National Institute of Standards and Technology
U.S. Department of Commerce

Impact of Process Parameters on Soft Nanoparticle Formulations for Capillary Rheology Studies

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NIST Center for Neutron Research

CHRNS CENTER FOR HIGH RESOLUTION NEUTRON SCATTERING NSF NIST

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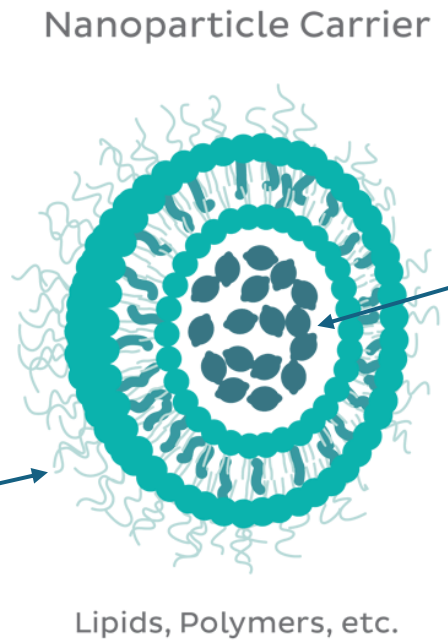
Nanomedicine (including the use of therapeutic nanoparticles) is a growing industry

- Enables targeted drug delivery & controlled release
- Micelle protects and stabilizes the pharmaceutical ingredients



Surface: Polymers to stabilize structure (e.g., Polyethylene Glycol (PEG))

Core: Typically contains an active pharmaceutical ingredient

Image from Precision NanoSystems (URL)

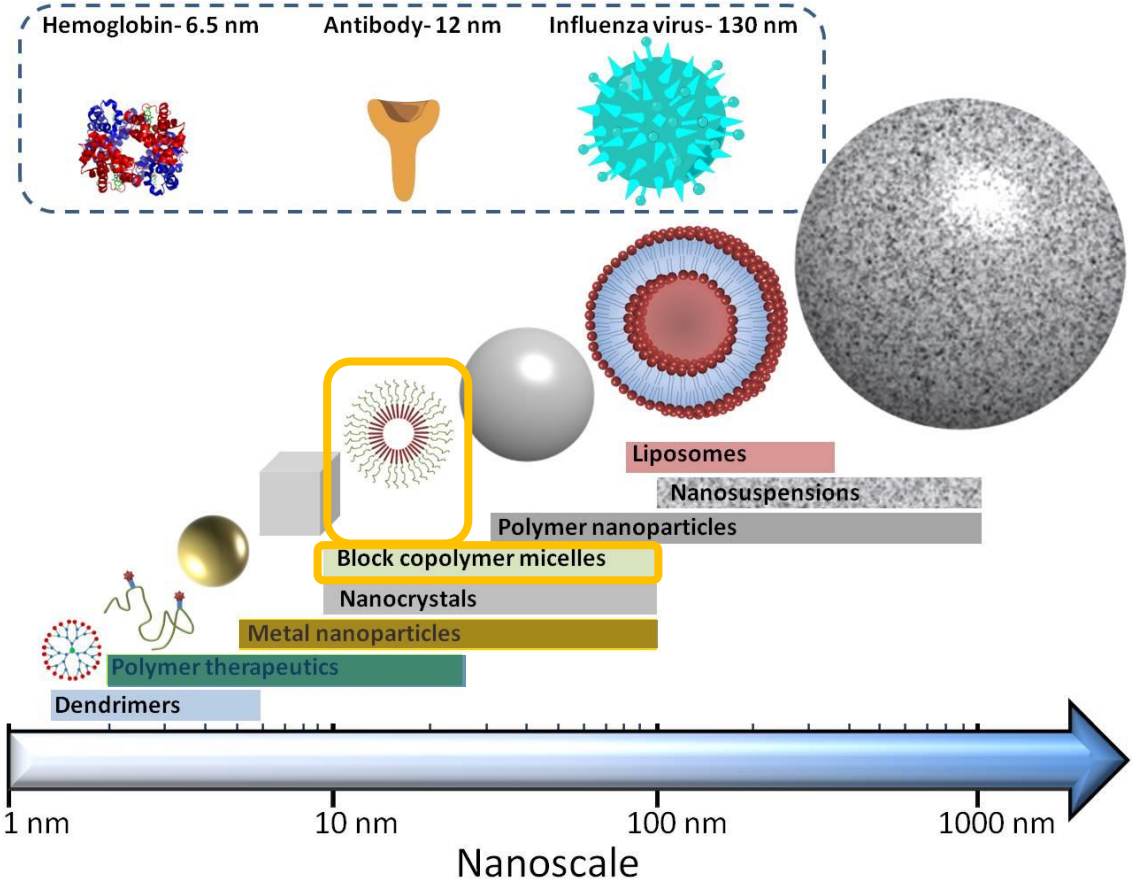
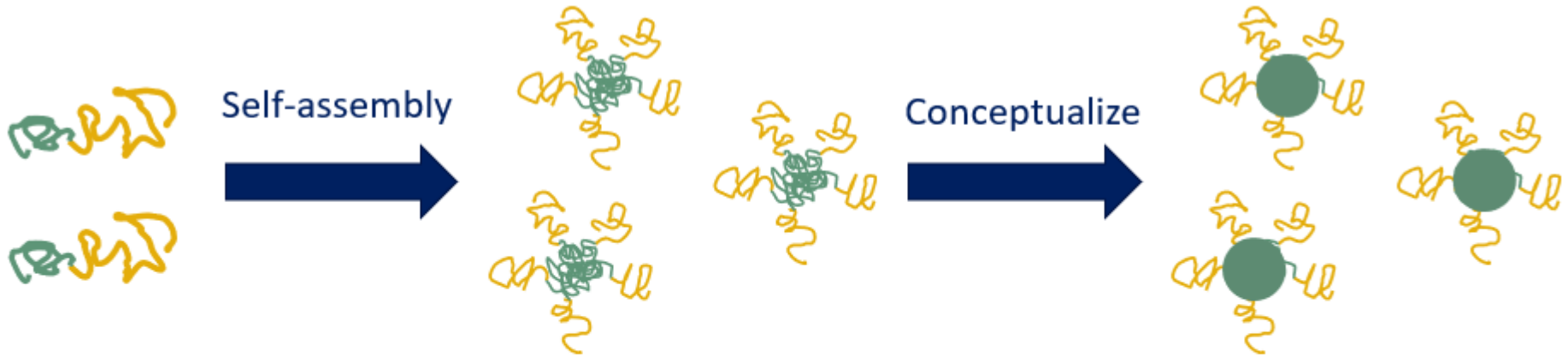


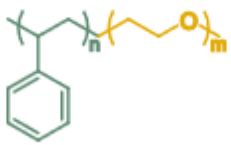
Image from British Society for Nanomedicine (URL)

Block Co-polymer Micelles

- Can self-assemble in water under proper mixing conditions



Poly(styrene-block- ethylene glycol)
(PS-b-PEG)



1.6-b-5 PS-b-PEG : 1600 Da PS, 5000 Da PEG:
spherical nanoparticles in water

Flash Nanoprecipitation Technique (FNP) for Nanoparticle formulation: Simple design

- Technique developed by a research group from Princeton University for high volume nanoparticle production
- Alternative to microfluidic based techniques

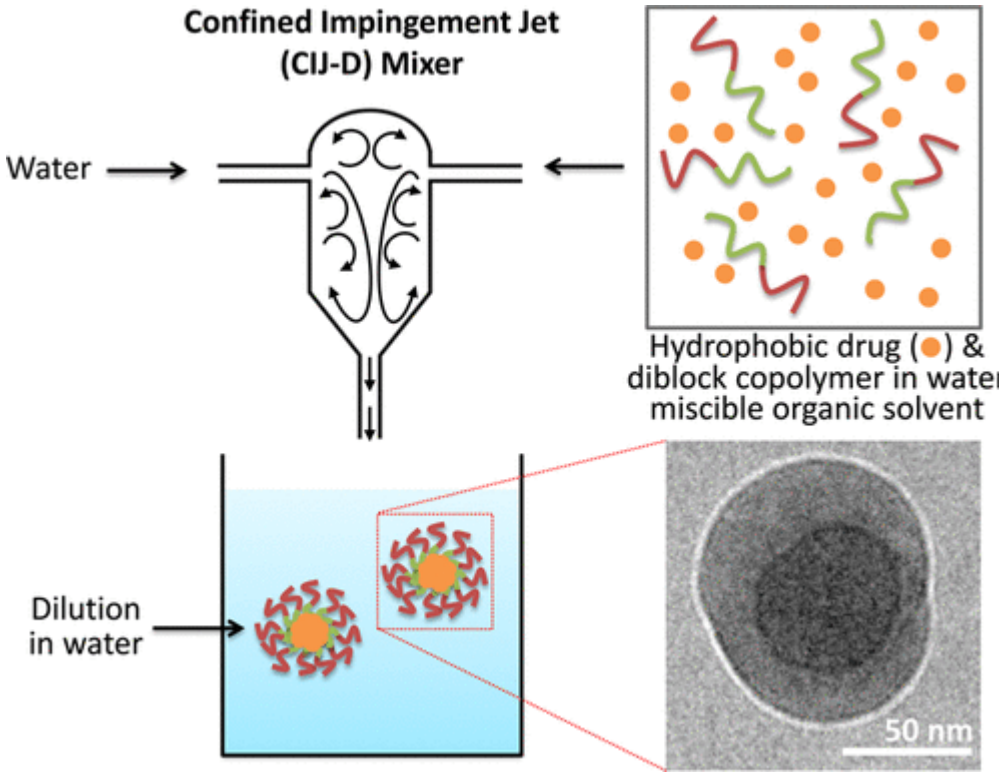


Image source: de Vos, W. "Brushes and particles". 2009. (URL)

Flash Nanoprecipitation Technique (FNP) for Nanoparticle formulation: Advanced design

- Chosen for this project due to its modular design
- Parameters involved:
  - Chemistry of selected polymer
  - Polymer concentration
  - Reynolds number (impacted by flow rate)
  - Mixer geometry

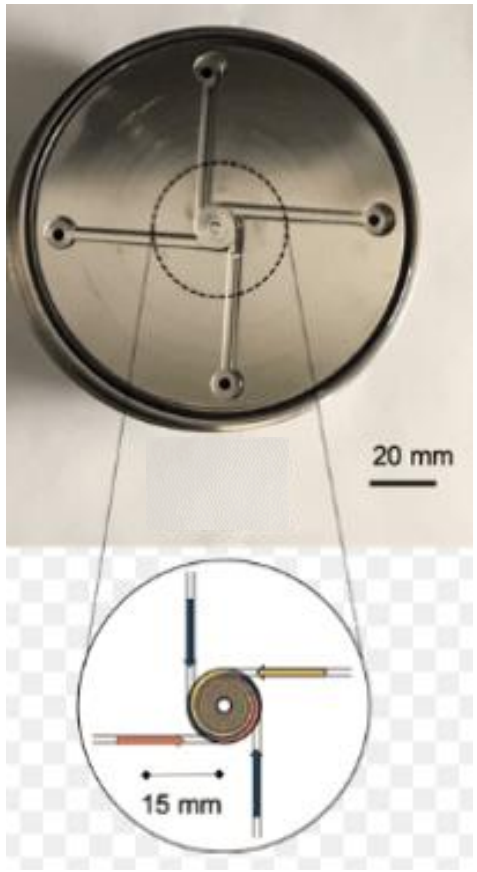
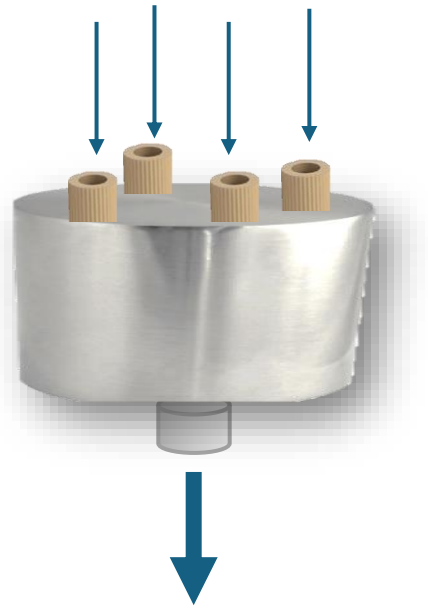


Image from Markwalter, et al. JOVE. 2019.



Structural changes in nanoparticles under high-shear conditions are measurable using the Rheo-SANS technique

Simplified Capillary Rheo-SANS set up

Sample flows through a capillary tube under high pressures to induce large shear forces

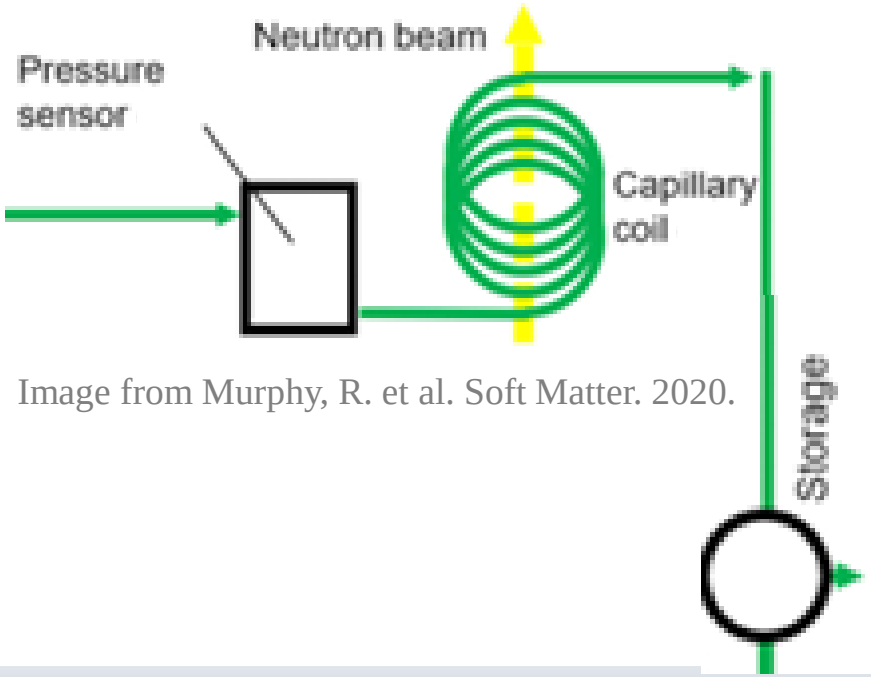
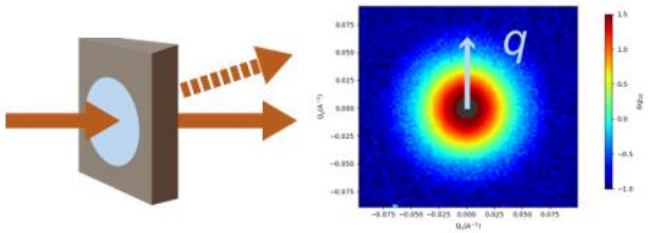
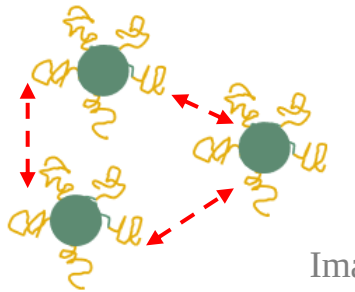


Image from Murphy, R. et al. Soft Matter. 2020.

Small Angle Neutron Scattering (SANS) can measure orientations and structure of nanoparticles

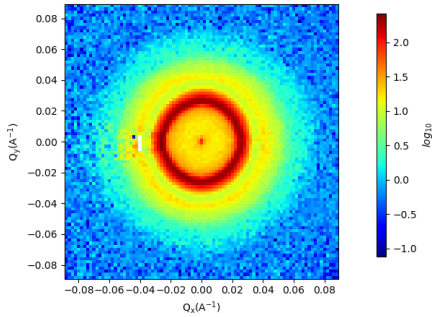




Images & data source: Rehmann, K.

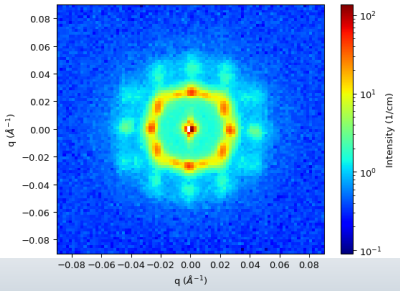
Shear could cause reorientation into more crystalline structures

No shear $\dot{\gamma} = 0\ s^{-1}$



Medium shear

$\dot{\gamma} = 3.4 \cdot 10^{2}\ s^{-1}$



Project Objectives

- Create nanoparticles with sizes comparable to production quality particles
- Optimize the Flash Nanoprecipitation process
    - Build and test equipment, gauge success by nanoparticle size and dispersity
- Prepare nanoparticle samples for future Rheo-SANS studies
    - Find and test repeatable methods for concentrating nanoparticle solutions
    - Concentrated solutions are ideal for capillary rheology studies
- Study structural characteristics of nanoparticles over time

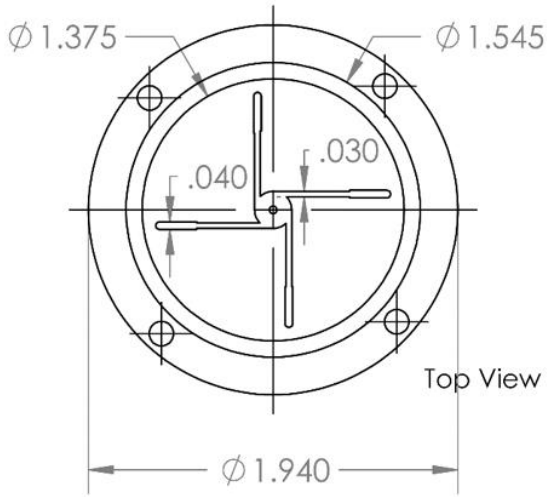
Project ties to manufacturing

Image source: getreskilled.com

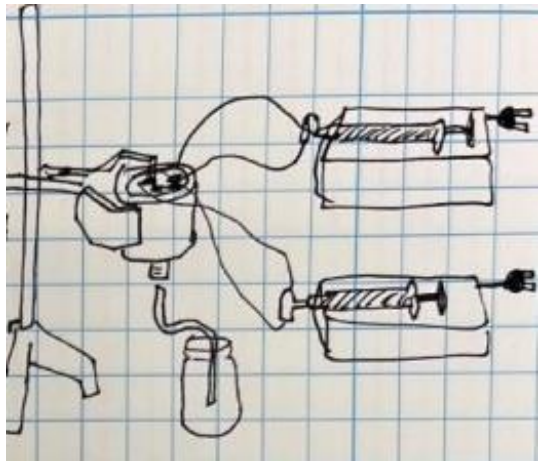
Setting up new equipment for FNP

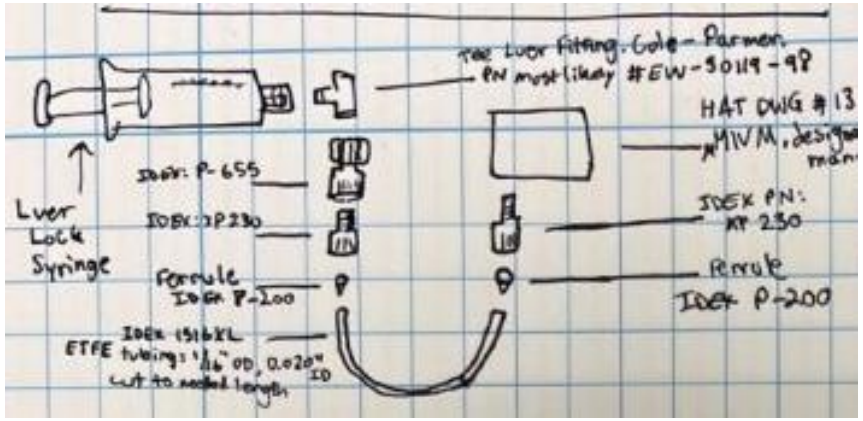
Studying manufacturer's engineering drawings

Mixing chamber

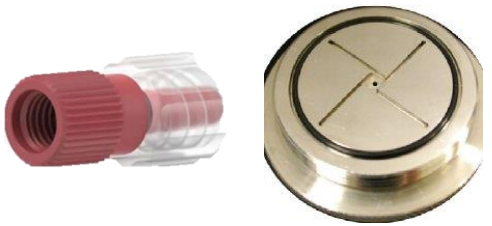


Sketching out potential set up designs

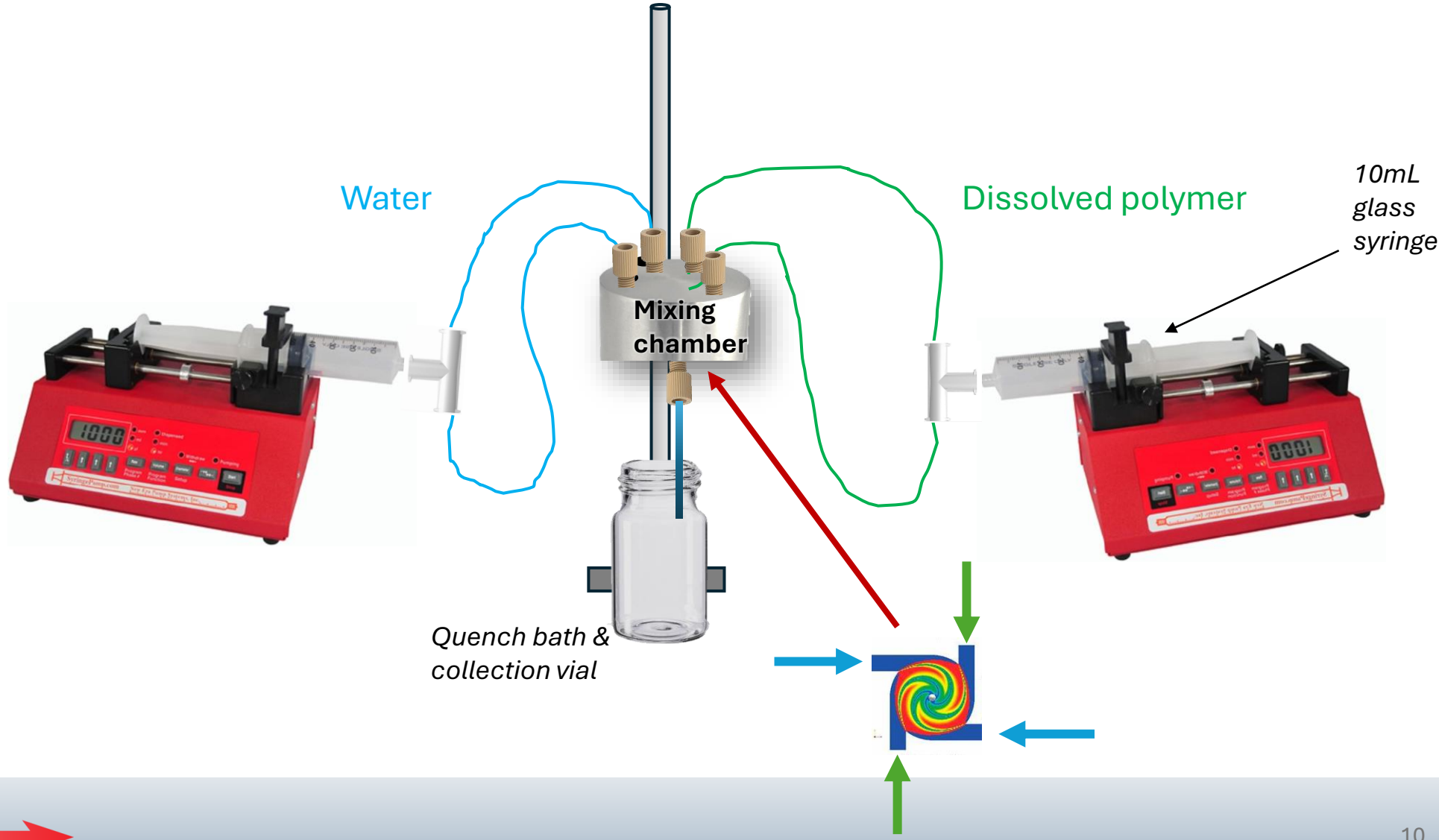




Ordering fittings and components

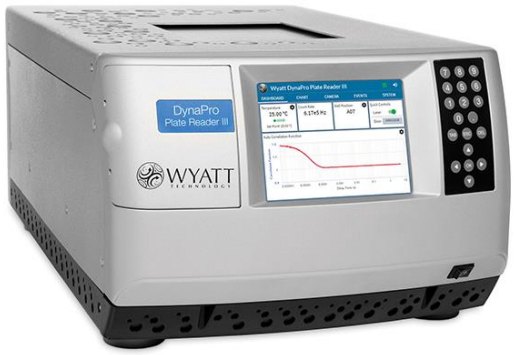


Full FNP equipment set-up



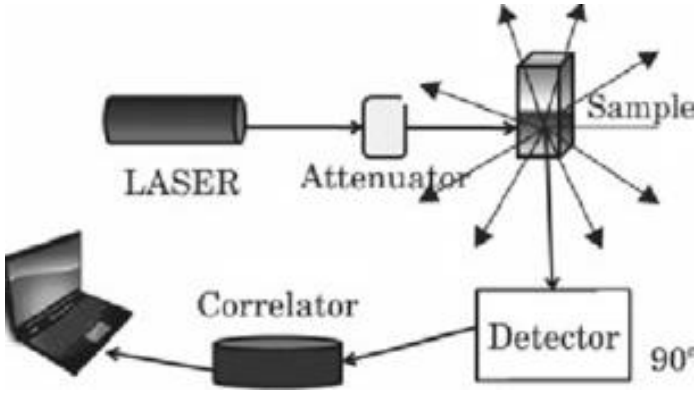
Optimizing Measurement Methods: Dynamic Light Scattering

- Dynamic Light Scattering (DLS) was selected for initial data collection
  - Rapid results, ease of set up

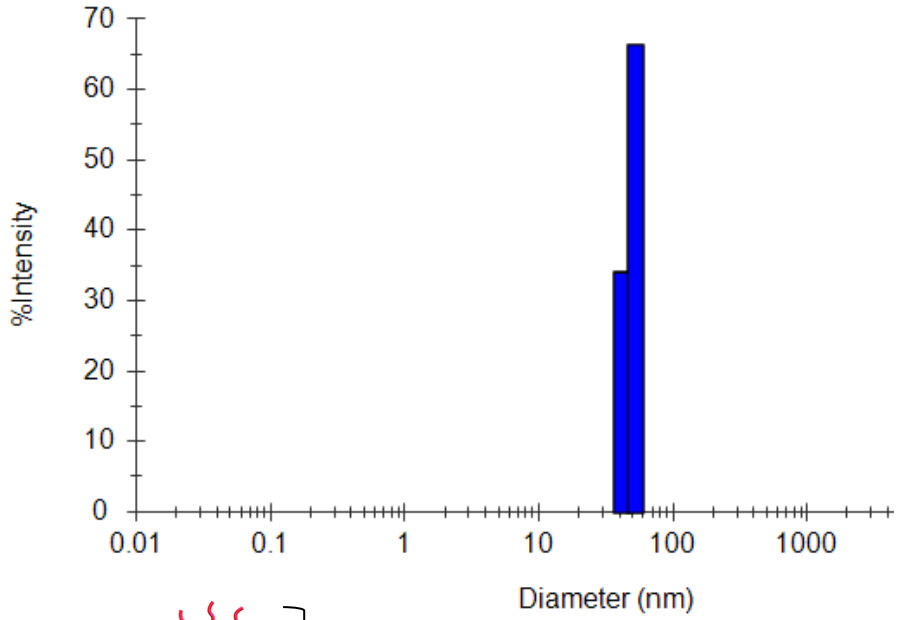


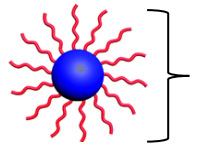
DLS Instrument

Quartz
Cuvette



Type of data that might come out of DLS

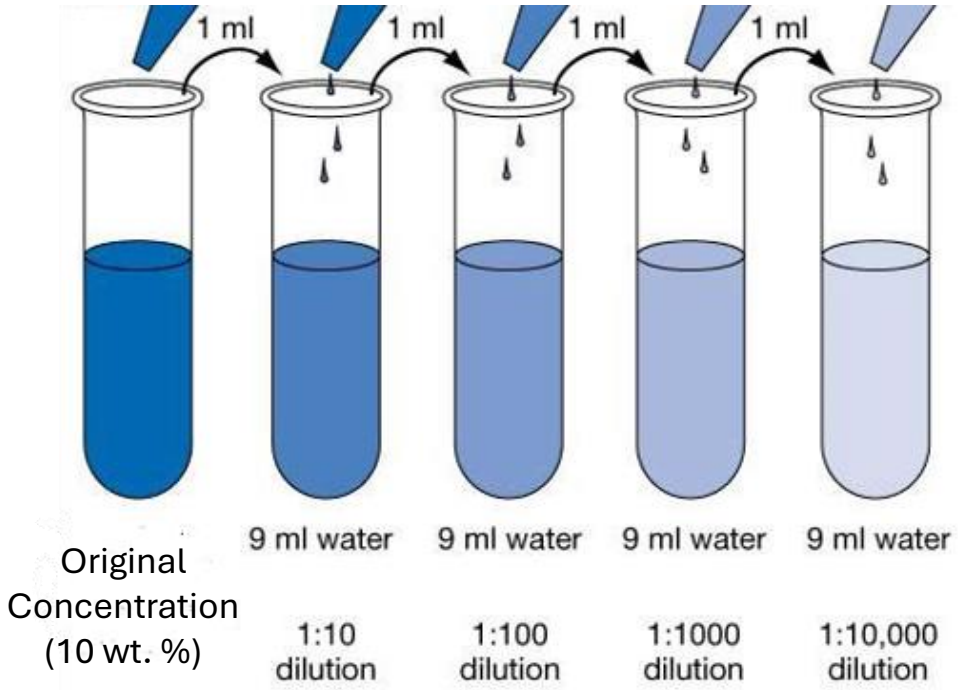


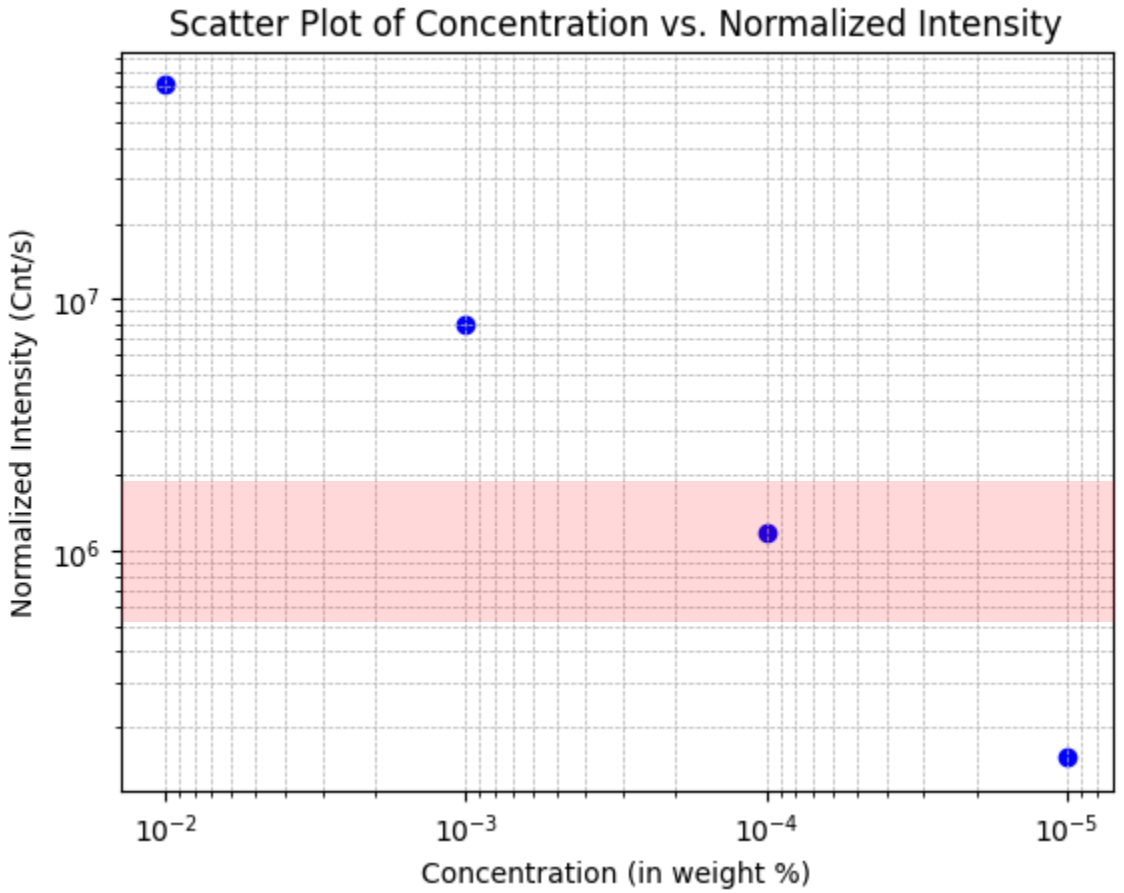


Measurement

Optimizing Measurement Methods: Dynamic Light Scattering

- Measured nanoparticle diameter using DLS for solutions from a serial dilution of known size particles
- A concentration of 0.0001 wt. % is ideal





Testing and validating the equipment

- Identified equipment operational limits (set by manufacturer)
- Set a target based on literature values
- Replicated the experiment & found comparable results

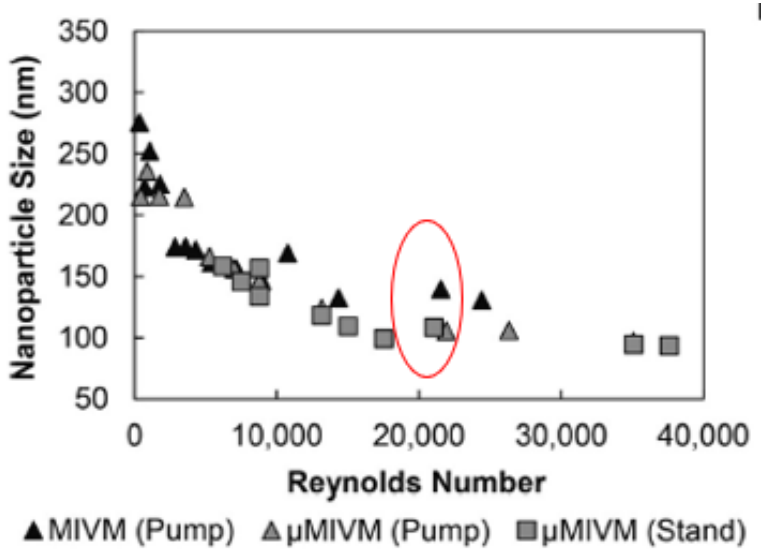
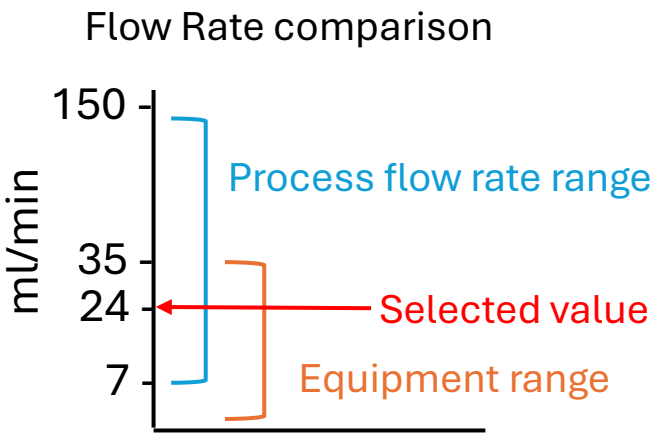
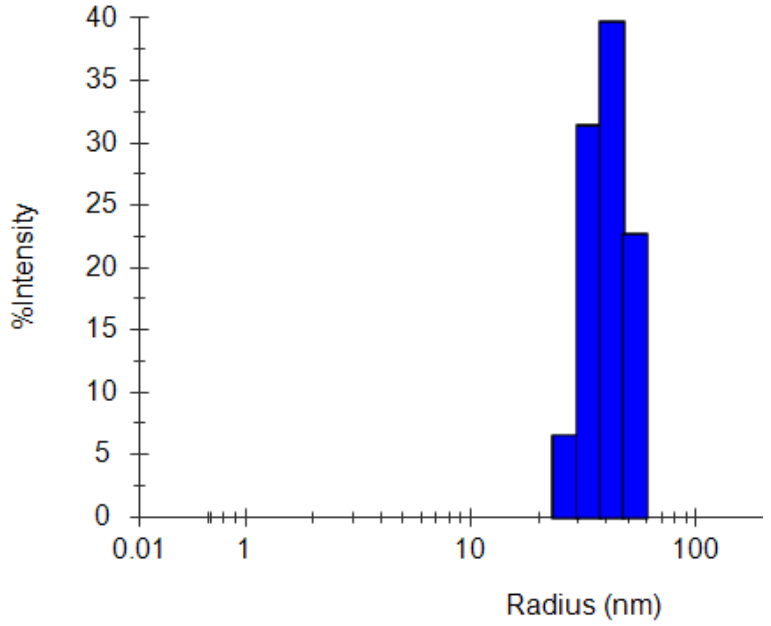


Image from Markwalter & Prud'homme. Journal of Pharmaceutical Sciences. 2018.

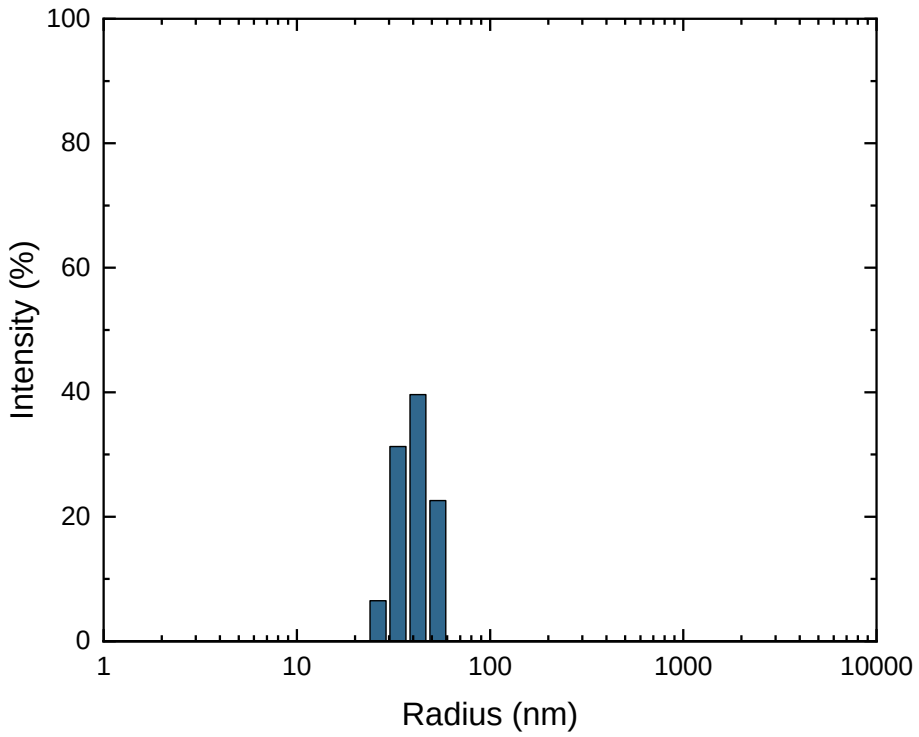




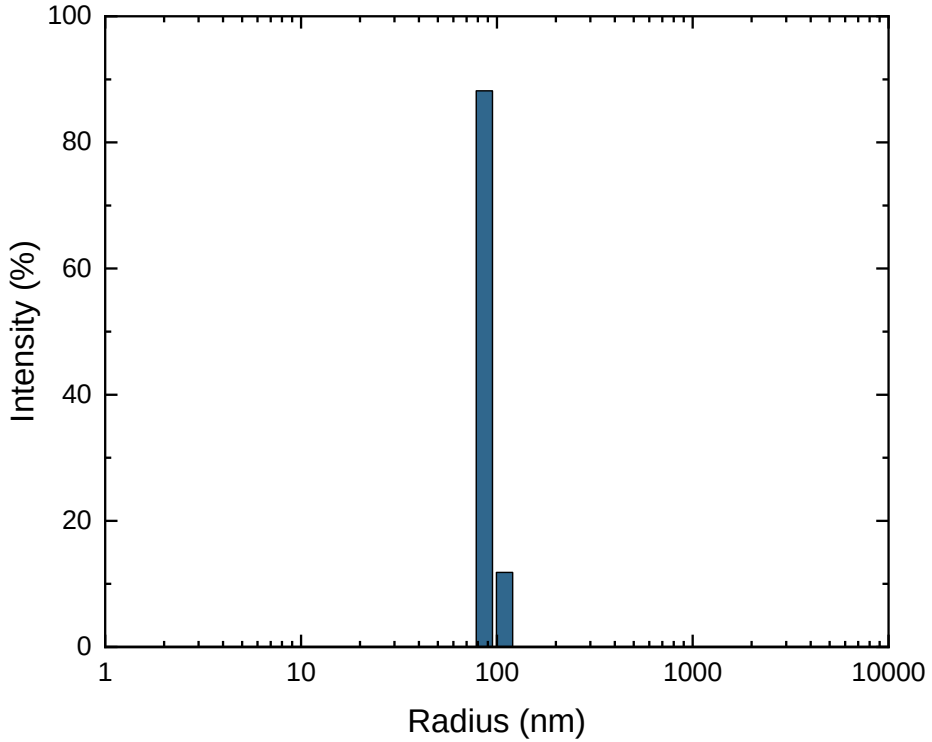
	My sample data	Researcher data
Diameter	82.7 nm	108 nm
Polydispersity Index	0.20	0.14

Verifying repeatability of performance

Sample tested: 20mg/mL PS-b-PEG with no therapeutic core



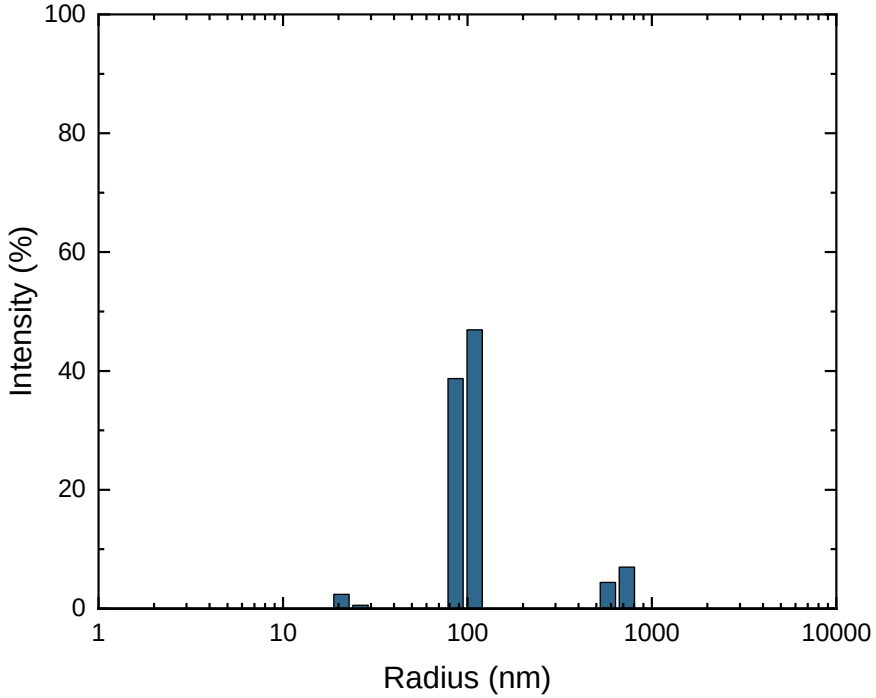
Trial 1
Diameter: 82.1 nm
Polydispersity Index: 0.20



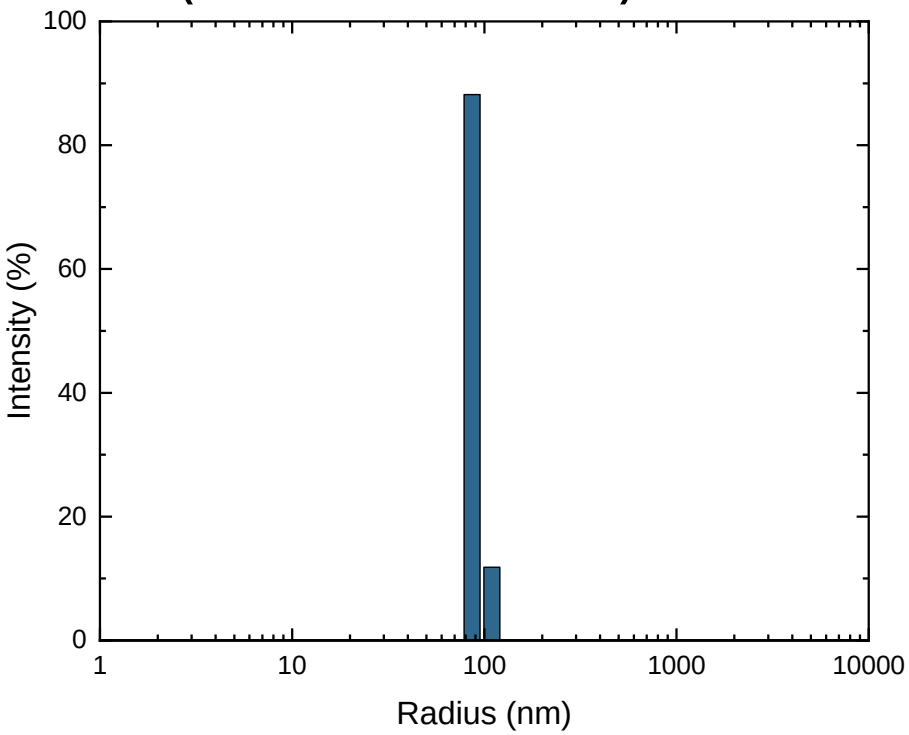
Trial 2
Diameter: 178 nm
Polydispersity Index: 0.08

Testing for Scalability: High Volume Sample

- We made 15x the amount we did the first time (3mL vs 75mL)



75mL sample
Diameter: 198 nm
Polydispersity Index: 0.12
Other peaks at 44nm and 1344 nm

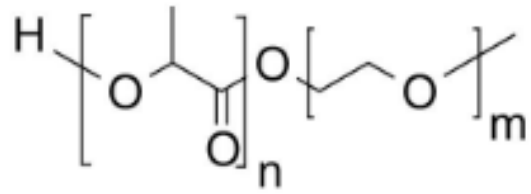


3mL sample
Diameter: 178 nm
Polydispersity Index: 0.08

Future Work

- Complete more replicates of the Flash Nanoprecipitation process
- Further concentrate solutions through evaporation or centrifuge filtering

- Create more nanoparticles with clinically relevant polymers
  - Example: Polyethylene Glycol-b-Polylactic Acid



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