

Developing Discriminatory IVRT Methods for Injectable Suspensions: *Start with Why*

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OPQ/OTR/DPQR

Challenge of Flocculated Suspensions

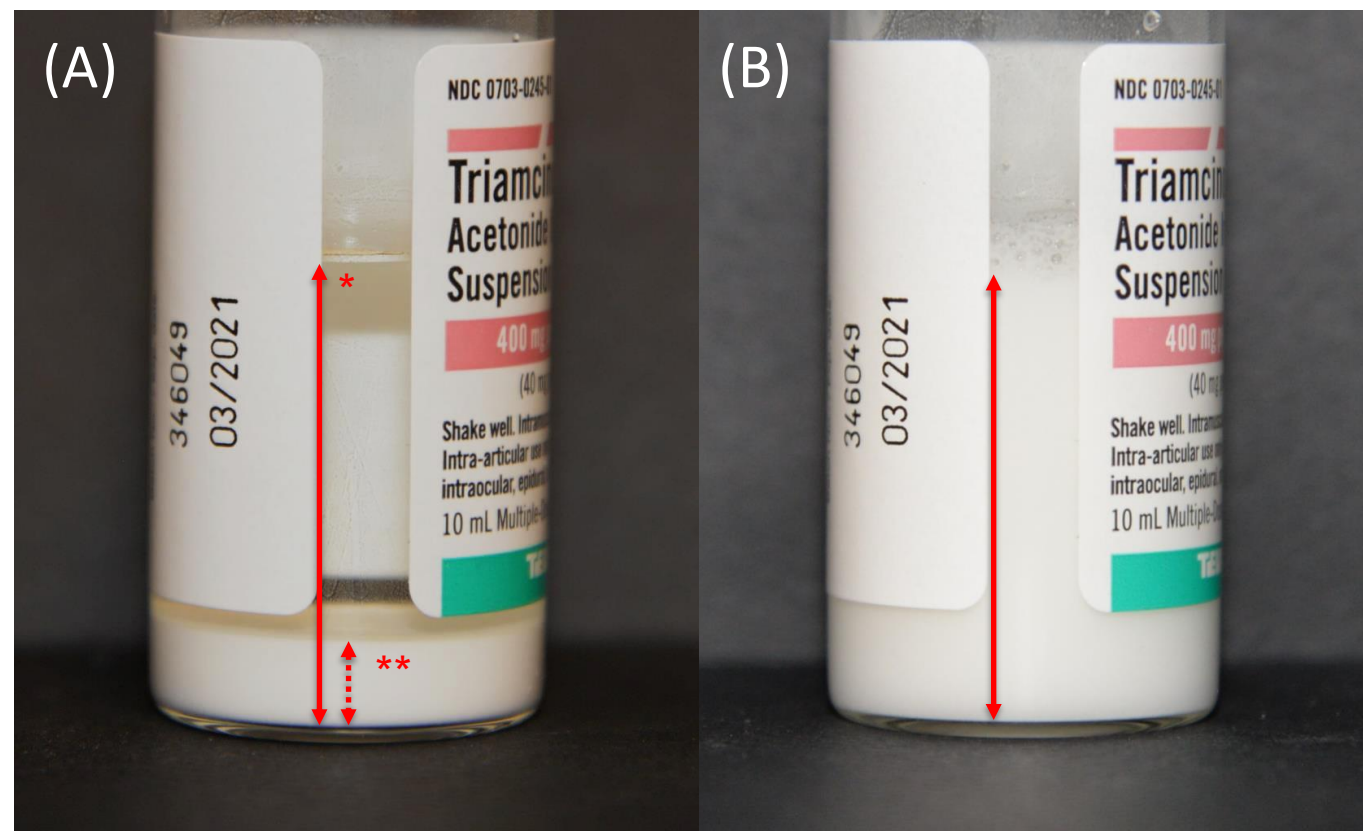
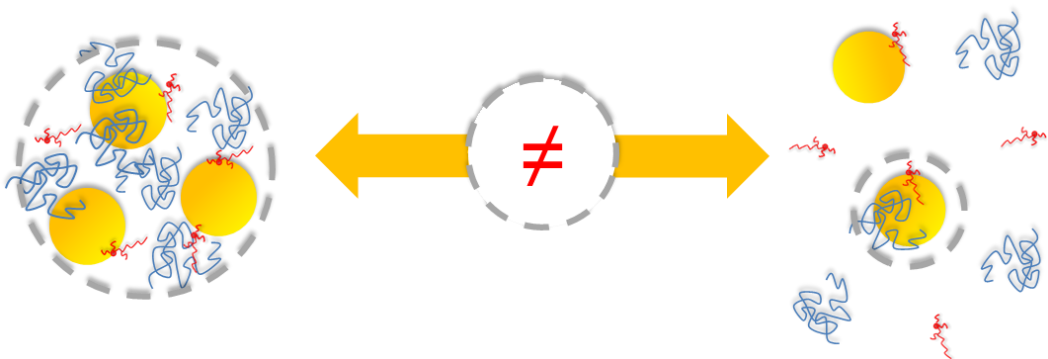


- How is particle size related to clinical performance?
- What exactly are we trying to measure?
- Is the method measuring what is intended?

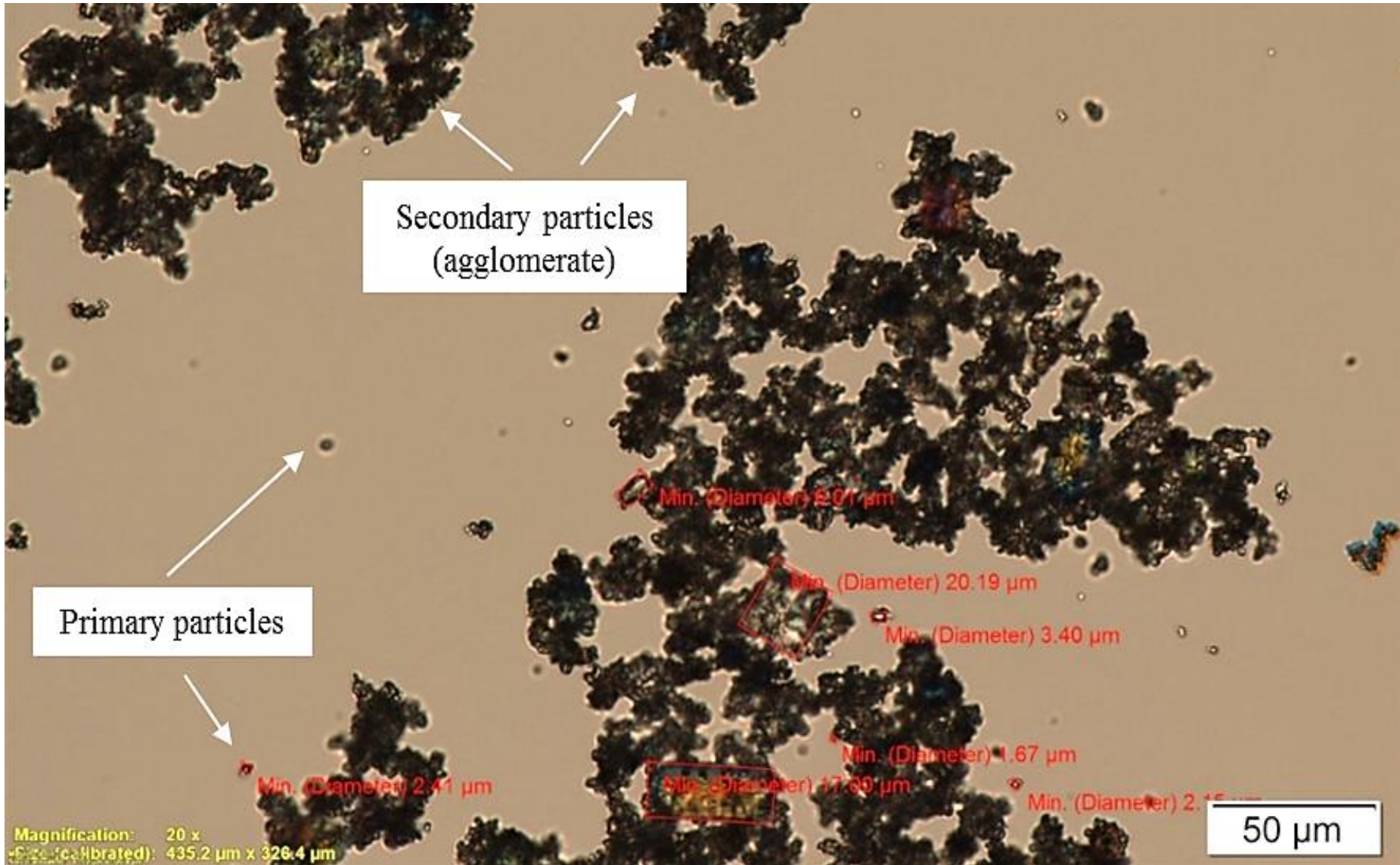
Impacts of Particle Flocculation



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



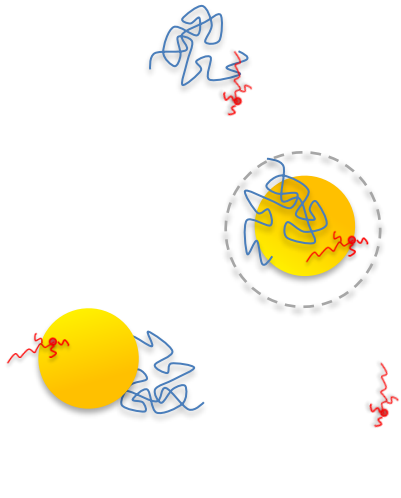
Cause and Effect: Flocculation and PSD



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

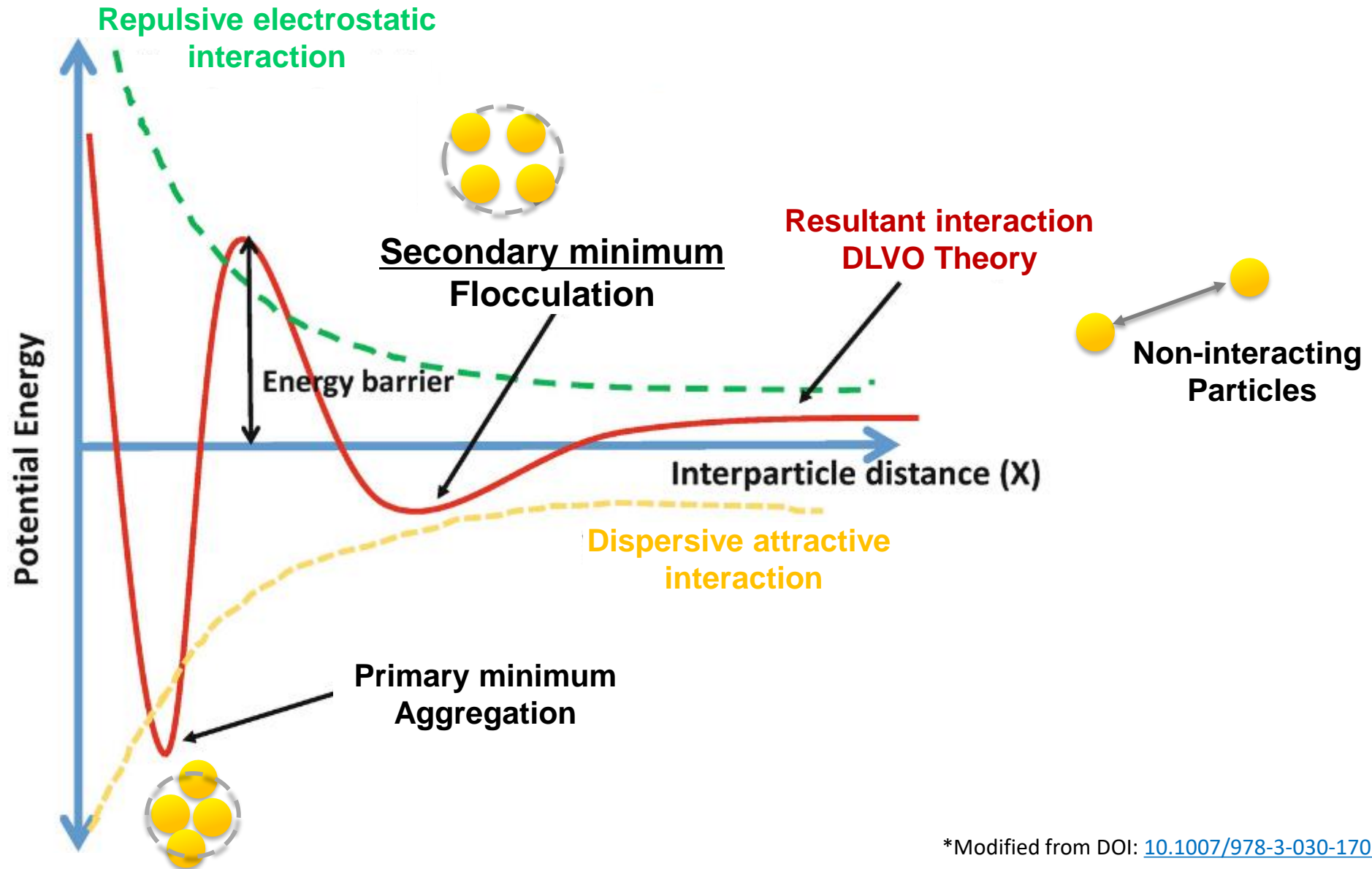
Formulation for Flocculation

Controlled Flocculation

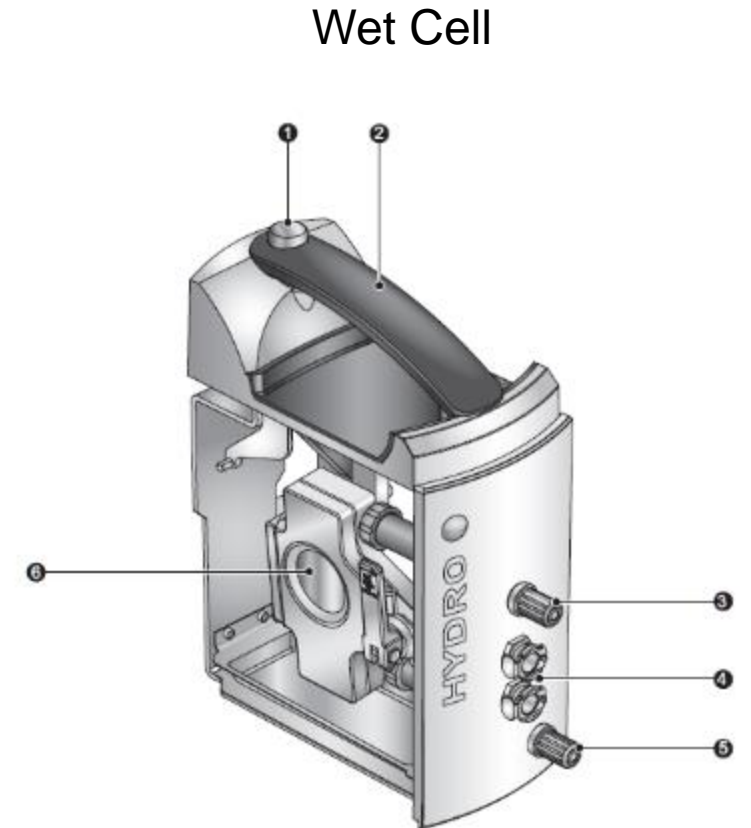
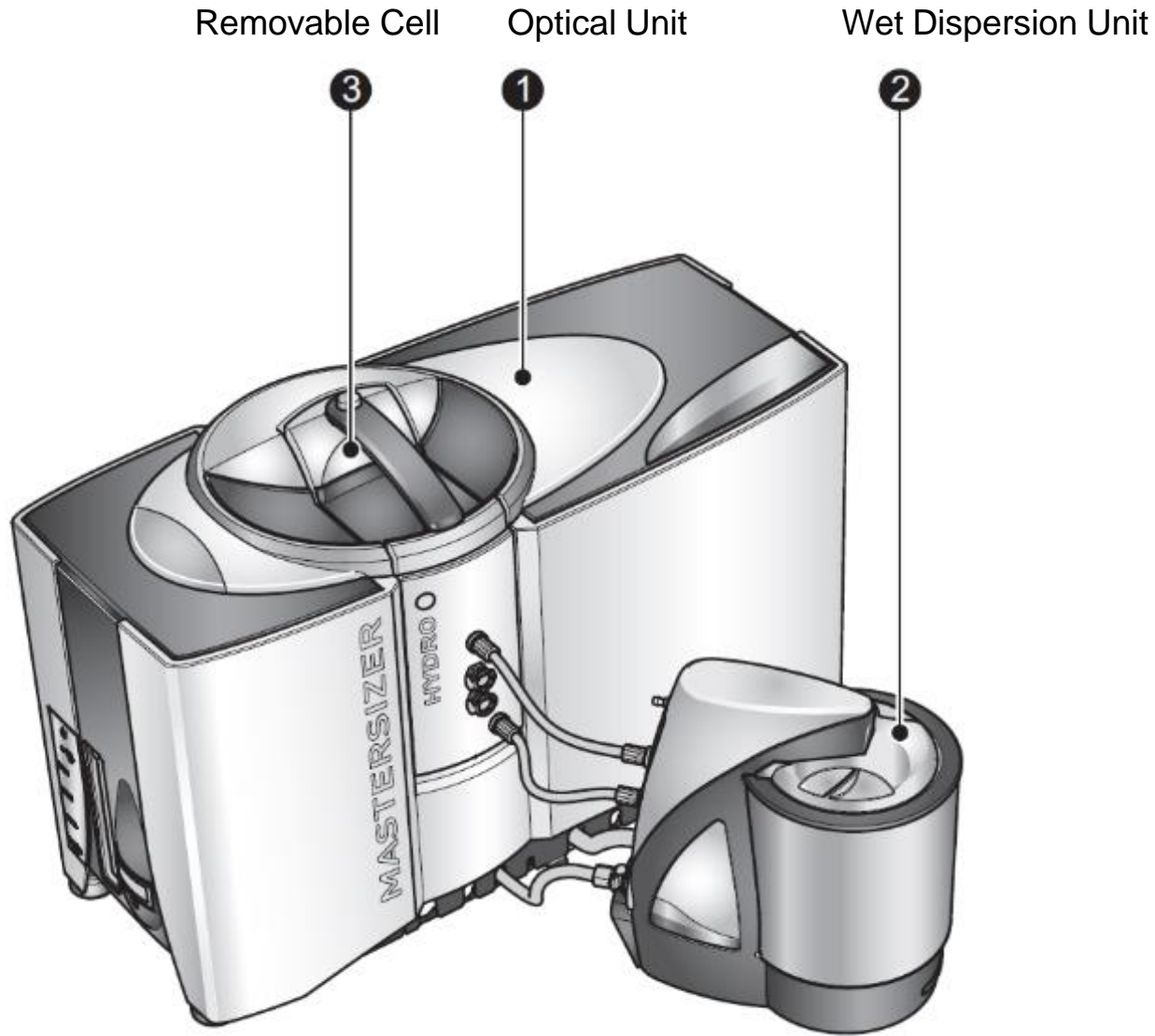


- Polymers
 - Suspending Agents, Sterics, and Electrostatics
- Surfactants
 - Wetting Agents, Hydrophobicity, and Electrostatics
- Electrolytes
 - Valency, Ionic Strength, and Electrostatics

Flocculation: Particle Interactions and DLVO Theory

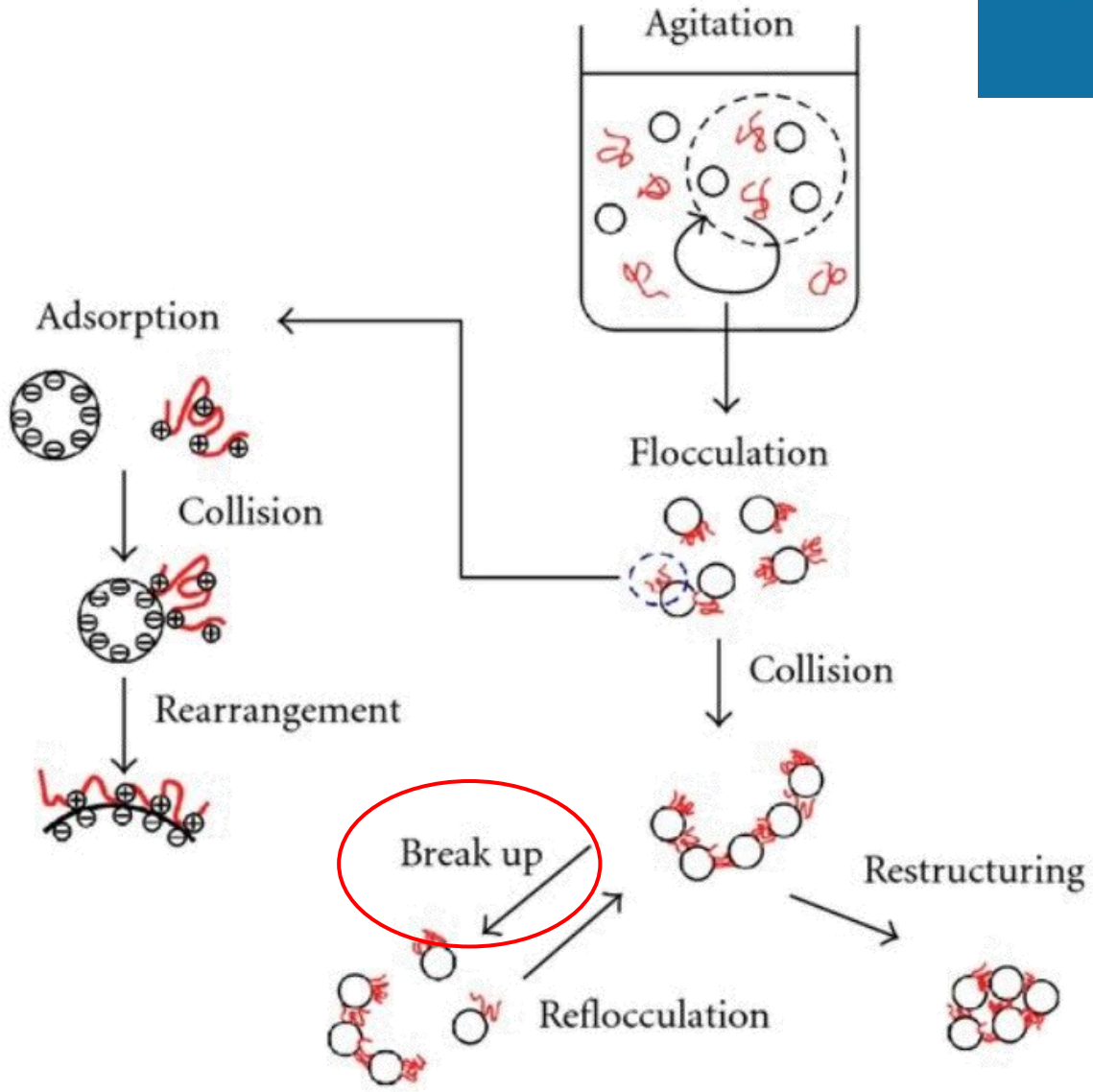
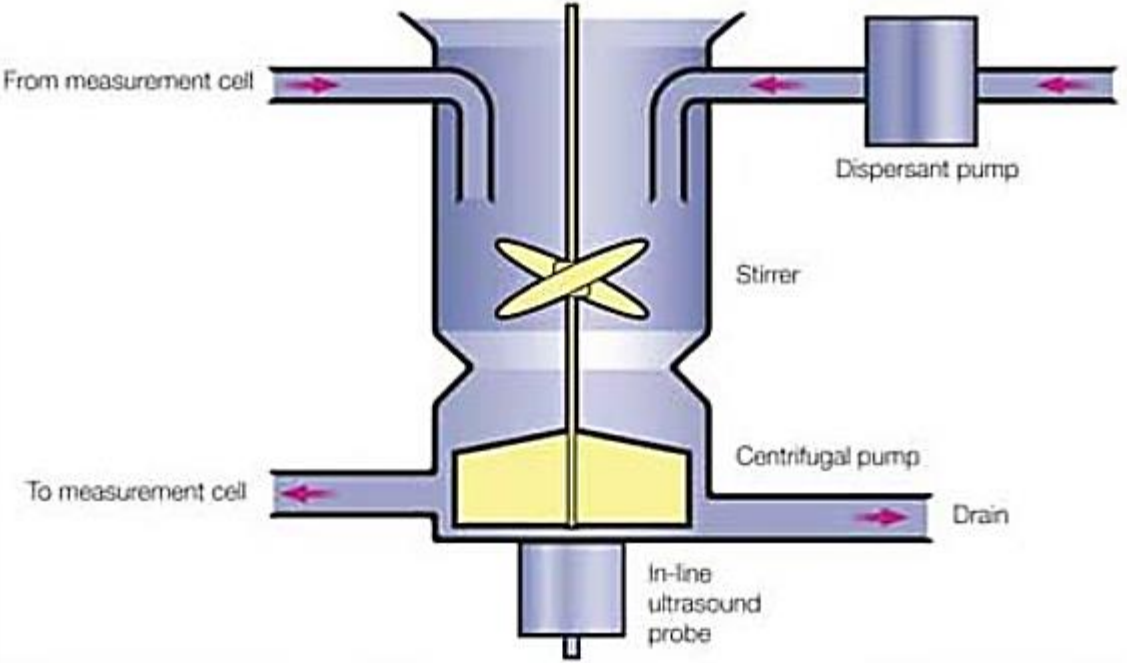


Laser Diffraction: Components and Setup

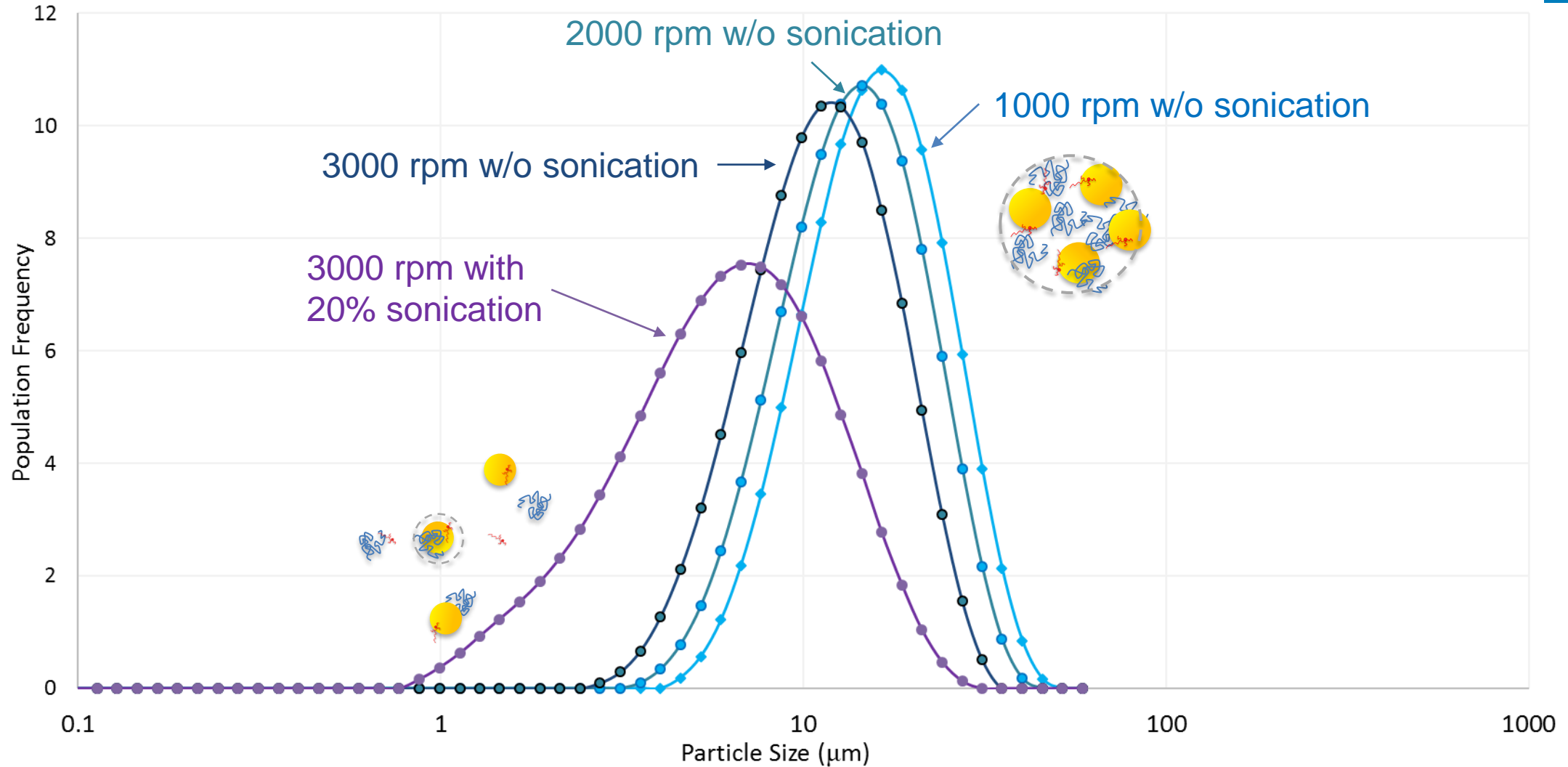


- | | |
|------------------------|------------------------------------|
| ① Cell release button | ④ Temperature regulator throughput |
| ② Cell handle | ⑤ Sample input (yellow) |
| ③ Sample output (blue) | ⑥ Cell windows |

Particle Flocculation State Is Shear Dependent

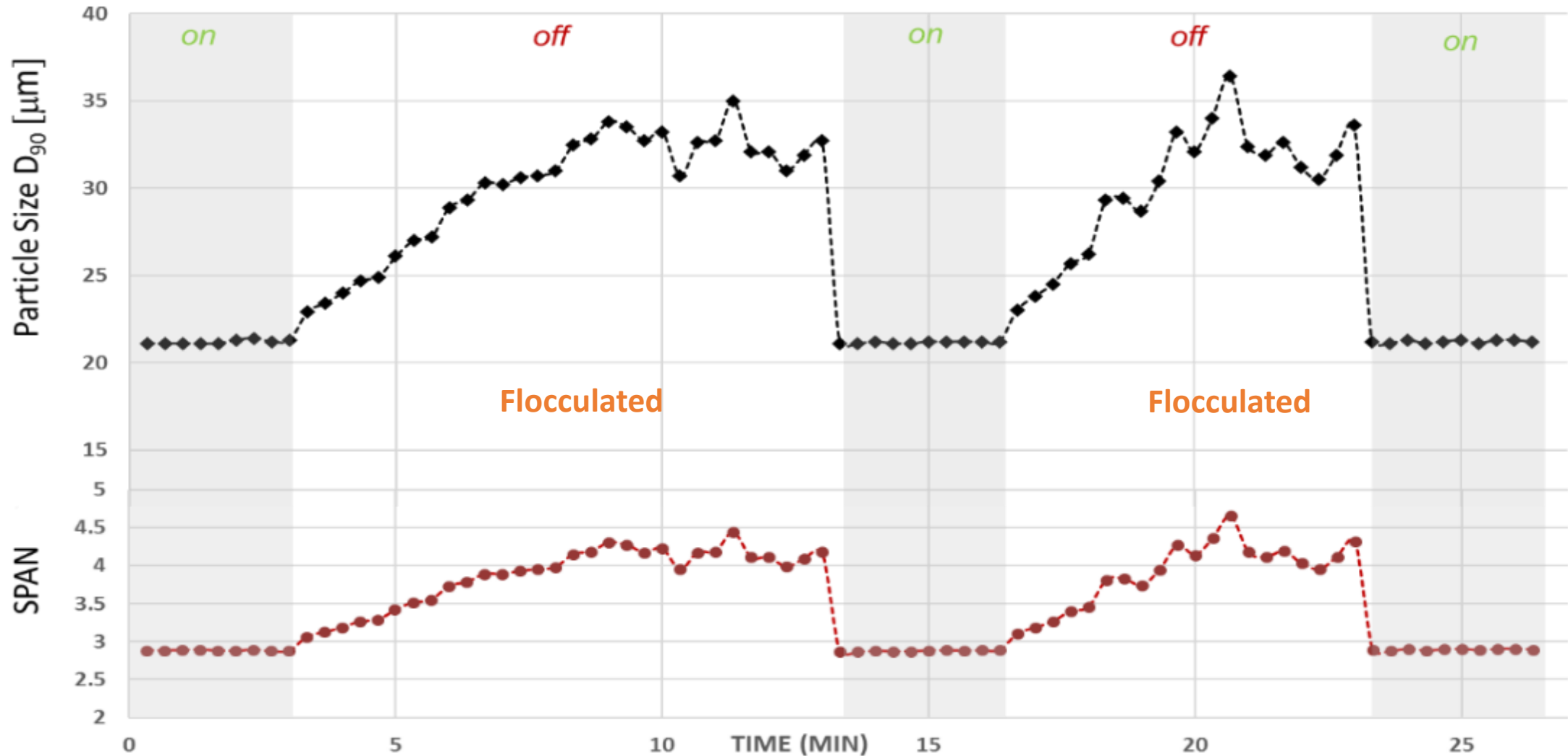


Shear Induced De-flocculation

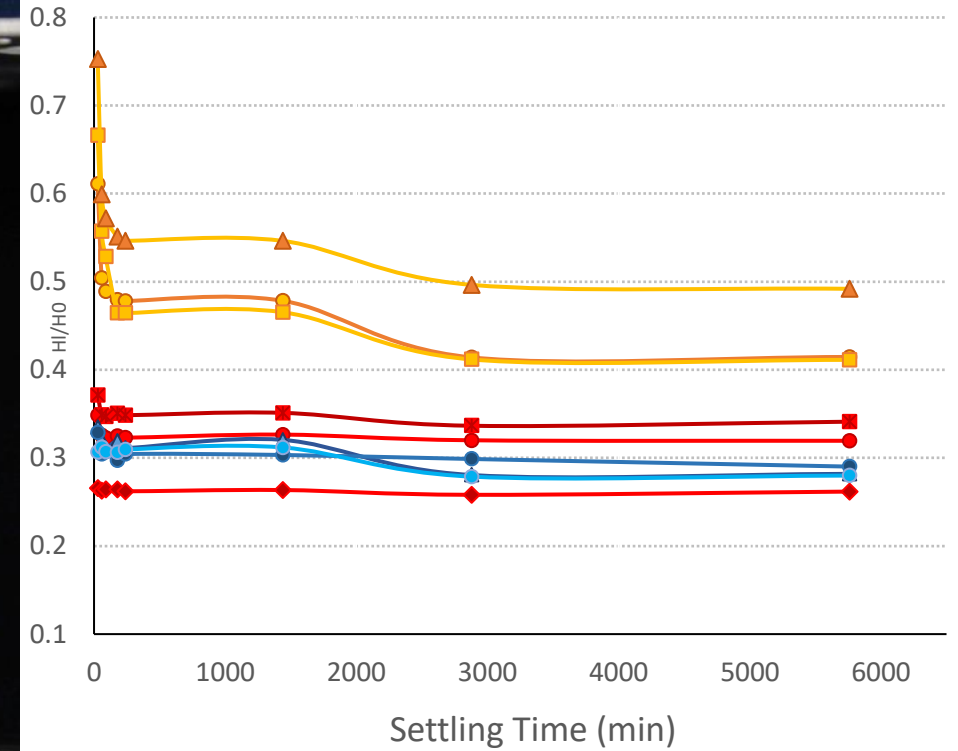


PSD becomes more broad and mean size decreases with increased stir rate and sonication

Flocculation of TA Suspension Is Reversible



Sedimentation as a Surrogate for PSD

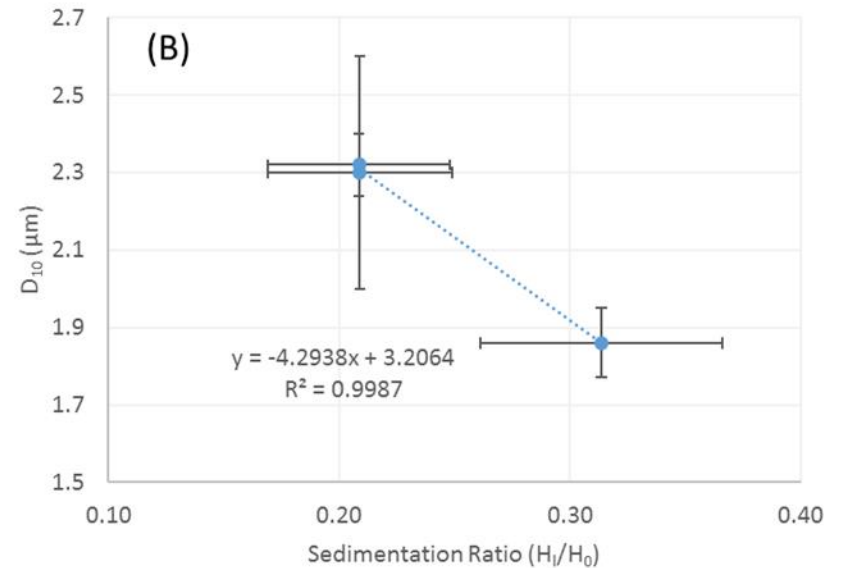
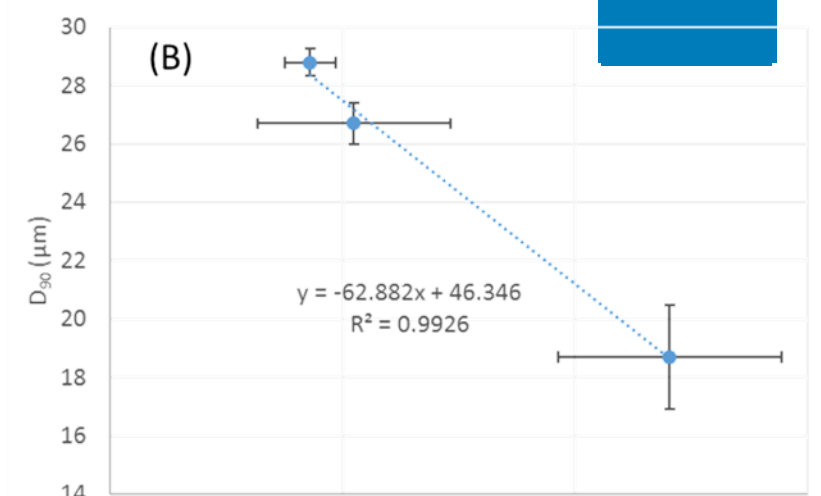
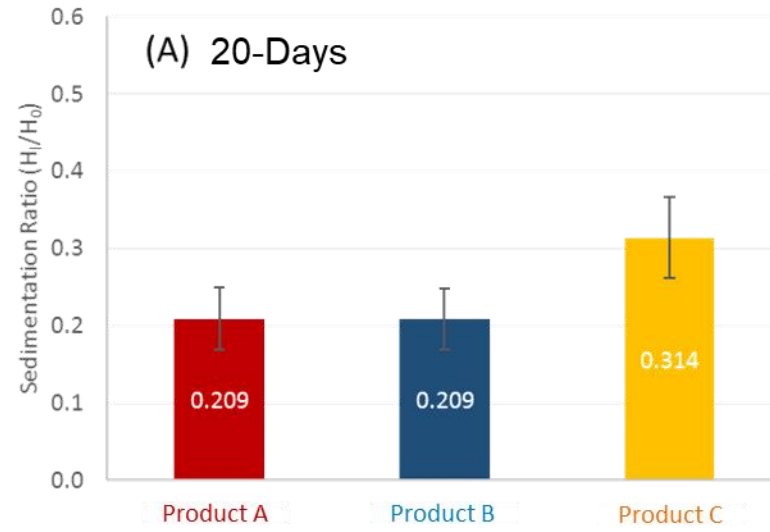
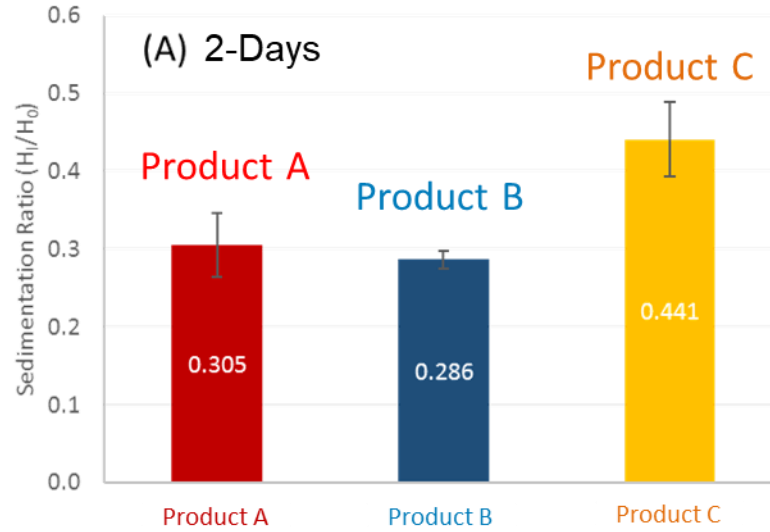
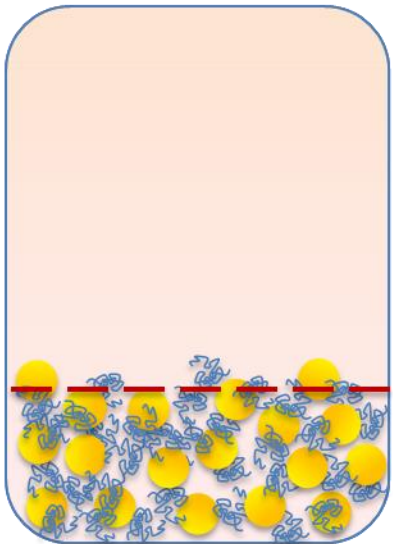
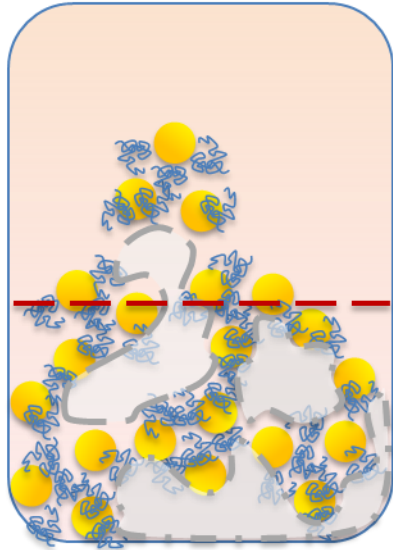


Flocculation → Sedimentation → Improved Long Term Stability

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

PSD and Sedimentation Take-Aways

- ❑ There are two types of particles:
 - ❑ Primary (Deflocculated) particles observable under aggressive dispersion conditions correlate to long term Sed. Ratios
 - ❑ Secondary (Flocculated) particles observable under gentle dispersion (low shear) conditions correlate to short term Sed. Ratios

- ❑ Sedimentation Ratio may be a useful surrogate for PSD

Kenalog-40 Package Insert and Guidelines

Administration

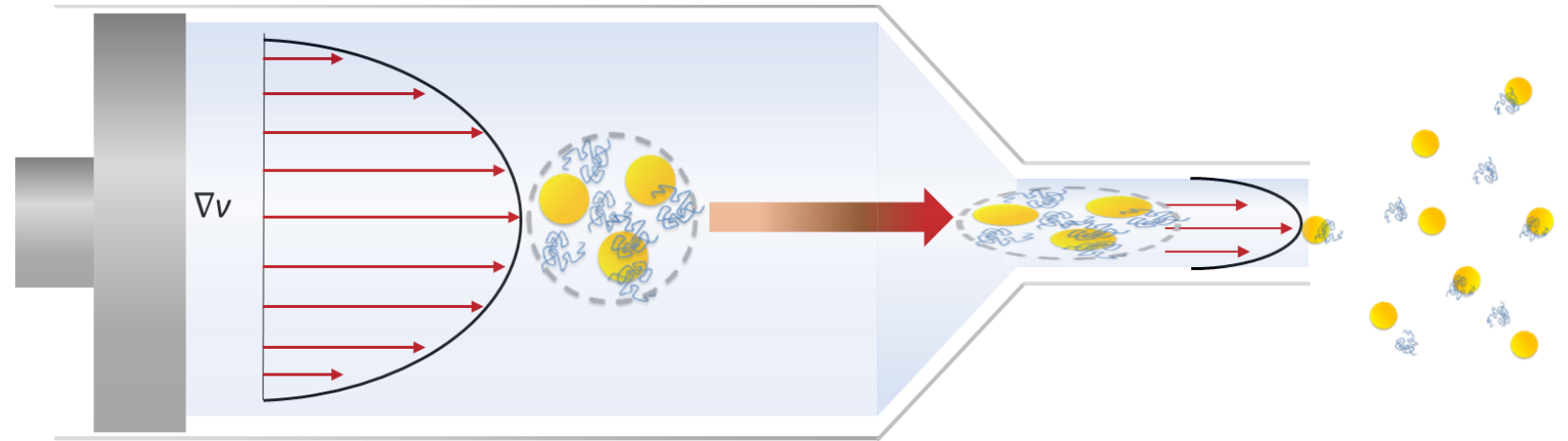
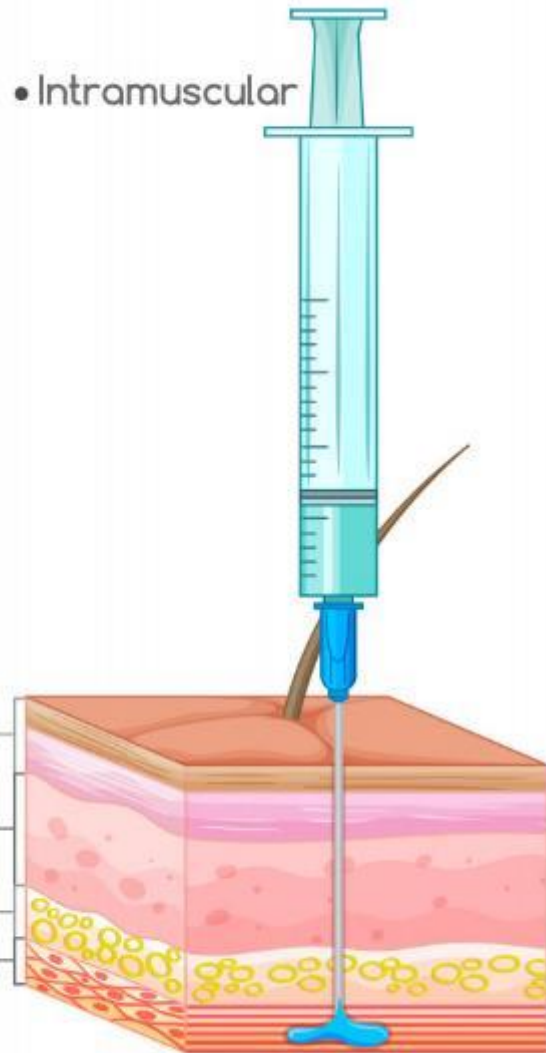
GENERAL

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



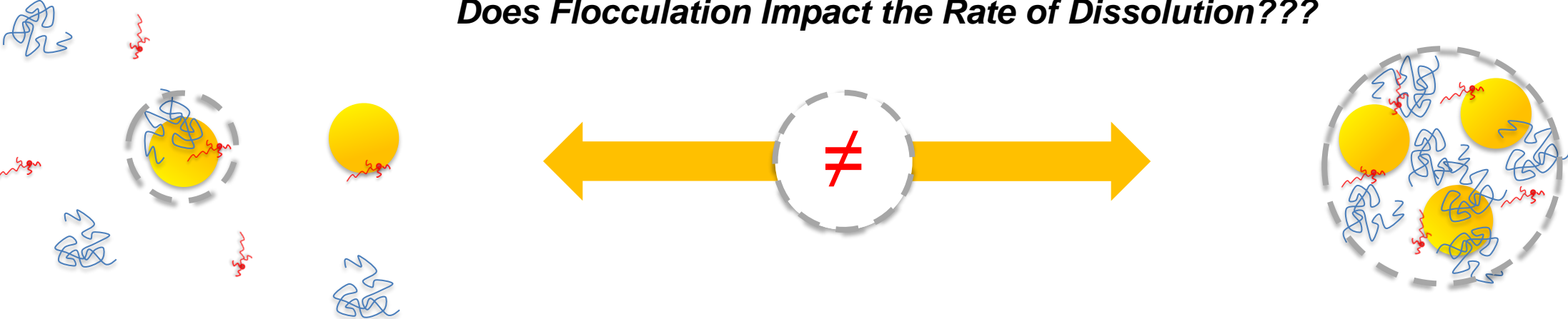
**Particle flocculates undergo shear during IM administration
Infusion Rate?? Syringe Gauge??*

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).*

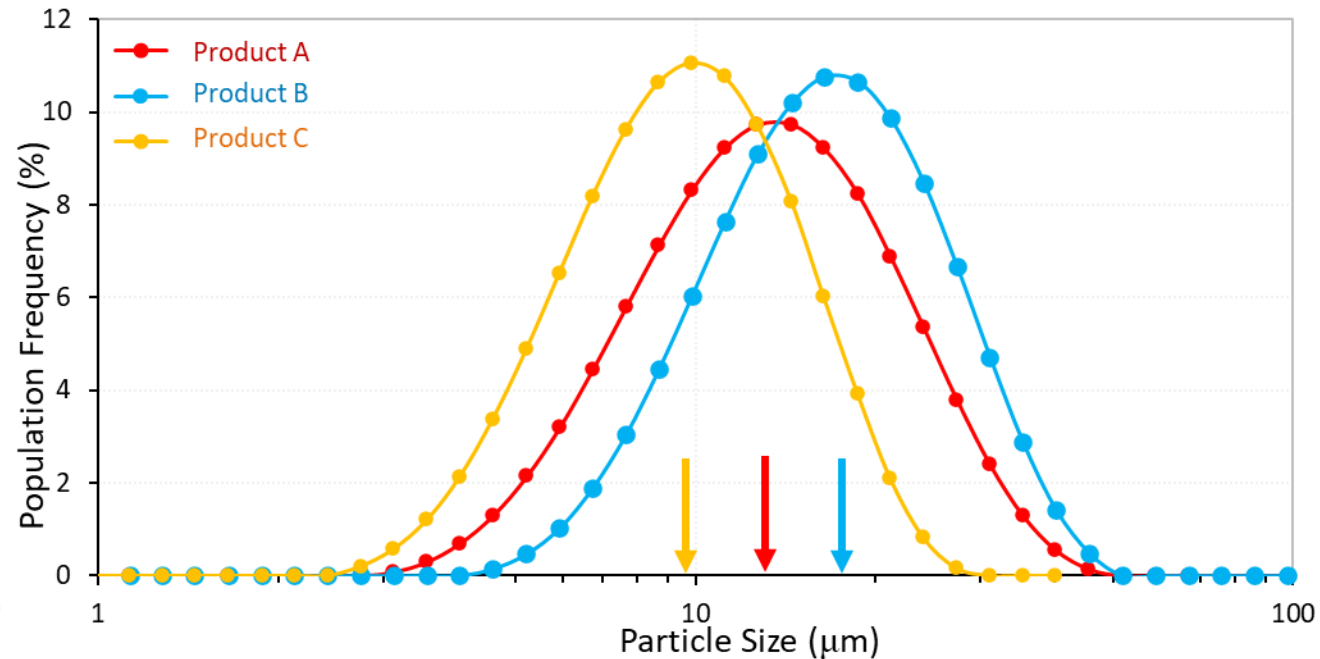
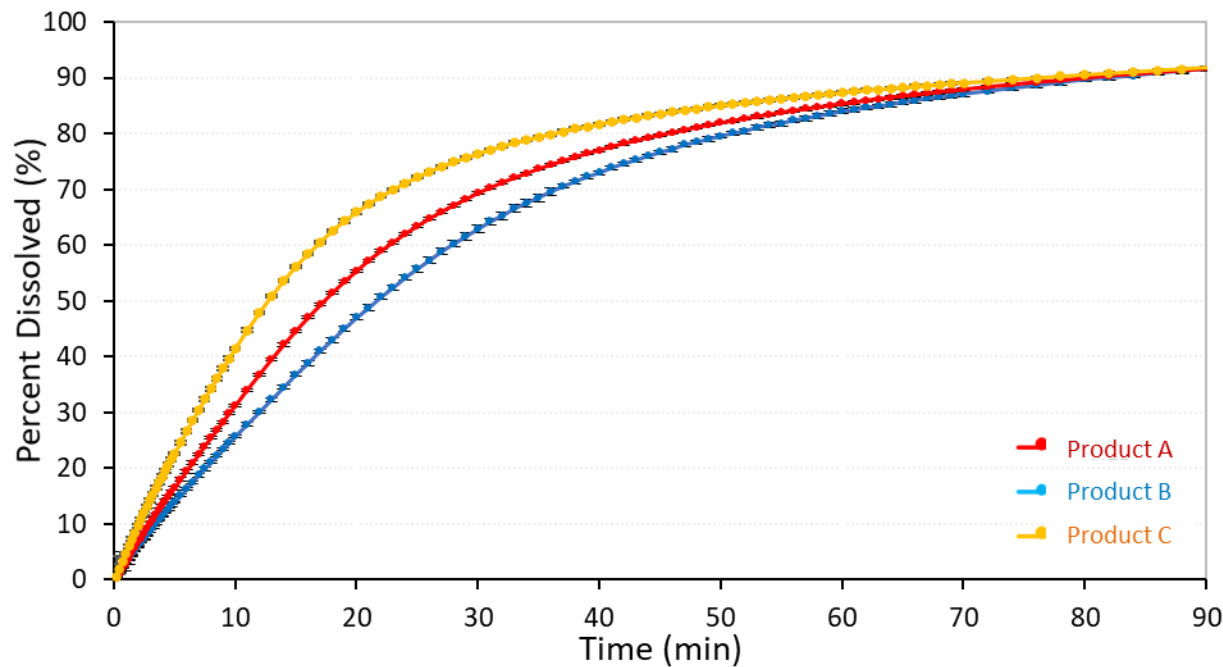
Noyes-Whitney Equation

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

Impact of Suspension PSD on Drug Dissolution



PSD directly impacts dissolution rates: Larger particles dissolve slower

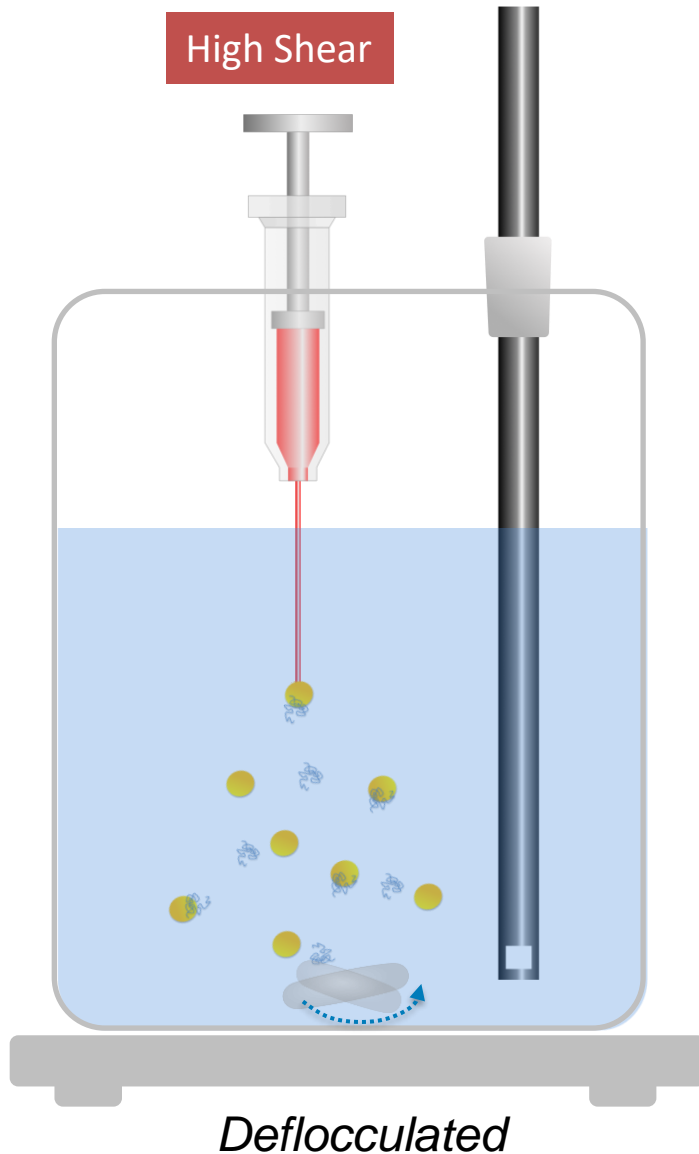


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Noyes-Whitney Equation

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

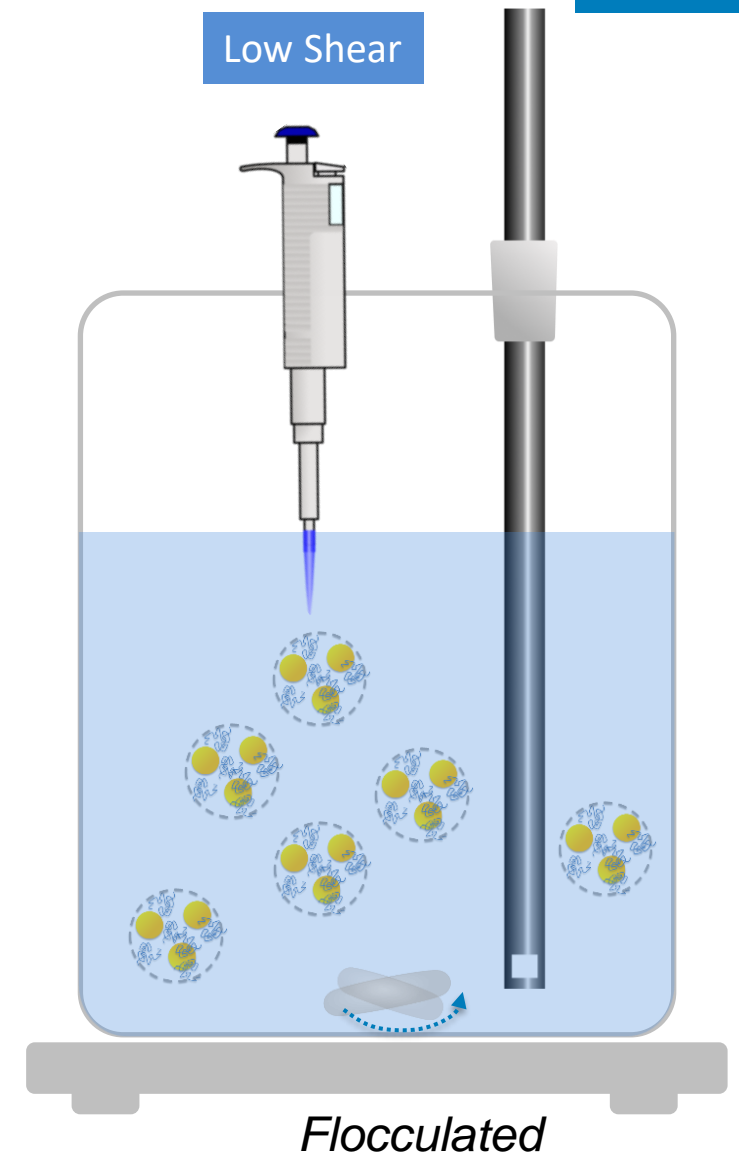
Shear-induced Deflocculation on Dissolution



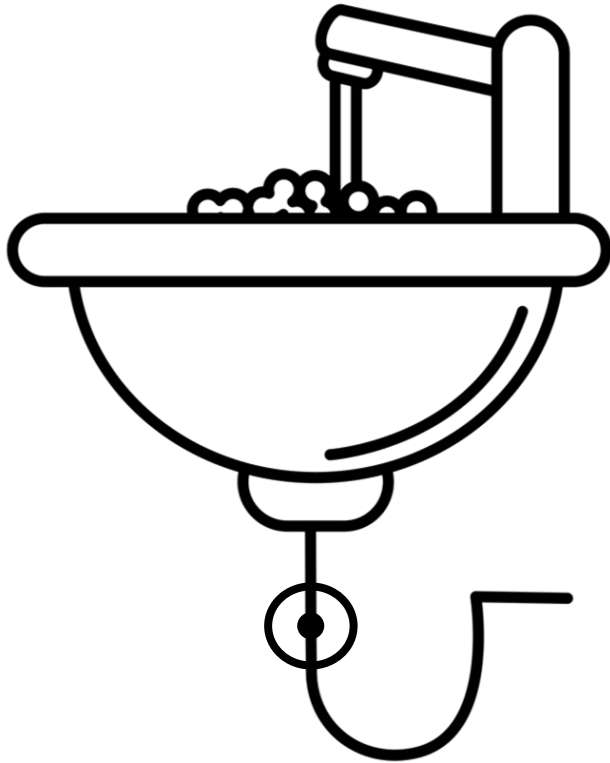
Controlling Shear: High vs. Low Shear

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

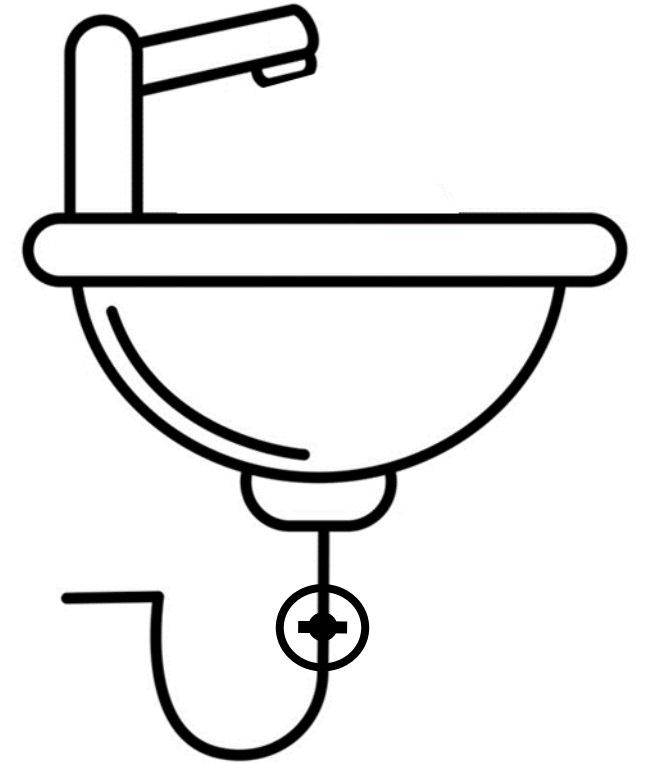
Dissolution Rate?



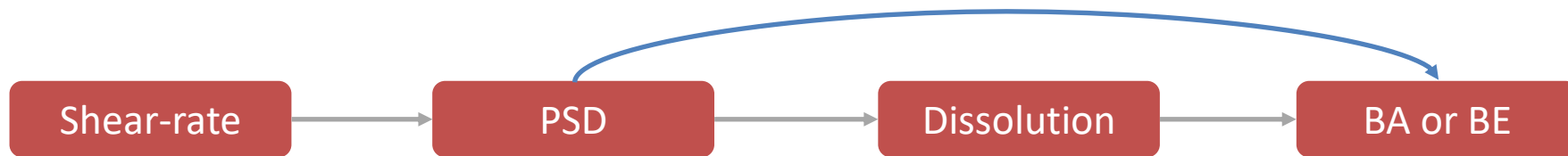
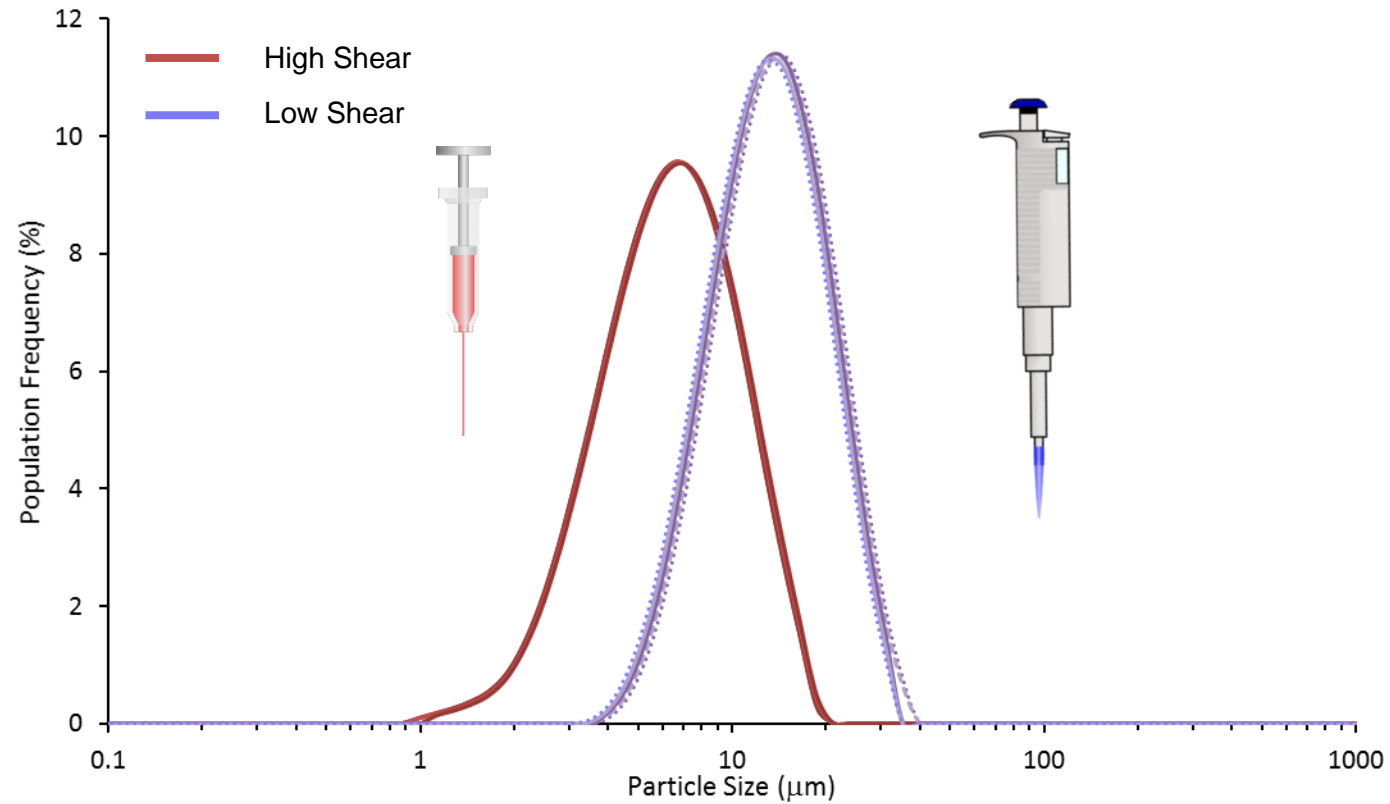
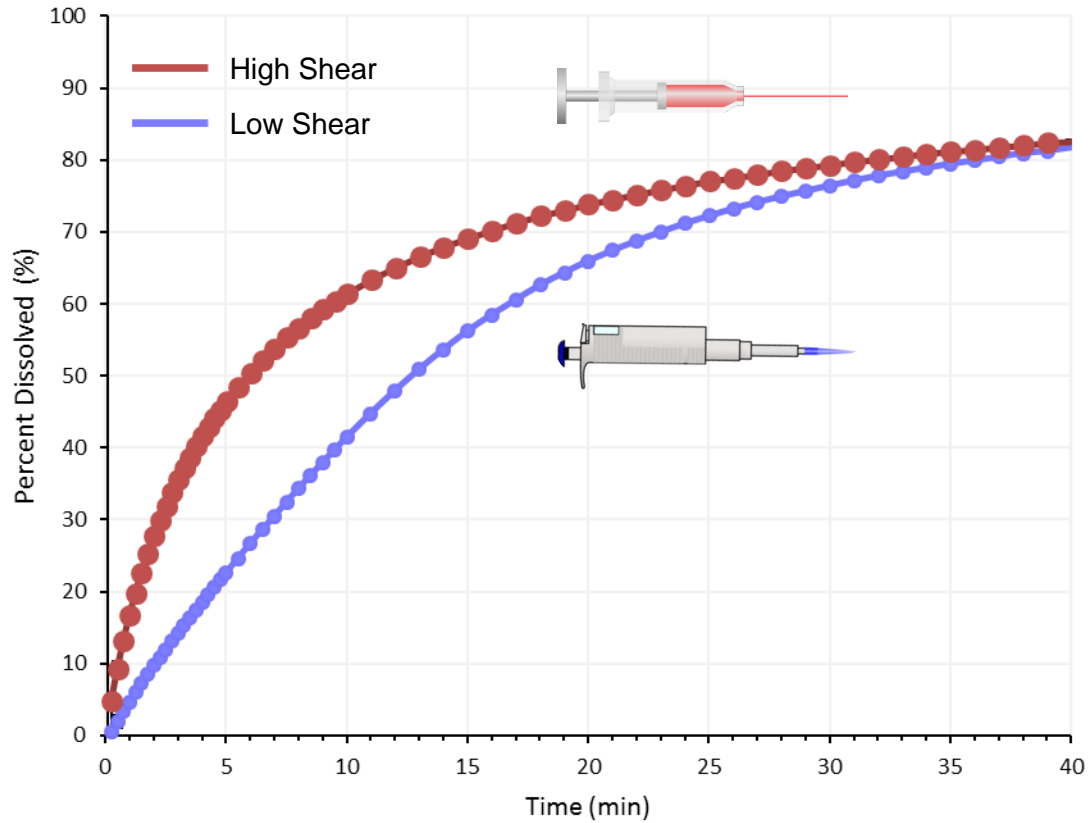
Choosing Sink or Non-Sink Conditions?



- Discrimination
- Relevance to In Vivo
- Release Rates
 - Zero Vs. First Order

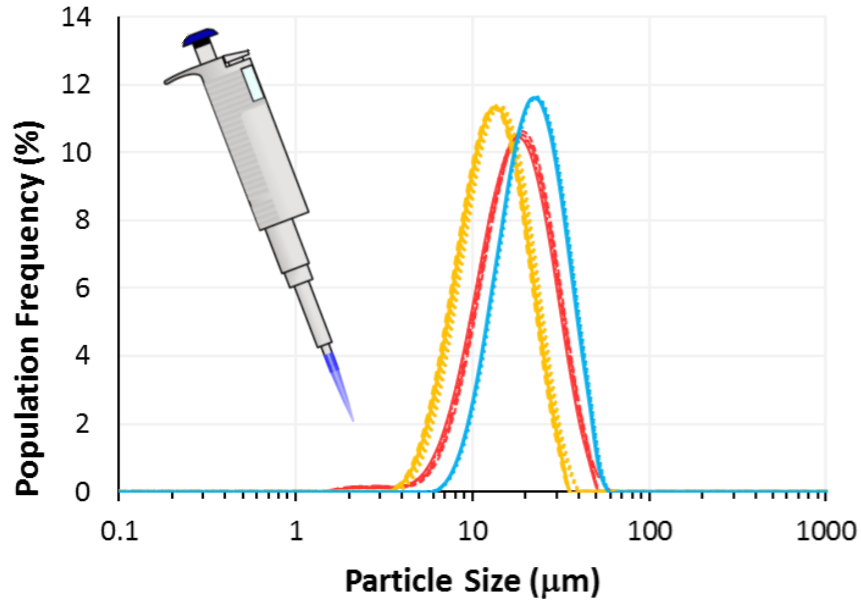


Impact of Suspension PSD on Drug Dissolution

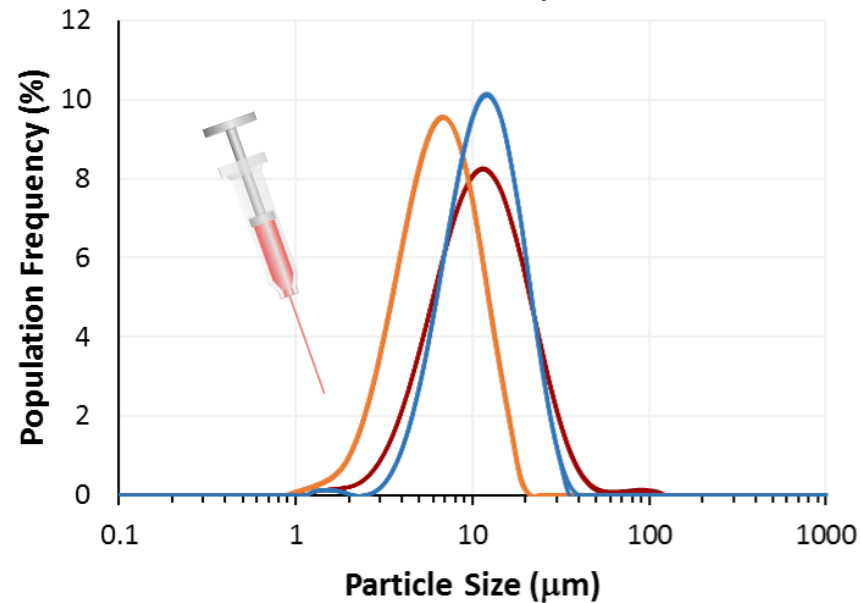
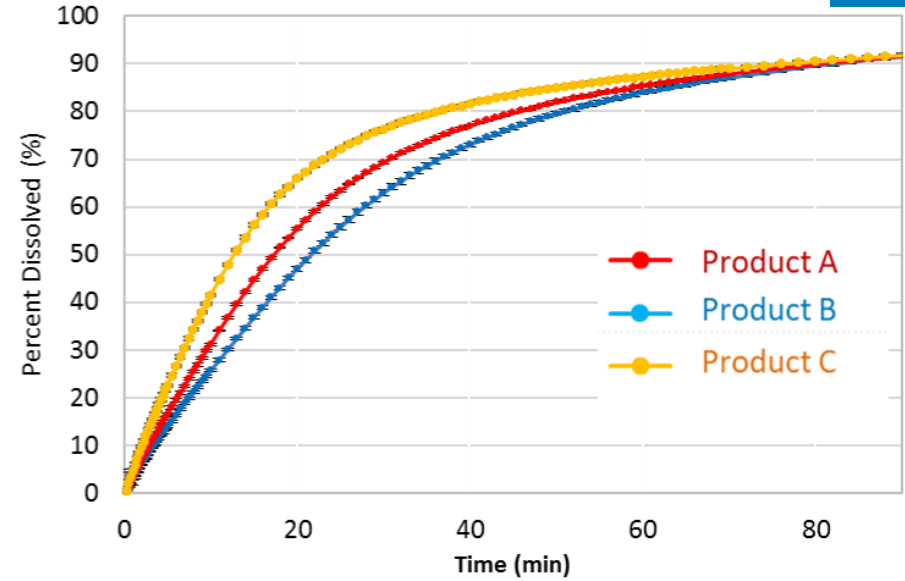
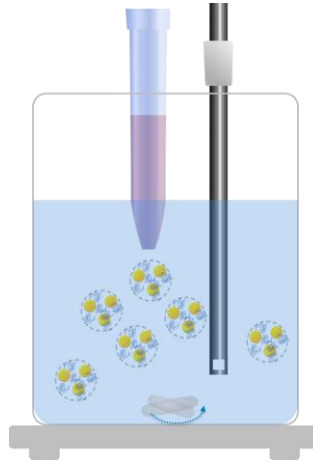


**Deflocculated suspension exhibits >4x higher dissolution rate than flocculated suspension*

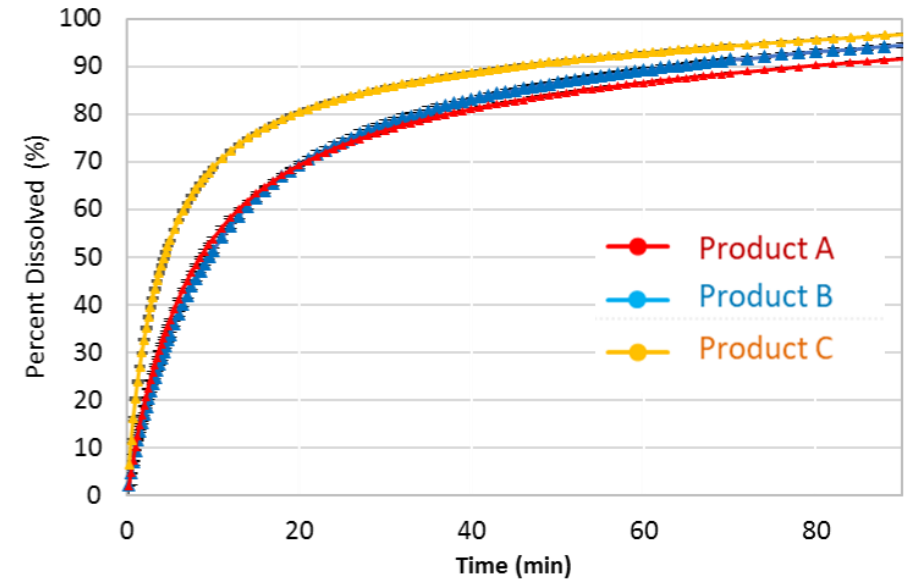
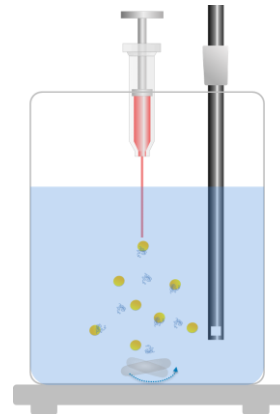
PSD and Dissolution at Shear Extremes



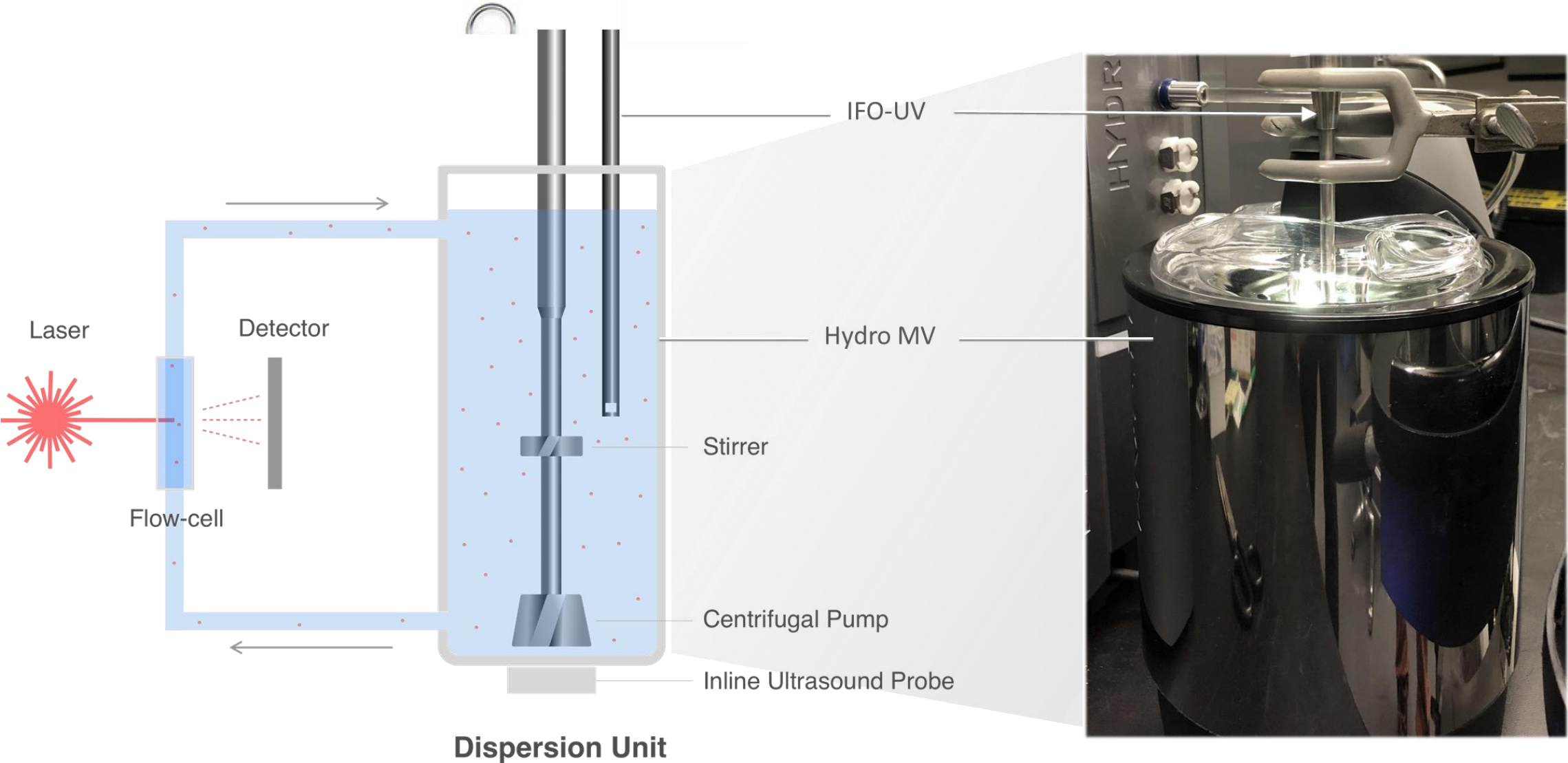
Low Shear



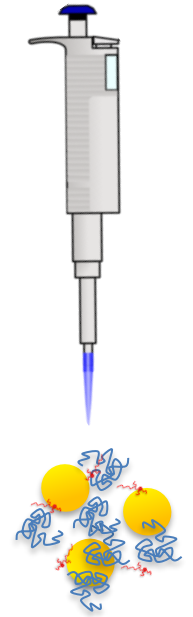
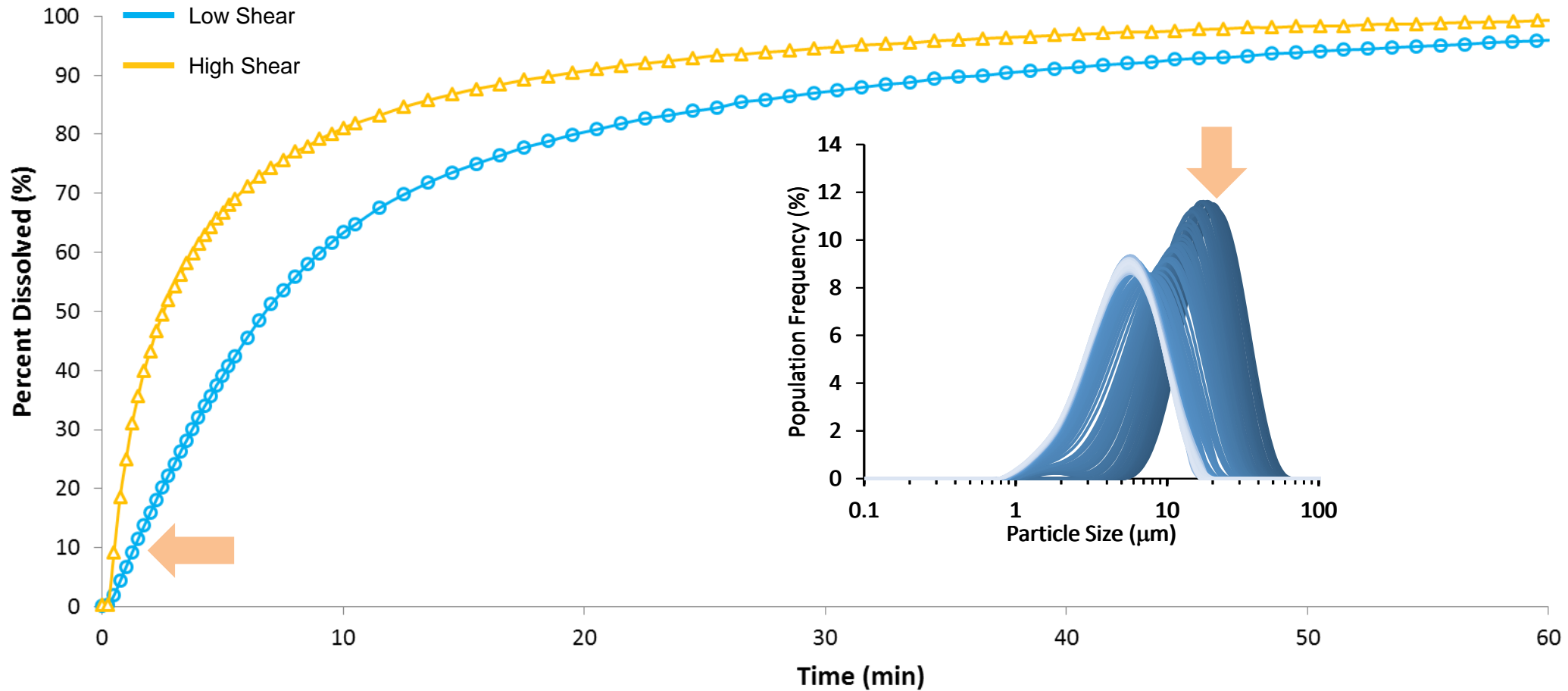
High Shear



Tandem Particle Sizing and Dissolution Setup

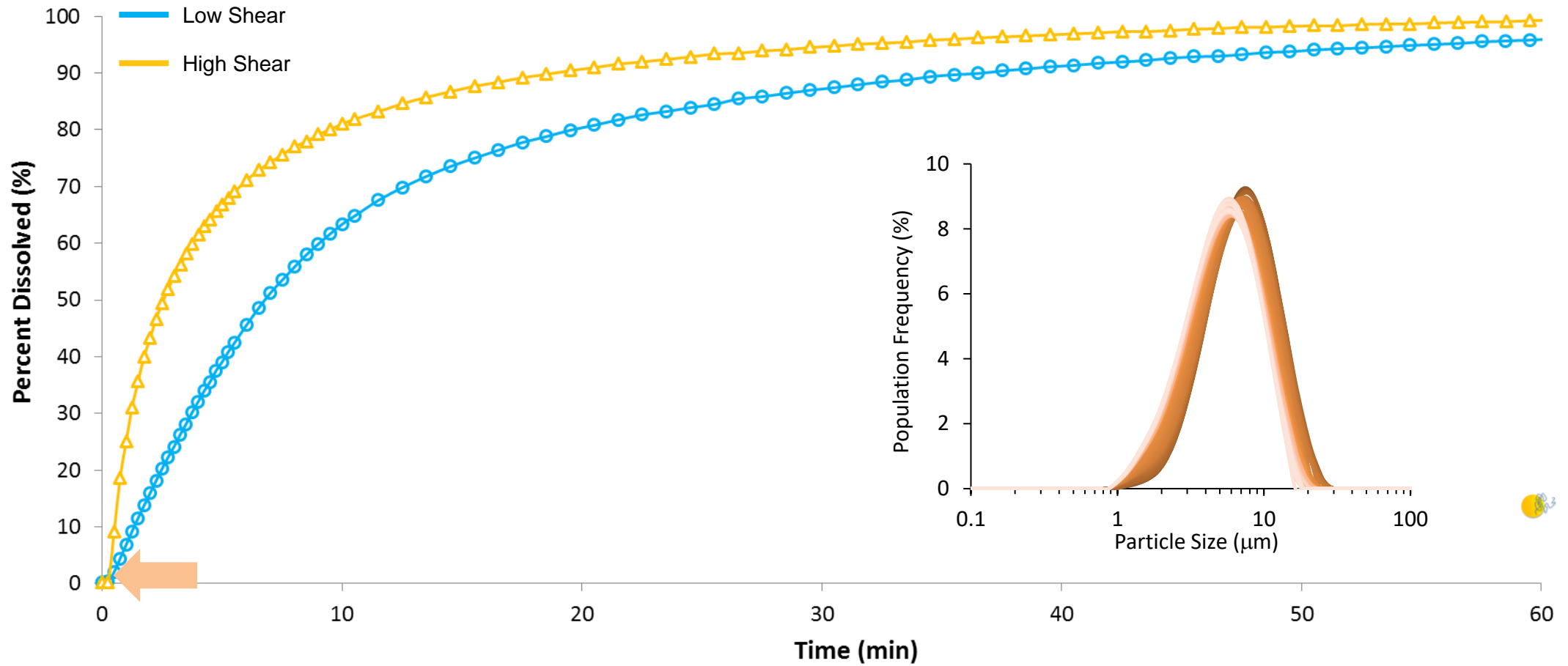


Simultaneous Particle Sizing and Dissolution



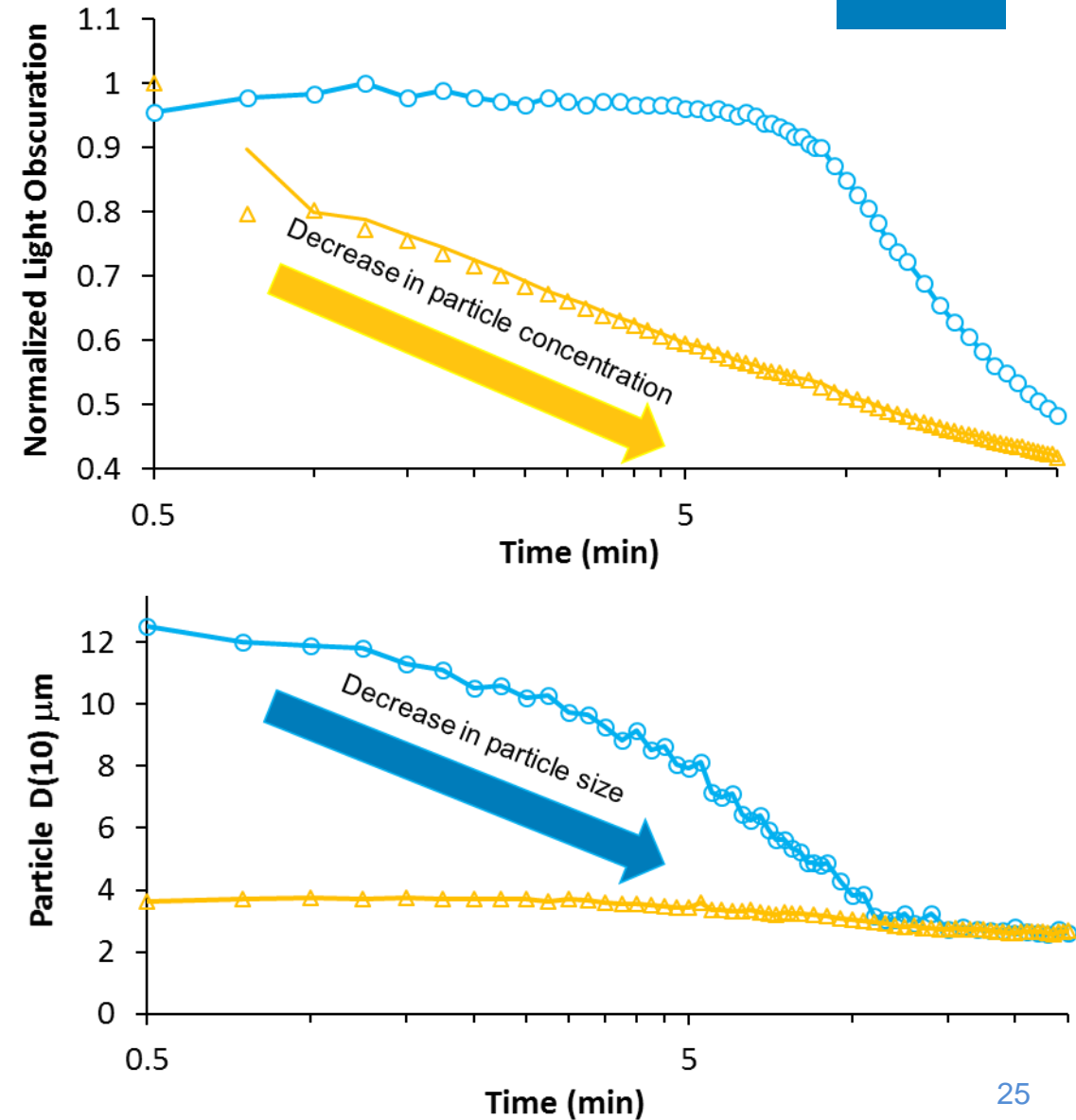
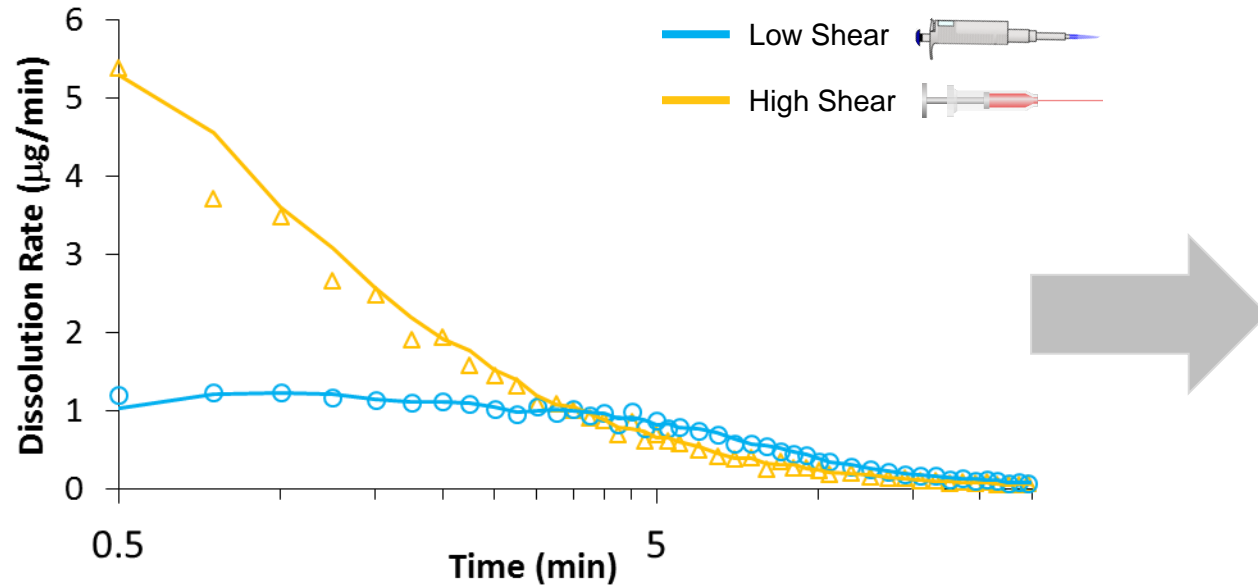
**Flocculated suspension exhibits large shift in Particle Size Distribution during dissolution*

Simultaneous Particle Sizing and Dissolution



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

Two Particles: Two Dissolution Pathways



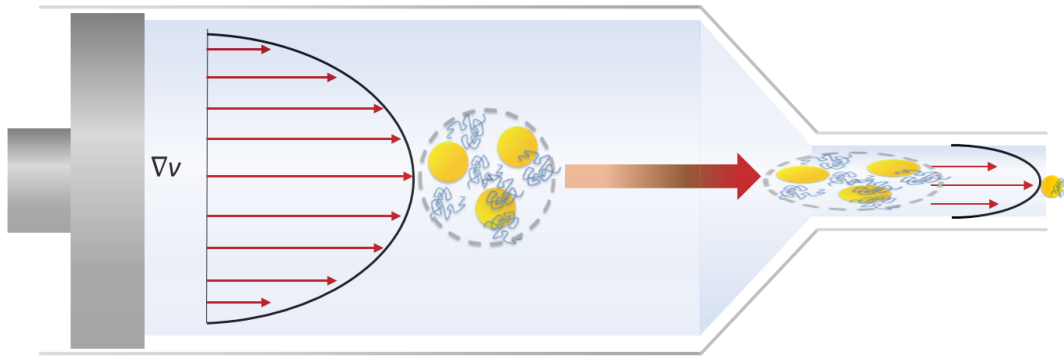
Dissolution follows two different pathways/mechanisms?

**Size Reduction and Particle Loss*

Syringe Induced Deflocculation: PSD and Dissolution

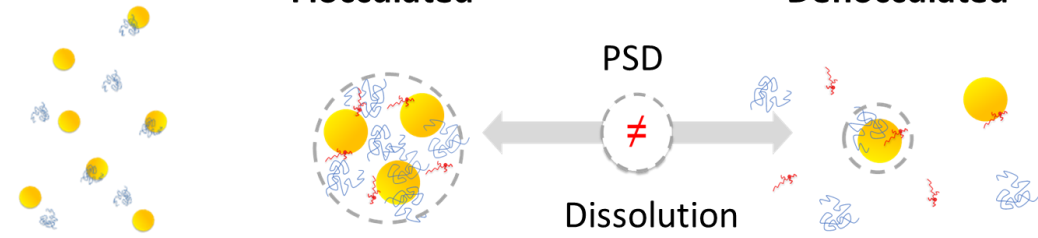


Syringe Induced Shear

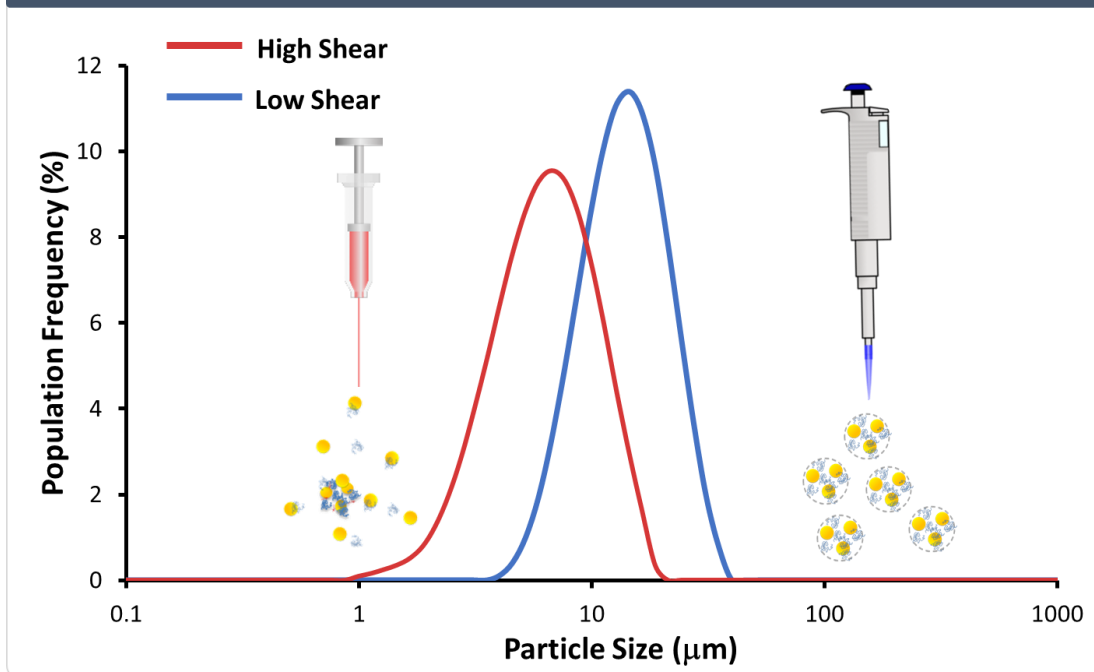


Flocculated

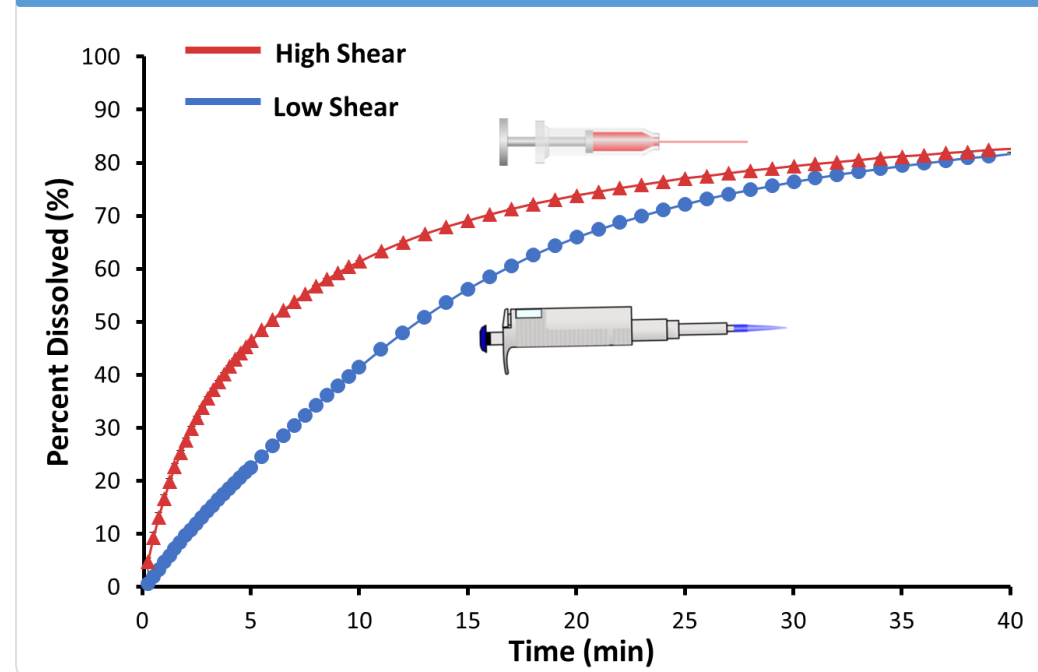
Deflocculated



Particle Size Distribution



Dissolution



**Particle shear via syringe leads to smaller PSD and faster dissolution (2-6x)*

Flocculation and Dissolution Take-Aways

- ❑ The flocculated state of particles is highly dependent on shear
- ❑ Flocculated and de-flocculated particles follow different dissolution pathways
- ❑ Choose dissolution methods that are dosage form appropriate
- ❑ **Bottom line:** *PK variability can be caused by changes in dissolution rate of suspension particles, which may be introduced during I.M. injection. This type of variability could possibly be preventable, if properly controlled.*

Acknowledgements



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