Duke UNIVERSITY

NIST CENTER FOR NEUTRON RESEARCH

# Optimizing Pharmaceutical Formulations

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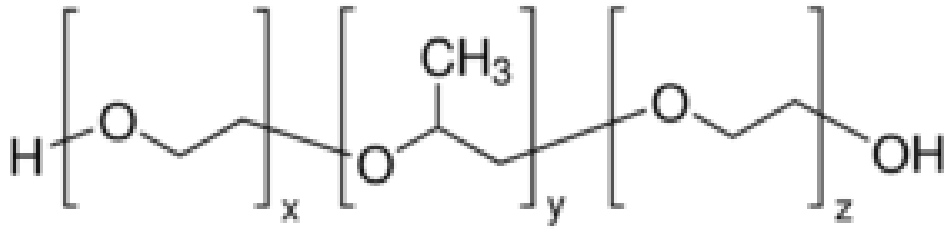
SURF Colloquium, August 1–3 2023

# Background

- Protein drug formulations include active protein, preservatives, and surfactants among other excipients
- Surfactants used to keep protein dispersed evenly in solution
- Preservatives used to prevent microbial growth
- Ideally maximize antimicrobial strength while remaining evenly dispersed in solution




Poloxamer 188
8780 g/mol
x = z ≈ 80; y ≈ 30

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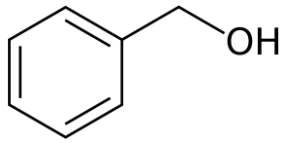
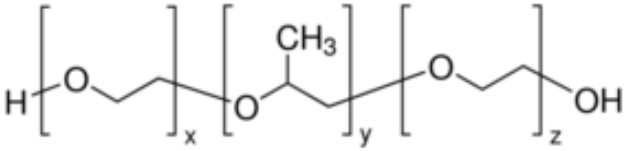
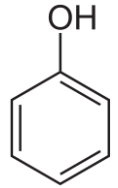



Benzyl alcohol



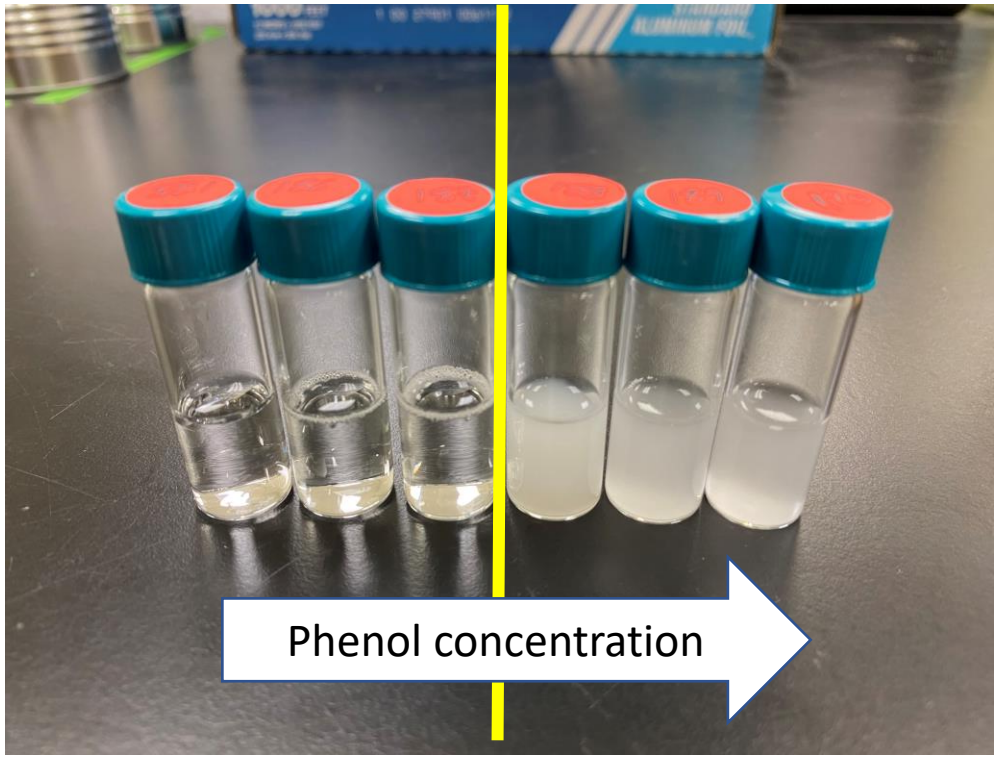

Poloxamer 188



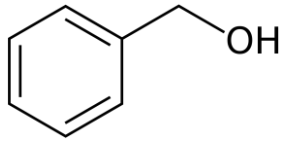

Phenol

# Problem

- Surfactants used to stabilize protein
- Surfactants and preservatives are aggregating below solubility limits
  - Phenol solubility is 84 mg/mL
  - Poloxamer 188 solubility is > 400 mg/mL
- Aggregation → less stable → degrade function, trigger immune response




Turbidity boundary @ 7 mg/mL phenol

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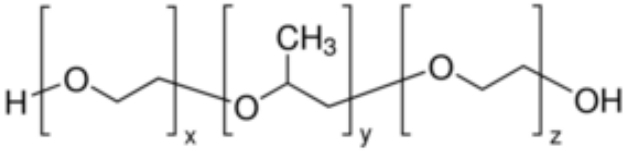
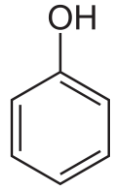


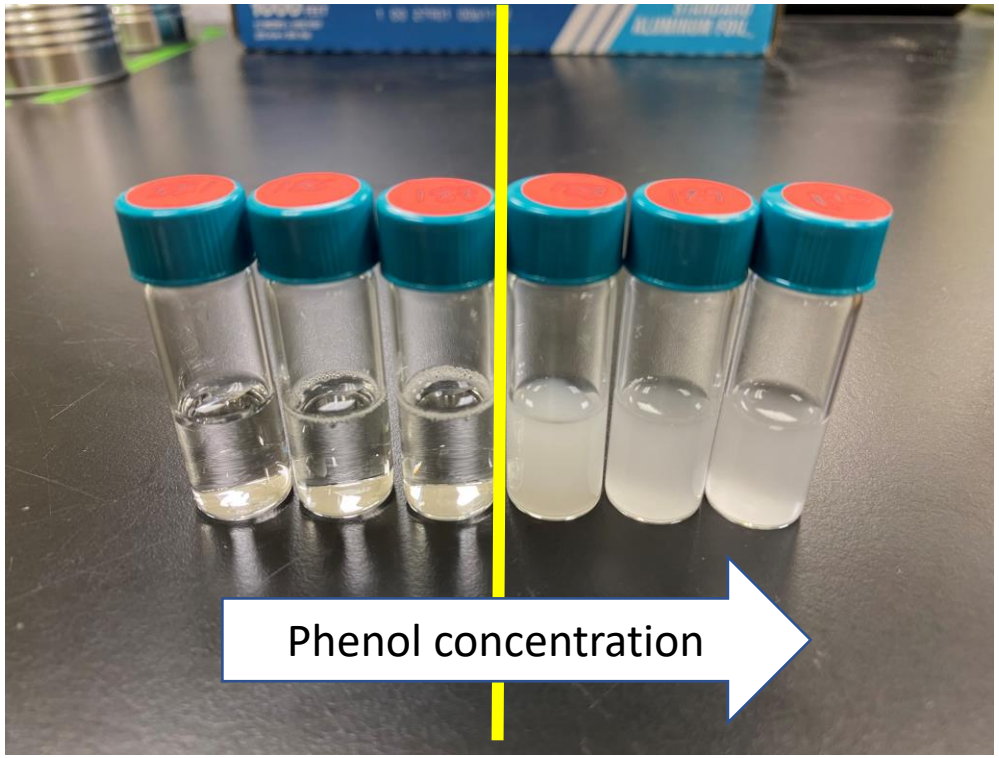

Poloxamer 188




Phenol

# Goal

- Create phase diagrams at varying conditions (Clear/Turbid)
  - Turbidity boundary is the first sample in phenol spectrum to exhibit turbidity
- Investigate impact of surfactants, preservatives, and temperature on stability of formulation
- Provide pharmaceutical industry with range of stable concentrations

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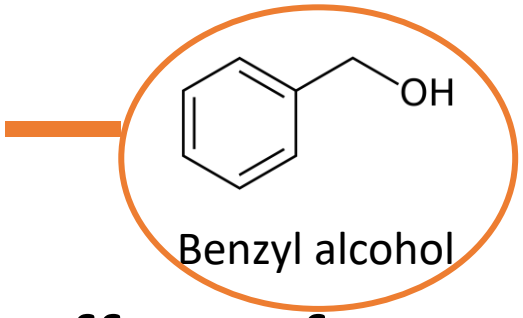
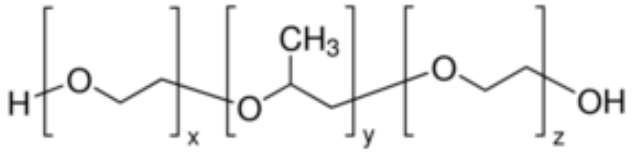


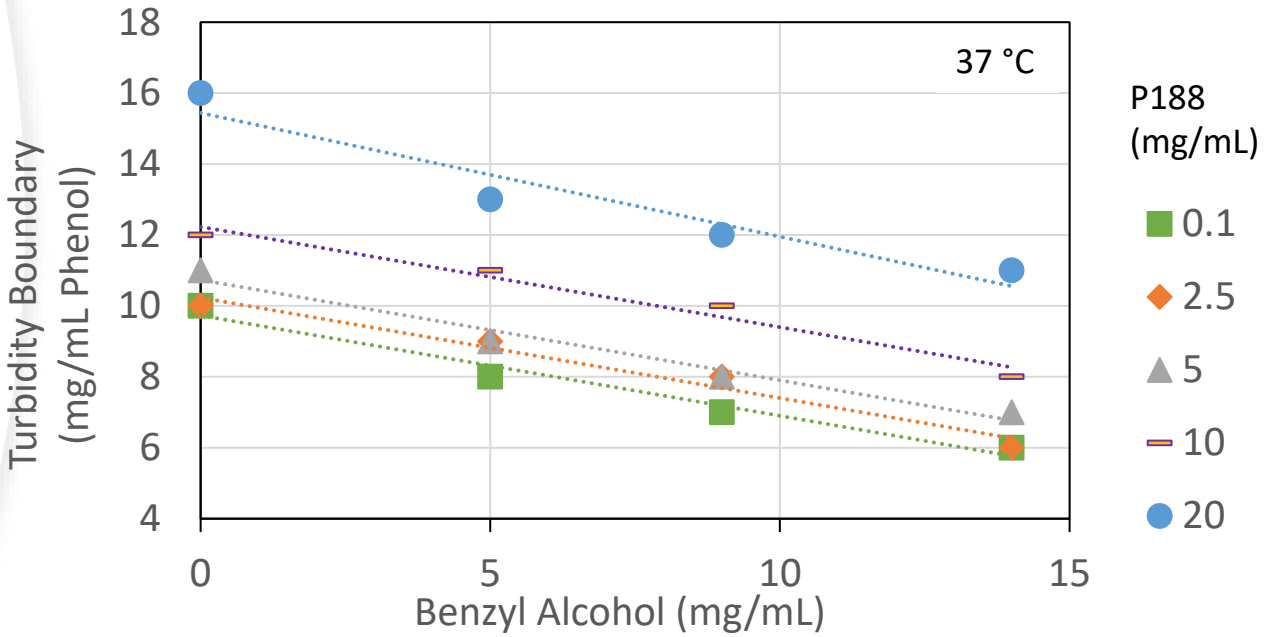

Benzyl alcohol

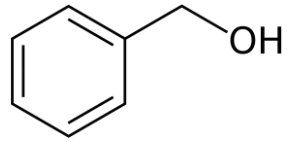



Poloxamer 188

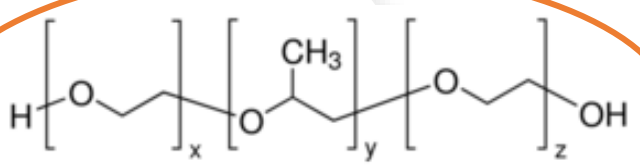
# Effect of Benzyl Alcohol

- Used as preservative
- Combined w/ phenol = more effective antimicrobial while below dose limits
- Decreases turbidity boundary by 0.28 mg/mL phenol per 1 mg/mL increment of benzyl alcohol





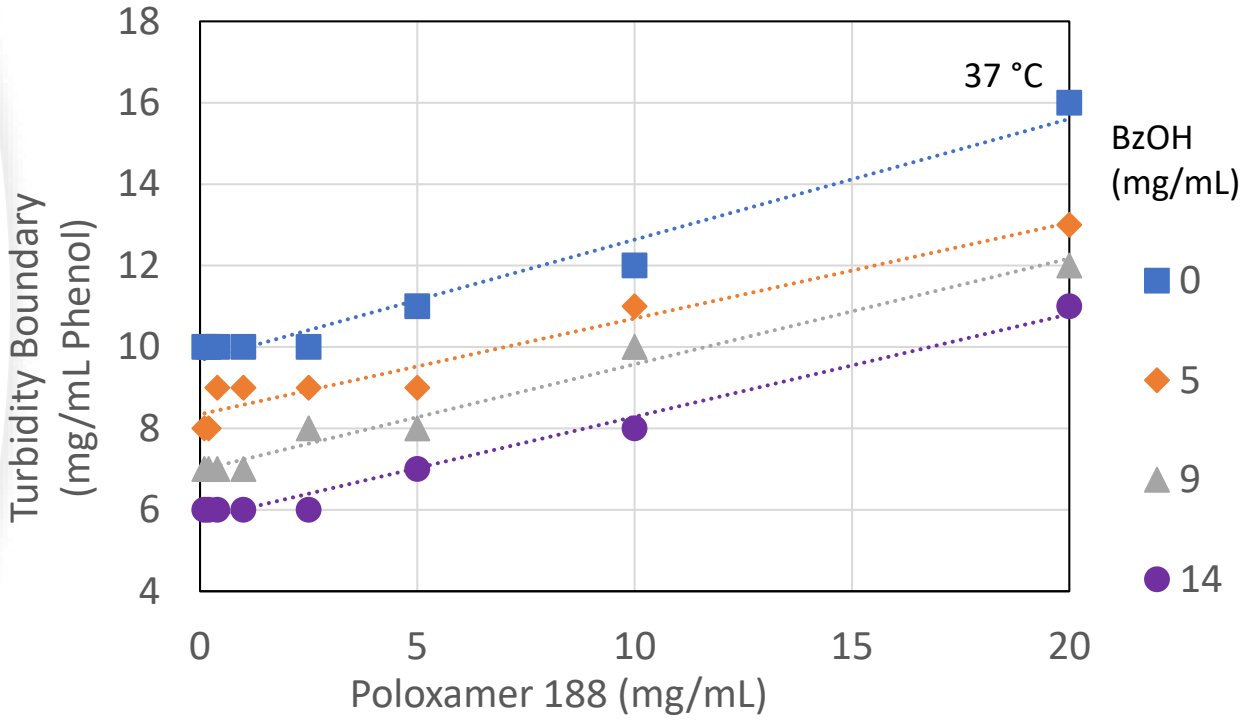

Benzyl alcohol

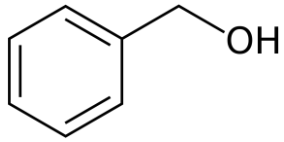



Poloxamer 188

# Effect of Poloxamer 188

- Commonly used as a surfactant
  - Consistency in production
  - Not susceptible to hydrolysis
- Increases turbidity boundary by 0.26 mg/mL phenol per 1 mg/mL increment of P188



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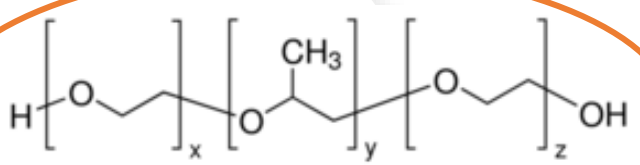


Poloxamer 188

# Effect of Poloxamer 188

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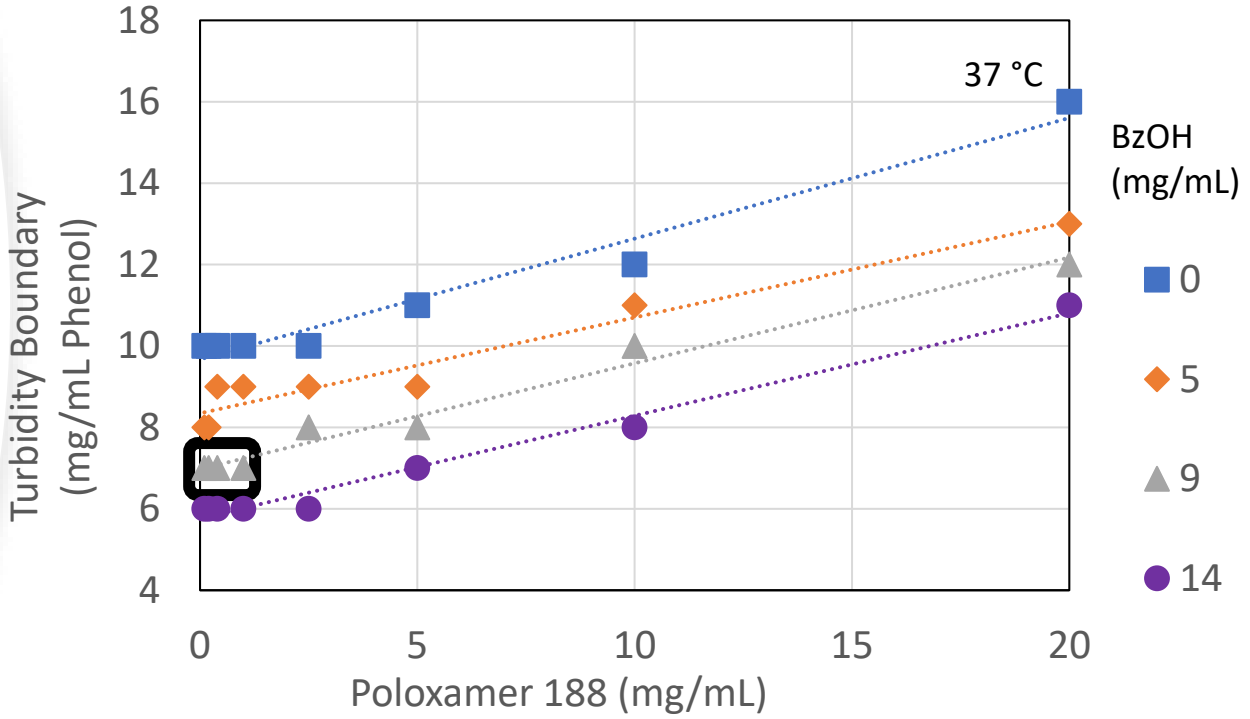
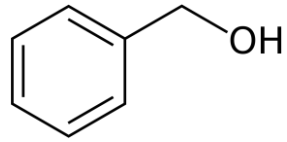
- Drug formulations typically use 0.2–0.6 mg/mL P188



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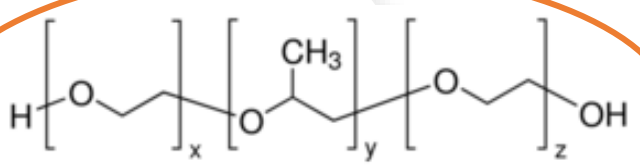
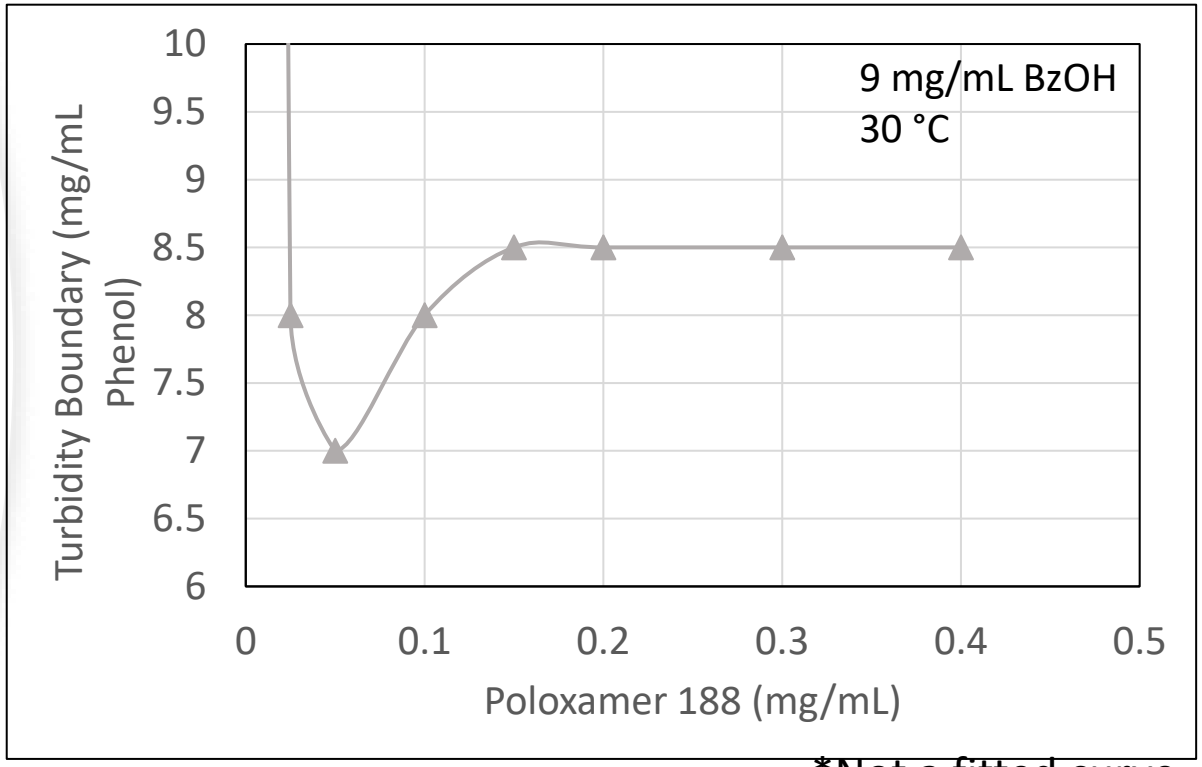


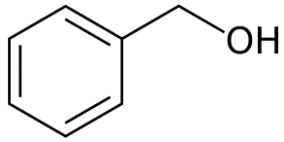

Poloxamer 188

# Effect of Poloxamer 188

- Below 0.05 mg/mL P188 opposite effect occurs
  - In absence of poloxamer 188 turbidity boundary ~80 mg/mL phenol
  - But poloxamer 188 increases turbidity boundary




*Not a fitted curve

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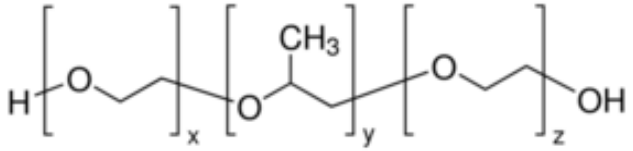
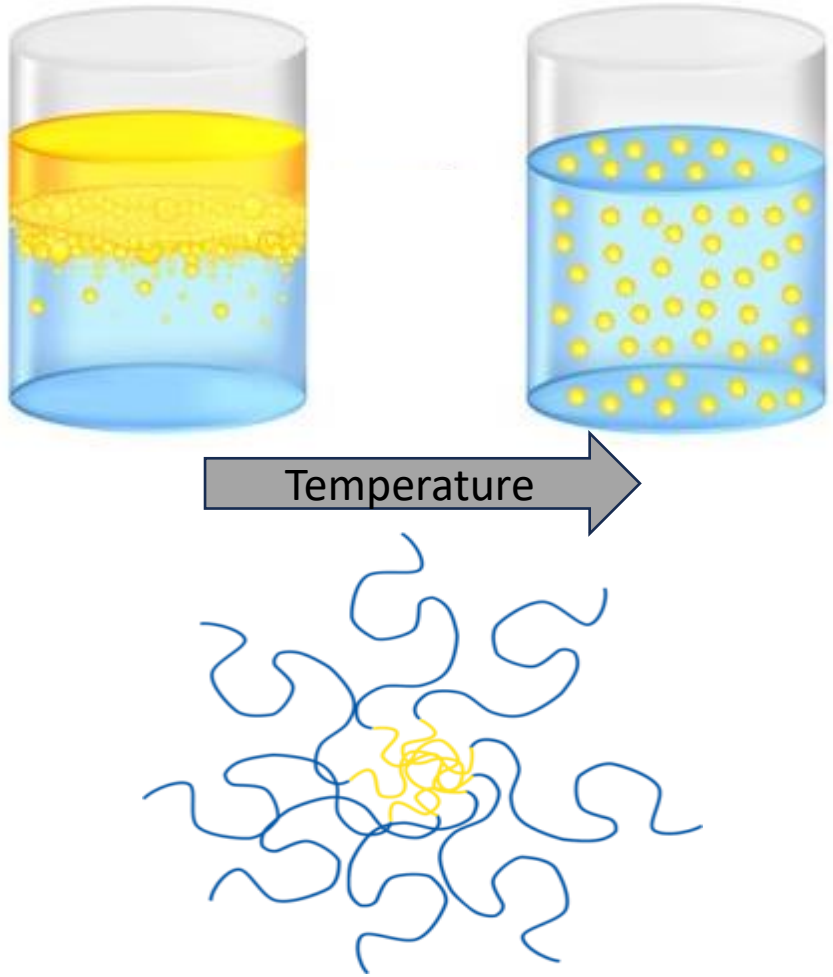


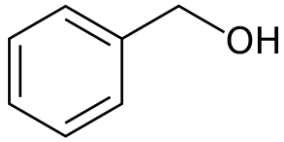

Poloxamer 188

# Effect of Temperature

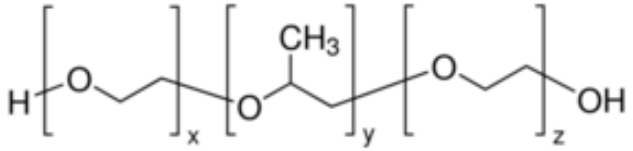
- Heating hydrophobic molecules like phenol and benzyl alcohol helps dissolve in water
- Poloxamer 188 has opposite relationship, T ↑ solubility ↓
- Which effect is most prominent?




Poloxamer 188 micelle




Benzyl alcohol




Poloxamer 188

# Effect of Temperature

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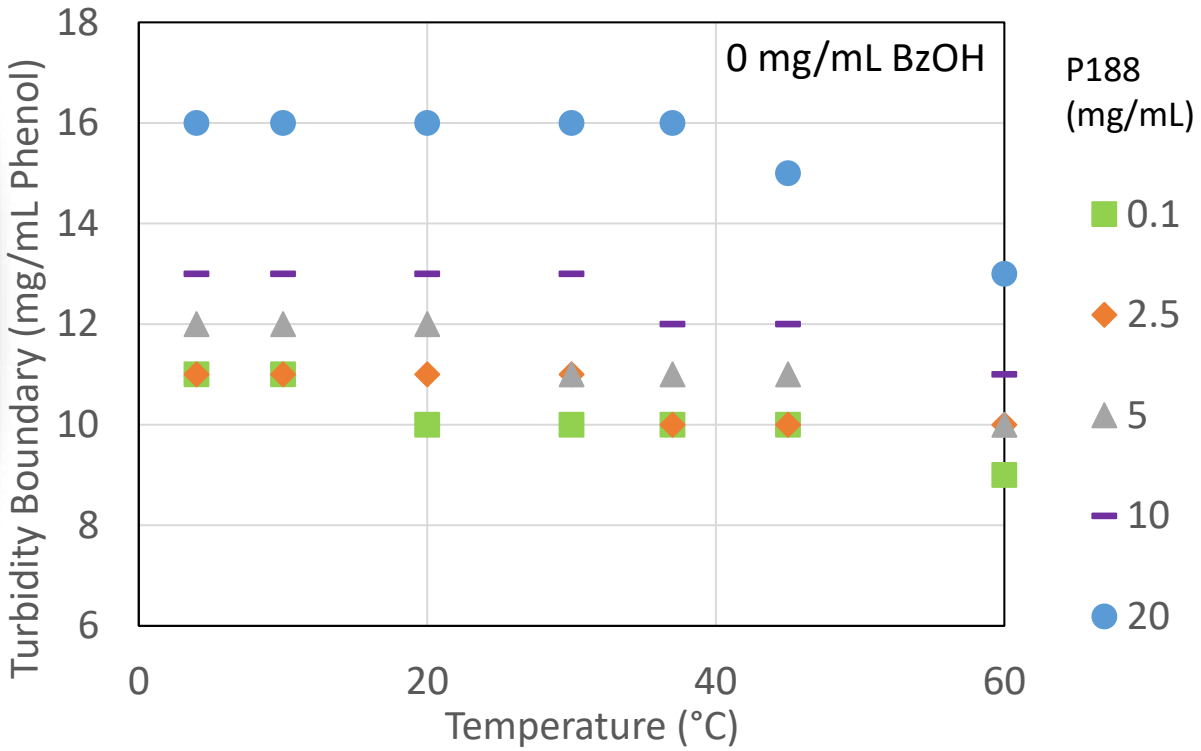
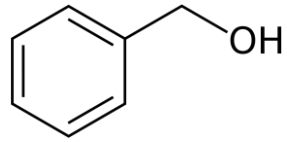
- Which effect is most prominent?
- Temperature decreases turbidity boundary



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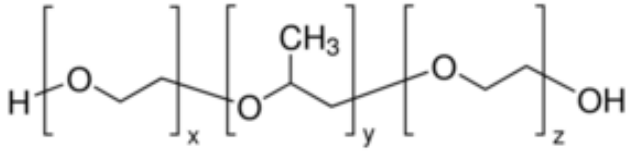
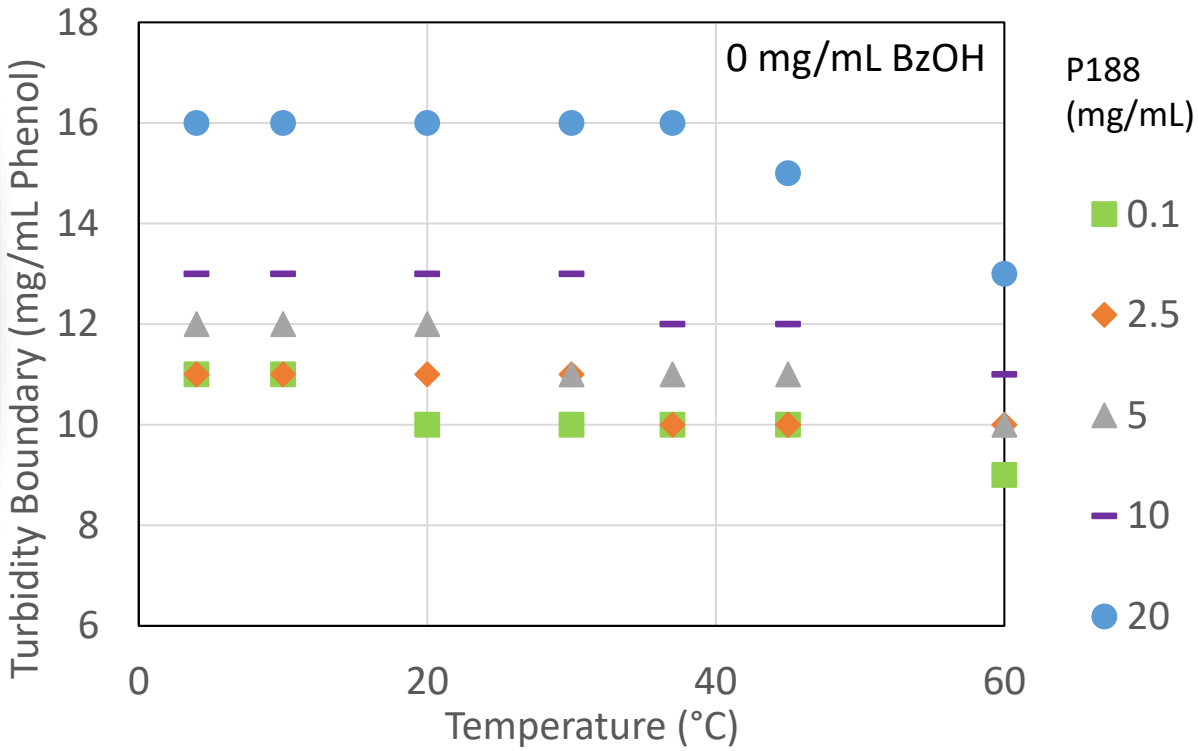



Poloxamer 188

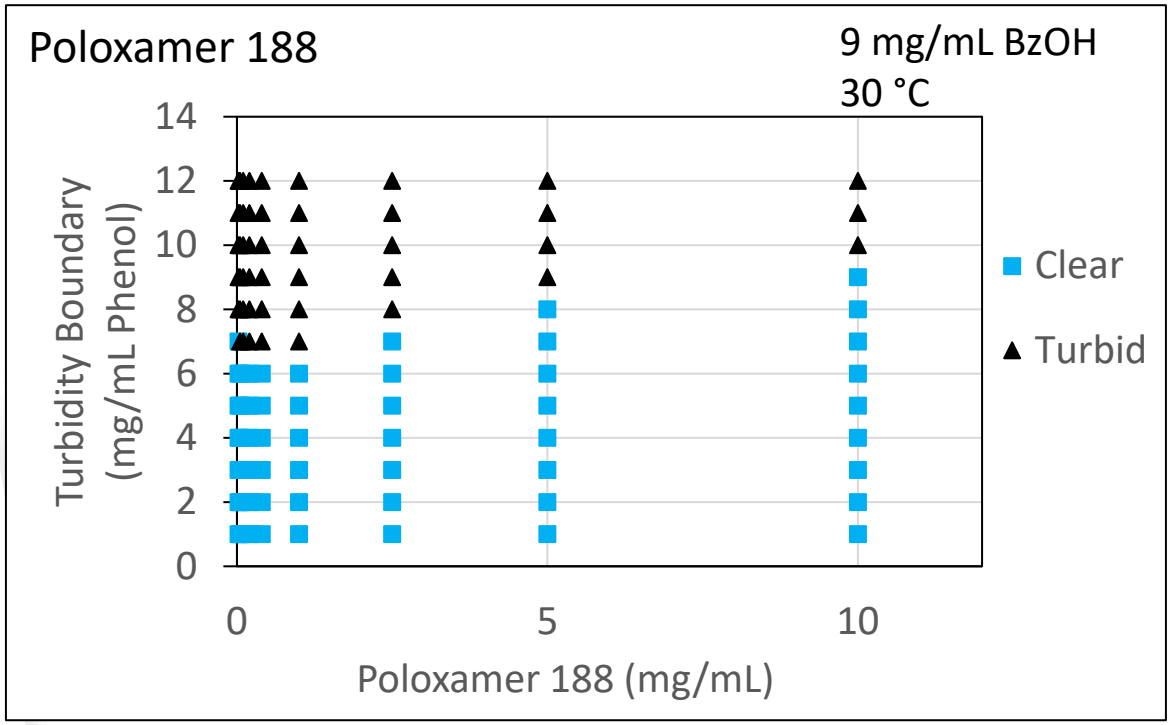
# Effect of Temperature

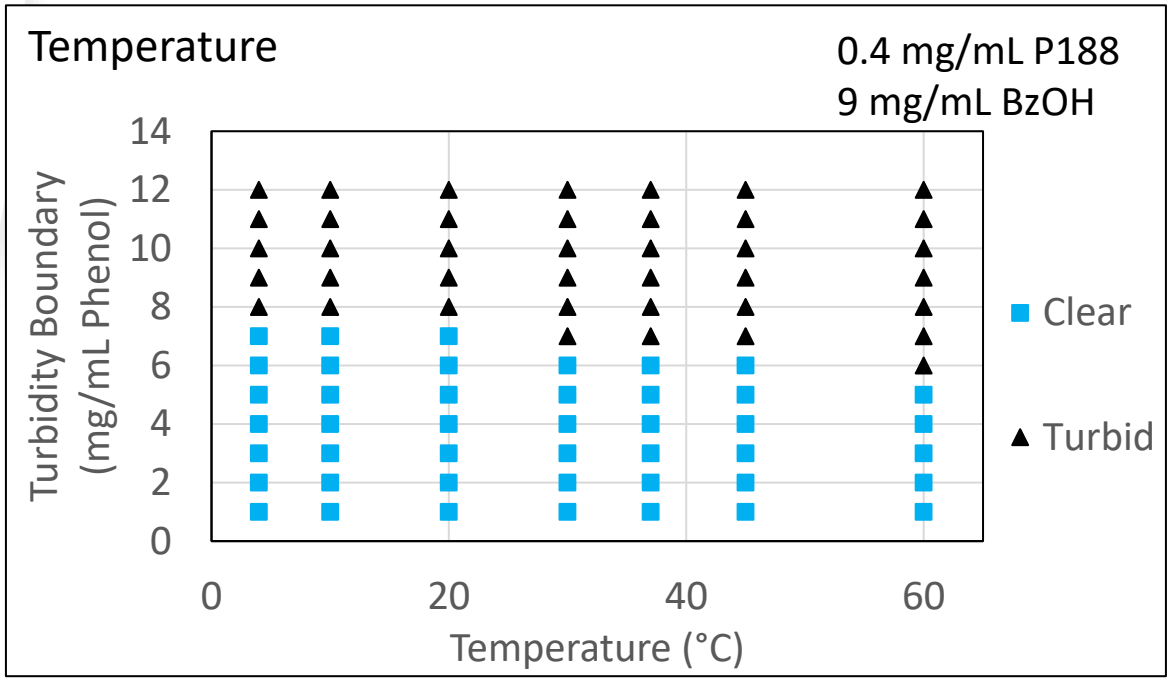
- Two regimes of turbidity
- 37 °C is critical micelle temperature for poloxamer 188
- Hypothesized mechanism for aggregation:
  - Poloxamer 188 T ↑ solubility ↓
  - Phenol prefers polypropylene oxide block over water



# Conclusion

- Provide a range of stable concentrations for pharmaceutical use
- Pharmaceutical formulations typically:
  - 0.2–0.6 mg/mL poloxamer 188
  - 9 mg/mL benzyl alcohol
- Phenol < 7 mg/mL



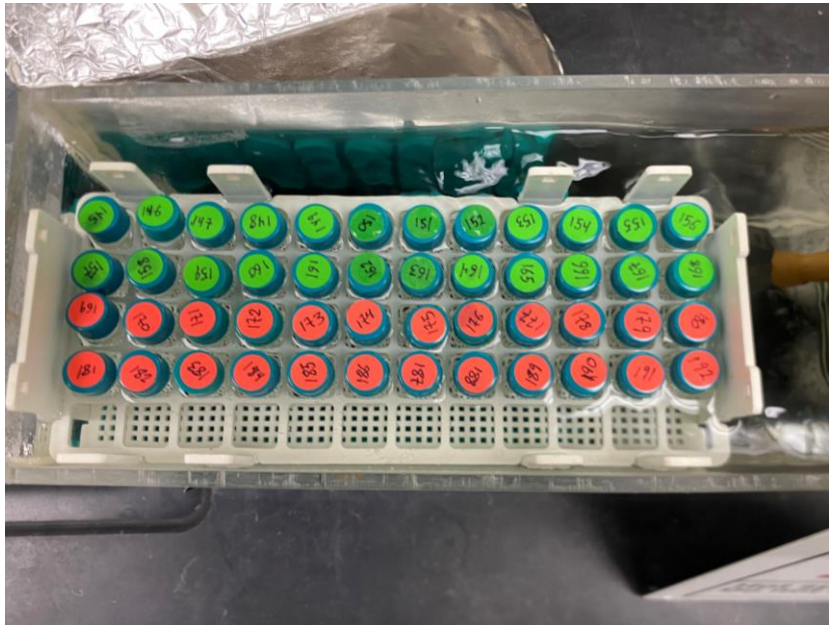
# Acknowledgements

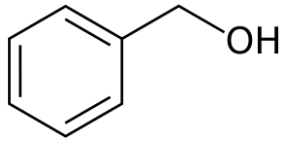

- Center for High Resolution Neutron Scattering, funding the SURF program at the NCNR
- Dr. Rachel Ford, amazing mentor
- The friendly scientists and staff at the NCNR



# Experimental Design

- Create samples varying phenol, poloxamer 188, and benzyl alcohol
- Place in temperature bath
- Record phase (T/C) at varying temperatures
- All samples repeated at least once for reproducibility



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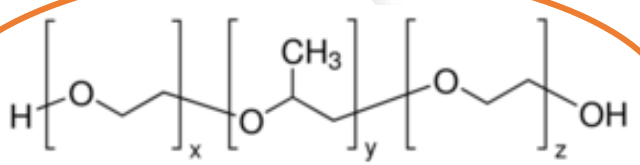
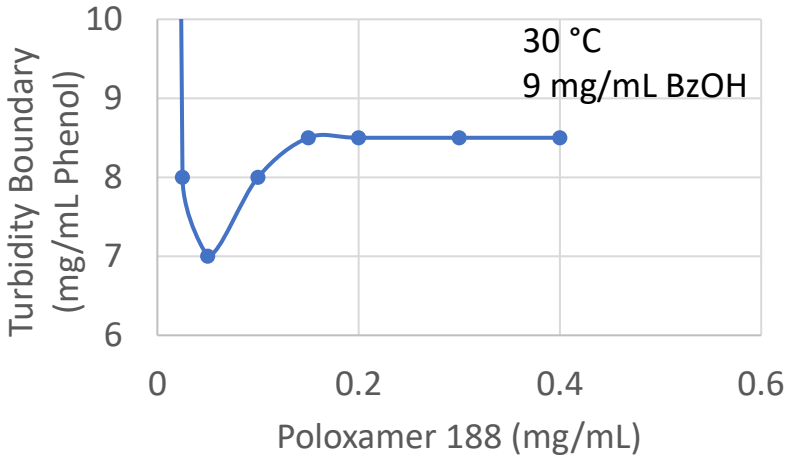


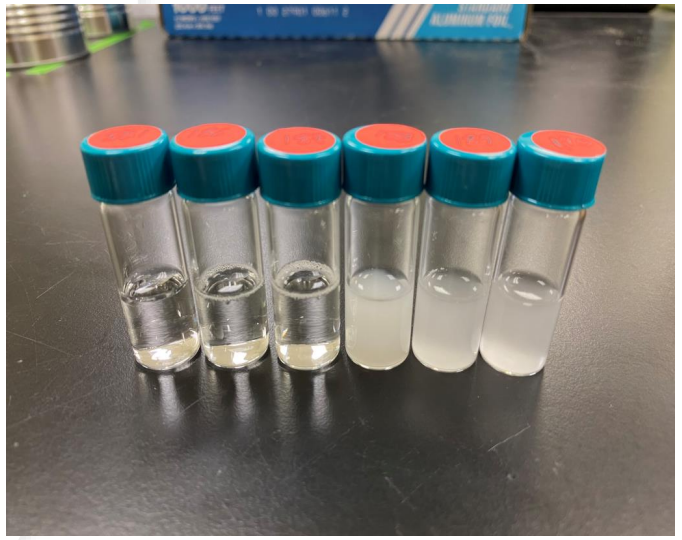

Poloxamer 188



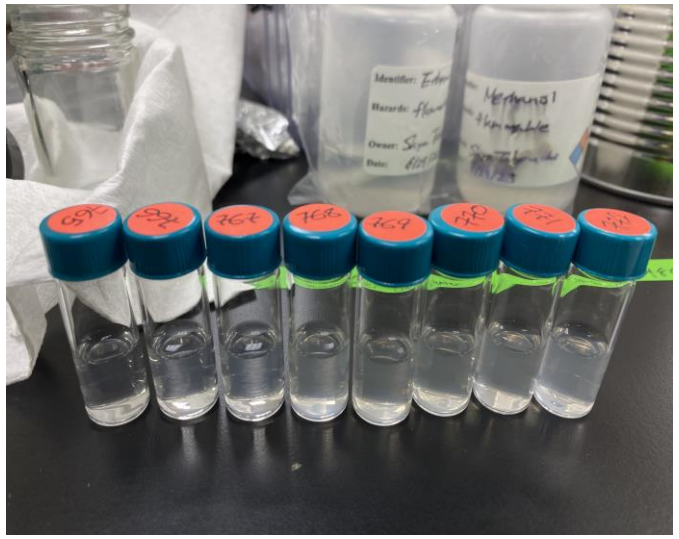

# Effect of Poloxamer 188

- Below 0.05 mg/mL P188 opposite effect occurs
  - In absence of poloxamer 188 turbidity boundary ~80 mg/mL phenol
  - But poloxamer 188 increases turbidity boundary
- Turbidity likely caused by micellization

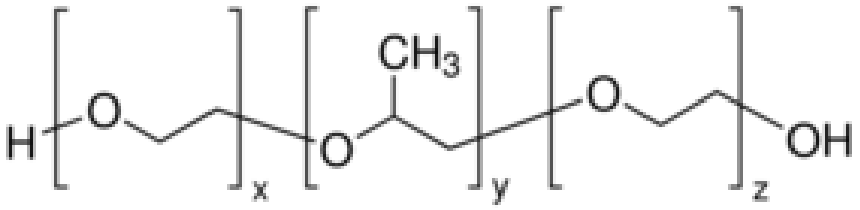
*Not a fitted curve



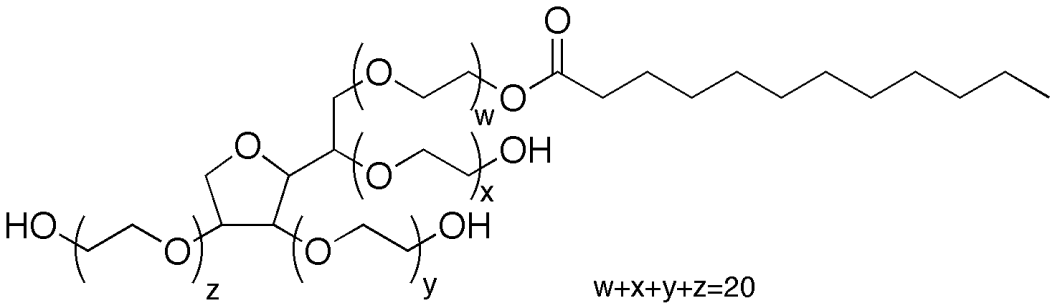
0.2 mg/mL poloxamer 188



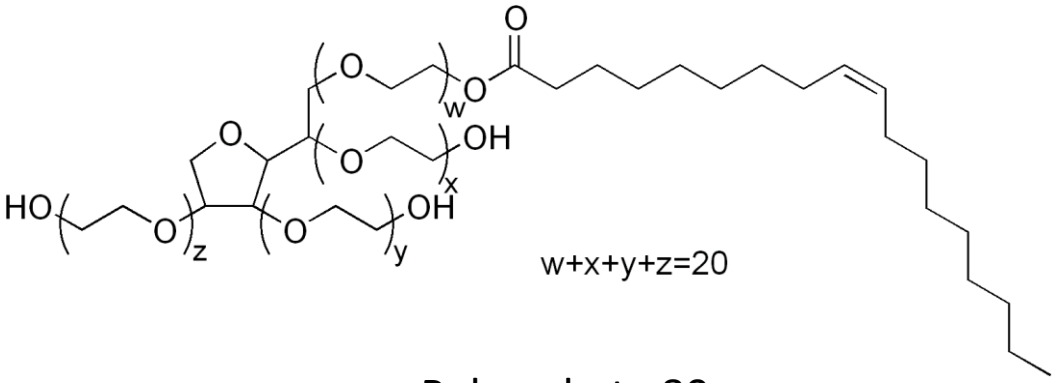
0.025 mg/mL poloxamer 188




Poloxamer 188
Molecular weight: 8780 g/mol




Polysorbate 20
Molecular weight: 1226 g/mol




Polysorbate 80
Molecular weight: 1310 g/mol