AAPS Workshop on

Locally Acting Drug Products: Bioequivalence Challenges and Opportunities

November 12–13, 2016

Colorado Convention Center, Denver

Beyond Q1/Q2—Comparing the Arrangement of Matter (Q3) and Performance

S. Narasimha Murthy Ph.D

Professor-Pharmaceutics and Drug Delivery

University of Mississippi, University, MS

Q1, Q2 and Q3

- Q1: Qualitative Similarity

  Same components are used in the formulations

- Q2: Quantitative Similarity

  Same quantities of the same components

- Q3: Structural Similarity

  Q1 and Q2 + Identical arrangement of matter

- **Q1/Q2 identical does not essentially mean Q3 similarity.**
- **Q3 differences could impact the performance of the products.**

Example: O/W Cream

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

Formulation Code	Variable
F1	500 rpm -20 min
F2	1000 rpm - 20 min
F3	3000 rpm - 20 min
F4	5000 rpm -20 min
F5	3000 rpm - 10 min
F6	3000 rpm - 40 min
F7	3000 rpm - 20 min Gradual cooling

pH Measurement

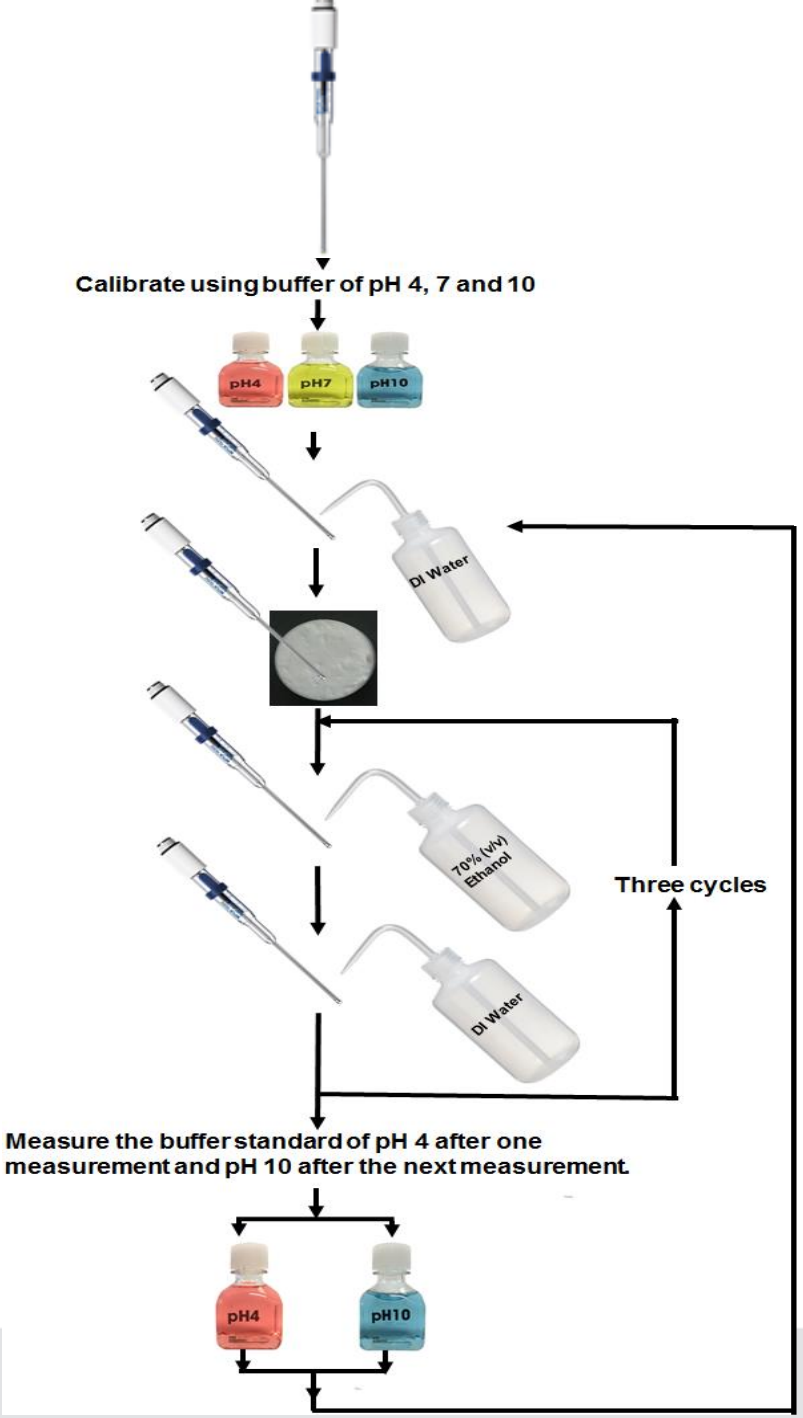
InLab Science

InLab Viscous

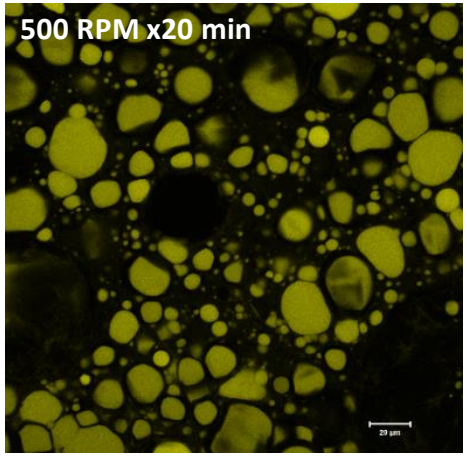
InLab Micro

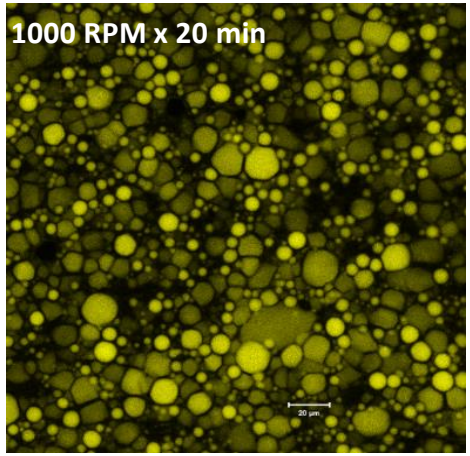
Suggestions

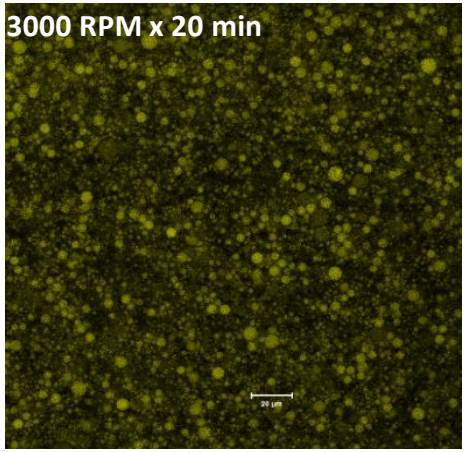
- *Standard buffers of pH 4 and 10 shall be alternated between each measurement.*
- *If it is a cream (o/w) use an electrode with smallest surface area for reproducible readings.*
- *Check the pH of aqueous Phase separated from the Cream.*

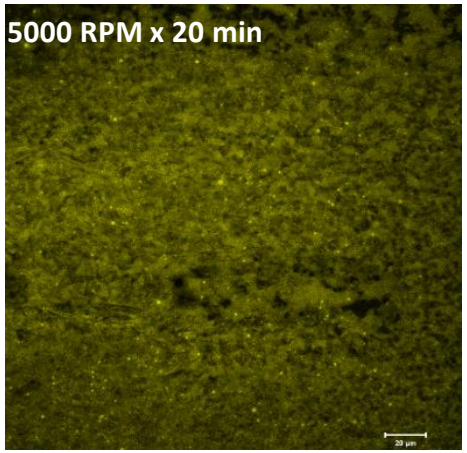


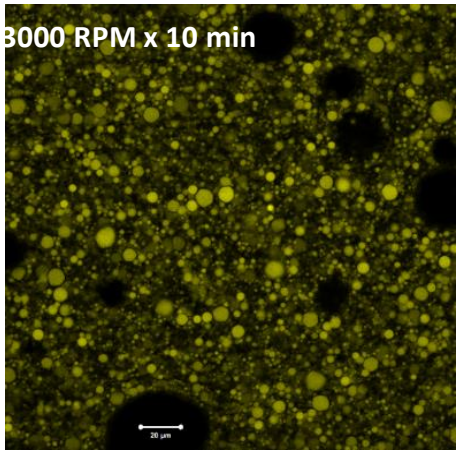
Globule Size

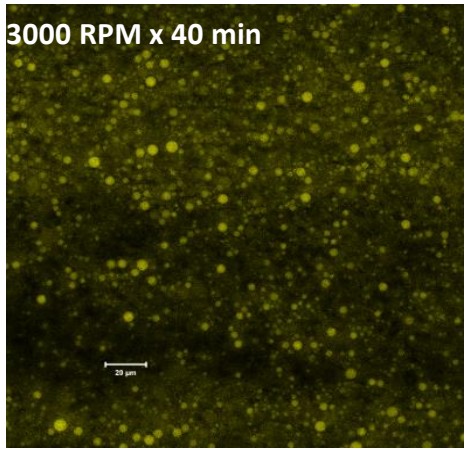


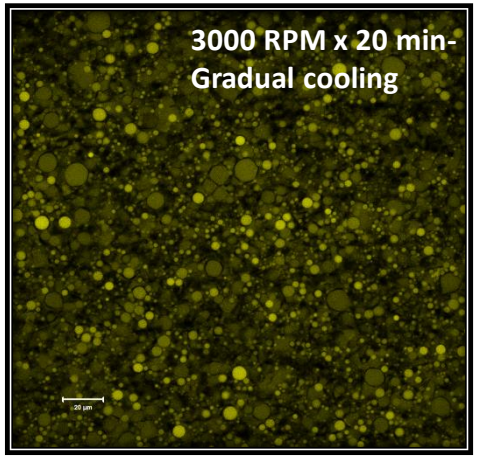






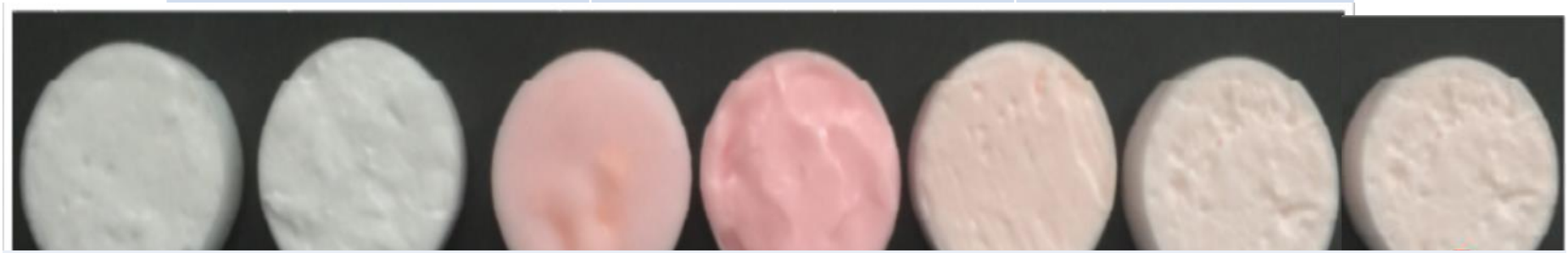






Globule Size

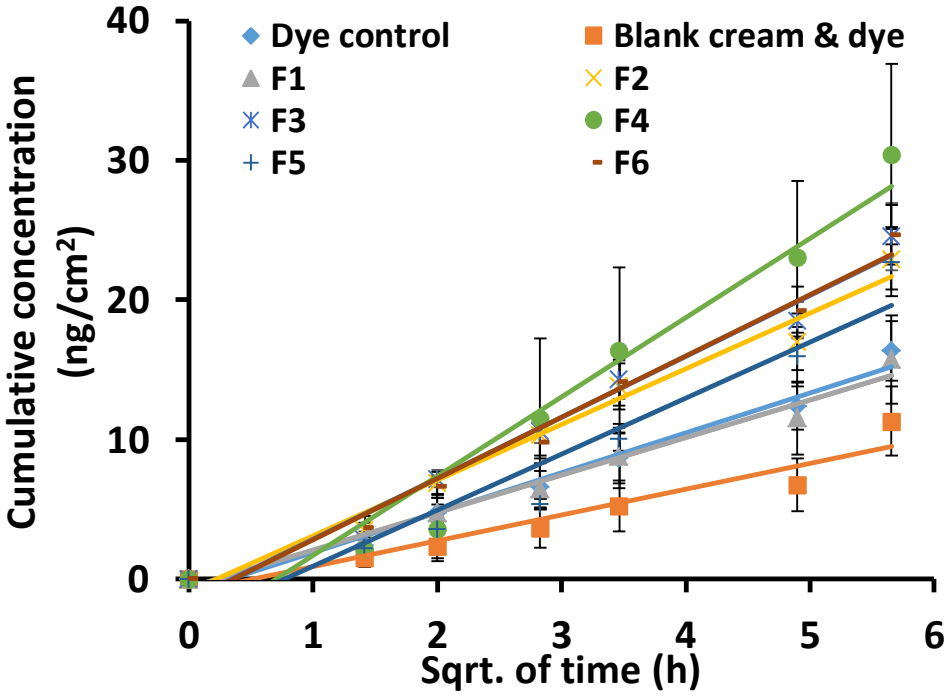
Formulation Code	Variable	Globule Size (um)
F1	500 rpm -20 min	11.37 ±7.03
F2	1000 rpm - 20 min	7.41 ±2.19
F3	3000 rpm - 20 min	2.98 ±1.25
F4	5000 rpm -20 min	1.71±0.41
F5	3000 rpm - 10 min	4.30±1.33
F6	3000 rpm - 40 min	4.36±0.88
F7	3000 rpm - 20 min Gradual cooling	4.25±0.99



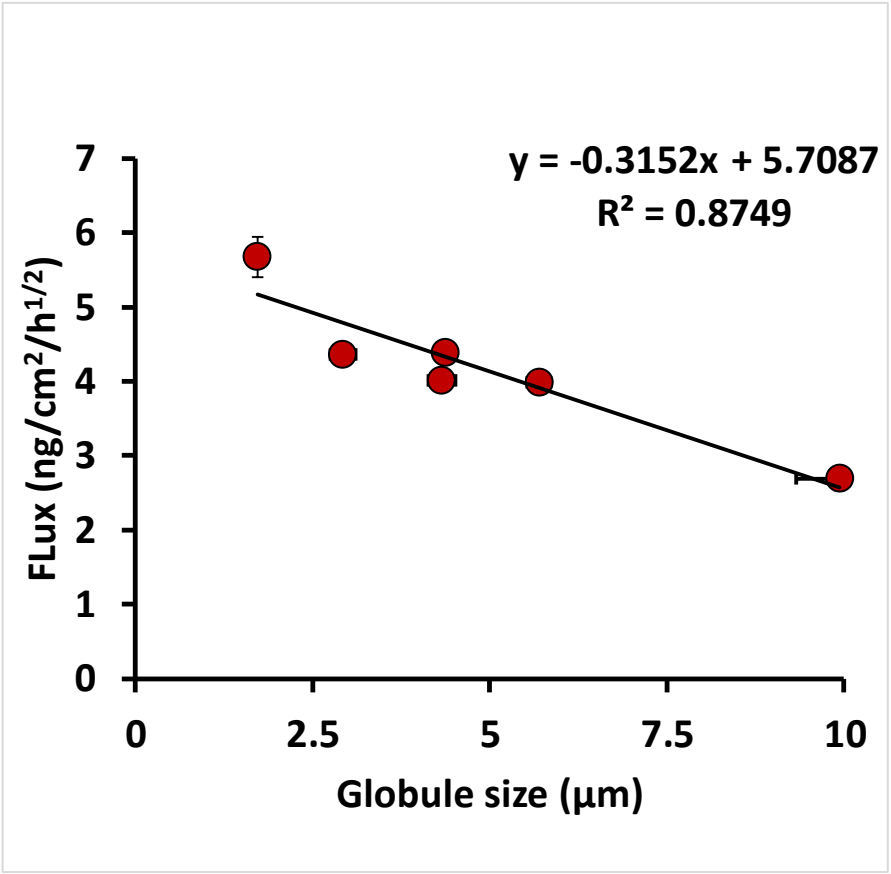
F1 F2 F3 F4 F5 F6 F7

In Vitro Permeation Testing (IVPT)

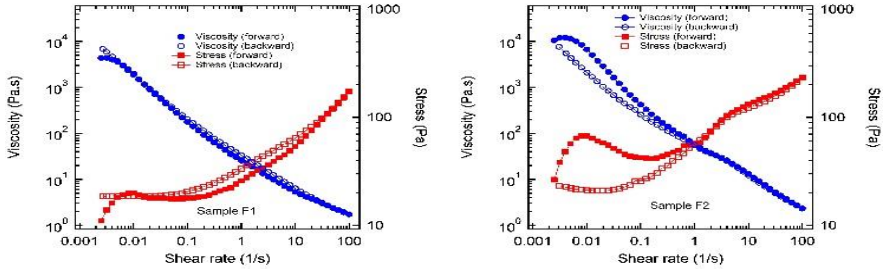
Cumulative permeation of NR across the porcine epidermis

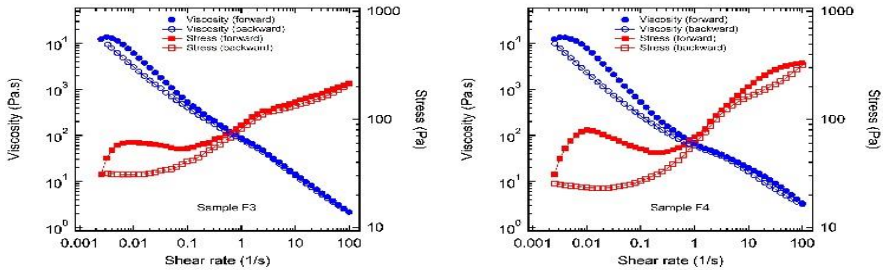


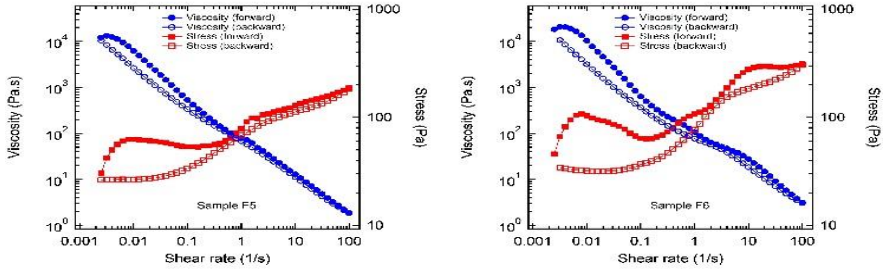
Permeation flux Vs Globule size of dispersed phase

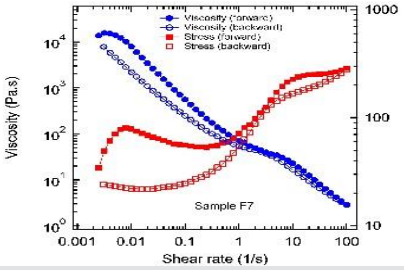


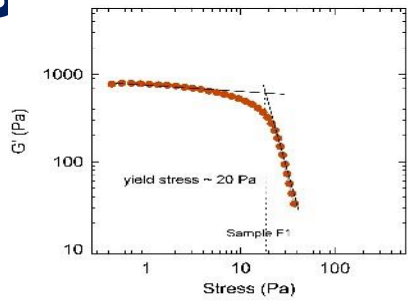
Rheological studies

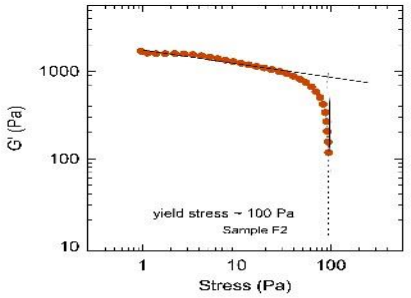


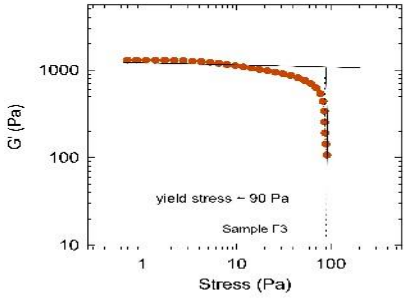


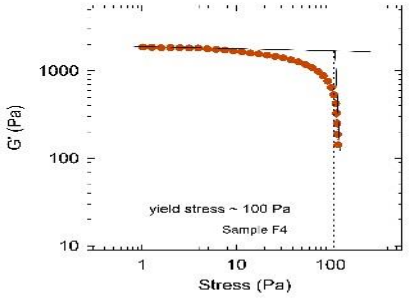


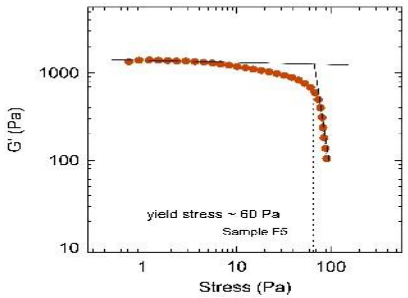


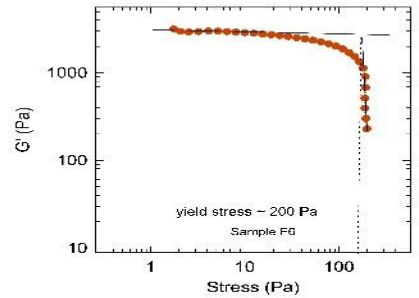


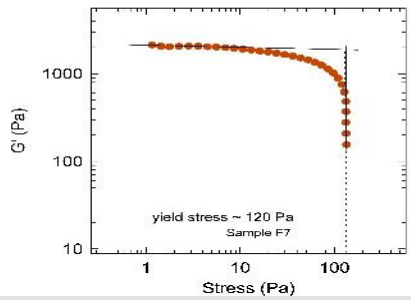












Shear Rate Estimation

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 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}

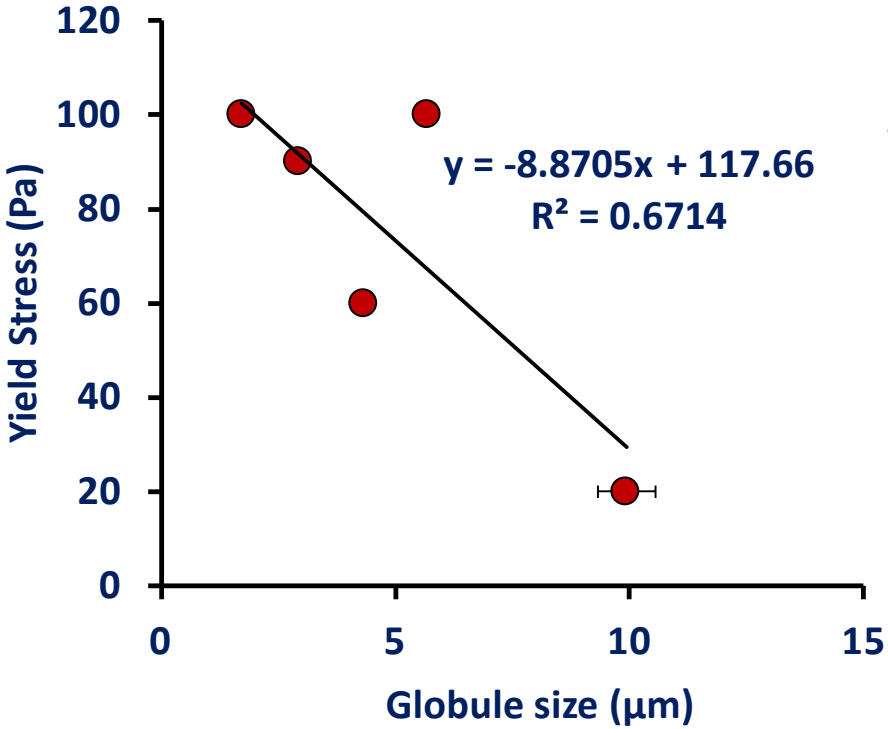
Product	Viscosity, Pa. s @ shear rate		Yield Stress, Pa
	20 s^{-1}	0.0025 s^{-1}	
F1	3.8	4388	20
F2	7.6	10589	100
F3	8.2	12338	90
F4	12.8	12337	100
F5	7.2	12161	60
F6	14.8	18318	200
F7	12.5	13711	120

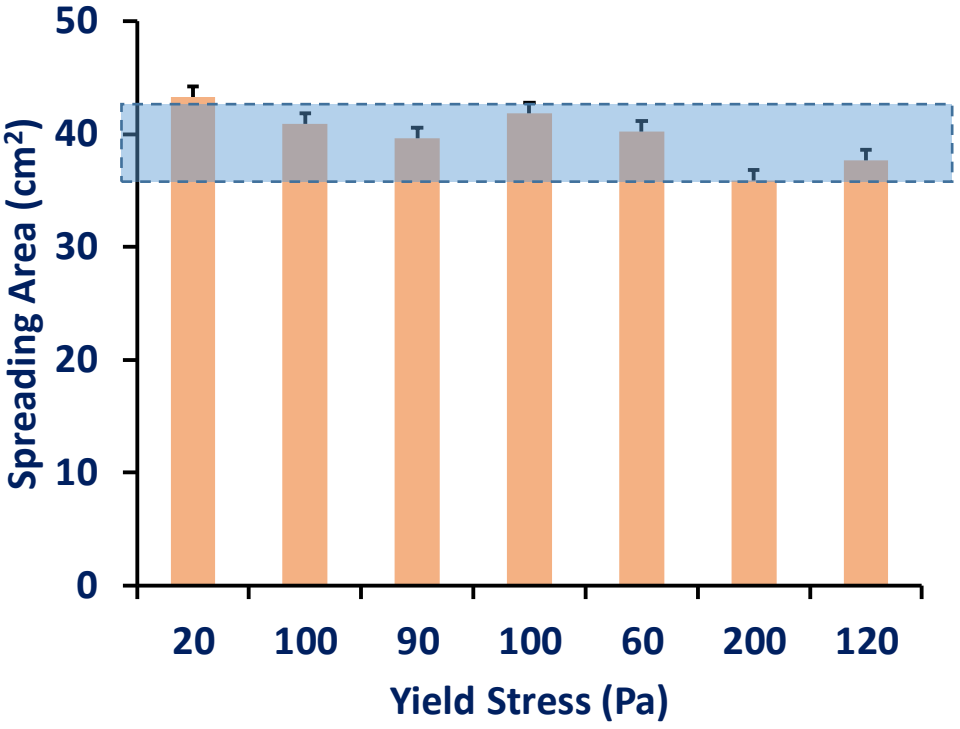
Dictates the behavior during the initial application

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

Influence of Rheology on the Spreading of Q1/Q2 Identical Creams

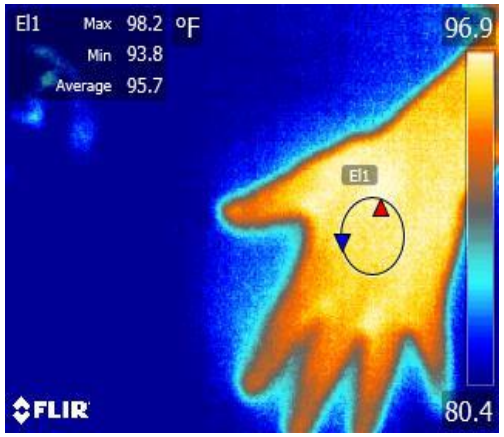
- Rheology of the sample would influence the area of application which in turn could affect the permeation profile.

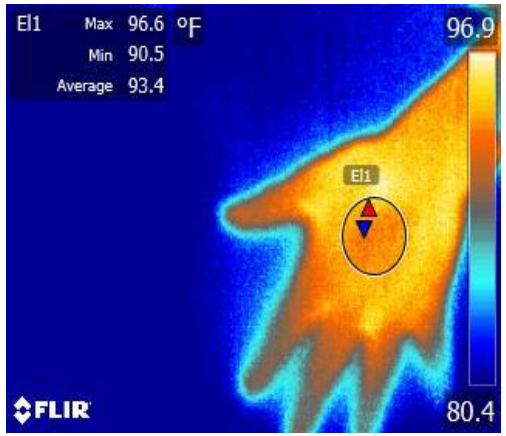




Area of formulation application by three individuals on six volunteers. (Each data point is a Mean n=3 (each expert applied on six different individuals) ± SEM)

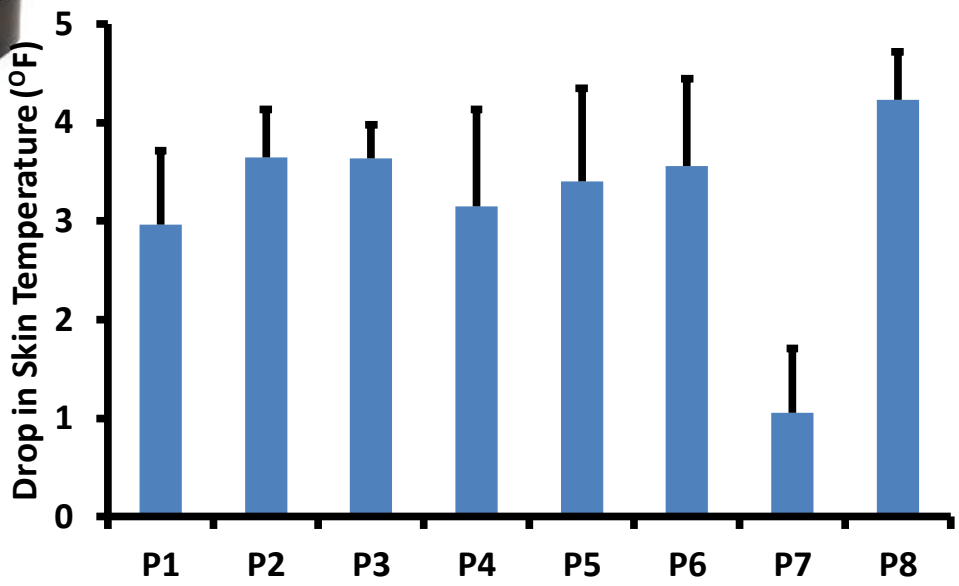
IR thermal Camera for Determining the Skin Cooling Effect



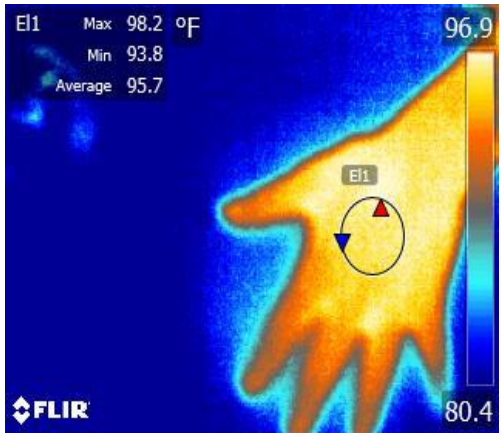


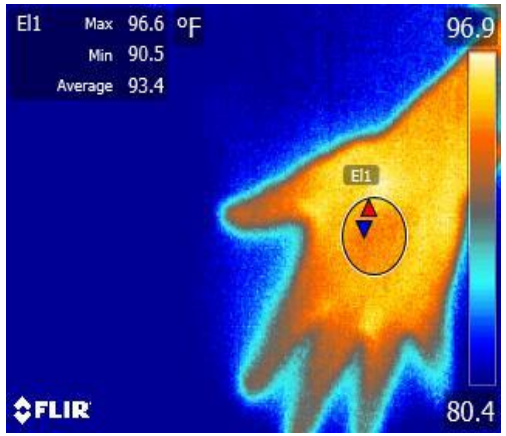
FLIR A35Sc Benchtop equipment

Evaluation of some commercially available cosmetic skin products



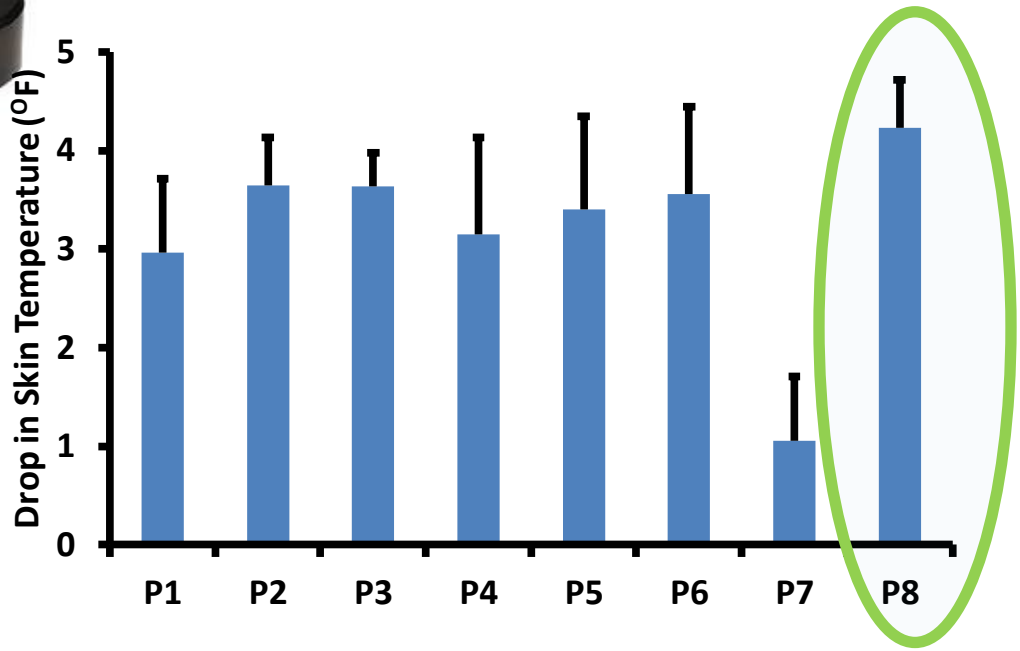
IR thermal Camera for Determining the Skin Cooling Effect



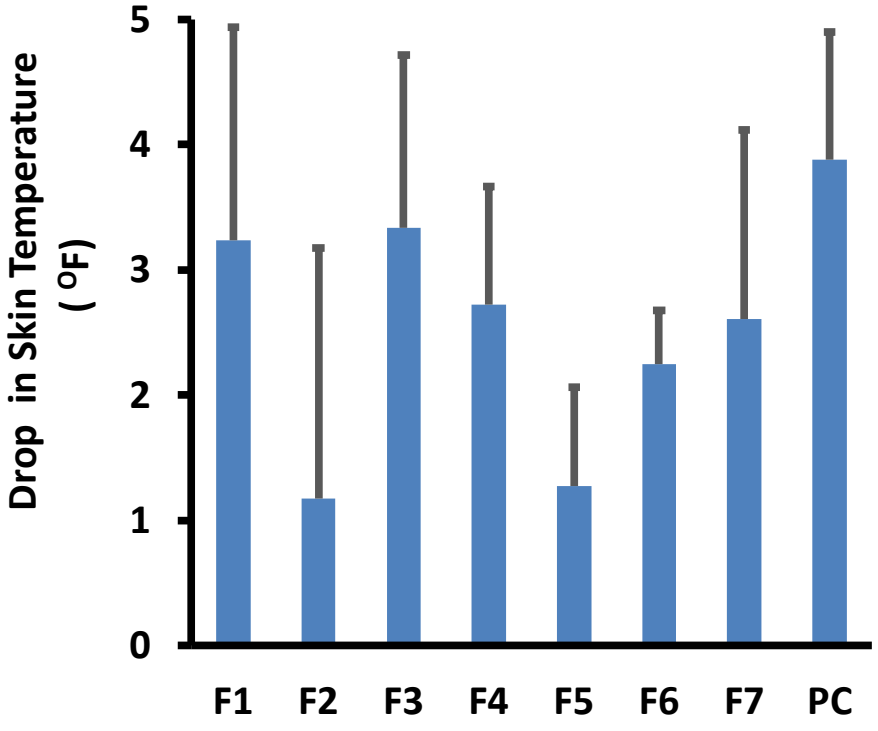


FLIR A35Sc Benchtop equipment

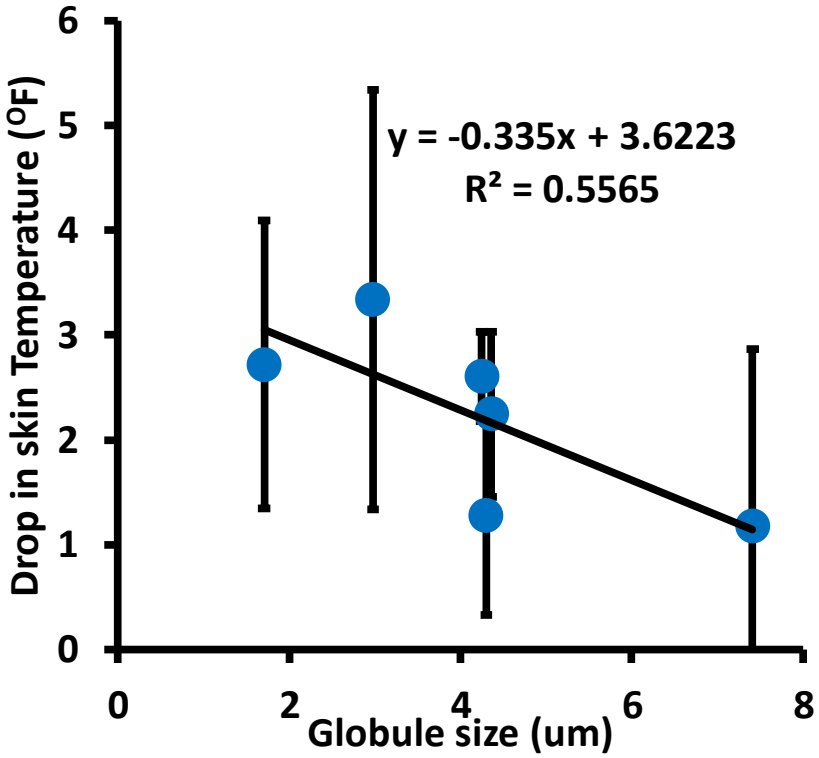
Evaluation of some commercially available cosmetic skin products



Influence of Microstructure of the Creams on Skin Cooling

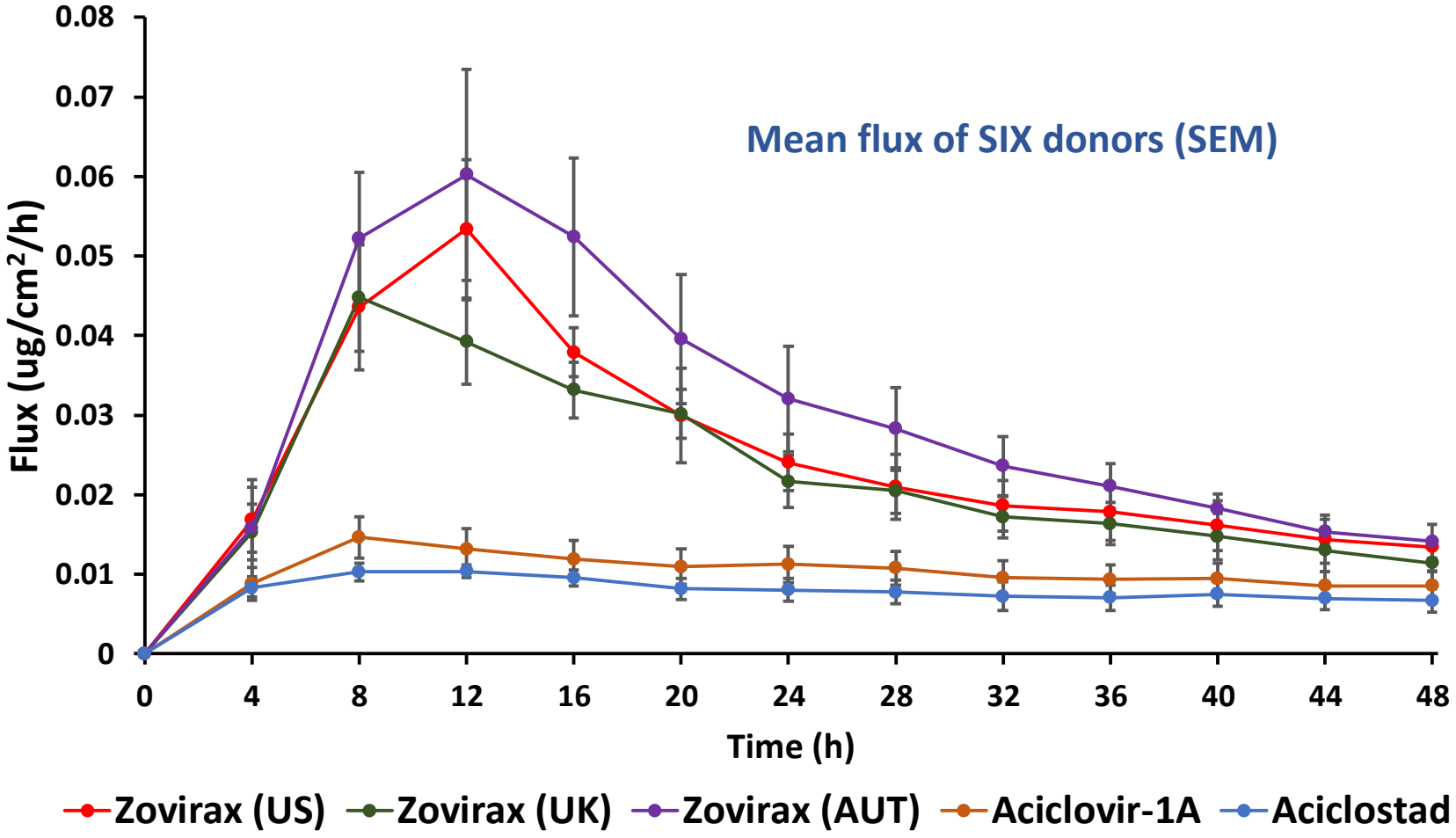


Skin cooling effect of custom made creams.

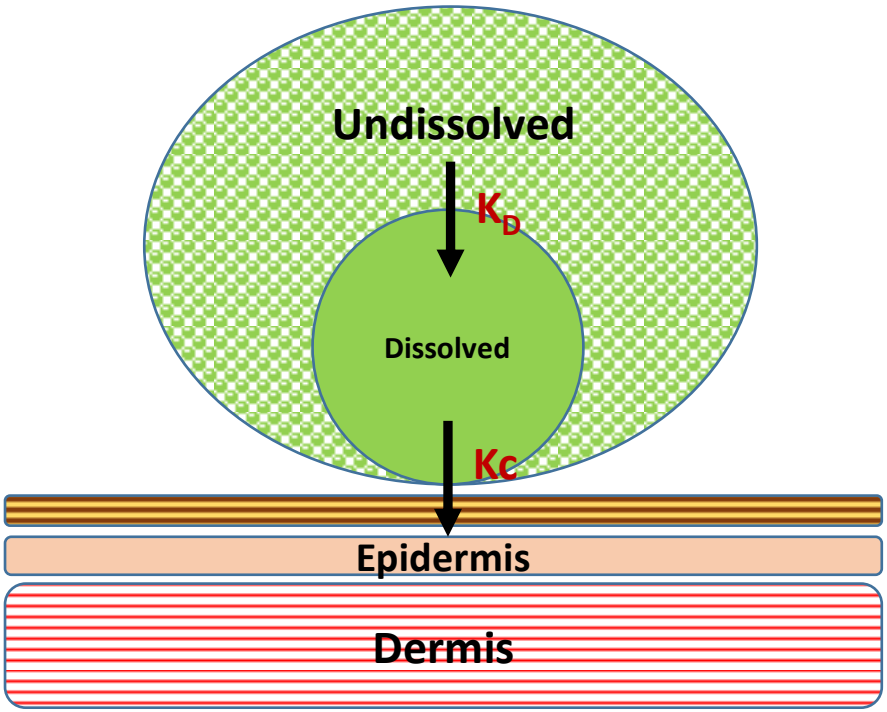


Influence of globule size on Skin cooling efficiency

In Vitro Permeation Testing of Acyclovir Creams



Drug Absorption from Topical Product



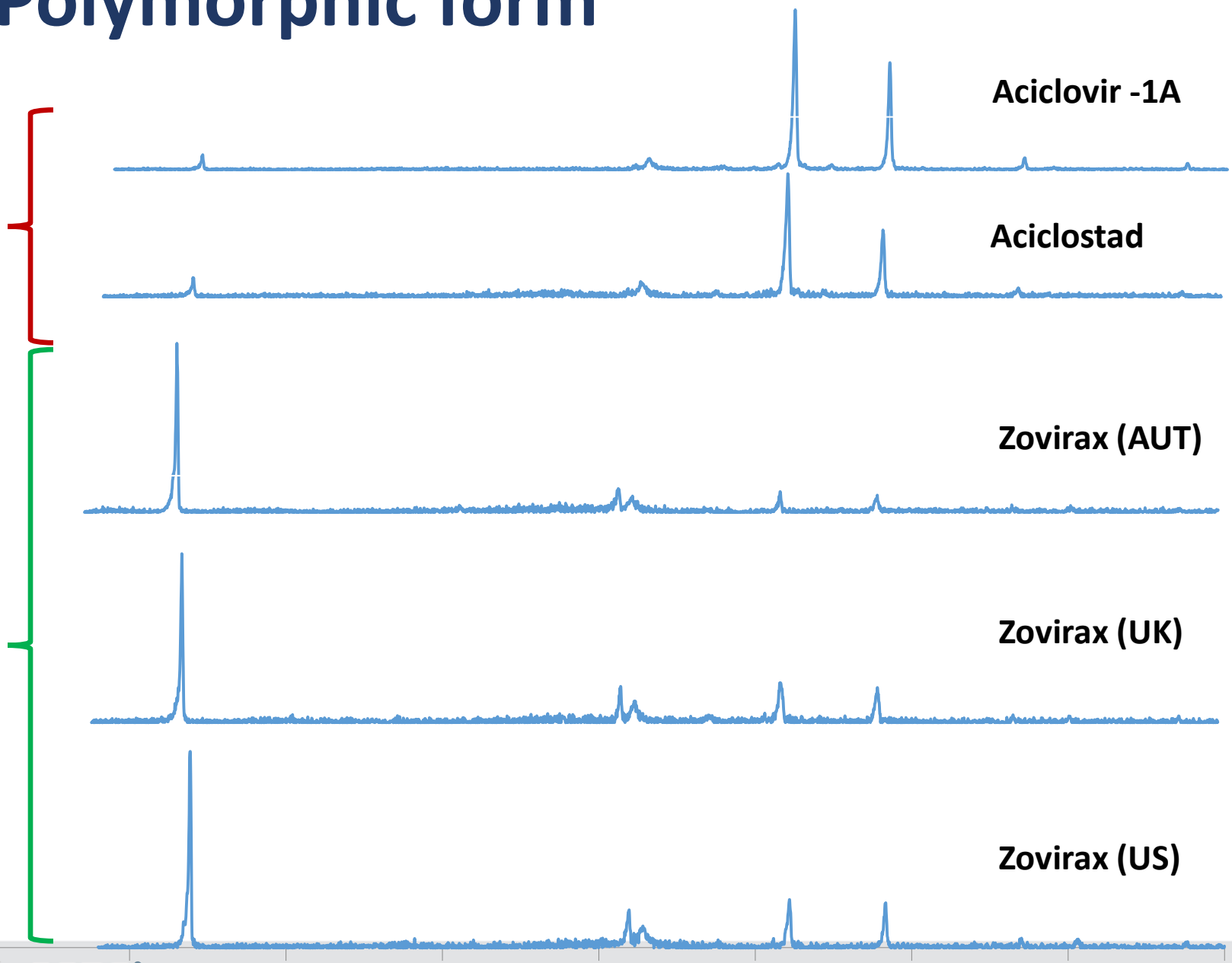
$$K_D \geq K_c$$

Rate of Dissolution of Drug

- Particle Size
- Polymorphic form
- Morphology of particles

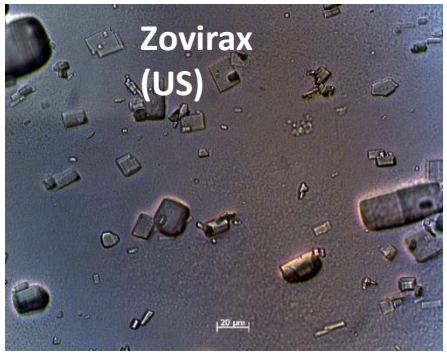
Dose	Total Drug	Dissolved Drug	Undissolved drug
5mg/cm^2	250 ug/cm^2	6.25ug/cm^2	243.75ug/cm^2

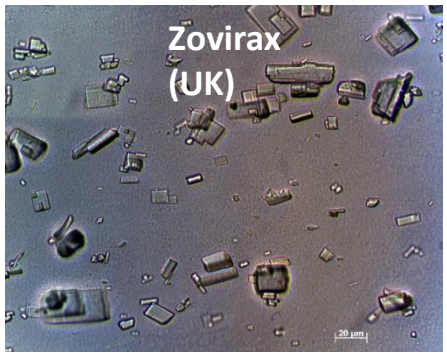
Polymorphic form

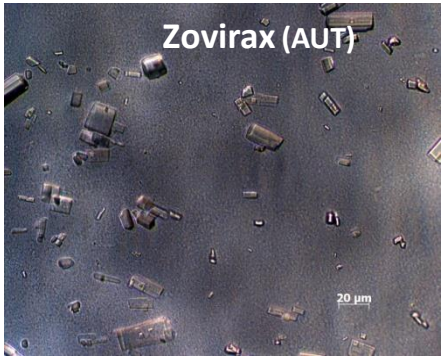


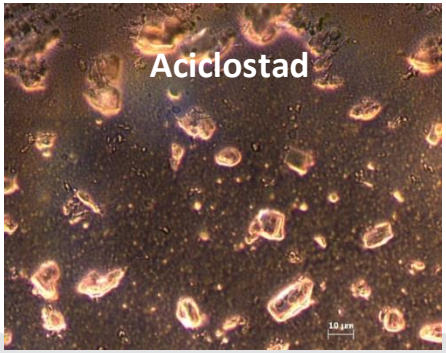
Particle Size and Morphology

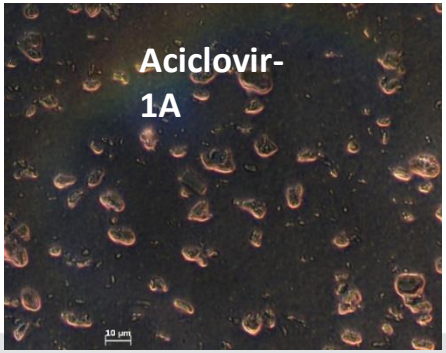
Product	d_{10}	d_{50}	d_{90}
Zovirax (US)	2.07	3.77	19.05
Zovirax (AUT)	1.76	3.43	20.76
Zovirax (UK)	1.36	2.50	24.18
Aciclovir -1A	4.0	5.95	10.94
Aciclostad	3.67	6.75	11.40











Water Activity (a_w)

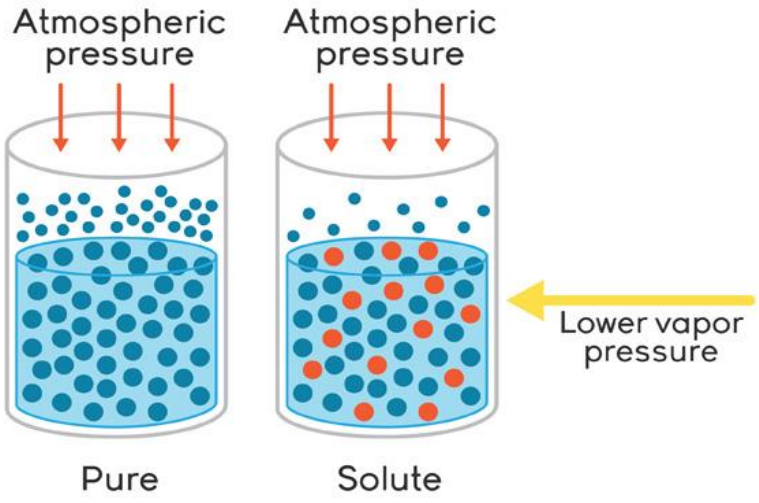
- Water activity is the measure of energy status of water in a chemical system. Pure water has water activity (a_w) = 1.

$$a_w = \rho / \rho_0$$

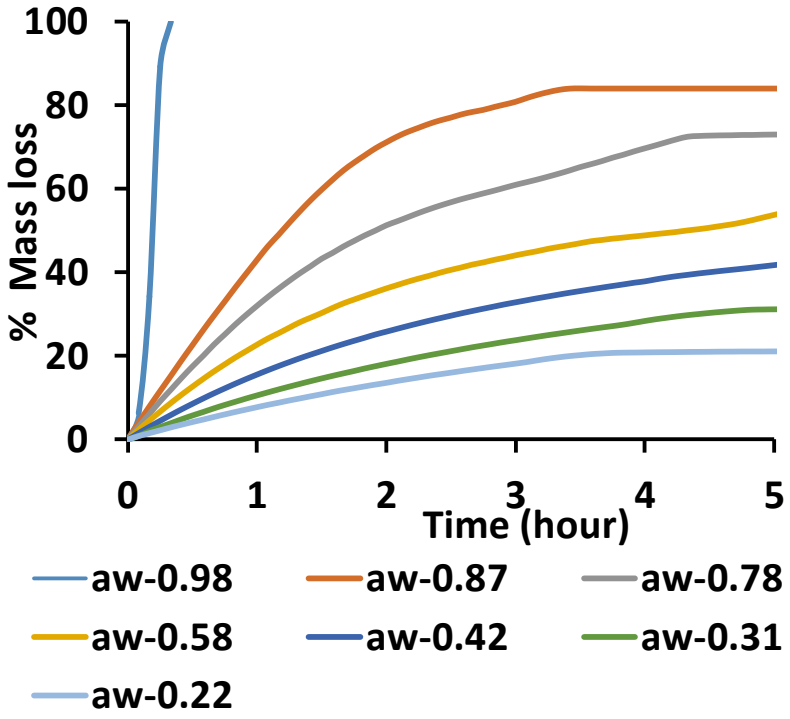
ρ = partial vapor pressure of water in material

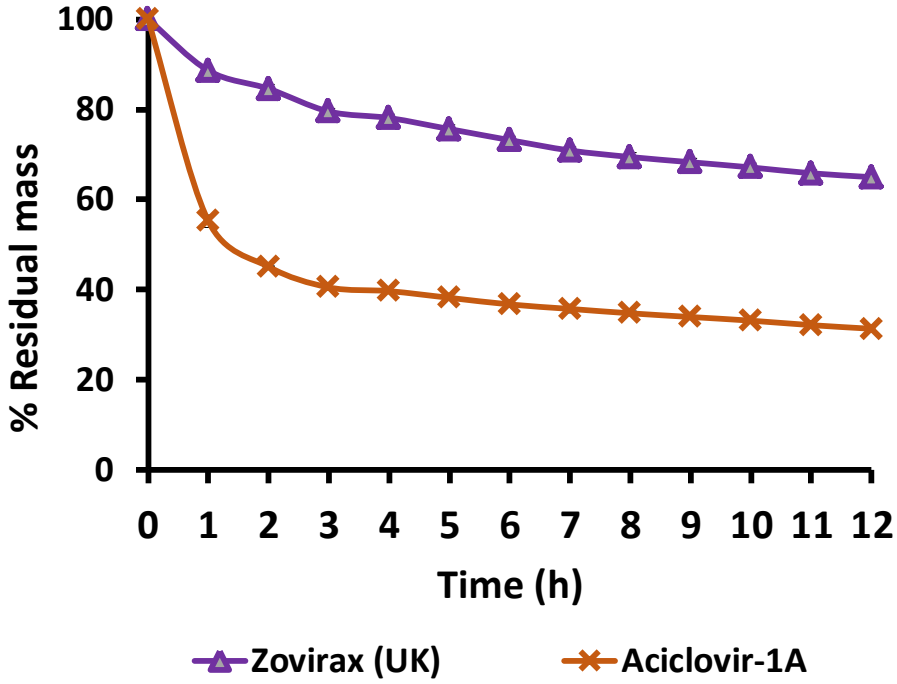
ρ_0 = vapor pressure of pure water

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



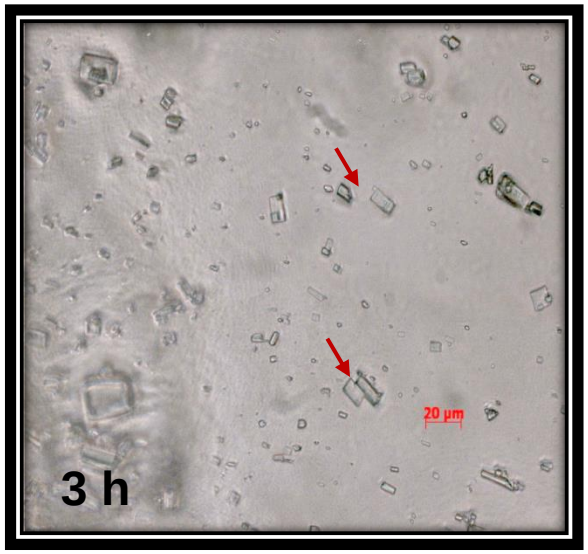
Effect of Solvent Activity on the Drying Rate

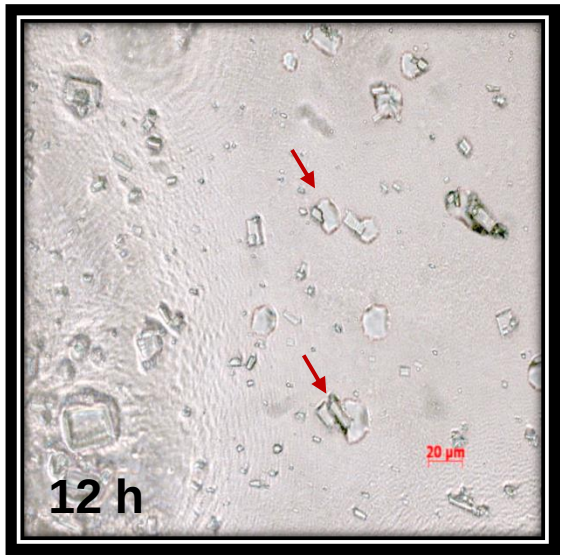




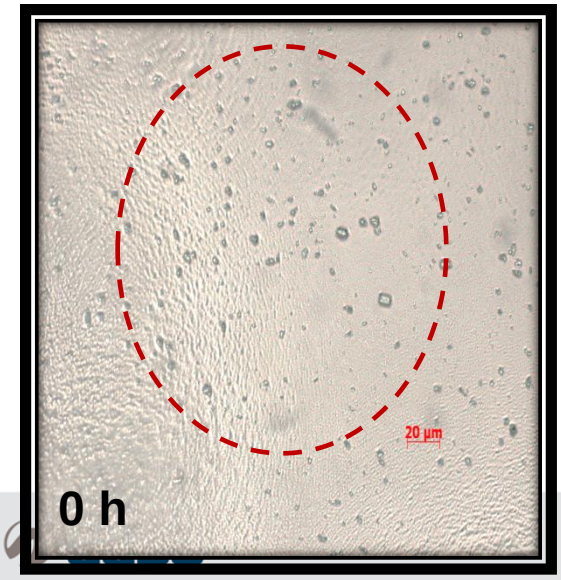
Solvent Evaporation and Precipitation of Acyclovir

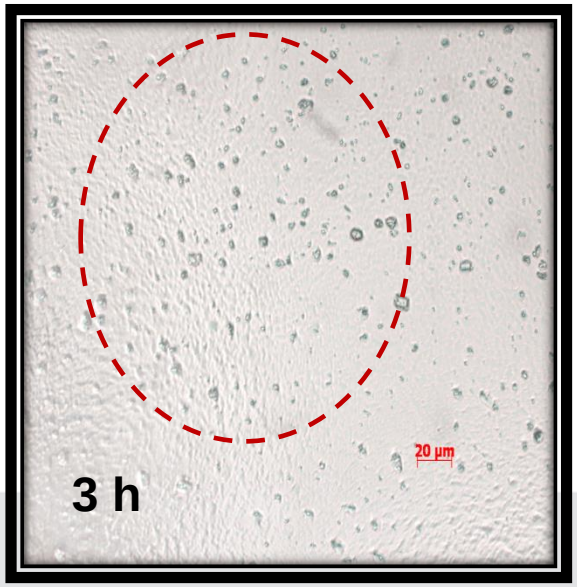
Zovirax-UK

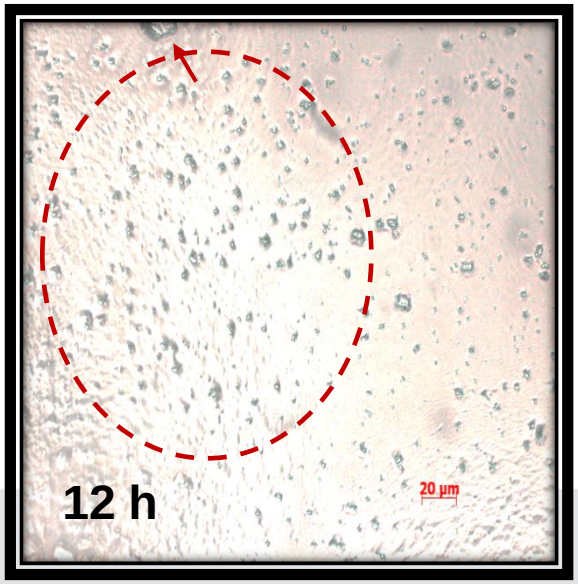




Aciclovir -1A







Q1 & Q2 Identical W/O Creams

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

Composition of a model w/o type cream formulation.

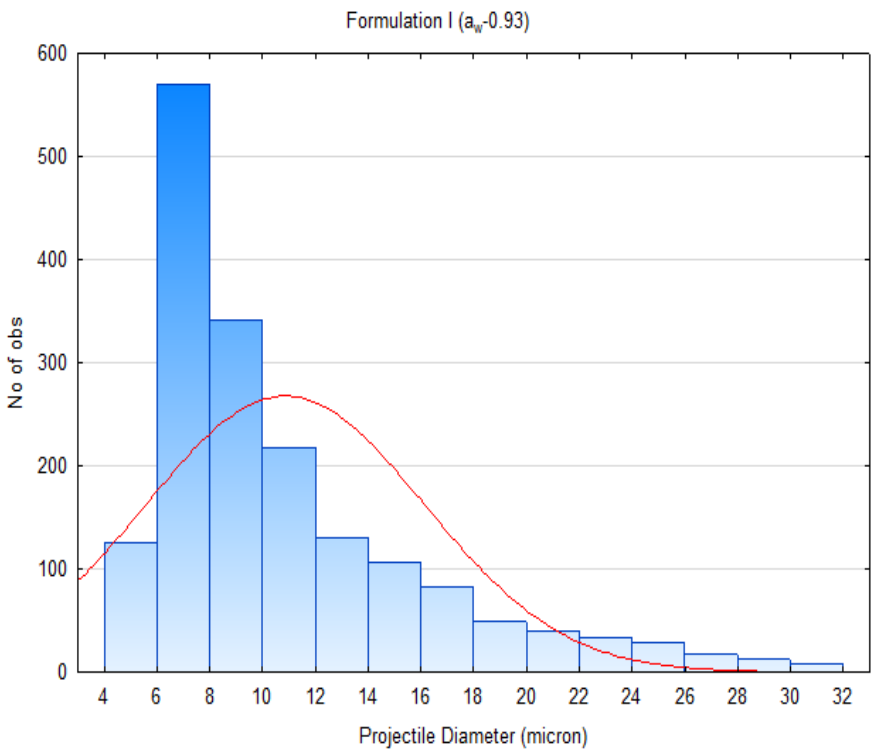
Code	Homogenization Speed (RPM)	Homogenization Time (minutes)
F1	3500	15
F2	7000	45

Process parameters for preparation of w/o cream formulations.

Globule Size Distribution

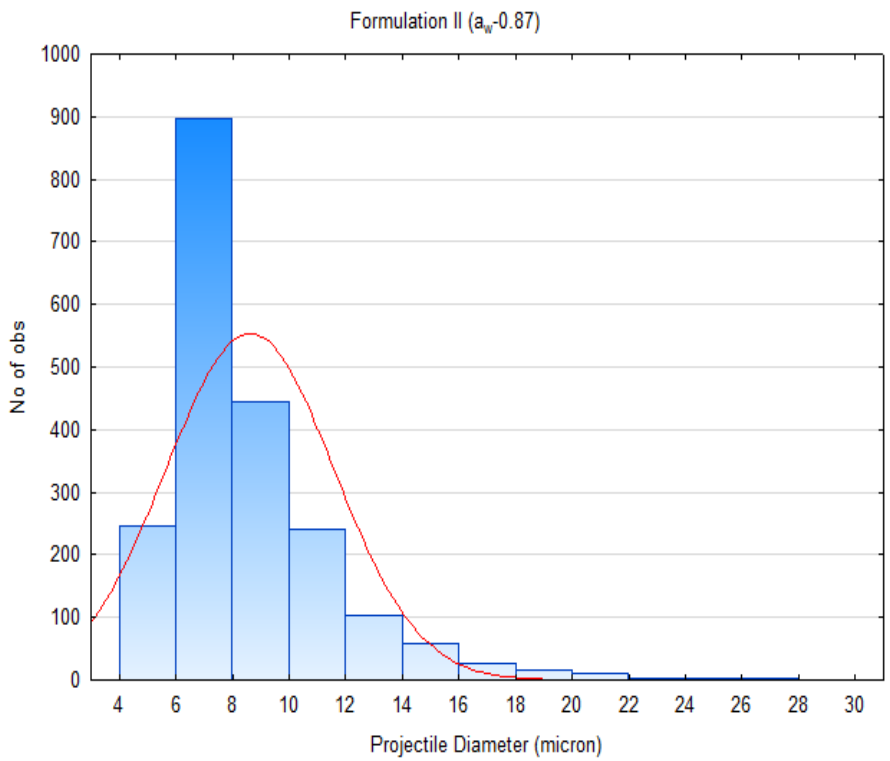
THE UNIVERSITY of MISSISSIPPI

F1



Histogram plot for globule size distribution in test formulation I (w/o type cream – a_w-0.93)

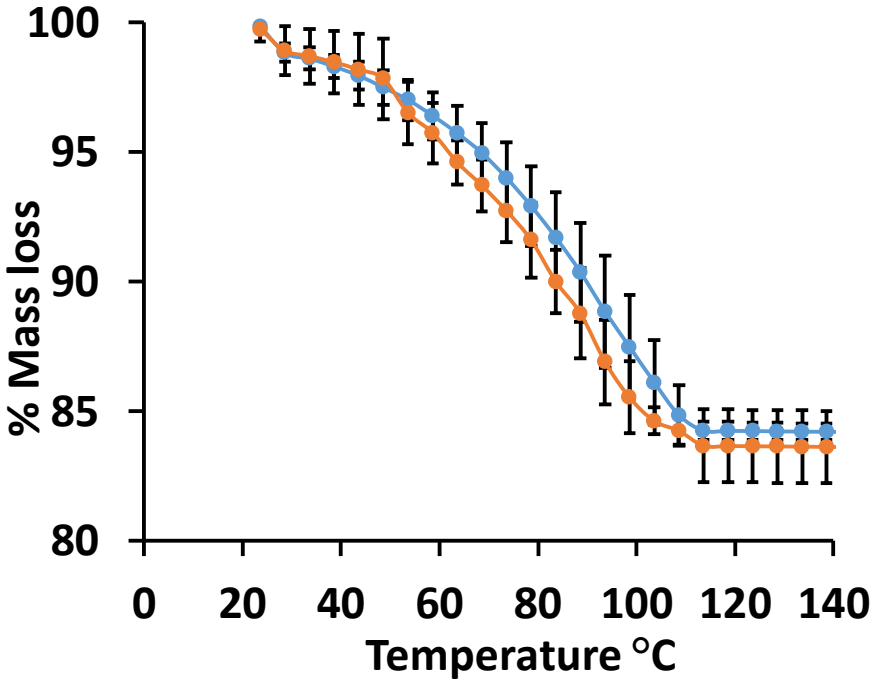
F2



Histogram plot for globule size distribution in test formulation II (w/o type cream – a_w-0.87)

Drying Rate of W/O Creams

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

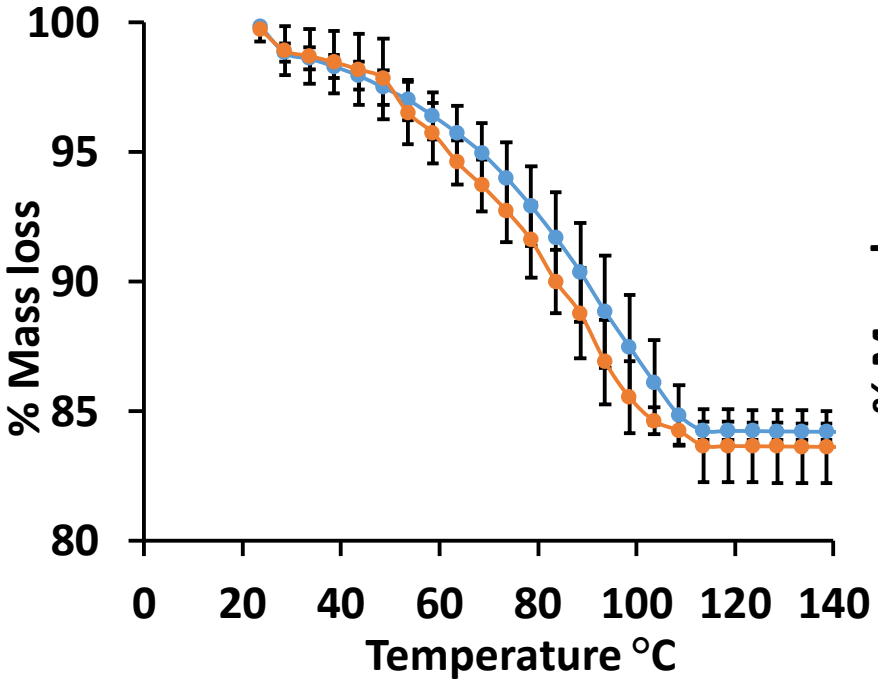


Determination of total water content in model w/o type cream formulation using thermogravimetry.

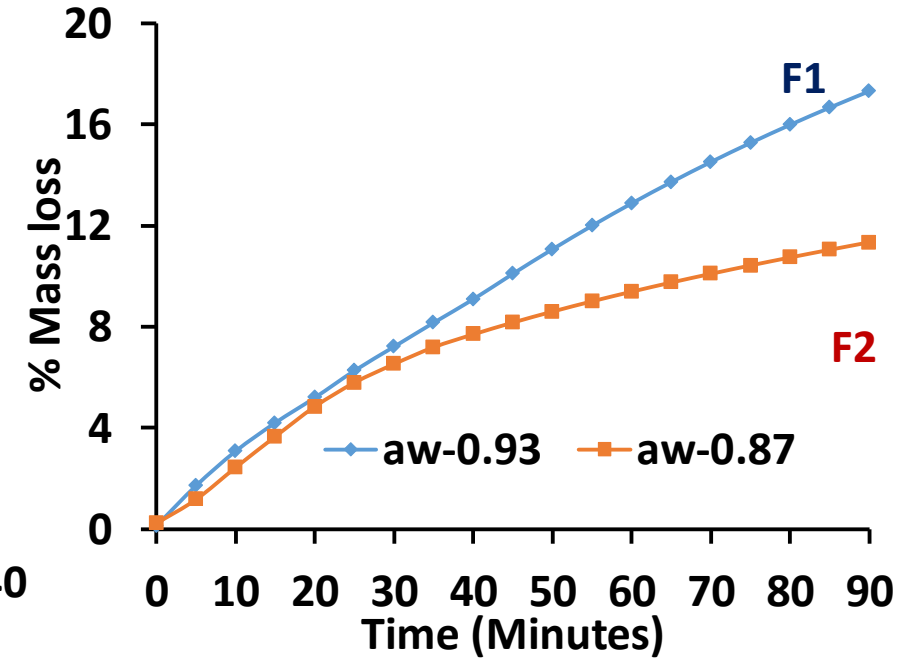
Drying Rate of W/O Creams

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

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

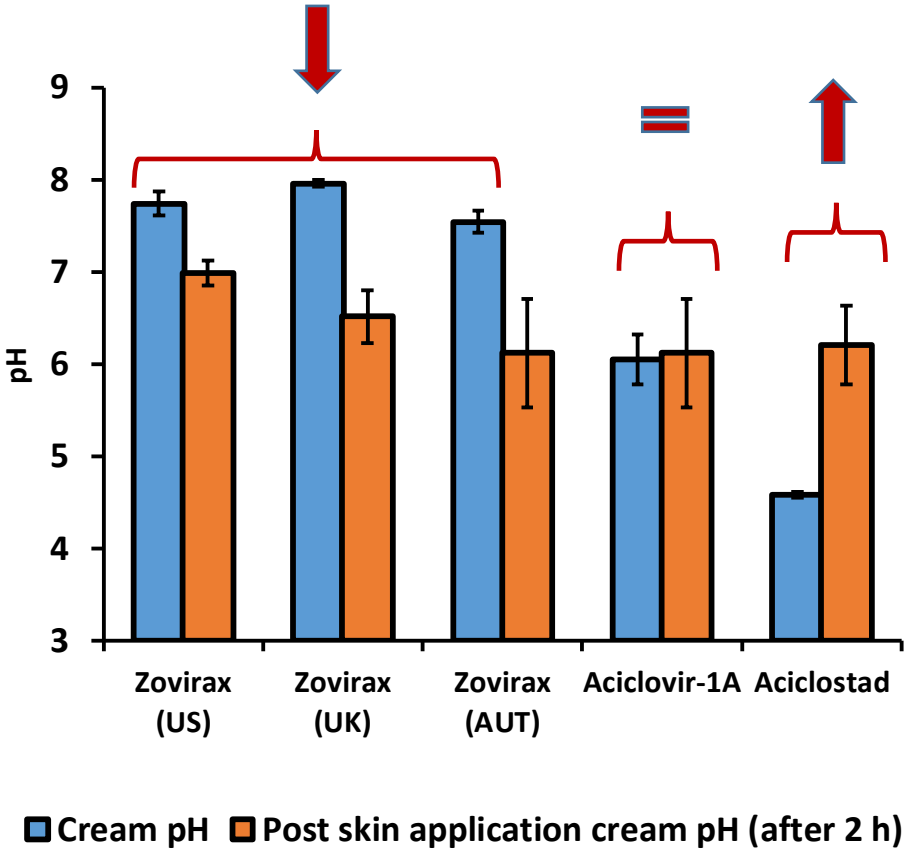


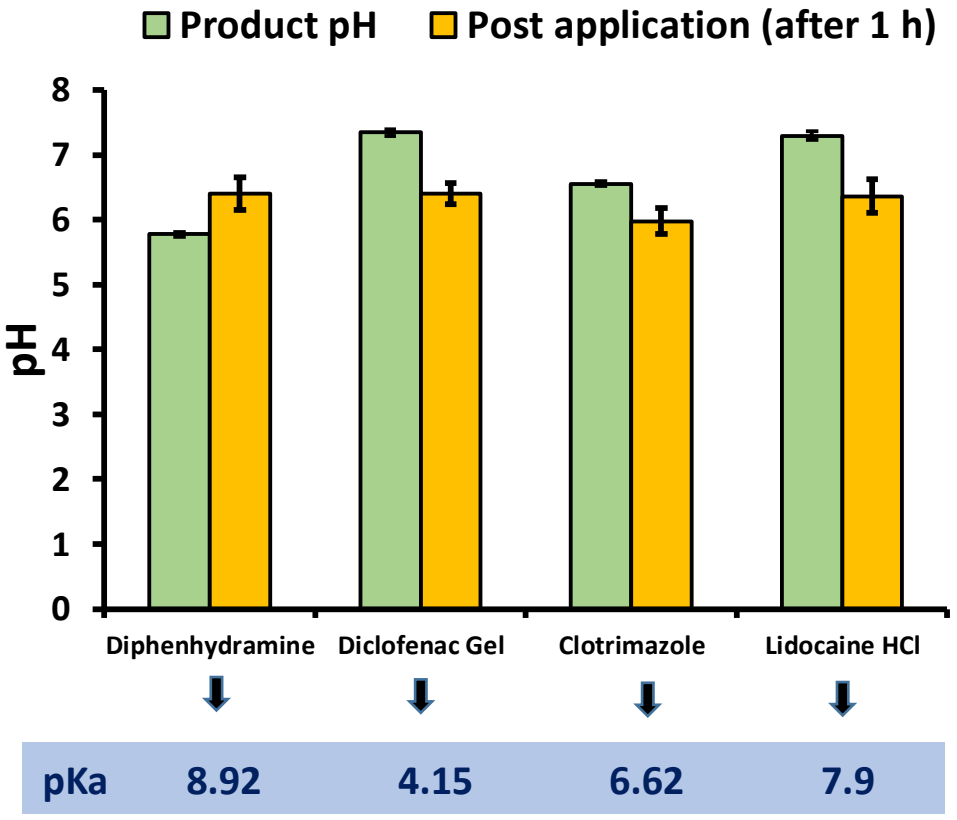
Determination of total water content in model w/o type cream formulation using thermogravimetry.



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

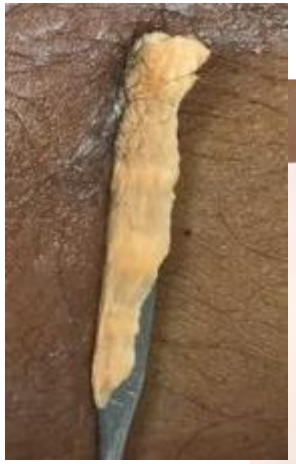
pH could change after application on the skin

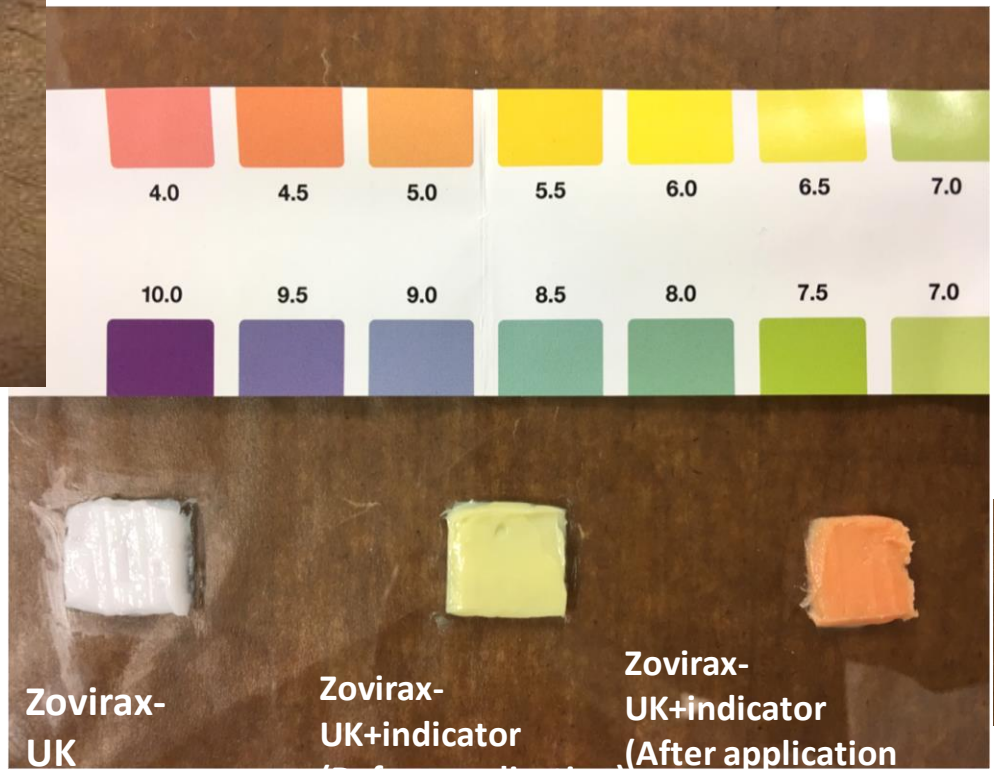




pKa	8.92	4.15	6.62	7.9

pH change of topical cream on the skin (1 h)





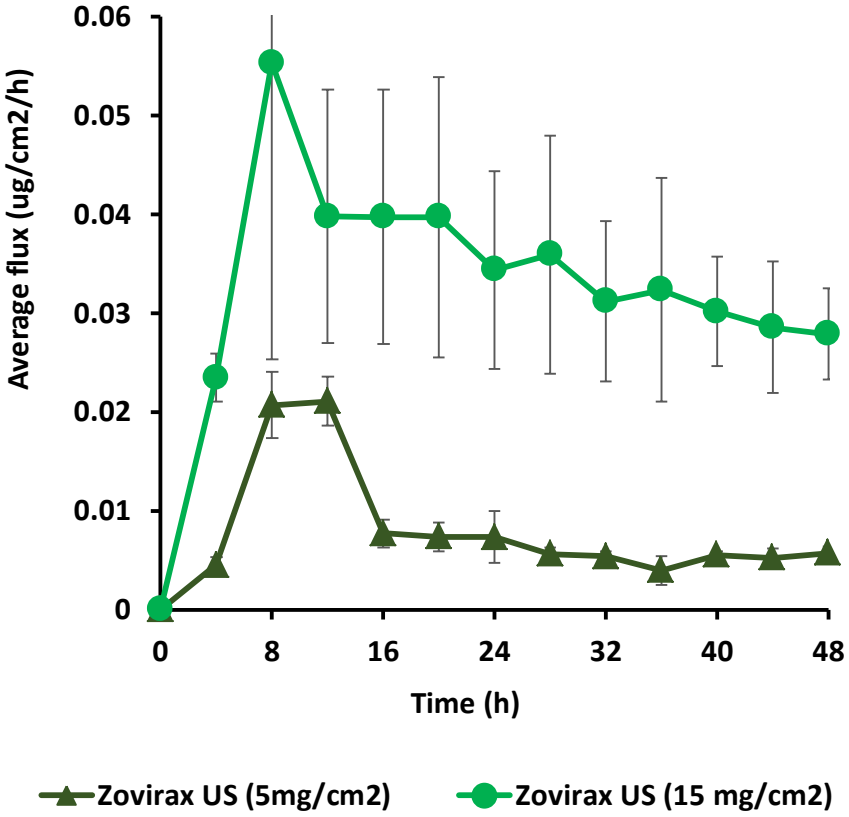
Zovirax-UK+indicator (After application on glass slide for 1h)

pH change could impact the drug permeation

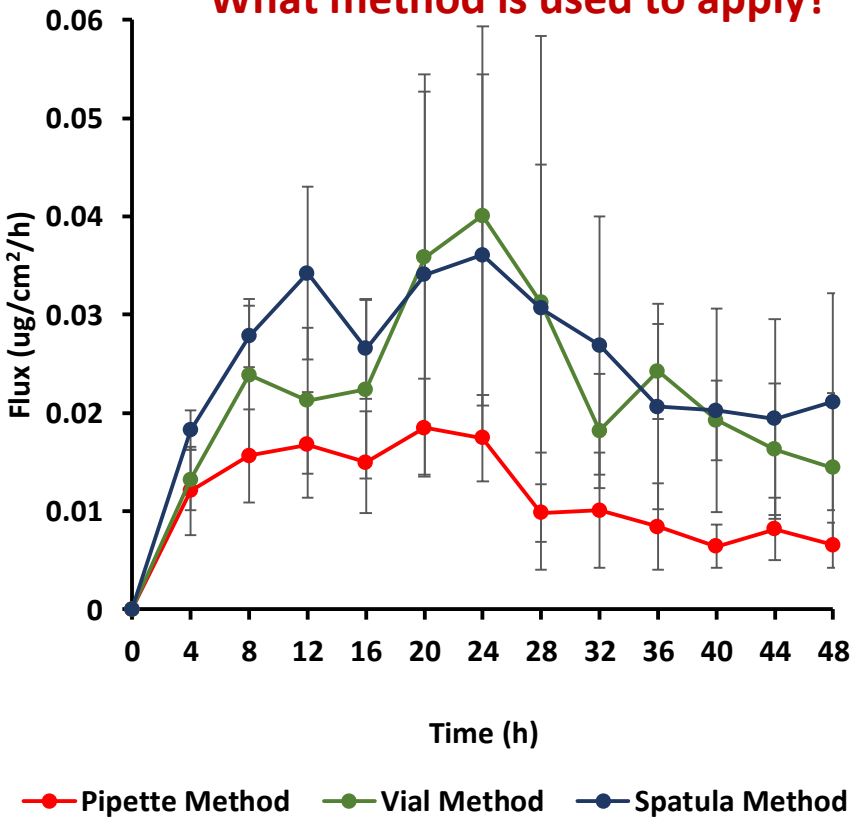
Product	pKa	% Unionized	
		Initial	After one hour
Clotrimazole	6.6	43.1% (pH 6.5)	7.1% (pH 5.5)
Lidocaine	7.9	20.1% (pH 7.3)	2.5%(pH 6.3)

In vitro Permeation Testing

How much is applied?

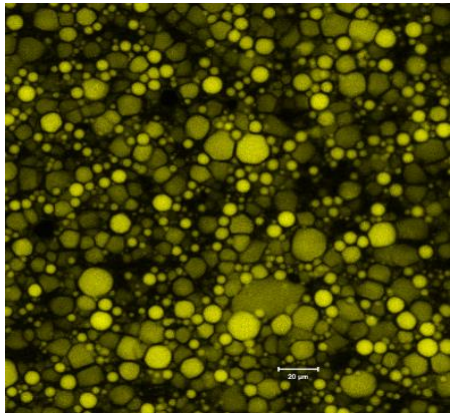
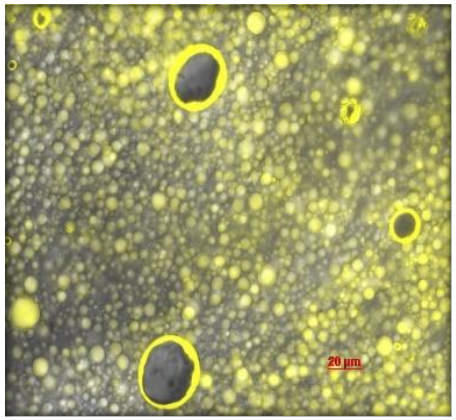
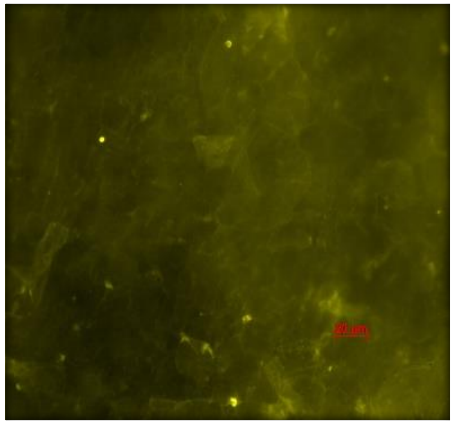


What method is used to apply?

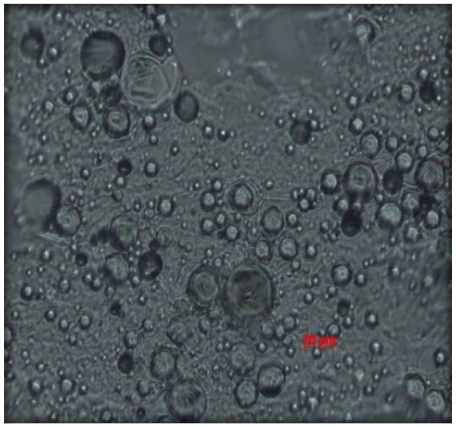
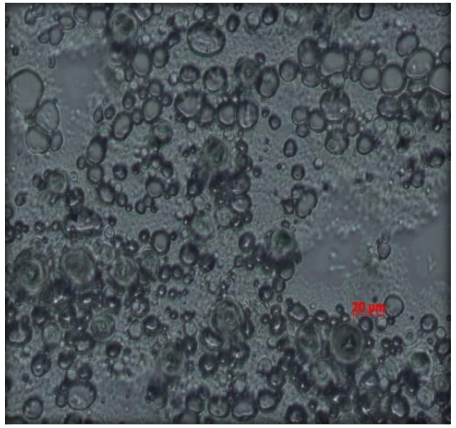
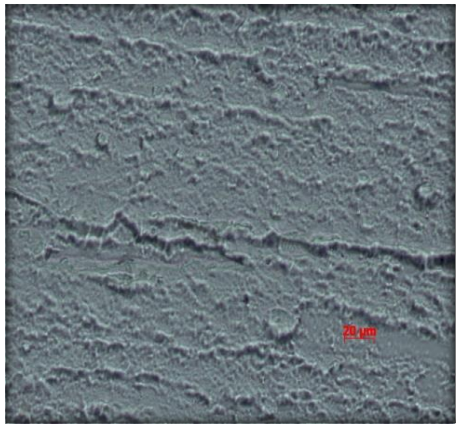


How Intensely was it applied?

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

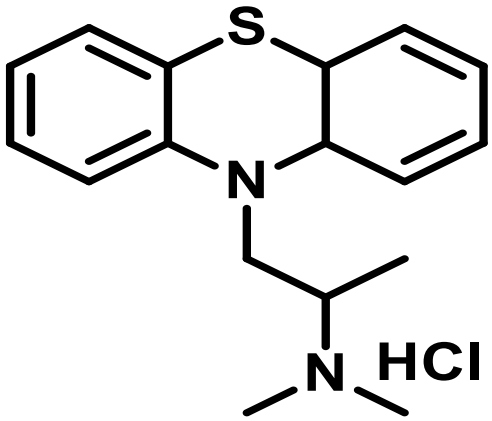




Gentle application → Rubbing → Intense Rubbing

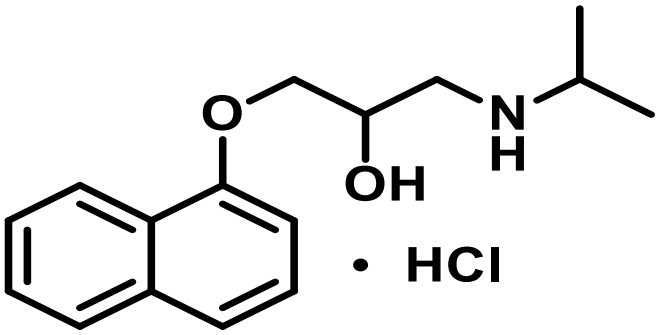




Benadryl cream on glass slide

Surfactant like Drug Molecules

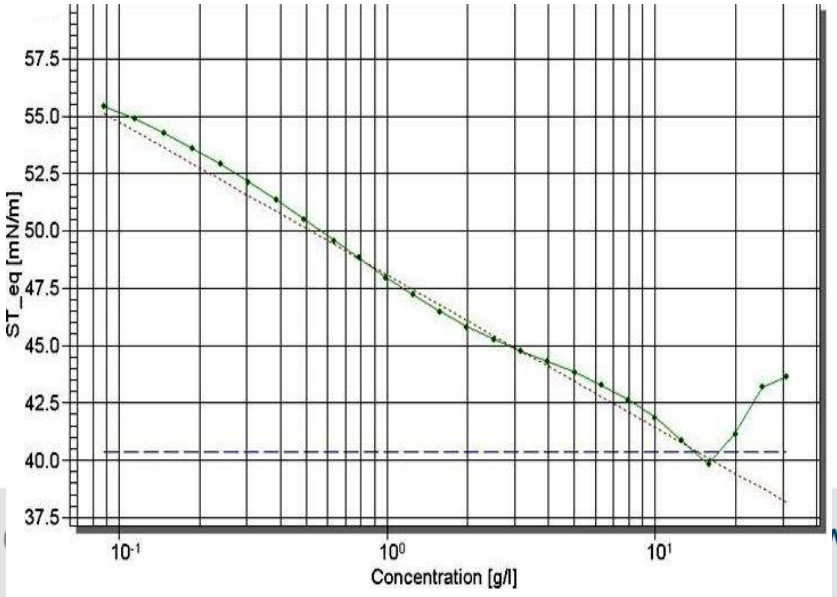


Promethazine hydrochloride structure

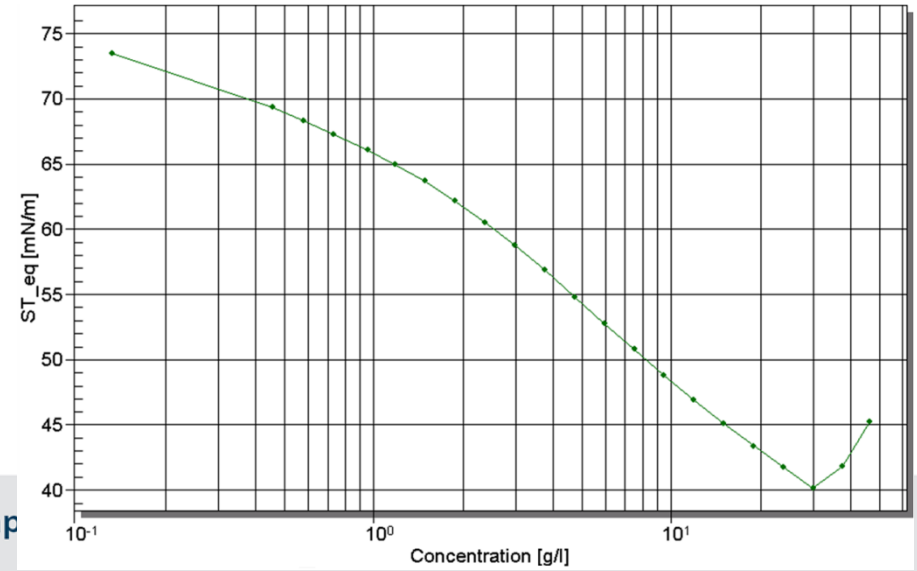


Propranolol hydrochloride structure

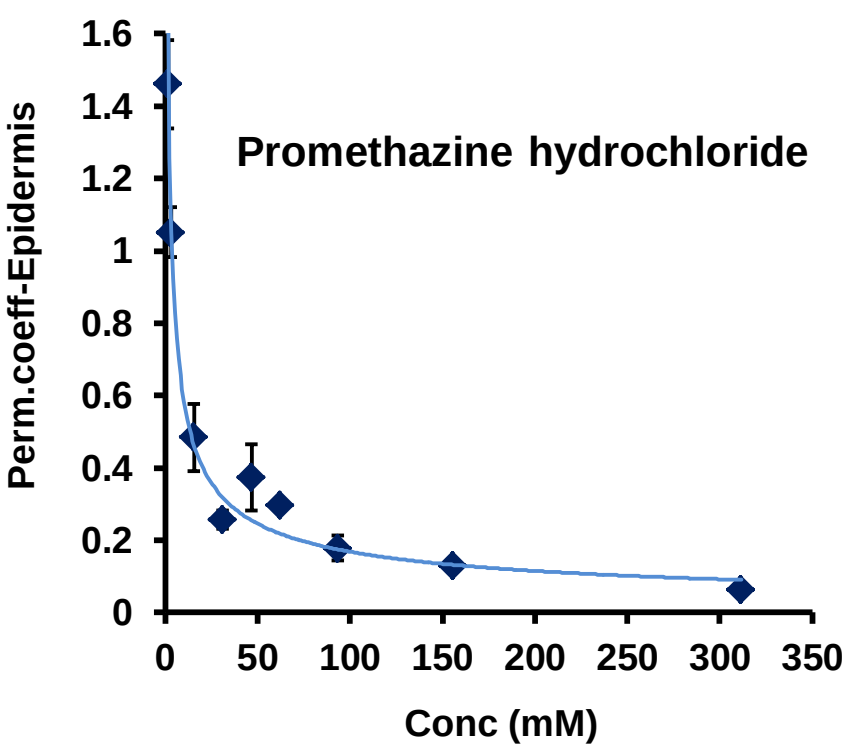
CMC = 49.2 mM

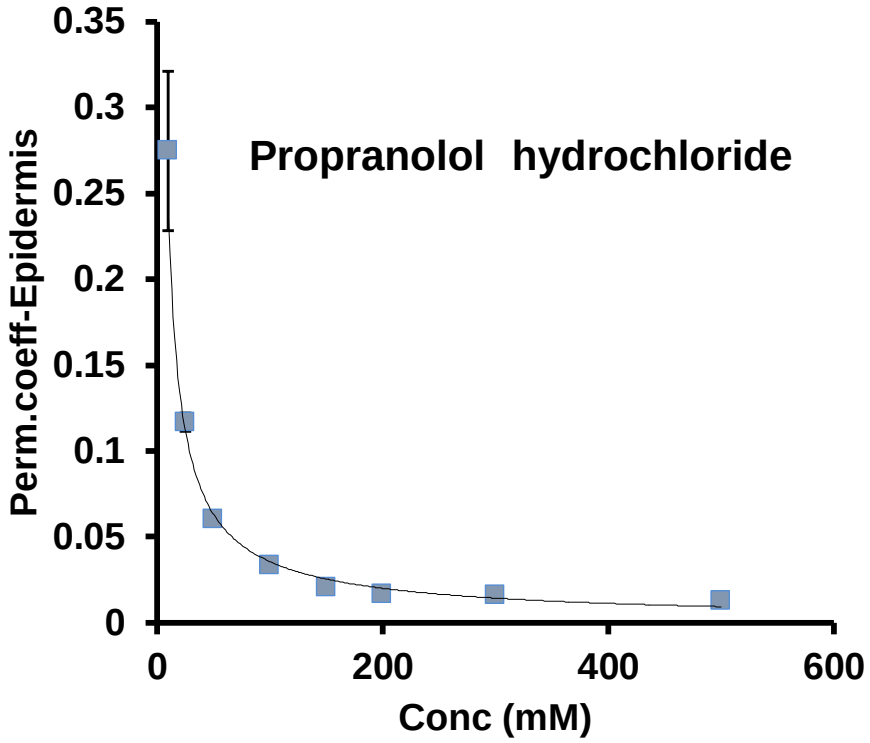


CMC = 98.4 mM



Permeability Coefficient Changes with Concentration





Conclusions

- The microstructural characterization is the predominant determinant of the performance of the product in vivo .
- Development of appropriate tools to characterize the microstructural characteristics of dosage forms needs to be developed and standardized.
- Post application changes in the formulation plays a major role in determining the BA/BE of the products.
- . Potential failure modes need to be understood clearly and robustness should be built in the products to resist any impact on the performance of the product.

Acknowledgments

- Dr.Howard Maibach (UCSF)
- Dr.Santanu Kundu (MSU)
- Dr.Repka –The Univ. of Mississippi
- Dr.Peter Wildfong (Duquesne University, PA)
- Dr.Srinatha-Post doctoral Associate
- Dr.Srinath-Post doctoral Associate
- MuraliKrishna Angamuthu (Grad.Student)
- Abhijeet Maurya (Grad. Student)
- Seyedmeysam Hashemnejad (Grad. Student)

The Office of Generics Drugs (OGD)/Office of Research and Standards (ORS)

Dr. Sam Raney

Dr. Bryan Newman

Dr. Priyanka Ghosh

Dr. Katherine Tyner

Dr. Elena Rantou

Dr. Ho-pi Lin

Dr. Susie Zhang

Dr. Darby Kozak

Grant Support-USFDA 1U01FD005223-01

Questions?

S.Narasimha Murthy
Professor-Pharmaceutics and Drug Delivery
The University of Mississippi
University, MS 38677
Tel: 662-915-5164
Fax: 662-915-1177
Email: murthygroup@gmail.com