Evaluation of the influence of some polymers on the physical stability of lipid self- double emulsifying systems loaded with Alendronate Sodium

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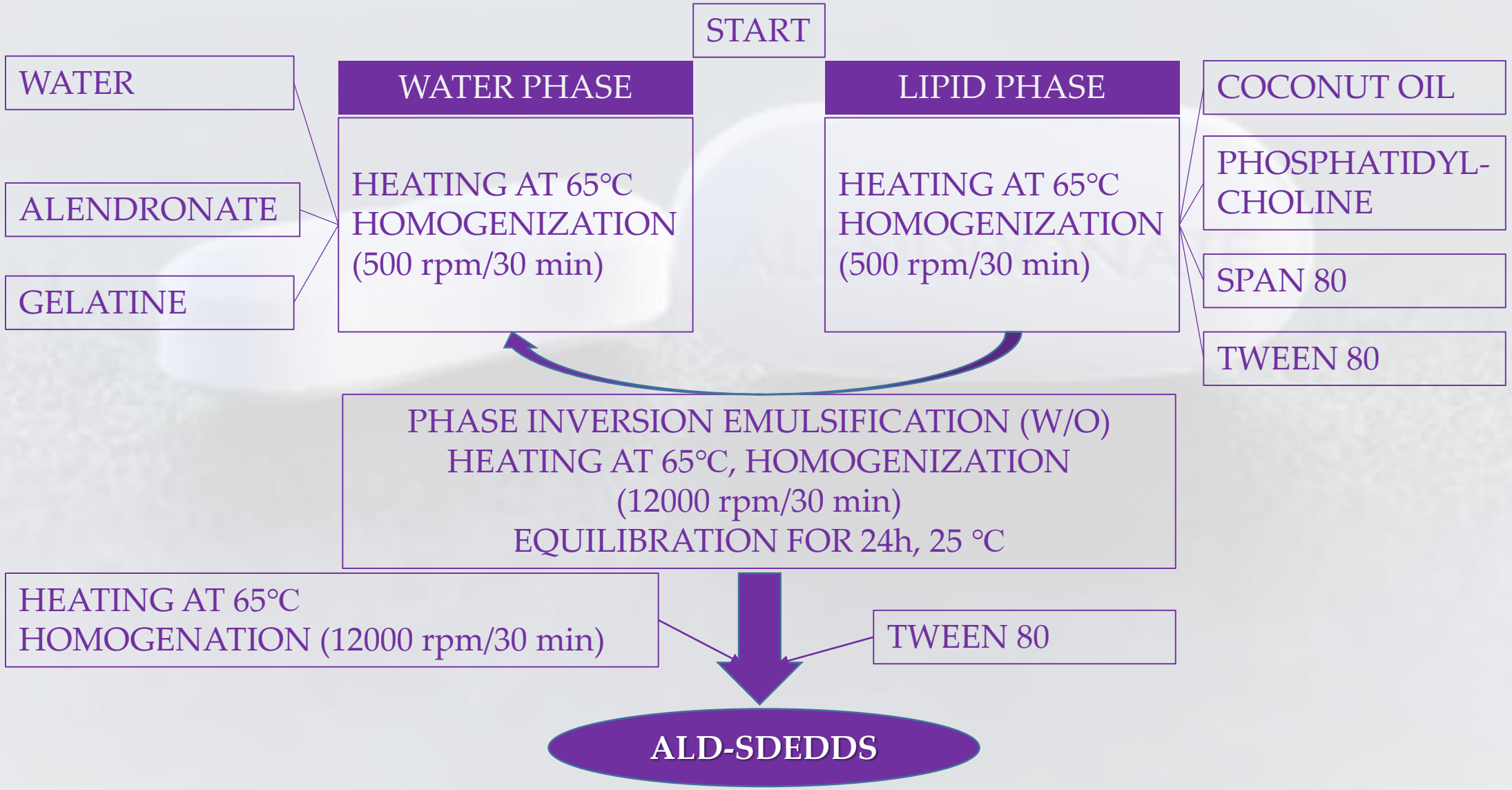
Introduction to the problem

- The Self-emulsifying drug delivery systems (SEDDS) composed of lipids, surfactants, and co-surfactants are a promising oral delivery platform for drugs with problematic solubility and/or permeability.
- However, especially those systems representing a liquid phase may show some shortcomings, such as in vivo drug precipitation, limited lymphatic transport, and storage problems. These shortcomings can compromise their application.
- The inclusion of some polymers in their composition would increase the system's stability both during storage and during dispersion in the gastrointestinal tract.

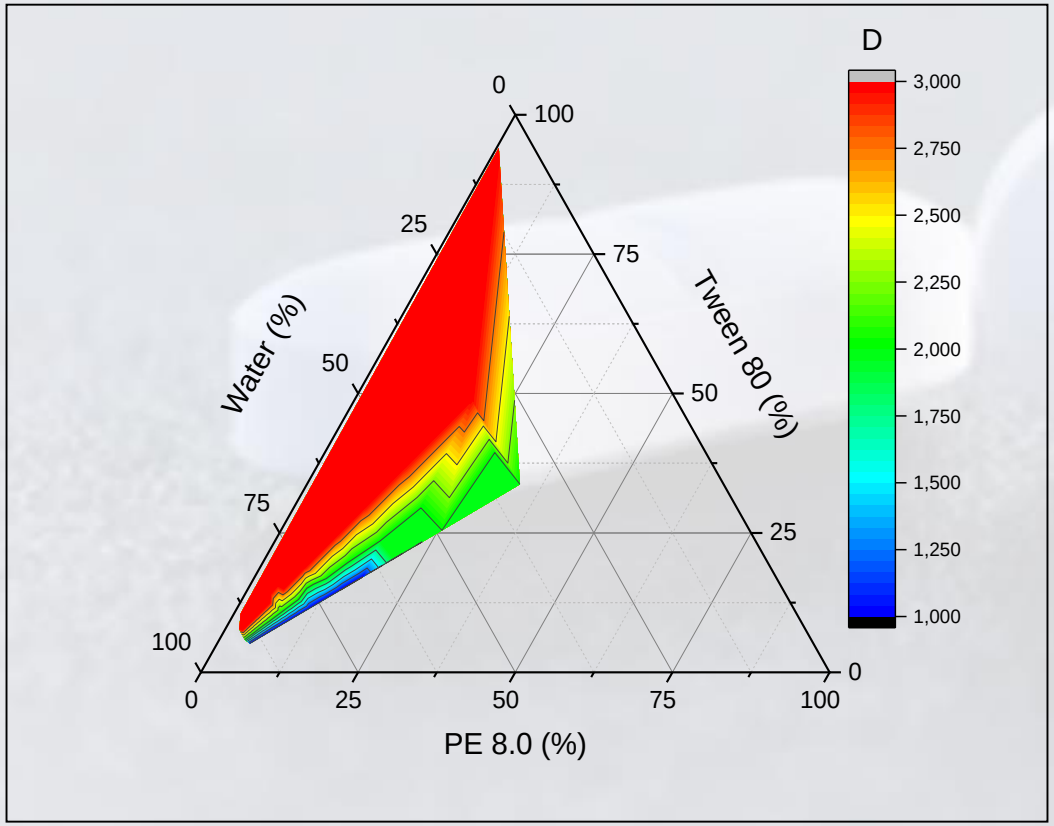
The aim

The present study was aimed to investigate the effect of the natural polymer gelatine and co-emulsifier soybean phosphatidylcholine on the physical stability of w/o/w self-double emulsifying drug delivery systems based on coconut oil loaded with Alendronate Sodium (w/o/w SDEDDS-NaALD).

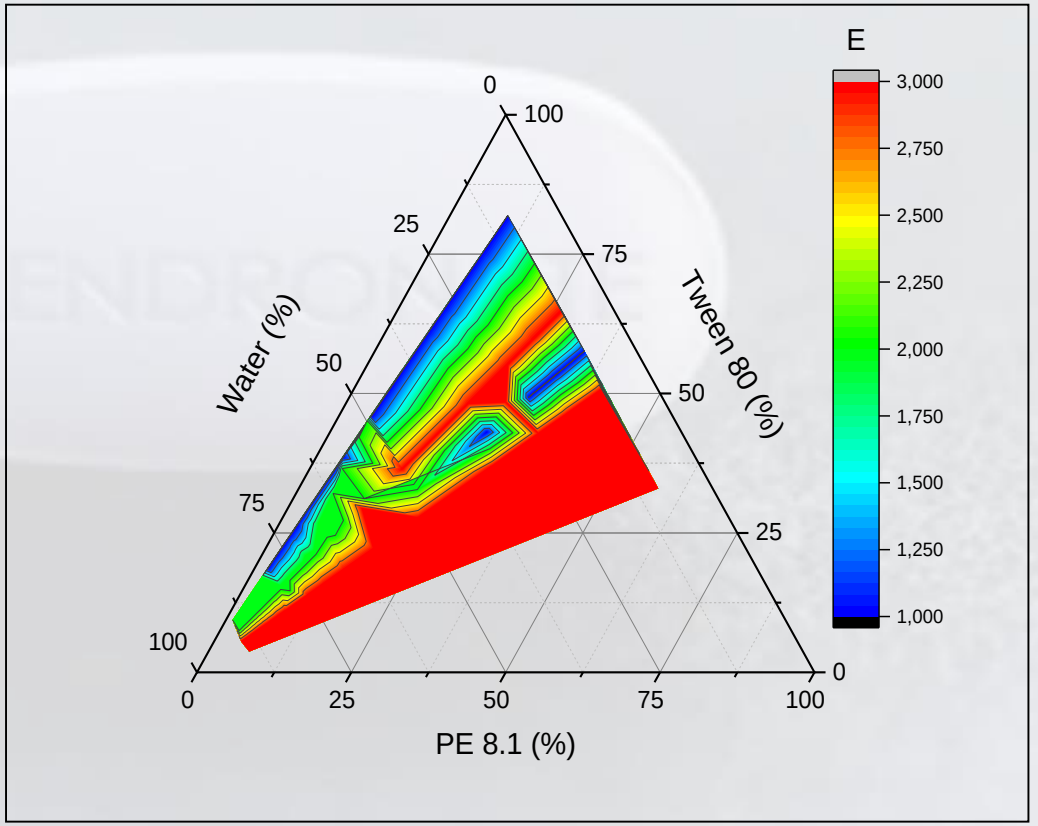
Technological scheme for obtaining the self-emulsifying systems.



Assessment of appropriate composition percentages



PE 8.0 – primary W/O, SPAN80/TWEEN80 AS EMULSIFIER/CO-EMULSIFIER



PE 8.1 – primary W/O, SPAN80/PHOSPHATIDYLCHOLINE AS EMULSIFIER/CO-EMULSIFIER

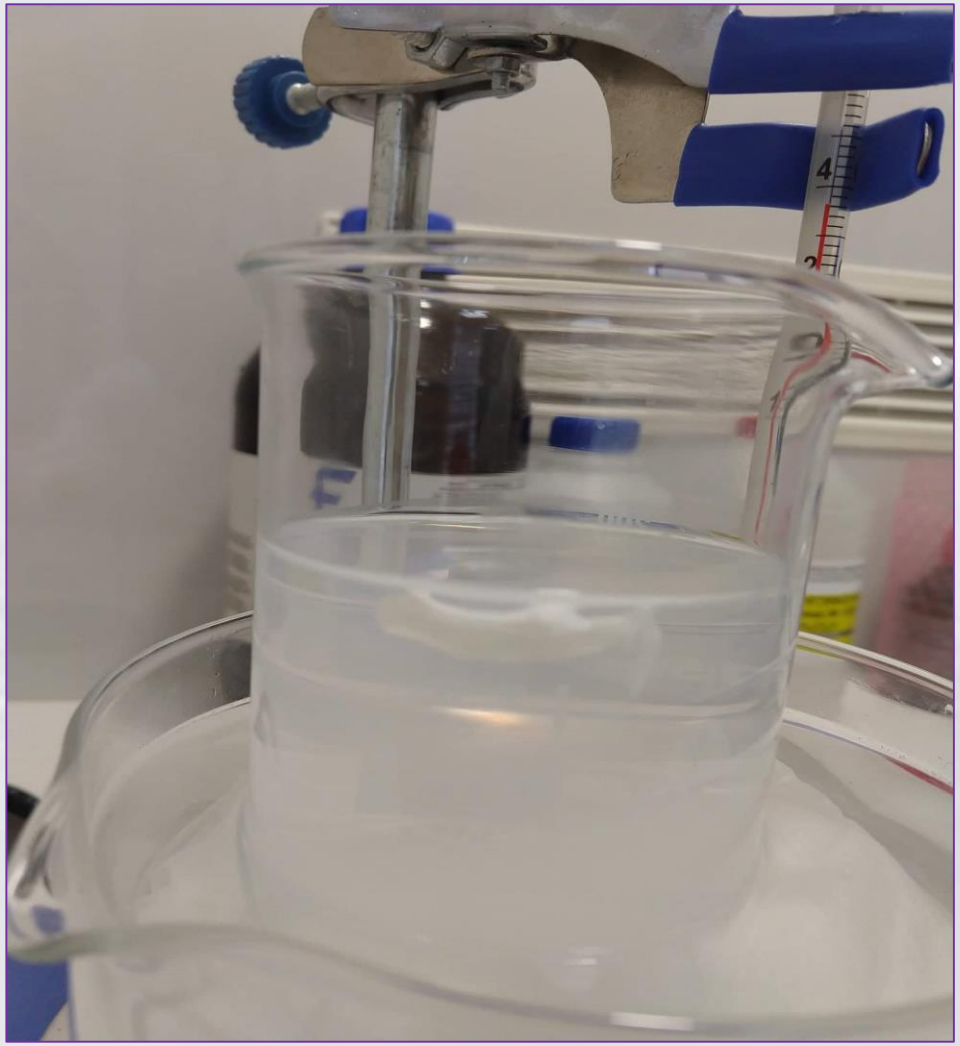
Formulation of models of self-emulsifying compositions

Ingredients, %	Model I	Model II	Model III	Model IV
Alendronate Sodium	6.42	6.42	6.42	6.42
Coconut oil	18.24	18.24	18.24	18.24
Soybean phosphatidylcholine	4.59	-	4.59	-
Gelatine	-	-	0.63	0.63
Span 80	2.96	2.96	2.96	2.96
Tween 80	45.00	49.59	48.92	53.51
Distilled water	22.79	22.79	18.24	18.24

Used methods

Assessment of physical stability	• Visual assessment • Centrifugation
Assessment of thermodynamic stability	• Spectroscopic methods
Assessment of particle size	• Dynamic Light Scattering
Viscosity	• Rheology at 20°C and 70°C

SDEDDS-NaALD characterization



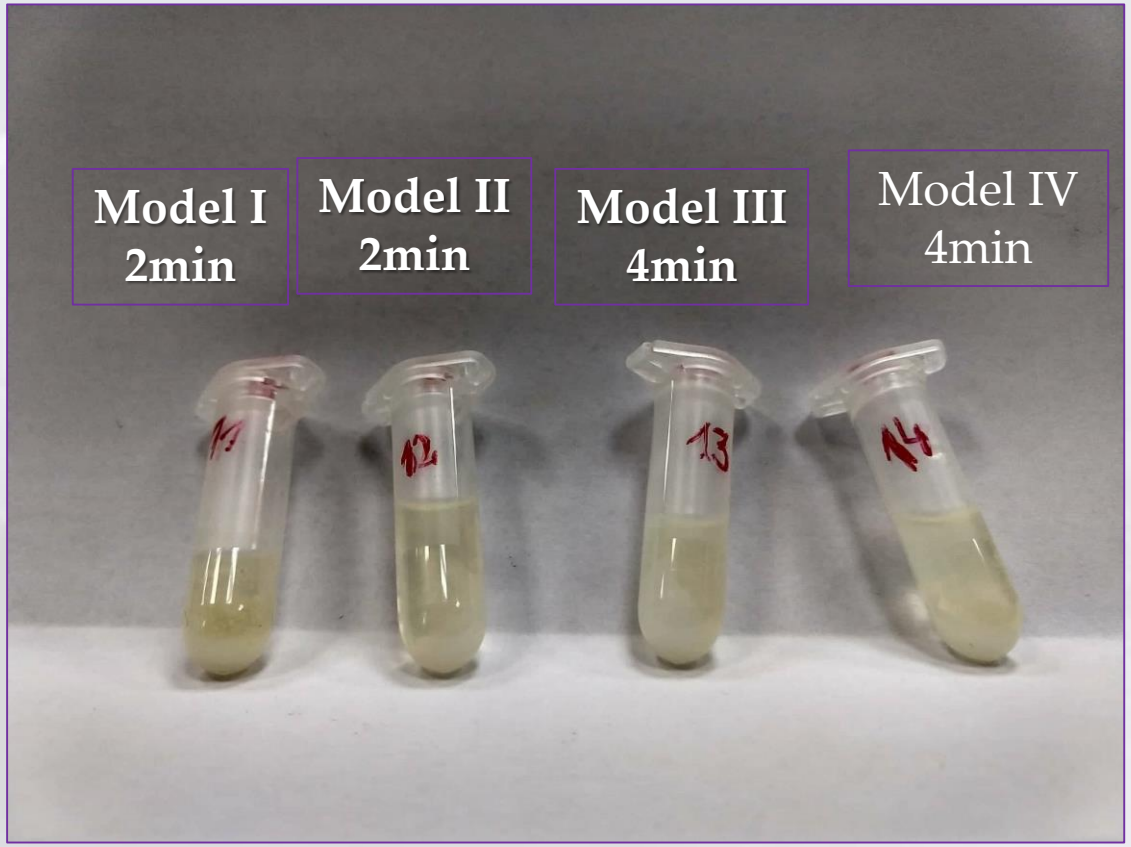
- Visual examination
- Self-emulsification time

75 rpm/ 37±1℃, 0.1 N HCl, 200 mL, pH= 1.2

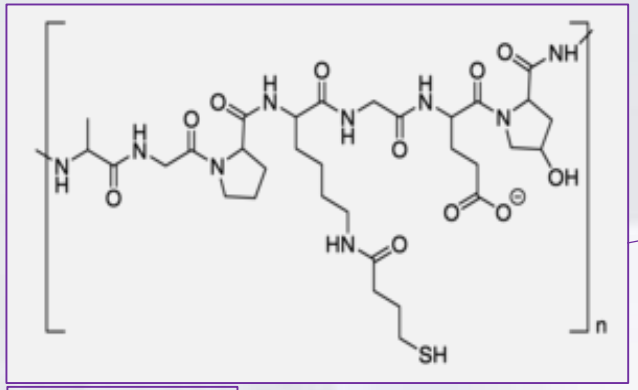
Assessment of physical stability

Freeze/thaw cycles:

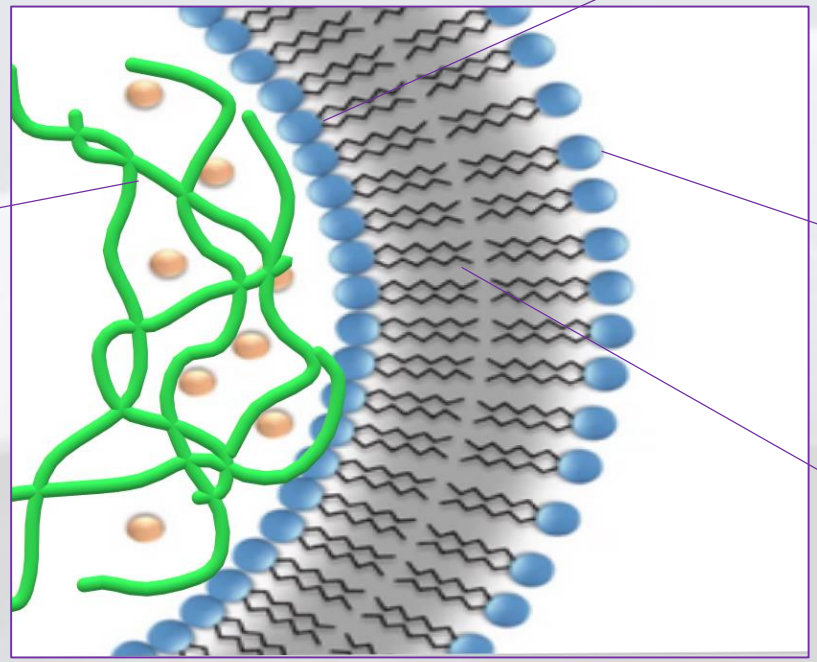
1. 3000 rpm for 1 min / visual inspection
2. Heating to 45°C
3. Centrifugation until phase separation
4. Re-homogenization
5. Freezing to -20°C + centrifugation
6. Centrifugation until phase separation

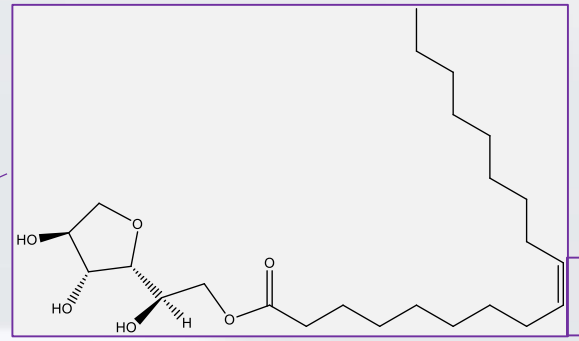


Emulsion structure

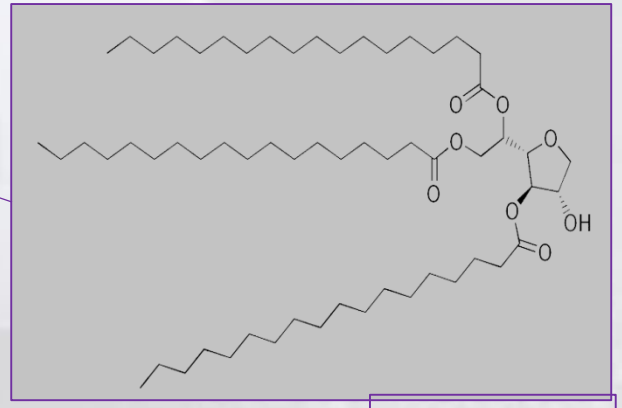


Gelatine

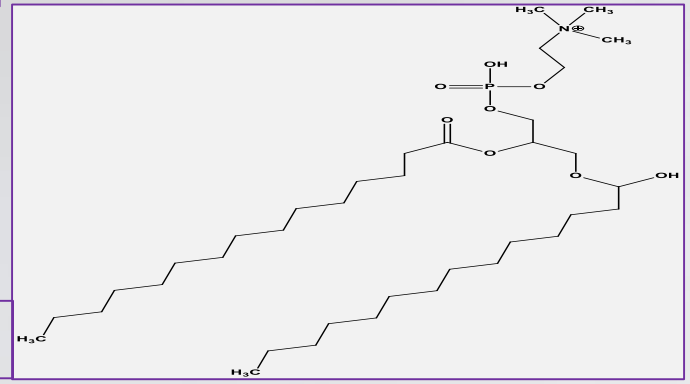




Span 80



Tween 80



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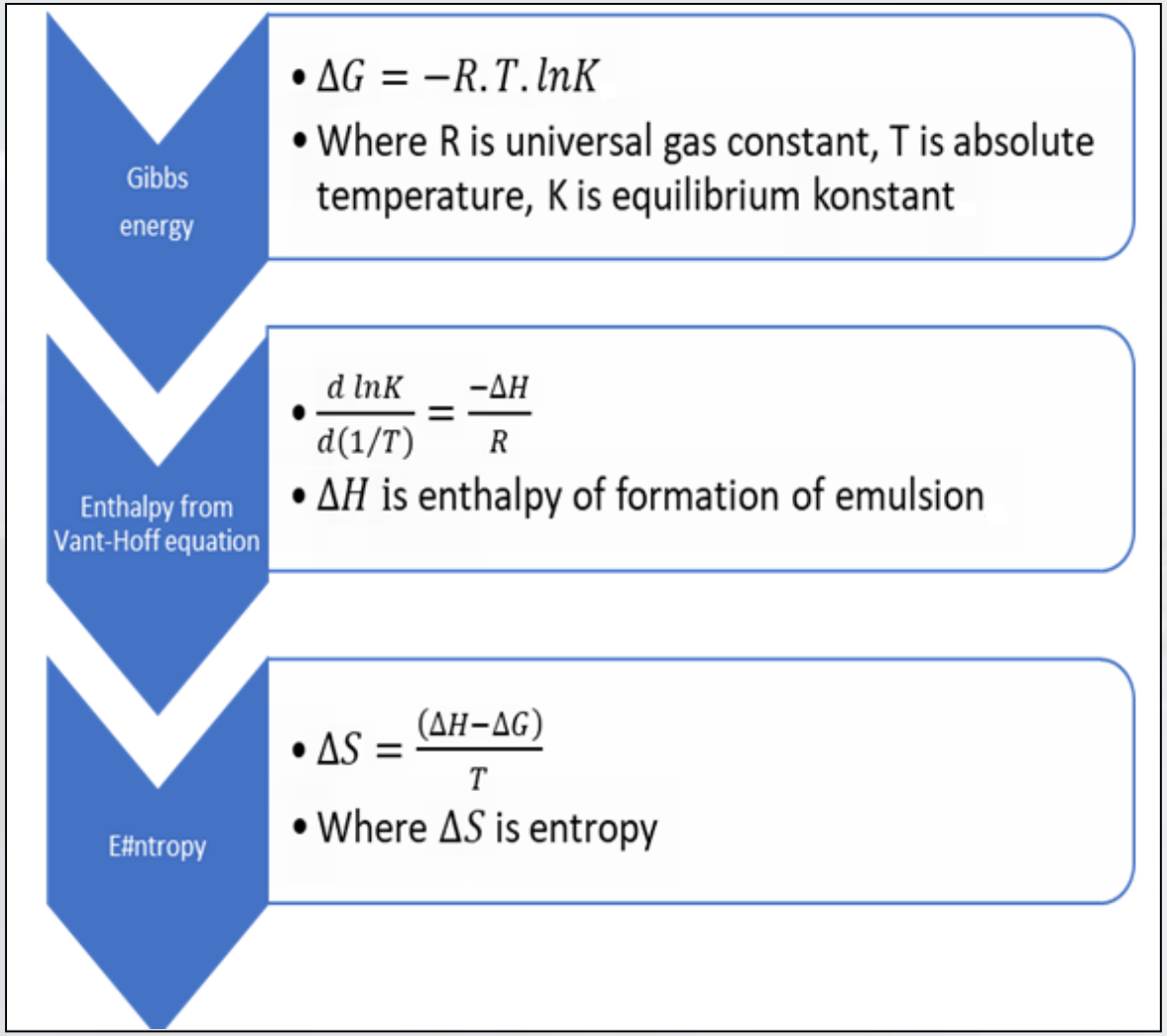
Thermodynamic stability – theoretical background

Spectroscopic method:

- ✓ At room temperature, the absorbance of a series of standard aqueous dispersions was measured with respective concentrations of 0.04, 0.08, 0.12, 0.16, and 0.2 . The absorption spectrum of the sample with the highest concentration is measured to determine the wavelength at which the sample absorbs most strongly.
- ✓ The operation λ-range is between 200 nm to 750 nm.
- ✓ The research is carried out with a Spectrophotometer with a cuvette of 1 cm path length, at λ= 230 nm.



Thermodynamic stability – main results

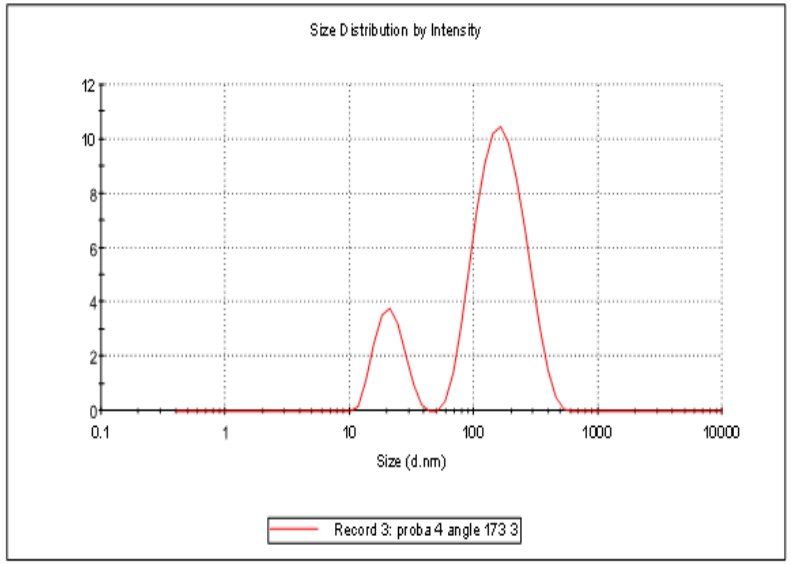
TYPE	ΔG [kJ mol^{-1}]	ΔH [kJ mol^{-1}]	ΔS [kJ mol^{-1} K^{-1}]	K
Model I	-1.89	-18.16	-0.06	2.14
Model II	-0.20	-17.43	-0.06	1.08
Model III	-6.37	-20.11	-0.05	13.06
Model IV	-1.91	-18.17	-0.05	2.17

- Model III has the highest total Gibbs energy, followed by Model IV.
- The calculated enthalpies of all emulsions have large negative values. This is associated with endothermic processes, which shifts the equilibrium in favor of the products formation.
- Entropies in the system have minimal negative values tending to zero.

Assessment of particle size

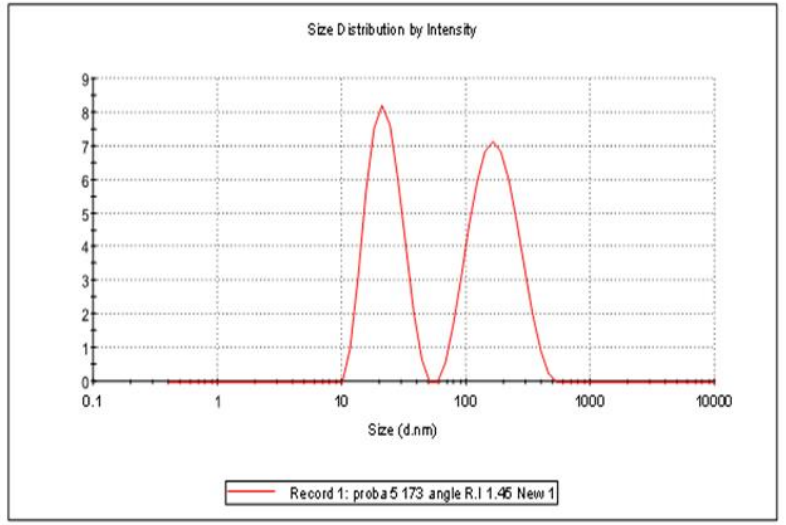
Model III

		Size (d.n...	% Intensity:	St Dev (d.n...
Z-Average (d.nm): 83,77	Peak 1:	178,4	82,4	77,72
PdI: 0,573	Peak 2:	21,47	17,6	5,419
Intercept: 0,962	Peak 3:	0,000	0,0	0,000

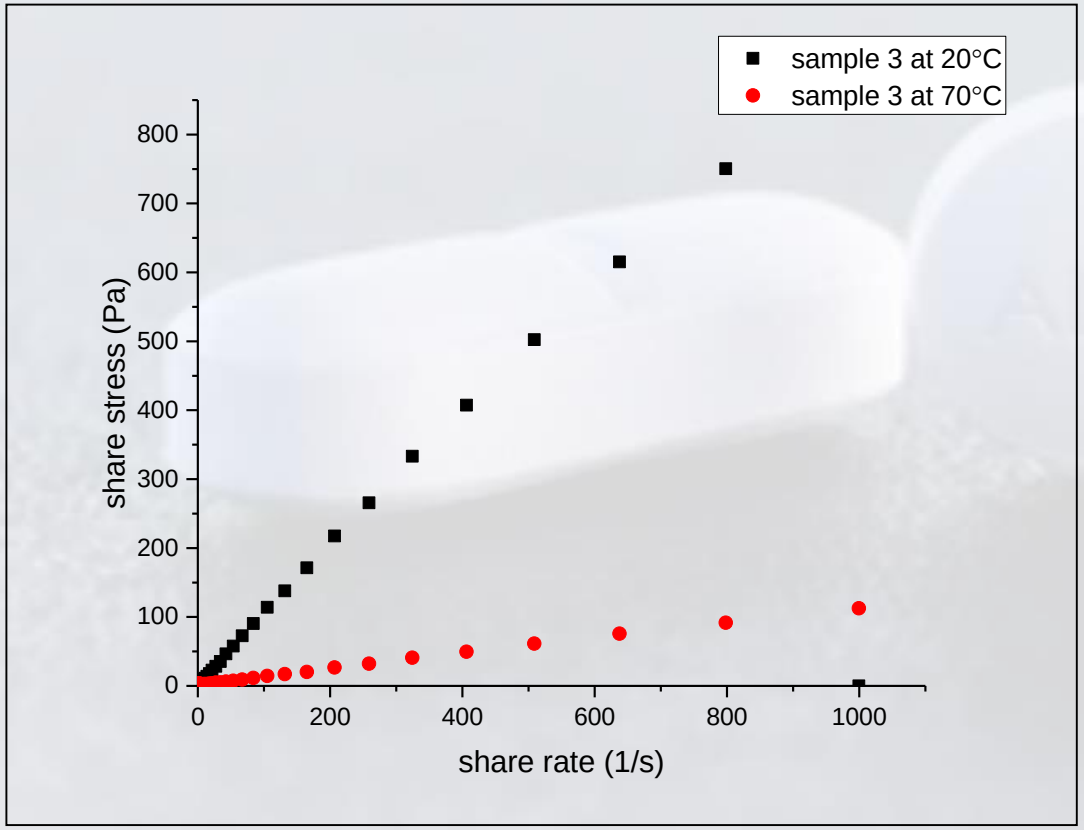


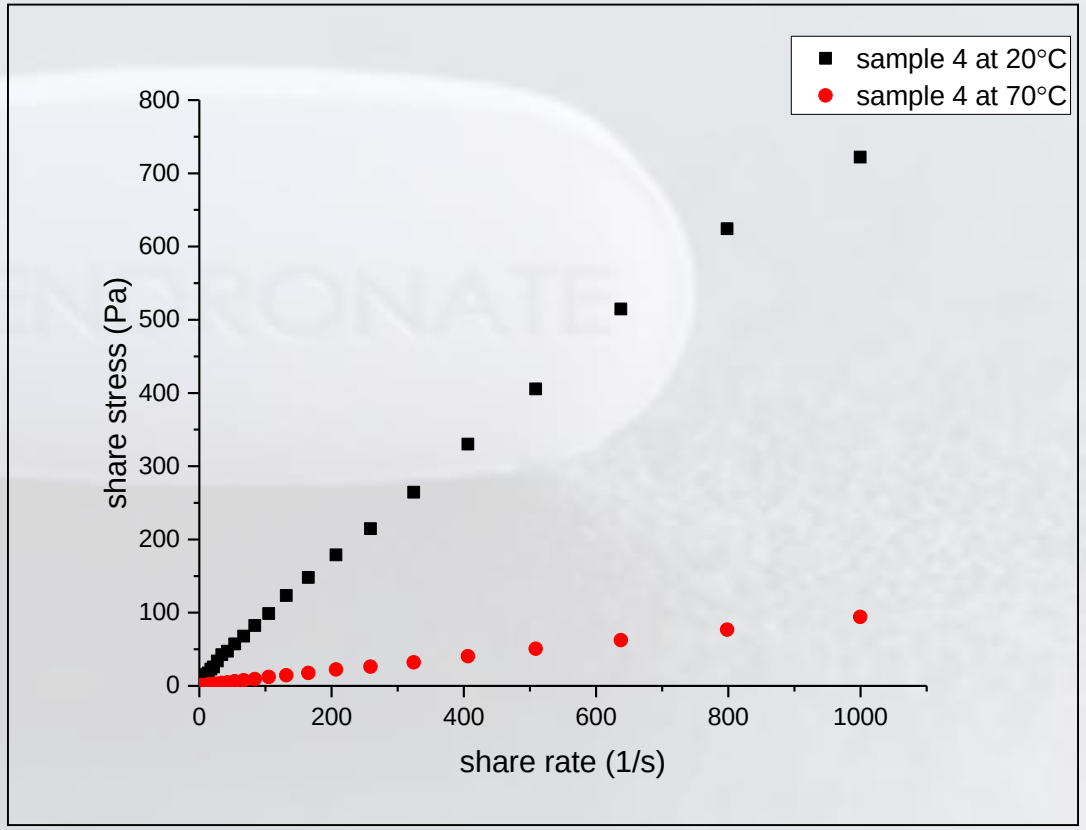
Model IV

		Size (d.n...	% Intensity:	St Dev (d.
Z-Average (d.nm): 42,14	Peak 1:	181,4	54,0	75,02
PdI: 0,518	Peak 2:	22,78	46,0	6,947
Intercept: 0,946	Peak 3:	0,000	0,0	0,000



Rheological models





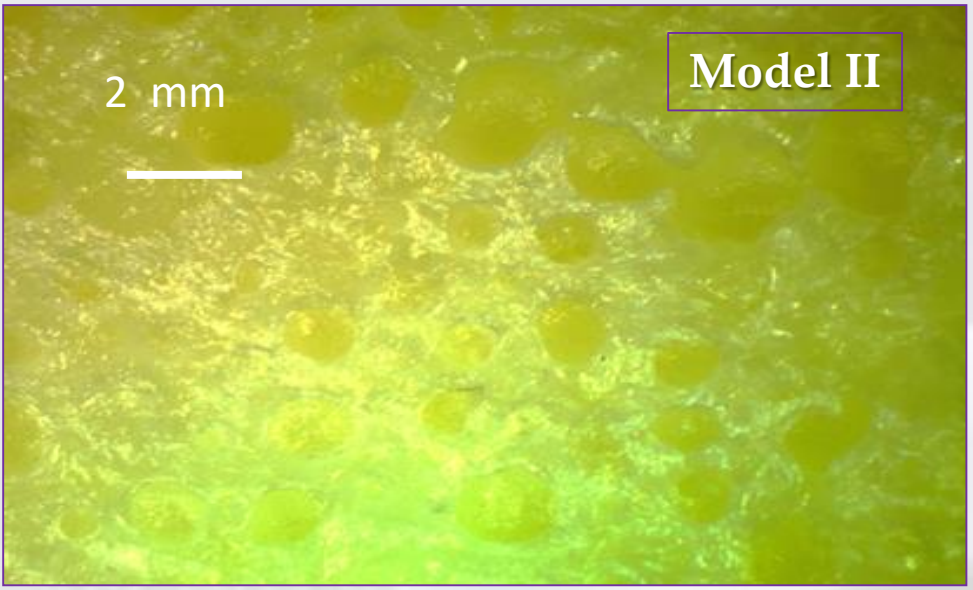
Rheological models

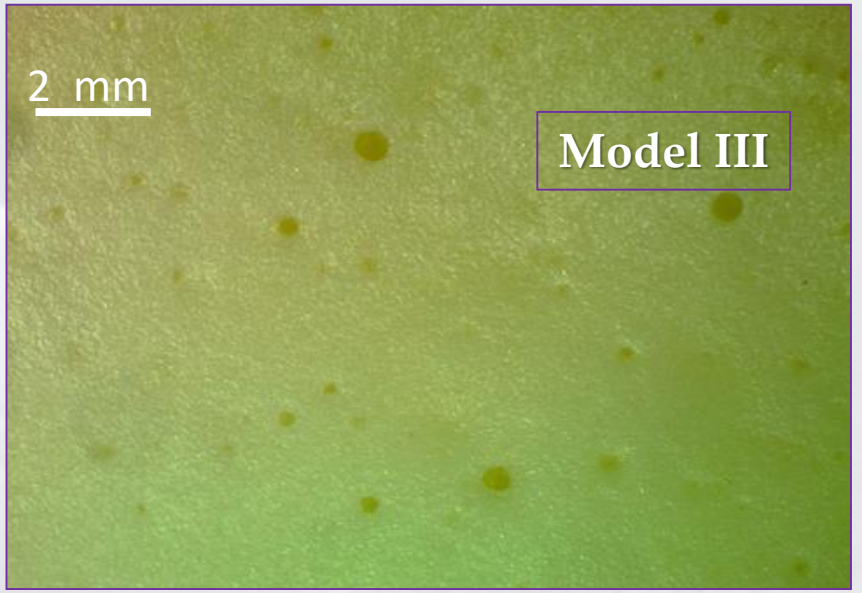
Type of model	Mathematical equation
Bingham Plastic Model (BPM)	$\tau = \tau_0 + \mu_p . \gamma$
Power Law Model (PLM)	$\tau = K . \gamma^n$
Hershcel-Bulkley Model (HBM)	$\tau = \tau_0 + K . \gamma^n$

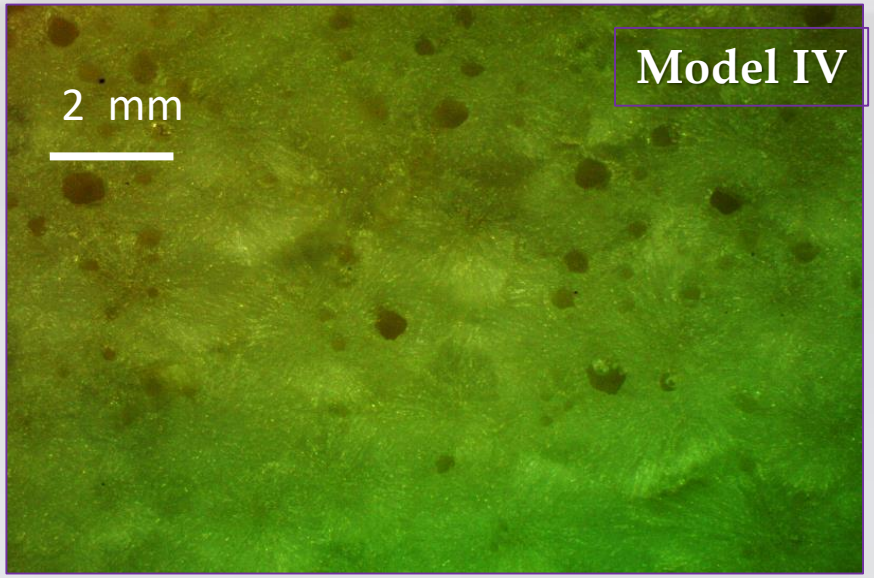
τ is shear stress, γ is share rate, τ_0 is yield stress, k is consistency index, and n is power law index, μ_p is plastic viscosity

Type of the model	*Model III*	*Model IV*
BPM	$\mu_p = 0.6 \pm 0.1$ $\tau_0 = 23.7 \pm 19$ $R^2 = 0.84$	$\mu_p = 0.8 \pm 1.7$ $\tau_0 = 7.6 \pm 1.8$ $R^2 = 0.995$
PLM	$K = 10.8 \pm 7$ $n = 0.6 \pm 0.1$ $R^2 = 0.85$	$K = 1.6 \pm 0.1$ $n = 0.89 \pm 0.1$ $R^2 = 0.999$
HBM	$\tau_0 = 0$ $K = 11.8 \pm 1.1$ $n = 0.55 \pm 0.1$ $R^2 = 0.84$	$\tau_0 = 1.4 \pm 0.1$ $K = 1.6 \pm 0.1$ $n = 0.89 \pm 0.1$ $R^2 = 0.999$

Microscopy of emulsions







Conclusion

- According to the particle size analysis, both Model III and IV are nanosized ;
- Model III was the most thermodynamically stable, followed by Model IV.
- The Gibbs free energy increased in modulus in the presence of gelatine and phosphatidylcholine in the emulsion.
- Model II was the most thermodynamically unstable. This was also confirmed by the microscopic photographs taken with a reflection microscope. Model II had the largest oil globule sizes.

Conclusion

- Model systems I and II were Newtonian fluids at room temperature, while III and IV were non-Newtonian fluids with pseudoplastic behavior;
- Sample IV had the highest plastic viscosity;
- At 70°C, all model systems exhibited Newtonian fluid behavior.


thank you
danke
謝謝
ngiyabonga
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рахмат
teşekkür ederim
Баярлалаа
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