

Advanced Characterization Approaches for Topical Formulations

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Session Description and Objectives

- The objective of the presentation is to discuss some knowledge gaps and novel tools used in the characterization of topical products.
- To understand the Importance of quality attributes of topical products.
- To learn about the fundamental principle behind tools and methodologies used to characterize the quality attributes of topical products.

Biography and Contact Information

- **Area of Research:** Topical and Transdermal Drug Delivery, Intranasal Drug Delivery, Trans-ungual drug delivery
- **Publications:** Over 100 research papers, Two books, 15 review papers.
- **Grants and Funding:** NIH, USFDA, Industry
- **Contact information:**

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Topical Products Characteristics

- pH
- Particle size
- Polymorphism
- Rheological Studies
- Globule size
- Dissolved/ Undissolved drug
- Sensorial Characteristics:
 - Color/Appearance
 - Texture characteristics
 - Odor
 - Skin cooling.

pH as a Quality Attribute

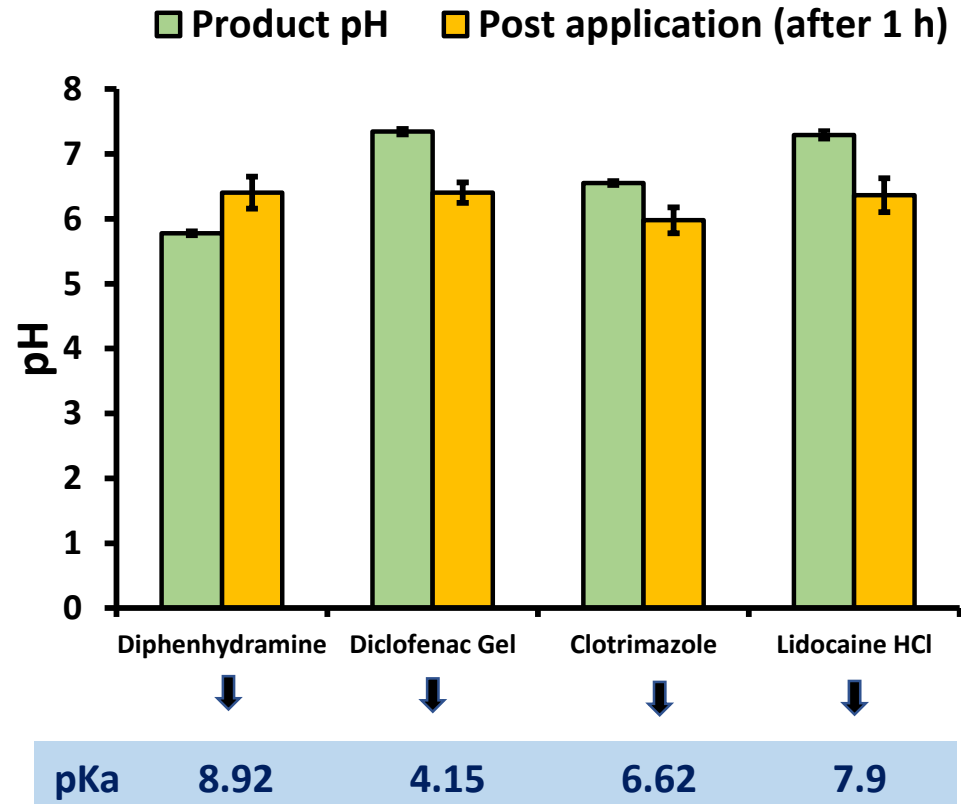
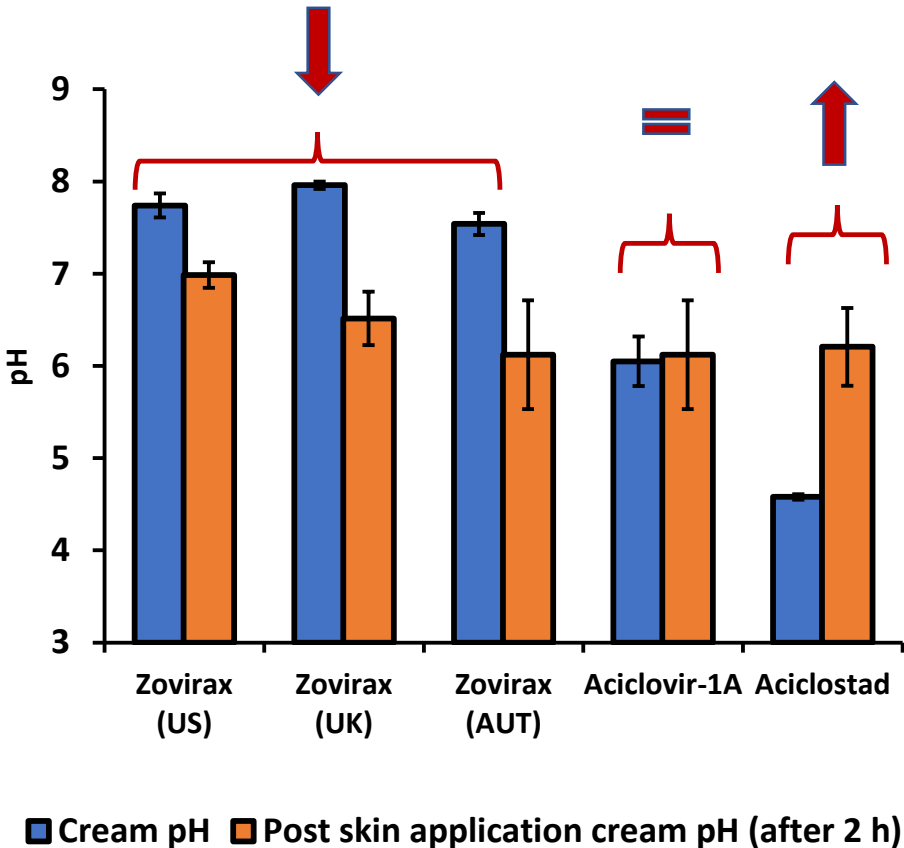
- pH of the product influences the extent of ionization of weakly acidic and basic APIs in the formulation.
- Unionized drug undergoes absorption relatively better than ionized form.
- pH changes in the formulation due to interaction with packaging material, loss of contents or due to changes in the excipient could impact the drug permeation from the formulation.

pH Change in Creams with Different Fatty Alcohols

Description	Purpose	w/w%
Propylene glycol	Solvent	8
Fatty alcohol	Viscogen	7
Octyldodecanol	Emollient	12
Macrogol cetostearyl ether 20	Emulsifier	3
Clotrimazole	API	1
Water	Solvent	69
Phenoxyethnol	Preservative	0.0005

Fatty Alcohol		pH of Fresh formulation (n=3±s.d)	pH of formulation after 3 months	
			25/65%RH	40/70%RH
Cetostearyl alcohol 50	CSA 50	5.75 ± 0.05	7.30 ± 0.05	7.15 ± 0.01
Cetostearyl alcohol 70	CSA70	5.89 ± 0.02	7.23 ± 0.02	6.65 ± 0.01
Myristyl alcohol	MA	5.79± 0.01	6.87 ± 0.01	6.32 ± 0.01
Cetyl alcohol	CA	5.79± 0.02	7.11 ± 0.01	6.96 ± 0.01
Stearyl alcohol	SA	5.79 ± 0.01	7.30 ± 0.01	6.89 ± 0.01

pH could change after application on the skin

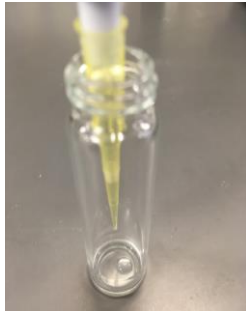


pH change could impact the drug permeation

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)

Should we consider Determining the Buffer Capacity as well?

Measurement of Buffer Capacity of Topical Products



Known volume of standardized Sodium hydroxide and dispersant solution



The solution is dried by constantly rotating the vial to form a thin film of about 5-7 mm depth



Measure the initial pH of the test cream and place a known weight/volume in the glass vial.



Thoroughly mix the contents with a spatula intermittently



pH is measured using InLab Micro probe until constant values are attained.

Product	Initial pH	β_{1h} (moles/pH)	β_{24h} (moles/pH)
RLD-Cream	4.82 ± 0.01	3.6 × 10 ⁻⁴	4.1 × 10 ⁻⁴
Generic Cream	5.05 ± 0.05	1.2 × 10 ⁻⁴	2.0 × 10 ⁻⁴

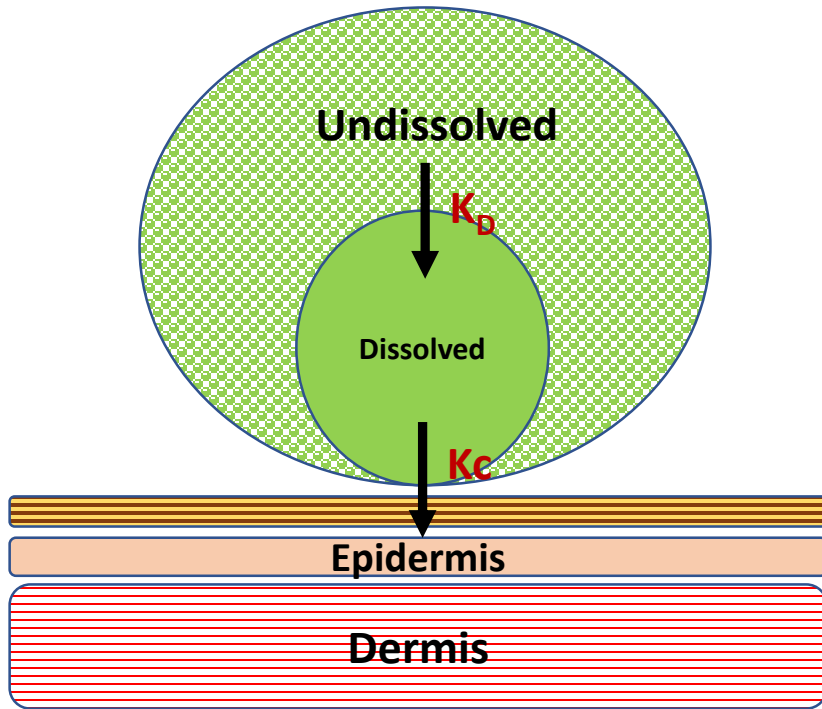


P > 0.05



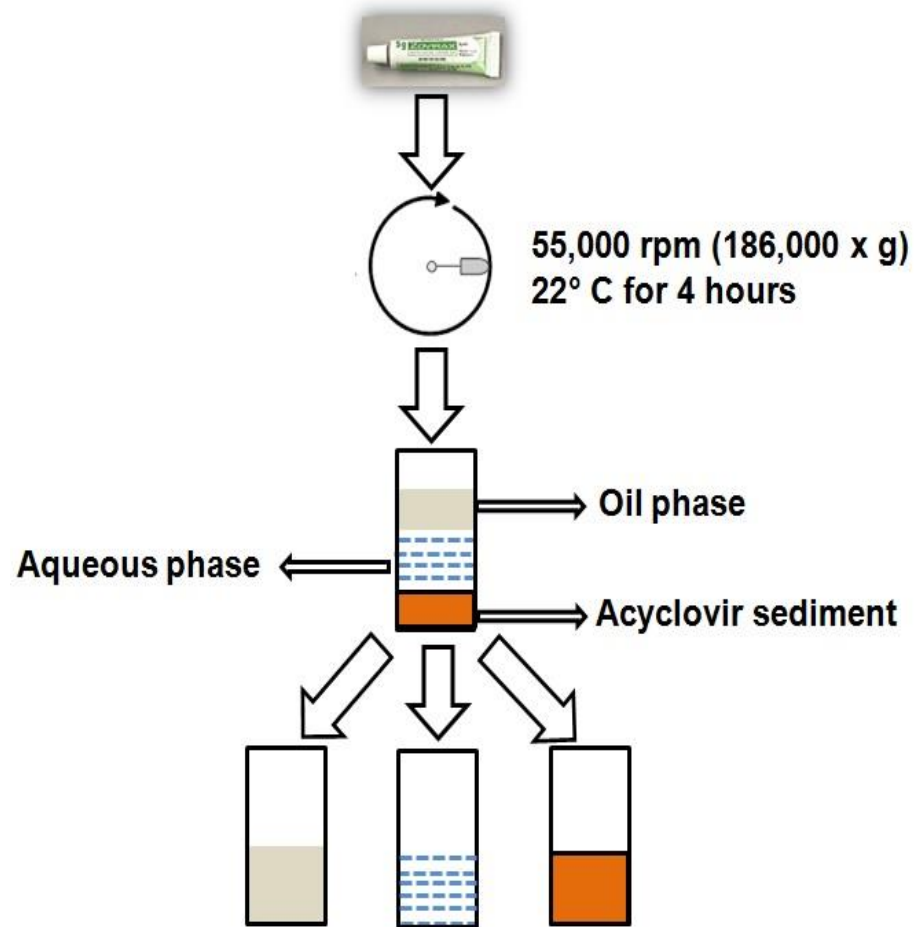
P* < 0.05

Dissolved/Undissolved drug



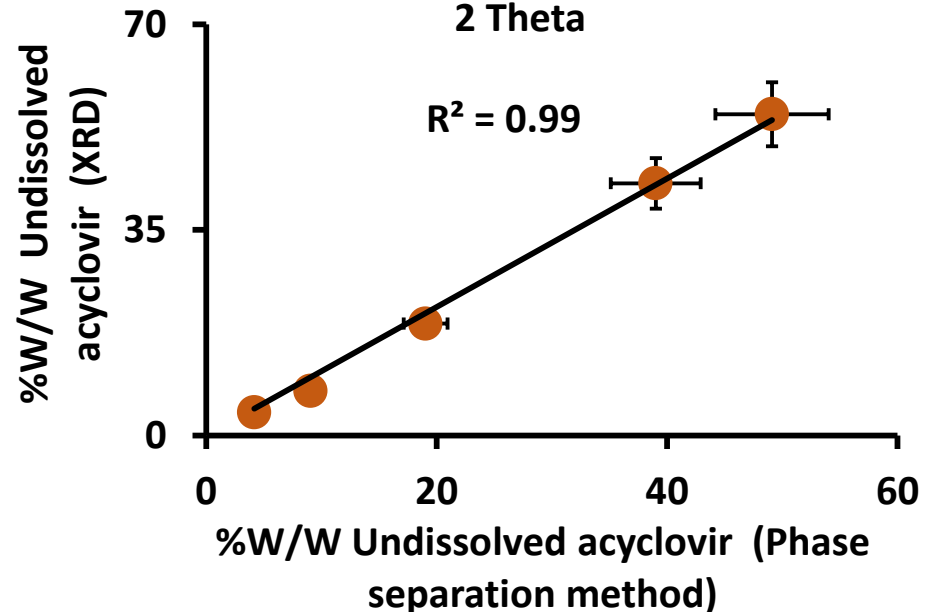
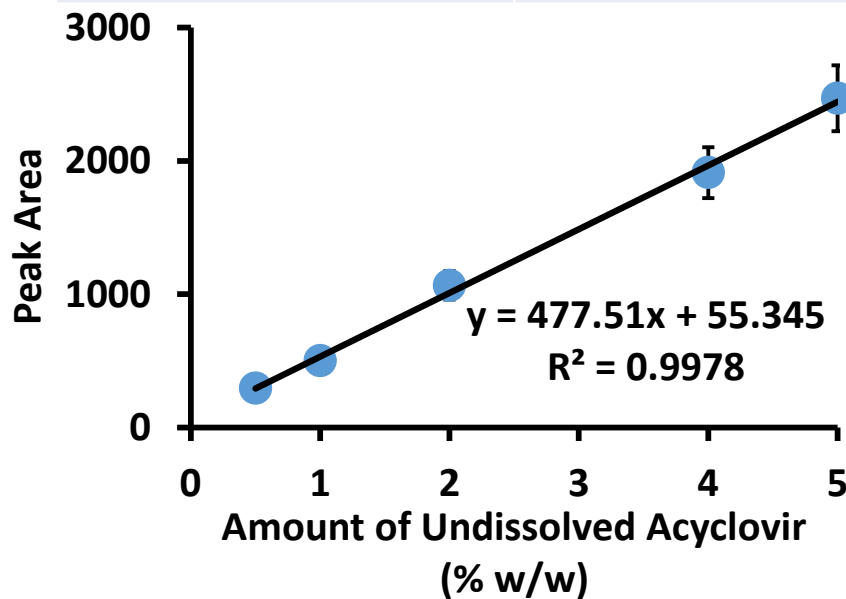
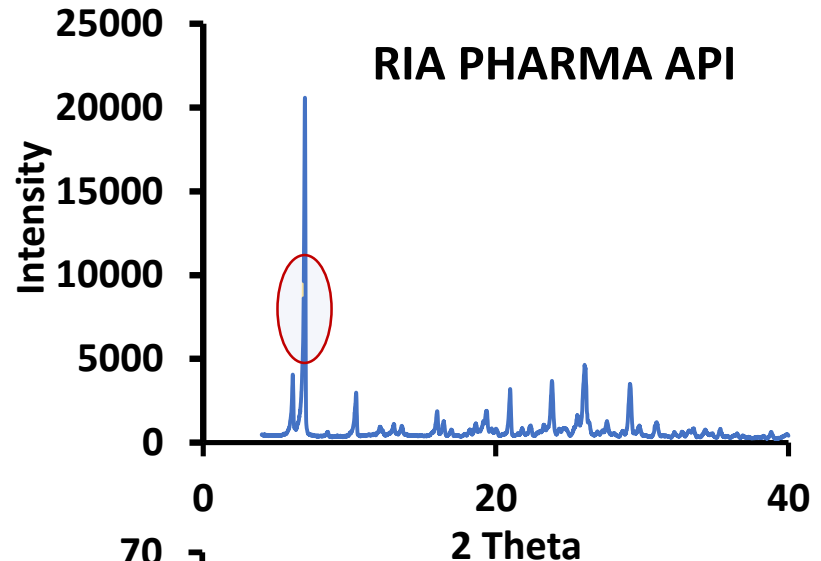
Dissolved Drug
Undissolved Drug

Phase Separation



D/UD – Quantitative XRD

Ingredient	Scale (g/100g)
Acyclovir	0.5-5%
Cetostearyl Alcohol	12
Cremophor A6	3
Cremophor A25	3
Liquid Paraffin	12
Deionized Water (q.s.)	100



Water Activity (a_w)

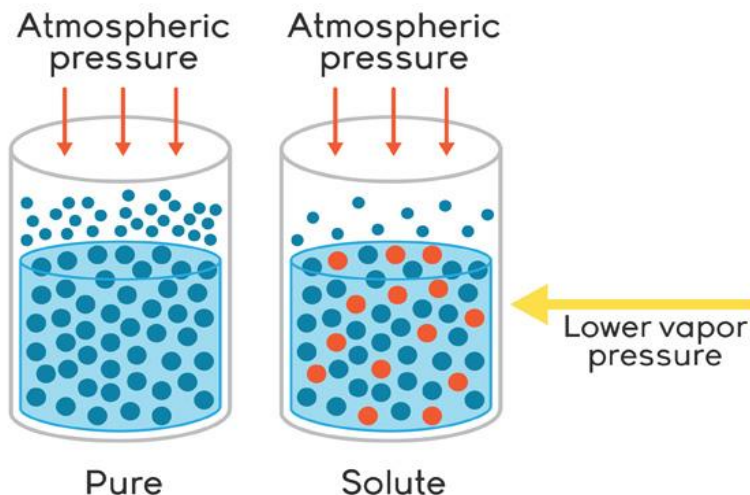
- Water activity is the measure of energy status of water in a chemical system. Pure water has water activity (a_w) = 1.

$$a_w = \rho / \rho_0$$

ρ = partial vapor pressure of water in material

ρ_0 = vapor pressure of pure water

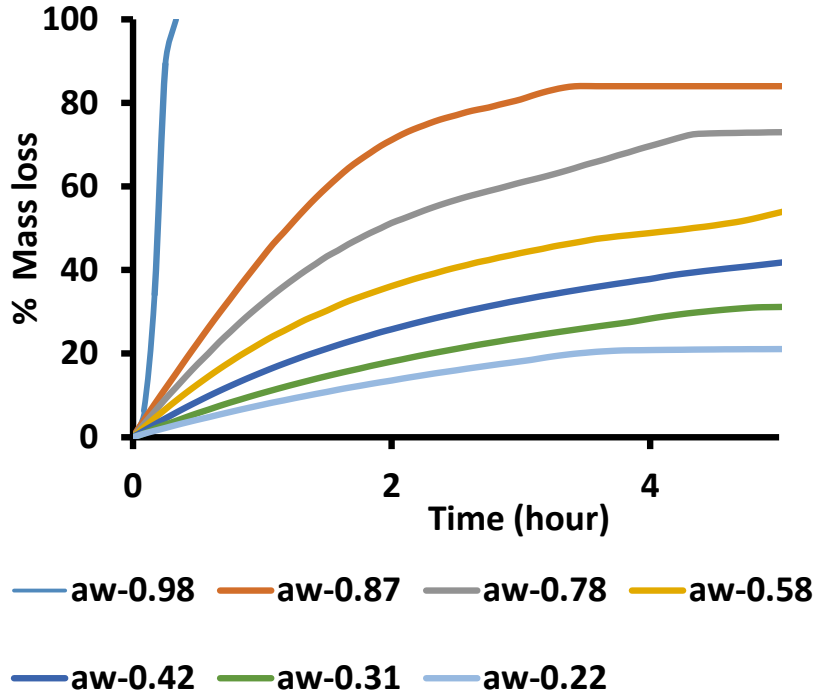
- Dissolved/suspended chemical species lower the thermodynamic activity of pure water.



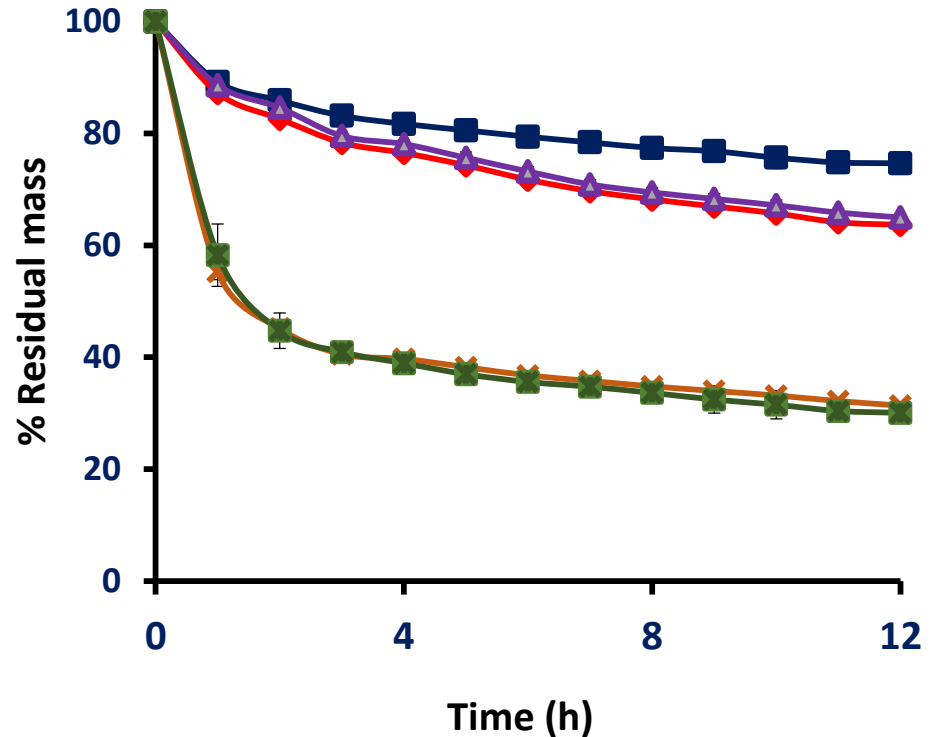
**AQUA
LAB**



Water Activity (a_w) and Drying Rate

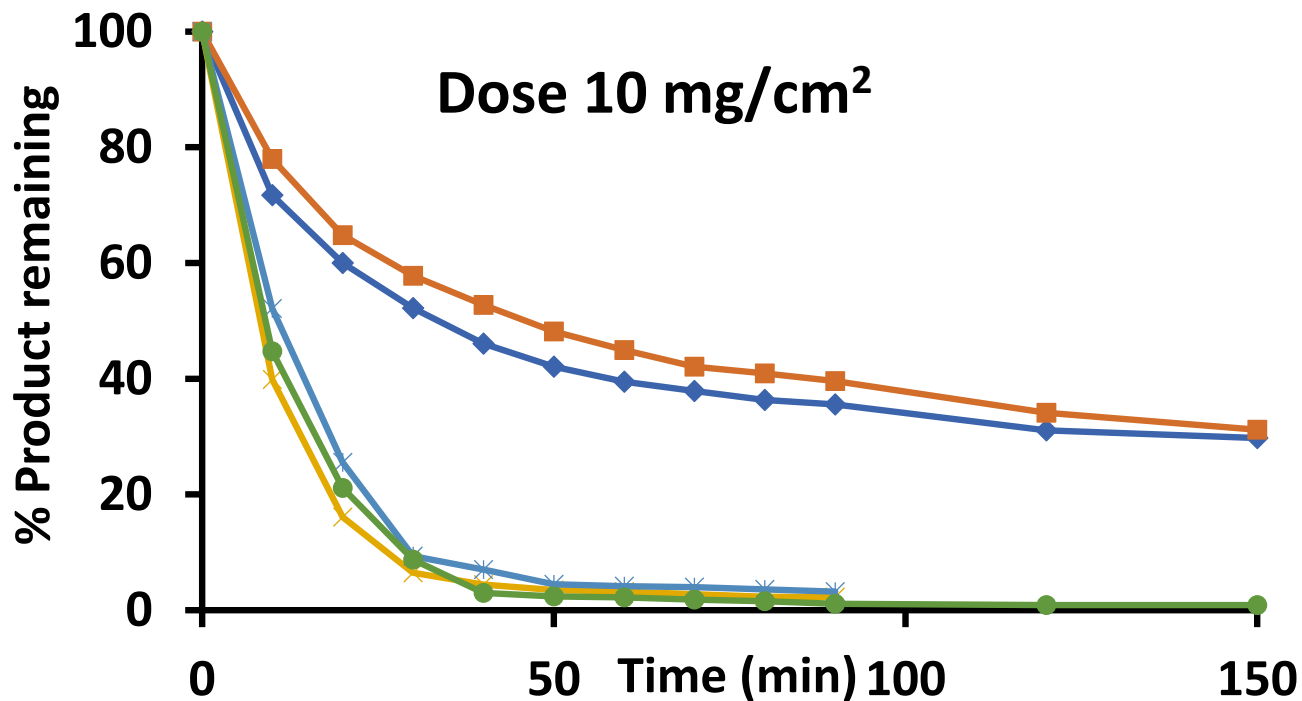


Product	Water Activity (a_w)
Zovirax (US)	0.753 ± 0.002
Zovirax (AUT)	0.735 ± 0.000
Zovirax (UK)	0.732 ± 0.002
Aciclovir-1A	0.948 ± 0.001
Aciclostad	0.948 ± 0.003



■ Zovirax (US) ◆ Zovirax (AUT) ▲ Zovirax (UK)
✕ Aciclovir-1A ■ Aciclostad

Drying Profile of Metronidazole Topical Products

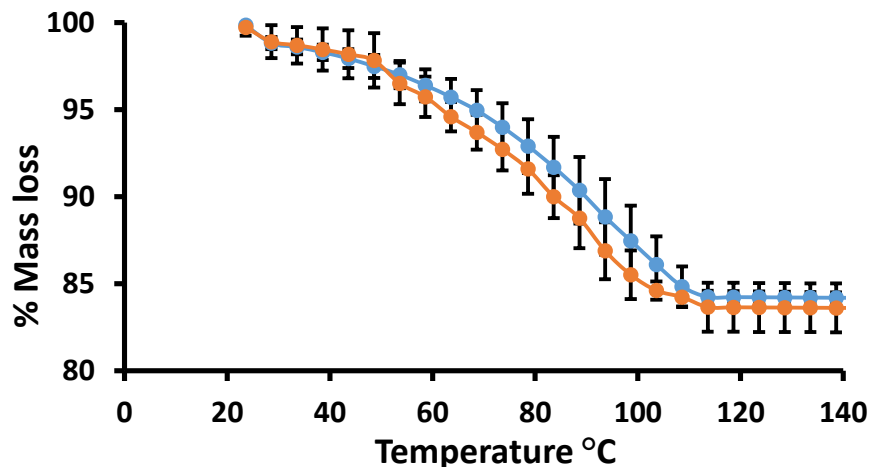


Quality Attribute	MetroCream [®] 0.75%, RLD cream (Galderma)	Metronidazole cream 0.75%, Generic cream (Fougera)	MetroGel [®] 0.75%, RLD gel (Prasco)	Metronidazole gel 0.75%, Generic gel - 1 (Tolmar)	Metronidazole gel 0.75%, Generic gel - 2 (Taro)
Water activity	0.977± 0.000	0.974± 0.002	0.992± 0.005	0.994± 0.004	1.002± 0.008
T ₃₀ % (min)	15.67± 0.76	11.40± 1.15	5.45± 0.45	4.70 ± 0.26	6.47± 0.55

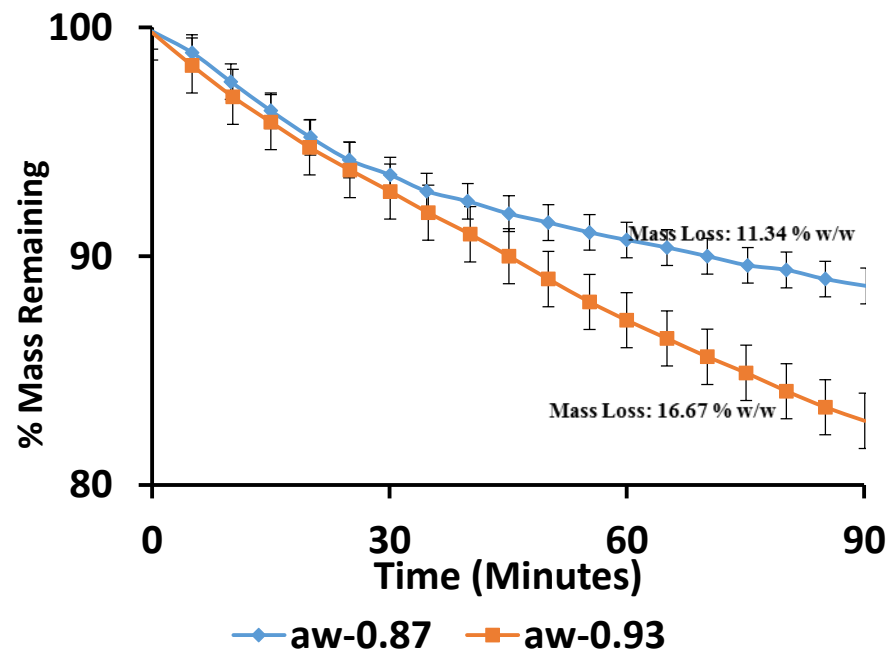
Water activity of Q1 & Q2 identical Creams

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

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



Formulation Code	Water Activity (aw)	% Mass loss at 90min
F1	0.93	16.67%
F2	0.87	11.34%



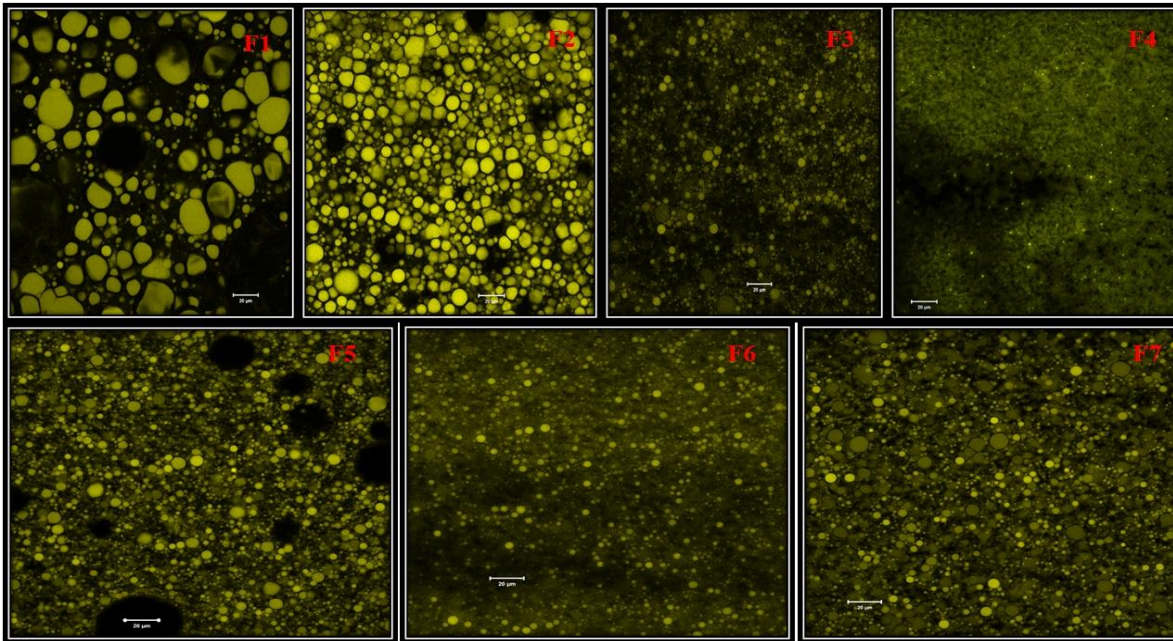
Determination of drying rate of model w/o type cream formulation using thermogravimetry at 32°C.

O/W Creams with Identical Composition and Different Globule size

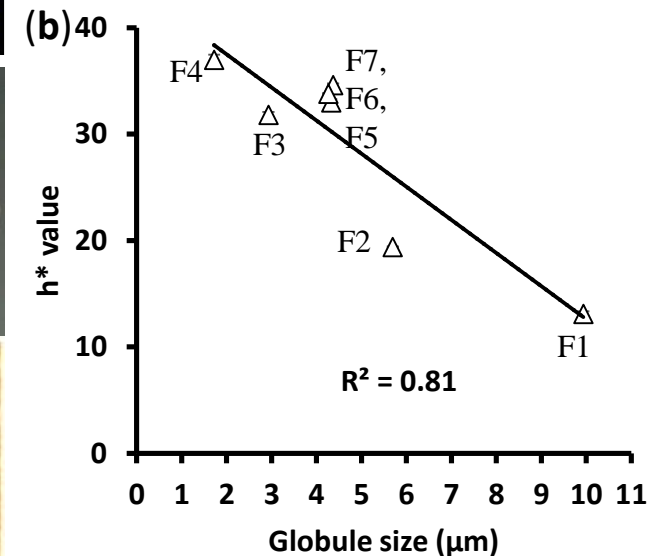
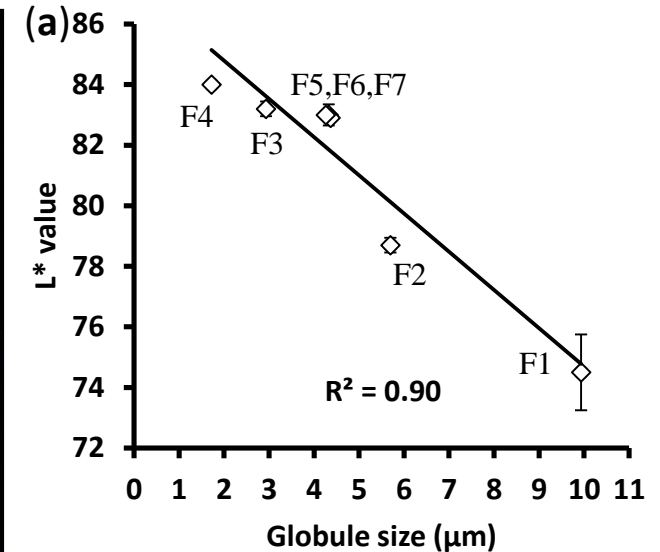
Ingredients (O/W)	Quantity (%)
Cetostearyl alcohol	7
Cremophor A6	1.5
Cremophor A25	1.5
Mineral Oil	12
Propylene Glycol	8
Water	70

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



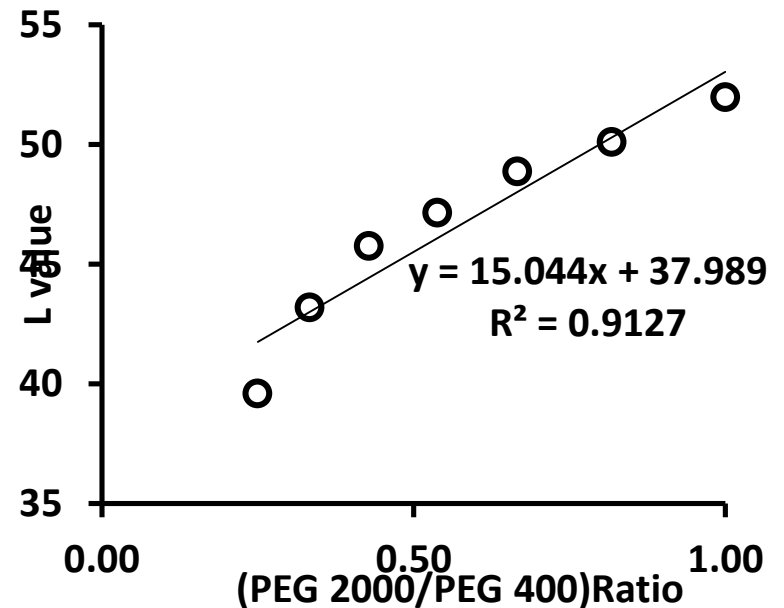
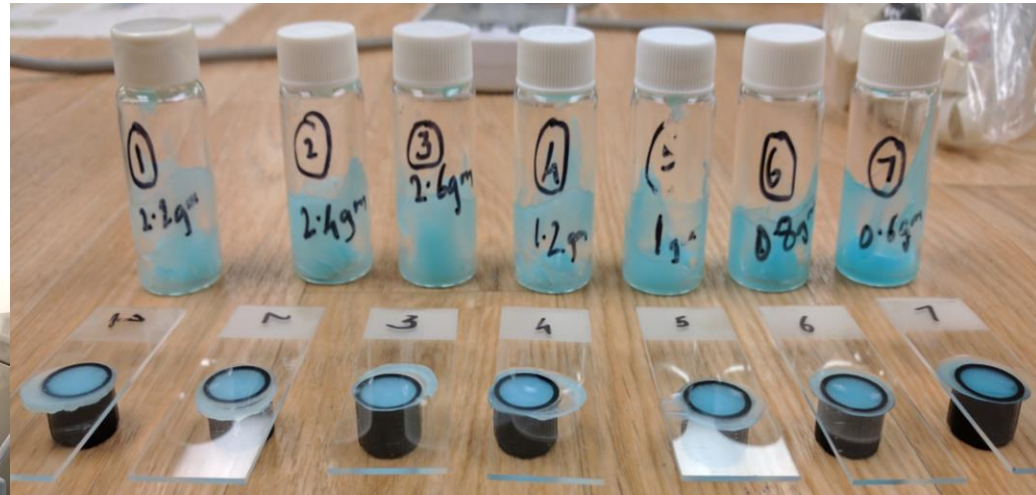
Colour Meter (PCE Instruments, PCE-CSM1)



Quantification of Color in Process optimization



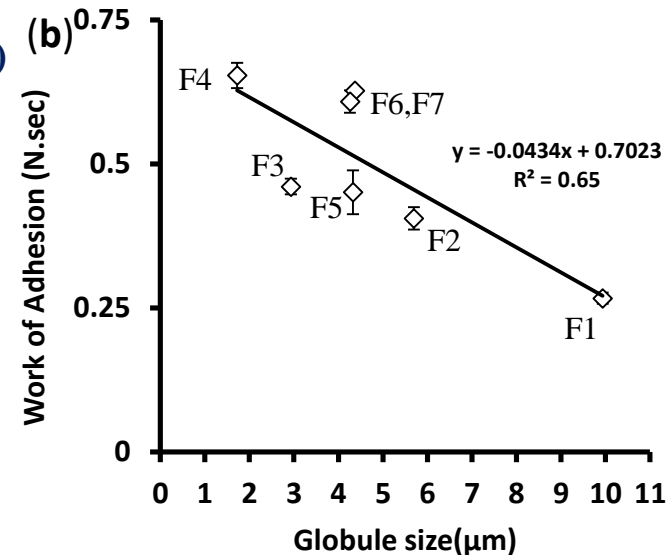
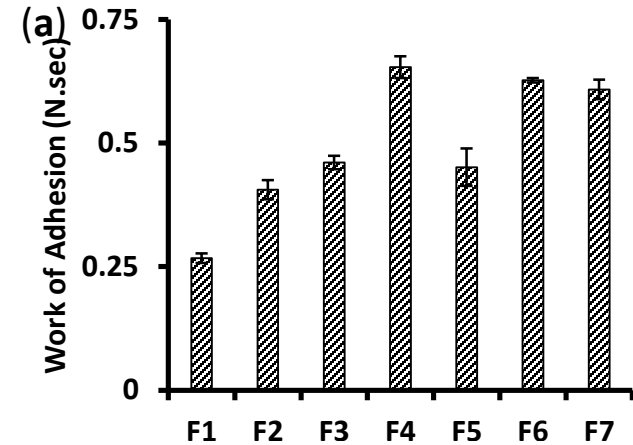
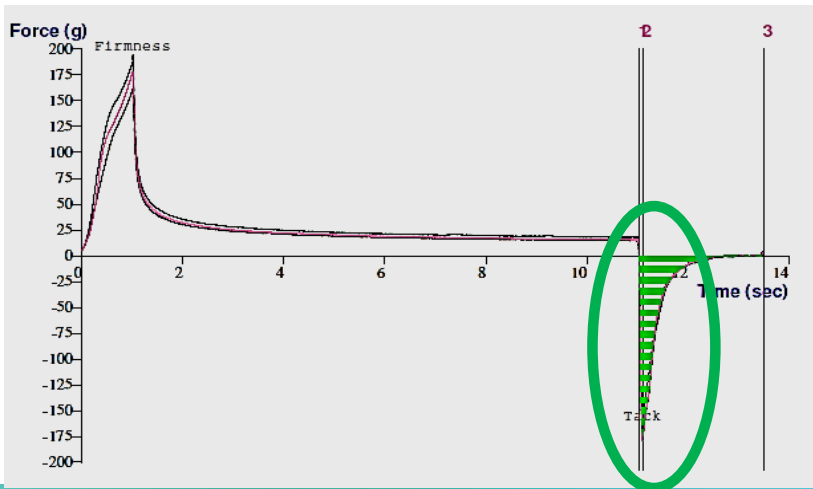
Omicron 10P, Steer America



Work of Adhesion- A sensitive Interfacial Characteristic



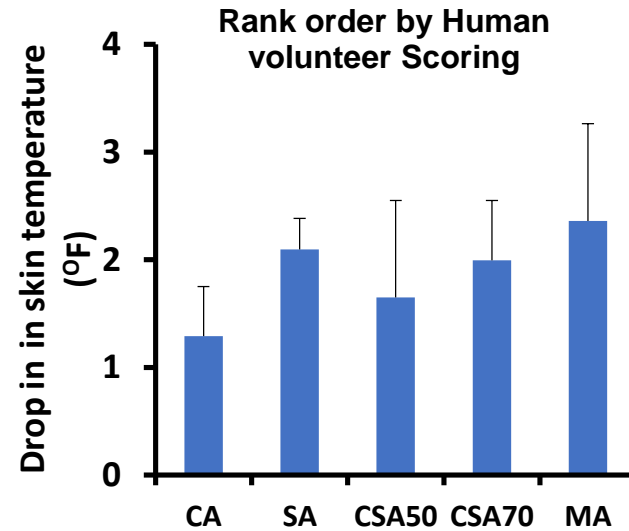
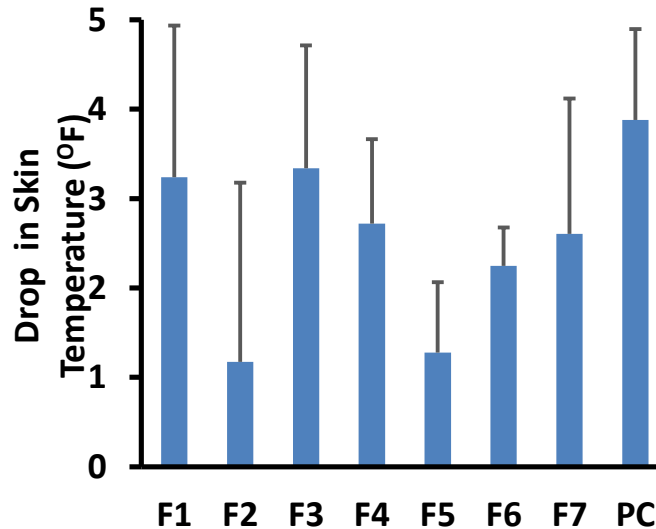
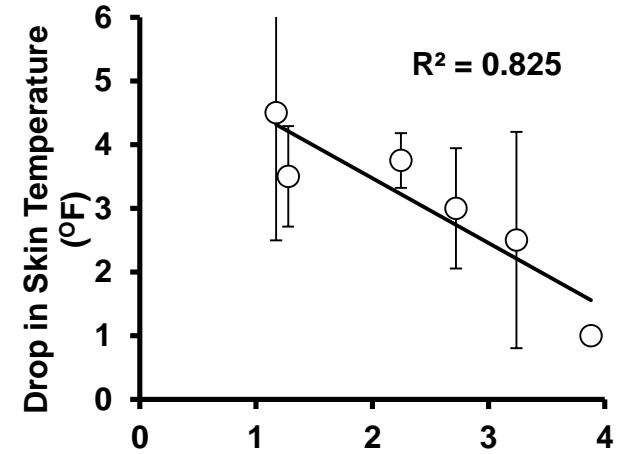
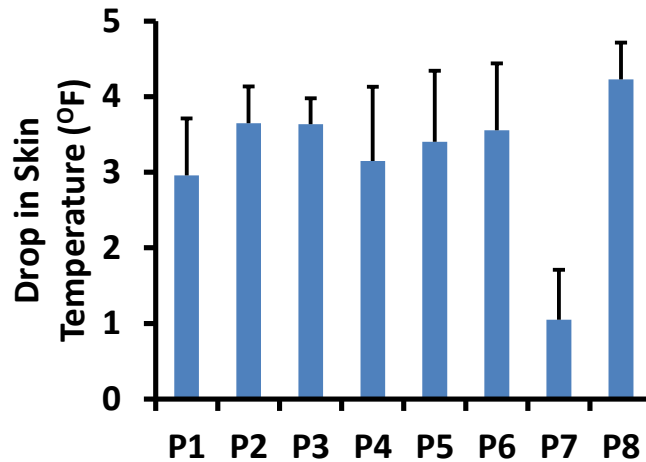
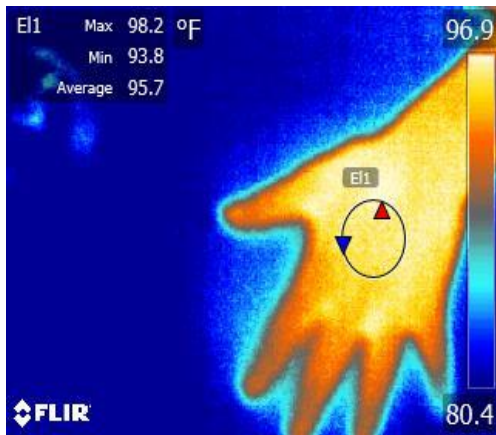
TA-XT2i Texture Analyser, Texture Technologies Corp)



IR thermal Camera for Determining the Skin Cooling Effect

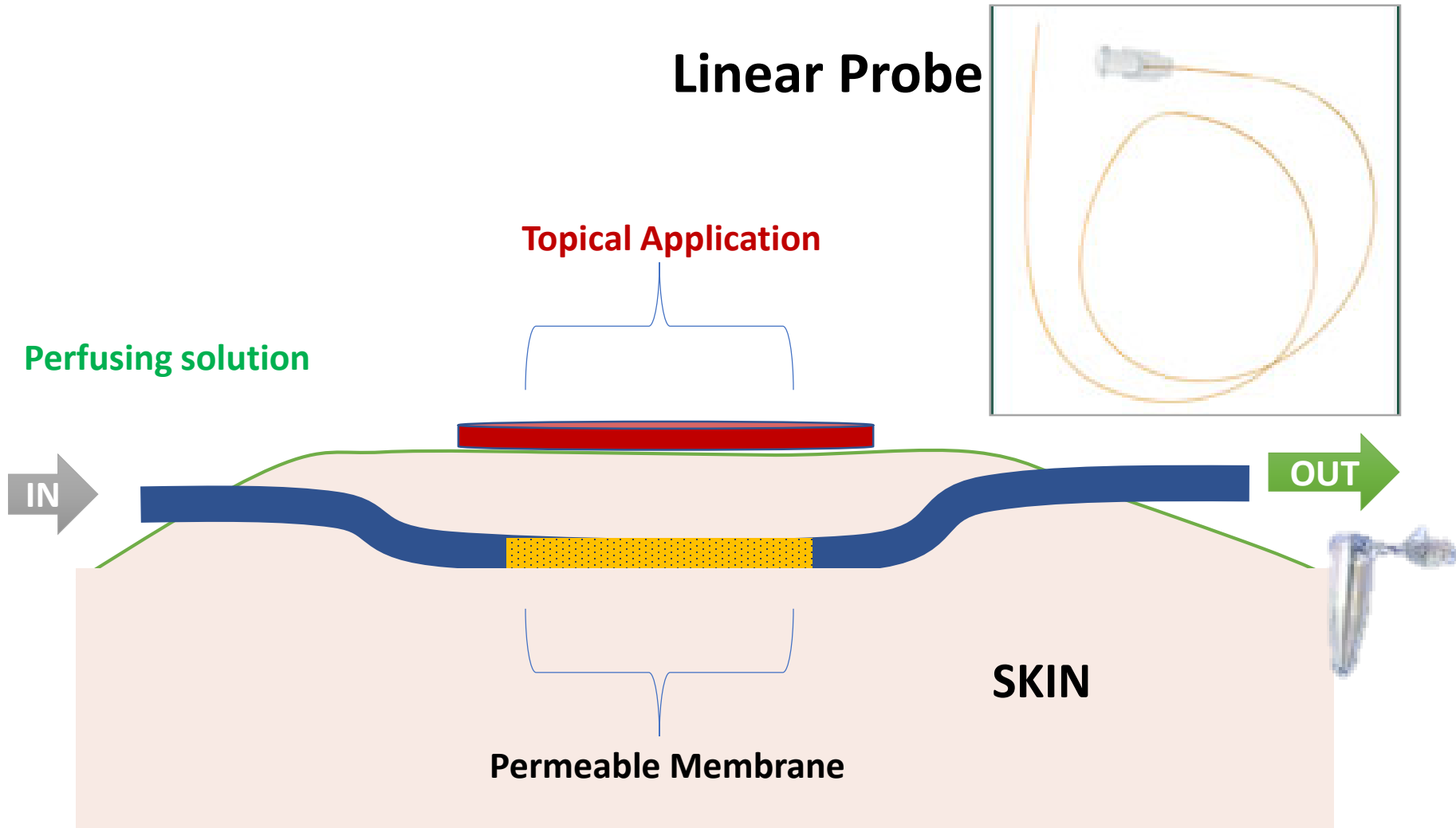


FLIR A35Sc Benchtop equipment



Cutaneous Microdialysis

Linear Probe



Microdialysis- Dermal Bioequivalence Studies

14 subjects: 7 female & 7 male

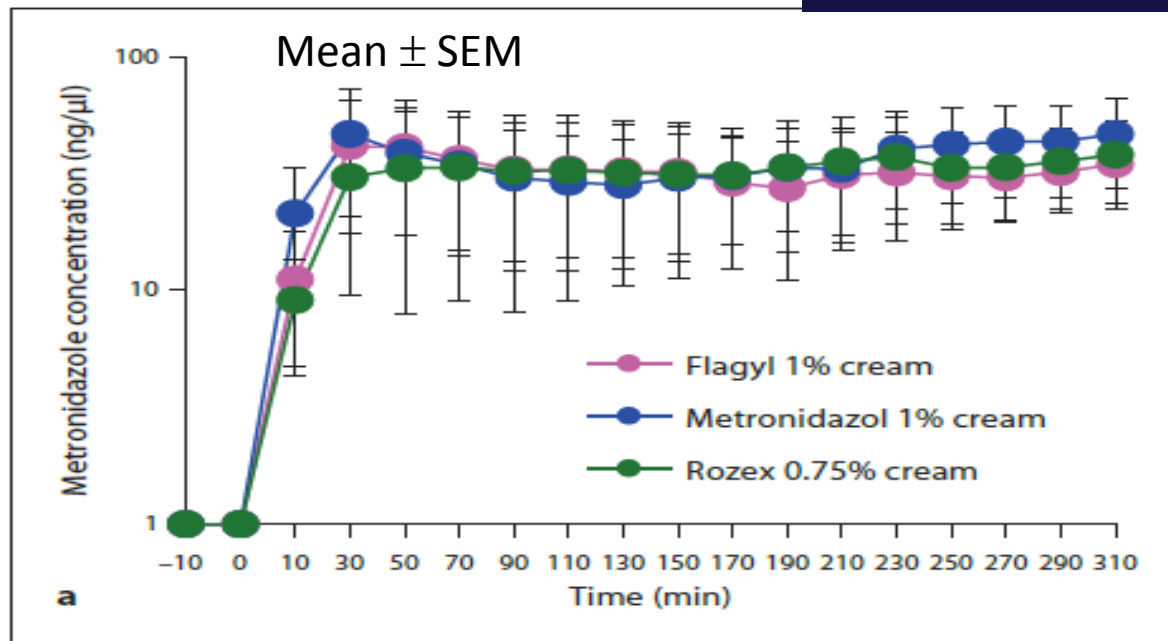
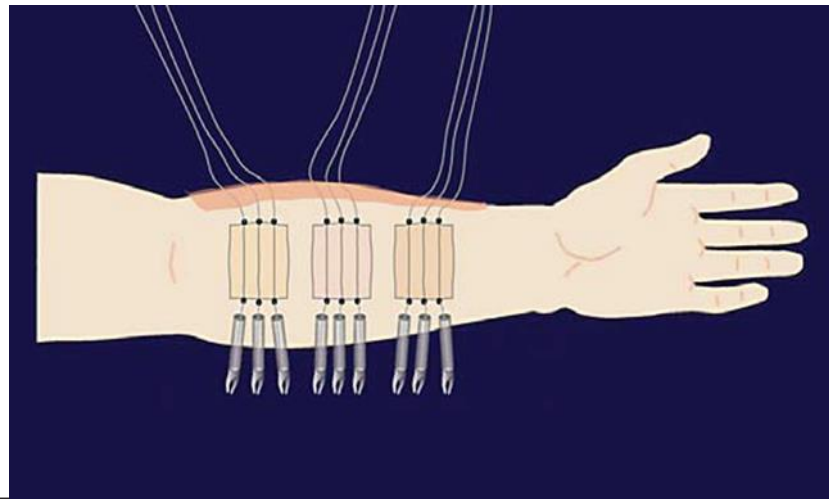
Three areas of application: one for each formulation

Three probes/area

Results

No effect of location on the arm

No difference between formulations

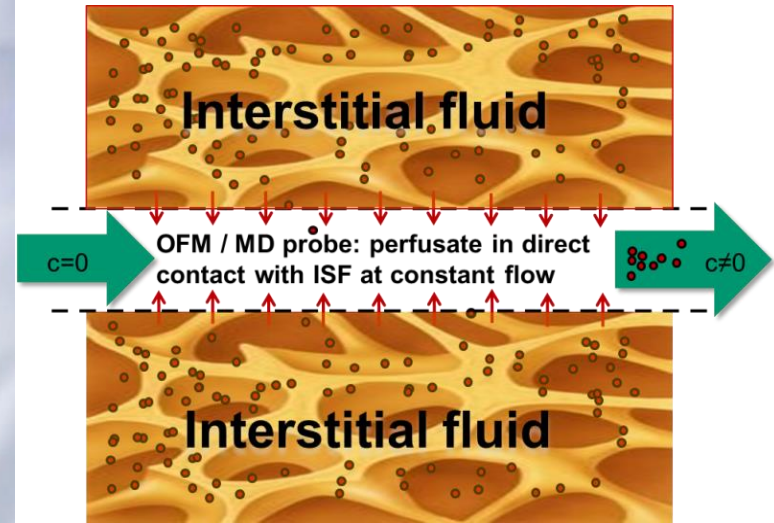


P. Garcia Ortiz et Al. 2011 "Are Marketed Topical Metronidazole Creams Bioequivalent? Evaluation by in vivo Microdialysis Sampling and Tape Stripping Methodology"; *Skin Pharmacol Physiol*, 24(1):44-53.

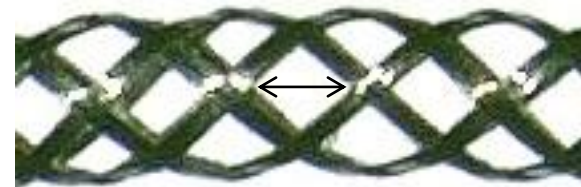
With permission from Prof. Stagni,
Long Island University

Open Flow Micro-perfusion Technique

Continuous dermal sampling
working principle



300 μ m



CE-certified for clinical use

With permission from Frank Sinner, JOANNEUM RESEARCH

Other Tools Under Development

- **Electro-microdialysis**: Enhanced recovery of ionic drugs.
- **EpSc™ Recovery Strips** for recovery of drug from stratum corneum and epidermis.
- **Impedance Spectroscopy** for characterization of o/w creams.
- **Electrochemical Method** of Determination of Buffer Capacity

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Thank you

