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Virtual via Adobe

Impact of Particle Flocculation on Determination of Bioequivalence and Clinical Performance of Injectable Suspensions

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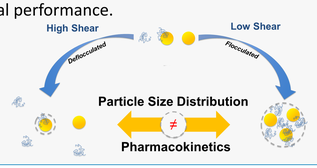
PURPOSE

Laser diffraction (LD) is the most commonly used particle sizing technique for commercial suspension-based products, which exhibit sizes ranging from a few hundred nanometers to tens of microns. The measured particle size distribution (PSD) is a critical quality attribute of suspension-based products. PSD affects not only the dose uniformity, physical stability, and dissolution properties of the product, but also its bioavailability. During formulation polymeric excipients and wetting agents can be chosen to induce particle flocculation through affecting particle-particle interactions which in turn imparts shelf stability. The process of flocculation inherently impacts measured PSD, causing possible unintended consequences in clinical performance. Using triamcinolone acetonide (TA) injectable suspensions as a model system, we intend to demonstrate the challenges and solutions to addressing the influences of particle flocculation on PSD measurement and in vitro release test (IVRT).

OBJECTIVE

Evaluate the role of particle flocculation on changing particle size and impacting clinical performance.



METHODS

PSD was determined by LD technique using Mastersizer 3000 equipped with a Hydro MV dispersion unit (Malvern Panalytical Ltd, Malvern, UK). A stepwise experimental design was used to determine the effect of various measurement conditions (e.g., stir rate, sonication power, dispersion media, etc.) on the accuracy and precision of LD measurements. Three commercial TA injectable suspension products were compared (color coded as shown in Figure 2). Particle-free water or drug saturated solutions were used as dispersants. Polarized light microscopy was used as an orthogonal technique to evaluate particle size.

A novel non-sink condition IVRT method was developed to investigate the impact of shear on the drug dissolution rate. IVRT was carried out using a PION Rainbow in situ fiber optic UV-vis spectrophotometer. Analysis was done in AuPro Advanced using a four component regression model. Samples were introduced to either LD unit or dissolution vessel via either high or low shear delivery method, 25 gauge, 1″ needle attached to 1 mL syringe or micropipette, respectively. Low and high shear conditions were also controlled by stir/pump rate during LD (500 or 1000 rpm) and stir rate during IVRT measurements (300 or 800 rpm).

RESULTS

Pharmacokinetic (PK) Variability of Triamcinolone Injectable

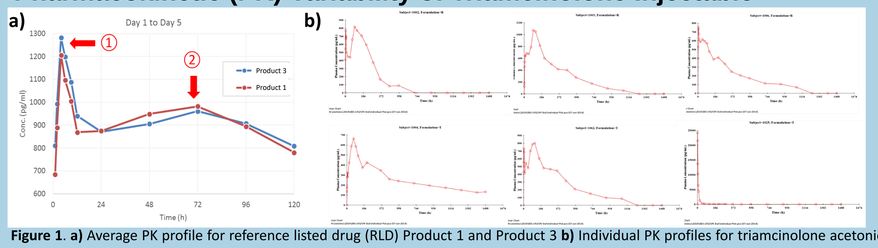


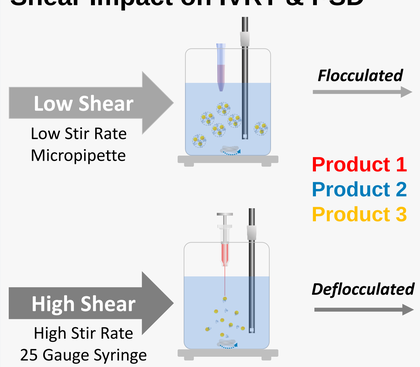
Figure 1. **a)** Average PK profile for reference listed drug (RLD) Product 1 and Product 3 **b)** Individual PK profiles for triamcinolone acetonide intramuscular depots.

Parameters (Units)	Mean ± SD (Un-transformed data)	
	Test Product-T (N = 157)	Reference Product-R (N = 158)
T_{max} (h)[#]	6.000 (1.000 - 552.050)	9.000 (1.000 - 216.000)
C_{max} (pg /mL)	1561.497 ± 3024.5646	1417.909 ± 2010.8860
AUC_{Inf} (pg.h /mL)	336083.023 ± 97146.0732	324108.348 ± 78850.7628

[#] T_{max} is represented as median (min-max) value. [^]N = 140 and [^]N = 141.

Table 1. Descriptive Statistics of Formulation Means for Triamcinolone Acetonide (N=315) demonstrating high variability in patient outcome. Excerpt from ANDA-207550

Shear Impact on IVRT & PSD



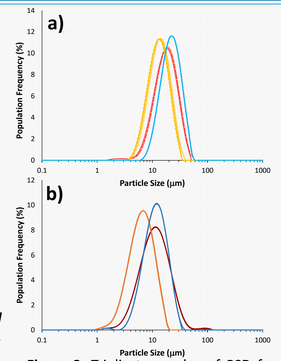


Figure 2. Triplicate overlay of PSD for products in **a)** lowest and **b)** highest shear conditions.

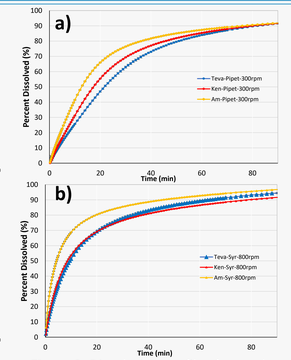


Figure 3. Dissolution profiles for products **a**) flocculated and **b)** deflocculated (n=3).

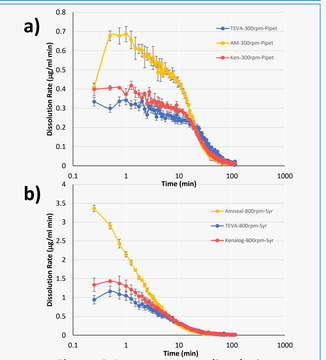


Figure 4. Instantaneous dissolution rate for **a)** flocculated and **b)** deflocculated (n=3).

In Situ IVRT in tandem with Laser Diffraction

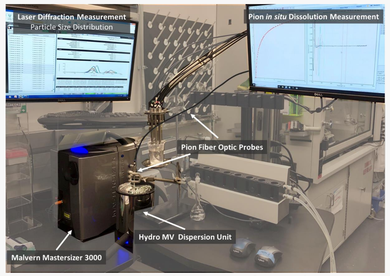


Figure 5. In situ LD dissolution setup for simultaneous measurement of particle size during drug dissolution.

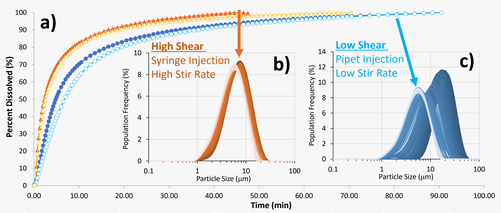


Figure 6. **a)** Dissolution profiles for high and low shear conditions: introduction method; syringe (triangles) and micropipette (circles), and stir/pump rate: 1000 rpm (dark blue/orange) and 500 rpm (blue/gold). Insets: Overlay of PSD during dissolution measured in **b)** highest shear and **c)** lowest shear conditions. *Results for ***Product 3***

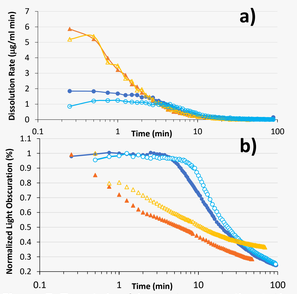


Figure 7. Trends in **a)** instantaneous dissolution rate and **b)** percent light obscuration showing similar behavior. **Labeled same as Figure 6a.*

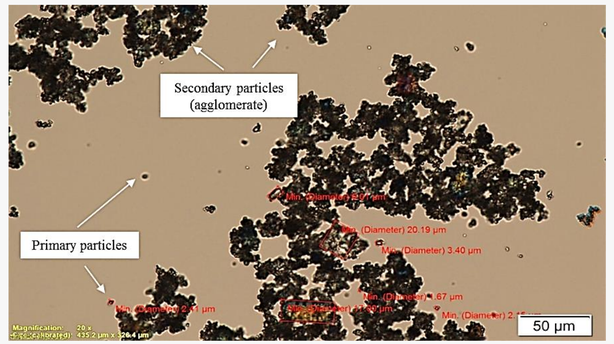


Figure 8. Polarized light micrograph (20x) of RLD product showing the presence of primary active pharmaceutical ingredient (API) particles (~ 2µm) and secondary flocculates-agglomerates (~ 20-30µm).

Syringe Induced Shear During Drug Administration

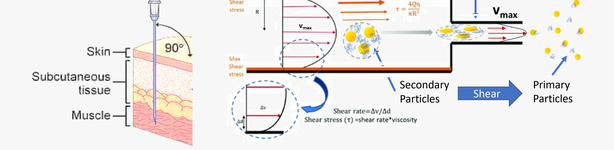


Figure 9. **a)** Illustration of intramuscular depot administration. **b)** Schematic of shear induced deflocculation. Suspension starts with a high concentration of flocculated particles which deform in the presence of steep velocity gradient as they travel from syringe body through the needle. Thus flocculates to break apart, increasing the primary particle population and shifting the PSD.

CONCLUSIONS

1. Shear during both introduction (micropipette or syringe) and measurement (stir and pump rates) affects both particle size distribution (Fig. 2) and rate of dissolution (Fig. 3).
2. Deflocculated particles show typical zero order dissolution (Fig. 4b), flocculated particles exhibit a multistep dissolution process (Fig. 4a).
3. Interplay of reversible flocculation during dissolution impacts not only the physical stability of the suspensions but also the variation in clinical outcomes.

ACKNOWLEDGEMENTS

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DISCLAIMER

This poster reflects the views of the authors and should not be construed to represent FDA's views or policies.