Characterizing the stability of surfactant-preservative mixtures for pharmaceutical use

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Background

- Protein drug formulations include many excipients
- Surfactants keep the protein dispersed evenly in solution
- Preservatives prevent microbial growth
- Ideally, formulations maximize antimicrobial strength while maintaining excipients evenly dispersed in solution

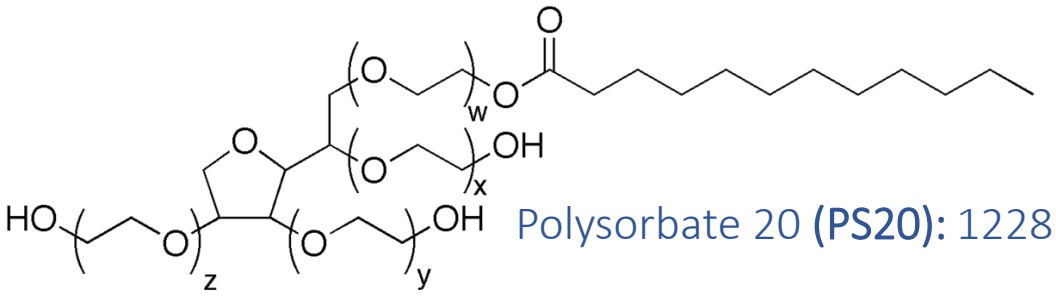
Excipients used in drug formulations

Surfactants

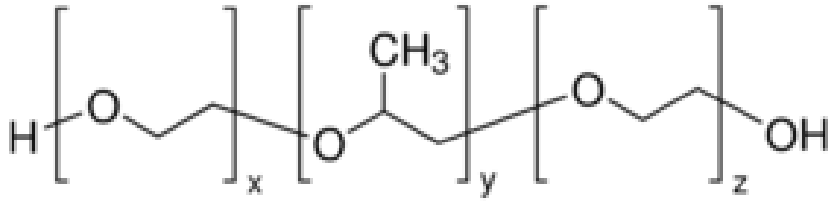
Polysorbate 20

Poloxamer 188

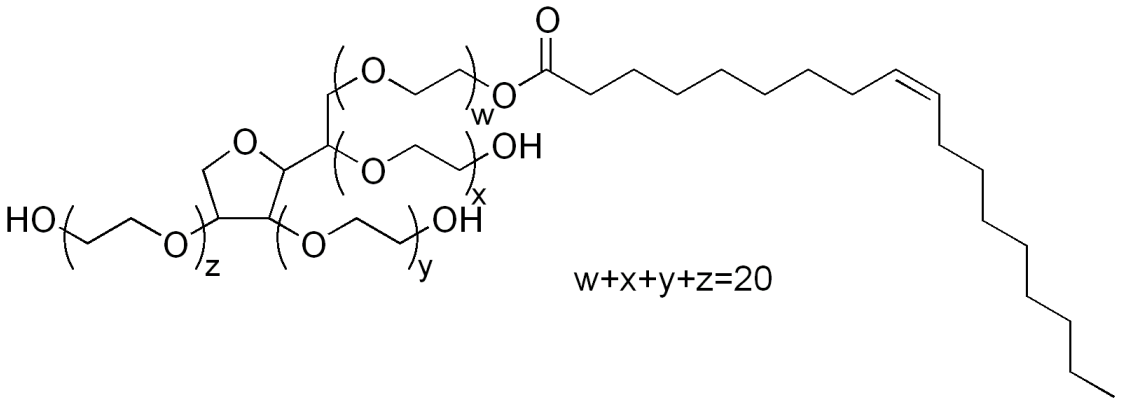
Polysorbate 80



Polysorbate 20 **(PS20):** 1228 g/mol



Poloxamer 188 (**P188**): 8780 g/mol



Polysorbate 80 **(PS80)**: 1310 g/mol

Excipients used in drug formulations

Surfactants

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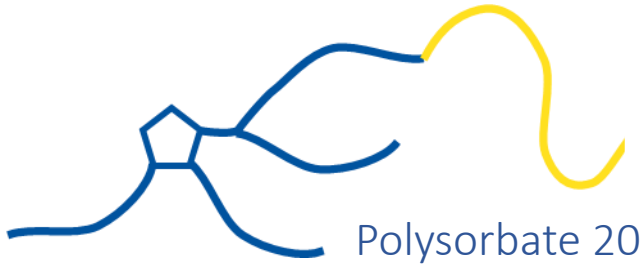
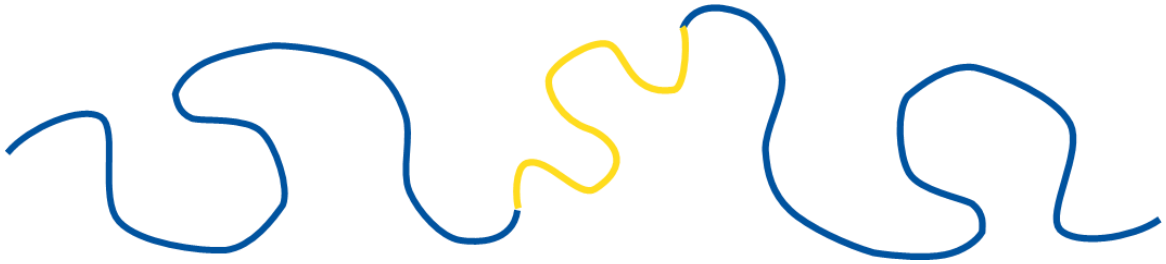
Poloxamer 188

Polysorbate 80



Polysorbate 20 **(PS20):** 1228 g/mol



Poloxamer 188 (**P188**): 8780 g/mol

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Poloxamer 188

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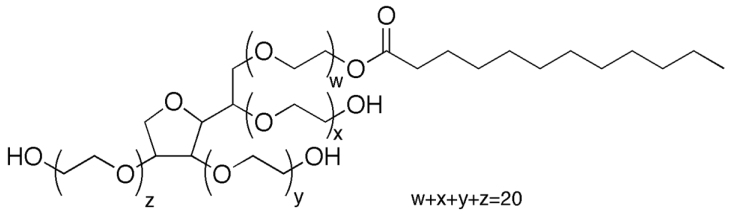
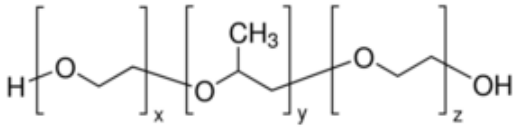
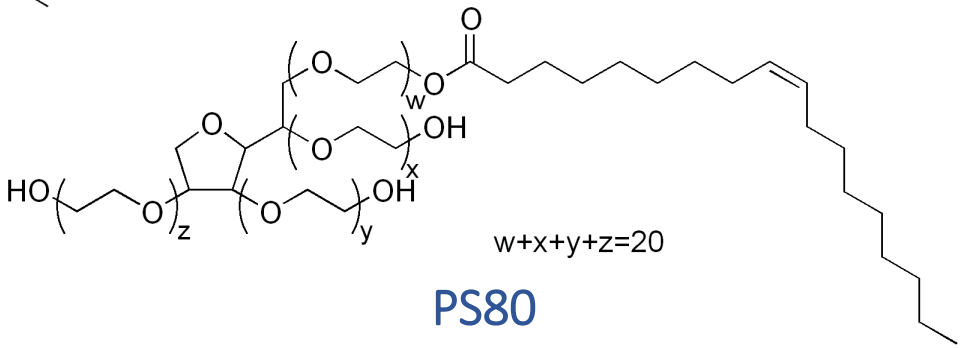


PS20



P188



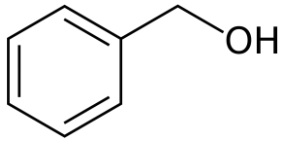
PS80

Preservatives

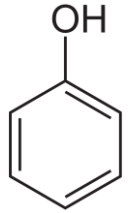
Benzyl alcohol

Phenol

Benzyl alcohol (BzOH)



Phenol PhOH

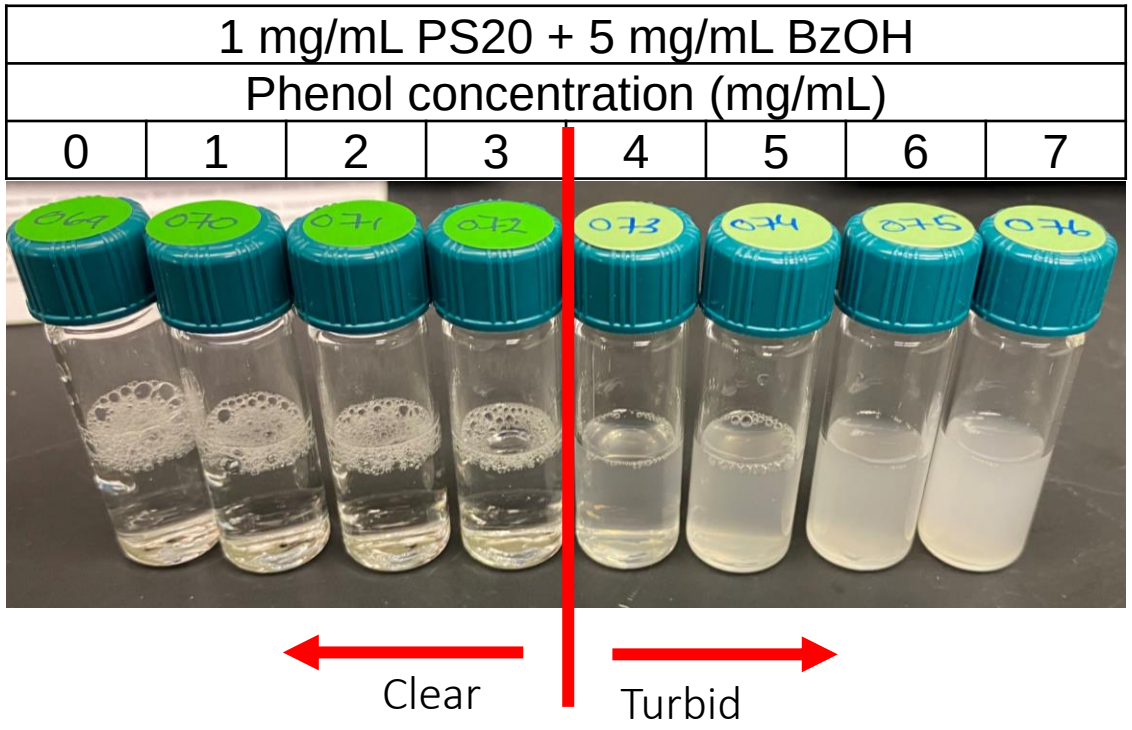


Turbidity Indicates Unstable Aggregates

- What is turbidity?

- Polysorbate 20 solubility: 100 mg/mL
- Benzyl Alcohol solubility: 40 mg/mL
- Phenol solubility: 80 mg/mL

- Aggregation indicates instability
  - 1) by observation, we've learned that turbidity in this system always precedes large-scale phase separation
  - 2) in injectable pharmaceutical formulations, turbid aggregates can induce an immune response.



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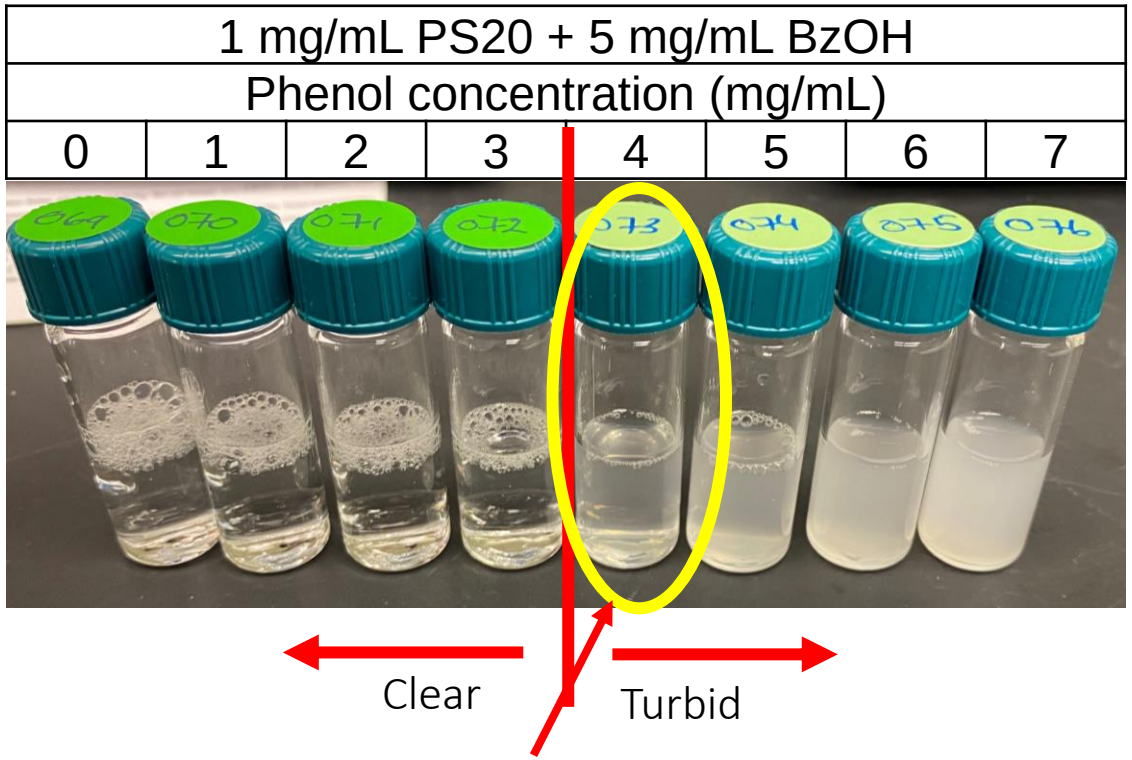

Visually turbidity indicates aggregation

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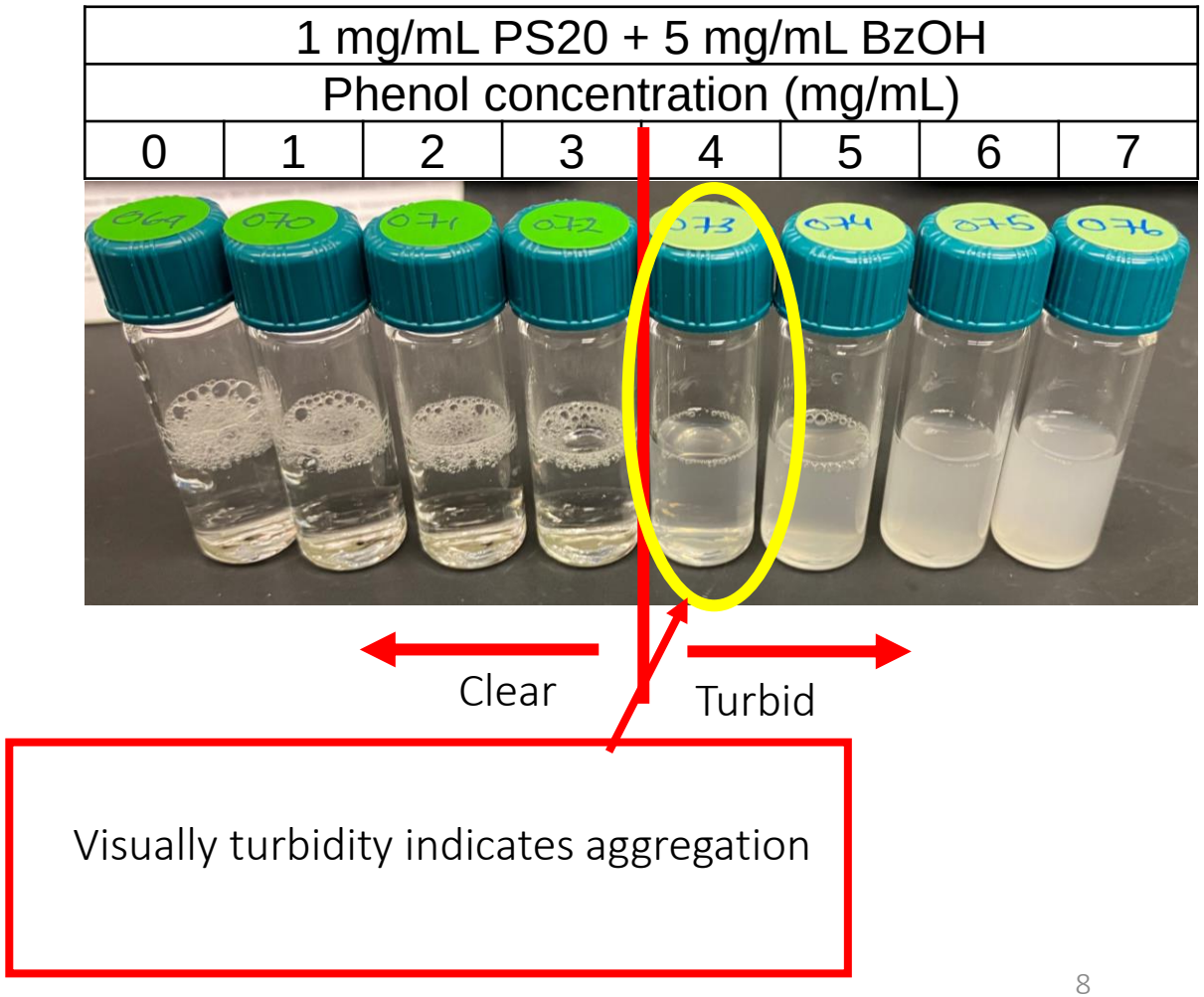
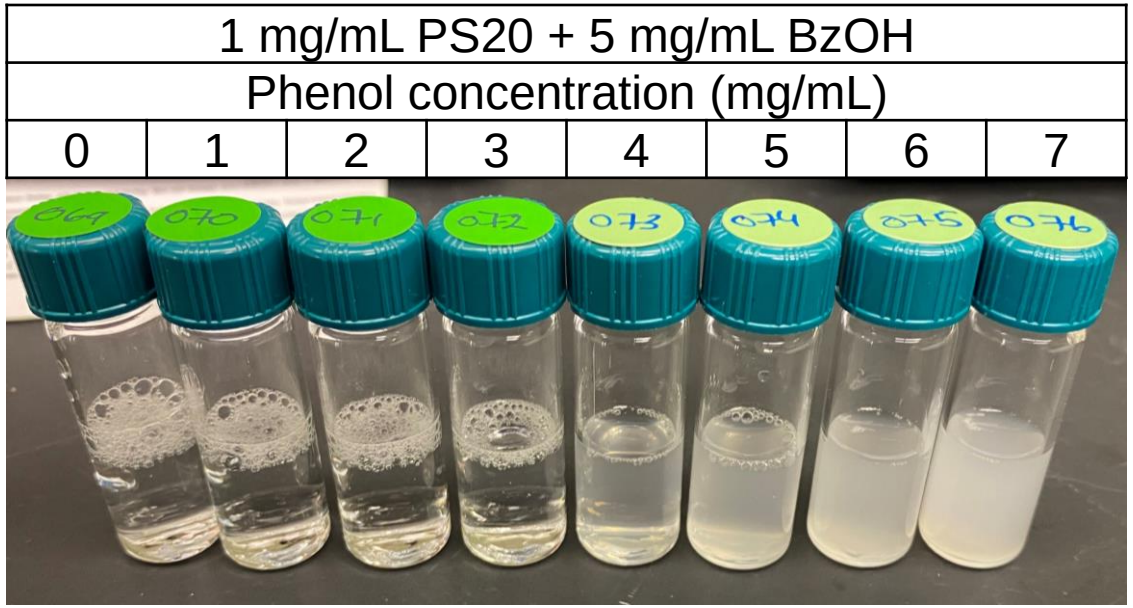


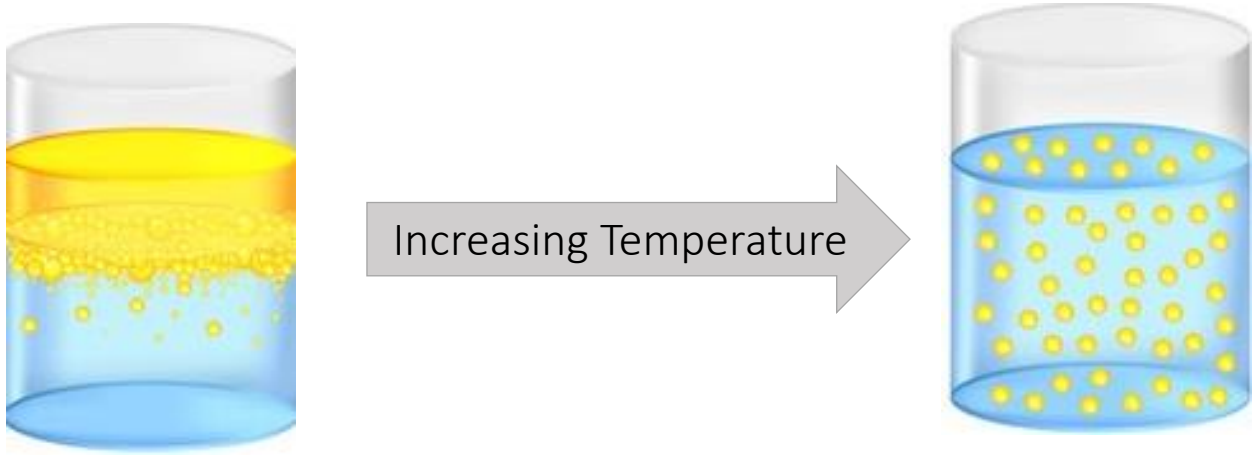
Experimental Design

- Turbidity response to
  - Record phase (T/C) at varying temperatures
  - Phase diagrams created at varying conditions (clear/turbid)
- Dynamic light scattering (DLS) used to gather information on aggregation at smaller length scales
  - DLS measurement of PS20 kinetics



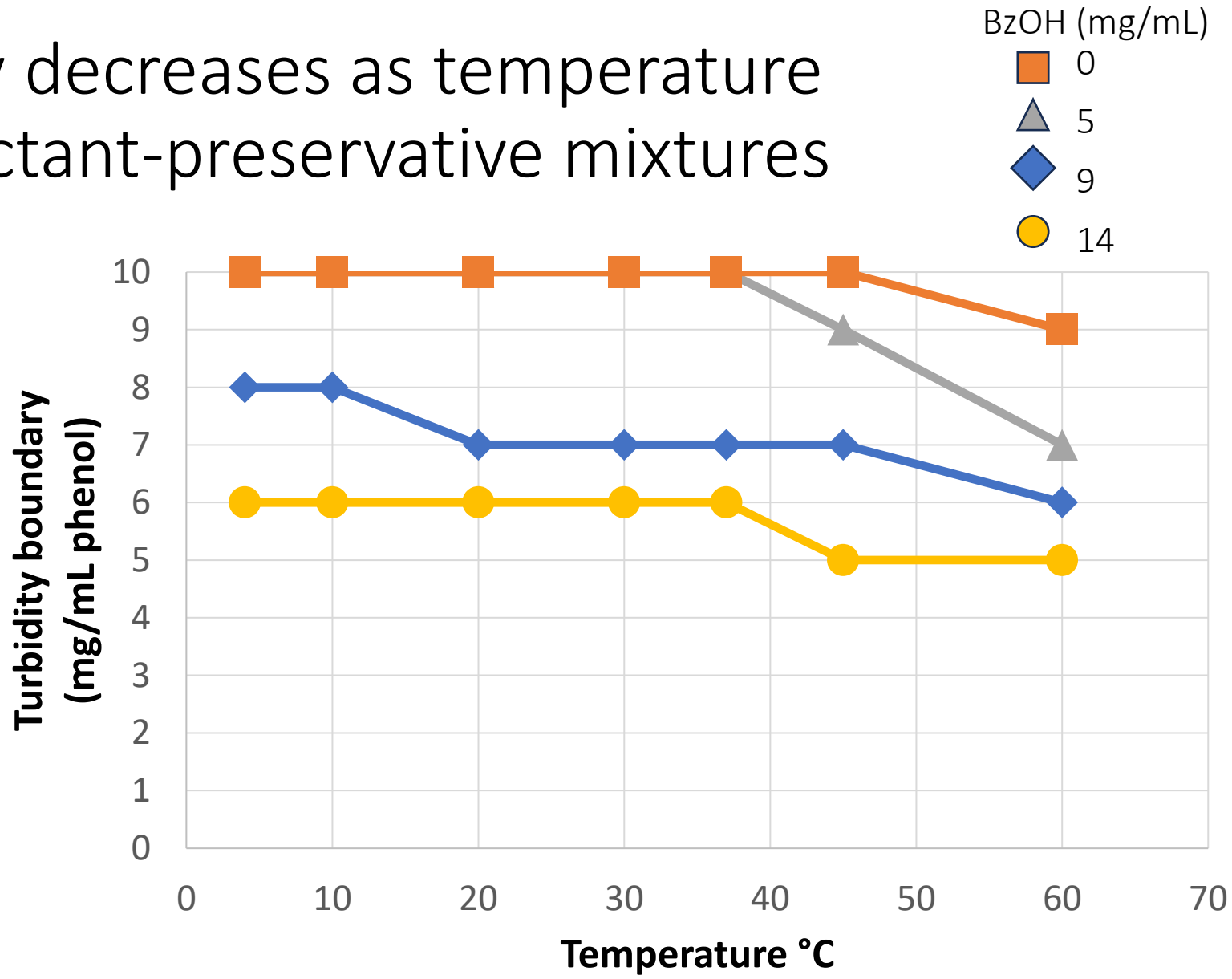
Effect of Temperature

- Phenol and benzyl alcohol solubility increase with temperature
- P188, PS20, PS80 solubility decrease with temperature
- Which component dominates the mixture’s response to temperature?



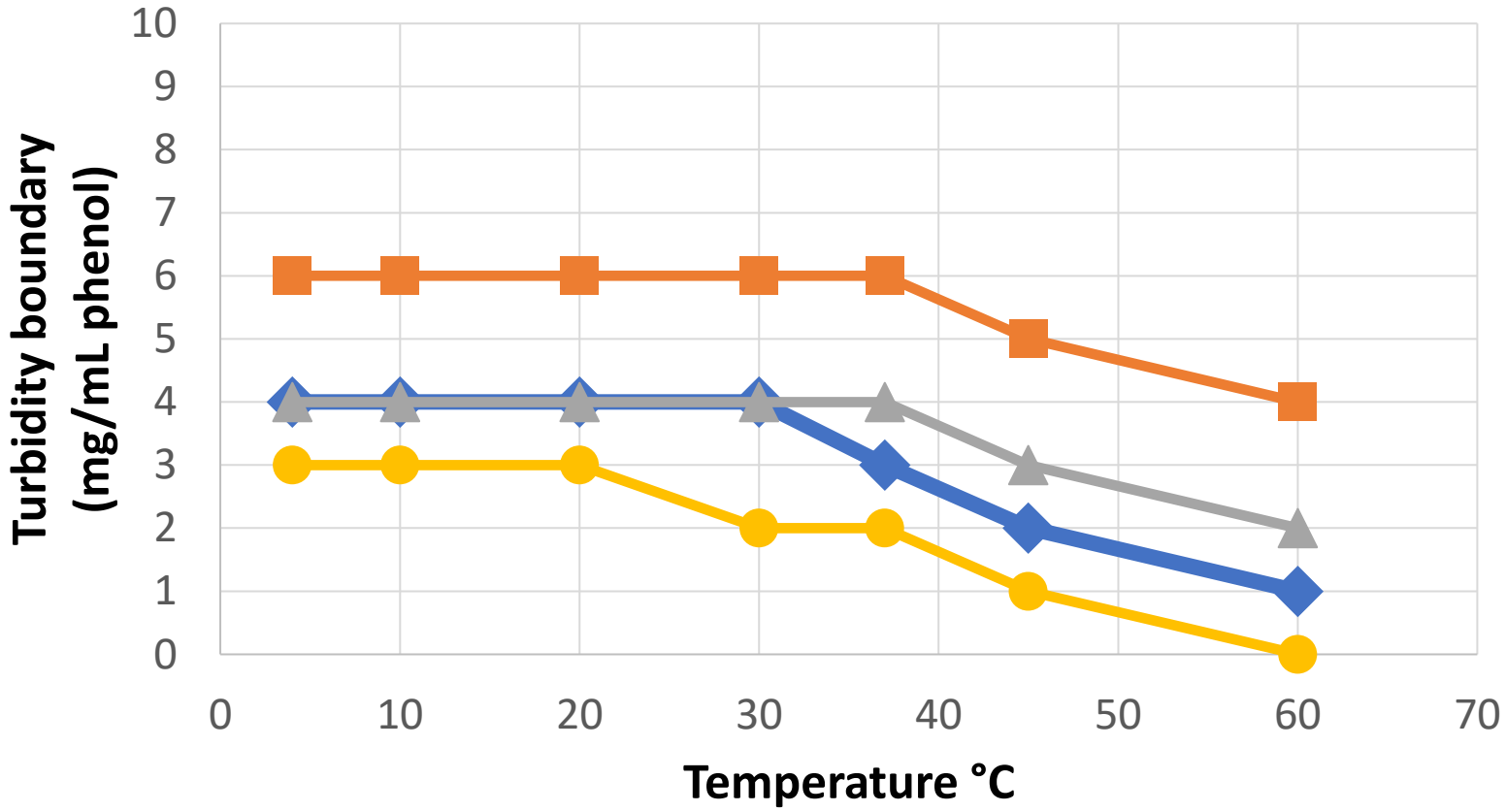
Turbidity boundary decreases as temperature increases for surfactant-preservative mixtures

- 1 mg/mL **P188**
- P188 dominates turbidity boundary
- Consistent across BzOH concentrations



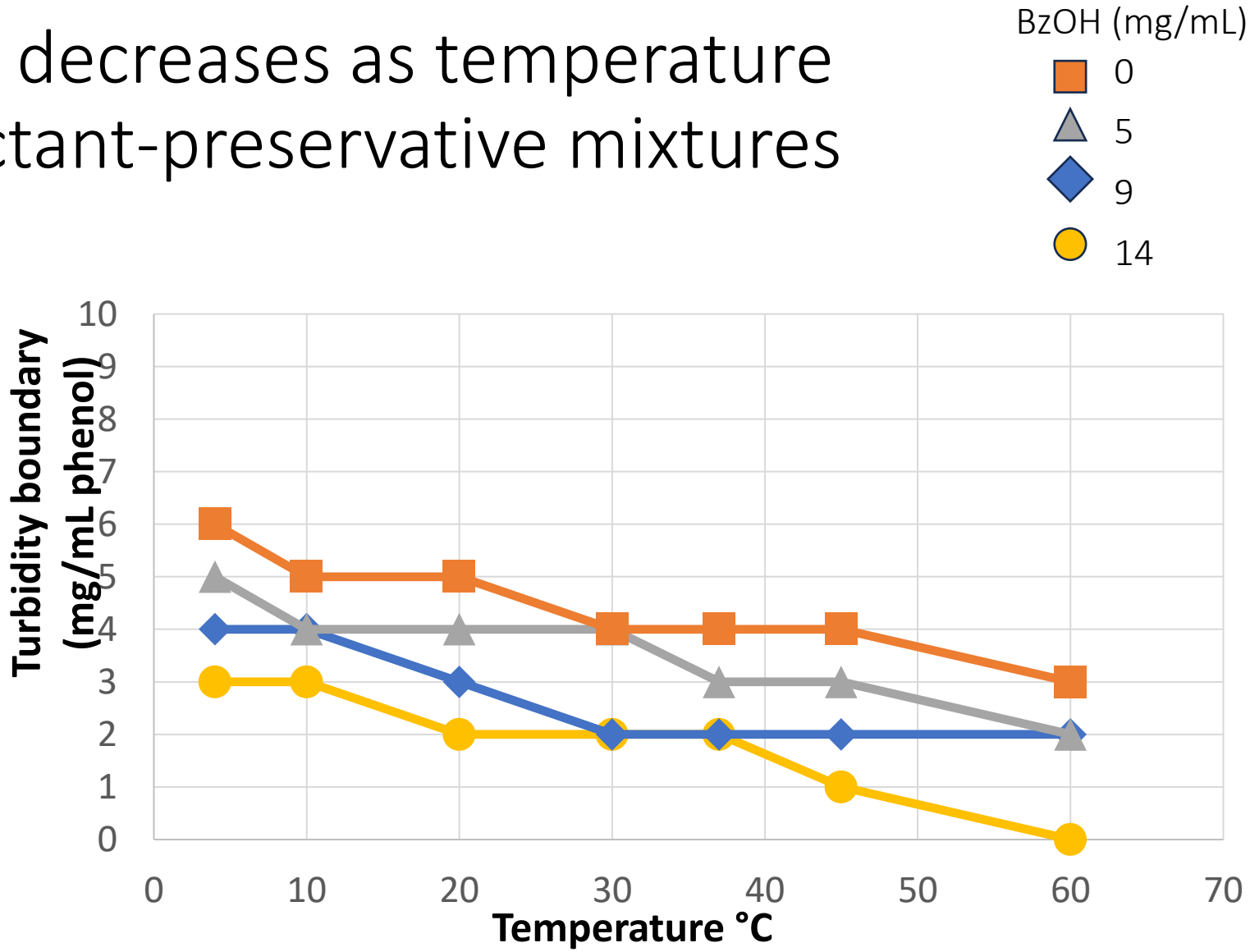
Turbidity boundary decreases as temperature increases for surfactant-preservative mixtures

- 1 mg/**ml PS80**
- 3 mg/mL turbidity shift
- Increased temperature response
- Consistent across BzOH concentrations



Turbidity boundary decreases as temperature increases for surfactant-preservative mixtures

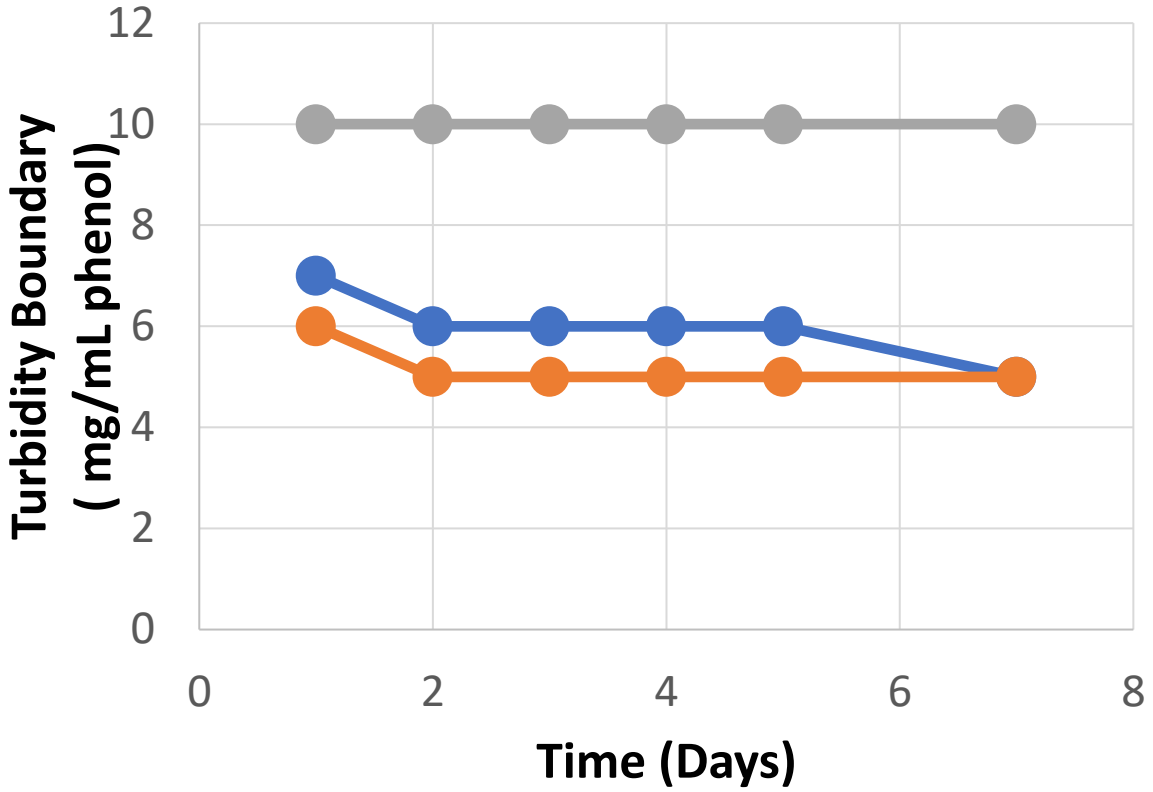
- 1 mg/ml **PS20** Turbidity shift of 4 mg/mL
- Substantial shift as temperature increases
- Consistent across BzOH concentrations



Delayed Turbidity Onset for Polysorbate Mixtures

- PS20, and PS80 show time dependent turbidity, indicates a kinetic component to phase separation
- P188 does not show time dependent turbidity

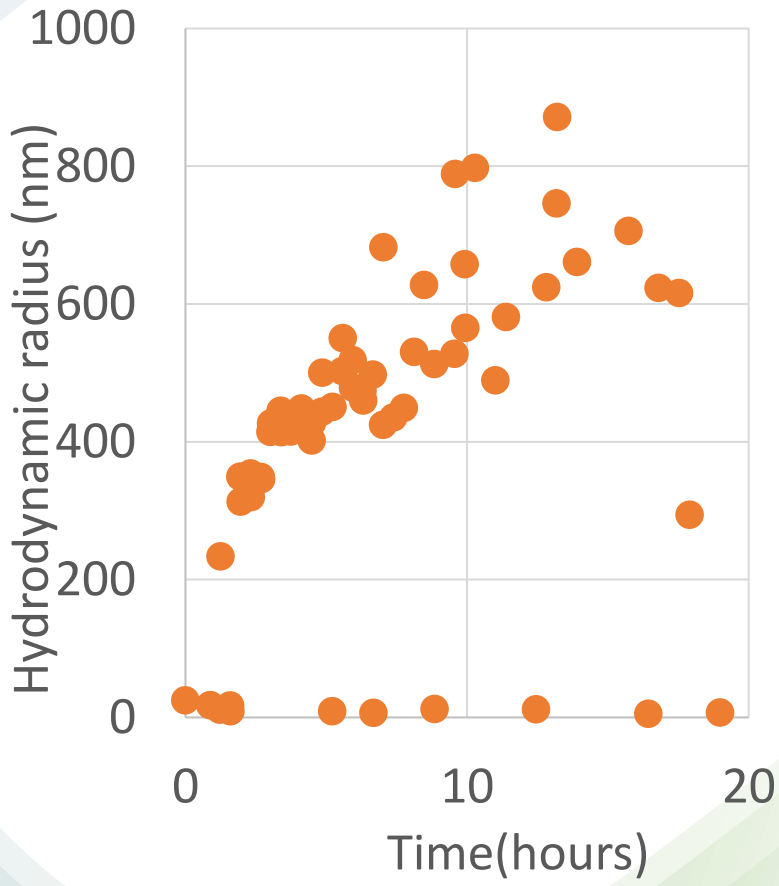
P188
PS80
PS20



DLS Shows Aggregate Growth Over Time

- 1 mg/mL Polysorbate 20
4 mg/mL Phenol
0 mg/mL Benzyl Alcohol

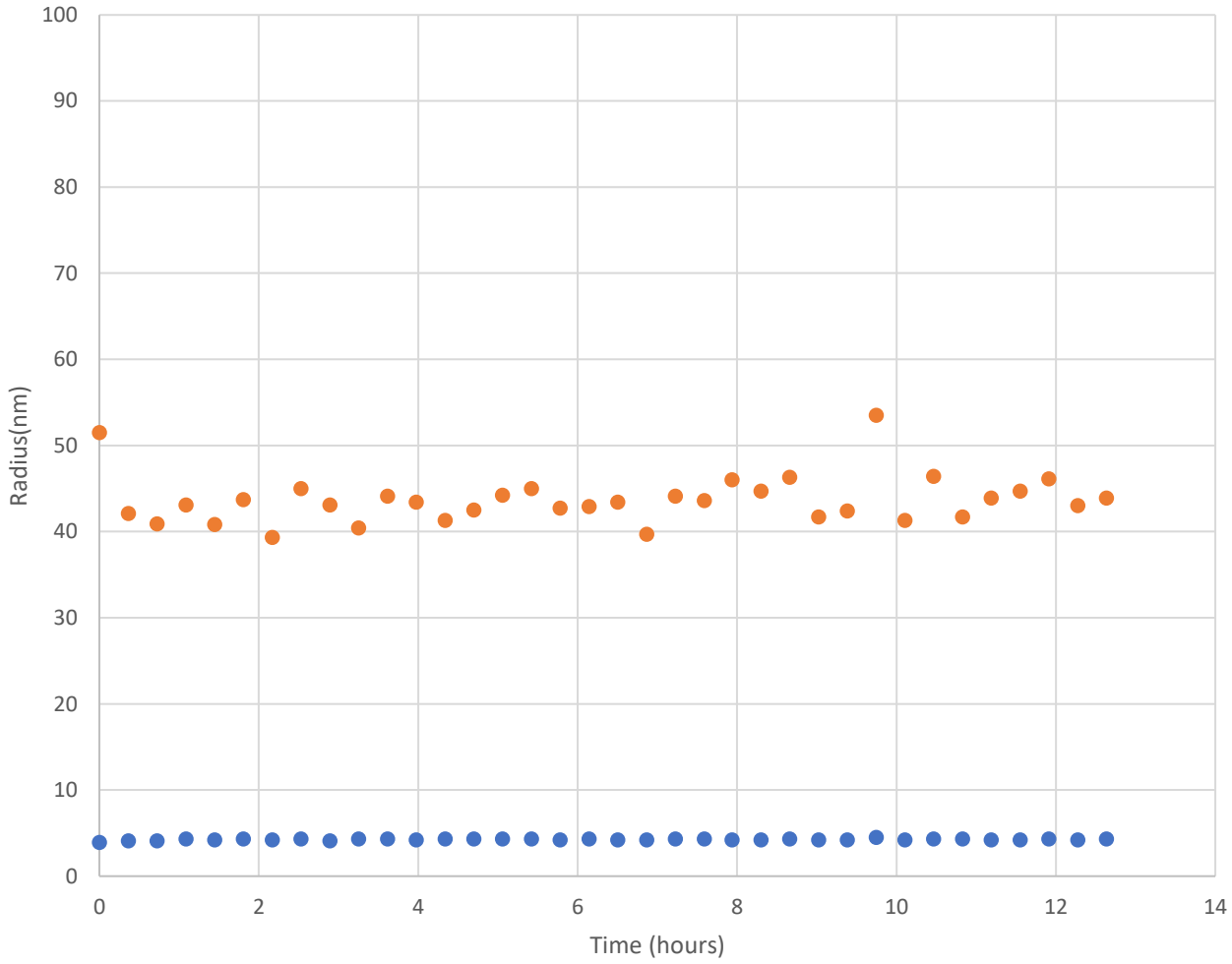
- Initially clear, became turbid
- Temperature was fixed at 37° C



DLS Shows Aggregate Growth Over Time

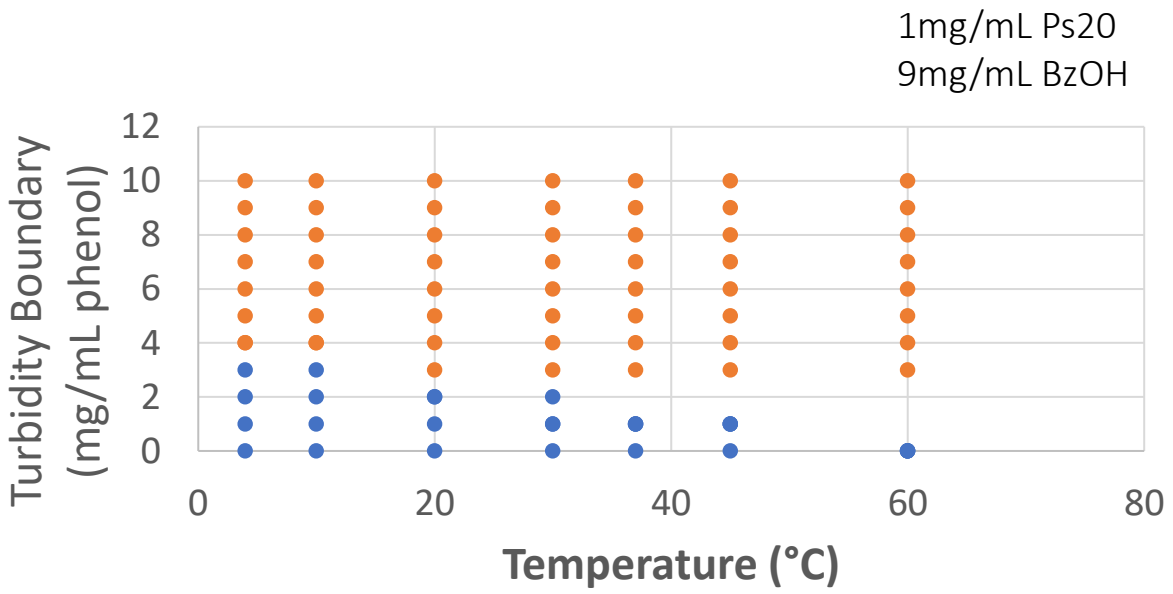
1 mg/mL Polysorbate 20
1 mg/mL Phenol
9 mg/mL Benzyl Alcohol

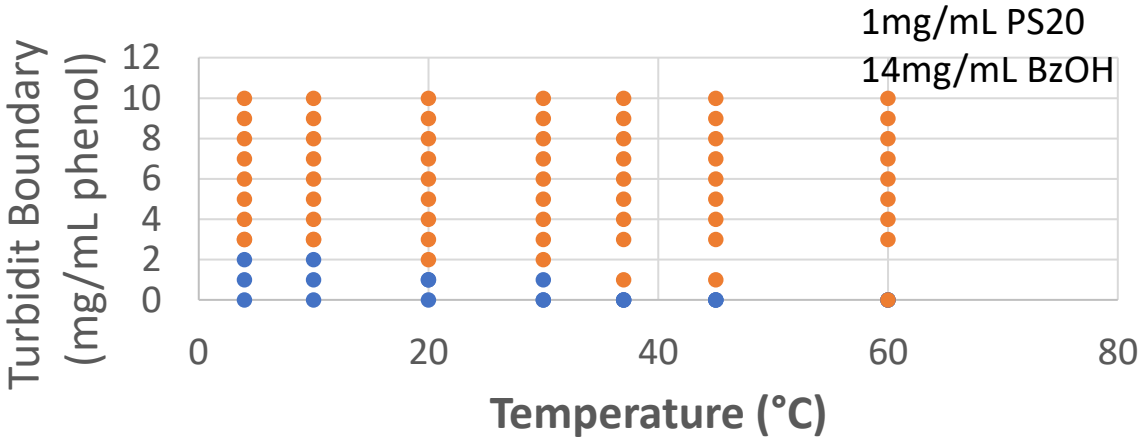
- Initially clear, became turbid
- Temperature was fixed at 37° C



Conclusion

- Identify stable concentrations for pharmaceutical use
- PS20 is more sensitive to BzOH than PS80 and P188
  - PS20 is not a suitable surfactant to be used with {BzOH + Phenol}
- Kinetics of phase separation are slower than P188
  - PS20 requires a more sophisticated characterization of stability





Acknowledgements

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To the shark tank, thank you!