Effects of Solvents on the Assembly of Nanoparticles from Poly(styrene-b-ethylene glycol)

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Forcing Polymers to Self-Assemble into Nanoparticles

- Polymers
  - Long repeating chains of identical molecules
  - Common uses: Hand sanitizer, rubber, and plastics
- Nanoparticles
  - Nanometer sized particles
  - Using polymer at different molar masses and using different synthesis processes to study the structure of nanoparticles
- Scattering Methods
  - Shot a beam of radiation (light/x-ray/neutrons) at the sample particles, parts of the radiation will scatter off, which is measured by a detector
  - Use the scattering data to determine the structure of the nanoparticles

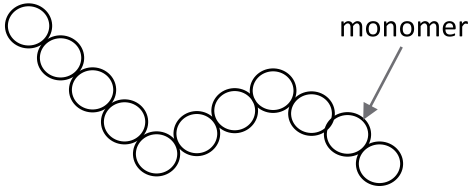
Using different synthesis conditions to change the structures of nanoparticles

- Study how different solvents, mixing methods of copolymers, and purification processes affect the synthesis of nanoparticles
- Understanding the structures and self-assembly of nanoparticles produced from blended polymers
- Studying the reproducibility of the process to make nanoparticles
- Improved targeted drug delivery
  - Drug delivery nanoparticles: nanoparticles that act as a transportation system for drugs to circulate through our bodies
- Our samples will act as a model system to more easily control the final structure, and study a variety of structures

Kelley, E. G., Smart, T. P., Jackson, A. J., Sullivan, M. O., & Epps, T. H. (2011). Structural changes in block copolymer micelles induced by cosolvent mixtures. *Soft Matter*, *7*(15), 7094. https://doi.org/10.1039/c1sm05506b

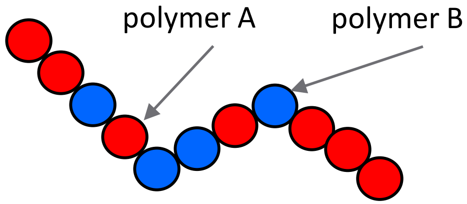
Dissolving Polymers with Solvents

Polymer:



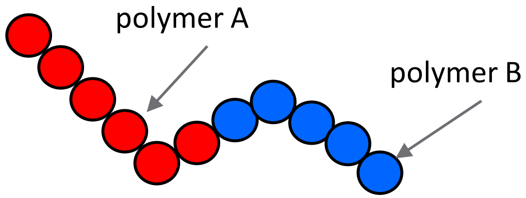
Long repeating chains of monomers/molecules

Copolymer:



Repeating chain of 2 or more different polymers (can be random or alternating)

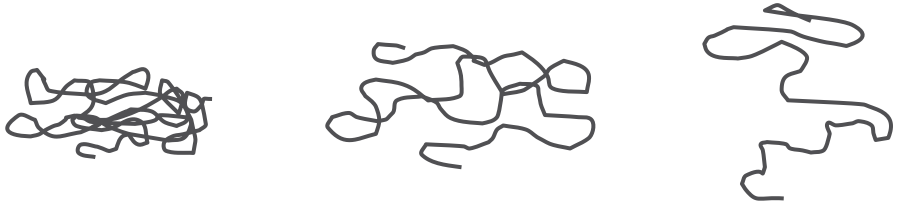
Block Copolymer:



Uninterrupted chain of 1 polymer connected to another uninterrupted chain of a second polymer

Solvents: swell and dissolve polymers

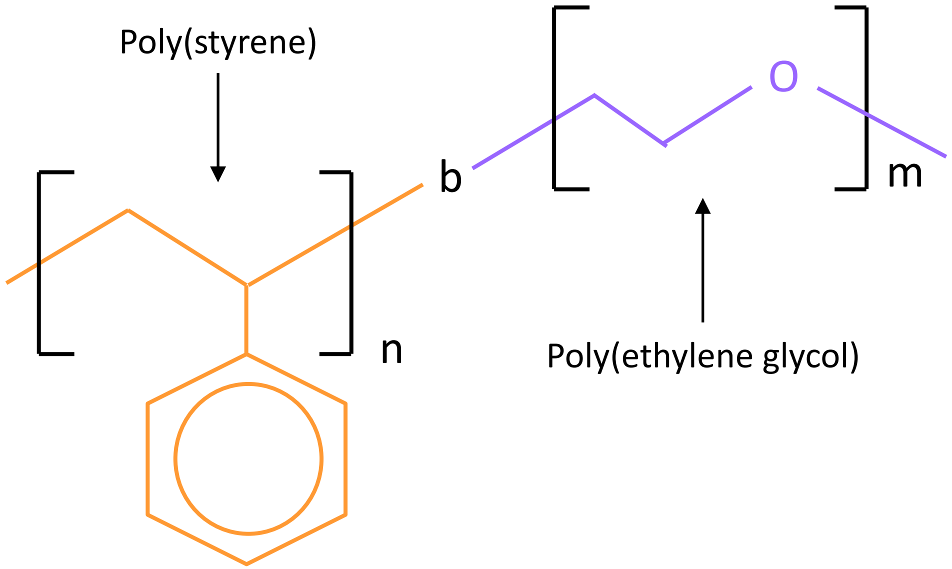
- Due to polymers' long chains, they can adopt different conformations based on the degree of solubility (how much a solvent will associate with a dissolved polymer)



Hiemenz, P. C., & Lodge, T. (2007). *Polymer chemistry* (2nd ed). CRC Press.

Polymer Solubility

- Poly(styrene-b-ethylene glycol) (PS-b-PEG) will be the block copolymer used to synthesize the nanoparticles we want to study

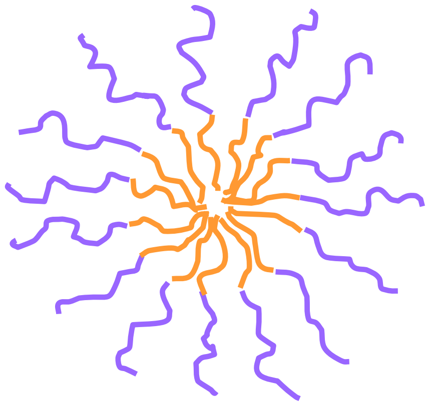


- Changing molar mass affects the solubility of polymers and other physical properties (polymer's ability to stabilize nanoparticles)
  - 1.6/3.8-b-5: molar mass of PS-b-PEG (M [=] kDa)
- The 2 different copolymer ends have different solubility
  - If both ends are soluble, the whole polymer is soluble
  - If only one end is soluble, then polymers can assemble into different structures

Hiemenz, P. C., & Lodge, T. (2007). *Polymer chemistry* (2nd ed). CRC Press.

How Polymers Form Nanoparticles

- The nanoparticles we are working with have a core-shell structure



Hydrophilic shell: Poly(ethylene glycol)
(hydrophilic: attracted to water)

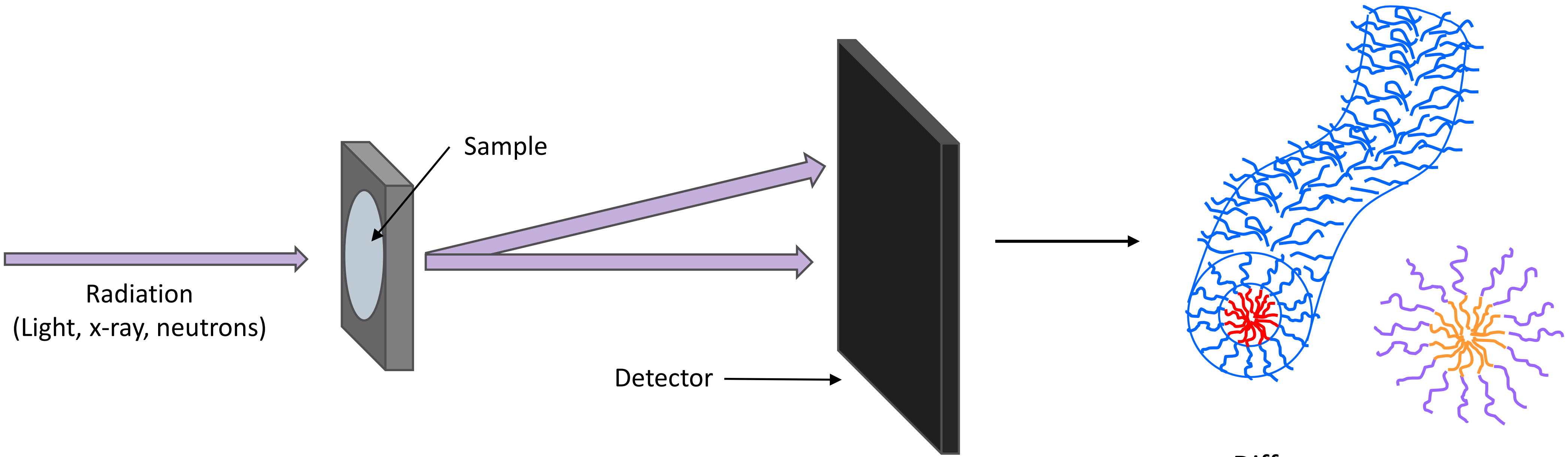
Hydrophobic core: Poly(styrene)
(hydrophobic: repels water)

- Forcing copolymers to assemble into nanoparticles by changing the solvent
  - Solvent good for both polymer ends $\longrightarrow$ Solvent (water) only good for 1 polymer end
- Block copolymers can form many different structures
  - Spheres and cylinders are primary examples, but others exist (Vesicles, Y-junctions, and more)
  - We are trying to make only spheres and learn when the nanoparticles stop assembling into spheres

Jain, S., & Bates, F. S. (2004). Consequences of Nonergodicity in Aqueous Binary PEO−PB Micellar Dispersions. *Macromolecules*, *37*(4), 1511–1523. https://doi.org/10.1021/ma035467j

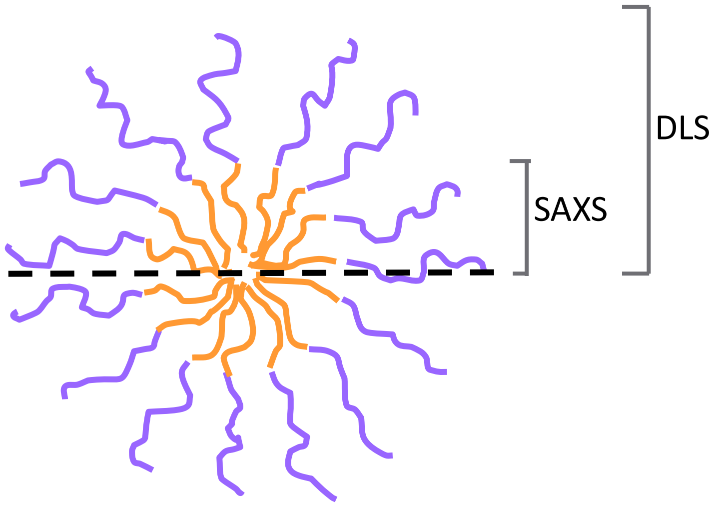
Why Scattering Methods are Used

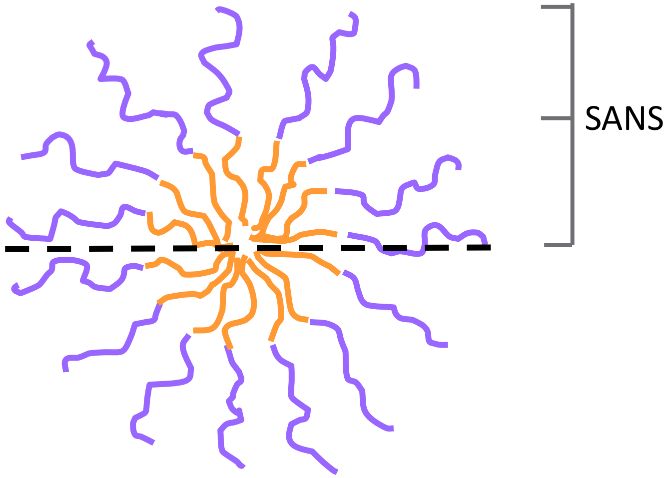
- A beam of radiation (light/x-ray/neutrons) is shot at the sample nanoparticles, parts of the radiation will scatter off, then be measured by a detector
- The detector measures the amount of scattered radiation at multiple angles, which is analyzed to determine particle structure and size



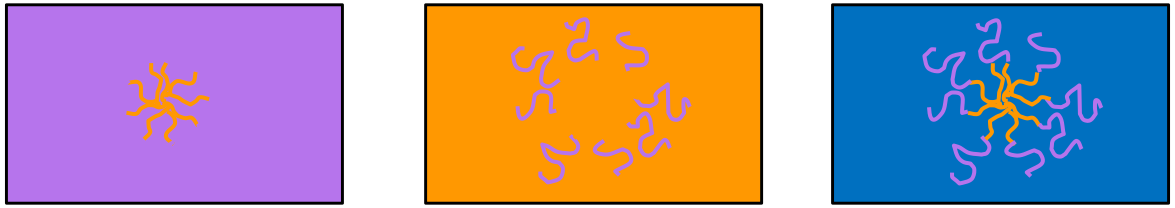
Different structures

Scattering Methods and What it Measures





- Dynamic light scattering (DLS):
  - Measures the radius of the whole structure of the nanoparticles (hydrodynamic radius)
- Small angle x-ray scattering (SAXS):
  - Depends on the polymers and solvent being used and their x-ray contrast
  - For PS-b-PEG in water, should be measuring the radius of the core and some PEG that is close to the surface
- Small angle neutron scattering (SANS):
  - Depends on the polymers and solvent being used and their neutron contrast
  - There is more contrast between H_2O and D_2O, and by mixing these solvents we can differentiate between the PS, PEG, and the whole particle



Overview of the Project

1. Synthesis of nanoparticles at different conditions

1a. Changing molar mass of copolymer

1b. Test solubility for different molar masses

2. Thin film rehydration (removing the solvent before water is added)

3. Solvent switch (removing the solvent while water is in solution)

2a. Using dichloromethane (DCM) solvent

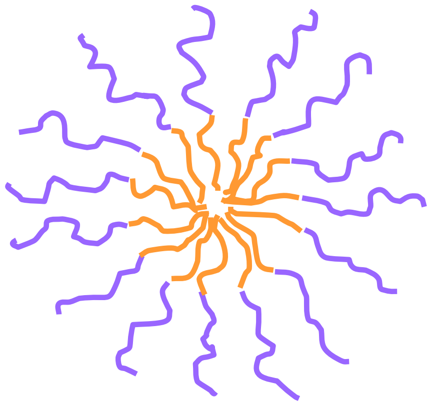
3a. Using tetrahydrofuran (THF) solvent

4. Use scattering methods to compare differences between the processes

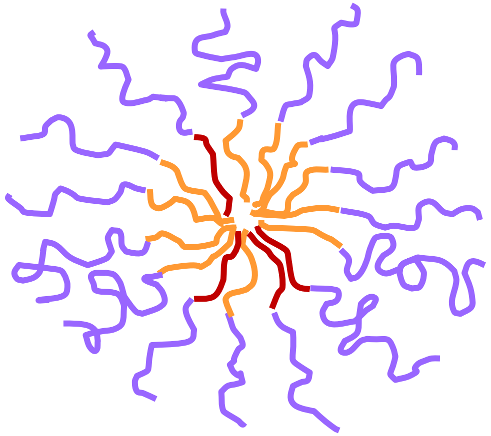
Wright, D. B., Patterson, J. P., Gianneschi, N. C., Chassenieux, C., Colombani, O., & O'Reilly, R. K. (2016). Blending block copolymer micelles in solution; obstacles of blending. Polymer Chemistry, 7(8), 1577–1583. https://doi.org/10.1039/C5PY02006A

Changing Molar Mass of Polymers

- 1.6-b-5 molar mass
  - Soluble in water and produces a clear solution of nanoparticles with a hydrodynamic diameter ~ 40 nm



- 3.8-b-5 molar mass
  - Slightly soluble in water
  - It was also found that blending small amounts of the 3.8 with a majority (> 70%) of 1.6-b-5 results in nanoparticles

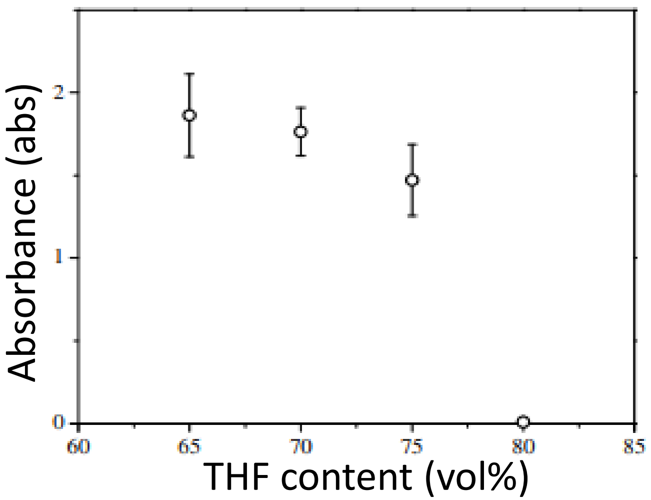


- We want to further study this finding and understand how mixing molar mass of polymer affects the structure of nanoparticles
  - Is the 3.8 polymer always insoluble in water, or is there a concentration where it forms nanoparticles in solution?
  - How does molar mass affect polymer solubility?
  - How do different processes affect the size of synthesized nanoparticles?

3.8 Polymer Solubility Test

- Is the 3.8-b-5 polymer soluble is water, and at what concentration?
- What is the structure if it is soluble?

Absorbance of PB homopolymer in H_2O/THF cosolvent mixtures

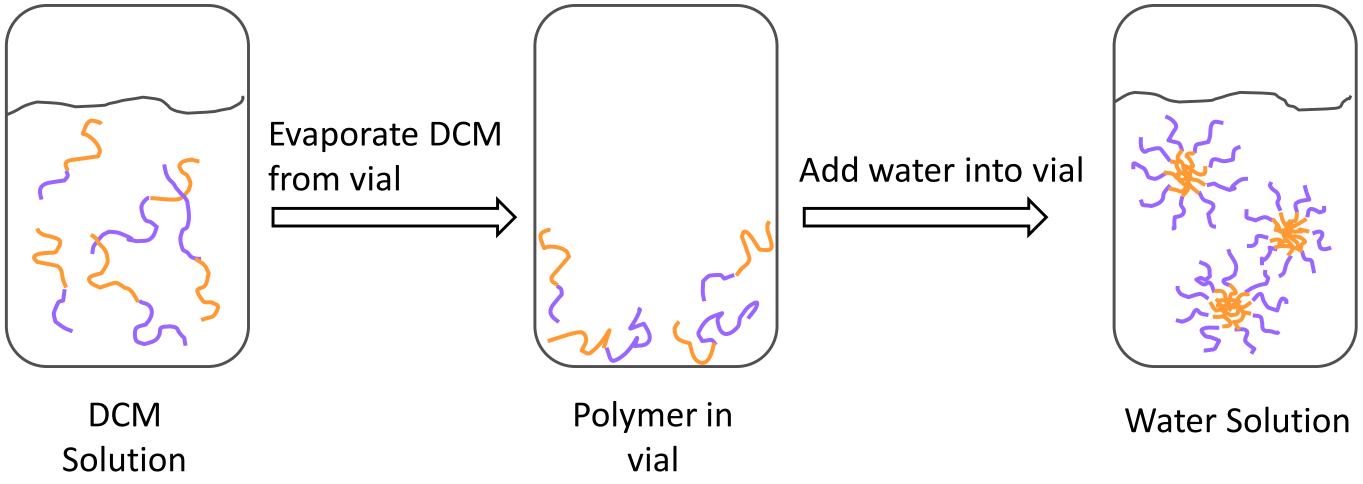


*Absorbance at 600nm wavelength

- Hard to measure solubility of both copolymer blocks
  - Literature: Using UV-Vis to measure absorbance and changing the solvent mixture to increase solubility
  - When abs reaches 0, polymer is soluble
  - Instead of changing the solvent mixture, we are changing polymer concertation to affect solubility
- Procedure
  - Create a concentration series of PS-b-PEG (3.8-b-5) in water
  - Use UV-Vis to determine the changes in absorbance and turbidity (cloudiness) of the sample

Kelley, E. G., Smart, T. P., Jackson, A. J., Sullivan, M. O., & Epps, T. H. (2011). Structural changes in block copolymer micelles induced by cosolvent mixtures. *Soft Matter*, *7*(15), 7094. https://doi.org/10.1039/c1sm05506b (ESI)

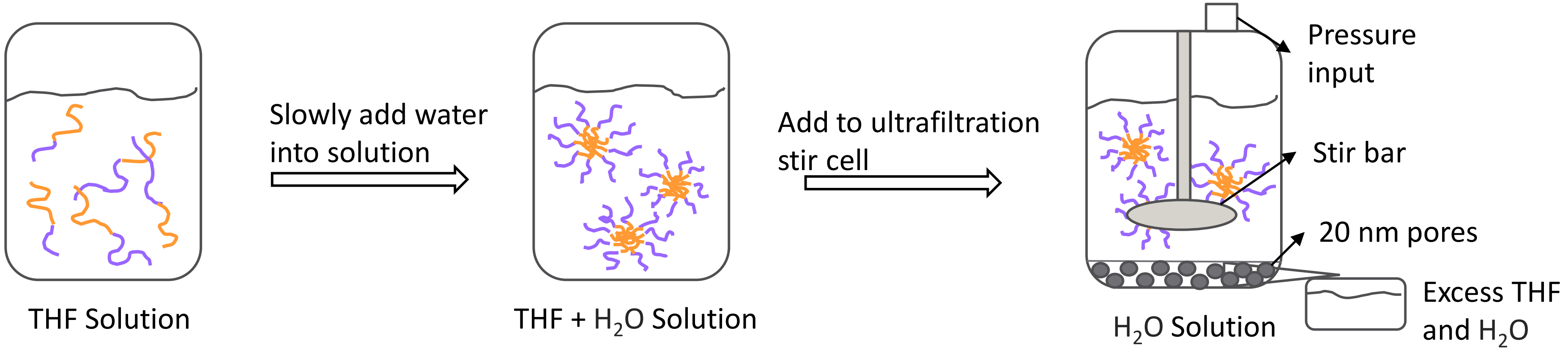
Thin Film Rehydration Procedure



- Mix 2 PS-b-PEG copolymers that have different molar masses of poly(styrene) in DCM solvent
- Evaporate DCM from the sample, add water to the thin film of polymer
- Add solution to a mixing plate to allow samples to reach a final structure

*Procedure completed by Kelsi Rehmann

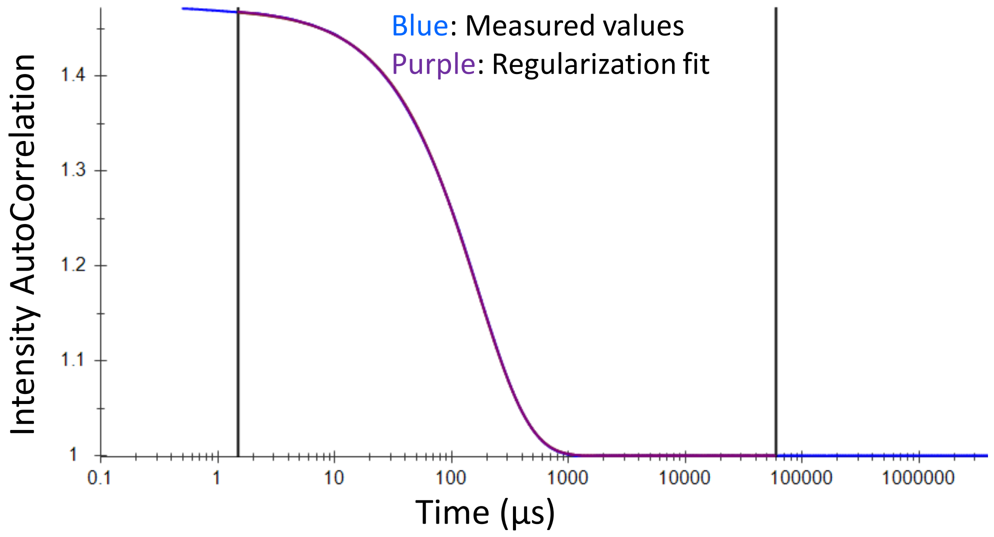
Solvent Switch Using an Ultrafiltration Stir Cell

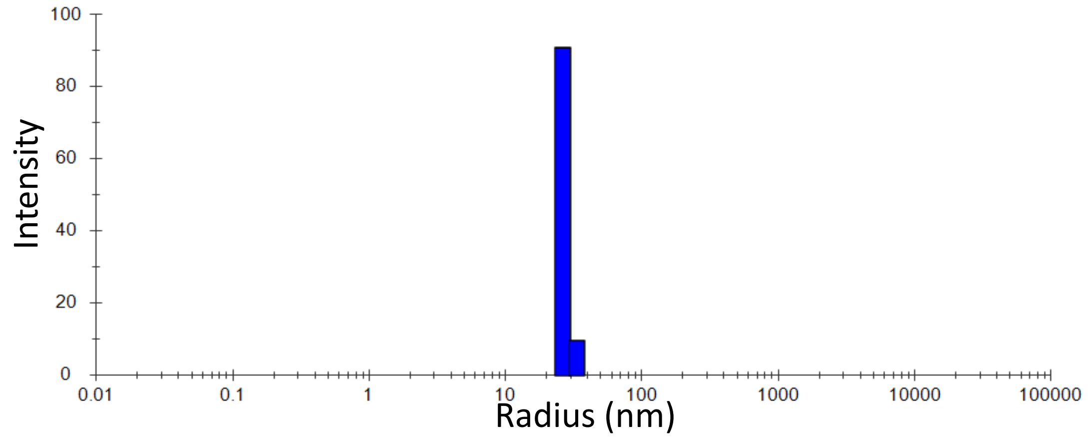


- Mix 2 PS-b-PEG copolymers that have different molar masses of poly(styrene) in THF solvent
- Slowly add water into solution to initiate self assembly of nanoparticles
  - Allows the particles to be closer to reach a final structure
- Add solution and extra water (H_2O) to ultrafiltration stir cell to remove the THF from the solution
  - Silica membrane with 20 nm pore diameter used to remove THF from solution

How DLS Works Differently from Small Angle Scattering

- Measures the movement of particles in solution over time, which can provide information about the particles size (assumes particle is a sphere)
- DLS will also pick up the movement of the solution surrounding the nanoparticles; therefore, hydrodynamic radius is larger than the actual radius
- Standardized 50nm PS nanoparticles (~0.09 wt% sample)





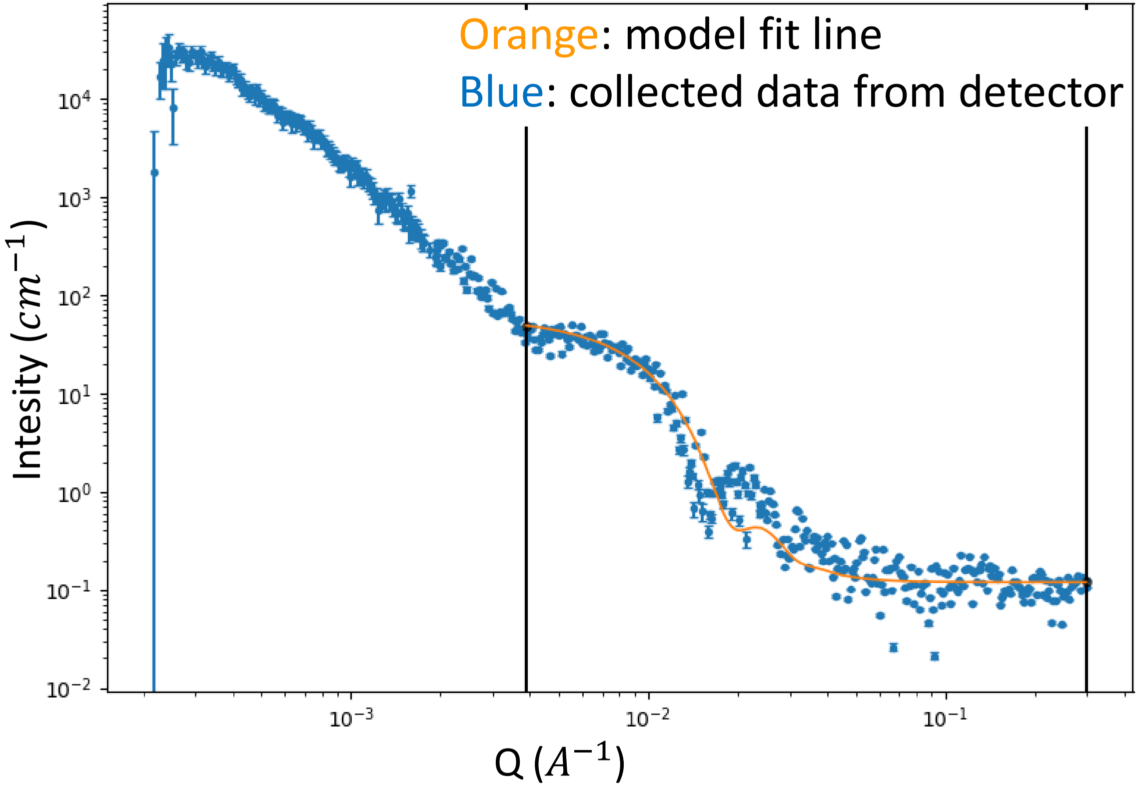
	Peak	Radius (nm)	Mw-R (kDa)	%Pd	%Intensity	%Mass	%Number
1	Peak 1	26.8	7395.1	7.6	100.0	100.0	100.0

Stetefeld, J., McKenna, S. A., & Patel, T. R. (2016). Dynamic light scattering: A practical guide and applications in biomedical sciences. Biophysical Reviews, 8(4), 409–427. https://doi.org/10.1007/s12551-016-0218-6

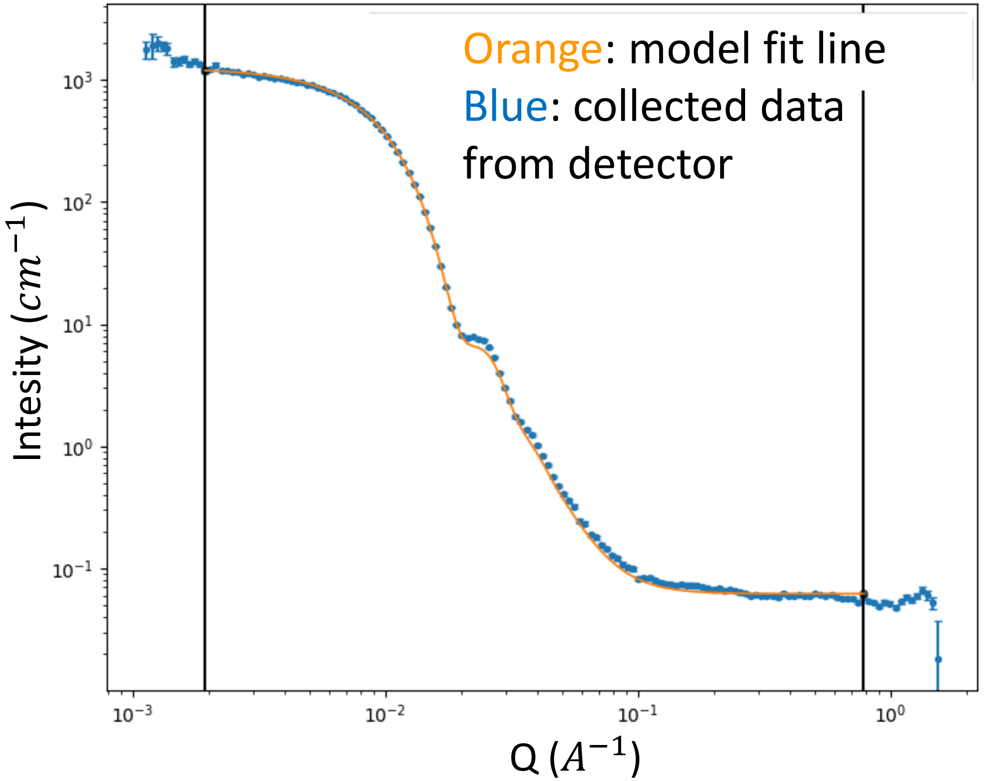
Small Angle Scattering Data

- Detector graphs data based on Intensity of radiation vs Q(angle of scattering)
- SAXS/SANS data is fitted to highly researched structural models
  - Spheres, core-shell spheres, cylinders, etc.

50nm PS nanoparticles SAXS data: sphere model fit
Radius: 21.5 nm



50nm PS nanoparticles SANS data: sphere model fit
Radius: 22.1 nm

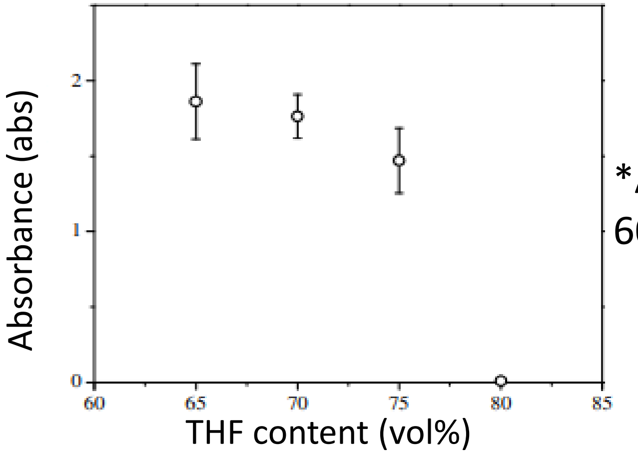


*SANS data collection: Kelsi Rehmann
*SAXS data collection: Caitlyn Wolfe

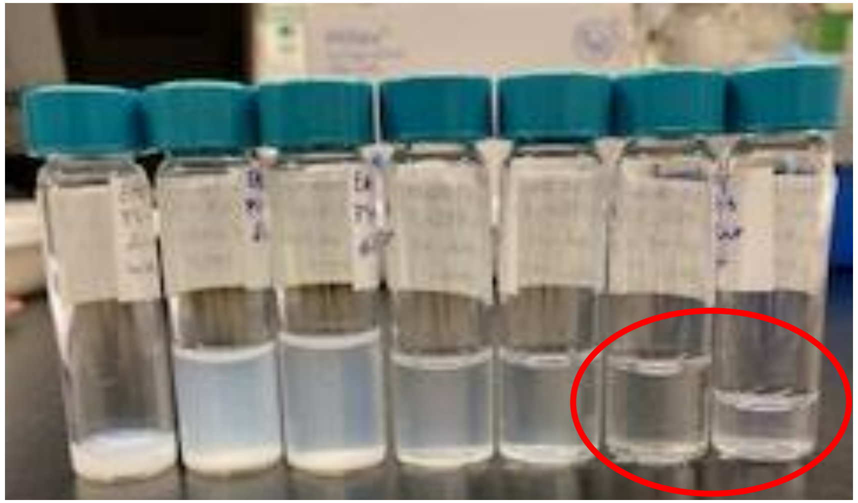
- USAXS measurements
- Low-q upturn is an artifact
- Noise at high-q

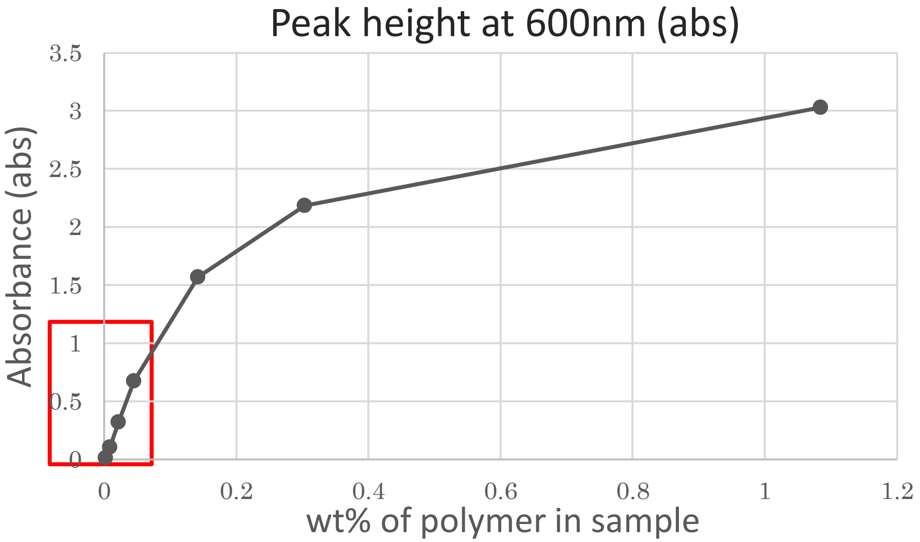
Absorbance of 3.8 Polymer in Water at 600nm Wavelength

Absorbance of PB homopolymer in H_2O/THF cosolvent mixtures



*Absorbance at 600nm wavelength



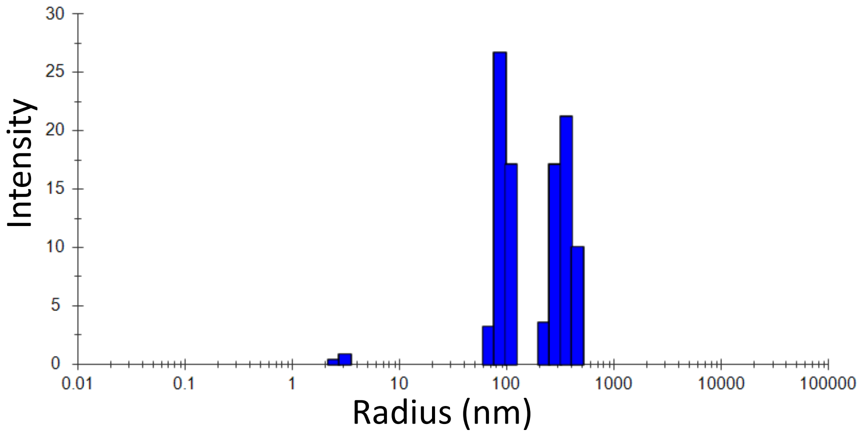


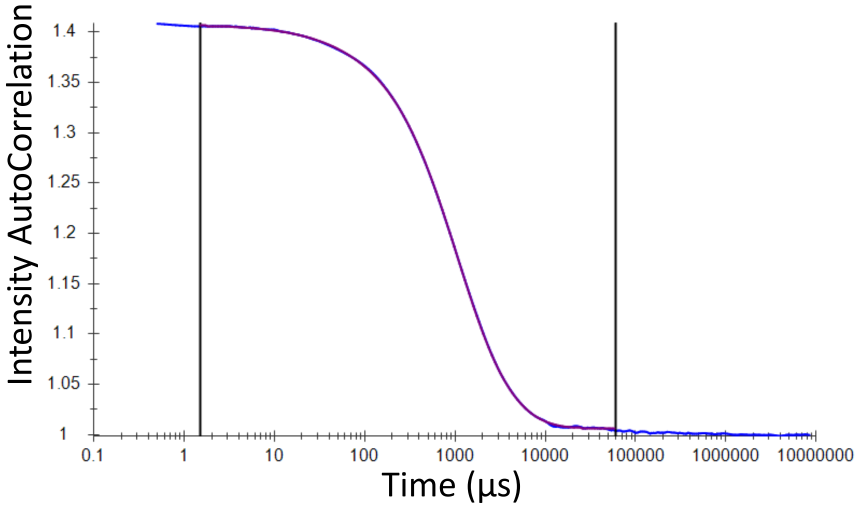
sample wt% (%)	peak height at 600nm (abs)	visual observations
1.09	3.031	turbid
0.30	2.182	turbid
0.14	1.568	slightly turbid
0.045	0.672	slightly clear
0.022	0.322	slightly clear
0.009	0.105	clear
0.002	0.010	clear

Kelley, E. G., Smart, T. P., Jackson, A. J., Sullivan, M. O., & Epps, T. H. (2011). Structural changes in block copolymer micelles induced by cosolvent mixtures. *Soft Matter*, *7*(15), 7094. https://doi.org/10.1039/c1sm05506b (ESI)

Structure of 3.8 Molar Mass Particles at Low Concentration

- Lowest Concentration sample



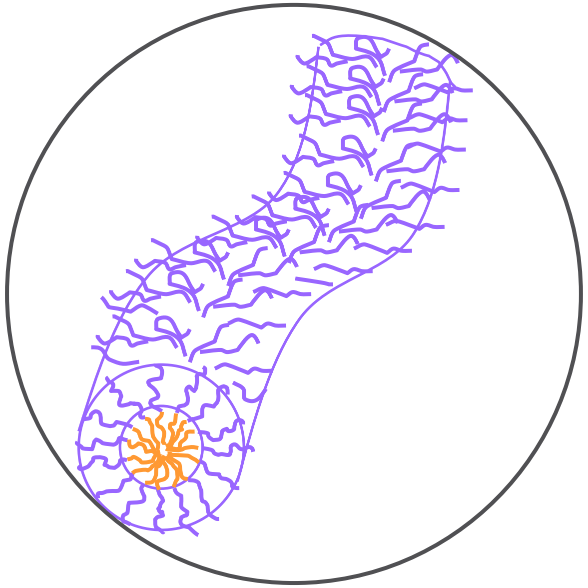


Sample wt% (clear)	Radius peak 1 (%Intensity)	Radius peak 2 (% Intensity)
2nd lowest conc.	126nm (65)	516nm (34)
Lowest conc.	93nm (47) 341.2	341nm (52)

*Radius is not correlated to size

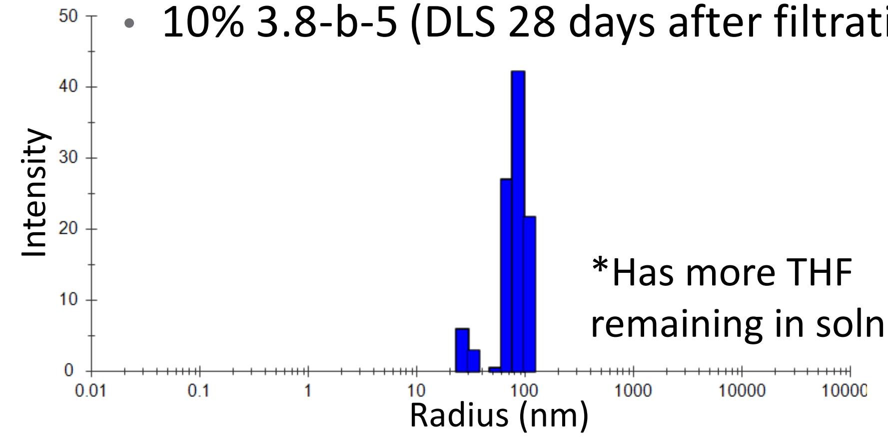
Take away from solubility test
- 3.8 is soluble and forms particles at low concentration

Hypothesis:
- Multiple structures in solution, resulting in multiple peaks



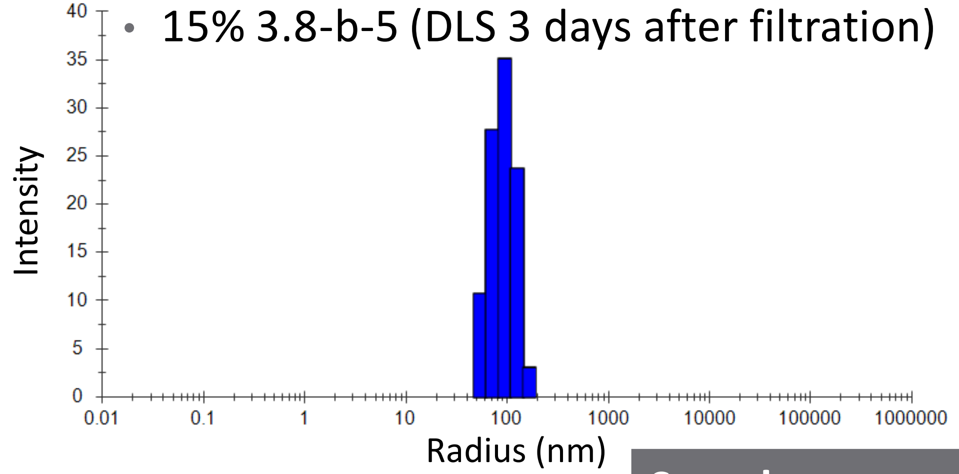
Structure for Mixed Solvent Switch Samples

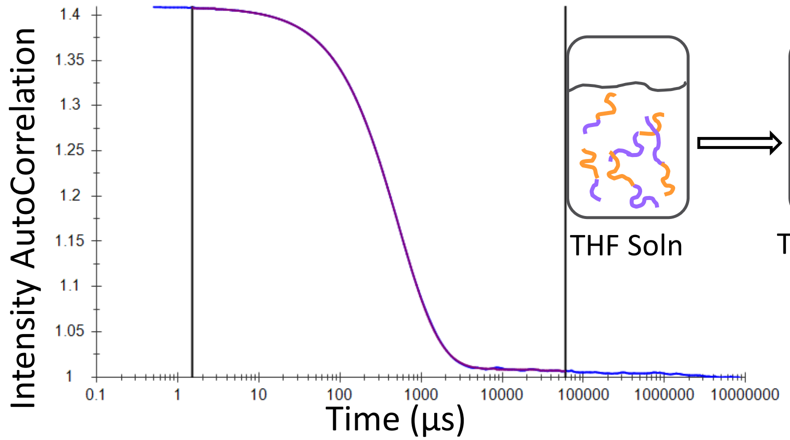
- 10% 3.8-b-5 (DLS 28 days after filtration)

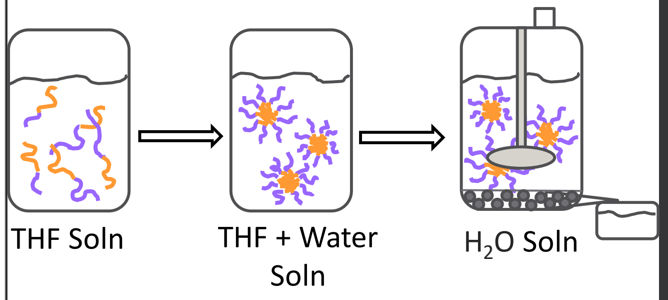


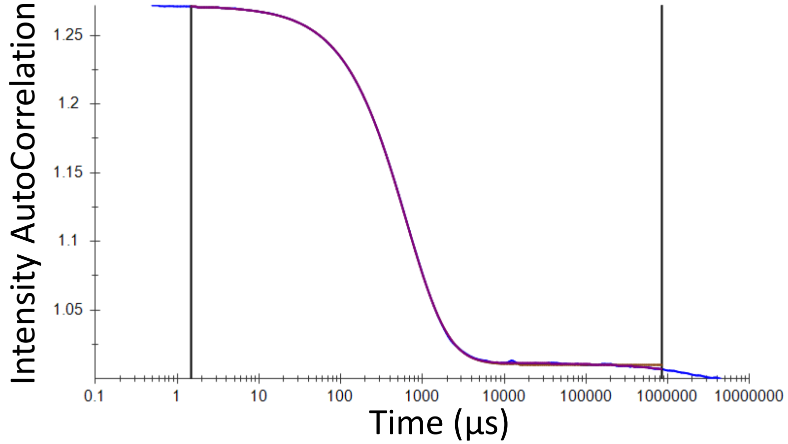
*Has more THF remaining in soln

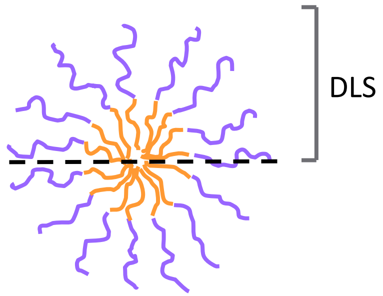
- 15% 3.8-b-5 (DLS 3 days after filtration)







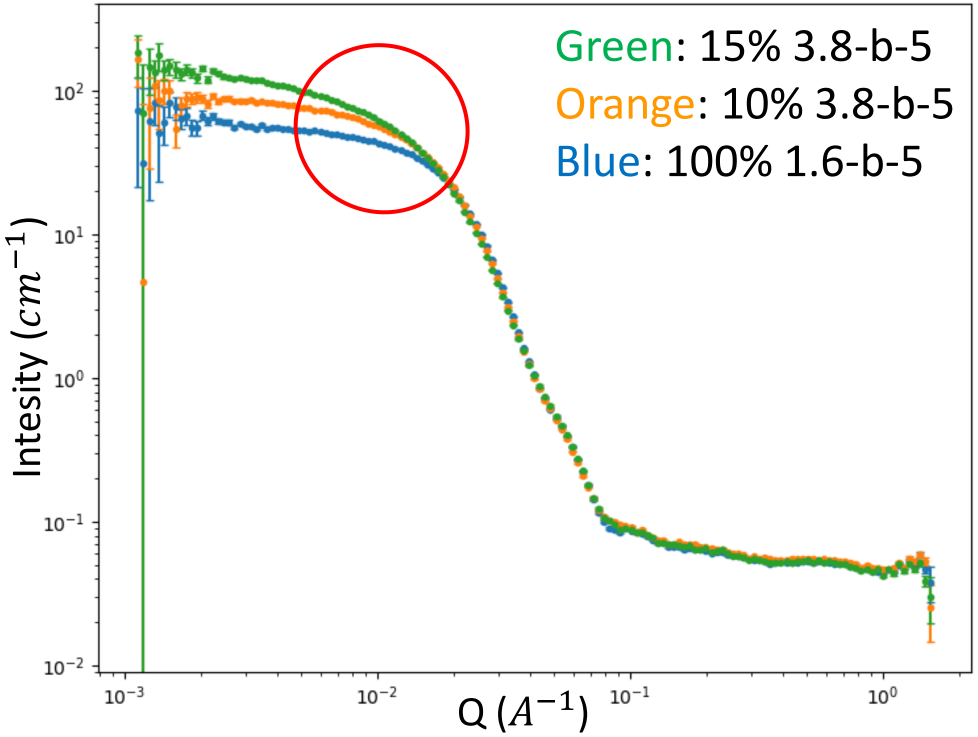




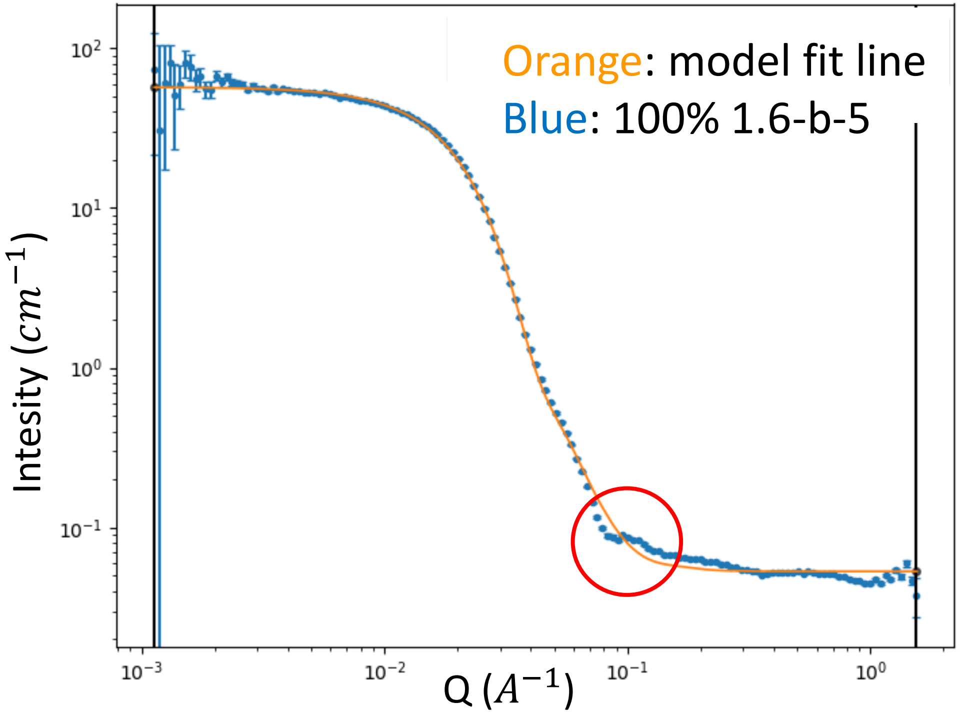
Sample type	Radius (nm)	% Polydispersity	% Intensity
10%	86	18	91
15%	93	26	100

Structure for Mixed Thin Film Rehydration Samples

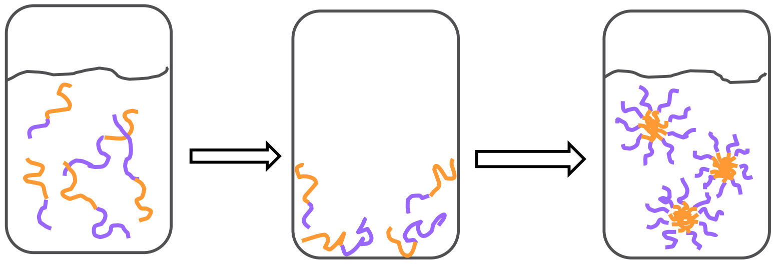
- SANS data for all samples



- SANS data: core-shell sphere model



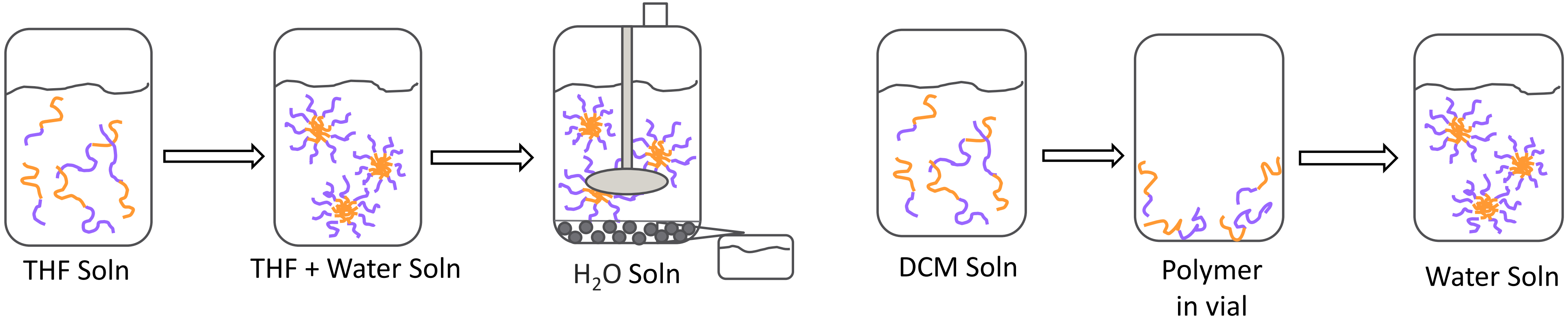
	DCM SANS data		
Sample type	Core radius (nm)	Shell radius (nm)	Total radius (nm)
100% 1.6-b-5	3	5.2	8.1
10% 3.8-b-5	3	4.9	8.0
15% 3.8-b-5	4.4	1.3	5.7



*Data collection: Kelsi Rehmann
Solvent: D_2O

Comparison Between the Two Processes

	DLS radius (nm)		DCM SANS data			DCM SAXS data		
Sample type	Solvent Switch	Thin Film Rehydration	Core radius (nm)	Shell radius (nm)	Total radius (nm)	Core radius (nm)	Shell radius (nm)	Total radius (nm)
100% 1.6-b-5		21	3	5.2	8.2	0.7	12	12.7
10% 3.8-b-5	86	27	3	4.9	7.9	8.1	6.4	14.5
15% 3.8-b-5	93	73	4.4	1.3	5.7	7.7	7.1	14.8



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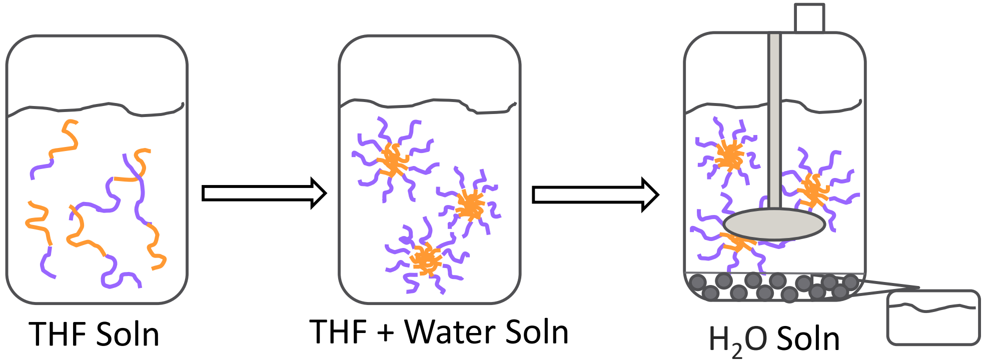

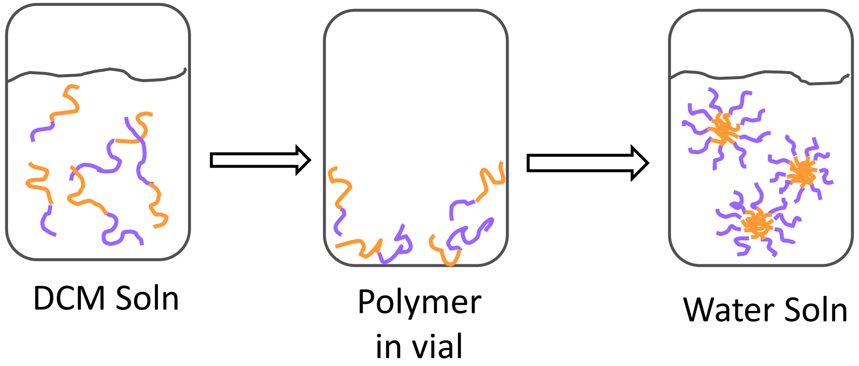

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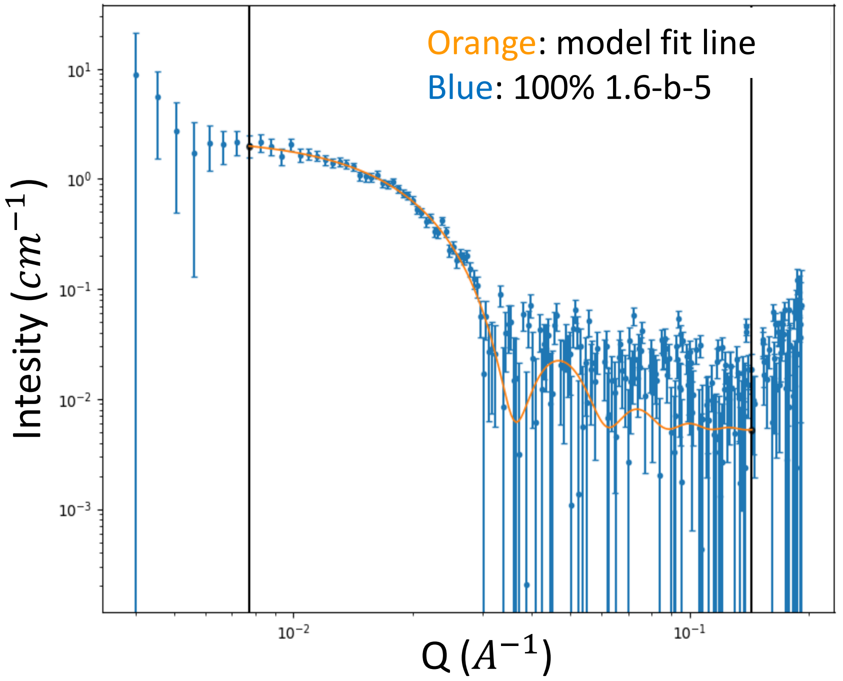
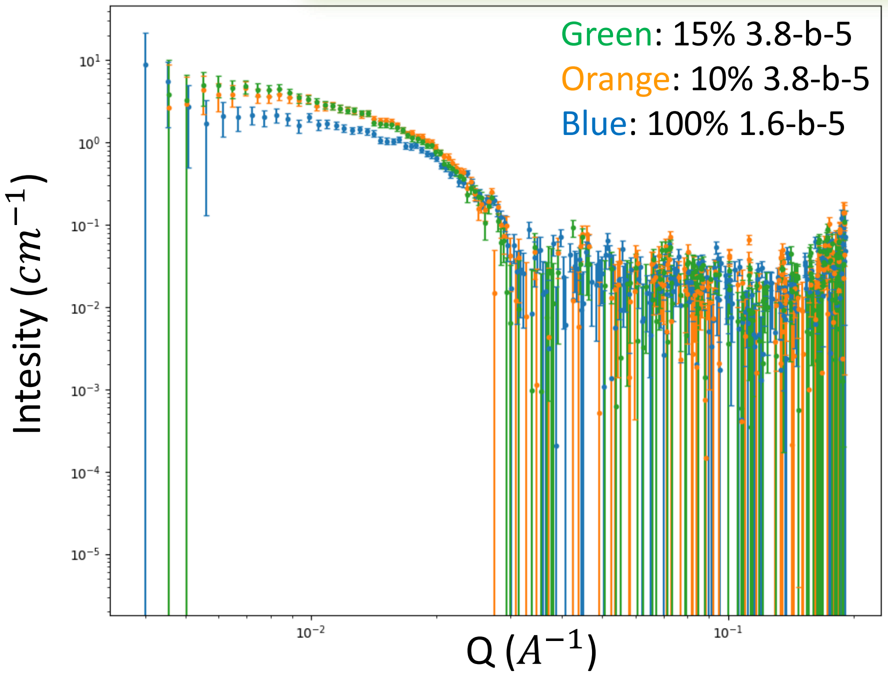
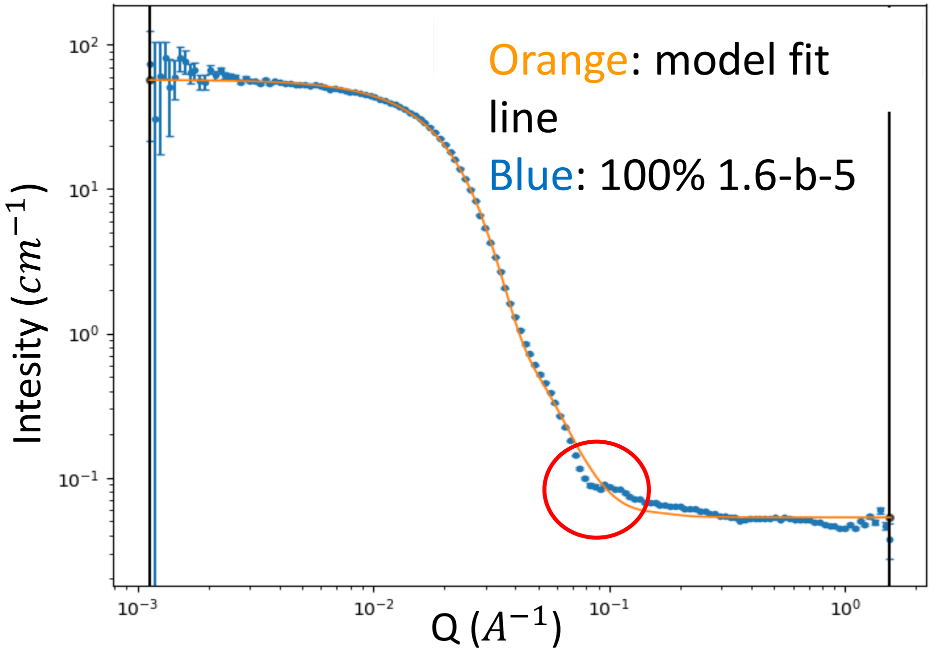
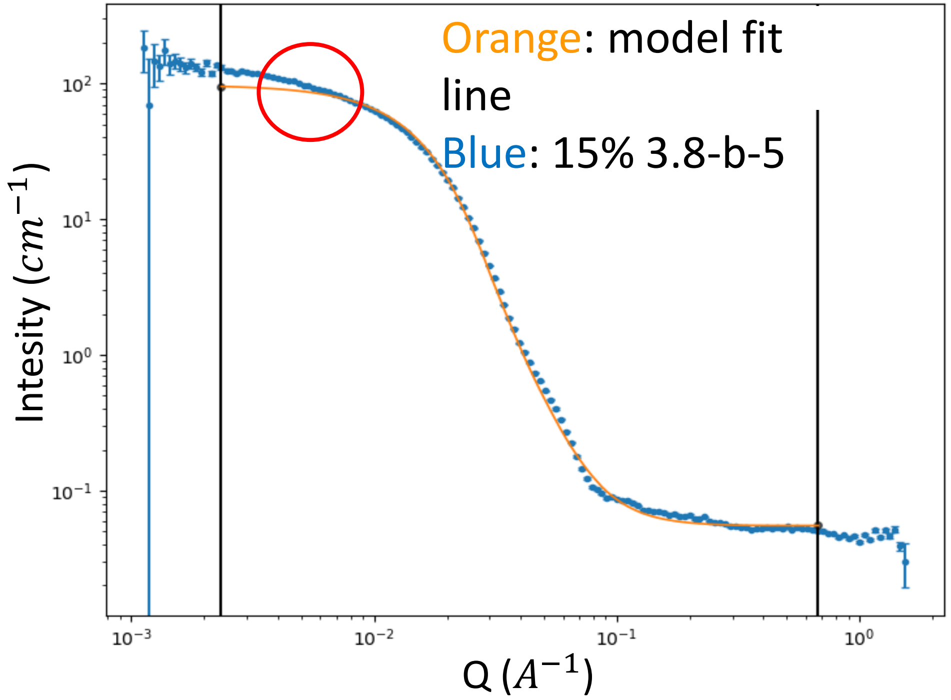




Ongoing Work

- **SAXS/SANS measurements and analysis**
- Low yield for Solvent Switch Ultrafiltration
- Processes to improve yield



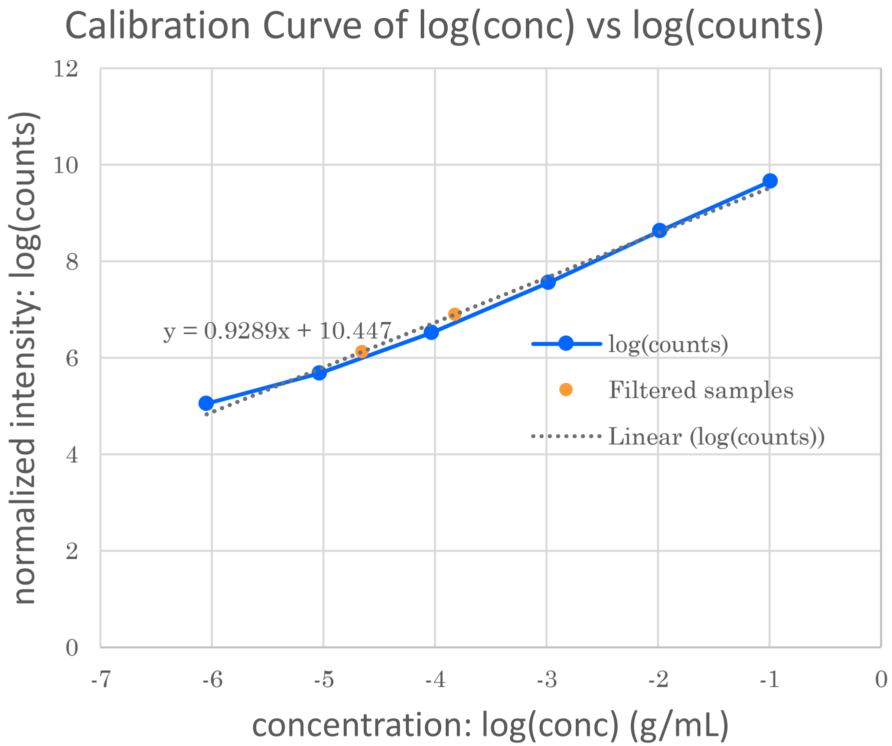


*Data collection: Kelsi Rehmann
Solvent: D_2O

Ongoing Work

- SAXS/SANS measurements and analysis
- **Low yield for Solvent Switch Ultrafiltration**
- Processes to improve yield

- Calibration Curve based on DLS data from standardized PS nanoparticles
  - Related DLS counts to concentration through PS nanoparticles concentration series to estimate % yield of the solvent switch method

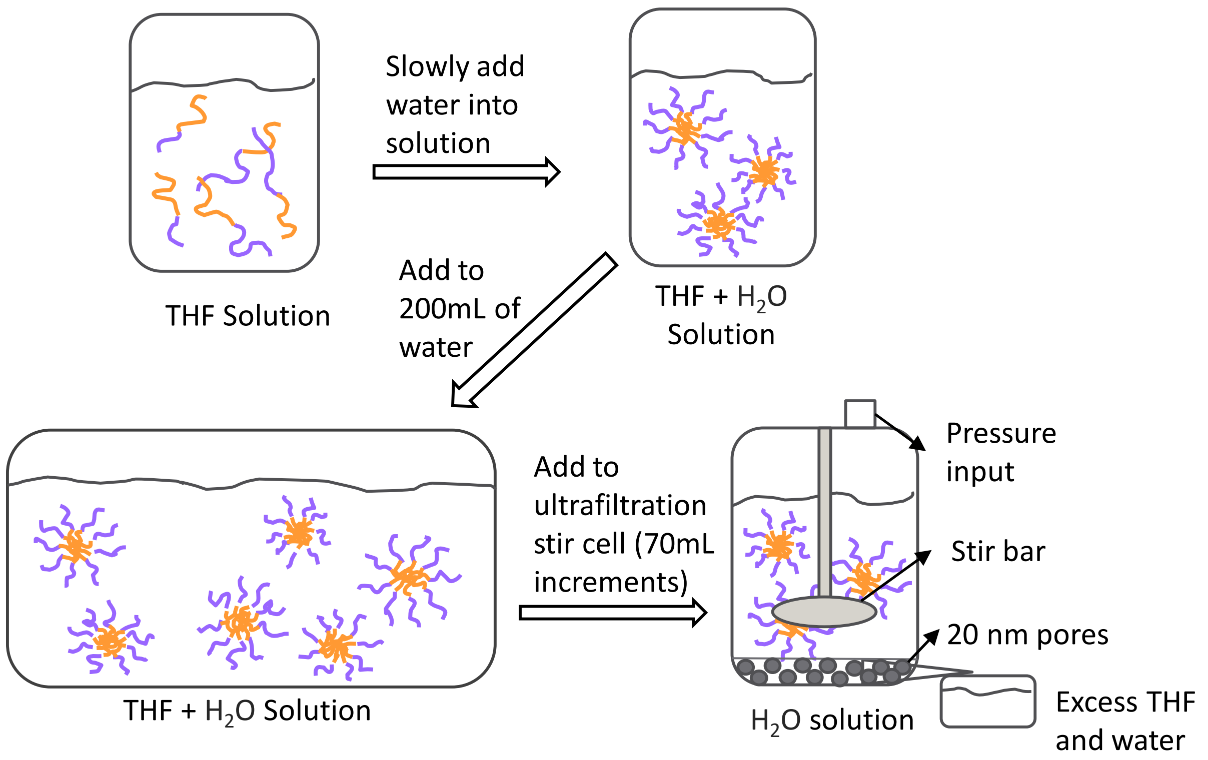


Sample type	expected conc (g/mL)	estimated conc (g/mL)	percent yeild (%)
10% 3.8-b-5	0.002	0.000151	7.55
15% 3.8-b-5	0.00202	0.0000222	1.10

Ongoing Work

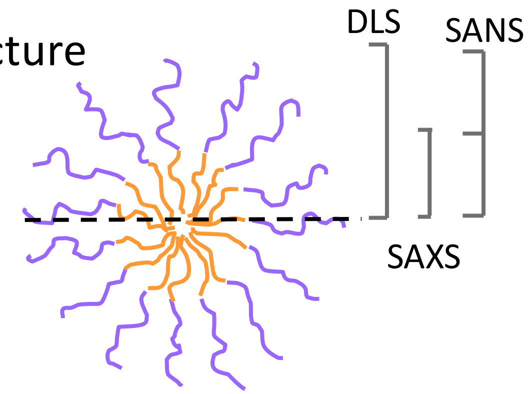
- SAXS/SANS measurements and analysis
- Low yield for Solvent Switch Ultrafiltration
- **Processes to improve yield**

- Have polymer in more water before filtration
  - Less THF concertation in solution, therefore, more likely for polymer chains to self-assemble into nanoparticles
- Reuse the same membrane
  - Already has water/polymer trapped in the membrane, won't trap much of the new sample
- Started using 100% 1.6-b-5 to compare data to previous findings



Conclusion

- Solubility test showed that 3.8-b-5 is able to form particles in water at low concentrations
- Ultrafiltration is usable for a solvent switch method, however, the process can still be optimized
- Higher molar masses of the polymer results in a greater particle size and changes in structure
- Possibility that changes in process can affect the nanoparticles size and structure
  - Continued work towards this finding



	DLS radius (nm)		DCM SANS data			DCM SAXS data		
Sample type	Solvent Switch	Thin Film Rehydration	Core radius (nm)	Shell radius (nm)	Total radius (nm)	Core radius (nm)	Shell radius (nm)	Total radius (nm)
100% 1.6-b-5		21	3	5.2	8.2	0.7	12	12.7
10% 3.8-b-5	86	27	3	4.9	7.9	8.1	6.4	14.5
15% 3.8-b-5	93	73	4.4	1.3	5.7	7.7	7.1	14.8

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