

Challenges and Considerations in Developing In Vitro Release Testing Methods for Parenteral Suspensions

*SBIA 2022: Advancing Generic Drug Development:
Translating Science to Approval
Day (1), Session (3): (Simple Injectables)*

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Learning Objectives

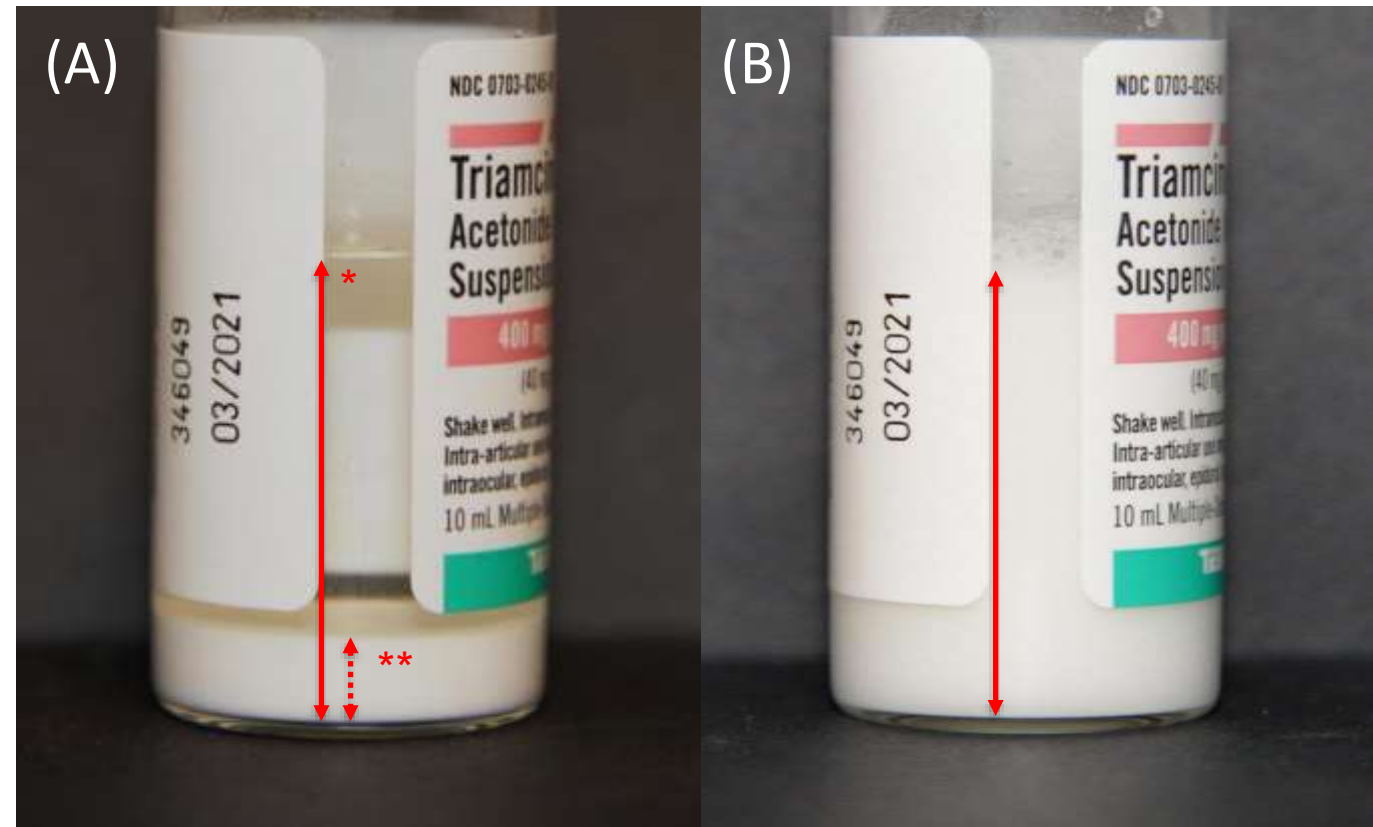
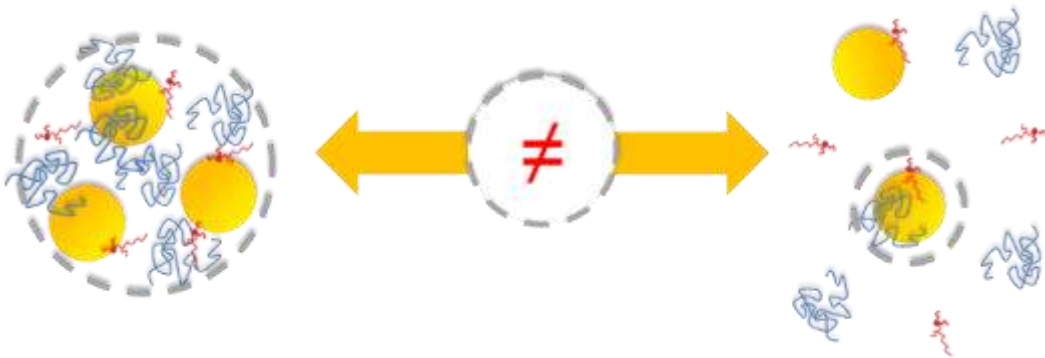


- **Understanding Flocculated Suspensions**
- **How is particle size related to clinical performance?**
- **Is your method measuring what is relevant?**

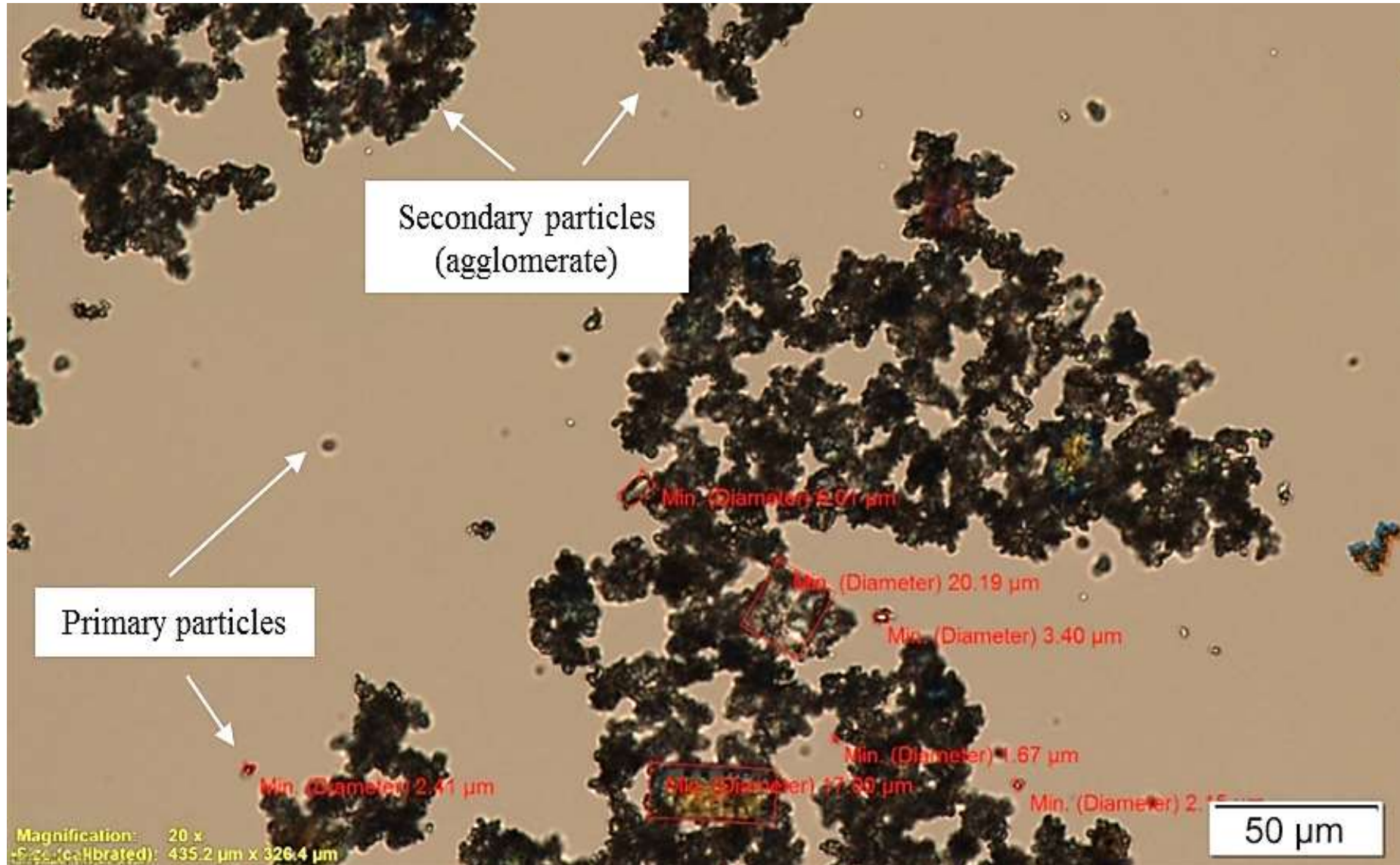
Impacts of Particle Flocculation



Particle flocculation, imparts shelf stability, but could potentially lead to variations in PK response for injectable suspensions



Cause and Effect: Flocculation and PSD

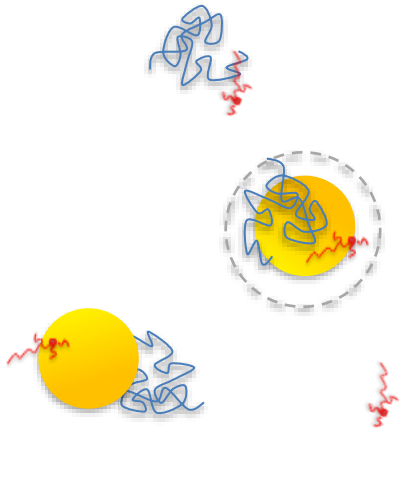


*Particle flocculation is a common phenomenon in suspension product (i.e., primary and secondary particles)

Formulation for Flocculation

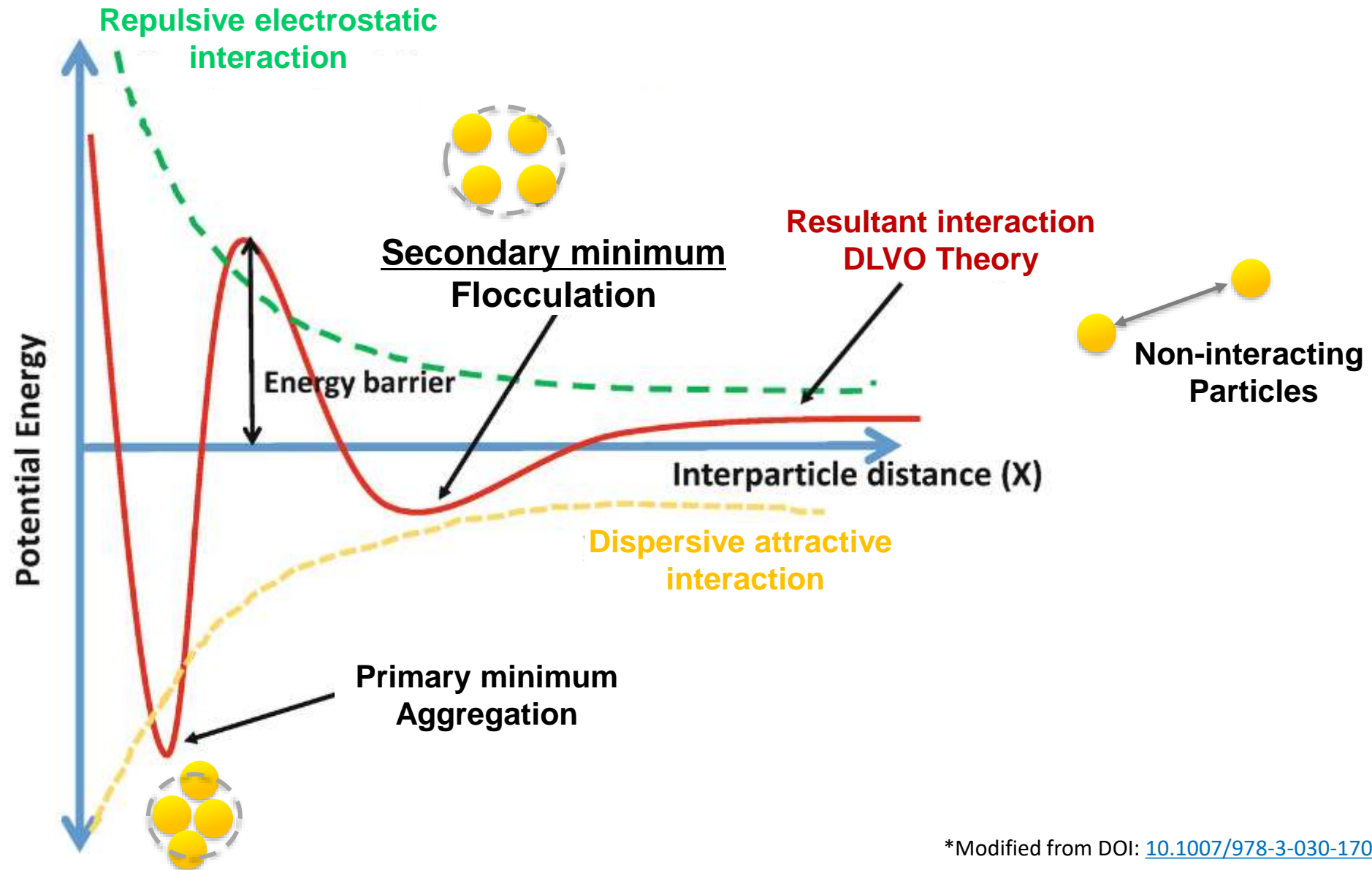


Controlled Flocculation

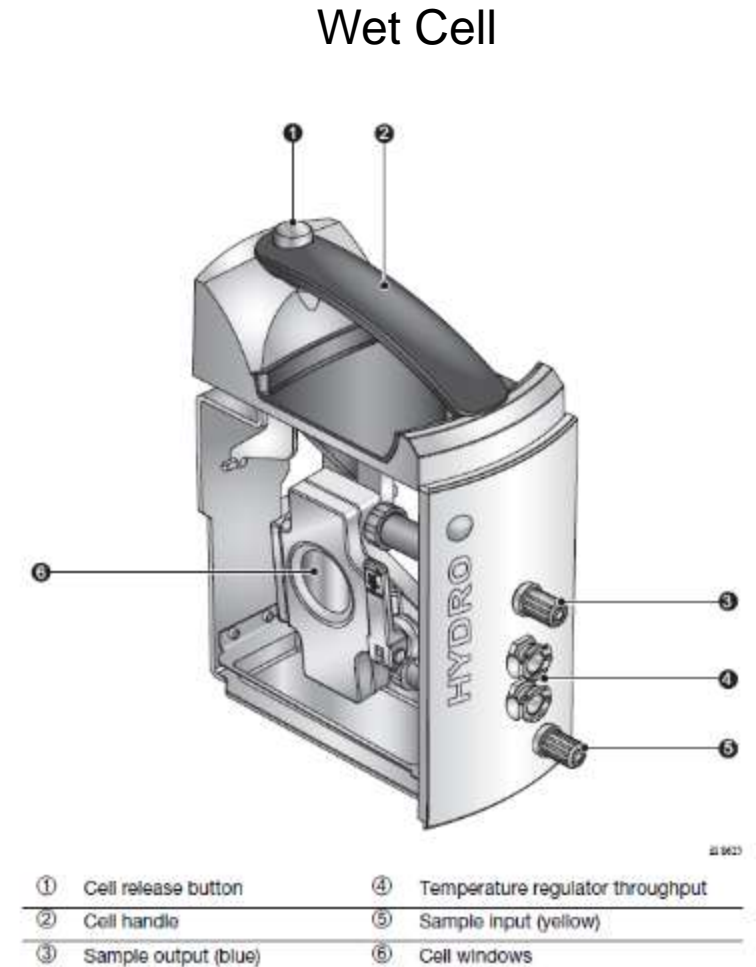
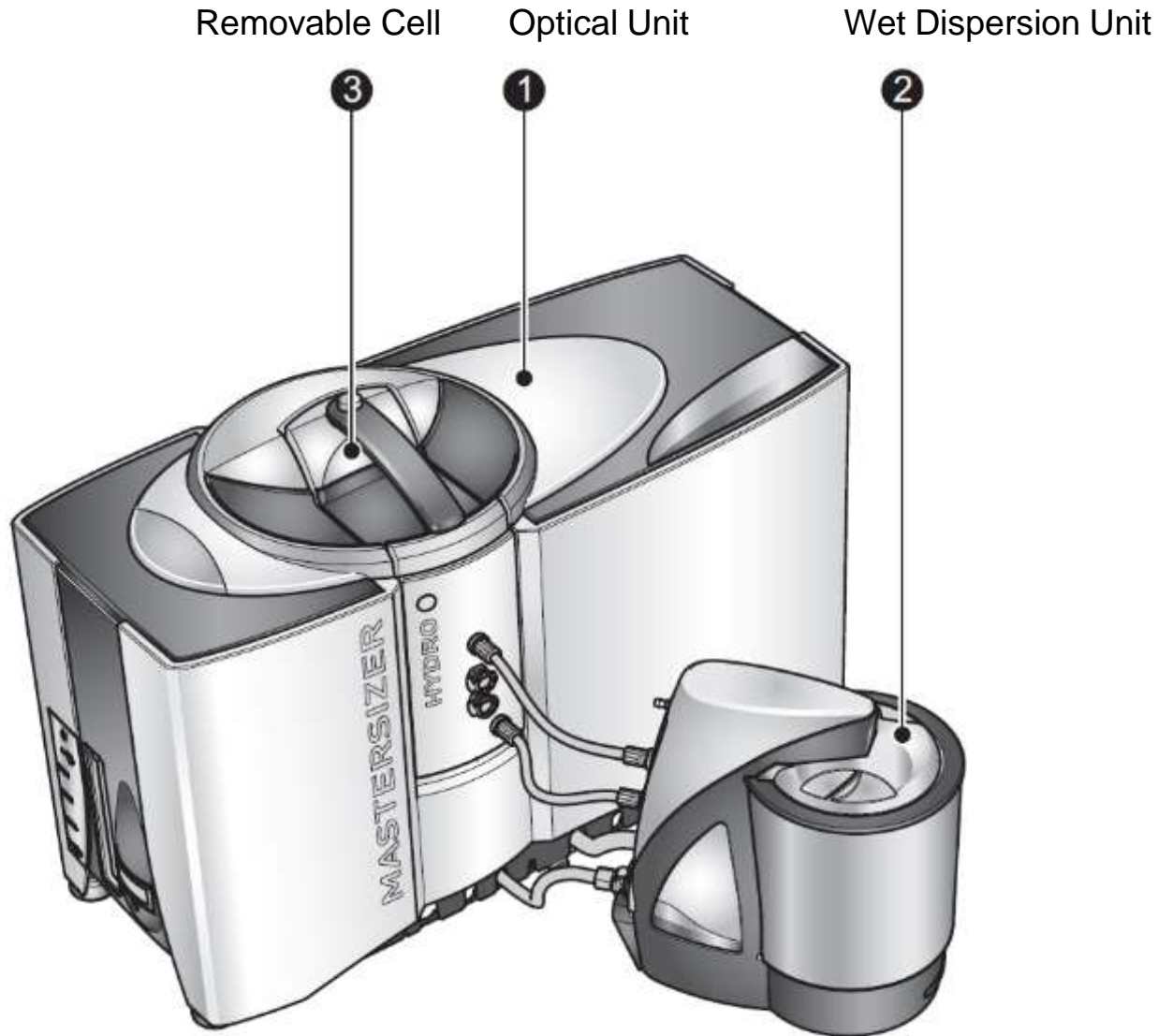


- Polymers
 - Suspending Agents, Sterics, and Electrostatics
- Surfactants
 - Wetting Agents, Hydrophobicity, and Electrostatics
- Electrolytes
 - Valency, Ionic Strength, and Electrostatics

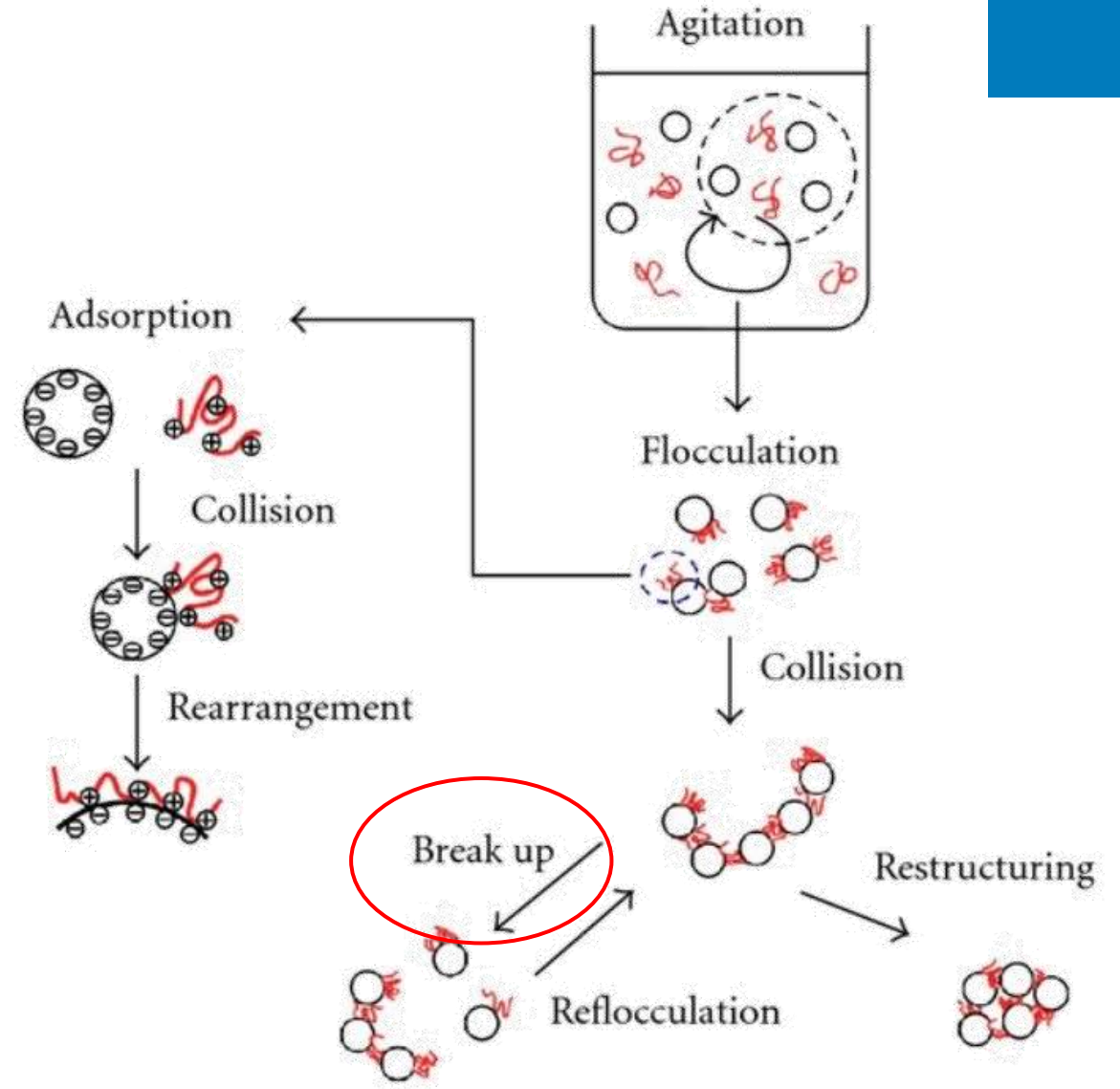
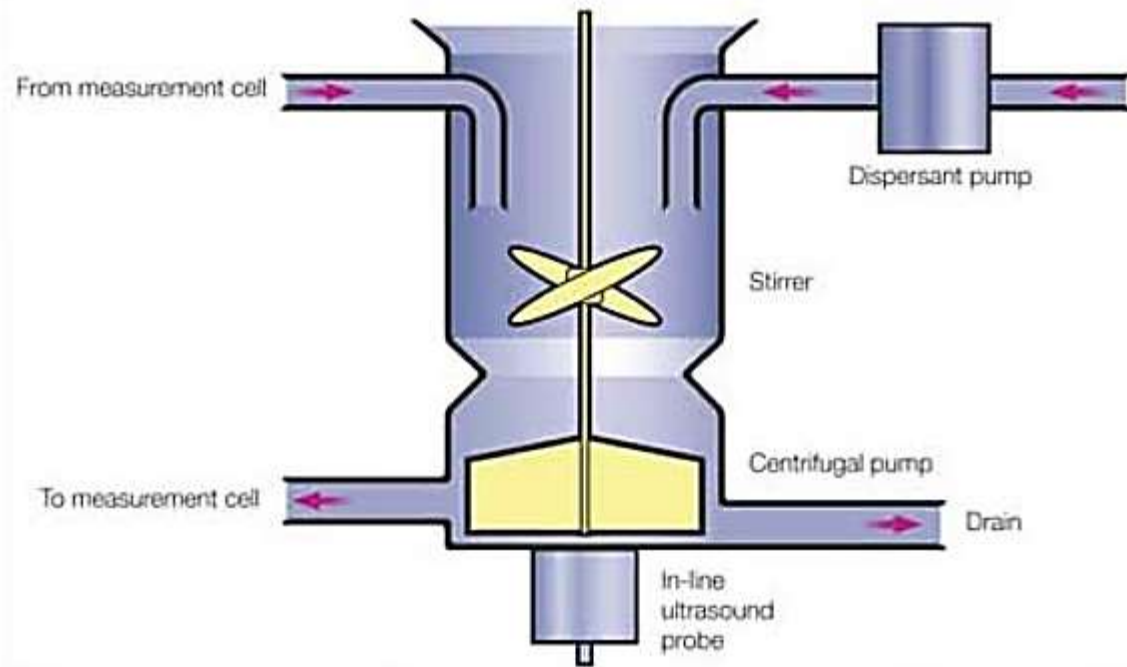
Flocculation: Particle Interactions and DLVO Theory



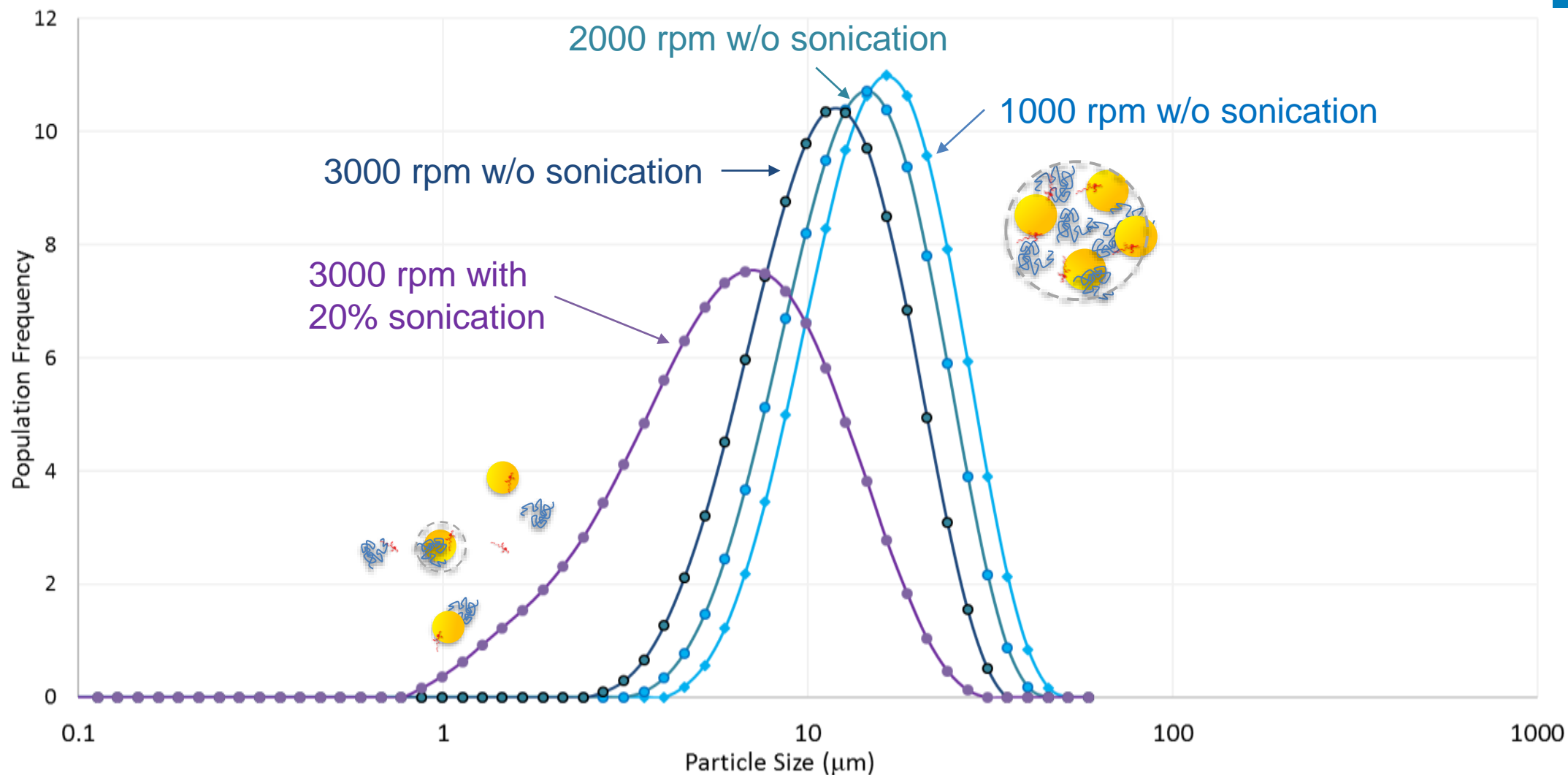
Laser Diffraction: Components and Setup



Particle Flocculation State Is Shear Dependent

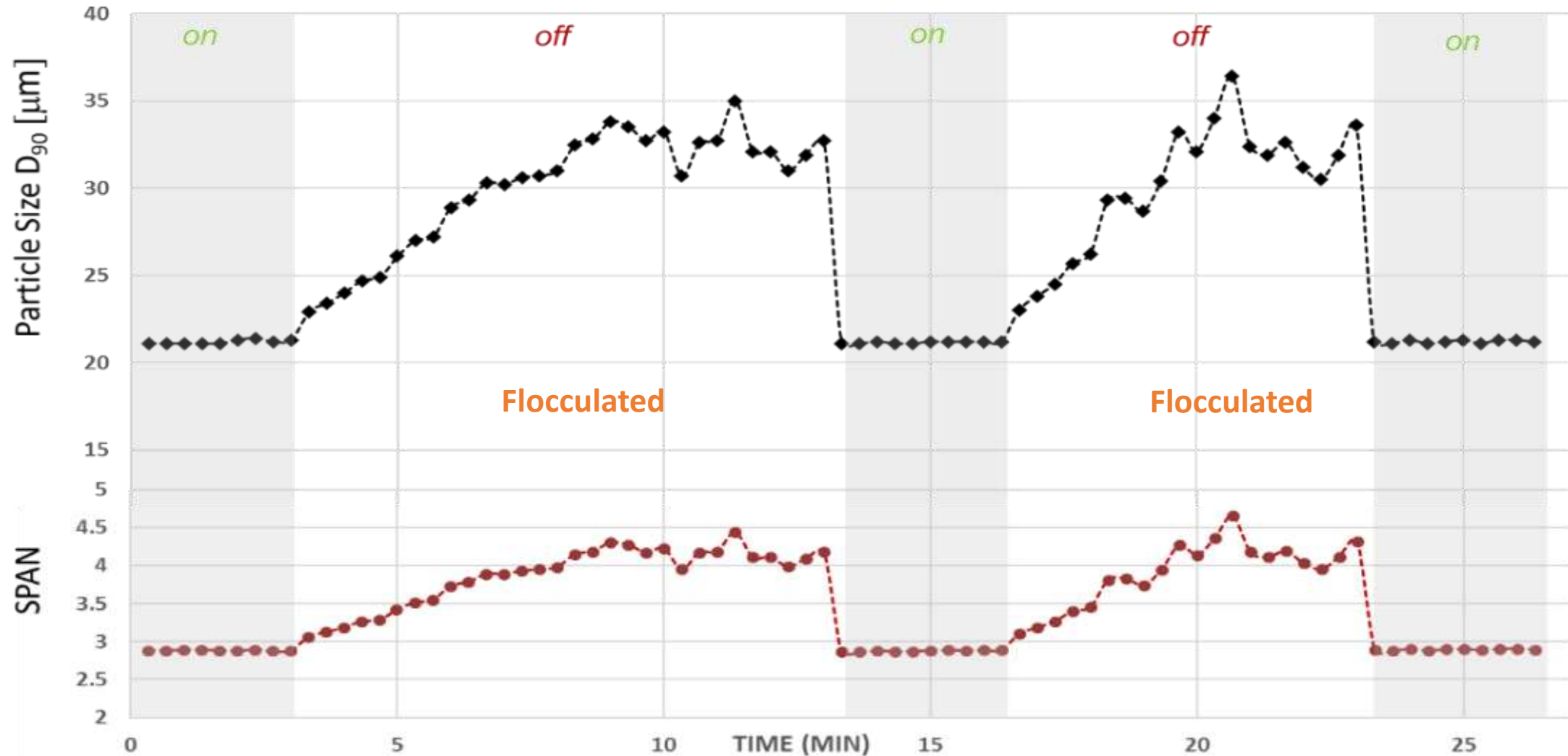


Shear Induced De-flocculation

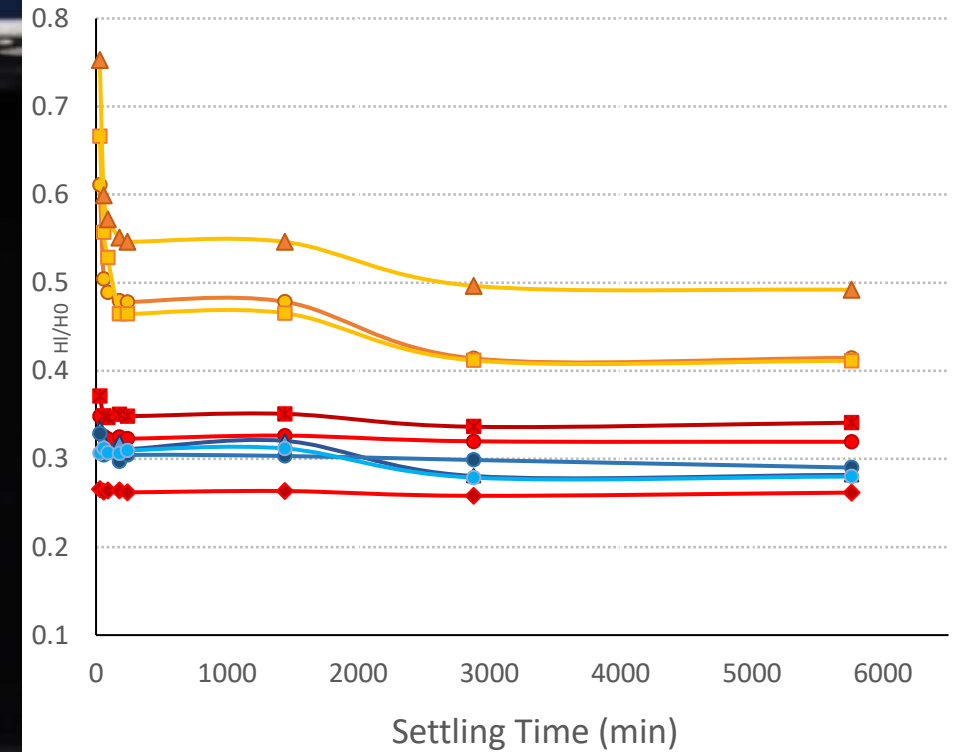


PSD becomes more broad and mean size decreases with increased stir rate and sonication

Flocculation of TA Suspension Is Reversible



Sedimentation as a Surrogate for PSD

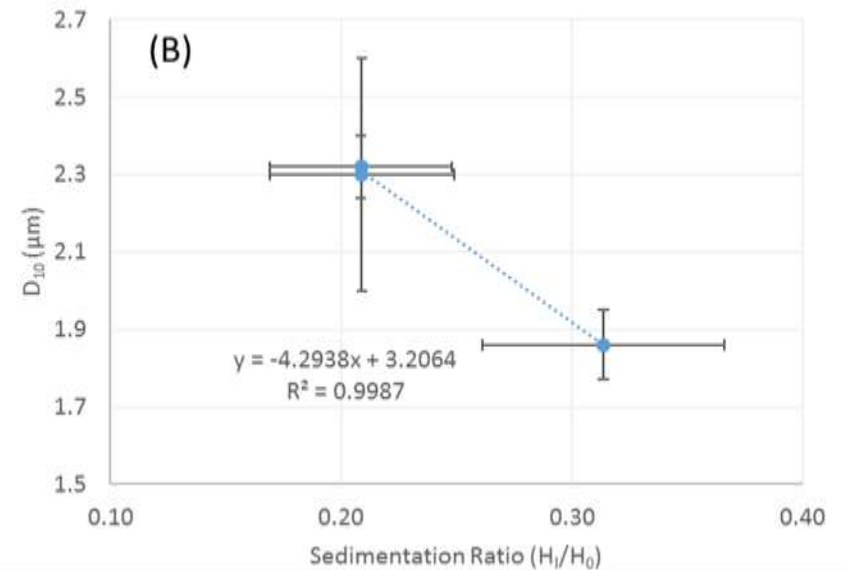
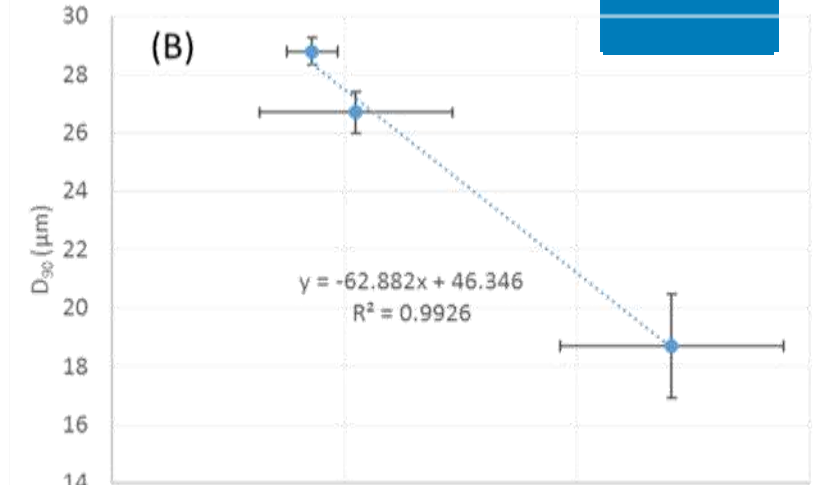
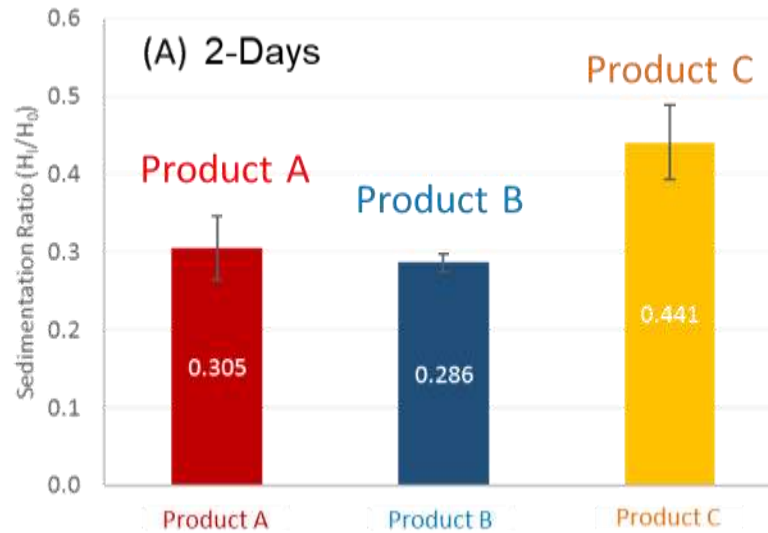
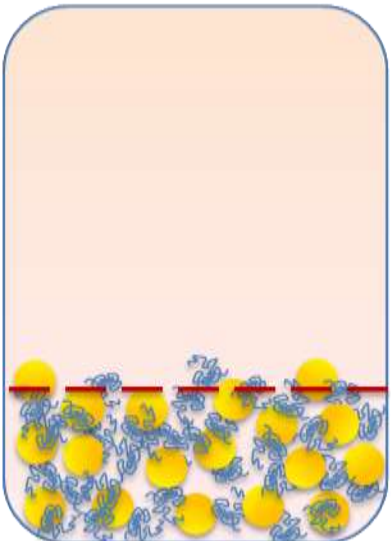
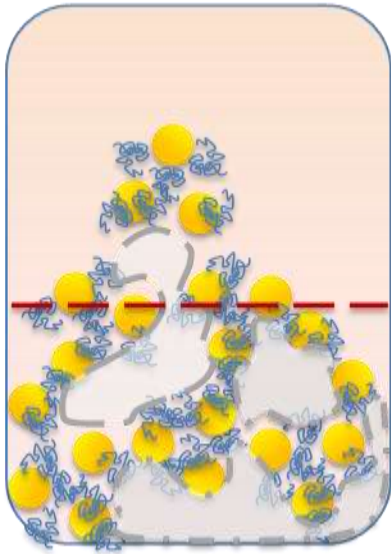


Flocculation → Sedimentation → Improved Long Term Stability

Sedimentation Ratios: $B < A < C$

**Sedimentation Ratios can be a useful surrogate for PSD*

Sedimentation of TA Injectable Suspension Products



Sedimentation correlates with: PSD D_{90} under gentle shear conditions
: PSD D_{10} under high shear conditions

Kenalog-40 Package Insert and Guidelines

Administration

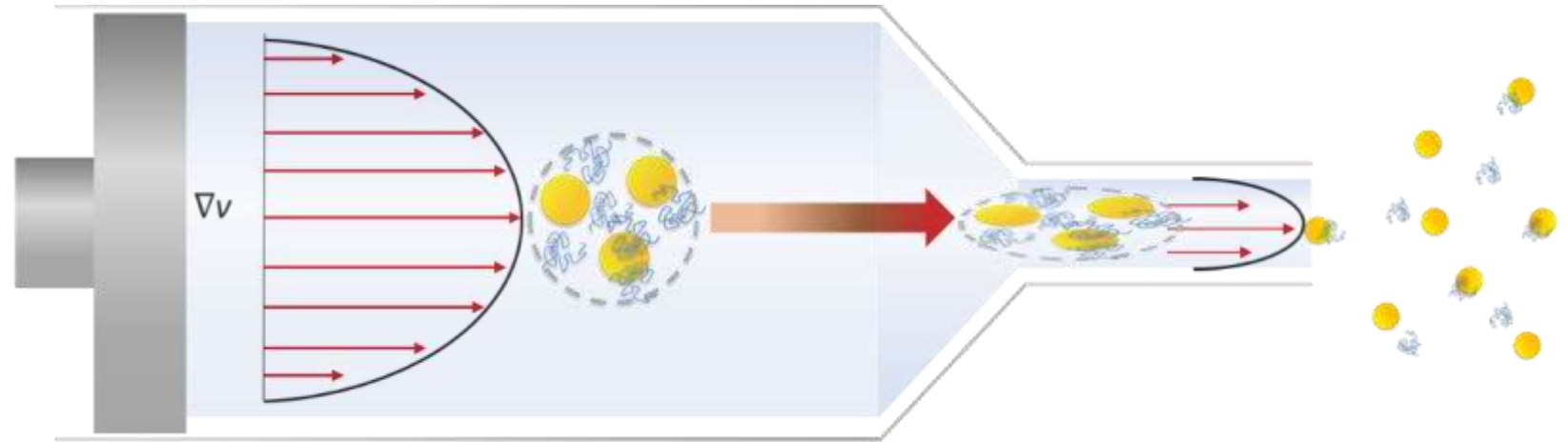
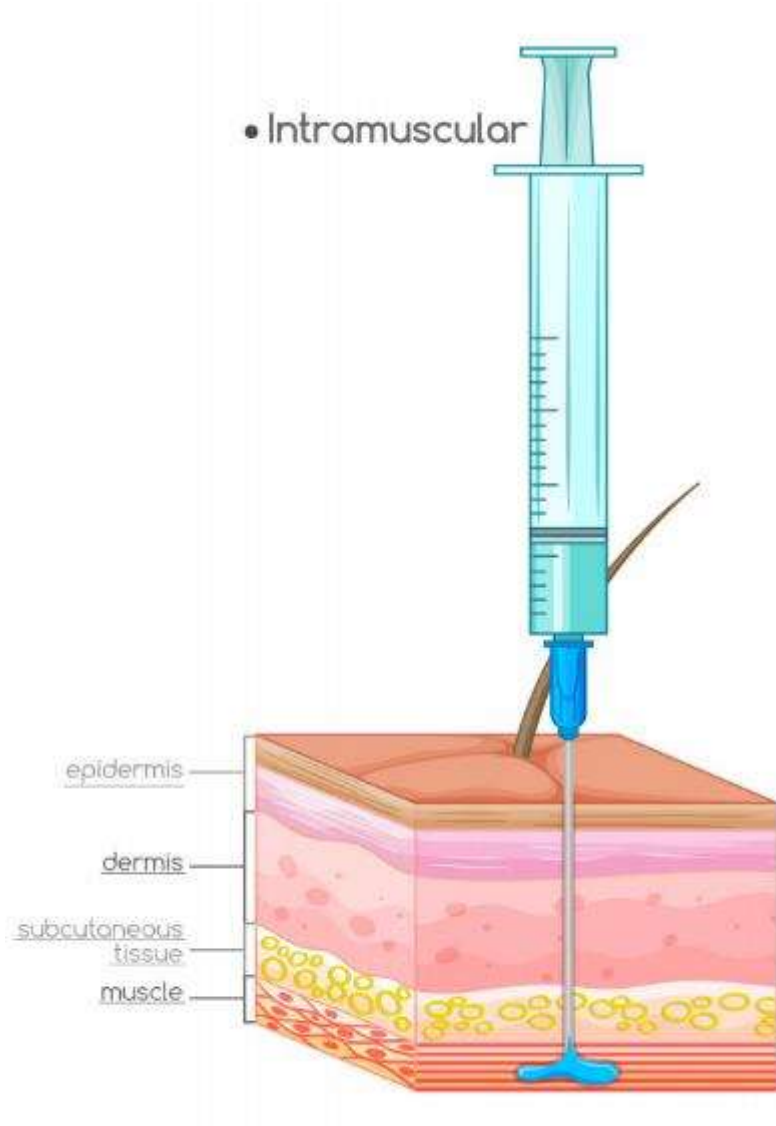
GENERAL

STRICT ASEPTIC TECHNIQUE IS MANDATORY. The vial should be shaken before use to ensure a uniform suspension. Prior to withdrawal, the suspension should be inspected for clumping or granular appearance (agglomeration). An agglomerated product results from exposure to freezing temperatures and should not be used. After withdrawal, Kenalog-40 Injection should be injected without delay to prevent settling in the syringe. Careful technique should be employed to avoid the possibility of entering a blood vessel or introducing infection.

SYSTEMIC

For systemic therapy, injection should be made **deeply into the gluteal muscle** (see **WARNINGS**). For adults, a minimum needle length of 1½ inches is recommended. In obese patients, a longer needle may be required. Use alternative sites for subsequent injections.

Shear-Induced De-flocculation During Injection



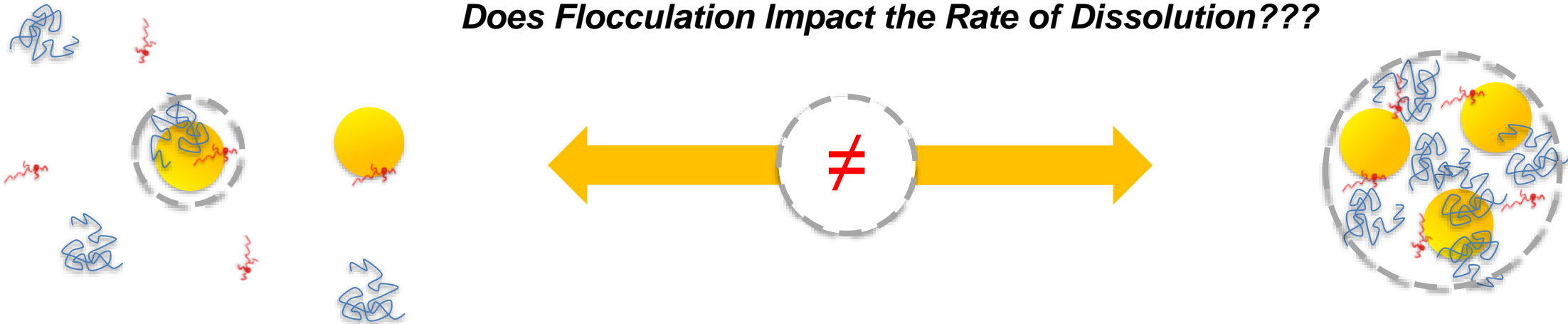
**Particle flocculates undergo shear during IM administration
Infusion Rate?? Syringe Gauge??*

Impact of Flocculation on Dissolution?

Deflocculated

Flocculated

Does Flocculation Impact the Rate of Dissolution???

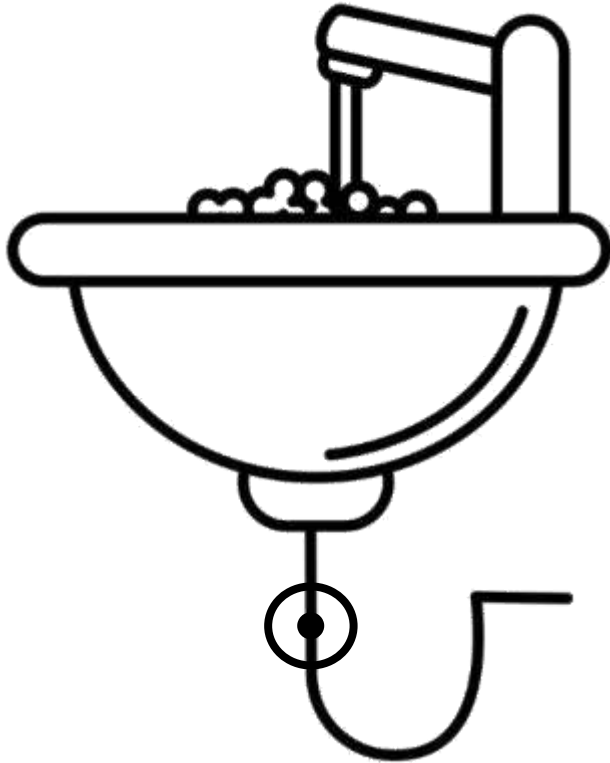


**According to Noyes-Whitney Equation, rate of dissolution depends on the specific surface area (i.e., particle size).*

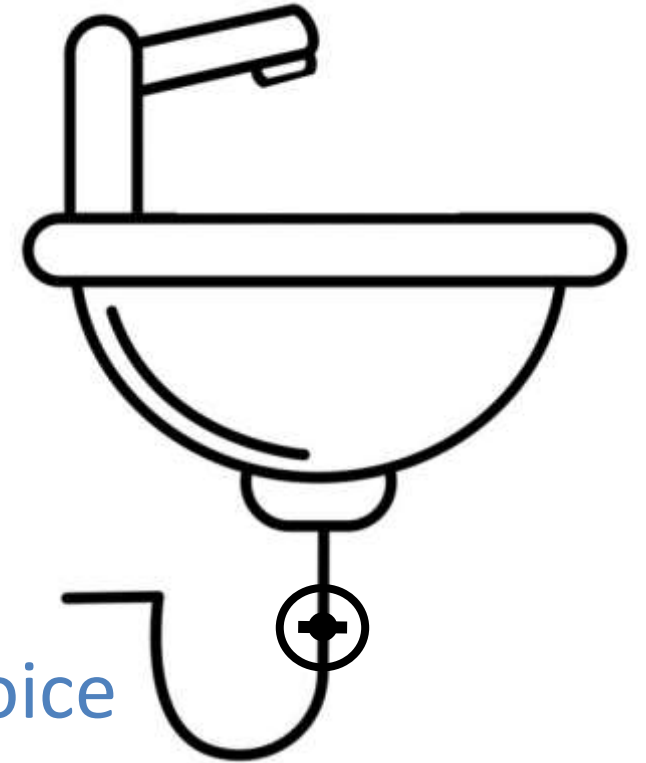
Noyes-Whitney Equation

$$\frac{dm}{dt} = \frac{D \times A}{h} \Delta C$$

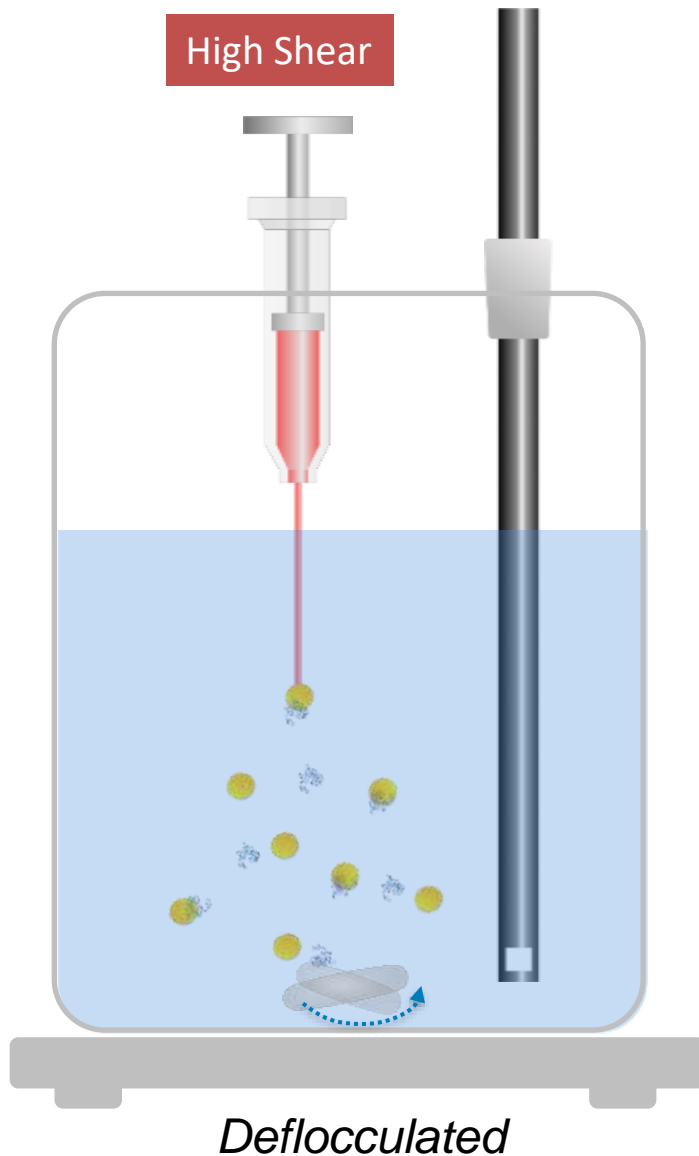
Choosing Sink or Non-Sink Conditions?



- Discrimination
- Relevance to In Vivo
- Shear and Apparatus Choice



Shear-induced Deflocculation on Dissolution



Controlling Shear: High vs. Low Shear

- Sample Introduction
 - 25G Syringe
 - Micro-pipet
- Stir Rate
 - 300 vs. 800 rpm

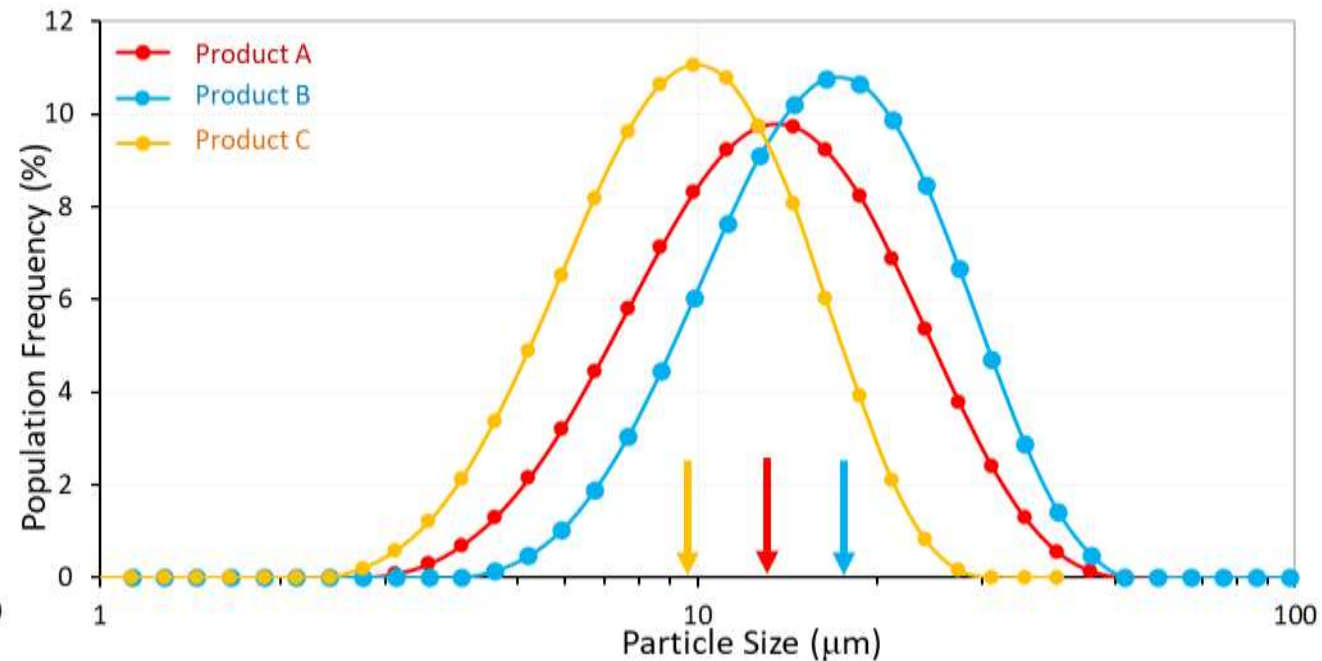
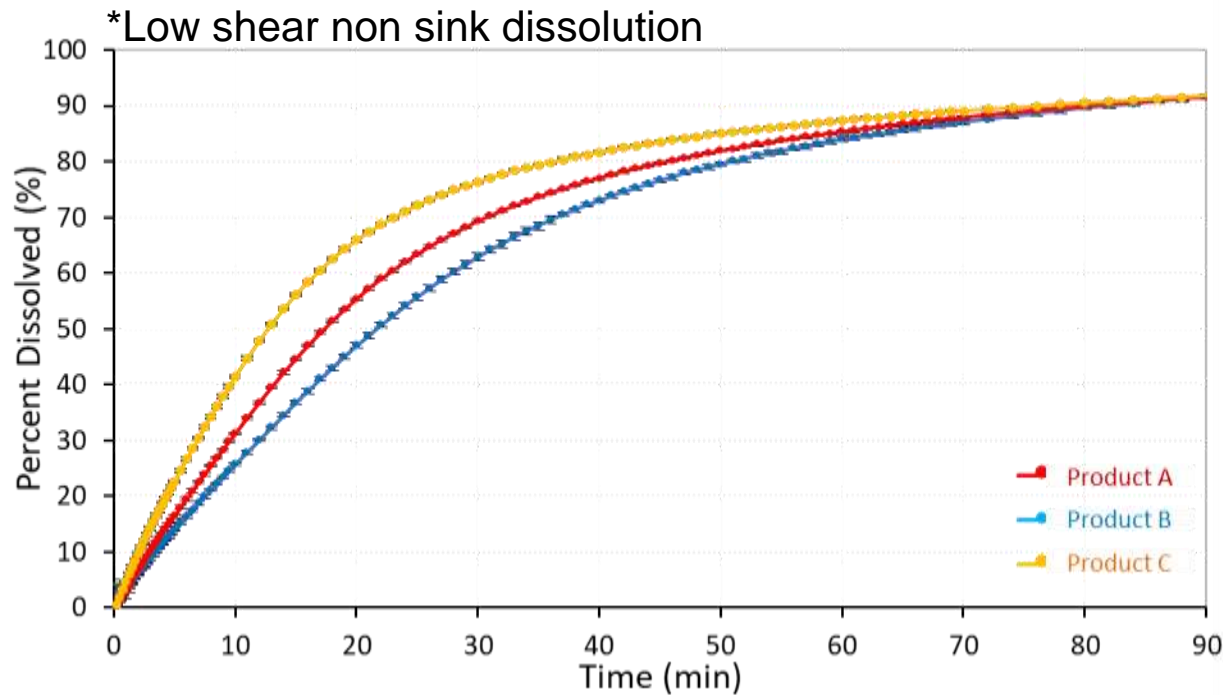
Dissolution Rate?



Impact of Suspension PSD on Drug Dissolution



PSD directly impacts dissolution rates: Larger particles dissolve slower

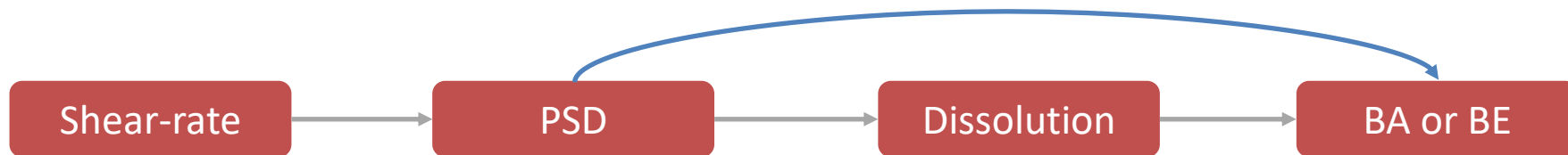
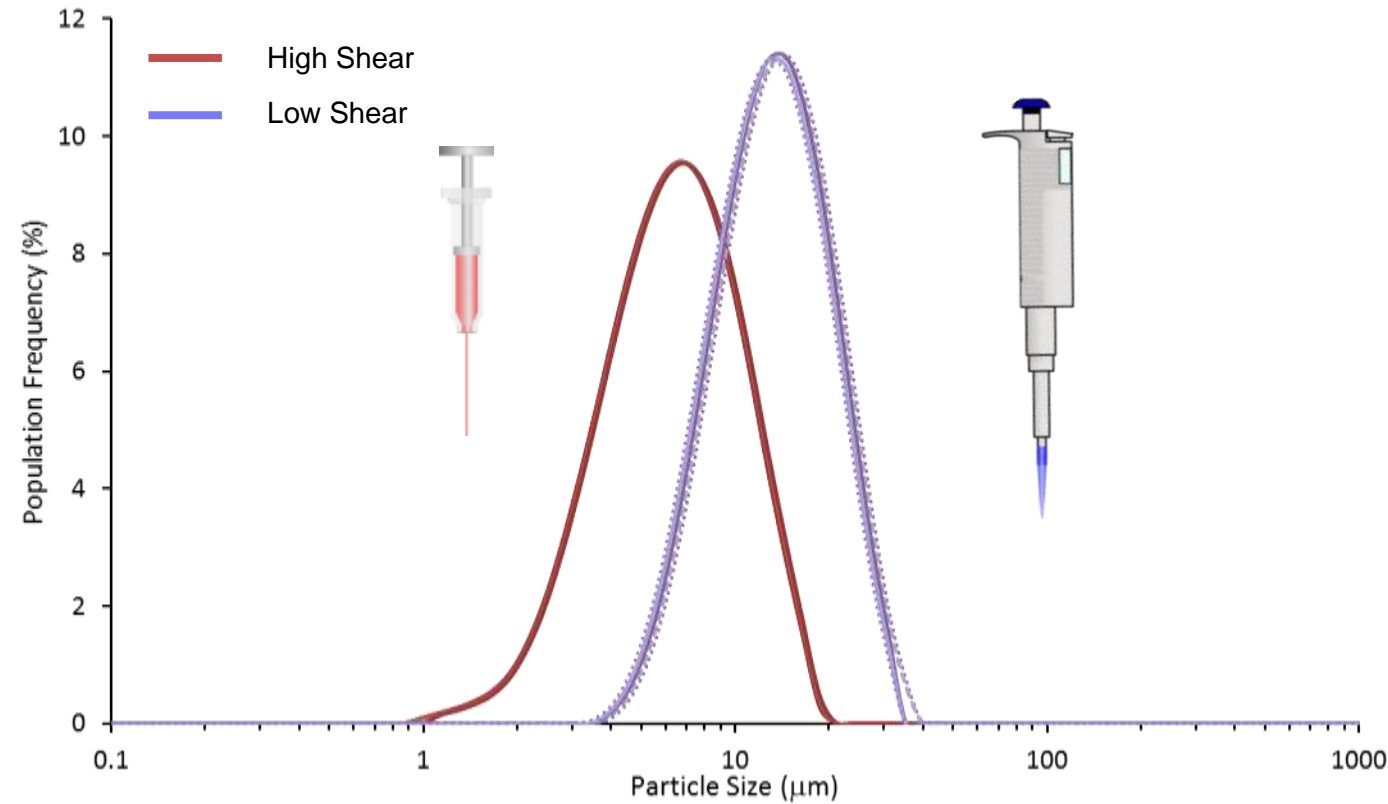
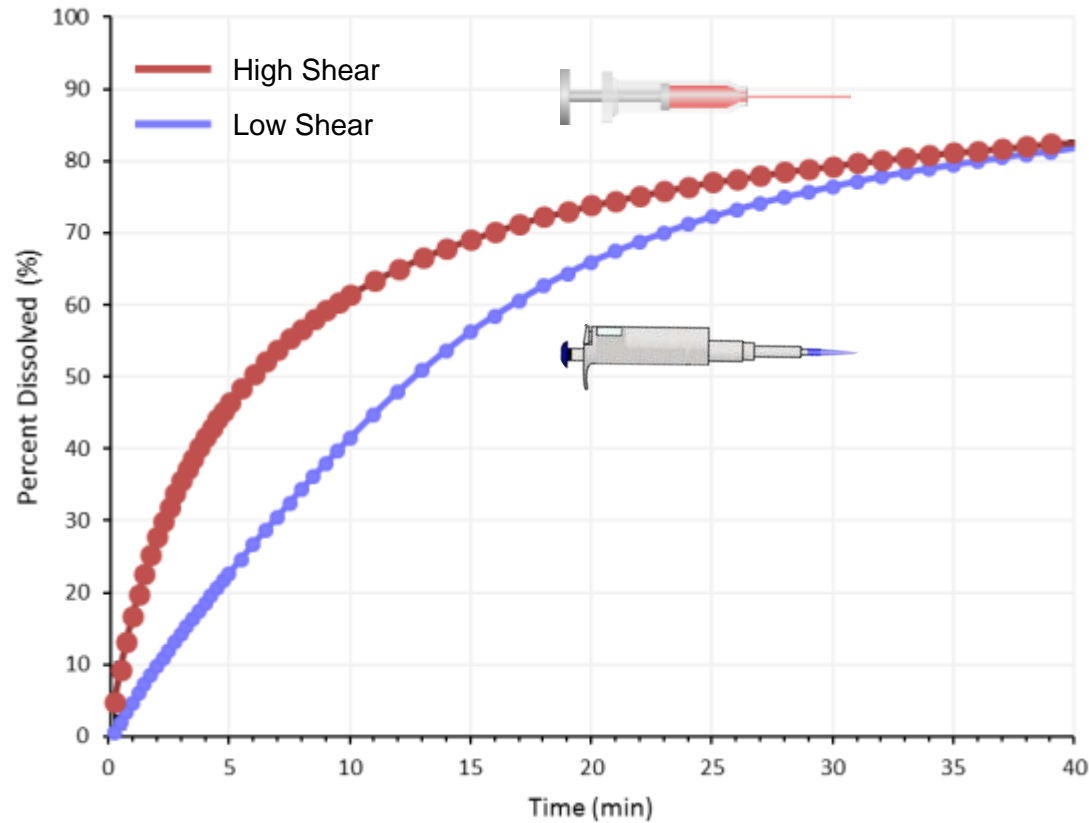


**According to Noyes-Whitney Equation, rate of dissolution depends on the specific surface area (i.e., particle size).*

Noyes-Whitney Equation

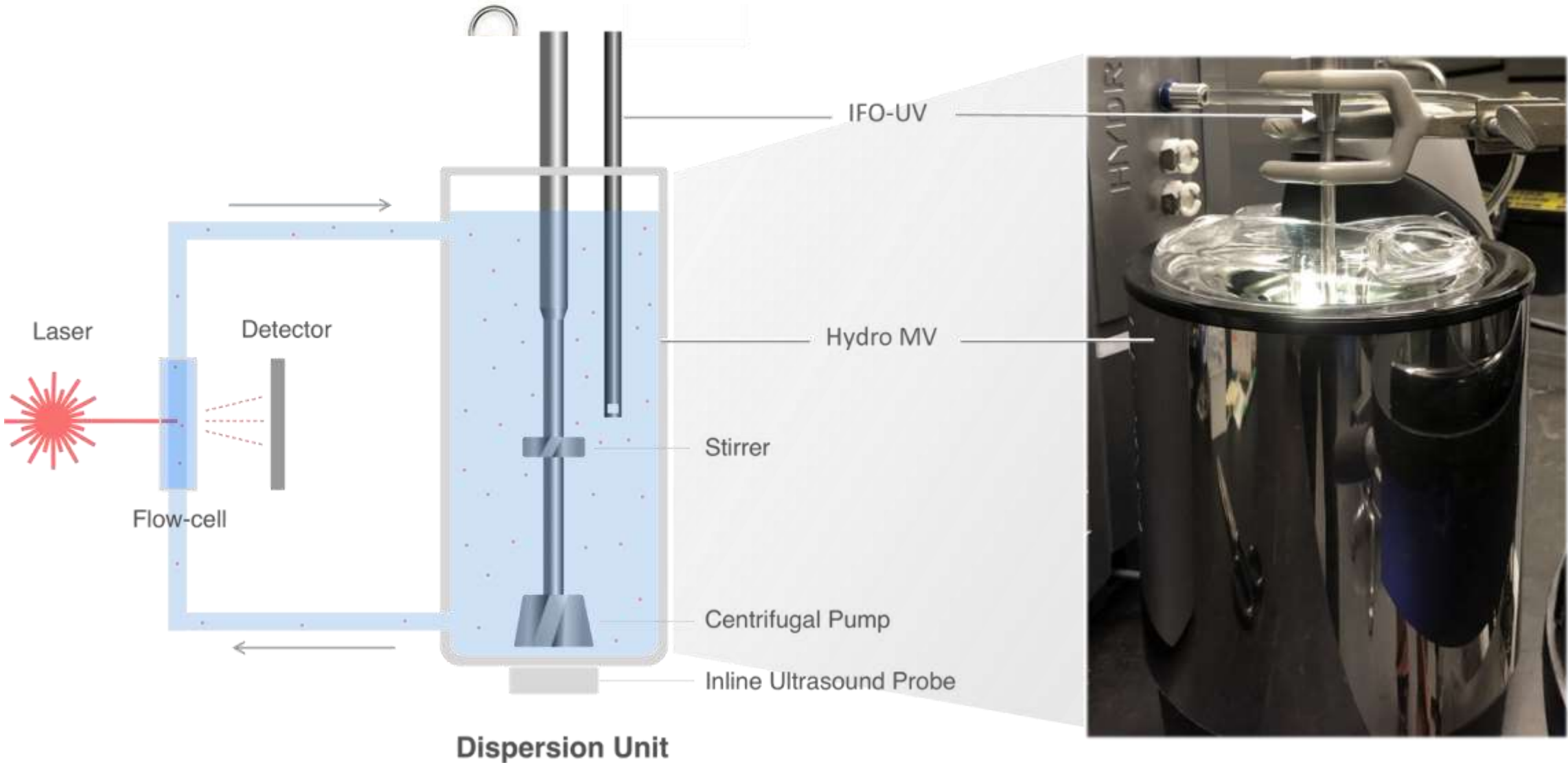
$$\frac{dm}{dt} = \frac{D \times A}{h} \Delta C$$

Impact of Suspension PSD on Drug Dissolution

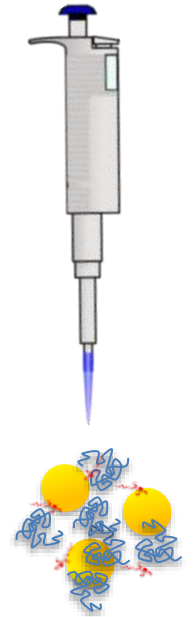
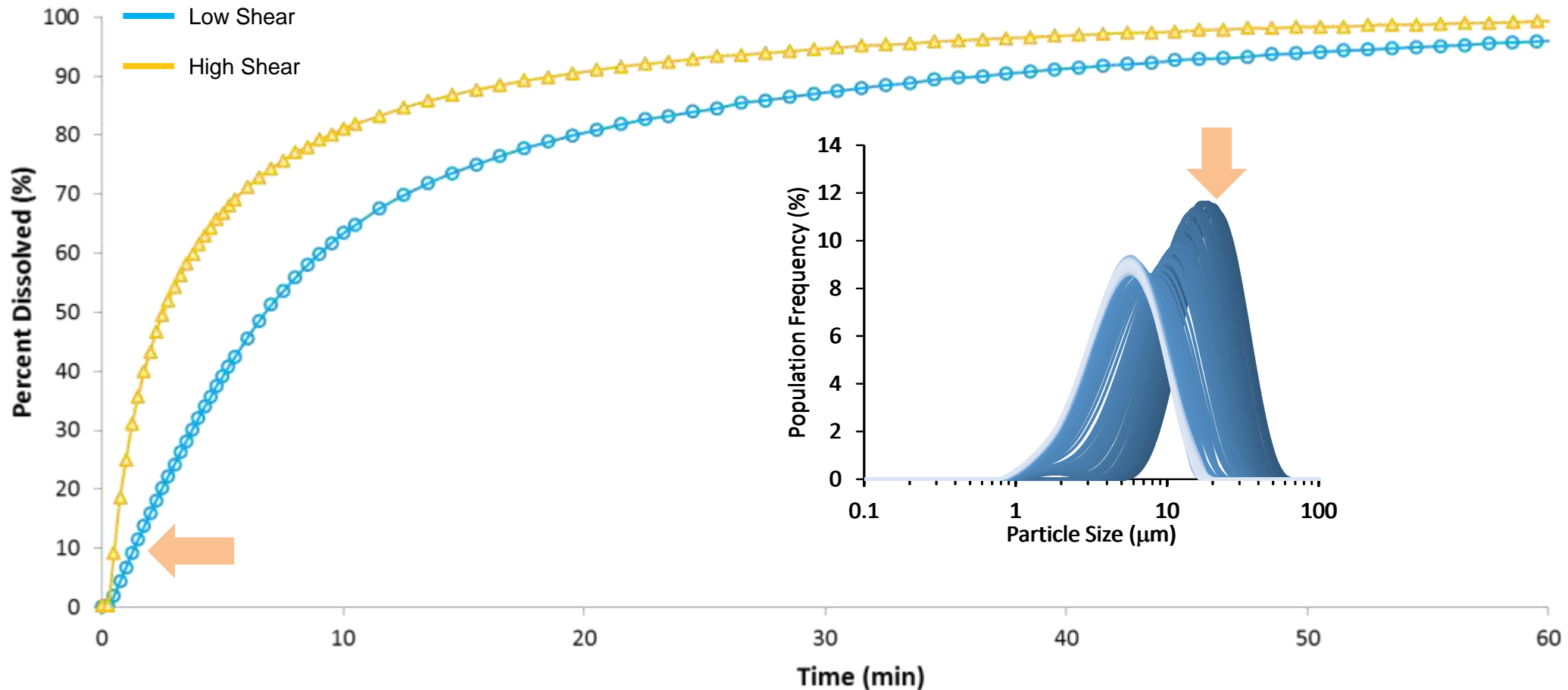


**Deflocculated suspension exhibits >4x higher dissolution rate than flocculated suspension*

Tandem Particle Sizing and Dissolution Setup

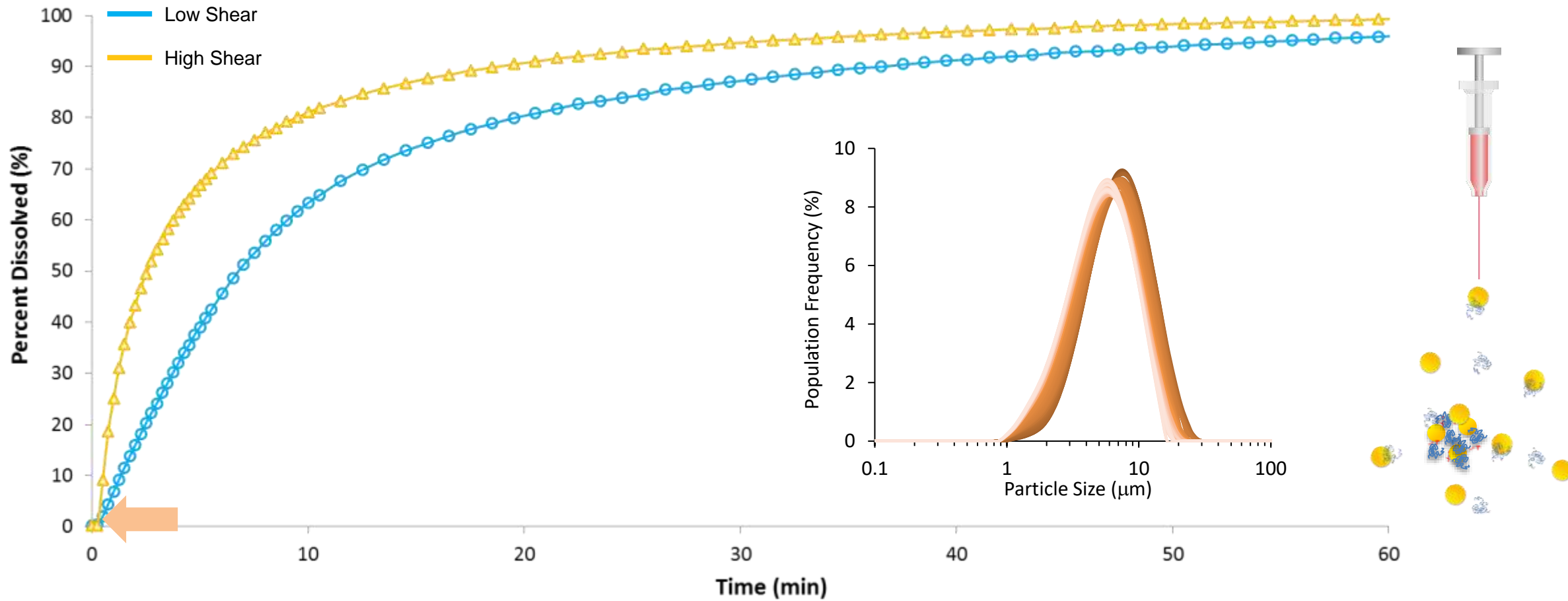


Simultaneous Particle Sizing and Dissolution



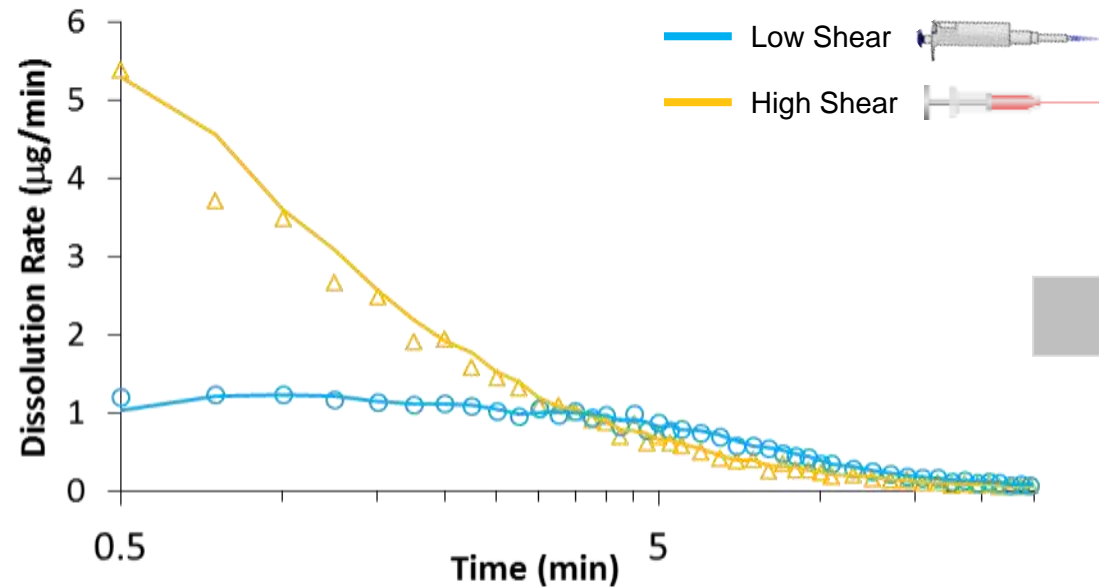
**Flocculated suspension exhibits large shift in Particle Size Distribution during dissolution*

Simultaneous Particle Sizing and Dissolution



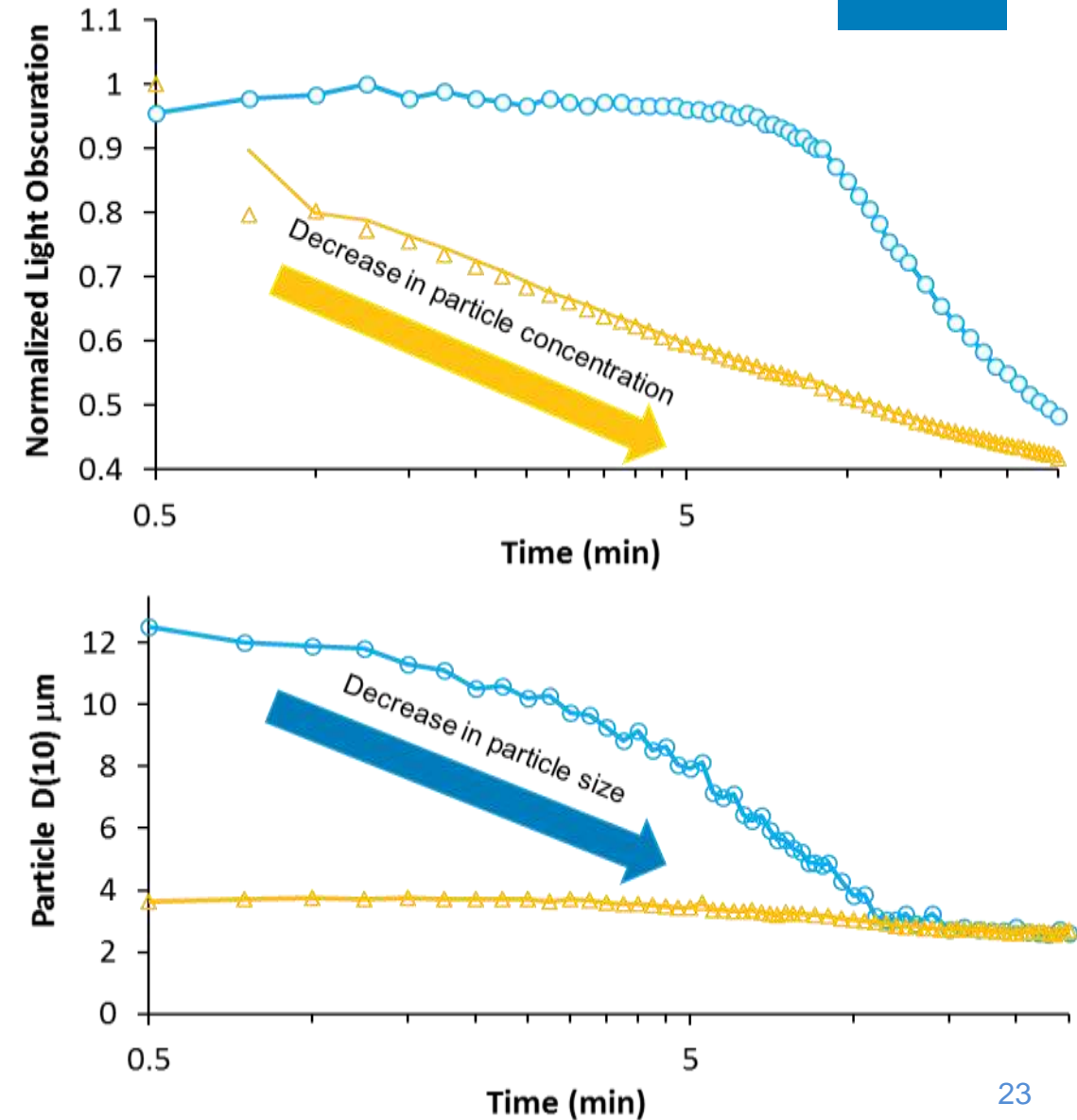
**Deflocculated suspension exhibits minimal change in Particle Size Distribution during dissolution*

Two Particles: Two Dissolution Pathways



Dissolution follows two different pathways/mechanisms?

**Size Reduction and Particle Loss*



Challenge Question #1



Which of these factors impact flocculation state?

- A. Ionic strength of dispersant or diluent
- B. Use of suspending agents or viscosity modifiers
- C. Agitation and temperature
- D. All of the above

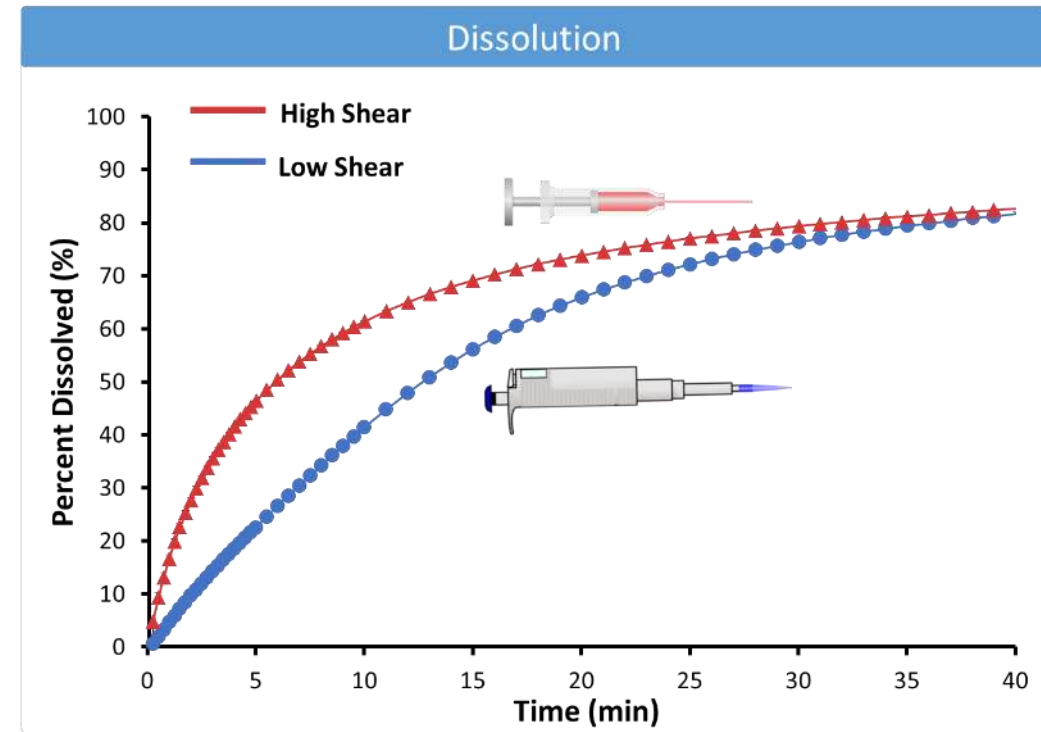
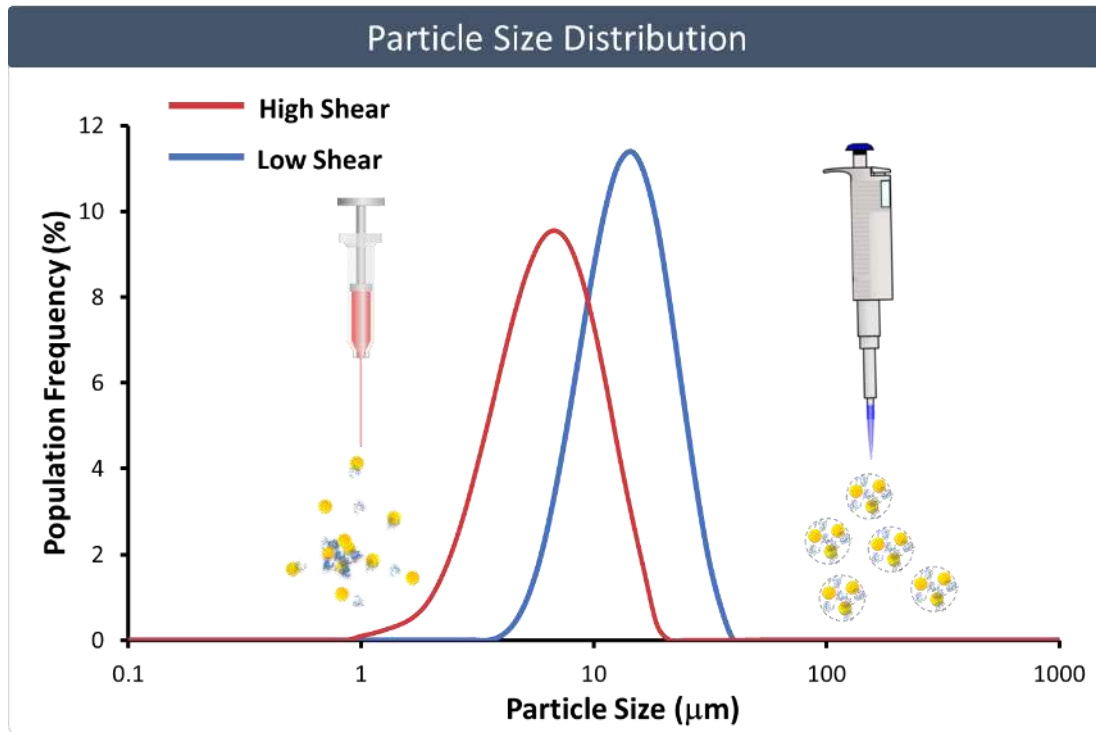
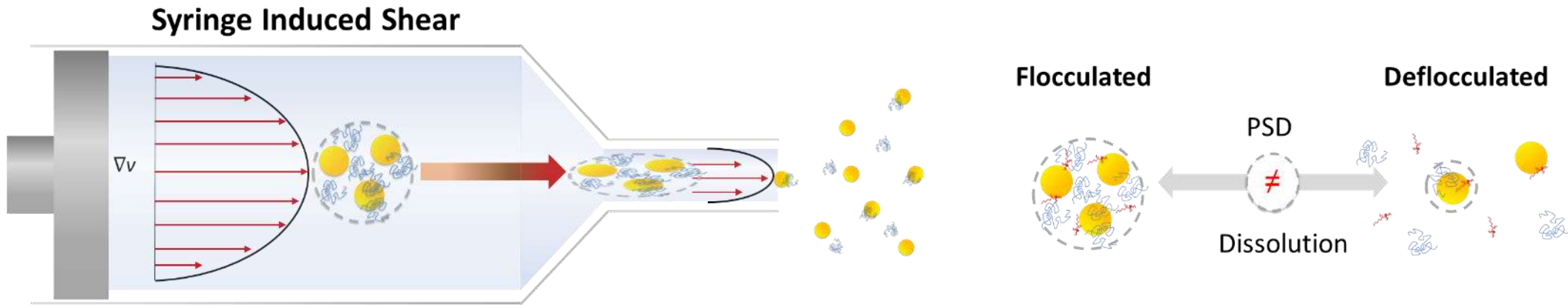
Challenge Question #2



When might you choose to use low shear non sink conditions for IVRT?

- A. Never
- B. Always
- C. For comparison of secondary particle population
- D. For comparison of primary particle population

Syringe Induced Deflocculation: PSD and Dissolution



**Syringe induced shear leads to smaller PSD and faster dissolution (2-6x)*

Acknowledgements

- ❑ Xiaoming Xu
- ❑ Jungeun Bae
- ❑ Ying Zhang
- ❑ Yan Wang
- ❑ Bin Qin
- ❑ Darby Kozak



Additional Resources

- ❑ Smith, W.C., et al. “Impact of particle flocculation on the dissolution and bioavailability of injectable suspensions”, Int. J. Pharm. 604 (2021), DOI:10.1016/j.ijpharm.2021.120767
 - ❑ [Link to our Journal Article](#)

- ❑ [FDA Newsletter on IVRT for Injectables](#)

- ❑ [I.M. Administration Guidelines](#)

- ❑ Flocculation Reading
 - ❑ [Flocculation in Pharmaceuticals](#)
 - ❑ [DLVO Theory Basics](#)

Questions?

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