Influence of Polymeric Excipients on the Precision of Particle Size Distribution Measurements of Suspensions Using Laser Diffraction

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PURPOSE

Particle size distribution (PSD) is a critical quality attribute of suspension-based drug products. PSD affects not only the dose uniformity, physical stability, and dissolution properties of the product, but also its bioavailability. Laser diffraction (LD) is the most widely used particle sizing technique for suspension-based drug products which typically exhibit sizes ranging from a few hundred nanometers to tens of microns. However, in LD, the presence of heterogeneous polymeric excipients can complicate PSD analysis, either via direct interference (overlapping signals) or through affecting particle-particle interactions, leading to potentially erroneous results. These concerns highlight the necessity for a more in-depth examination and comparison of the LD methodology. Using loteprednol etabonate (LE), brinzolamide (BRZ), and triamcinolone acetonide (TA) suspensions as model systems, we intend to demonstrate the challenges and solutions to addressing the influences of excipients on PSD measurement.

METHODS

Particle size distribution was determined by LD technique using Mastersizer 3000 equipped with a Hydro MV dispersion unit (Malvern Panalytical Ltd, Malvern, UK). A suitable amount of samples was added into the dispersion unit, followed by dispersing and recirculating to the measurement cell. Particle sizes in the suspensions were also examined using polarized light microscopy (Olympus BX51) coupled to ImageJ software. The impact of excipients on the LD measurement results was determined using leave-one-out approach, and National Institute of Standards and Technology (NIST) traceable size standards (STD) were used as reference. The commercial drug products; Azopt (brinzolamide ophthalmic suspension, 1%), Lotemax (loteprednol etabonate gel, 5%), and Kenalog-40 (triamcinolone acetonide injectable suspension) were procured from DBA-Brookville Pharmacy & Wellness Center (5454 Wisconsin Ave Suite 400, Chevy Chase MD 20815).

To prepare formulations, polyacrylic acid PAA (or other polymers) was dispersed in 7 g of particle free water and stirred overnight. The remaining ingredients were added and dissolved. Subsequently, pH was adjusted to 6.5 followed by autoclaving at 121°C for 30 min. Lastly, 1 mL of a known STD (0.9, 2 or 5 µm) was spiked into each formulation and water was added to make up a total weight of 10 g.

Table 1: Example study design (leave-one-out) using the placebo formulations

No.	Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Polycarbophil	+	+	+	+	+	+	+	-	+
2	Boric acid	-	+	+	+	+	+	+	+	+
3	Glycerin	+	-	+	+	+	+	+	+	+
4	Propylene glycol	+	+	-	+	+	+	+	+	+
5	Tyloxapol	+	+	+	-	+	+	+	+	+
6	Benz. Cl	+	+	+	+	-	+	+	+	+
7	NaCl	+	+	+	+	+	-	+	+	+
8	EDTA	+	+	+	+	+	+	-	+	+
9	0.9 µm STD	+	+	+	+	+	+	+	+	+
10	NaOH	q.s.								
11	HCl	q.s.								
12	Water	q.s.								

RESULTS

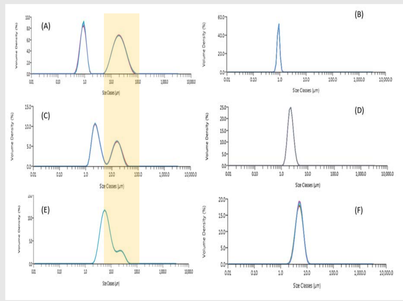

Figure 1. Comparison of PSD histogram of placebo + 0.9 µm, 2.0 µm, or 5.0 µm STD without (A, C, E) and with (B, D, F) background subtraction, respectively.

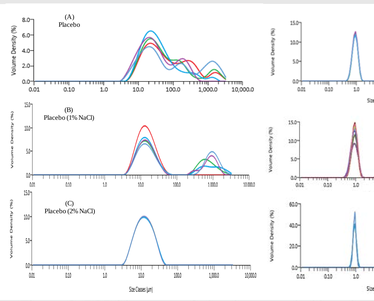

Figure 2. PSD histogram of placebo treated with various of NaCl solutions (A) 0%, (B) 1%, (C) 2%, and placebo formulations with 1 µm size standard, (D) F6 (no NaCl), (E) F1-F5, F7, F9, (F) F8 (no polycarbophil).

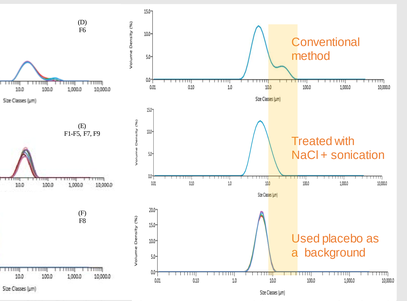

Figure 3. PSD histogram of placebo spiked with 5 µm STD measured using various approaches

PSD Measurement of Commercial Loteprednol Etabonate Gel, 0.5%

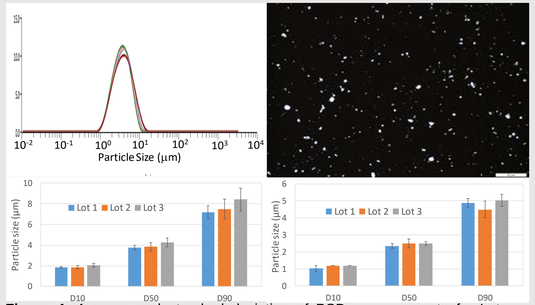

Figure 4. Average and standard deviation of PSD measurements for Lotemax (loteprednol etabonate gel, 5%) using LD total background subtraction technique (volume based n=6, left) and polarized microscope (number based n=3, right).

- *The excipient interference was eliminated, results were consistent in three commercial lots.*
- *The PSD measurement results were comparable between two techniques confirming the suitability of the newly developed method.*

- *The PAA excipients were in micrometer range, generating signals that could interfere with the PSD measurement.*
- *Use of sodium chloride exhibited concentration-dependent reduction of the polycarbophil interference.*
- *False interpretation of the PSD could arise, if the LD peak generated by the excipients overlaps with the peak from the particles of interest.*
- *Pretreating samples containing PAA with sodium chloride can reduce excipient interference, rather than eliminate it.*
- *Using placebo dispersion as a background could eliminate the interference of excipients.*

PSD Measurement of Commercial Triamcinolone Acetonide (TA) Injectable Suspension

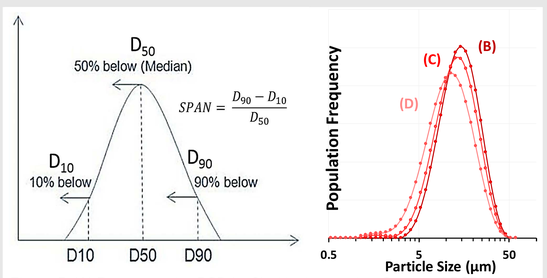

Figure 5. (A) Representative PSD (n=3) with size metrics; Overlay of PSD histograms of Kenalog-40 at different recirculation speeds; (B) 1000 rpm, (C) 2000 rpm, (D) 3000 rpm.

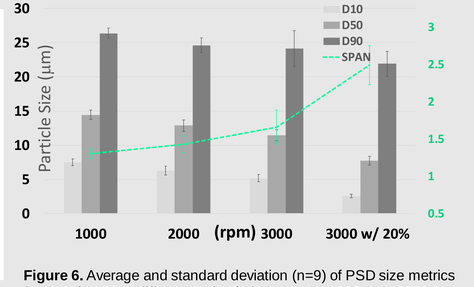

Figure 6. Average and standard deviation (n=9) of PSD size metrics for Kenalog-40 at different recirculation speeds; 1000 rpm, 2000 rpm, 3000 rpm, and 3000 with continuous sonication at 20% power.

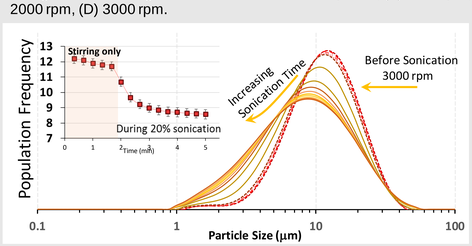

Figure 7. Overlay of PSD histograms during sustained sonication for a representative sample Kenalog-40 at constant 3000 rpm stir rate, sonication (20% power) is applied continuously for 5 min. *Inset:* Change in average and standard deviation of D_{50} during measurement in the presence of sonication (n=3).

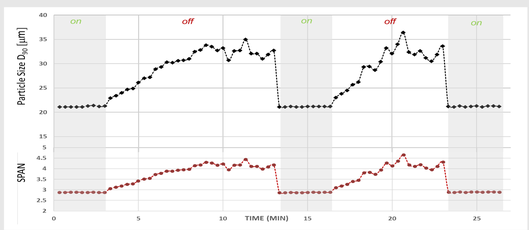

Figure 8. Trend in particle D90 and SPAN upon the cycling of sonication. Dispersion of Kenalog-40 TA sample stirred at constant 3000 rpm stir rate, sonication (20% power) is applied continuously (shaded region) for 10 measurements.

- *Different conditions led to different PSD with broadness and mean size depending on stir rate and sonication.*
- *Upon removal of sonication particle size increased indicating quick reversible flocculation.*

PSD Measurement of Commercial Brinzolamide (BRZ) Suspension, 1%

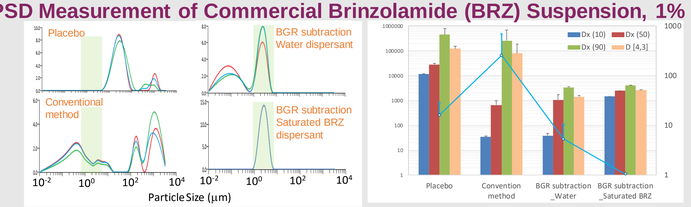

Figure 9. Representative PSD histogram of Azopt (BRZ Suspension, 1%) and its placebo (every constituent excluding the API), measured using different approaches (left and middle), and corresponding average and std-dev of PSD measurement results (n=3, right). *BGR: background*

- *Placebo background subtraction method eliminated the interference of carbomer.*
- *Dissolution of brinzolamide during measurement led to underestimation of PSD as well as appearance of a bimodal distribution.*
- *The combination of placebo background subtraction and saturated BRZ dispersant was critical.*

CONCLUSIONS

The newly developed LD method successfully eliminated the interference of excipients, and thus allowed more reliable measurement of the PSD in suspensions. Depending on the type of excipients used, LD measurement conditions can strongly influence observed PSD. Similar method development strategies could be applied in the future to other heterogeneous dispersed systems where the excipients interferences could be of concern.

ACKNOWLEDGEMENTS

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