Influence of Metamorphosis on the Performance of Topical Formulations

March 26, 2021

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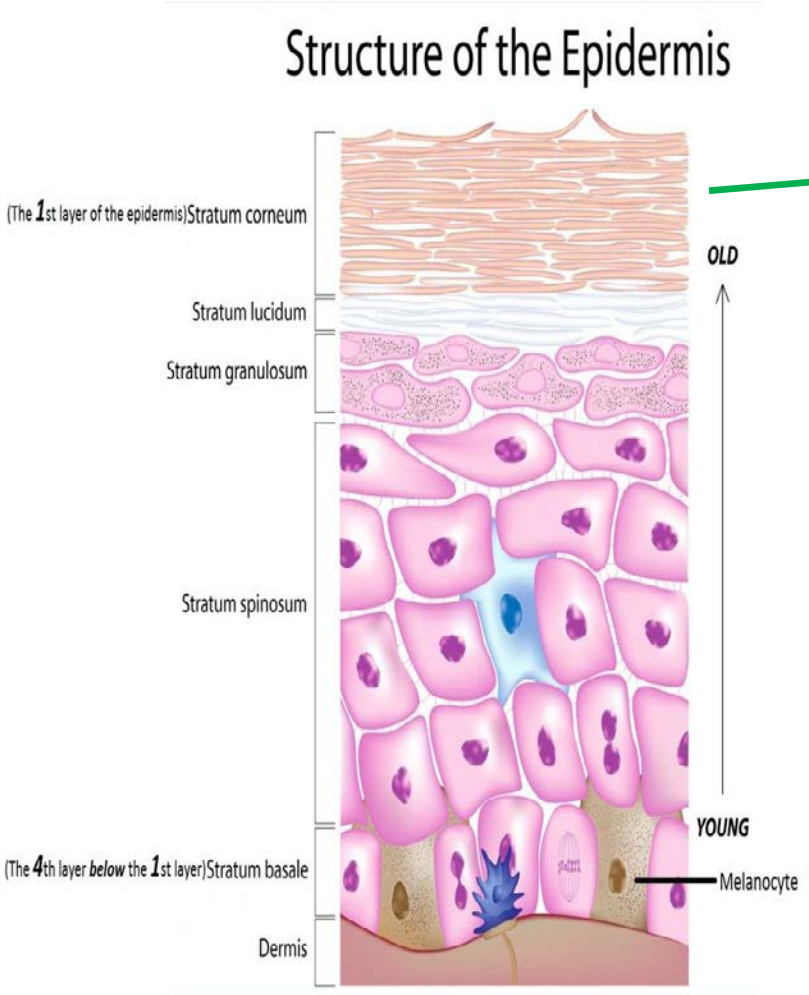
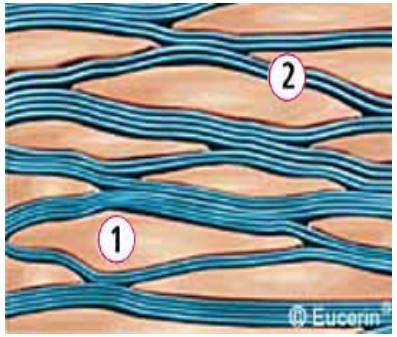
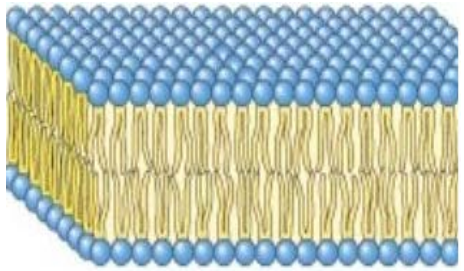
Skin and drug permeation through skin





Stratum corneum (SC)



Lipid domains in SC (Bilayer lamellae formed with ceramides, cholesterol, fatty acids)

$$Percutaneous\ Flux, J\ \alpha\ \frac{\alpha . D}{h}$$

α – Thermodynamic activity

D – diffusivity

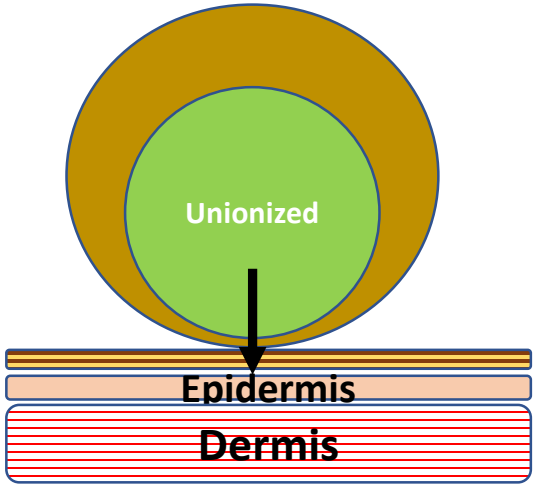
h –Thickness of the membrane

API related factors affecting permeation

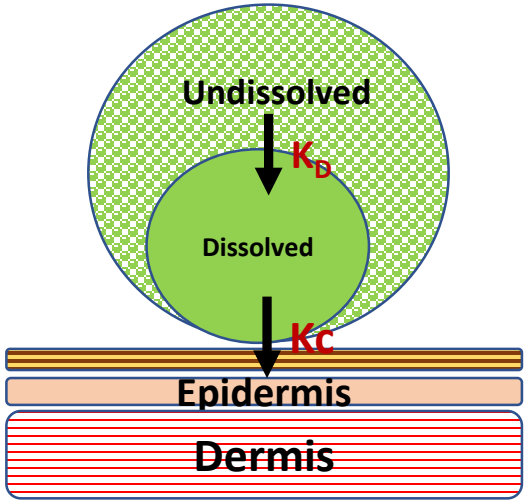
- Molecular weight
- Partition co-efficient
- Ionization (pKa)
- Melting point
- Solubility
- Number of hydrogen bonding groups

Formulation factors influencing drug permeation through skin (CQA)

pH of the formulation



Dissolved/Undissolved drug



Solvent Activity (a_w)

$a_w = \rho/\rho_0$

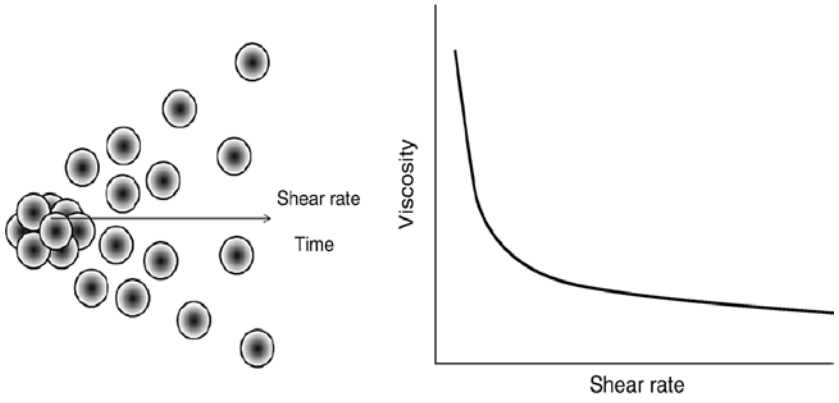
ρ = Partial vapor pressure of solvent in the product

ρ_0 = Vapor pressure of pure water

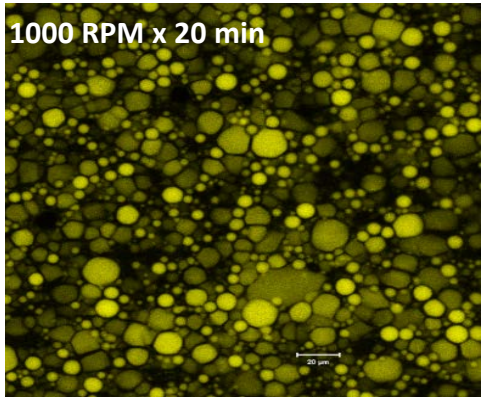
Rate of dissolution of drug

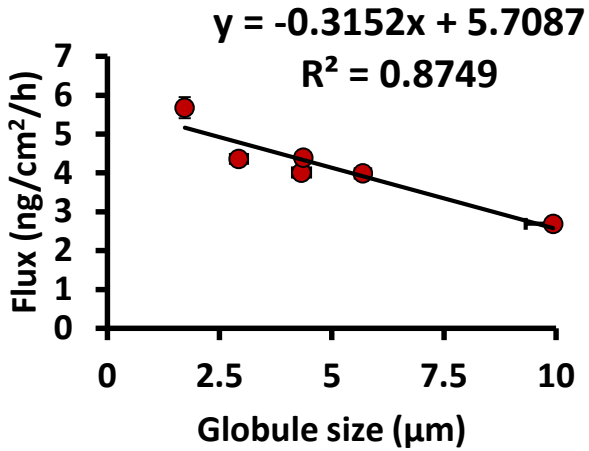
- Particle Size
- Polymorphic form
- Morphology of particles

Rheological Behavior



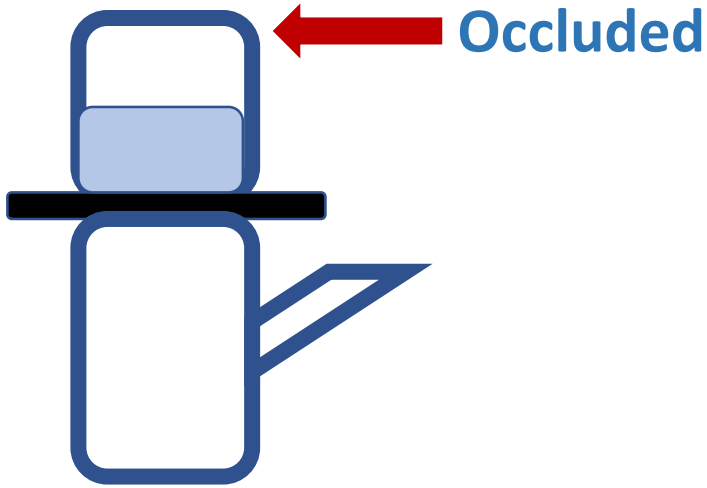
Globule Size





In Vitro Permeation Testing

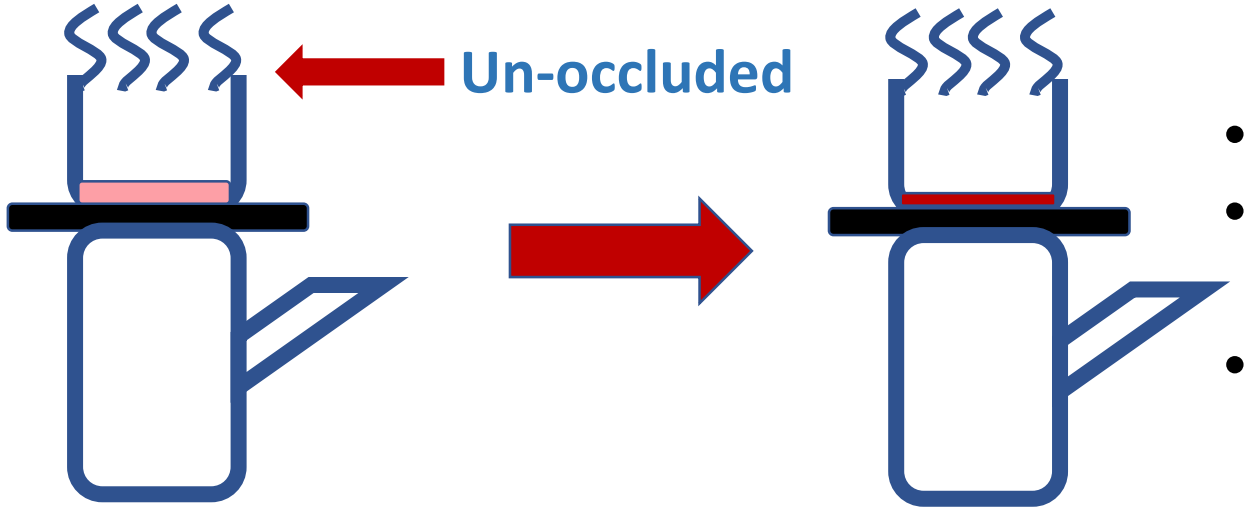
Infinite Dose



- No evaporation
- No change in composition
- Drug concentration change is negligible
- No change in CQA

Finite Dose

- Evaporation of solvents
- Mimics in vivo condition



- Change in composition
- Change in conc. of drug is significant
- Change in CQA

Metamorphosis

Application induced changes in the formulation characteristics

Evaporative metamorphosis

Drug penetration from remnant vehicle of drug

Primary Phase

Changes in the formulation due to mode of application.

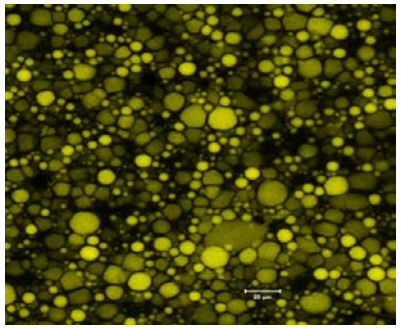
Secondary Phase

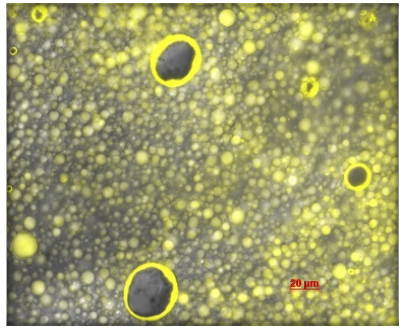
Changes predominantly due to evaporation of solvents

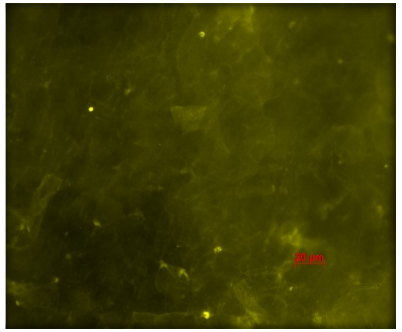
No major changes in the composition

Phases of Metamorphosis

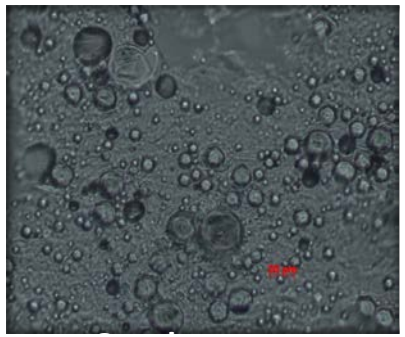
Primary Phase

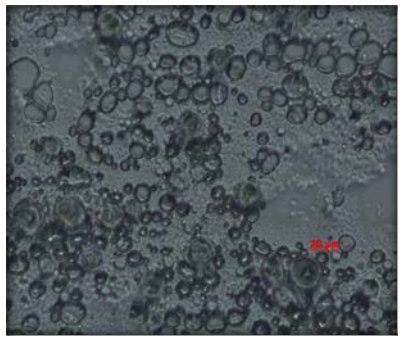


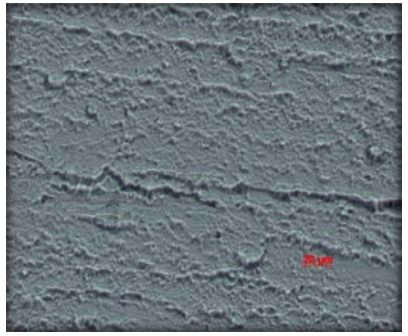




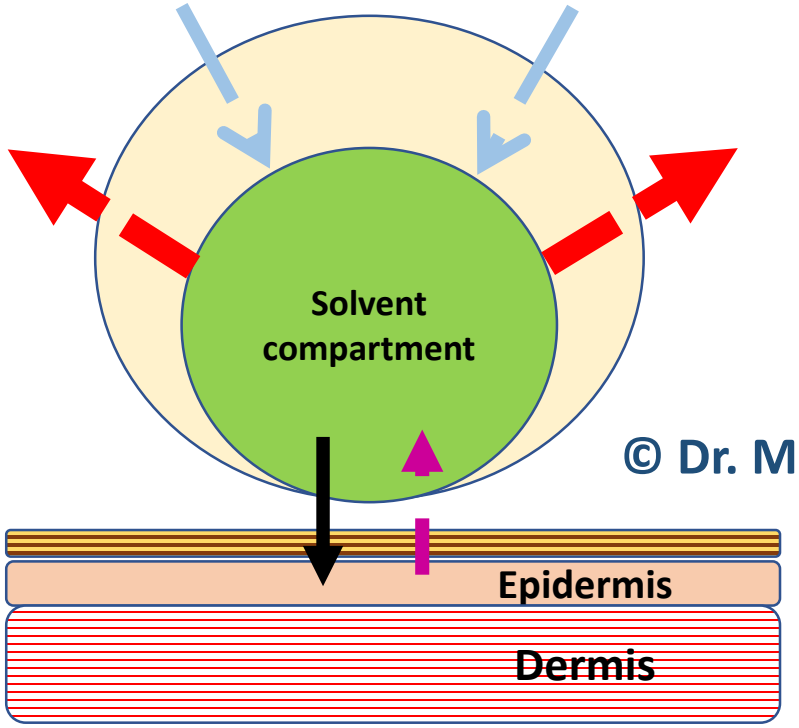
Gentle application → Rubbing → Intense Rubbing





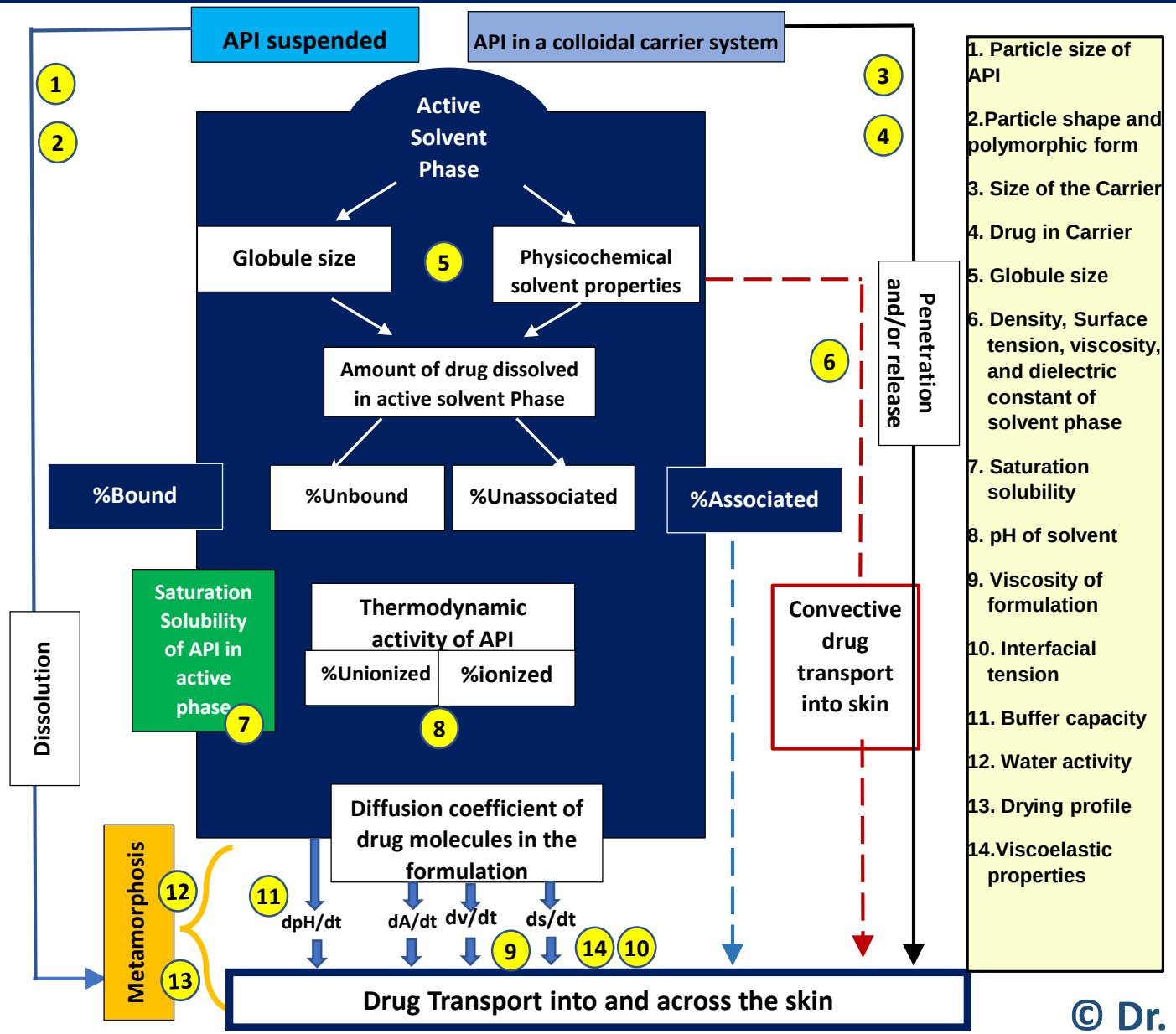


Secondary Phase

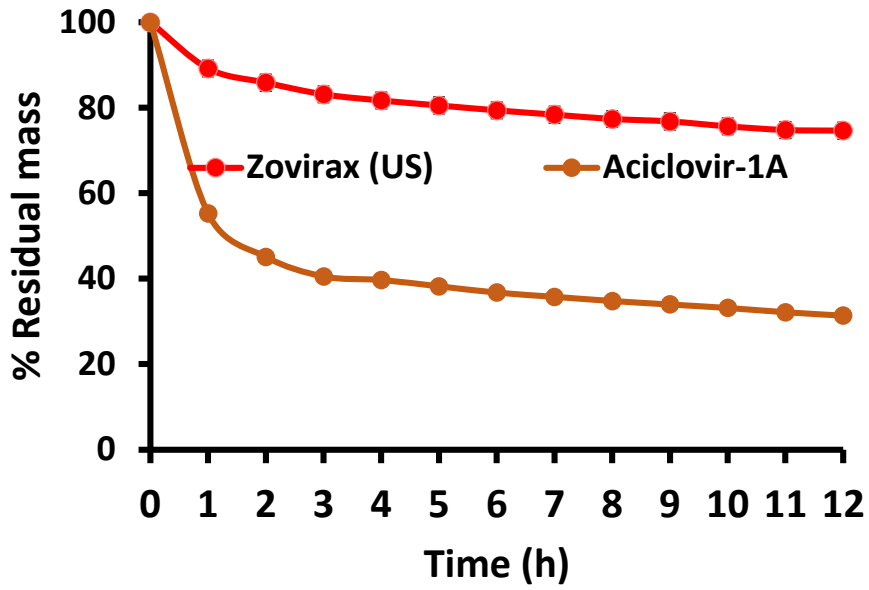


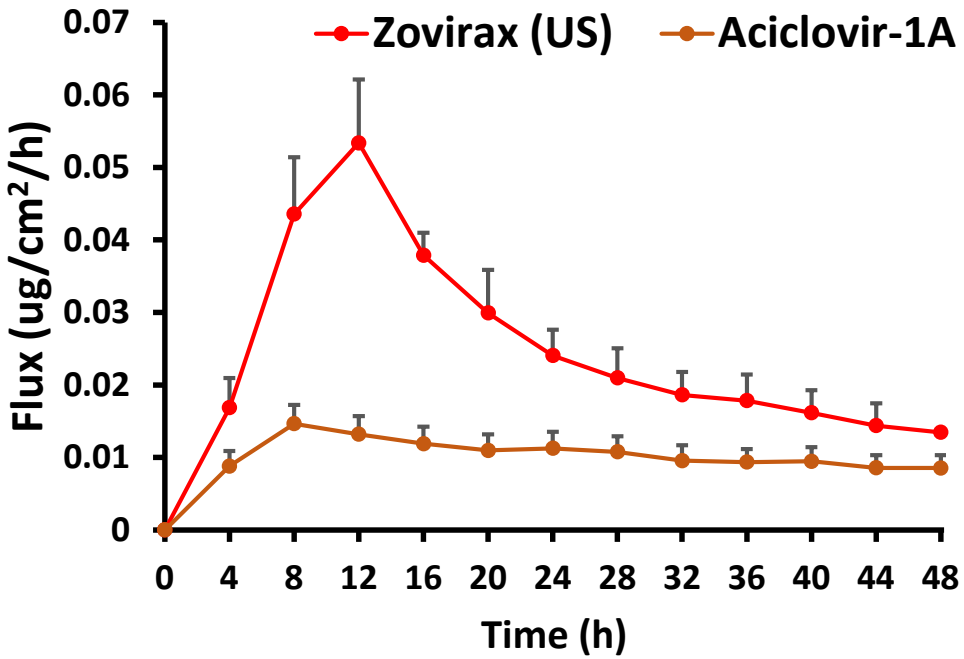
- Solvent loss due to evaporation
- Solvent that is absorbed from the atmosphere
- Solvent penetration into the skin
- Solvent that could potentially get incorporated from skin.

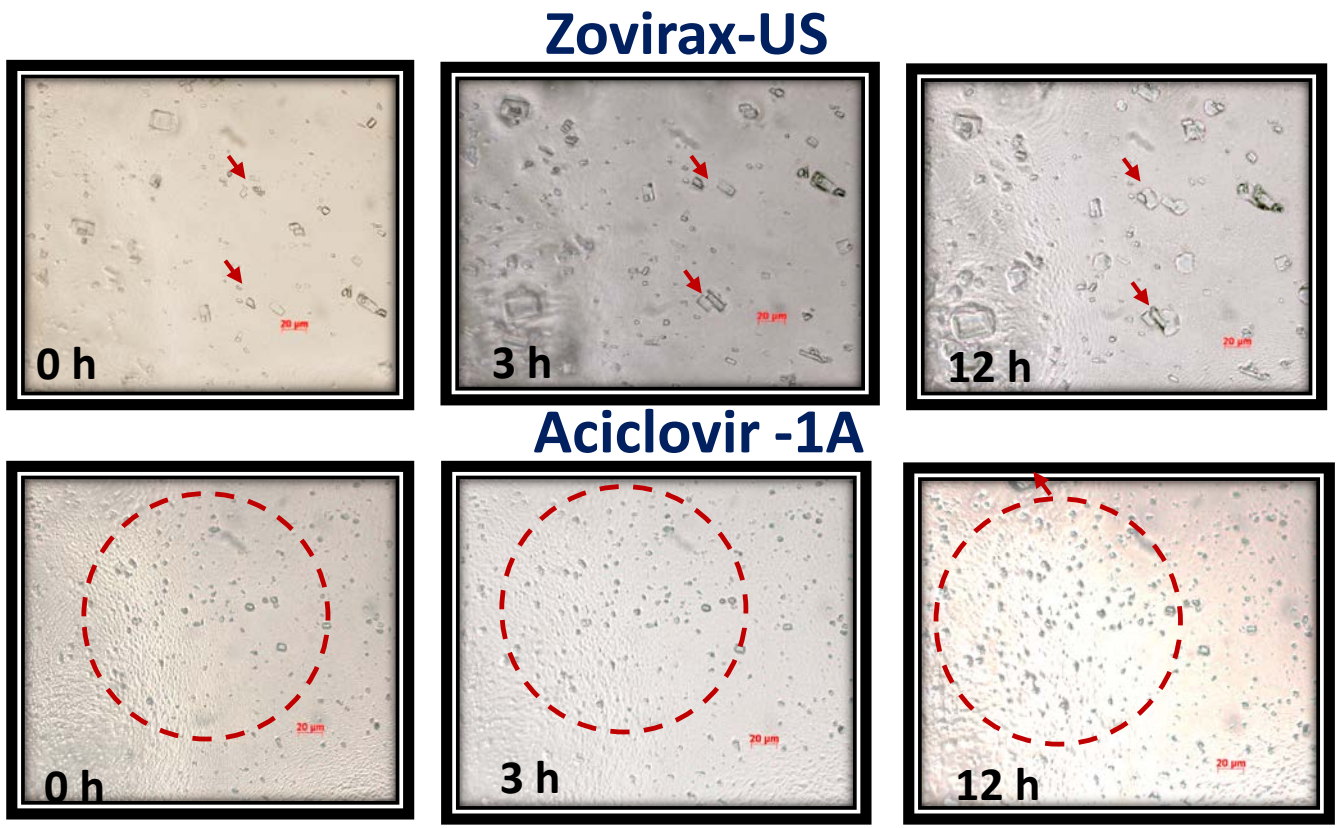
Fundamental factors that govern topical dosage form performance



Solvent Evaporation and Precipitation of Acyclovir

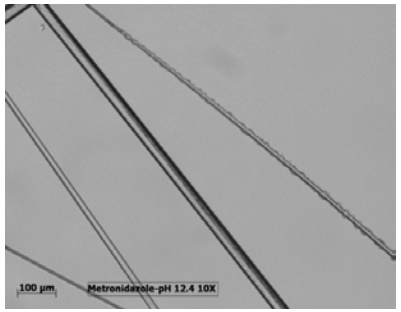




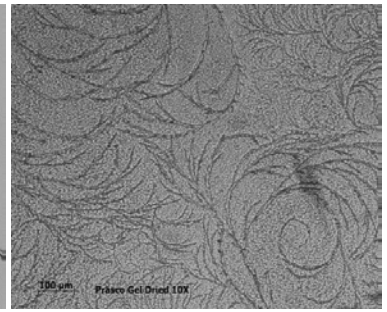


Product	AUC (µg/cm²)
Zovirax (US)	1.20 ± 0.42
Aciclovir-1A	0.53 ± 0.10

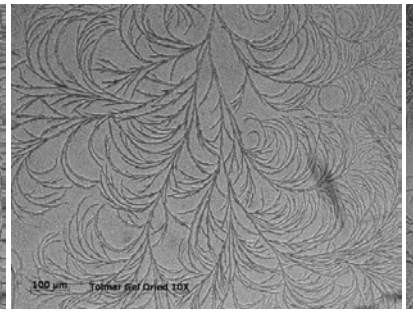
Crystal pattern in gels after drying



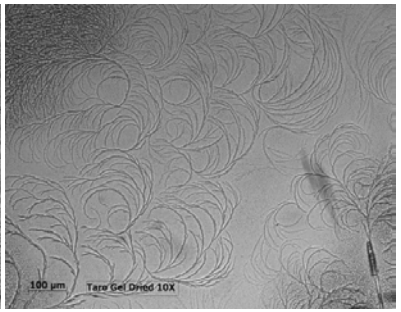
Metronidazole solution



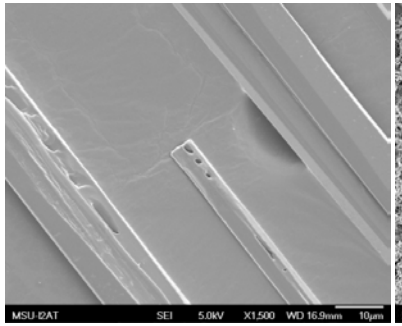
MetroGel® 0.75%, RLD gel (Prasco)



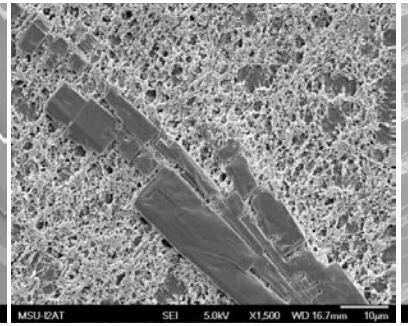
Metronidazole gel 0.75%, Generic gel (Tolmar)



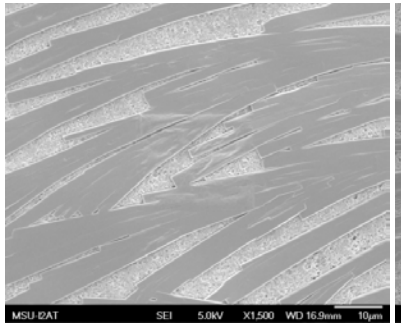
Metronidazole gel 0.75% , Generic gel (Taro)



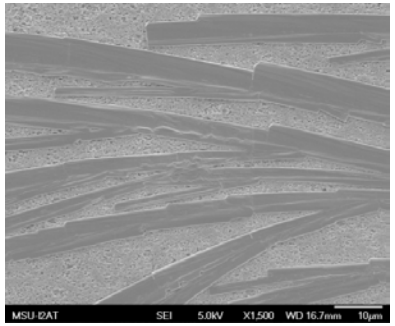
Metronidazole solution



MetroGel® 0.75%, RLD gel (Prasco)

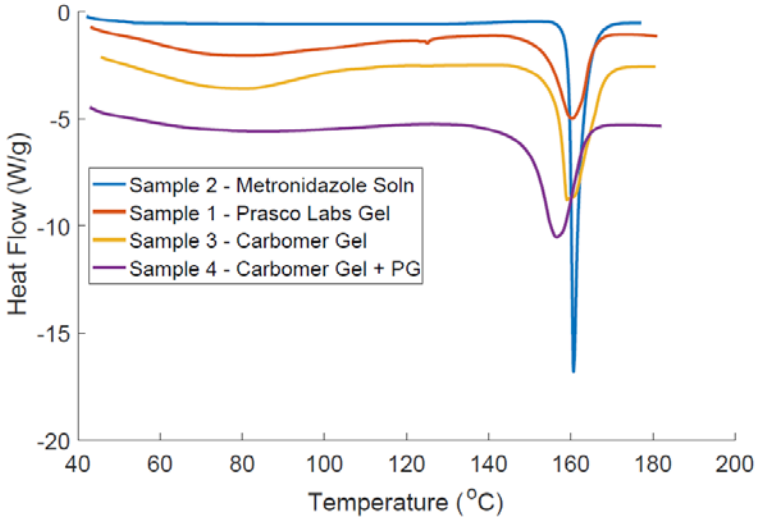


Metronidazole gel 0.75%, Generic gel-1 (Tolmar)

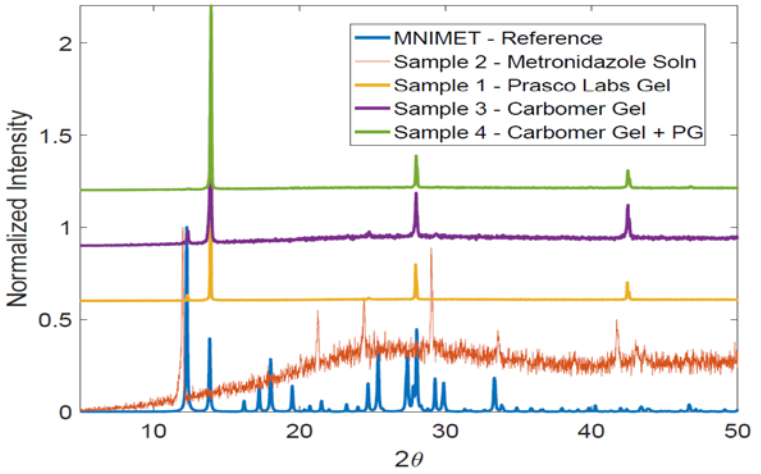


Metronidazole gel 0.75%, Generic gel-2 (Taro)

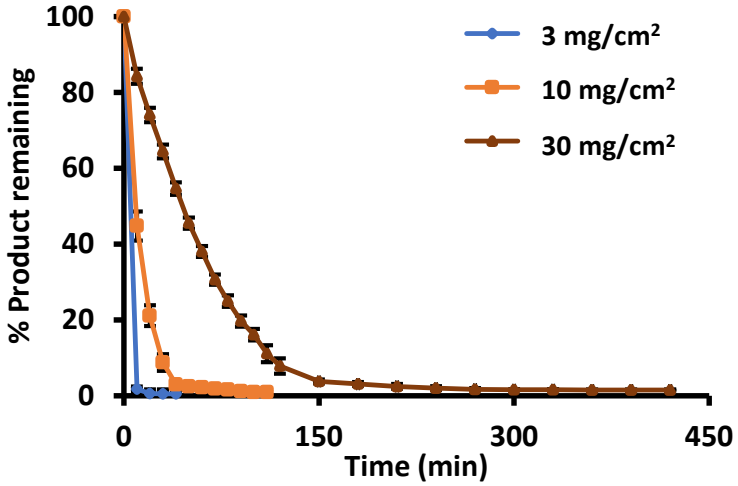
Differential Scanning Calorimetry



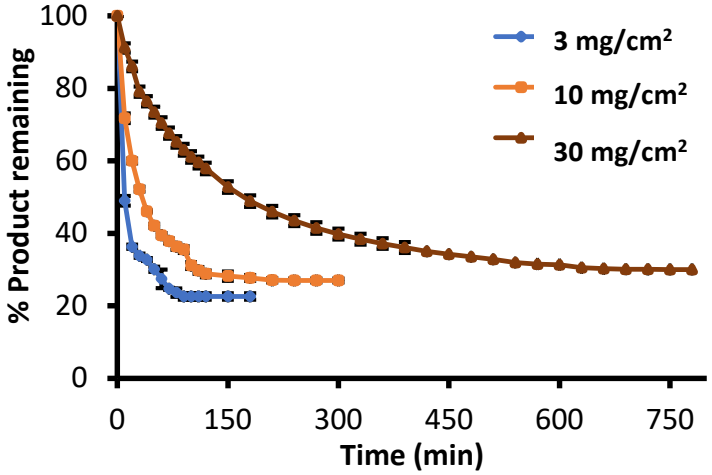
PXRD



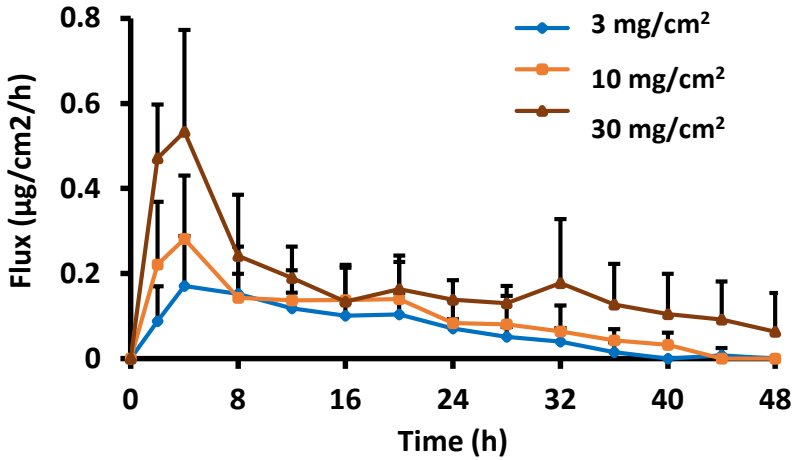
Dependence of dose on drying rate and its effect on performance



Drying rate

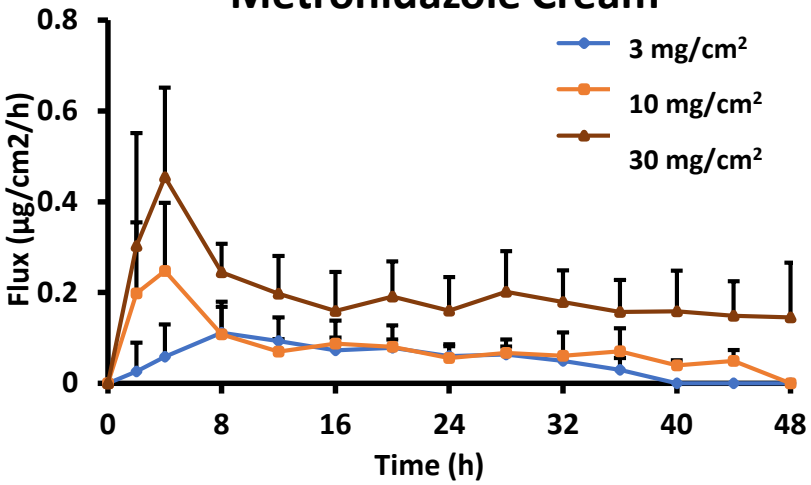


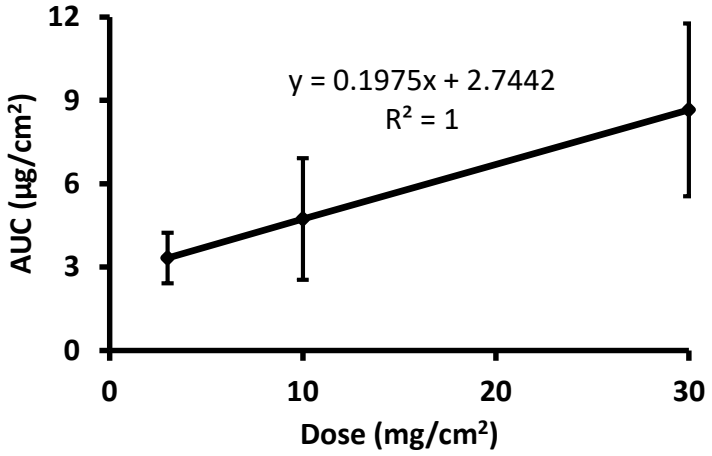
Metronidazole Gel



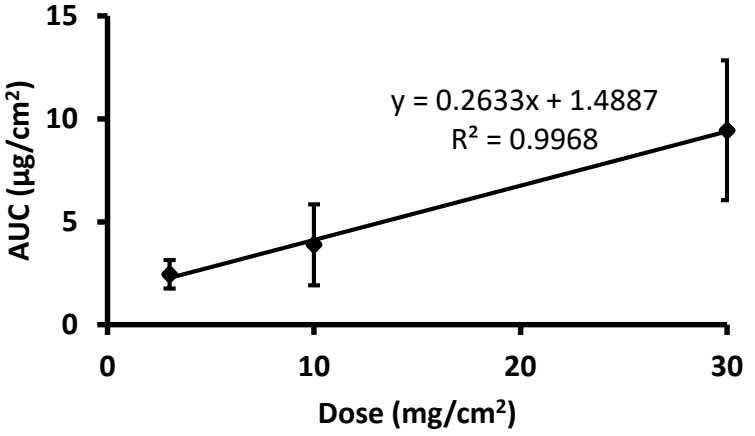
IVPT

Metronidazole Cream



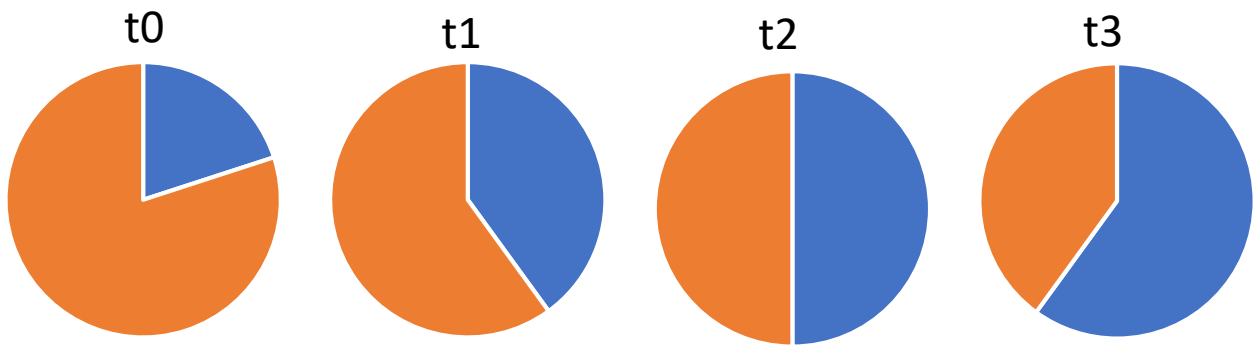


Dose Vs AUC

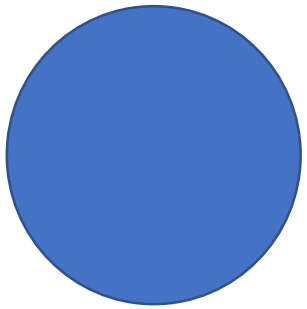


Impact of changes in the degree of saturation during metamorphosis of topical formulations on drug permeation

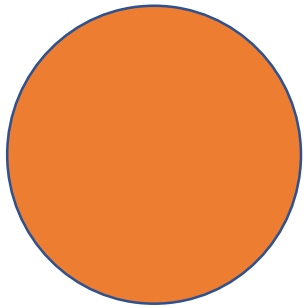
- **It is seen that in some cases, the products that are compositionally different could match in their performance.**
- **Often, we also observe that in formulation that are compositionally same, the performance is different due to difference in rates of drying despite most of the Q3 characteristics are matching between them.**
- **Can we explain these kind of situations based on the change in degree of saturation with time?**



Impact of changes in the degree of saturation during metamorphosis of topical formulations on drug permeation

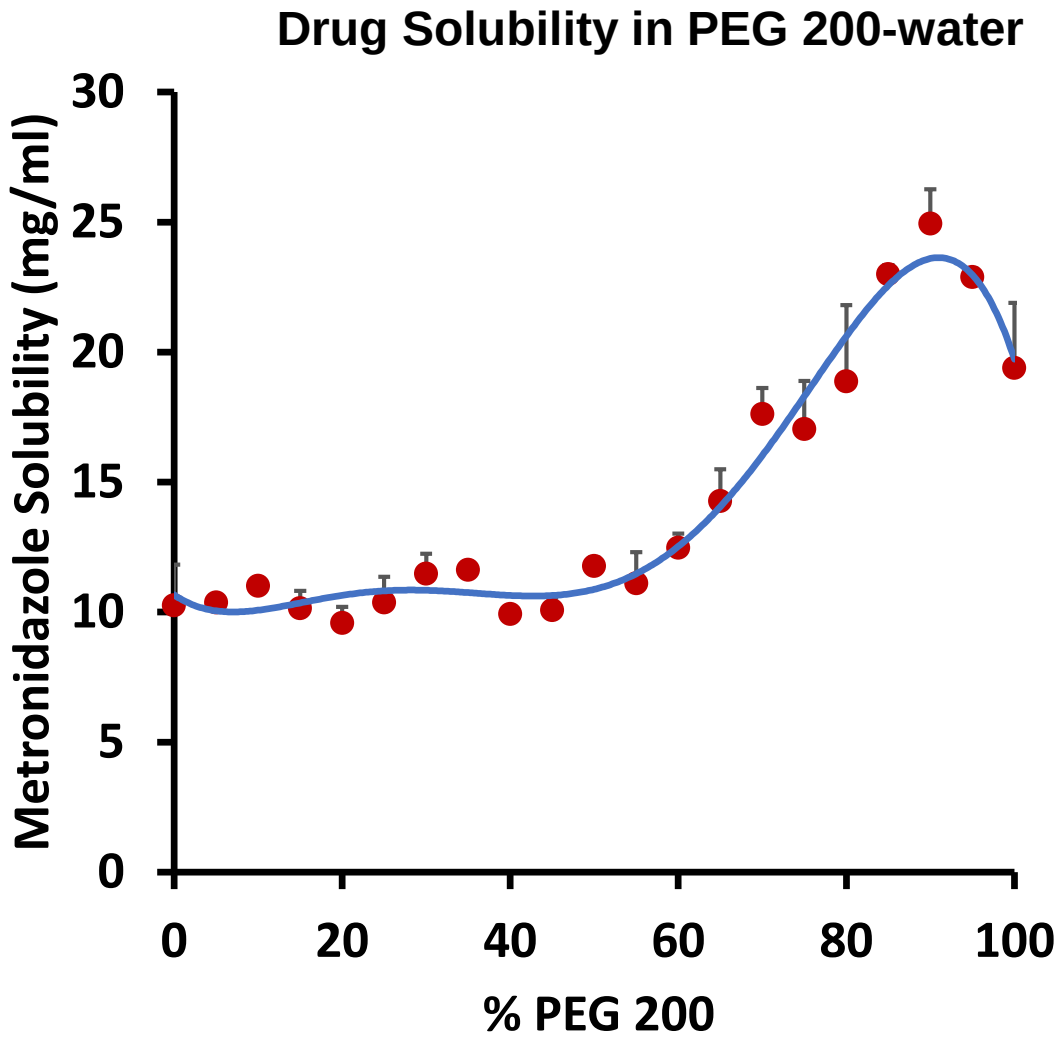


Water
BP:100°C



PEG 200
BP:150-160°C

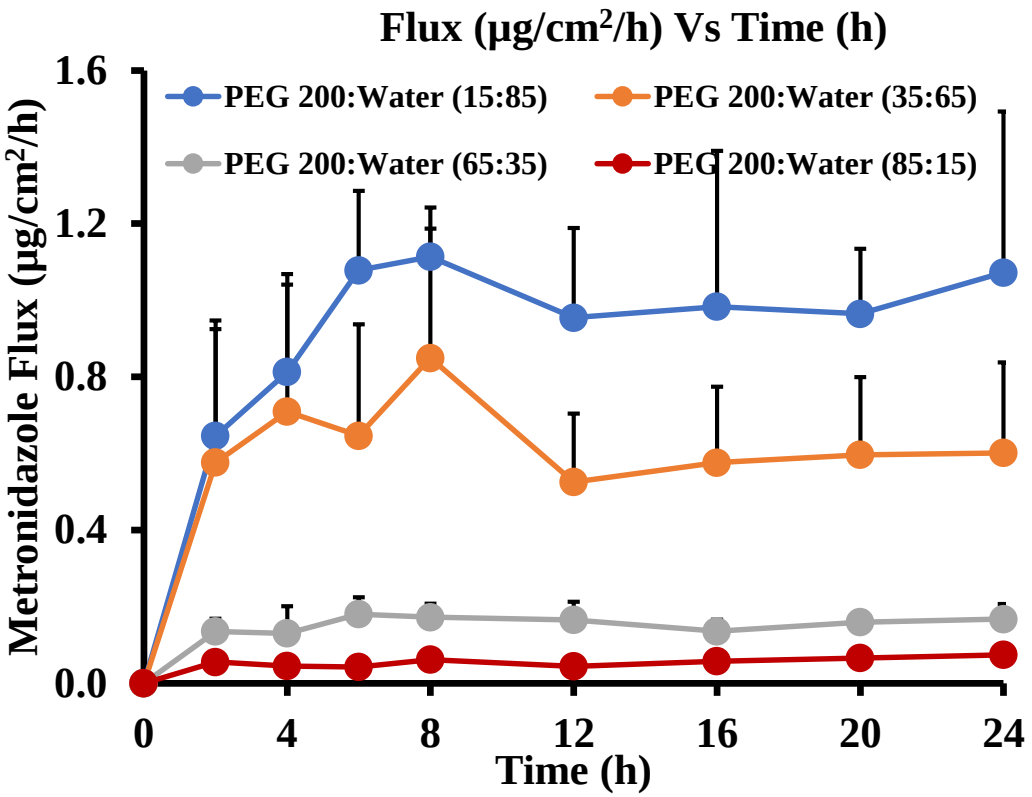
Solubility of metronidazole (mg/mL)	
Water	PEG 200
10.26 ± 1.56	19.39 ± 2.50



Effect of viscosity on drug permeation for binary solvent systems

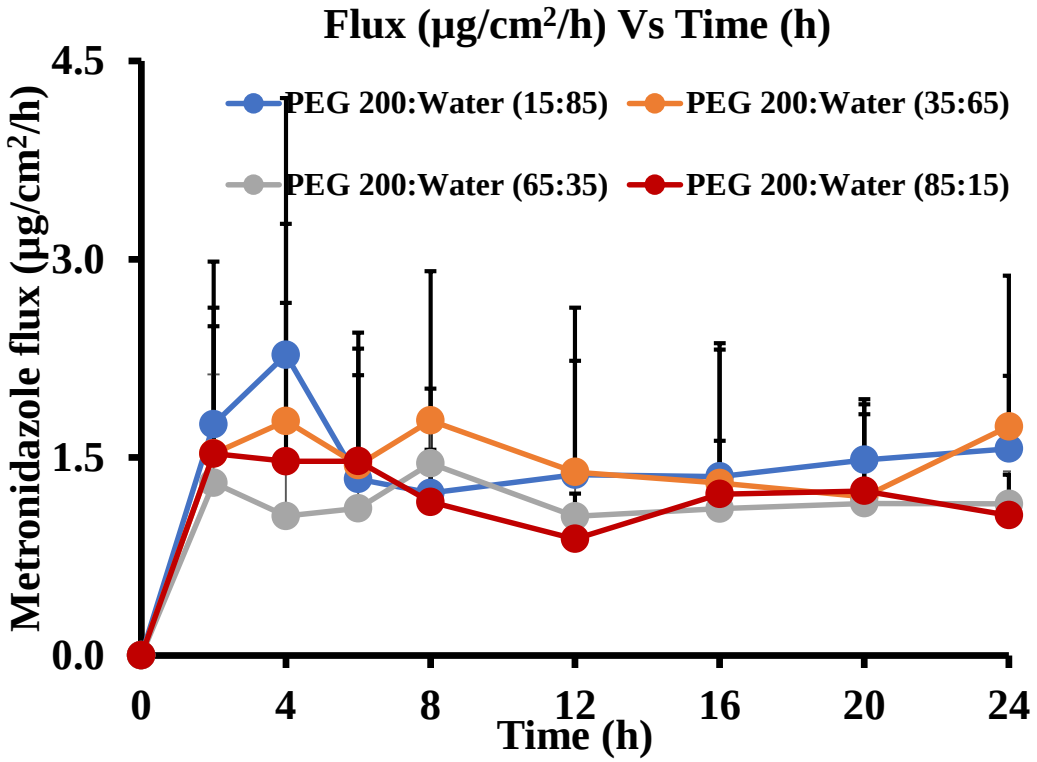
PEG 200:Water	Viscosity (mPa.S)	Solubility (mg/ml)	Conc (mg/ml)	Degree of Saturation (α)
15:85	1.09	10.15 ± 0.67	7.50	0.74
35:65	1.49	11.62 ± 0.31		0.65
65:35	8.55	14.27 ± 1.22		0.53
85:15	17.55	22.99 ± 0.36		0.33
15:85	1.09	10.15 ± 0.67	5.08	0.50
35:65	1.49	11.62 ± 0.31	5.81	
65:35	8.55	14.27 ± 1.22	7.14	
85:15	17.55	22.99 ± 0.36	11.50	

Effect of viscosity on drug permeation for binary solvent systems



Degree of saturation: varied, Viscosity : varied

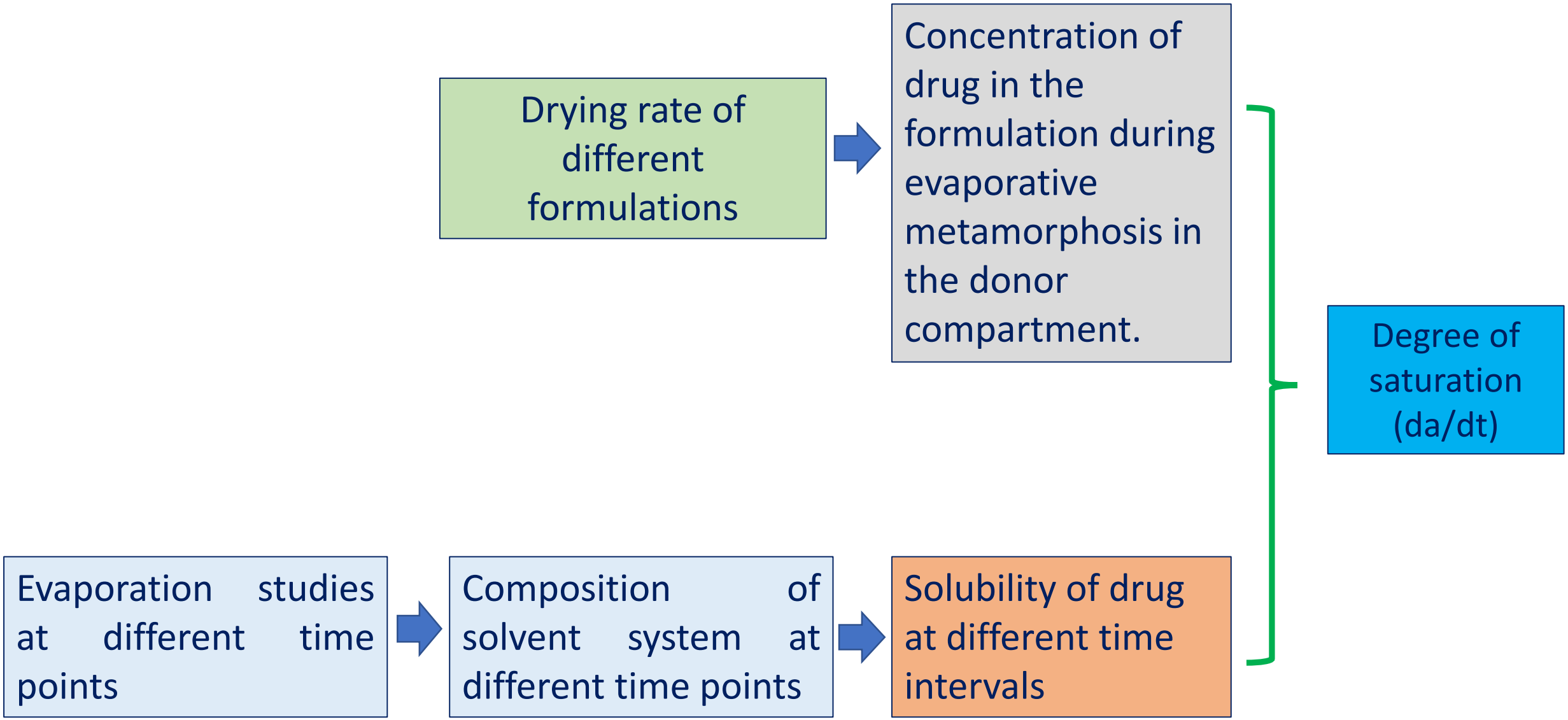
Flux increased with increase in degree of saturation
Flux increased with decrease in viscosity



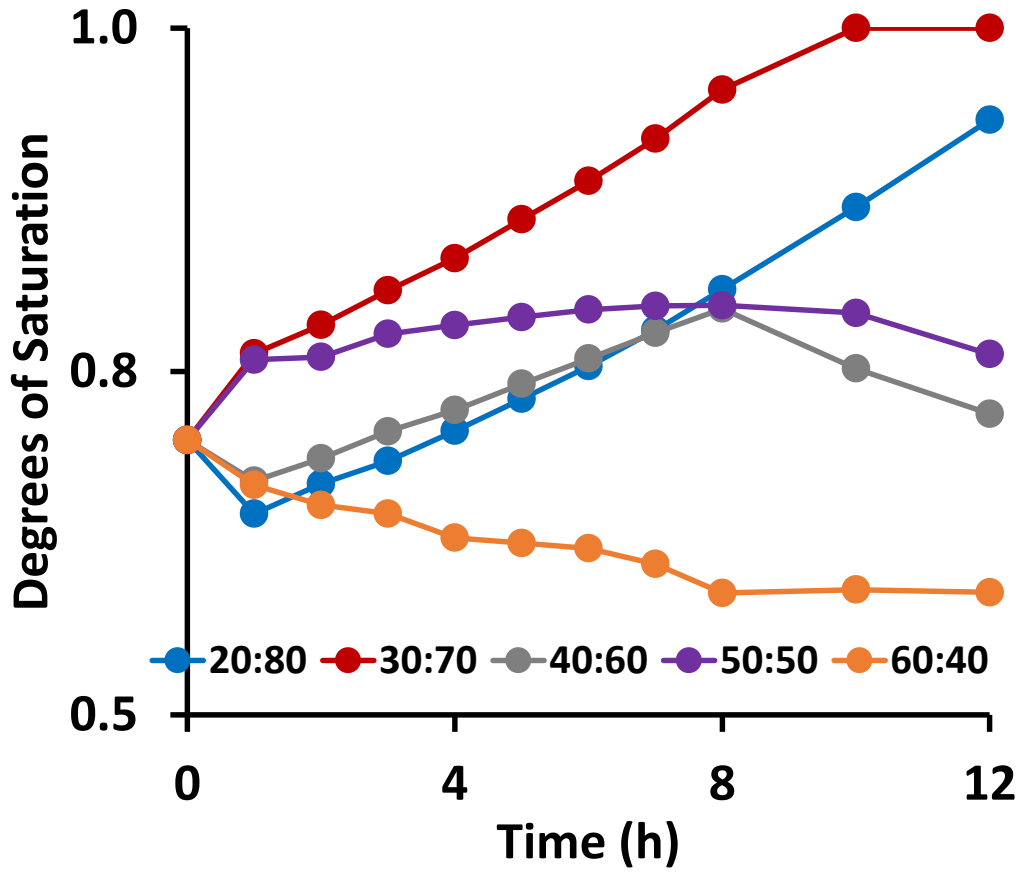
Degree of saturation: constant, Viscosity : varied

Flux remained constant with same degree of saturation solutions though viscosity varied

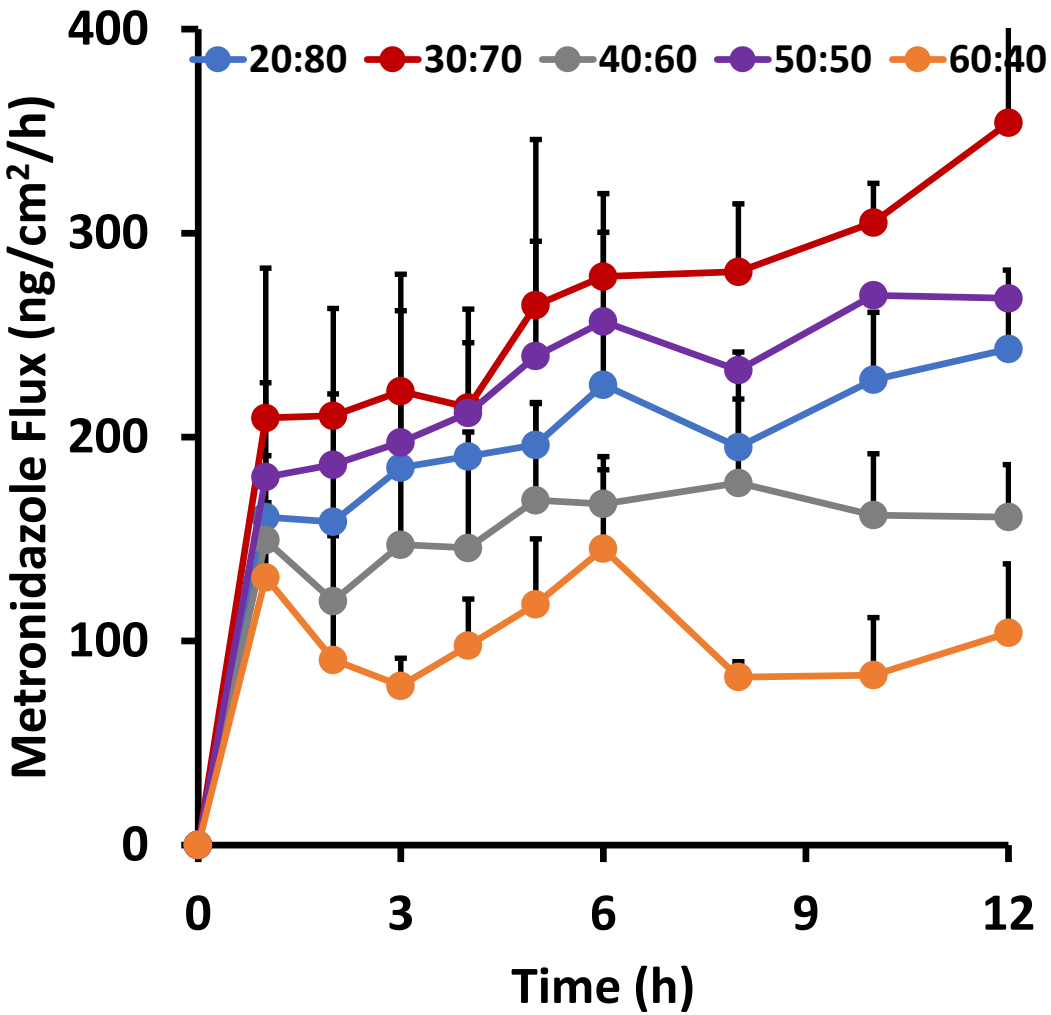
Impact of changes in the degree of saturation during metamorphosis of topical formulations on drug permeation



Impact of changes in the degree of saturation during metamorphosis of topical formulations on drug permeation

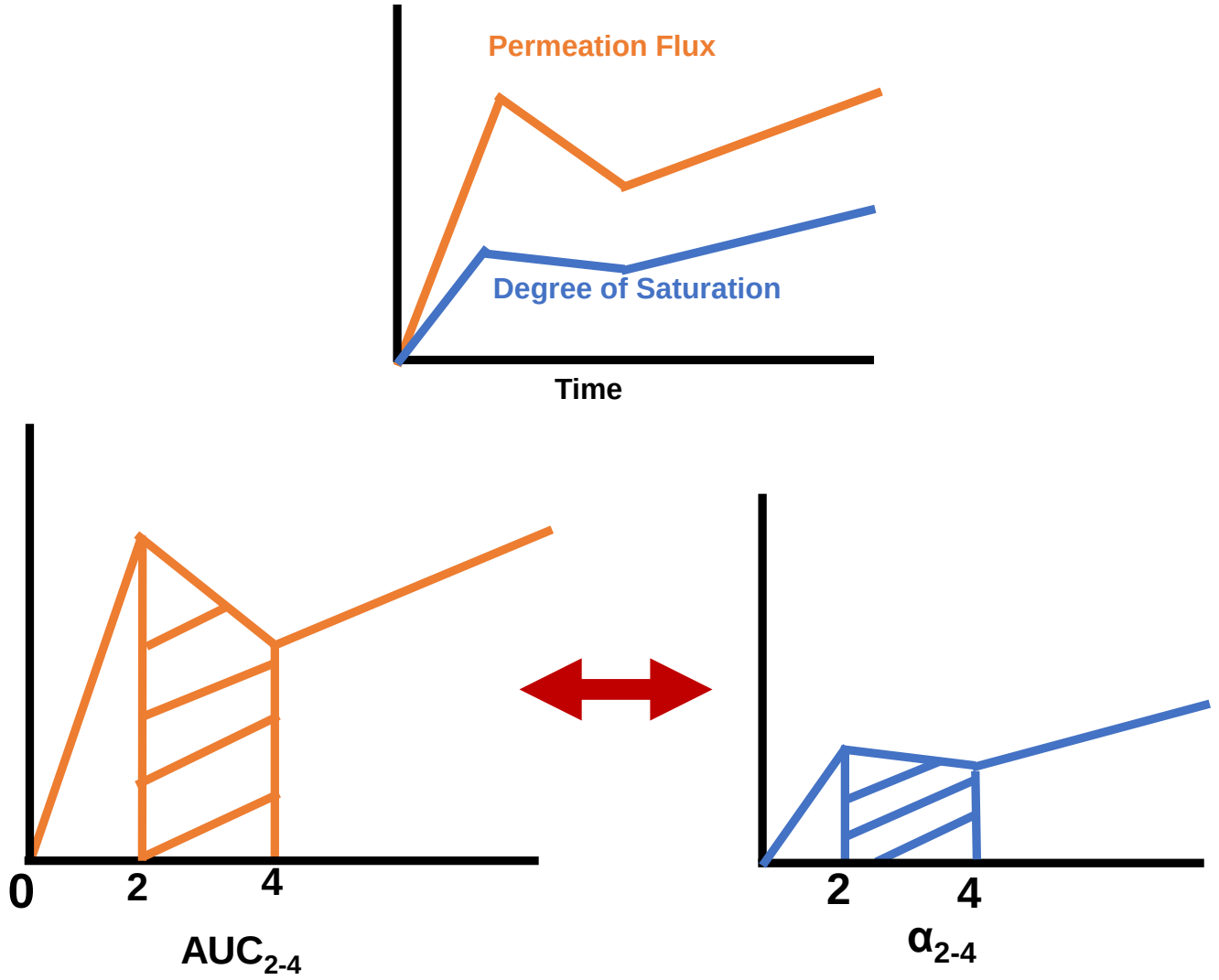


Degree of saturation of metronidazole during evaporative metamorphosis

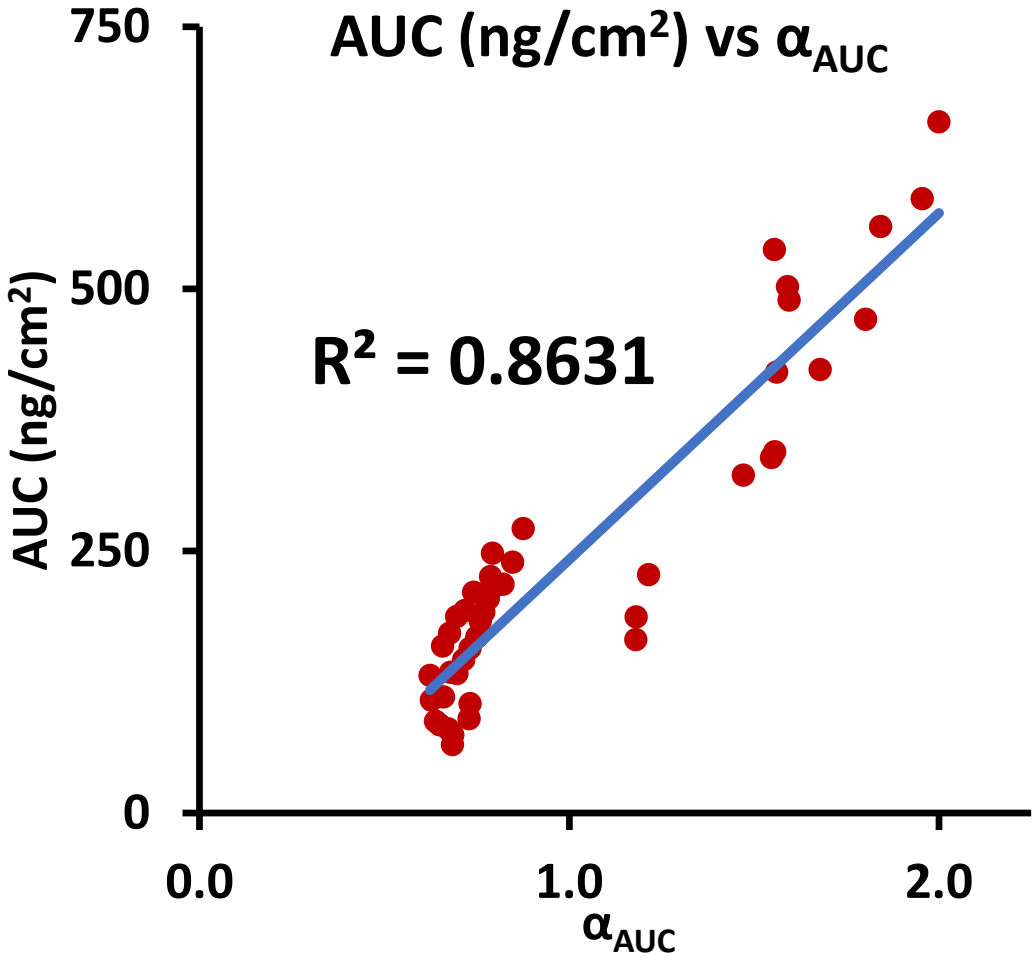


Finite dose IVPT

Segment to Segment Correlation (Finite dose IVPT)

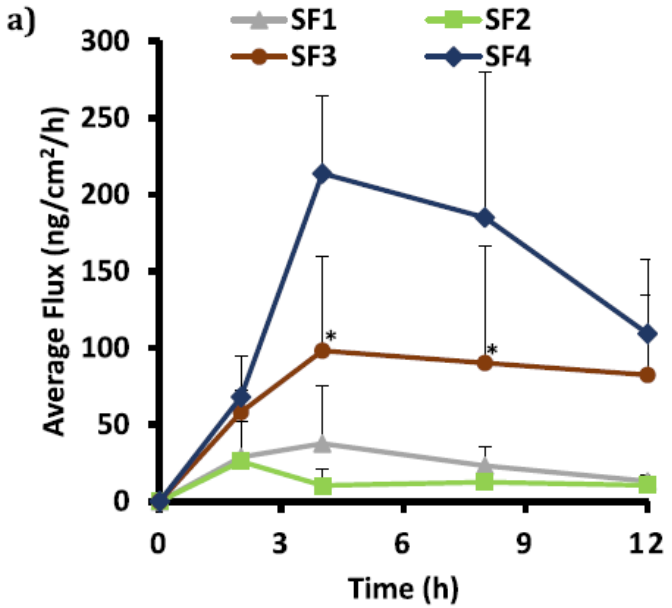


PEG 200-water solutions

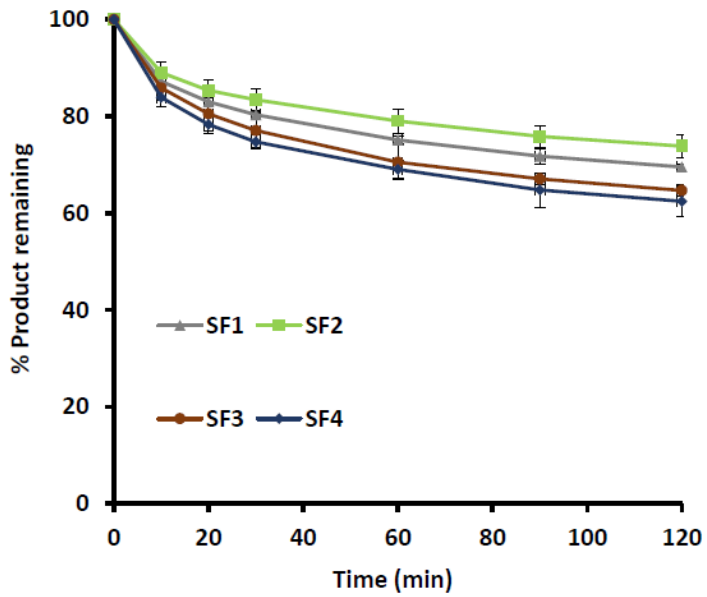


Effect of surfactant on quality and performance attributes

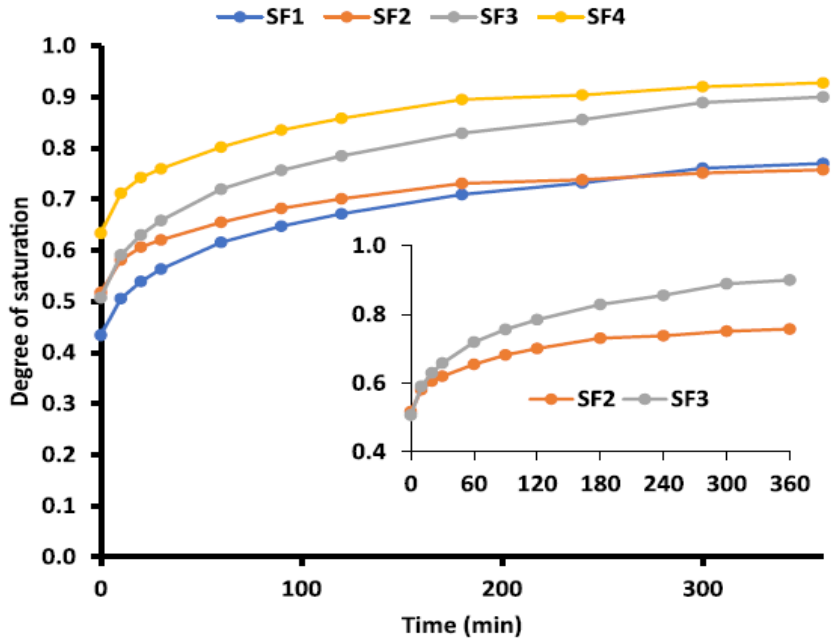
- Four creams with metronidazole as model drug
- Varied Tween concentration (± 5%w/w)
- Similar in the all the critical quality attributes – pH, water activity, viscosity, globule size, in vitro drug release rate



IVPT



Drying rate



Time course of degree of saturation

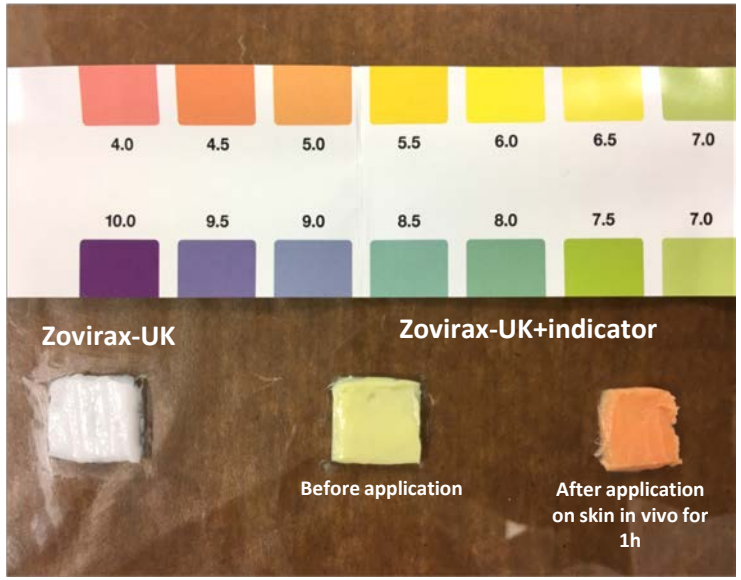
Sharma, Purnendu Kumar, A. Panda, S. Parajuli, RM Badani Prado, S. Kundu, M. A. Repka, E. Ureña-Benavides, and S. Narasimha Murthy. "Effect of surfactant on quality and performance attributes of topical semisolids." *International Journal of Pharmaceutics* 596 (2021): 120210.

Ongoing Studies

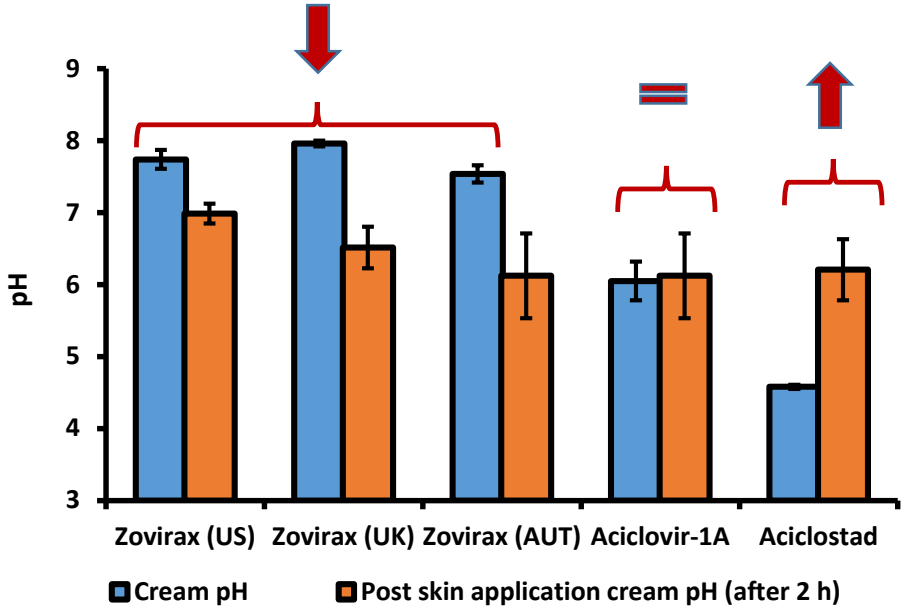
- **Complex formulations**
- **Gels using different drugs**
- **Improvise the methodology by determining**

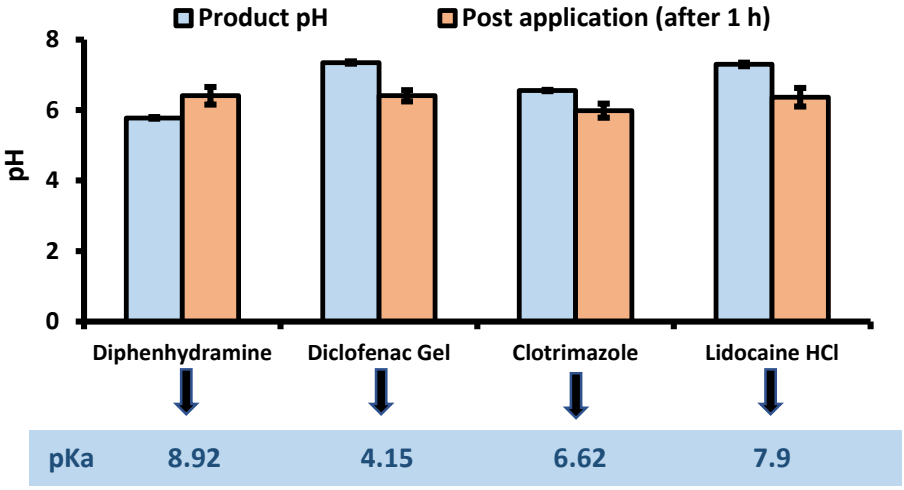
- The drug concentrations simultaneously from the donor chamber
- Analyzing the composition of formulation by direct analysis

pH could change after application on the skin



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





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)

Conclusion

- It is important to investigate the Critical Quality Attributes of topical formulation to understand the performance
- Critical quality attributes will not remain the same due to metamorphosis
- Tools to access the time course in change in different quality attributes
- In case of metronidazole products, the performance was dependent on the degree of saturation
- Further studies need to be performed if this work can be extended to complex products for proving equivalence between 2 products

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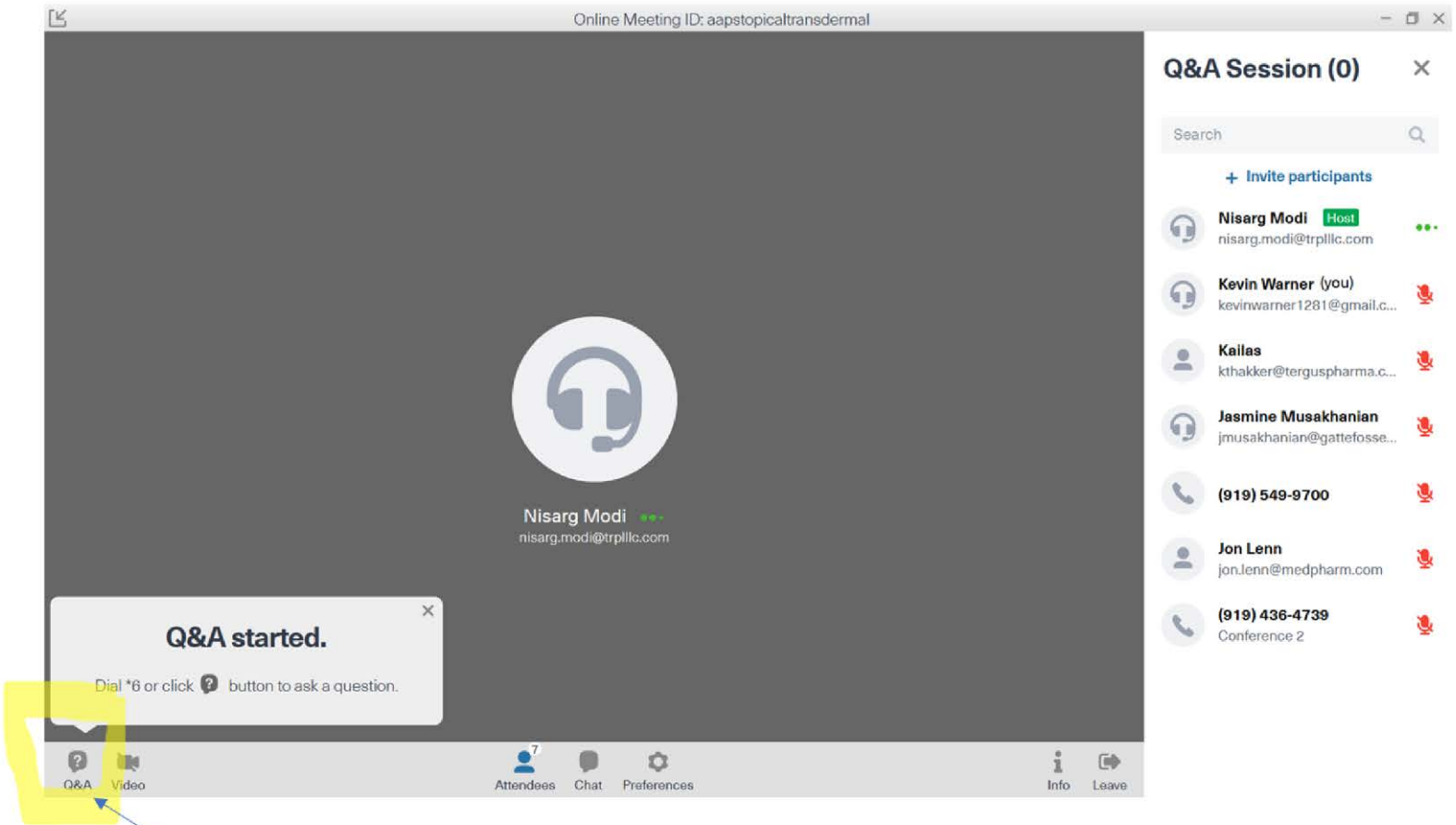
How to Ask A Question…



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