

Monitoring of droplet size changes in a suspension pMDI by Laser diffraction on a Sympatec™ instrument

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Summary

A laser diffraction method was developed to characterise droplet size in a suspension pMDI (Pressurised Metered Dose Inhaler) product. Measurements were made with a Sympatec™ instrument, consisting of a Helos/BF™ laser diffraction sensor and an Inhaler™ dry dispersion unit.

Experiments conducted show that differences are observed between product strengths and there is an increase in droplet size through the unit container life. Work was also undertaken to determine the sources of variability in the droplet size distribution response. The most likely causes of this variability were inconsistent sampling due to the dynamic nature of the actuation plume and sensitivity to environmental conditions such as relative humidity.

Introduction

A laser diffraction method was developed to characterise droplet size in a suspension pMDI (Pressurised Metered Dose Inhaler) product, as a faster alternative to an existing Cascade Impactor method.

This was considered appropriate as the measured droplet size would be influenced by the particle size of the active pharmaceutical ingredient (API) within the formulation in two ways. Firstly, the dry API particles would be present in the actuation plume after atomisation; Also, the droplet formation during atomisation may be influenced by the particle size of the API. Both of these factors would be exacerbated by increased particle loads and, hence, any trend could be expected to be more evident for the highest product strength.

Experiments were conducted to characterise droplet size behaviour in this pMDI with respect to product strength, position through unit life and changes in environmental conditions.

Measurements were made with a Sympatec™ instrument, consisting of a Helos/BF™ laser diffraction sensor and an Inhaler™ dry dispersion unit. A pMDI unit is manually actuated into the dry dispersion unit under constant pressure. The actuation plume spreads across the laser (He/Ne @ 633nm) where light is scattered then focussed by a chosen lens onto a detector array. A particle size distribution is inferred from the scattering pattern based on the chosen optical model, allowing for background levels (Size range of 0.5 – 80 µm). The Mie optical model was chosen using the Refractive Index of a major formulation component. This was considered suitable for the size range being analysed and was shown to give robust measurements.

Results and discussion

Three product strengths (n=4) were evaluated in a suspension pMDI along with a matching placebo (n=8). Although the placebo signal shows the droplet size is being measured, the strength dependence shows that the droplet size is likely related to powder load (see Figure 1).

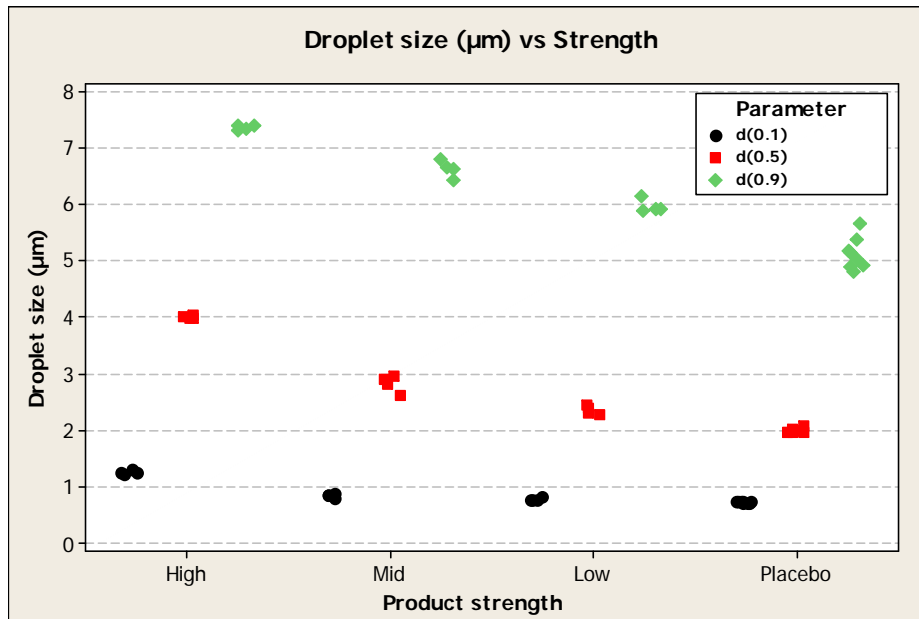


Figure 1. Droplet size vs API Strength

An evaluation of droplet size at the beginning and end of container life was performed for all three product strengths. A through life droplet size increase was observed although this was less evident for the low strength product (see Table 1) which may be due to a lesser influence from the API on the overall droplet size distribution.

Product strength	Through unit life position	Average of d(0.1) (µm)	Average of d(0.5) (µm)	Average of d(0.9) (µm)
Low	Start	1.112	2.711	5.639
	End	1.116	2.774	5.819
Mid	Start	1.200	3.128	6.378
	End	1.326	3.316	6.656
High	Start	1.448	3.791	7.163
	End	1.562	3.997	7.447

Table 1. Droplet size at beginning and end of container life

During method development, suitable sampling criteria (Trigger conditions) must be chosen to ensure measurements are made of the sample and not the background. This involves setting of a suitable optical concentration (OC) threshold at which to “trigger” the measurement. The plot in Figure 2 shows how variable the OC is within the dynamic plume and therefore there is potential for shot-to-shot variability in the measurements made. It is critical to optimise the sampling conditions to minimise this.

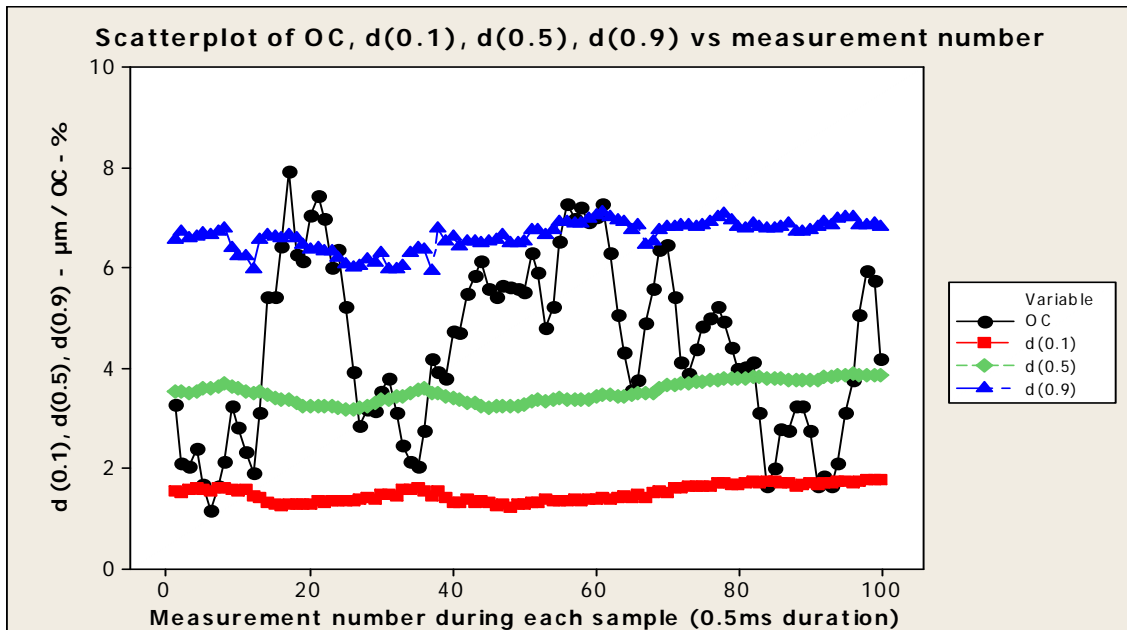


Figure 2. Droplet size and Optical Concentration throughout a sample (50ms)

Environmental measurements were made during testing over a number of days, using a single product strength at the Start of Life. An apparent trend is present for humidity with respect to measured droplet size (see Figure 3), similar to that observed by Ziegler and Wachtel¹. It is therefore critical to control RH (Relative Humidity) during these measurements.

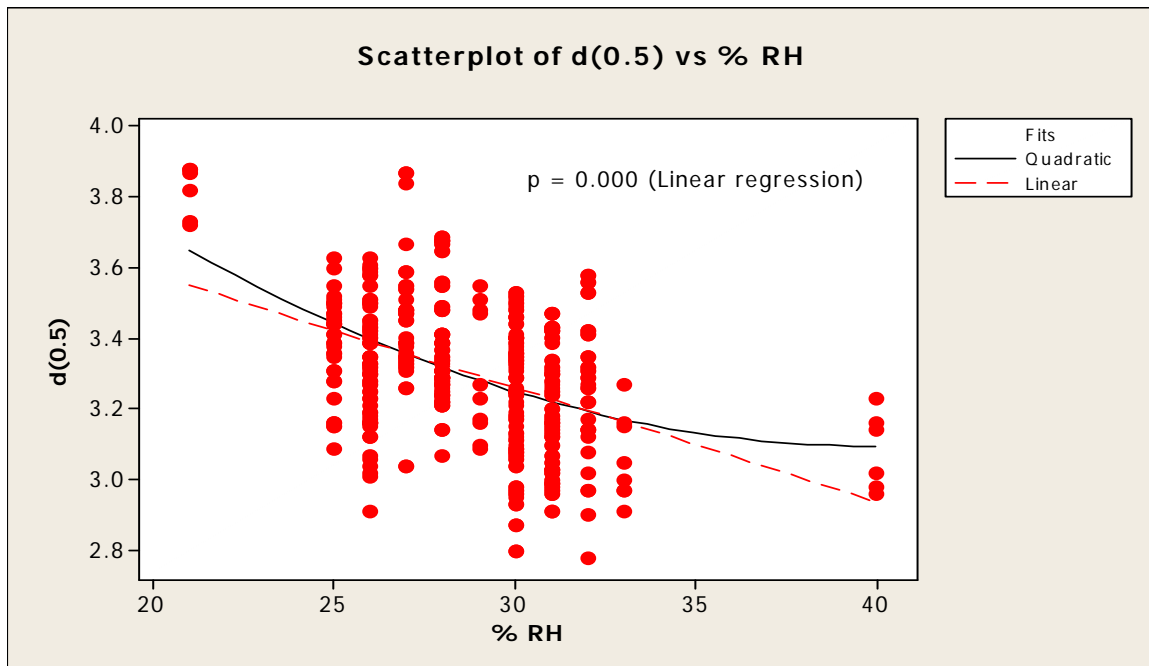


Figure 3. Median droplet size versus RH with linear and quadratic regression fits.

Conclusion

Laser diffraction measurements using a Sympatec™ instrument were conducted to characterise the droplet size of a suspension pMDI. Trends have been observed between product strengths and through the unit container life.

The through unit container life trend is most apparent for the high strength product, likely due to the increased signal from the higher particle load and the observed measurement variability obscuring any differences for the lower API strengths. The variability arises from inconsistent sampling due to the dynamic nature of the actuation plume and sensitivity to environmental conditions such as relative humidity.

References

¹ - Ziegler, J., and H. Wachtel. 2005. Comparison of Cascade Impaction and Laser Diffraction for Particle Size Distribution Measurements. JOURNAL OF AEROSOL MEDICINE. Volume 18, Number 3, p. 311–324