Interplay Between Particle Flocculation and Dissolution Leading to Variation in Bioavailability and Clinical Performance of Injectable Suspensions

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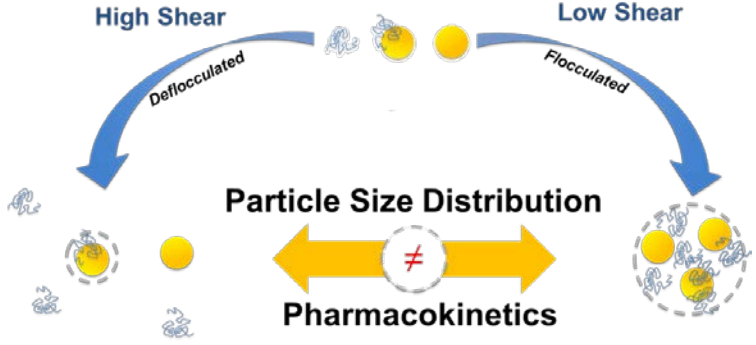
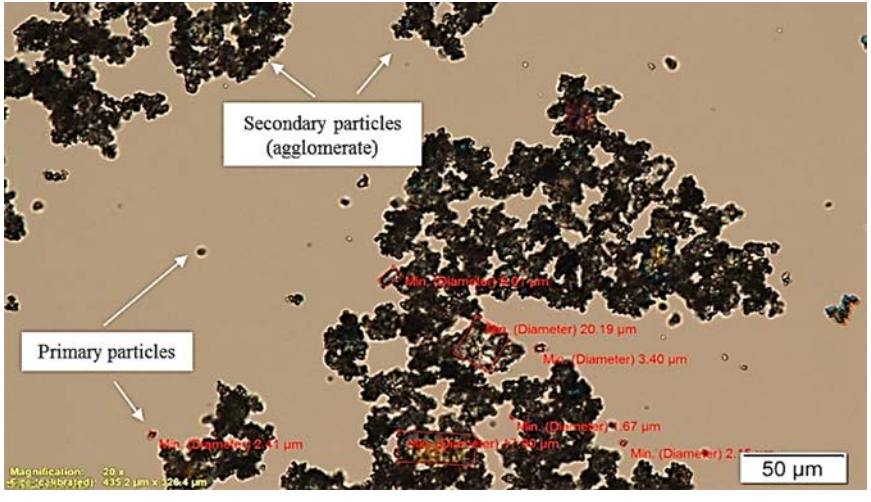
Purpose:

- Crystalline suspensions are often formulated with specific excipients and wetting agents to induce flocculation for increased shelf stability.
- Flocculation inherently impacts particle size distribution (PSD) and conversion between primary and secondary particles is highly dependent on shear.
- Using triamcinolone acetonide (TA) injectable suspensions as a model system, we demonstrate the challenges and solutions to addressing the influences of particle flocculation on PSD measurement and in vitro release test (IVRT).

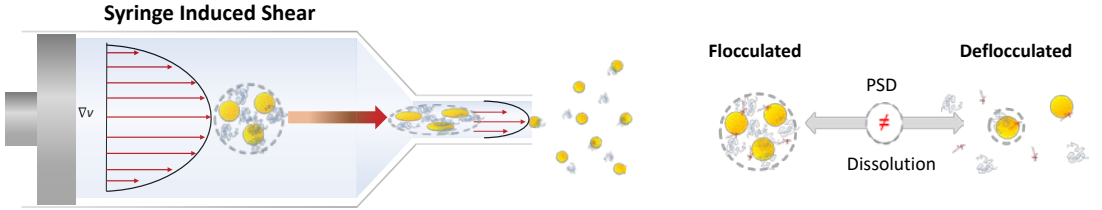


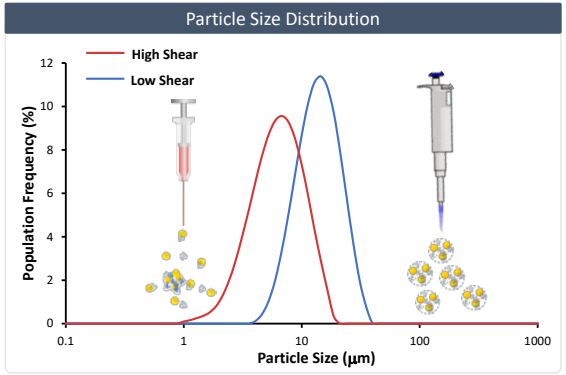
Methods:

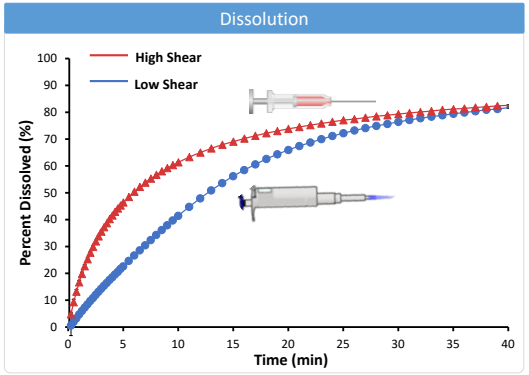
- PSD was determined by Mastersizer 3000 with a Hydro MV dispersion unit (Malvern Panalytical Ltd, Malvern, UK) and examined using polarized light microscopy (Olympus BX51) coupled to ImageJ software.
- Monitoring of the dissolved drug was carried out using an in-situ fiber optic (IFO) UV-Vis system (Pion µDiss Profiler, Billerica, MA) (200–720 nm). Comparing introduction via either micropipette or 1 mL syringe with 25-gauge, 1.5-inch needle.
- Kenalog-40 (triamcinolone acetonide injectable suspension) were procured from DBA-Brookville Pharmacy & Wellness Center (5454 Wisconsin Ave Suite 400, Chevy Chase MD 20815).

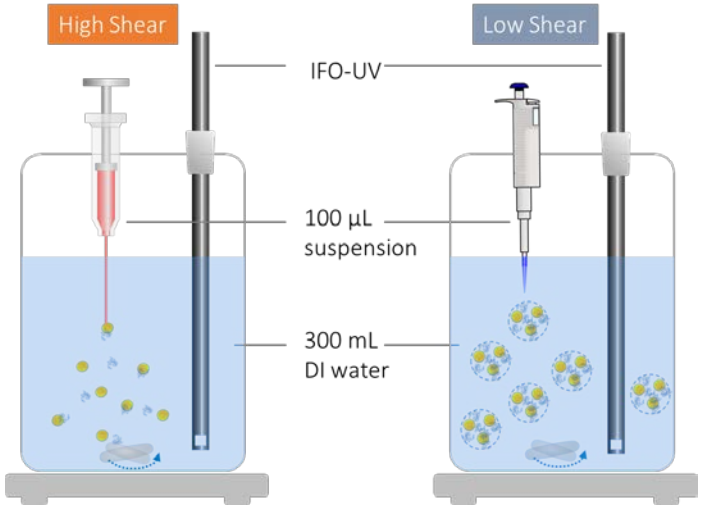


Impact of Flocculation State on Particle Size Distribution and Dissolution





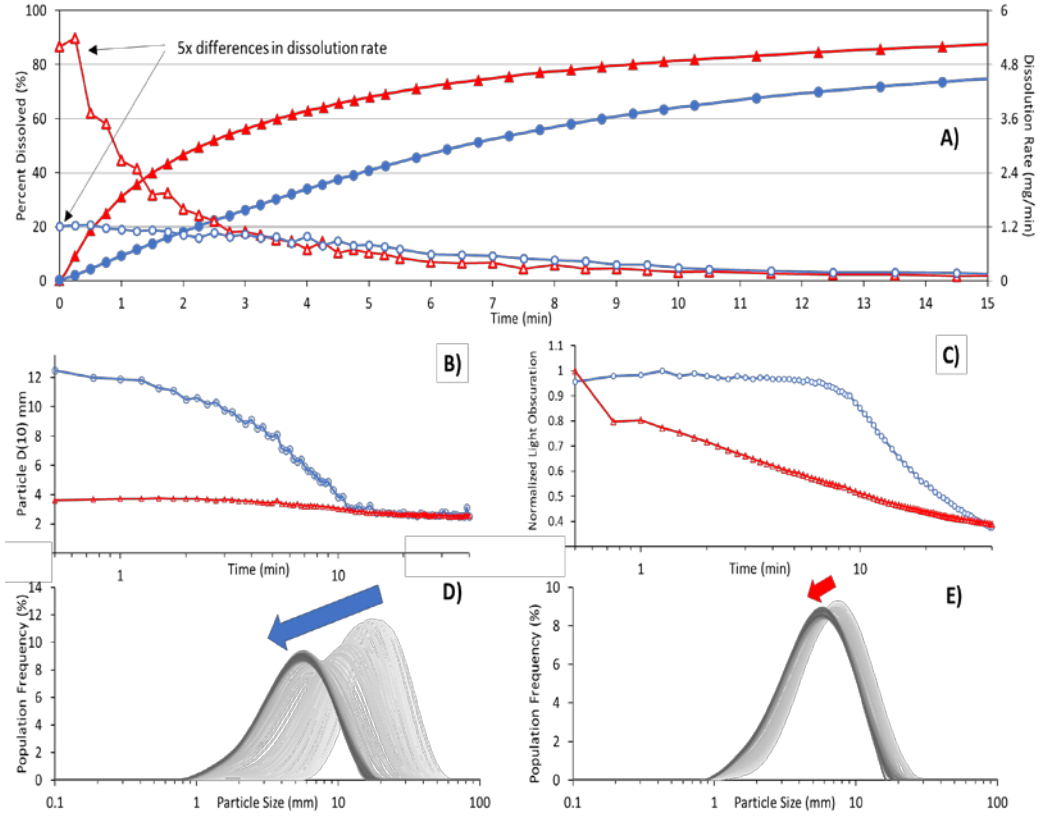




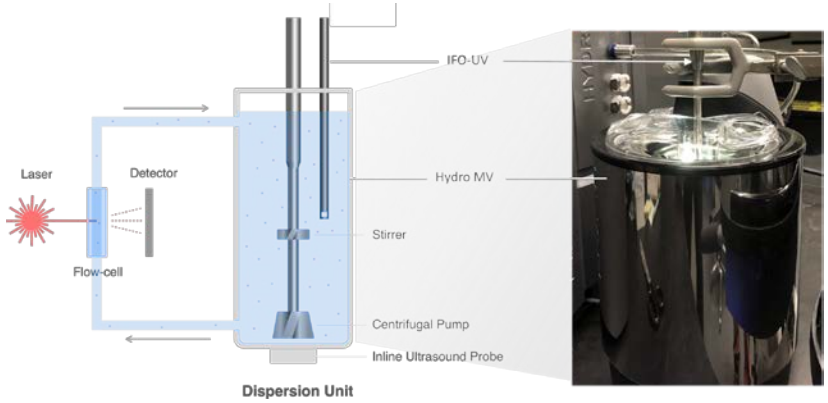
IVRT Setup: *Non-sink dissolution setup with continuous IFO-UV monitoring: effect of shear on suspension dissolution.*

- When expelling suspension through a 25-gauge syringe, the suspension experienced ~100x higher shear than during stirring (1000 s^{-1}).
- Syringe induced stress shifts particle size distribution from large secondary particles (flocculates/agglomerates) to a mixture of primary and secondary particles, with an increase in SPAN approximately 40% and a decrease in mean size D_{50} of approximately 60%.
- Samples introduced via high shear 25-gauge needle method exhibited significantly higher initial dissolution rates (approximately 6x) than the low shear micropipette method.

Probing the Mechanism of Dissolution via Tandem IVRT-PSD Measurements



A) Dissolution profiles under high shear (syringe, solid red triangles) and low shear (micropipette, solid blue circles) at constant stirring rate; overlaid instantaneous dissolution rates (empty triangles and circles); **B)** Particle size D_{10} µm, low shear (blue) and high shear (red); and **C)** percent light obscuration. Overlay of PSD measured simultaneously during dissolution **D)** low shear and **E)** high shear conditions; curves are color coded lightest to darkest from initial to final PSD (indicated by arrows) with one curve for each time point on the dissolution curve.



Tandem IVRT-PSD: *Internal flow path between laser diffraction flow cell and dispersion unit with IFO-UV probe, for simultaneous dissolution and particle size determination.*

Conclusion

The significance of these findings lies in the fact that there is a strong correlation between the (reversible) flocculation behavior of the particles (the cause), particle size distribution and dissolution rate results (the effects), which may impact not only the physical stability of the suspensions but also possible variations in clinical outcomes. Furthermore, measuring both PSD and dissolution behavior under varying shear conditions may be critical to the understanding of in vivo product performance.

Acknowledgements

WCS, JB, and YY acknowledge support of fellowships from the Oak Ridge Institute for Science and Education, administrated through an interagency agreement between the U.S. Department of Energy and U.S. Food and Drug Administration.

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