/w)	SF3 (% w/w)	SF4 (% w/w)
Mineral oil	15	15	15	15
Cremophor® A6	1.5	1.5	1.5	1.5
Cremophor® A25	1.5	1.5	1.5	1.5
Cetostearyl alcohol 70	7	7	7	7
Isopropyl myristate	3	3	3	3
Tefose® 63	1	1	1	1
Labrafil® M 1944 CS	1	1	1	1
PEG 400	5	5	5	5
TPGS	1.2	1.2	1.2	1.2
Tween 80	1.21	1.27	1.33	1.40
Span 60	2	2	2	2
Propylene glycol	10	10	10	10
Drug (Metronidazole)	0.75	0.75	0.75	0.75
Water (q.s.to 100%)	49.84	49.78	49.72	49.65

Microstructural Characteristics

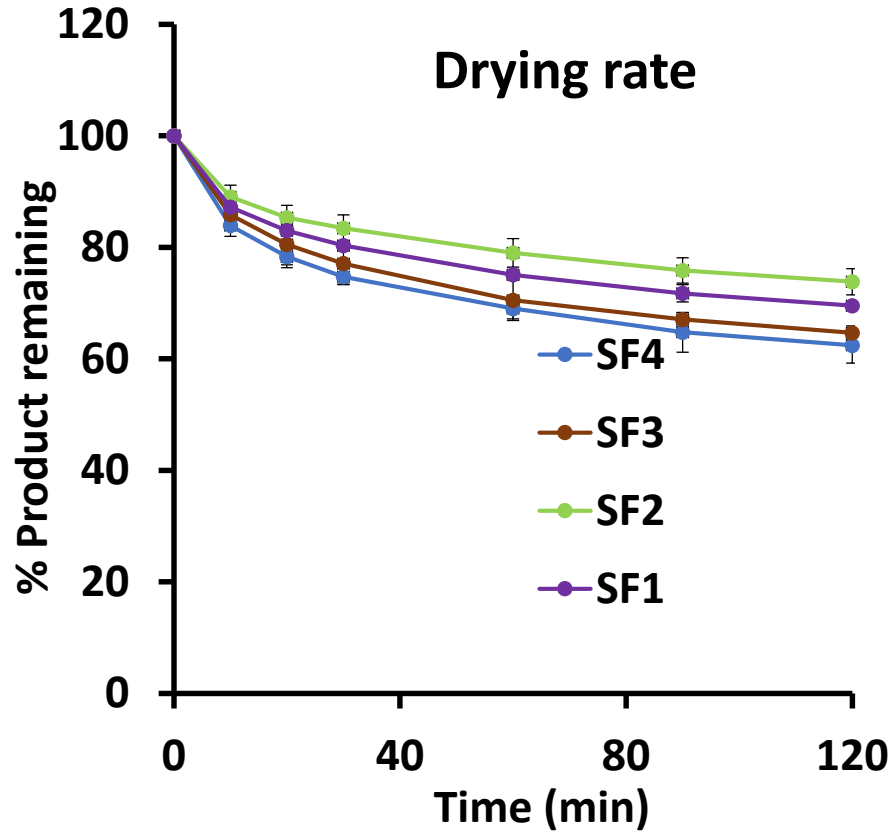
Code	Amount of surfactant (% w/w)	Average globule size (μm)	Cream pH	Amount in Aqueous phase (mg/g)	Water activity (a_w)	IVRT slope ($\mu\text{g}/\text{cm}^2/\text{h}$)	Work of adhesion (g.sec)	Viscosity (Pa.s) at Shear rate 100 1/s	Yield stress (Pa)
SF1	1.21	20.7 \pm 16.54	5.60 \pm 0.15	5.17	0.894 \pm 0.025	245.2 \pm 36.3	214.4 \pm 14.45	3.37	190
SF2	1.27	19.3 \pm 14.81	5.49 \pm 0.08	5.54	0.890 \pm 0.008	258.1 \pm 32.9	217.1 \pm 13.03	3.40	132
SF3	1.33	19.1 \pm 16.79	5.54 \pm 0.04	6.09	0.894 \pm 0.003	266.1 \pm 40.9	221.8 \pm 13.90	2.95	132
SF4	1.40	14.4 \pm 10.98	5.57 \pm 0.04	4.42	0.917 \pm 0.007	233.8 \pm 27.4	244.3 \pm 26.48	3.56	122

IVPT of Cream Formulations

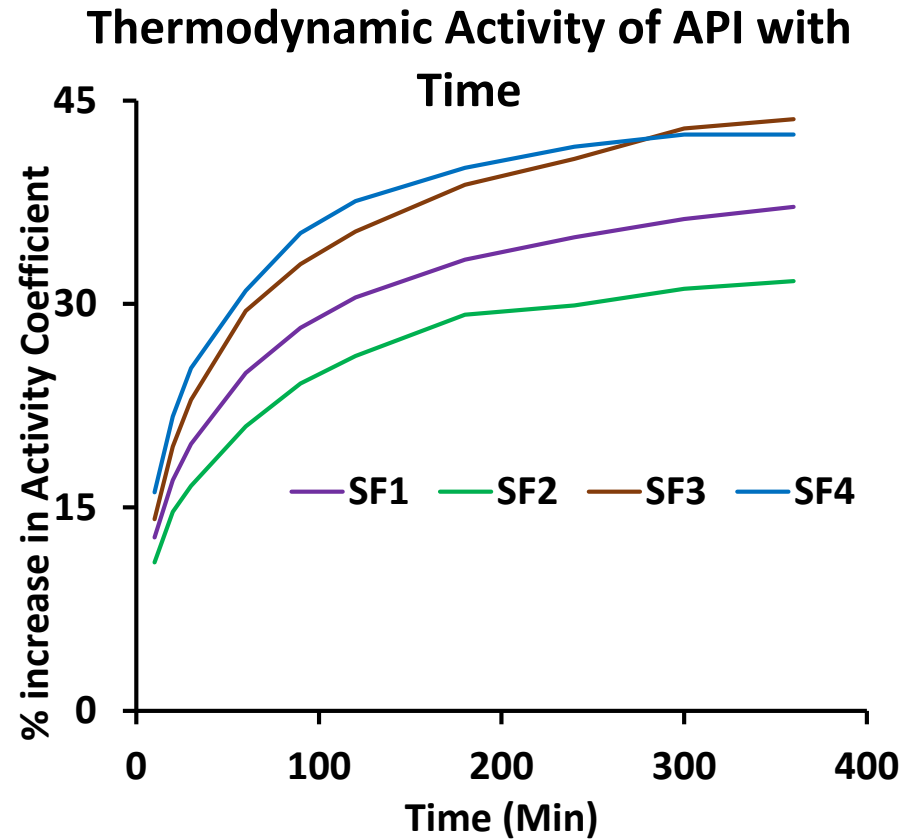
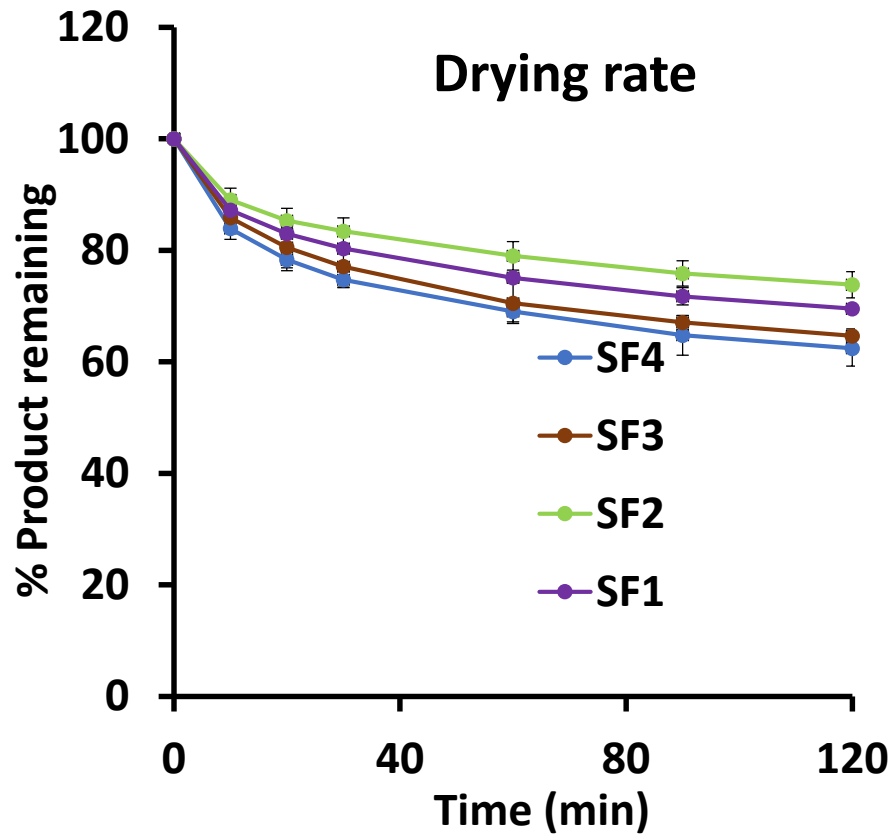


Dermatokinetics	SF1	SF2	SF3	SF4
J_{\max} (ng/cm ² /h)	51.2±45.53	41.2±32.71	149.4±93.96	308.0±138.89
AUC_{0-12}	289.2±258.93	154.0±117.65	936.8±669.55	1736.5±636.14

Drying Rate and Thermodynamic potential



Drying Rate and Thermodynamic potential

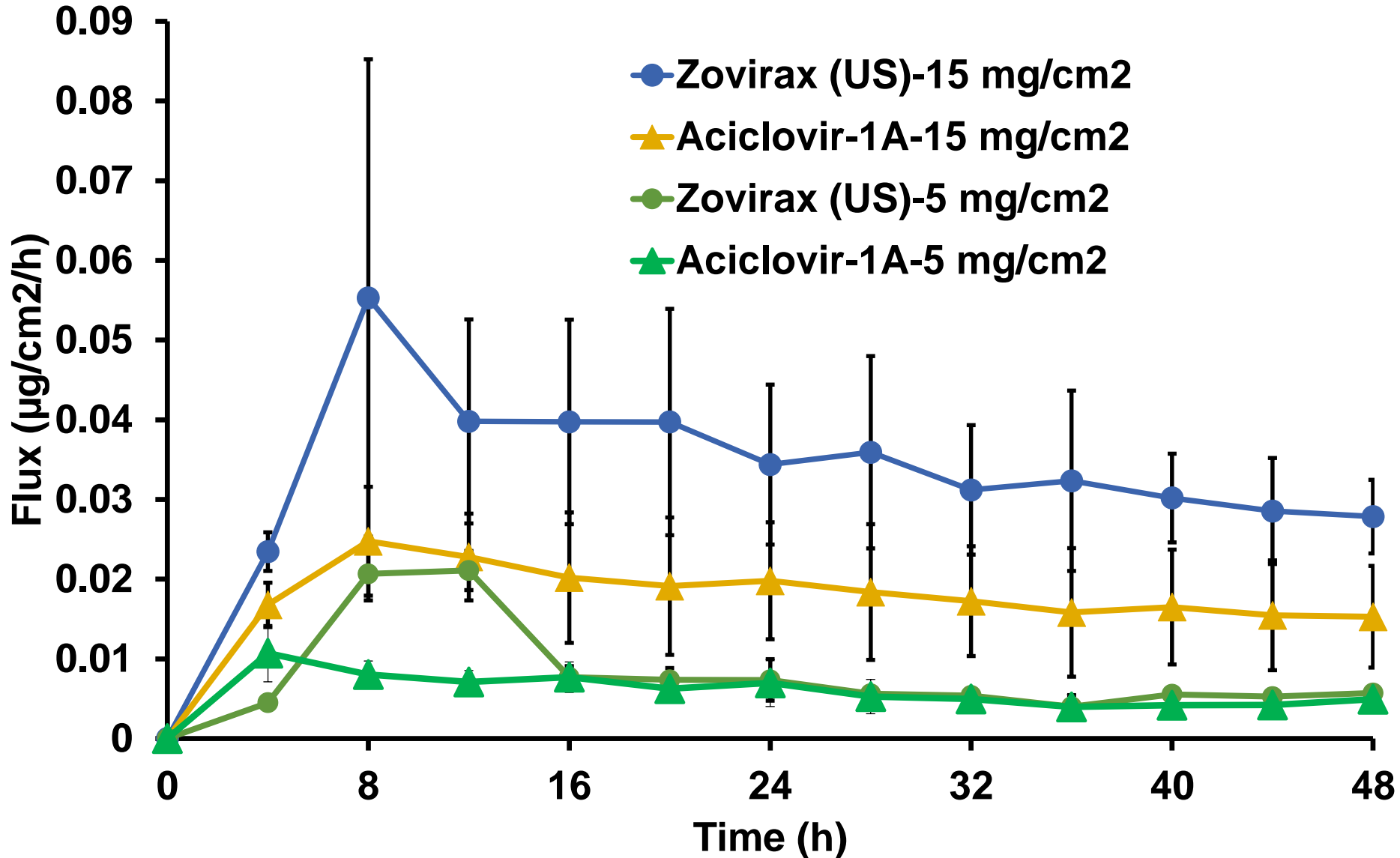


In Vitro Permeation Testing

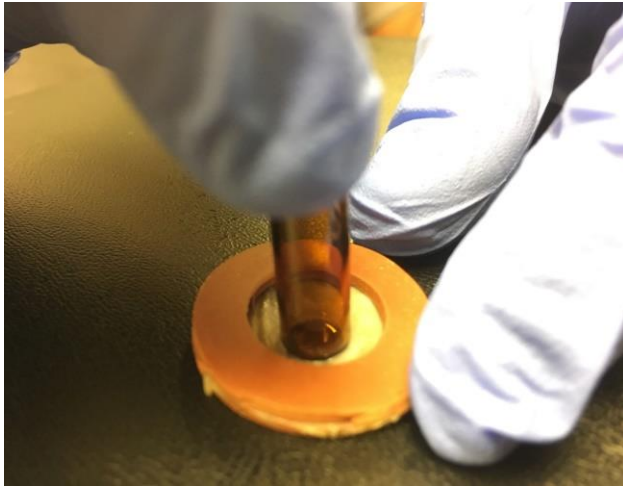
Method Development

- **Dose selection**
- **Method of Application**
- **Sampling time points**

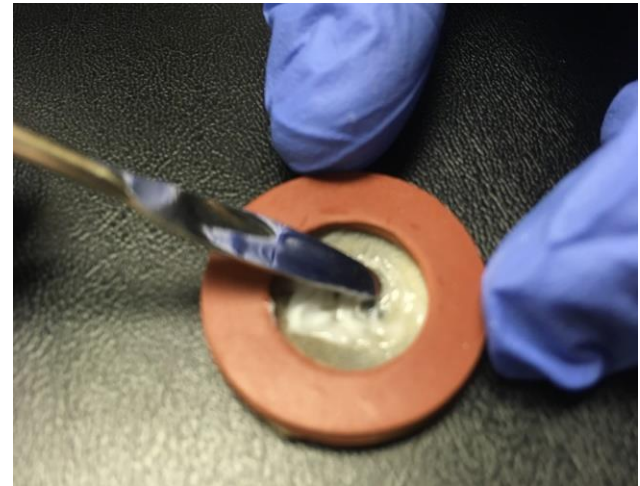
Dose Selection for IVPT in Acyclovir Creams



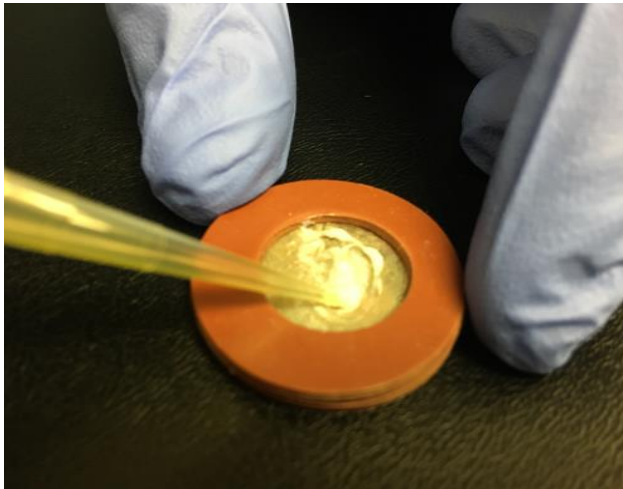
Dose Application Techniques for IVPT



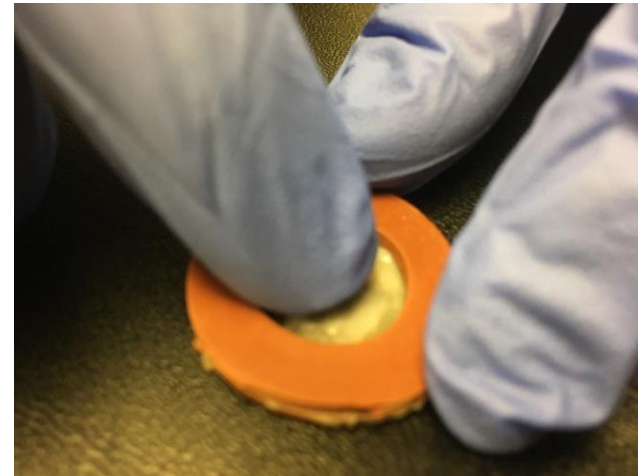
Vial Technique



Spatula Technique

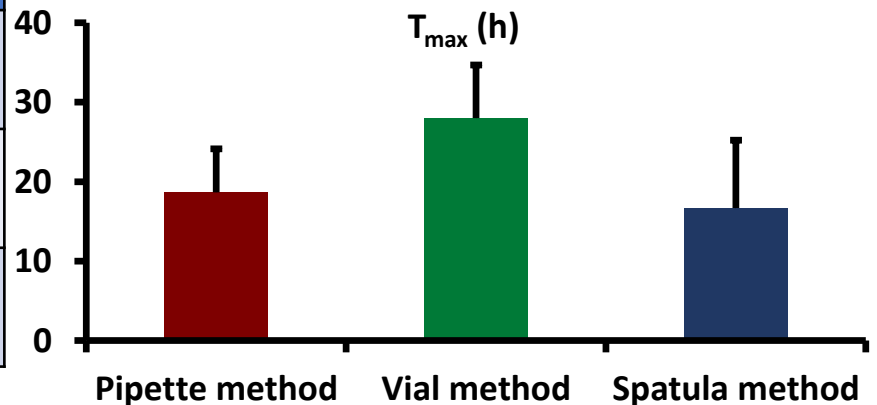
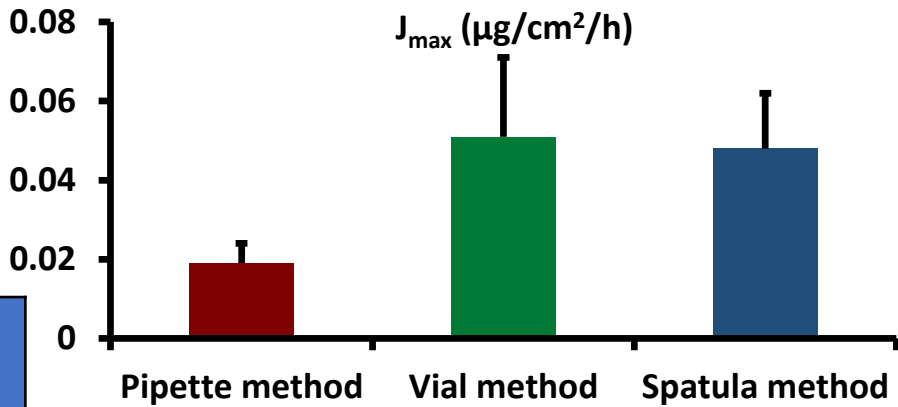
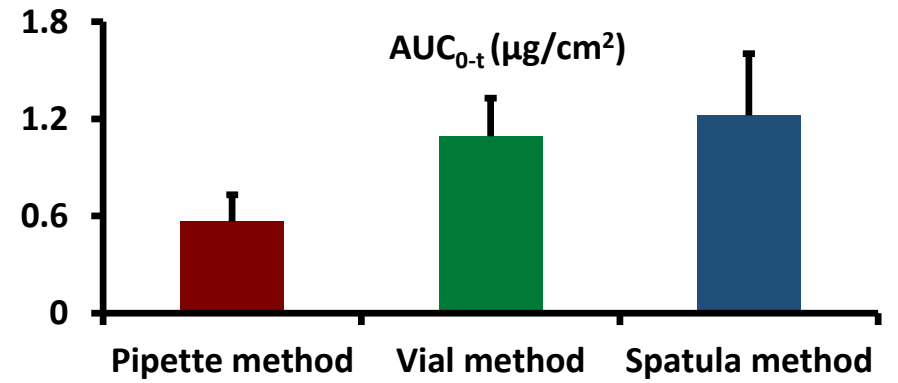
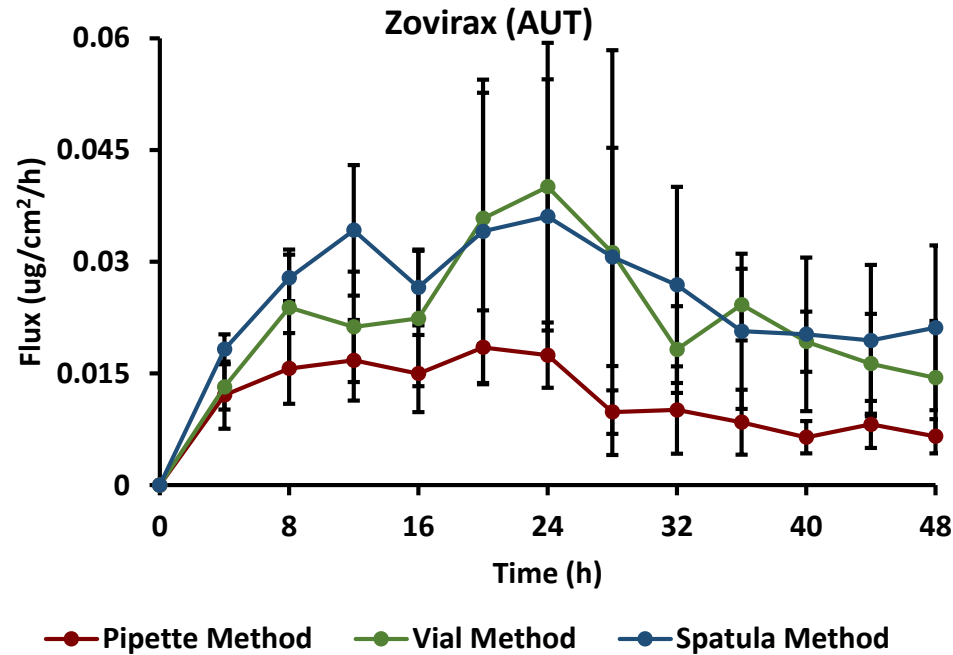


Pipette Technique



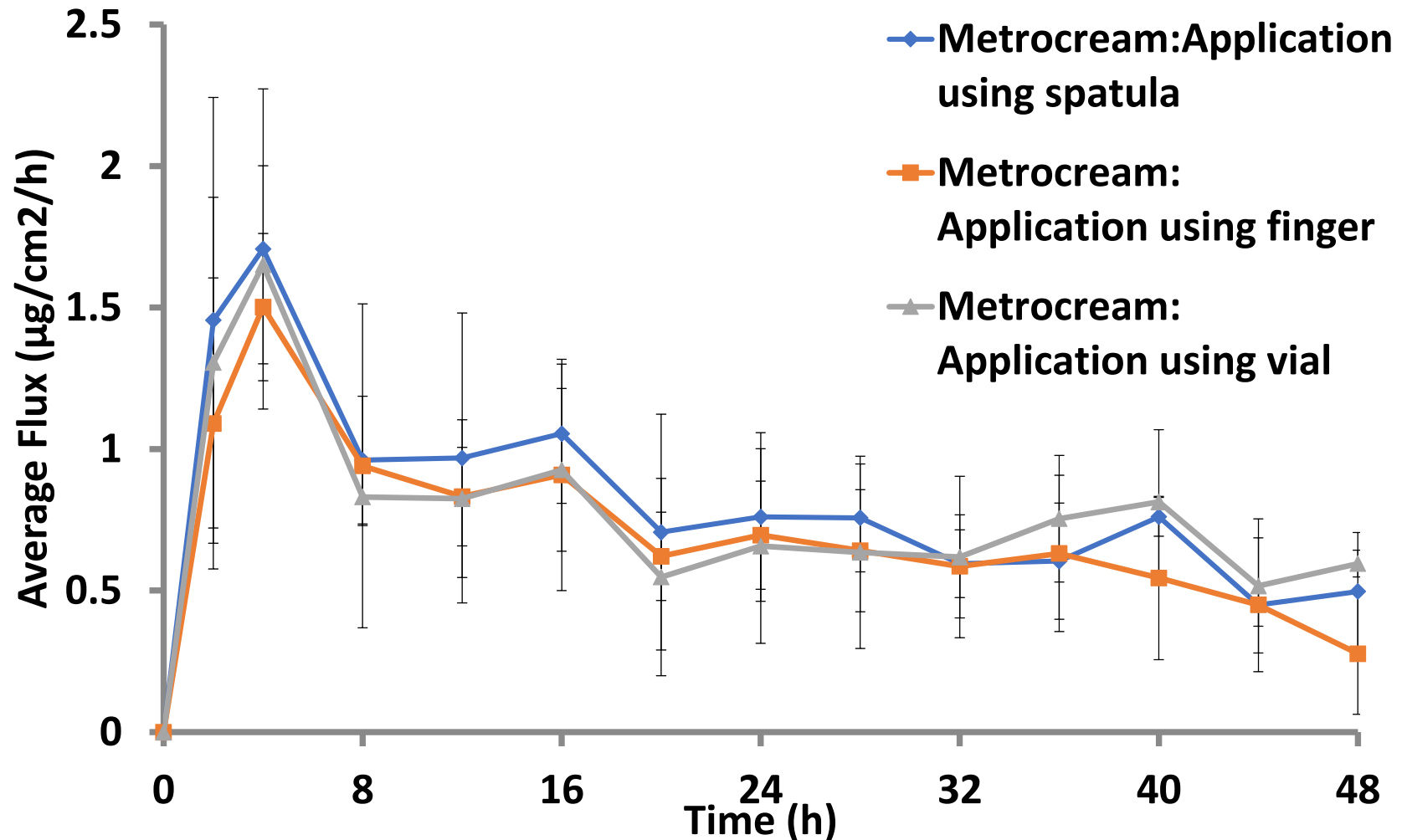
Finger Technique

Method of Dose Application

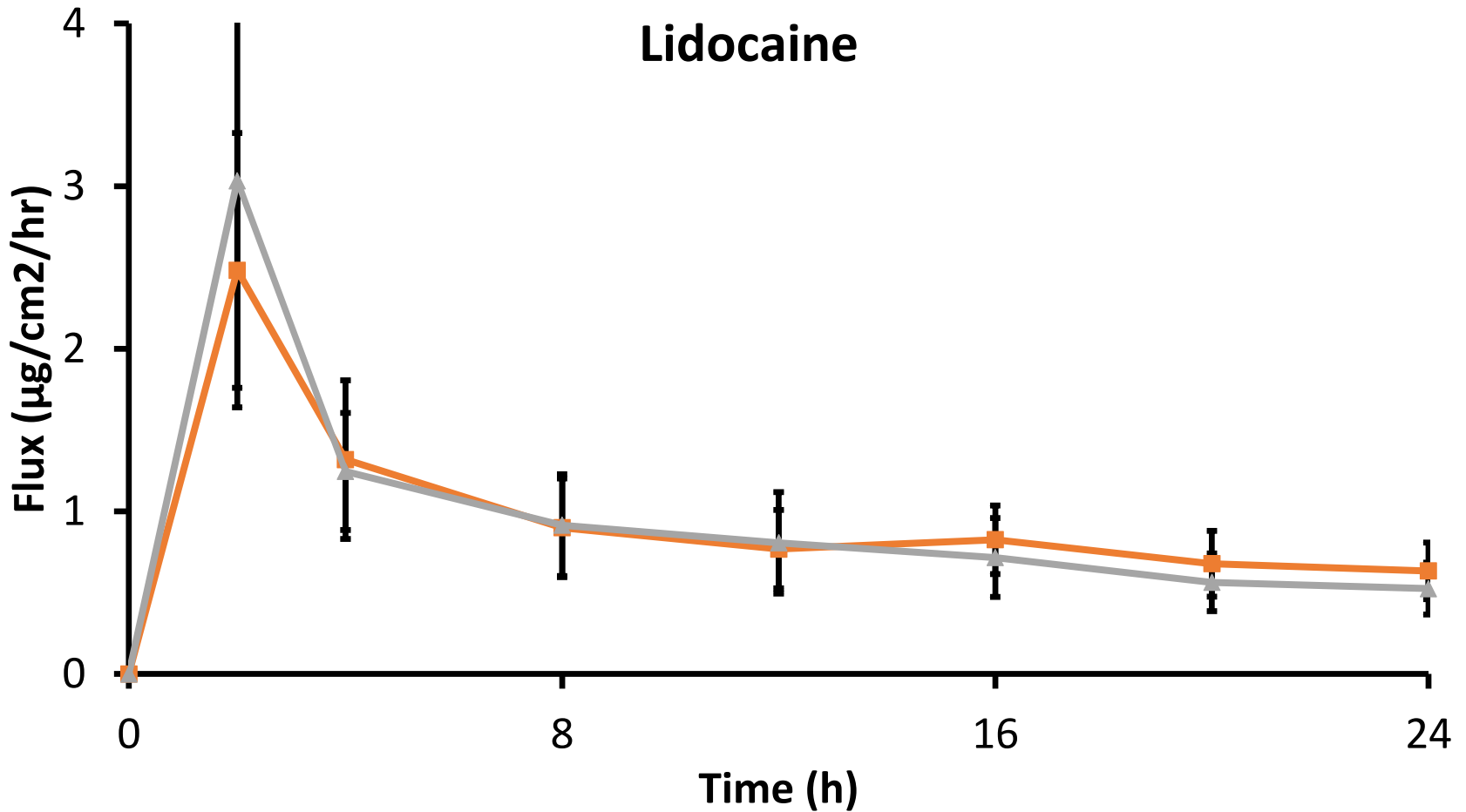


Method	AUC_{0-t} ($\mu\text{g}/\text{cm}^2$)	J_{\max} ($\mu\text{g}/\text{cm}^2/\text{h}$)	T_{\max} (h)
Pipette method	0.57 ± 0.17	0.02 ± 0.01	18.67 ± 5.46
Vial method	1.09 ± 0.24	0.05 ± 0.02	28.00 ± 6.69
Spatula method	1.22 ± 0.38	0.05 ± 0.01	16.67 ± 8.54

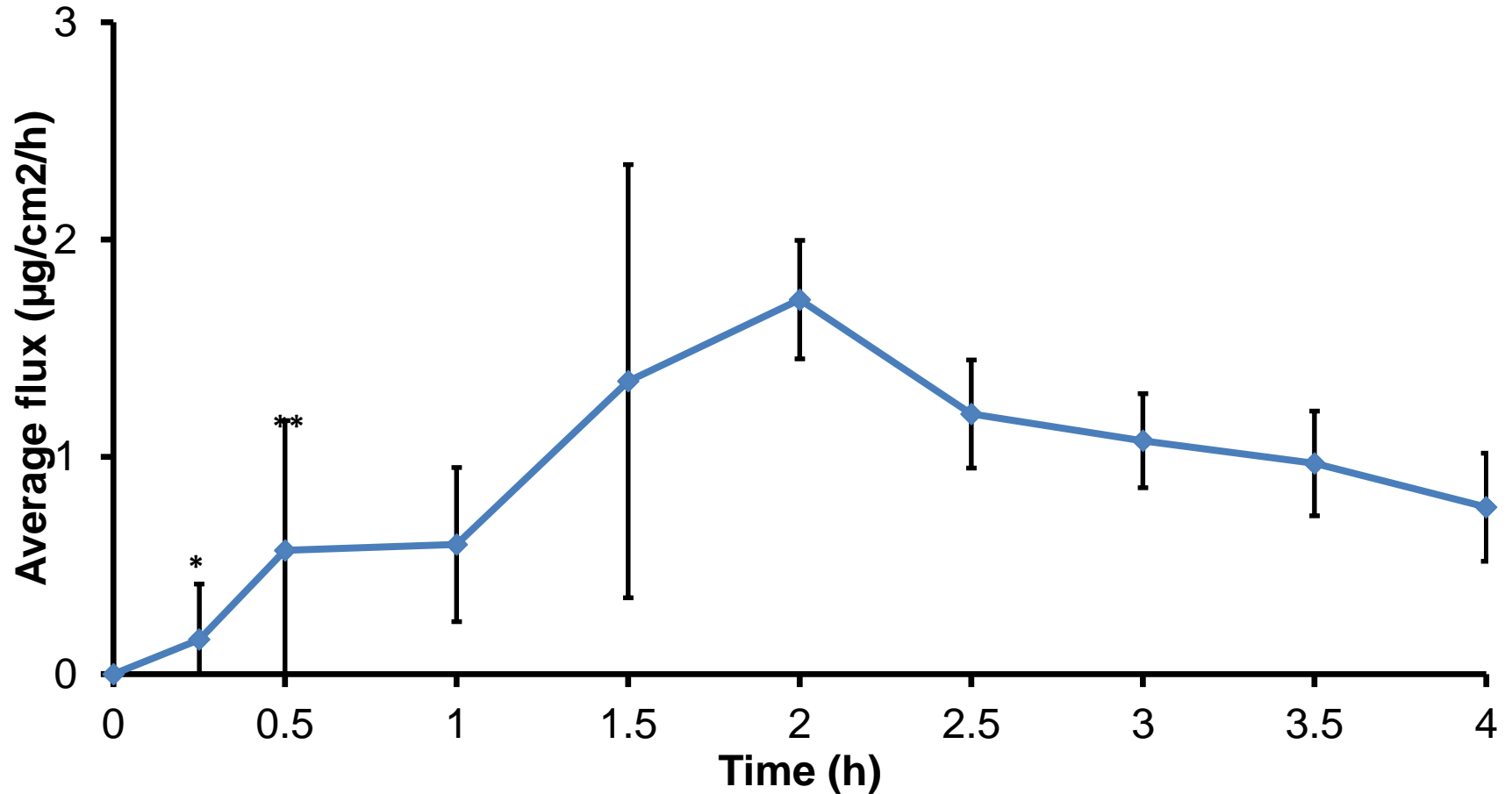
Effect of method of application of topical products on *in-vitro* permeation profile of Metronidazole



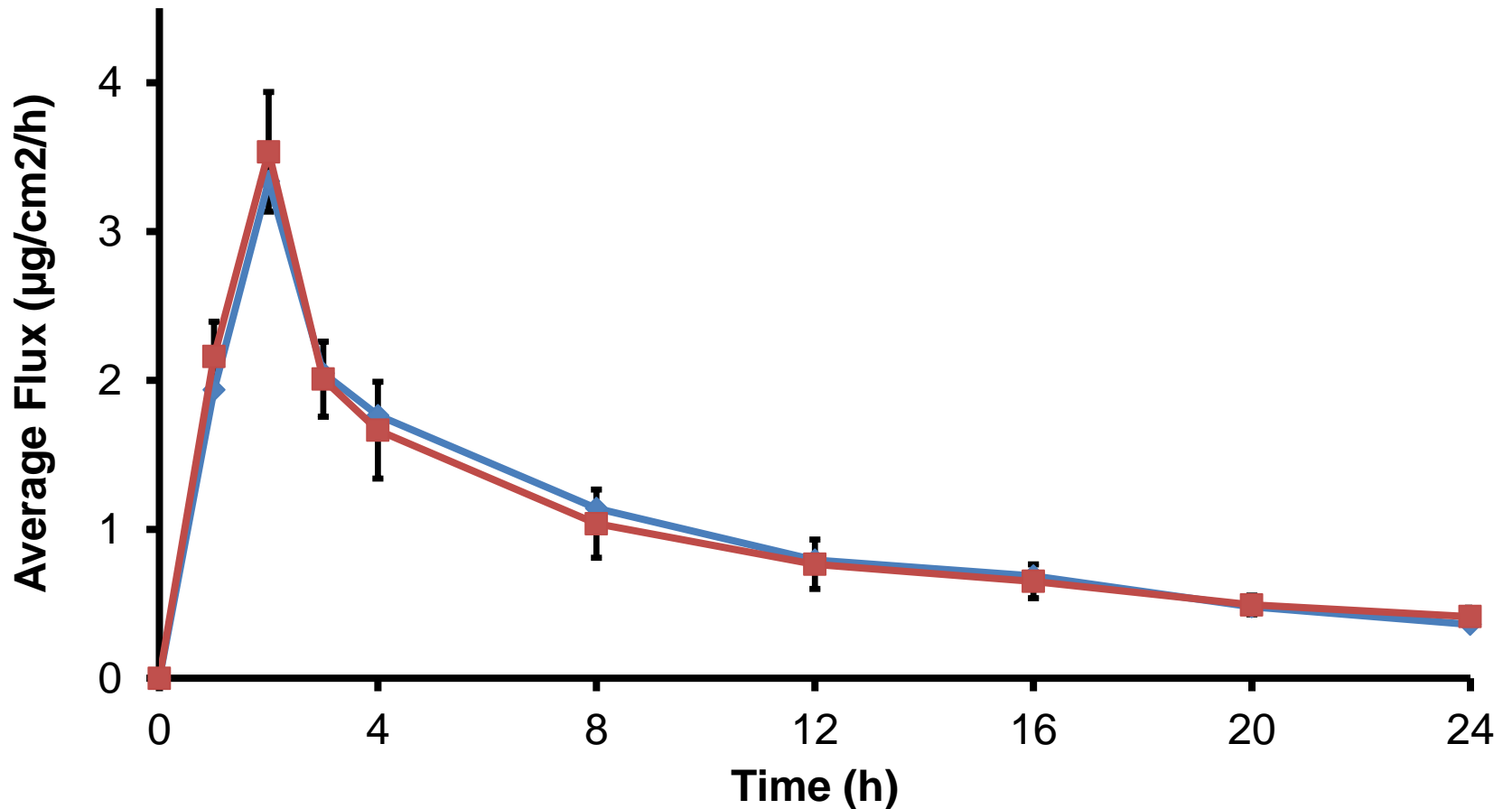
IVPT of Lidocaine-Prilocaine Cream



IVPT of Lidocaine-Prilocaine Cream



IVPT of Lidocaine-Prilocaine Cream



Conclusions

- Not just the pH, Buffer capacity is also important.
- The manufacturing protocol could influence the microstructure in the end product in gels containing molecules undergoing self association.
- Microscopy could be challenging in high water activity products.
- Water activity influences the post-application metamorphosis of topical products.
- IVPT is a great tool to measure bioequivalence. However, dose, method of application, sampling times need to be determined in a sequence of pilot studies during development.

Acknowledgements

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- Dr. Srinatha-Postdoctoral Associate
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- Srinivas Ajarapu (Grad. Student)

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