

Impact of Fractional Solubility on Drug Permeation from Topical Formulations

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Session Description and Objectives

Description

- Fractional solubility is used as a measure of the thermodynamic activity, one of the main driving forces that impact the drug release from the topical formulations, and thereby the amount of drug that is available for permeation. The presentation will discuss theoretical concepts related to the influence of fractional solubility on permeation of drug from topical formulations and empirical data that illustrates the impact of changes in the fractional solubility during metamorphosis, on drug permeation.

Objectives

- Learn about the approaches that can be used to evaluate the fractional solubility during metamorphosis.
- Understand the influence of fractional solubility on drug permeation from topical formulations.
- Understand the impact of changes in the fractional solubility during metamorphosis of topical formulations on drug permeation.

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Drug Permeation through Skin and Thermodynamic Activity

$$\text{Percutaneous Flux, } J = \frac{A \cdot D}{\gamma \cdot h}$$

A – Thermodynamic activity

D – diffusivity

γ – Eff. activity co-efficient in the membrane

h – Thickness of the membrane

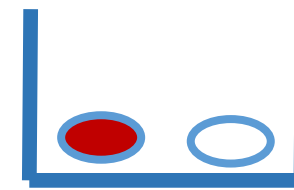
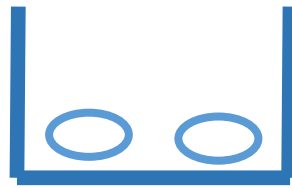
Thermodynamic Activity: Ability of drug to escape from the formulation

$$\text{Fractional Solubility, } \alpha = \frac{\text{Conc. of Solute}}{\text{Solubility of solute in the solvent}}$$

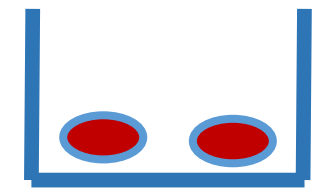
Solvent A

Solubility:

2 parts of solute in 100 parts of solvent



Conc. – 1%

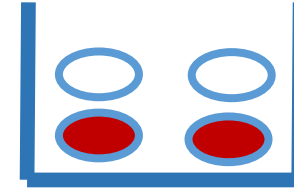
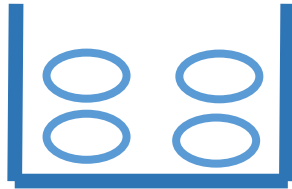


Conc. – 2%

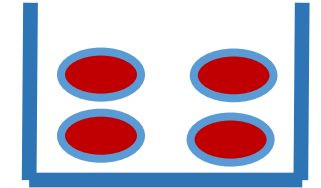
Solvent B

Solubility:

4 parts of solute in 100 parts of solvent



Conc. – 2%

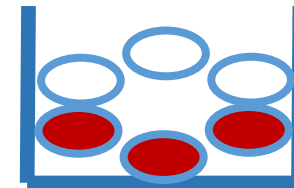
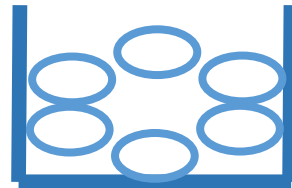


Conc. – 4%

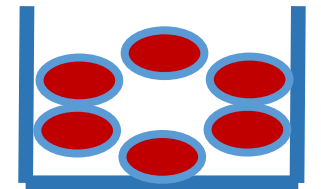
Solvent C

Solubility:

6 parts of solute in 100 parts of solvent



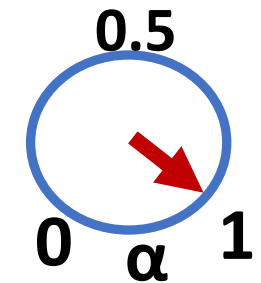
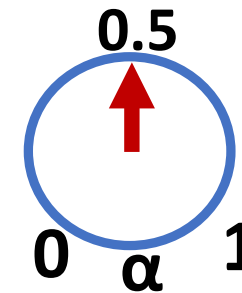
Conc. – 3%



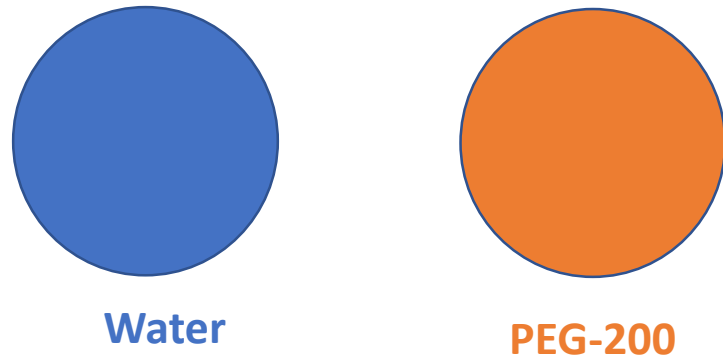
Conc. – 6%

Saturation Solubility

Fractional Solubility



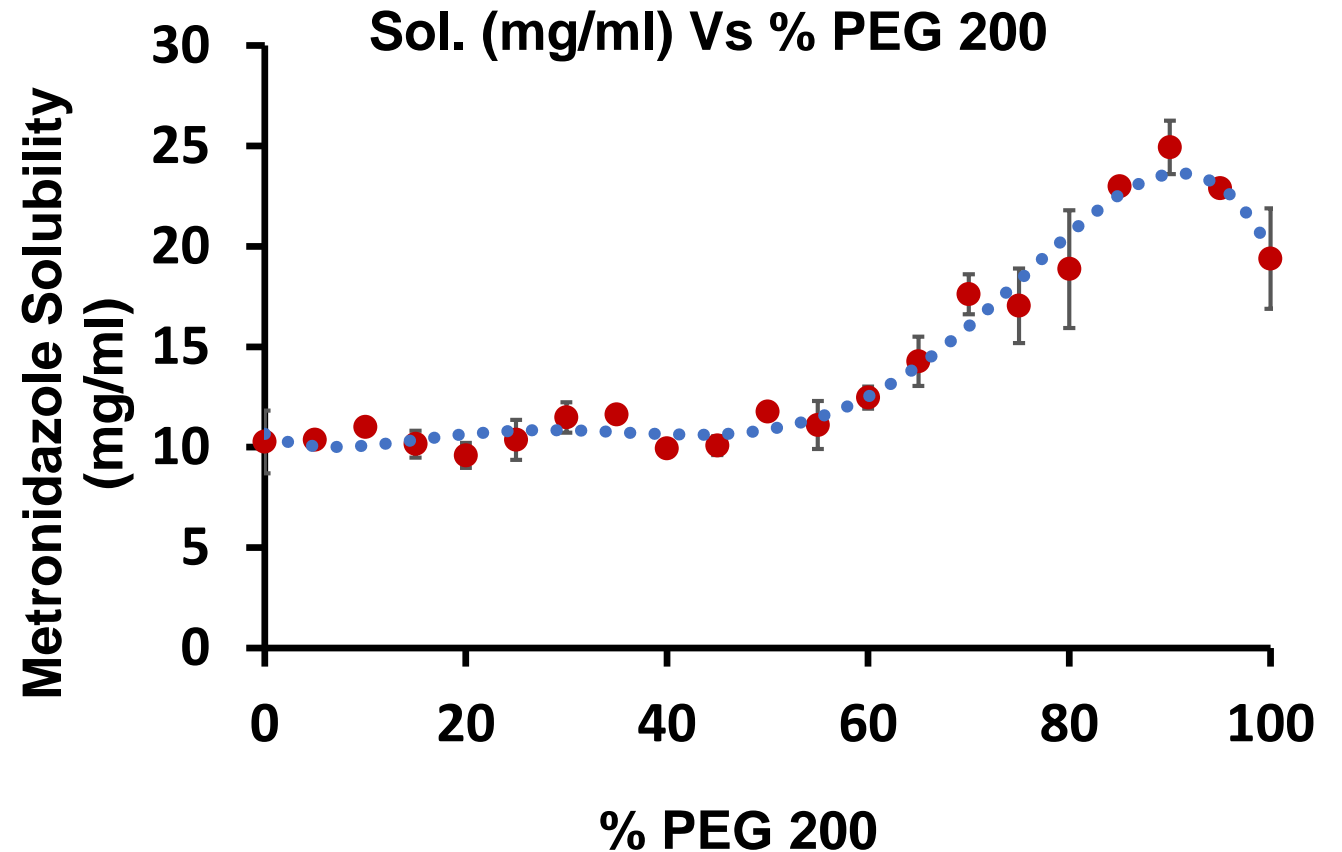
Influence of Fractional Solubility on Drug Permeation from Topical Formulations



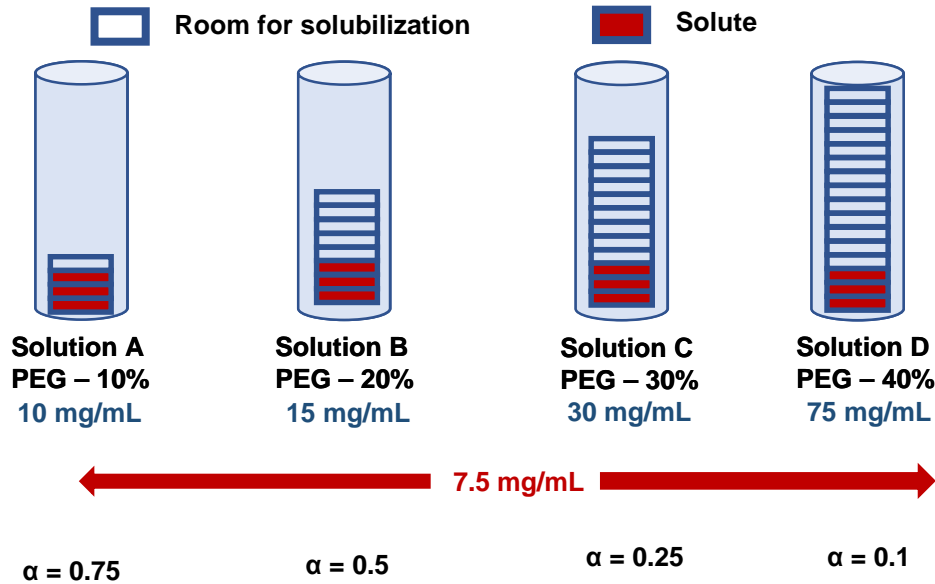
Do not alter the barrier properties of skin

Model drug - Metronidazole

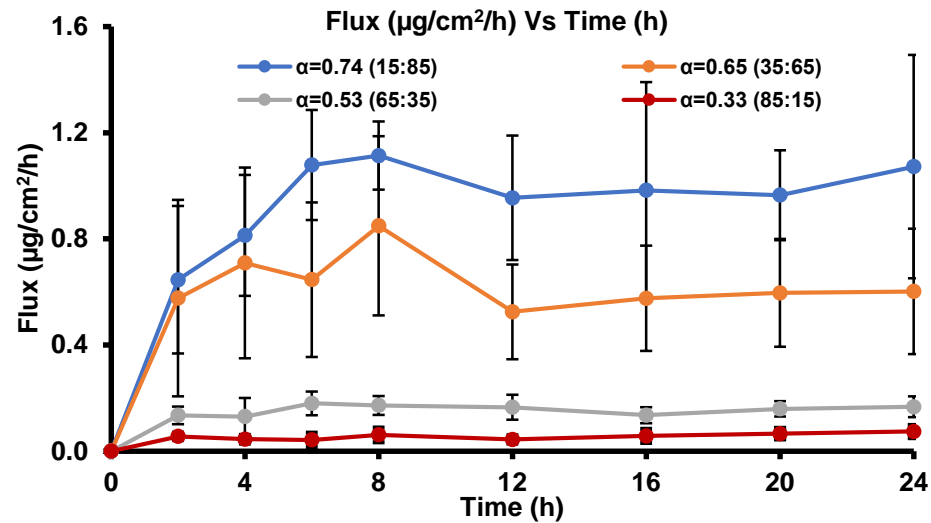
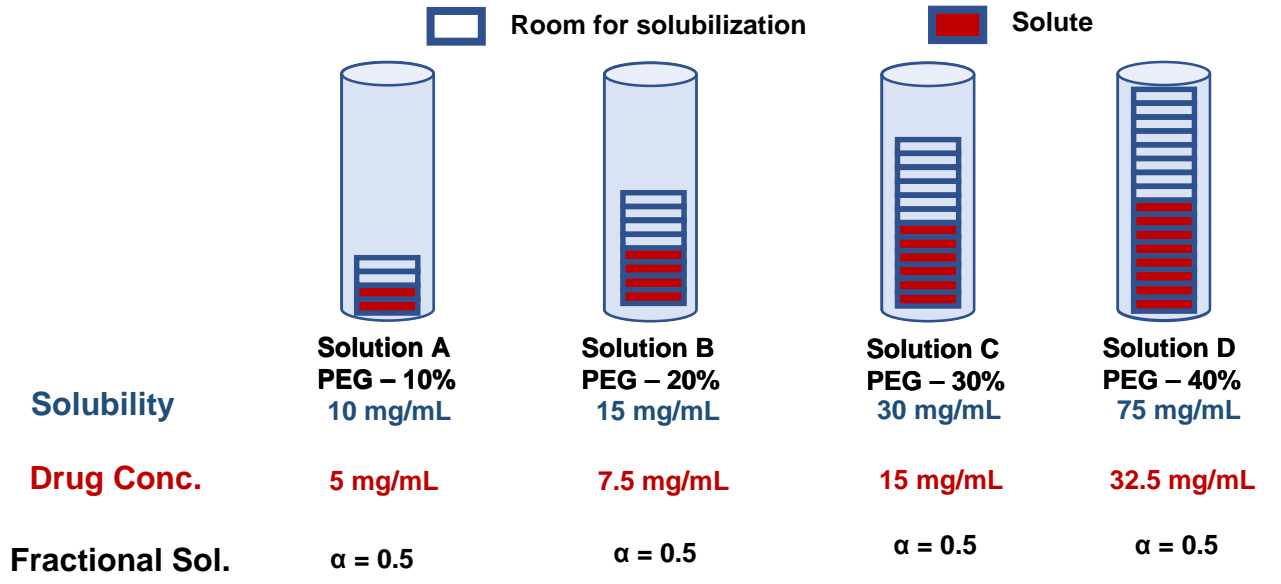
Solubility (Shake Flask method)



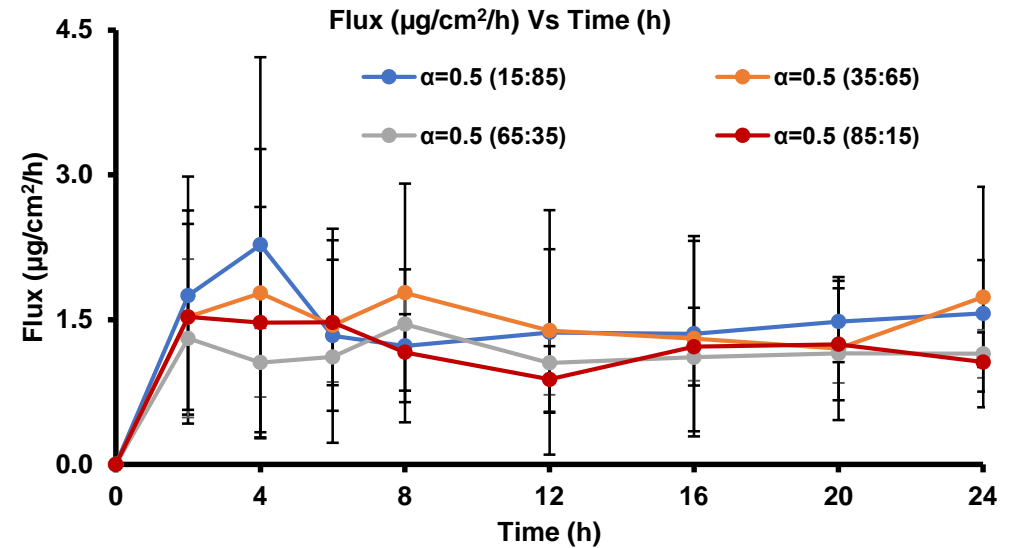
Different Fractional Solubility Solutions



Same Fractional Solubility Solutions



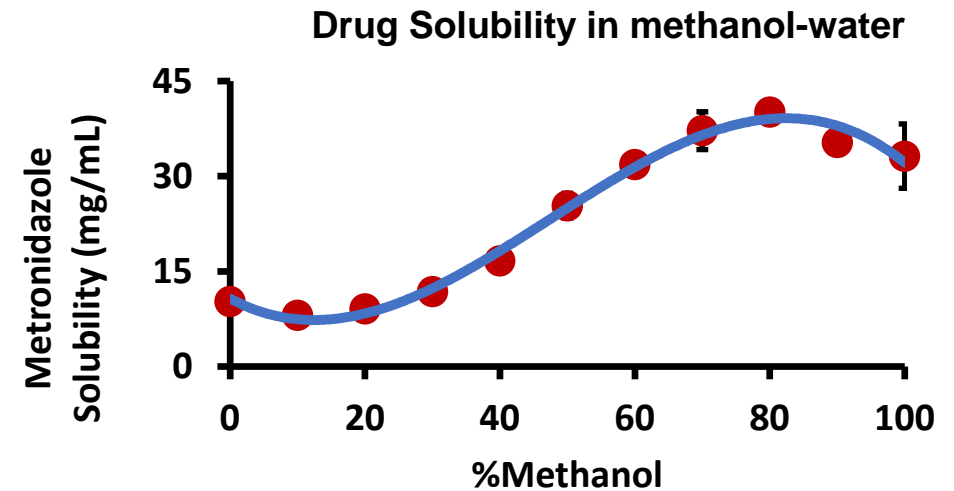
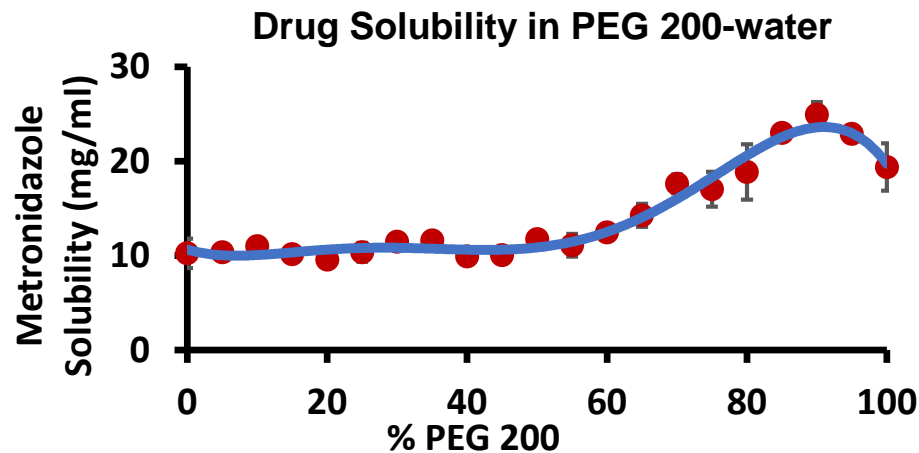
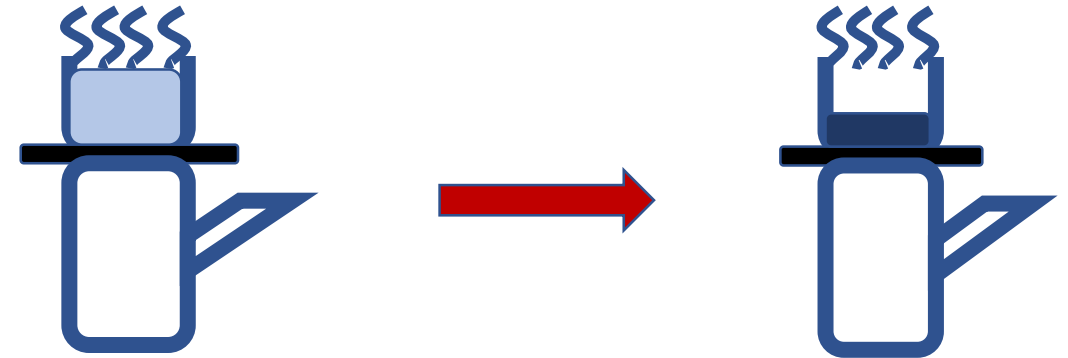
IVPT



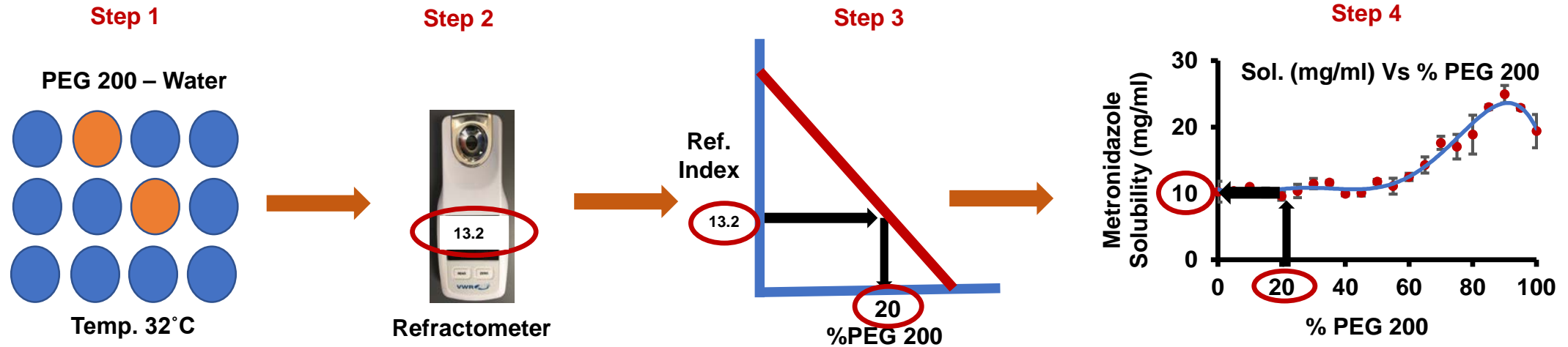
Impact of changes in the fractional solubility during metamorphosis of topical formulations on drug permeation

Evaporation of solvent from the formulation at the site of application leads to

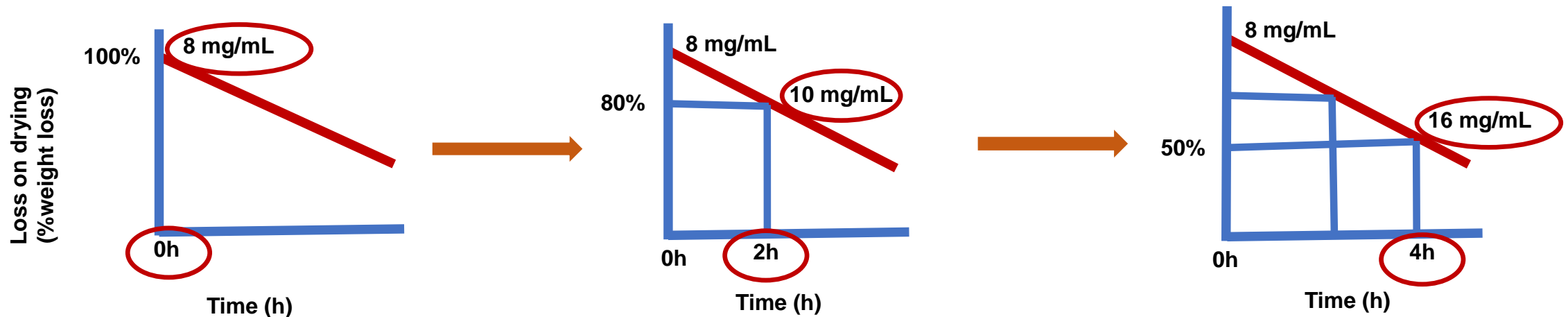
1. Change in drug concentration
2. Change in formulation composition
3. Change in drug solubility
4. Change in viscosity
5. Change in microstructure



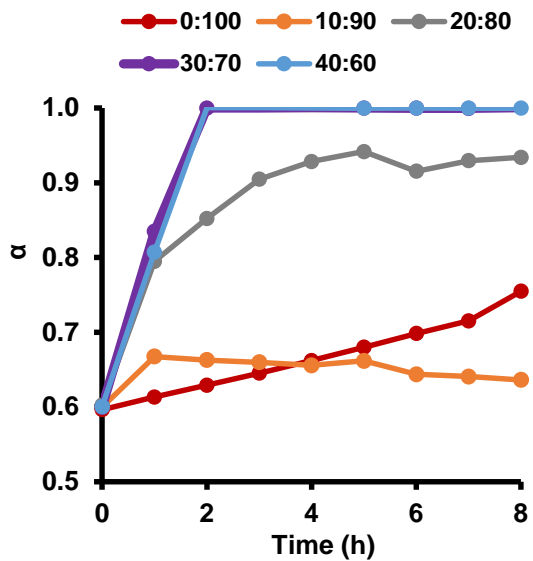
Determination of saturation solubility at each time interval



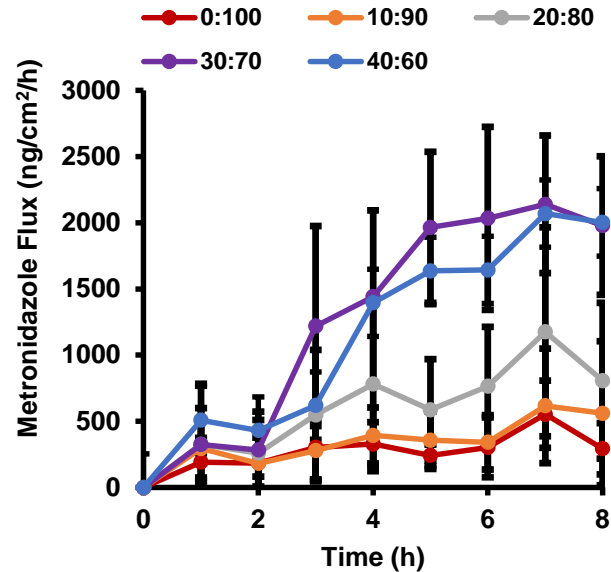
Determination of drug concentration in the donor compartment at each time interval



PEG-Water

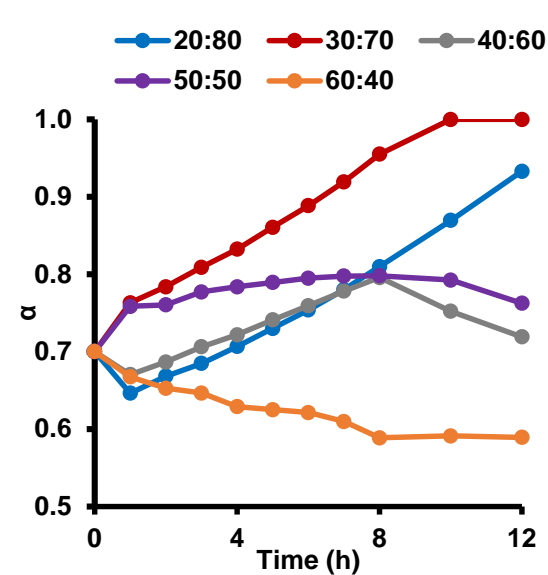


α-time profile

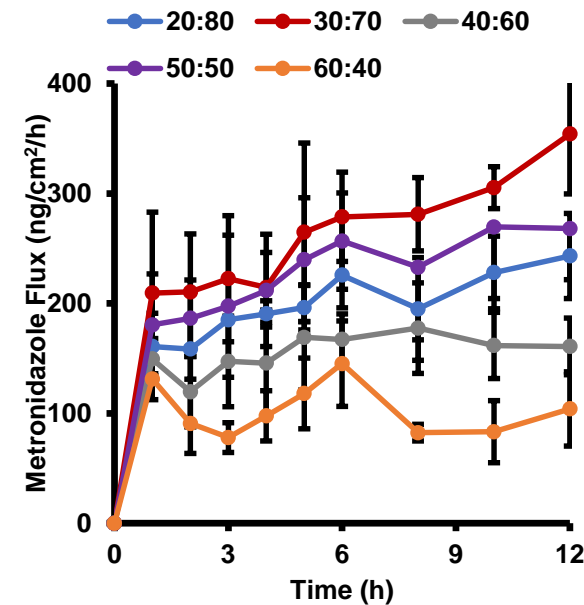


Flux-time profile

Methanol-Water

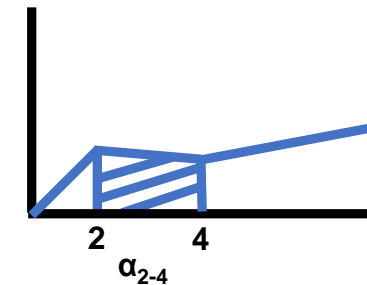
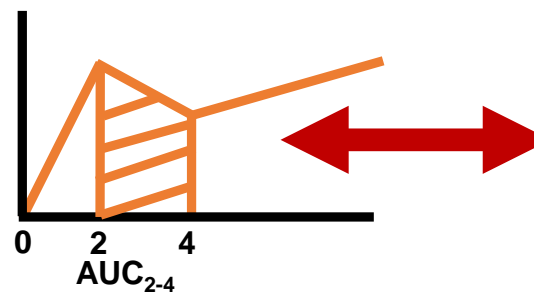
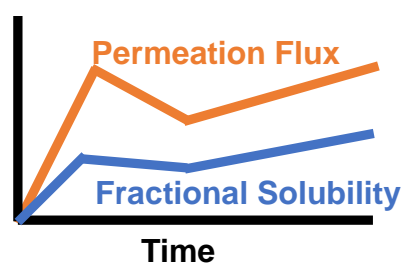


α-time profile

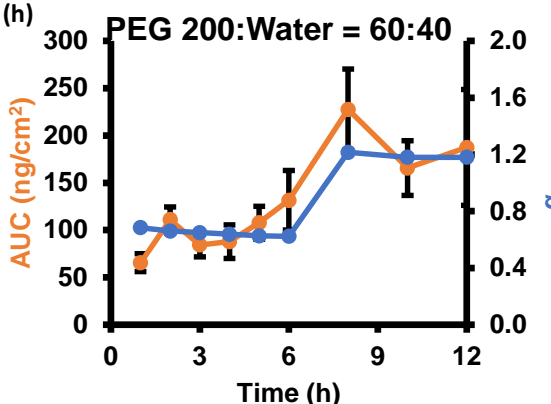
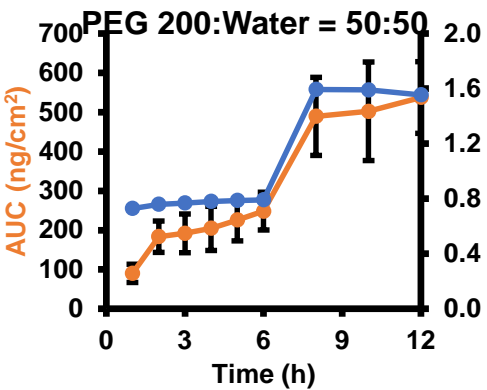
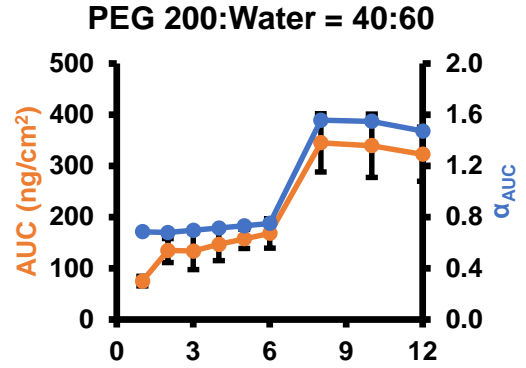
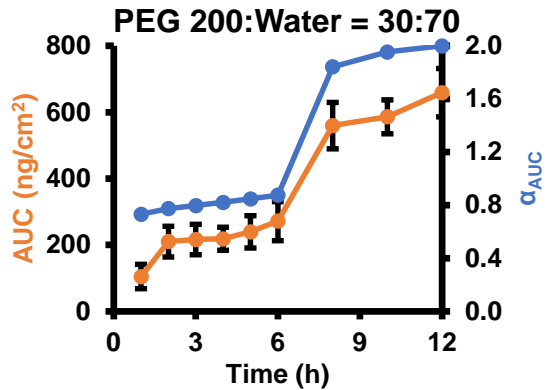
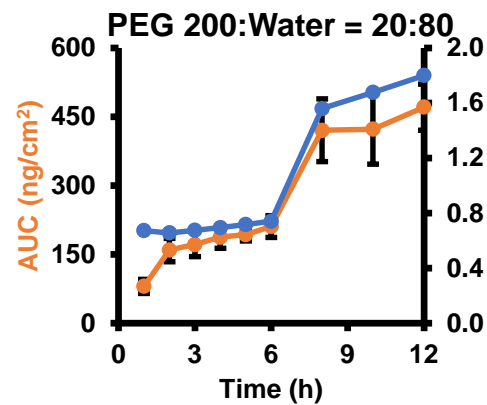


Flux-time profile

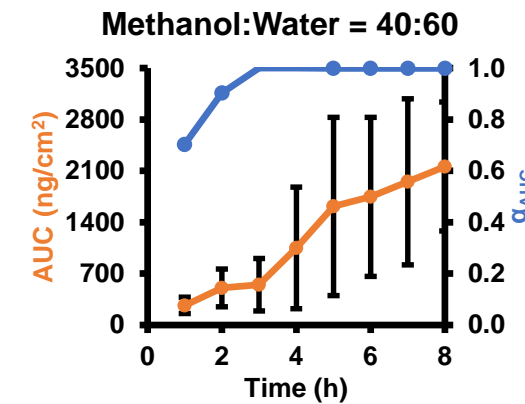
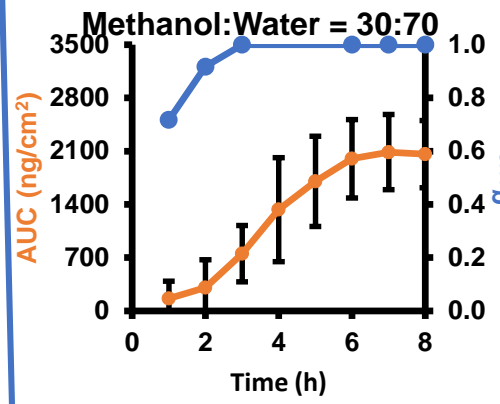
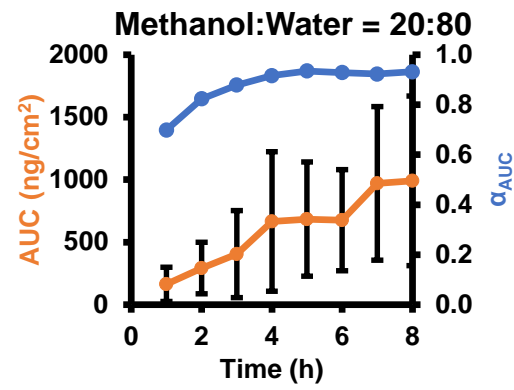
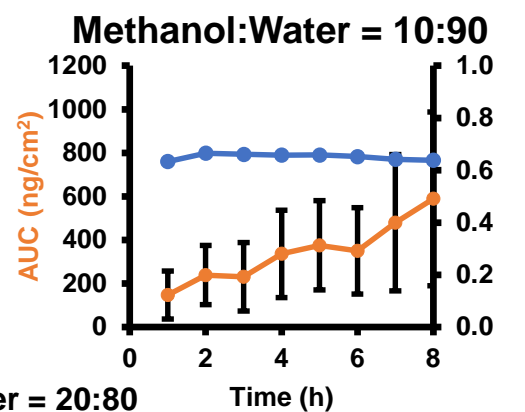
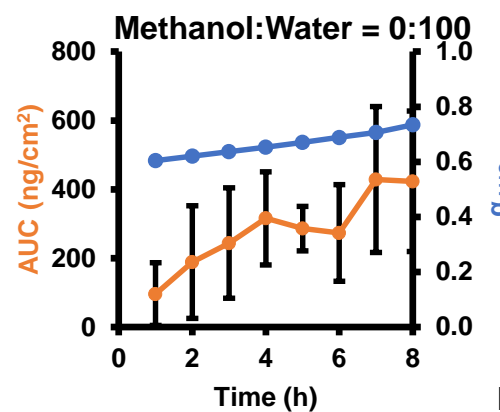
Segment-Segment Correlation of Finite Dose Data



PEG-Water



Methanol-Water



Conclusion

- Fractional Solubility plays role in controlling the permeation of metronidazole from topical formulations into and across skin.
- BA of metronidazole appeared to correlate with fractional solubility (α) during the metamorphosis of a formulation. Based on the limited data, it appeared that this correlation may be somewhat stronger in the case of the PEG 200-water systems vs. the methanol-water systems.
- Additional studies are warranted to understand the mechanistic basis for these observations

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- Dr. Ross Walenga



The views expressed in the presentation are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by FDA/HHS, or the U.S. Government.

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