

A comprehensive approach in the development and validation of a laser diffraction method for determining the particle size and size distribution of an active pharmaceutical ingredient

Viktor Popovski^{1,2}, Maja Simonoska Crcarevska¹, Marija Glavas Dodov¹,
Katerina Goracinova¹, Nikola Geskovski¹

¹ Institute of Pharmaceutical technology, Faculty of Pharmacy, University Ss Cyril and Methodius in Skopje, Majka Tereza
47, Skopje, N. Macedonia

² ReplekFarm AD, Kozle, 1000, Skopje, N. Macedonia

Introduction

Particle size (PS) and particle size distribution (PSD) are one of the most important characteristics of powder materials that play an important role during the development of pharmaceutical dosage forms and their manufacturing processes. The PSD of an active ingredient affects the final characteristics of the pharmaceutical dosage form, its dissolution profile, formulation bioavailability, uniformity and stability (Hintz et al., 1989).

Aripiprasole is a BCS II class drug and to enhance its bioavailability, several formulation strategies can be employed. One approach involves the utilization of micronization, to improve drug solubility and dissolution.

Considering the abovementioned, it can be assumed that Aripiprazole PS is critical material attribute that can affect the dissolution profile of the solid dosage form and therefore needs to be closely monitored. The aim of our study was to develop and validate a laser diffraction based method for PS and PSD determination using a comprehensive approach.

Materials and methods

The sample, Aripiprazole, was obtained from Alembic pharmaceuticals. All other chemicals used were of analytical grade

Morphological analysis and was performed using microscopic analysis with static image analyzing on CX3 (Olympus, Japan). The refractive index was determined

using extrapolation from the standard curve constructed from the RI of DMSO solutions of Aripiprazole that were measured on digital refractometer RX 40 (Mettler Toledo, Spain) on 25°C. The PS and PSD laser diffraction analyses were performed using Mastersizer 2000 equipped with dry dispersion unit Sirocco 2000 (Malvern Instruments, UK). The method development and validation were performed according to the criteria and tests described in ISO 13320.

Results and discussion

The microscopic analysis performed using various levels of energy for particle dispersion revealed that under mild dispersion conditions (1 min ultrasound) spherical and irregularly shaped particles were observed divided into two fractions: fine (3-5µm) and coarse particles (20-50µm). The particles from the fine fraction demonstrated aggregation behavior, which was drastically reduced when the dispersion energy was increased (5 min ultrasound). However, when the ultrasound dispersion time for the sample preparation was increased to 10 min, a noticeable breakage of the primary particles was observed.

The RI of the solid API was determined to be 1.5892, and for the purpose of the laser diffraction method, 1.59 was employed.

The measuring conditions were optimized by using an OFAT approach in varying the measurement time (6-12s) and air pressure for dispersion of the sample (0.5- 4bar). The variation of particle size and RSD (%) in relation to the measurement time are presented on Figure 1.

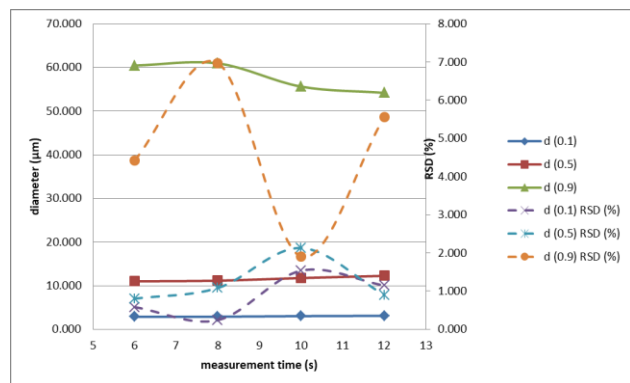


Figure 1. Particle diameter (μm) percentile ranks (solid lines, left vertical axis) and RSD (dashed lines, right vertical axis) as a function of measurement time

Given that the measurements were made under the same conditions (rate of sample addition in the measurement cell, sample air dispersion 1 bar), it can be concluded that by increasing the measurement time, the amount (volume) of the sample being analyzed increases, thereby increasing the statistical significance of the obtained result. The measuring time of 10s was considered as optimal in regards to the PS and RSD of the analysis. Further on, the sample dispersion air pressure was varied, while all other parameters were kept constant. The results are presented in Figure 2.

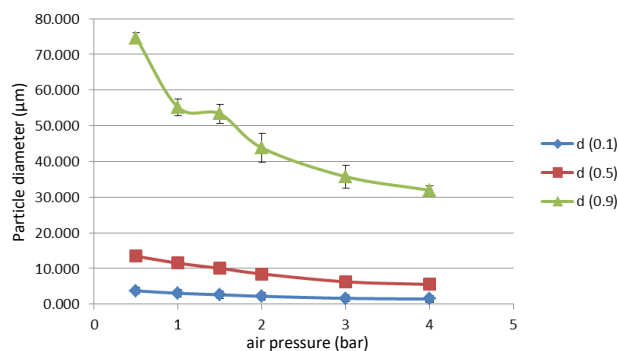


Figure 2. Particle diameter (μm) percentile ranks as a function of sample dispersion air pressure

Increasing the air pressure for dispersing from 1 to 3 bar will give an increase in the air speed from 240 to 522 m/s, which will also result in a different coalition energy of the particles (Ali et al., 2015). Considering that the higher coalescence energy can cause breakage of the primary particles, which was also observed in the morphological analysis, it was decided to choose conditions under which the particle size is stable (in this case it was the range from 1 to 1.5 bar). The results showed that with a further increase in air pressure, a significant decrease in the diameter of the particle size was observed. It is assumed

that this change occurs due to the reduction of size of the primary particles. Therefore, a pressure of 1 bar is chosen as optimal for performing the analysis.

The method demonstrated adequate linearity in the range of 2-6.5% laser light obscuration. In addition, the reproducibility testing (measured on six separately prepared samples) revealed RSD (%) of 0.38, 0.8 and 4.31 for d 0.1, d 0.5 and d 0.9, respectively. While the intermediate precision resulted with RSD of 0.75, 0.88 and 4.65% for d 0.1, d 0.5 and d 0.9, respectively. The above results clearly demonstrated that the method is compliant to the requirements of ISO 13320.

Conclusion

In the development of methods for the determination of particle size, it is necessary to use several complementary techniques.

Optical microscopy with static imaging was used for preliminary morphological analysis of the sample, as well as to evaluate the behavior of the sample under different dispersion conditions.

A laser diffraction method using dry optical cell setup was developed for measurement of particle size of Aripiprazole. The statistical indicators point out that the developed method is reproducible and with satisfactory precision, according to the requirements of ISO 13320, and as such can be used for further routine analysis of such samples from this API.

References

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