

# Phytonadione – Self-Assembled System & Thermodynamics Systems

*SBIA 2023—Advancing Generic Drug Development: Translating Science to Approval*  
Day 1, Session 4: **Noteworthy Complex Generic Drug Approvals: Multiphase Systems**

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# Learning Objectives

- “Recognize the difference in macro-emulsion, nano-emulsion, and *microemulsion* properties”
- “Identify key aspects of manufacturing macro-, nano-, and micro-emulsion formulations”
- “Describe the difference between thermodynamically and kinetically stable systems”

# Phytonadione Injectable Formulations



Each milliliter contains:

Phytonadione .....	2 mg or 10 mg
Inactive ingredients:	
Polyoxyethylated fatty acid derivative.....	70 mg
Dextrose .....	37.5 mg
Water for Injection, q.s.....	1 mL
Added as preservative:	
Benzyl alcohol .....	9 mg

RLD

INJECTION  
**AquaMEPHYTON®**  
(PHYTONADIONE)  
Aqueous Colloidal Solution of Vitamin K<sub>1</sub>

RS

Contains 5 of NDC 0409-9158-31  
**VITAMIN K<sub>1</sub> Injection**  
Phytonadione Injectable Emulsion, USP  
**10 mg/mL**



# Dosage Form and Regulatory Pathways



Solution-Like?



Emulsion?

*Which BE Pathway?*

# A Tale of Two States

**Kinetically Stable**

100 $\mu$ m – 0.5 $\mu$ m

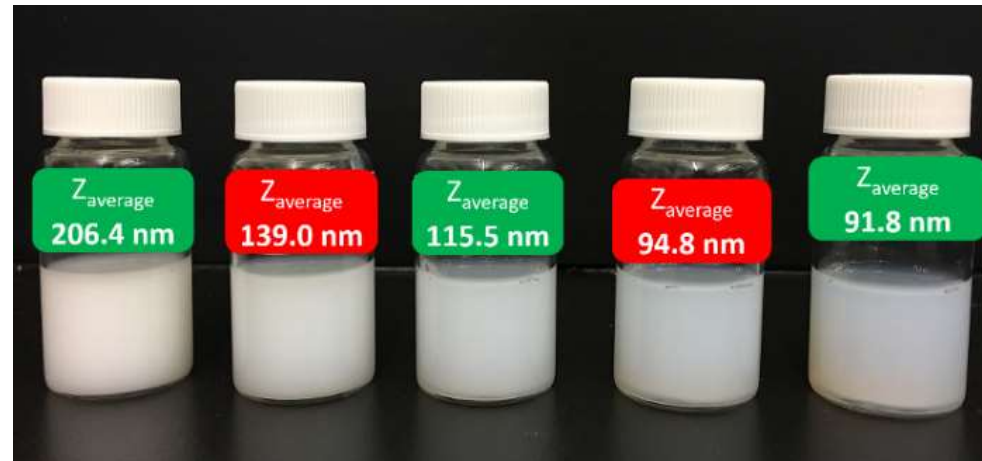
**Emulsion**  
(macro-emulsion)



**Thermodynamically Stable**

0.5 $\mu$ m – 0.1 $\mu$ m

**Nanoemulsion**



100nm – 10nm

**Microemulsion**



- **Kinetic vs Thermodynamic Stability**
- **Components (Composition)**
- **Process (Equipment & Conditions)**
- **Particle Size Distribution**
- **Appearance (Turbidity, etc.)**

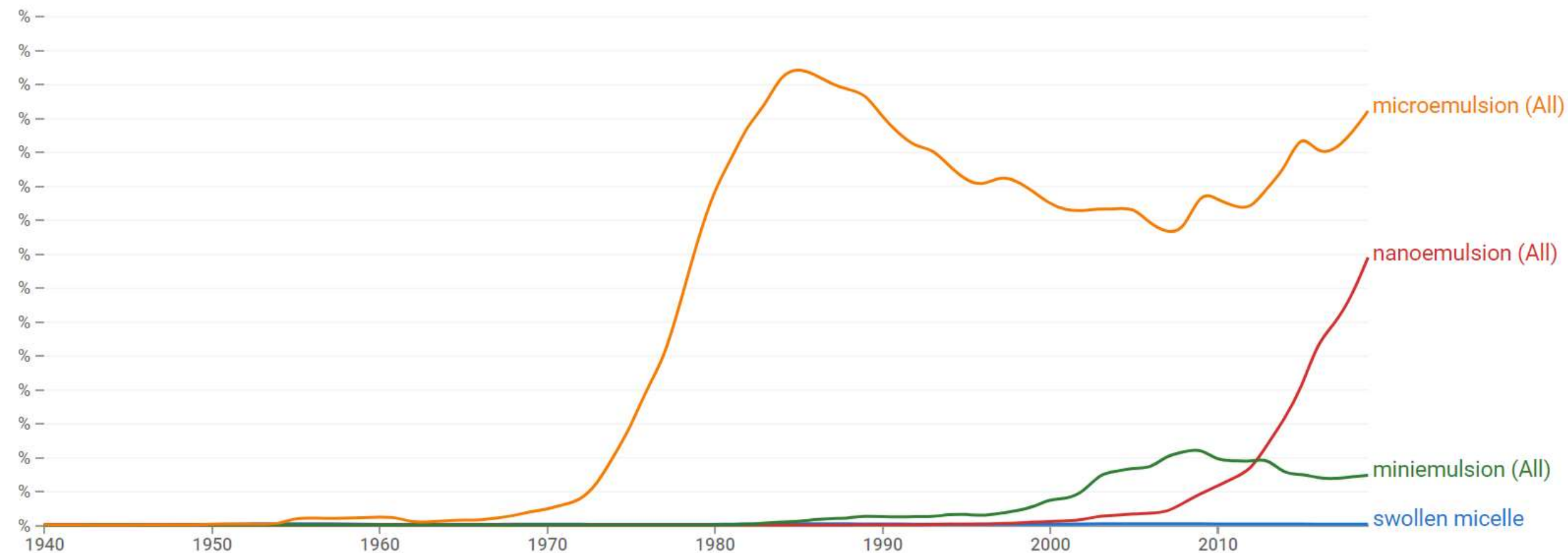
# Point of Interest: *Nomenclature*



Micellar systems or *microemulsions* are a special class of “dispersions” (transparent or translucent) which are better described as “swollen micelles.”

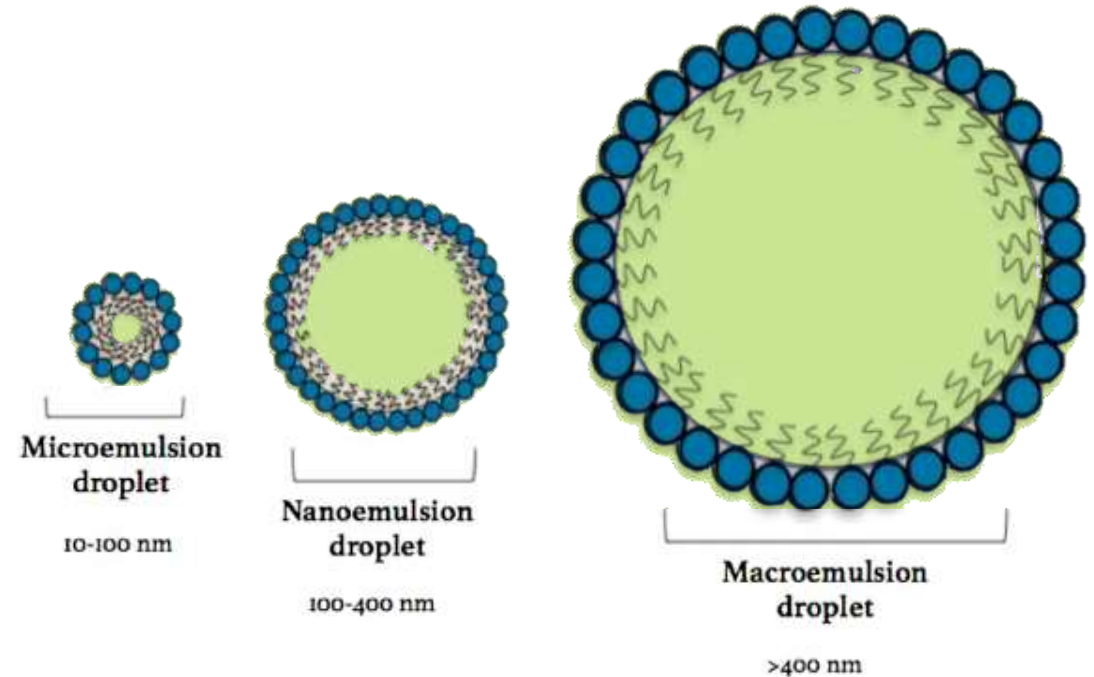
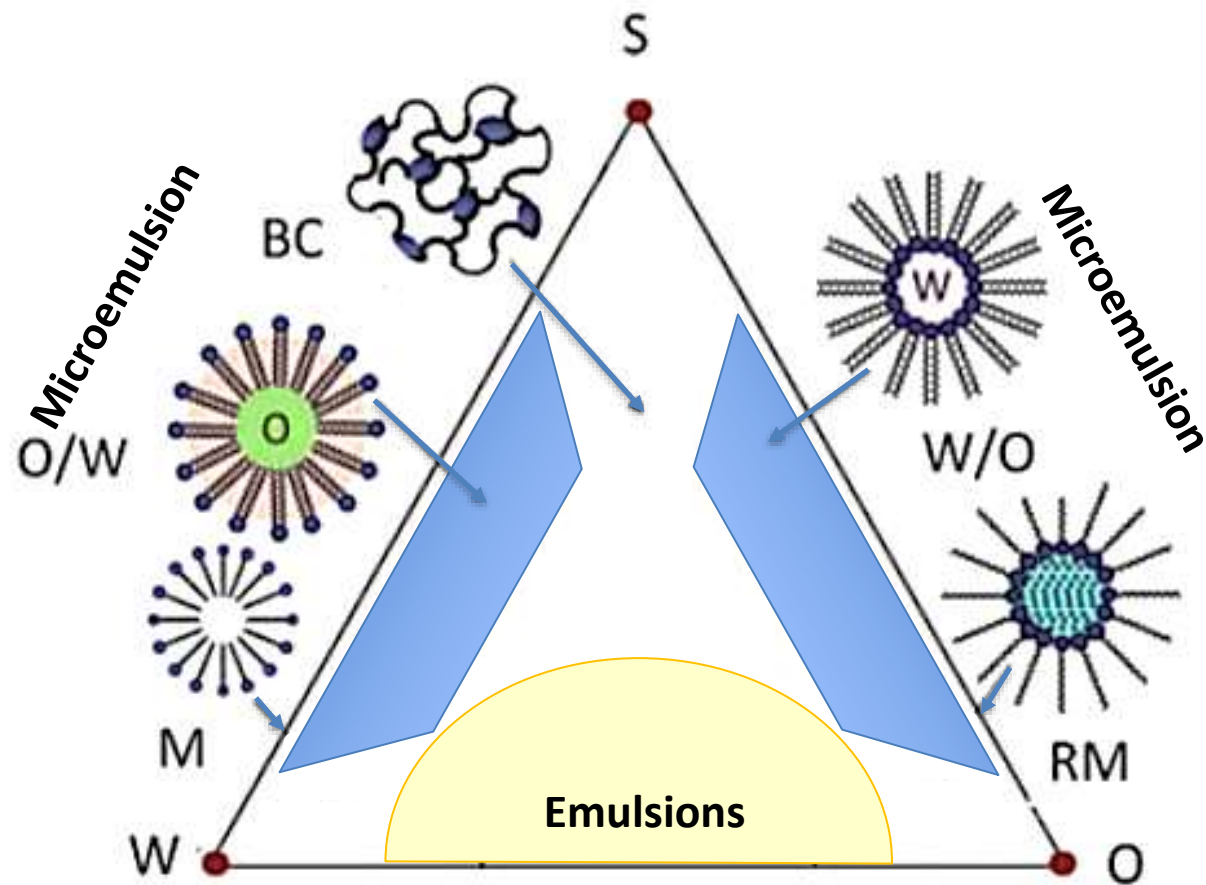
-Encyclopedia of Colloid and Interface Science

# Terminology Over Time





# Ternary Phase Diagrams and Surfactant Assembly



$$\Delta G = \gamma \Delta A - T \Delta S$$

Enthalpy

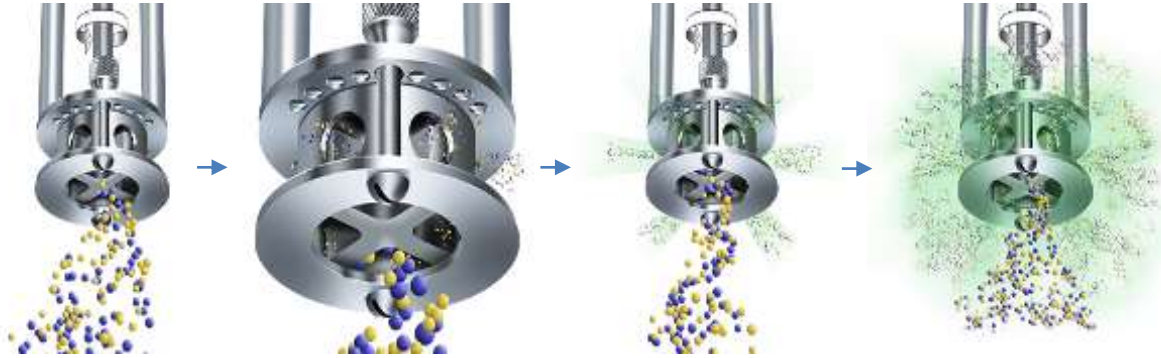
Entropy



# Nanoemulsion Manufacturing Process

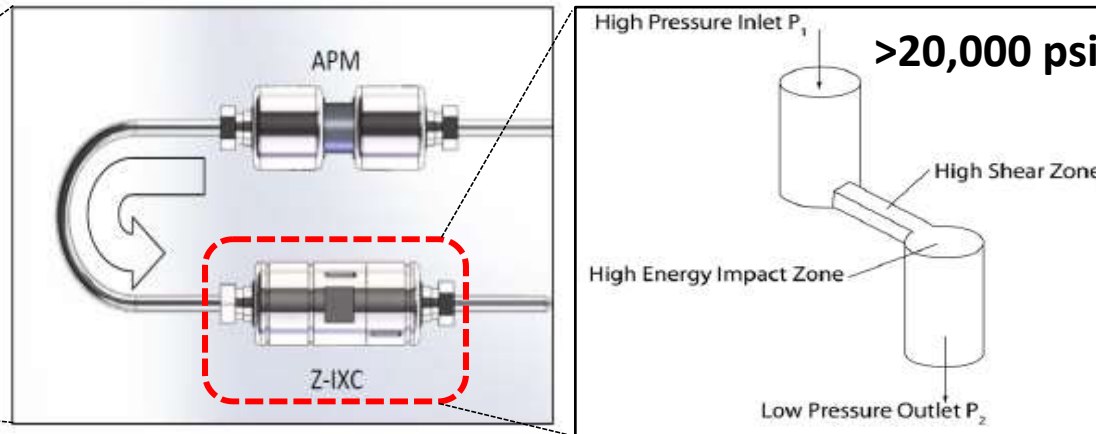
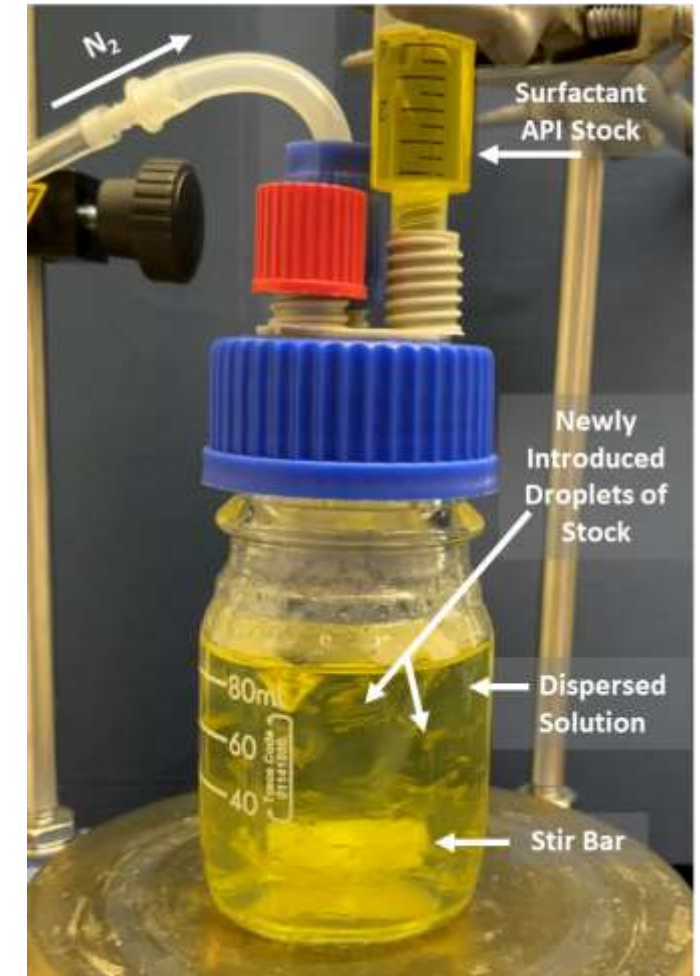


Kinetically Stable



5000 to 10000 rpm with high shear

Thermodynamically Stable



High energy inputs (e.g., high shear, high pressure) are required to disperse the globules, reaching sub-micron size range (nanoemulsion).

Microemulsion: Low energy input (ambient temp and low shear) <sup>9</sup>

# Mixing Independent Formation of Particles

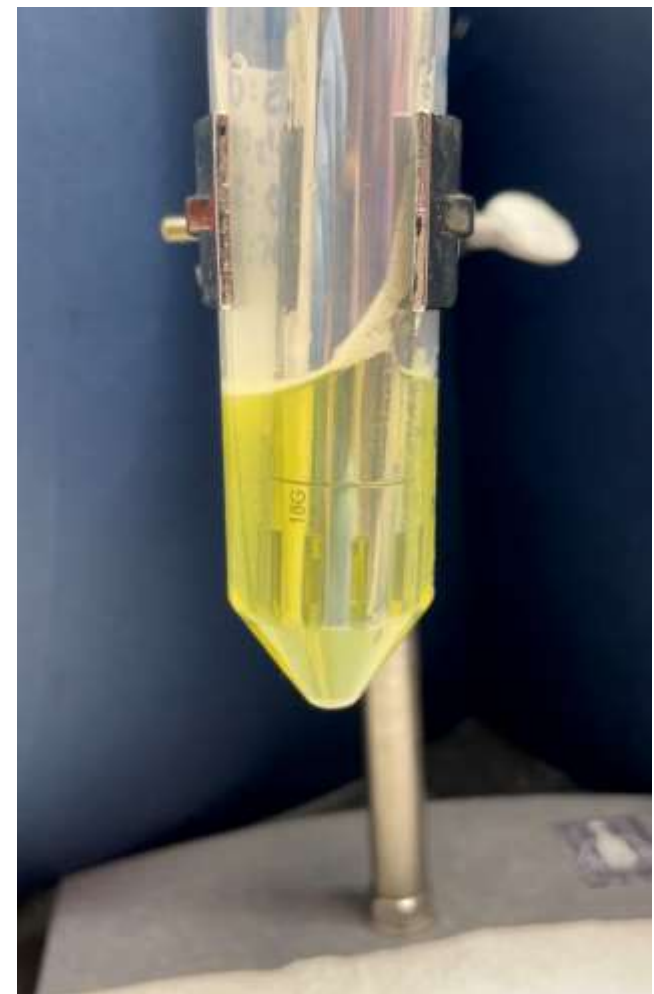


**Particle Size:**

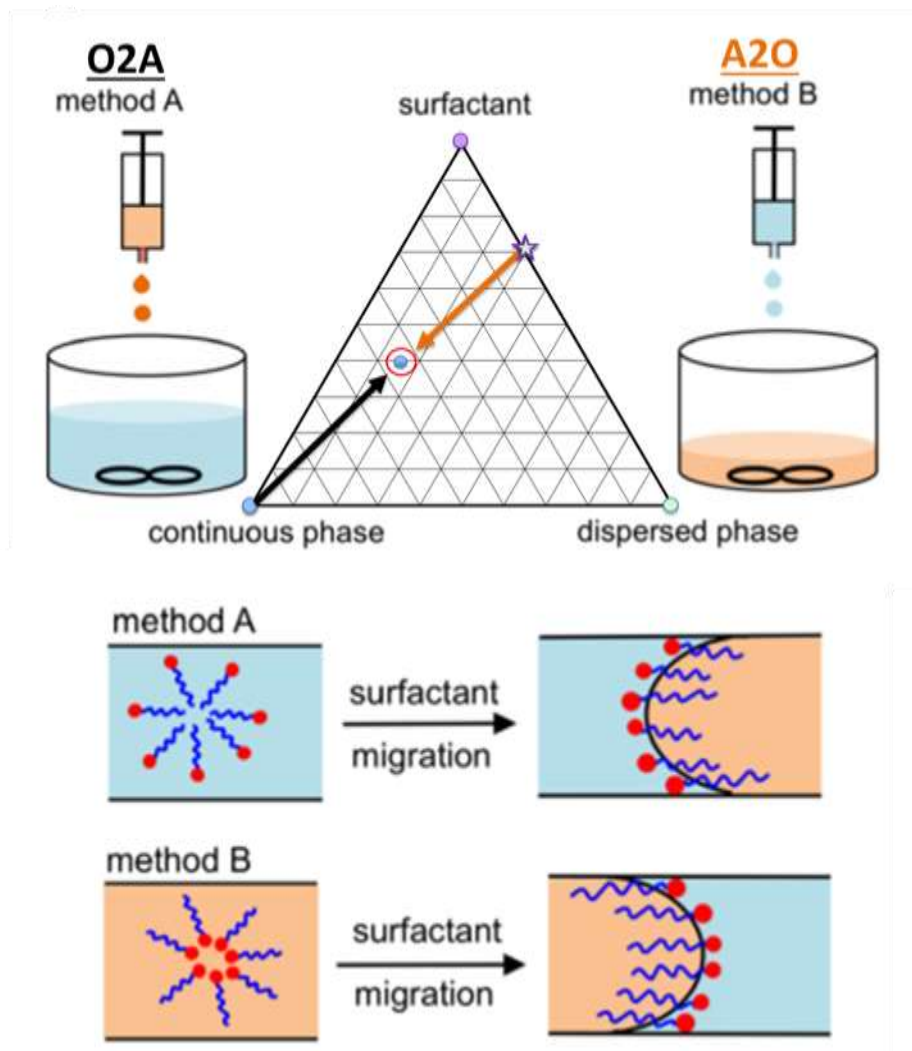
*Slow Mixing:*  
 $15.2 \pm 0.7$  nm



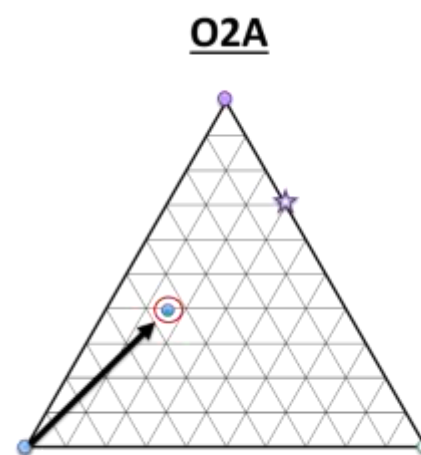
*Homogenizer:*  
 $15.0 \pm 0.2$  nm



# Micro- and Nano-emulsion Manufacturing

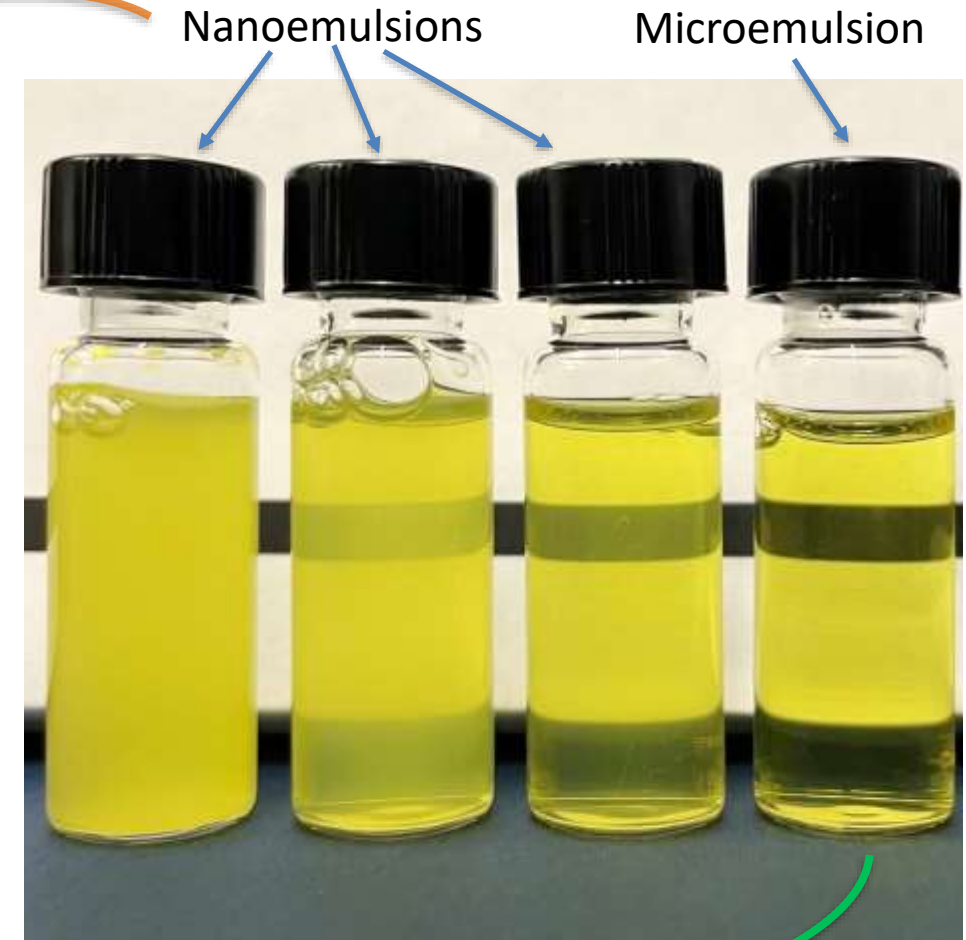
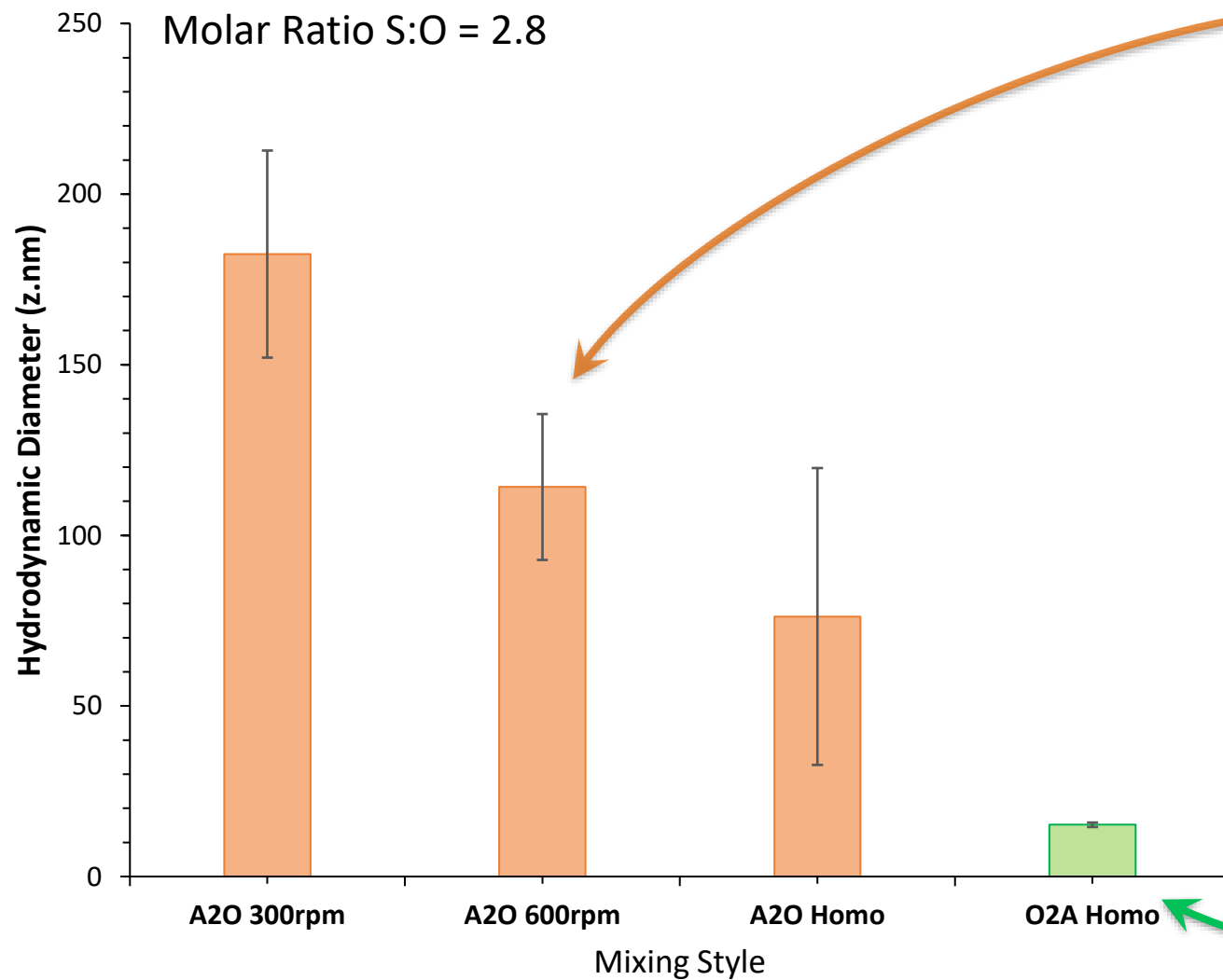


**Composition** (molar ratios of surfactant, continuous and dispersed phases) and **Processing Conditions** (equipment, shear, temperature, and order of mixing) *can directly impact the initial and final dispersion state (nano- vs. micro emulsion) of the product.*



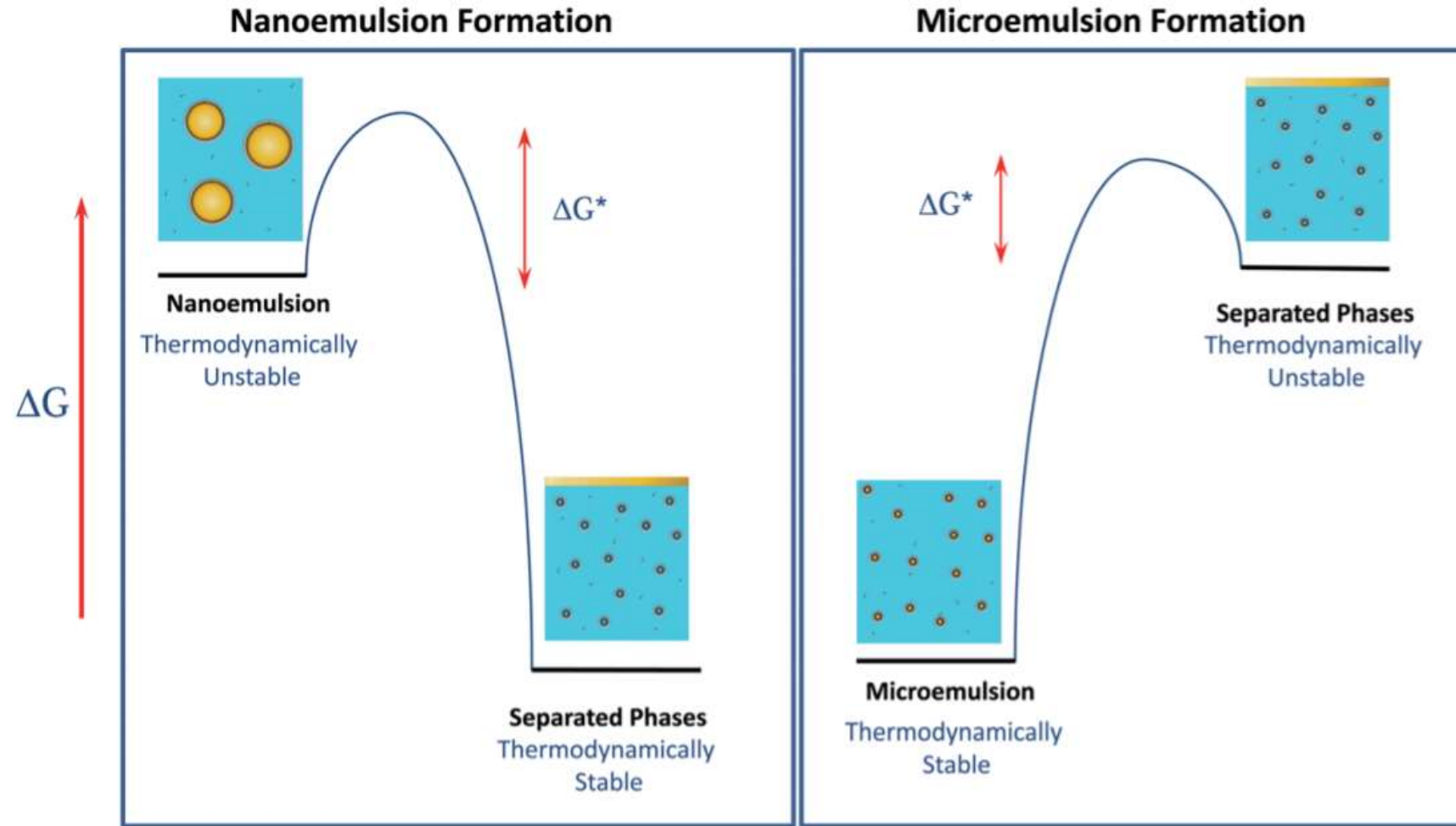


# Addition of Aqueous to Oil Phase



\*Particle size from Batch DLS

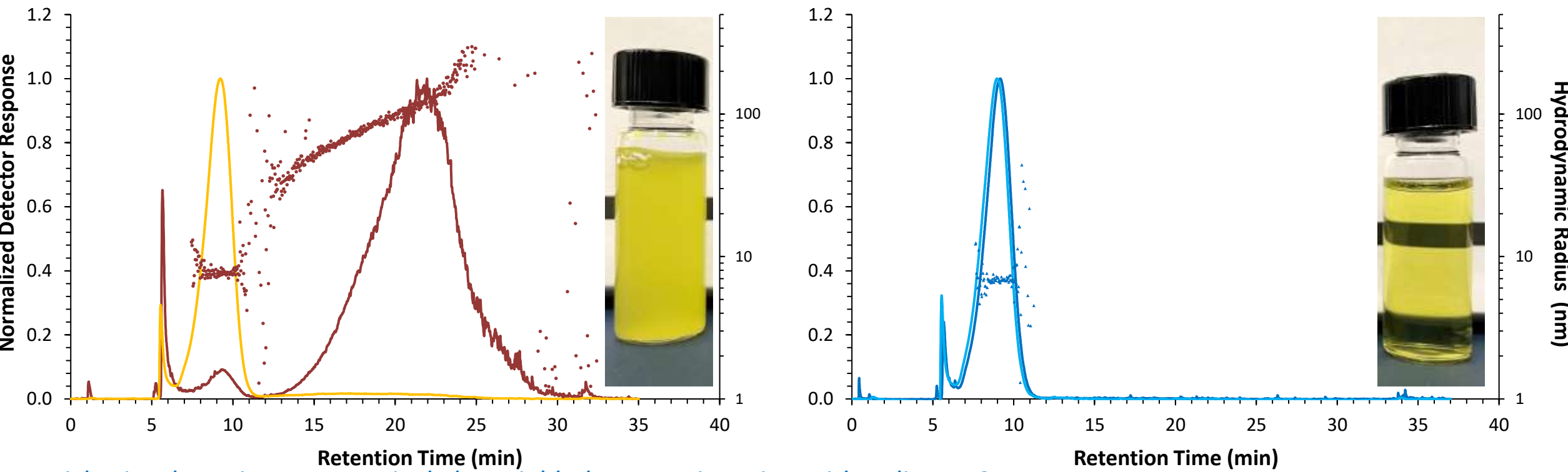
# Identifying the Thermodynamically Favored State



# What Happens Upon Heating the Formulations?



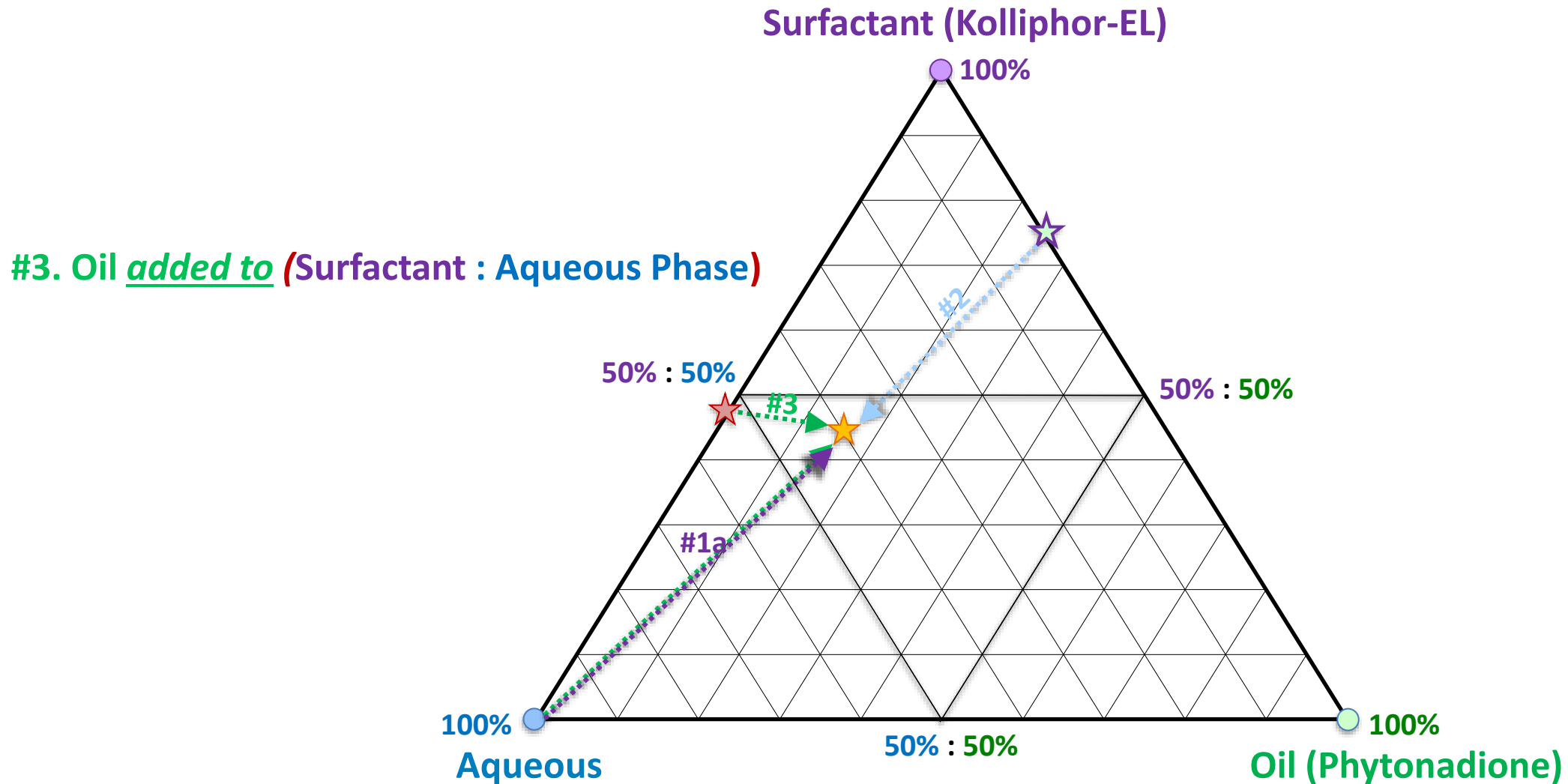
Incubation of nanoemulsions at 70°C for 30 min



Particle size data via Asymmetrical Flow Field-Flow Fractionation with online DLS

At the Product Composition the *initial* Nanoemulsion turns into a Microemulsion!

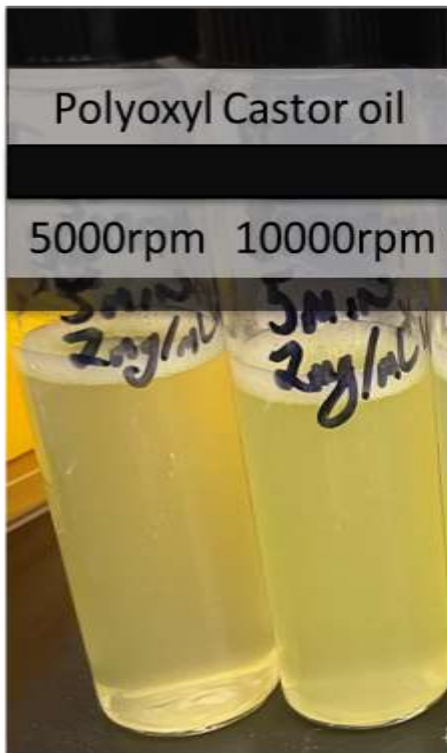
# The Three-Fold Formulation Pathway





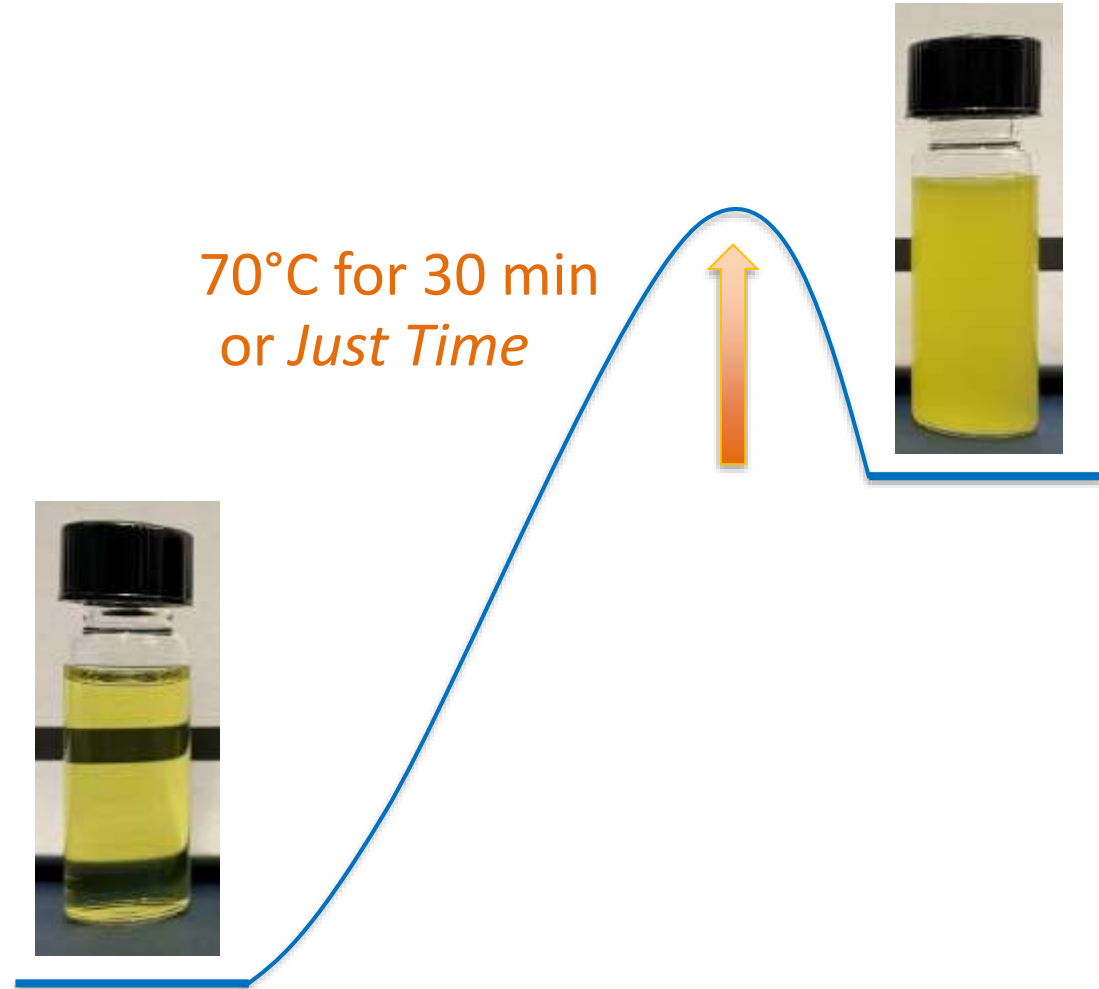
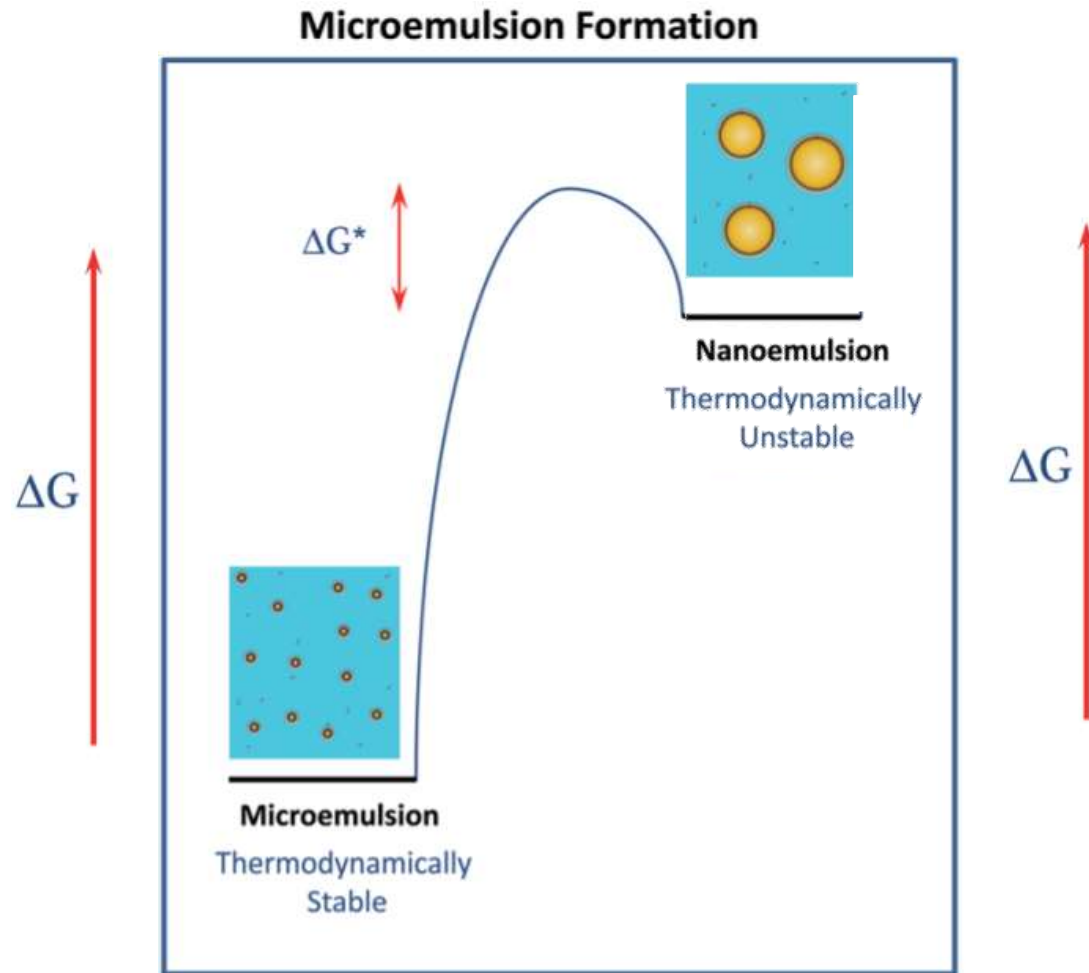
# Time Matters...

## Initial Macro- Nanoemulsion



\*Microemulsion has spontaneously formed after approx. one month of storage at 20°C

# Transition from *Nano-* to *Micro-* Emulsion



\*Microemulsion is the thermodynamically favored state for phytonadione injections.

# Challenge Question #1

**True or False: Microemulsions can only be produced using high shear mechanical processes?**

- A. True
- B. False
- C. No Clue

## Challenge Question #2



**Ranks these dispersions in order of increasing particle size:**

- A. Macroemulsion, Microemulsion, Nanoemulsion
- B. Nanoemulsion, Microemulsion, Macroemulsion
- C. Microemulsion, Nanoemulsion, Macroemulsion
- D. None of the Above

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*BE Pathway?*