Impact of Particle Flocculation on Dissolution and Implications on Bioavailability of Injectable Suspensions

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PURPOSE

Particle size distribution (PSD) is a critical quality attribute of suspension-based injectable products, impacting dose uniformity, physical stability, dissolution and bioavailability. During formulation development, polymeric excipients and wetting agents are often included to induce particle flocculation to impart shelf stability, by controlling particle-particle interactions. The process of flocculation inherently changes PSD and may also cause unintended changes in drug release rate leading to variation in clinical performance. Using triamcinolone acetonide (TA) injectable suspensions as a model system, we intend to understand the relationships among particle flocculation, PSD and drug dissolution.

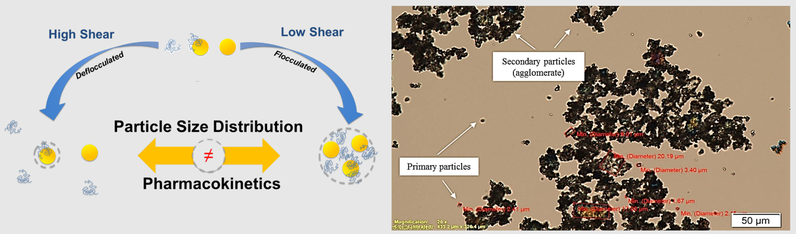

Figure 1. Polarize light micrograph (20x) of a representative TA injectable suspension sample.

METHODS

The PSD of three different commercial TA injectable suspensions were measured by laser diffraction (LD) (Malvern Mastersizer 3000) and compared. Impact of various measurement conditions (e.g., stir rate, sonication power, dispersion media, etc.) on the accuracy and precision of LD measurements were examined. Particle-free water or drug saturated solutions were used as dispersants. A non-sink in vitro drug release test (IVRT) method was developed to investigate the impact of shear on drug dissolution rates, by varying the introduction procedure: via 25-gauge syringe to simulate high shear and a micropipette to simulate low shear. In addition, a novel tandem LD-IVRT system was devised to simultaneously determine PSD and dissolution rate (**Figure 1**). [1]

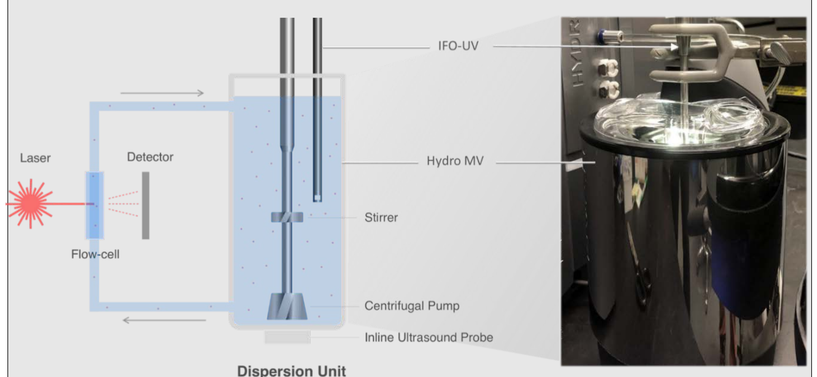

Figure 2. View of internal flow path between laser diffraction flow cell and dispersion unit with an in situ fiber optic UV (IFO-UV) probe, for simultaneous dissolution and particle size determination**.**

RESULTS

- *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 D50 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.*

Impact of Flocculation State on Particle Size Distribution and Dissolution

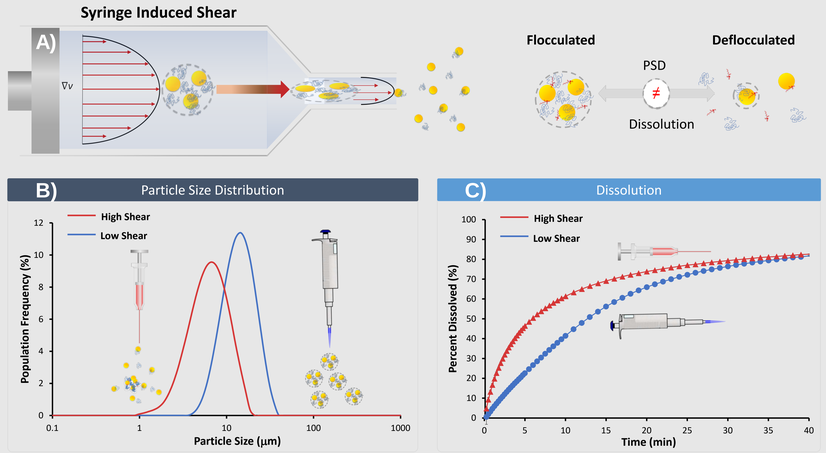

Figure 3.
A) Schematic of particle flocculates undergoing shear induced dissociation during injection.

B) Difference in particle size distribution caused by shear from differing introduction method (syringe vs. micropipette)

C) Difference in dissolution rate based on shear induced change in PSD**.**

Probing the Mechanism of Dissolution via Tandem IVRT-PSD Measurements

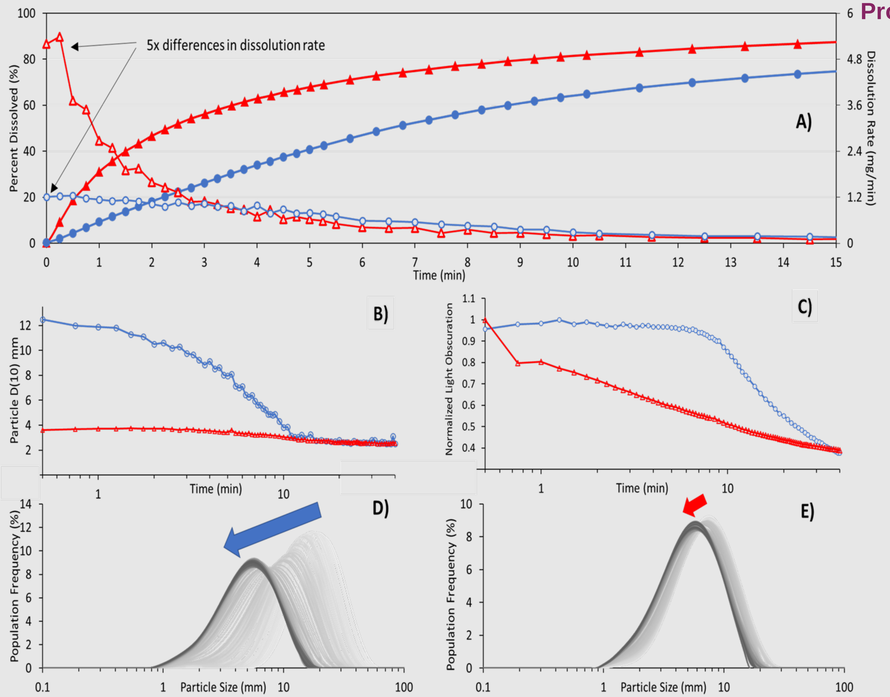

Figure 4. A) Dissolution profiles under high shear (syringe, solid red triangles) and low shear (micropipette, solid blue circles) at constant stirring rate; overlaid instantaneous dissolution rates (empty triangles and circles); **B)** Particle size D10 µm, low shear (blue) and high shear (red); and **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**.**

CONCLUSIONS

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

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REFERENCES [1] Smith, W.C., *et al.* Int. J. Pharm. 604 (2021), DOI:10.1016/j.ijpharm.2021.120767