

Particle size analysis – important points

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In this article I would like to summarize different aspects and to represent my point of view regarding particle size analysis (by laser diffraction). While developing methods for particle size analysis for different pharmaceutical substances by different PSD machines/analyzers (by laser diffraction) researchers/analysts may have difficulties in choosing appropriate dispersant. There is no need to choose dispersant while performing measurements in a dry manner (for example on Mastersizer 2000 dry powder feeder , Alpine jet and similar apparatus , using air pressure to achieve good dispersion of sample) . When sample dispersion occurs in the liquid dispersant, the right choice of dispersant is very important issue [2]. It is preferable to use safe (non toxic), low cost dispersants, - and of course matter of its polarity and viscosity should be taken into account too. Some pharmaceutical substances (powders) are freely soluble in water and some in Ethanol, and there is a need to find the "right" dispersant for sample dispersion. In many cases oils – for example silicone oil of viscosity 20 centistokes or lower may be found to be a good dispersant. It can take some time to fill the wet dispersion units of apparatus with Silicone oil but advantages of using it can be seen during method development, - for particles from 60 μm to 1000 μm and more good dispersion is generally achieved during period of time – from 1 to several minutes by mixing / stirring (at moderate speed) or with help of shaking by hand. When micronized powders are need to be tested on particle size analyzers in a wet manner choosing of right dispersant and sample preparation methods must be taken care very carefully , - for particles bellow 10 microns the forces of attraction between particle can be huge – from 10 g at 10 microns to about 100000 g at 0.1 microns . I think there is no need to say how it is important to find the correct value of particle Refractive index to obtain accurate results while using Mie theory ¹. I would like to discuss method for particle size analysis of one of micronized powders, using Mastersizer 2000 particle size analyzer –Hydro 2000S wet dispersion unit and in this example to discuss several important factors of method development of micronized powders, using wet dispersion. After finding the correct value of particle refractive index and absorption, in this case it was: RI – 1.526, absorption – 0.001, I started to look for conditions of good dispersion, water was used as dispersant. Correct optical settings should give a good fit .The using of Fraunhofer theory (particle RI = 0, absorption = 0) instead of Mie theory gives an overestimation in results for micronized powders (i.e. 43% less than 3 μm by Mie theory, and 60 % less than 3 μm by Frounhofer theory) .Ultrasonic probe was set to low value (for Hydro 2000 at 30%) and ultrasonic probe can be turned on during the measurements. After sample addition ultrasonic was turned on for 30 minutes. Sample was added until obscuration is about 4 % to avoid multiplied scattering. Low intensity of ultrasonic is required to avoid oscillating of particles , besides that at great frequency of Ultrasonic wave the refractive index of dispersant can undergo some changes , and together with particles oscillating it can affect

accuracy of results and to "spoil" fit data . Long period of ultrasonic action at low intensity is needed to achieve good dispersion of the particles and to overcome adhesion forces, which can be strong enough for micronized powders.

For some micronized powders it is better to perform analysis in a dry manner , good dispersion (when fine fractions are not overestimated) can be achieved under pressure of 1,5 - 2 bar , - feed rate and sample measurement time should be chosen according to technical specifications of apparatus . With regard to wet method development, sample preparation is a very important issue by itself. Generally addition of 2-3 drops of 10% tween 80 can strongly improve wetting of particles (especially in case of micronized powders). Using of silicone oil as dispersant for micronized powders (and generally any liquid/medium, having viscosity greater than viscosity of water) can make method development process more complex and difficult. For example in Silicone oil of viscosity of example 20 centistokes, it can take a lot of time of stirring and mixing of powder until good dispersion will be achieved , but good dispersion of micronized powder also can be achieved in next way : add about 10-15 mg of micornized powder in small glass vial , pour about 10-15 ml of silicone oil over it and put into Ultrasonic bath for 10-15 minutes or more , after that sample can be added into the wet dispersion unit – optimal conditions and settings must be found as part of method development . For thin and long particles ultrasonic energy, applied to break up agglomerates should be chosen very carefully because of particles shape (thin and long particles can be fragile enough - because of its shape), and significant amount of ultrasonic energy during long time period (that should be verified) can break up particles. In any case while developing method in a wet manner the next tip can be very helpful (I used it many times): before starting the measurements it is recommended to look at particles of powder under the microscope (to get information on their shape and transparency) to set correct values: absorption, distribution type (by Volume, by Surface, etc) that should be used, some estimation of particles and sizes of agglomerates.

When you see that good dispersion is achieved , according to data , obtained from measurements (i.e. trend graphs , etc ...) , do another effort to be sure that good dispersion is achieved , if it is possible - take a small amount of the sample that has just already been measured (from the tank or from the measurement unit) and look at it under the microscope , in addition to it you can compare it with particles of powder (in the same medium (dispersant) - before sample measurement).

For example pictures, obtained from observation under the microscope are represented below. Under the microscope particles were observed as thin, transparent and elongated.

Figure A: Sample was prepared in next way: about 10 mg of powder were added into 10 ml container (with cover top), 10 ml of Silicone oil were poured over it, and container was put into Ultrasonic bath for 5 minutes, after that sample was added into the tank until obscuration is about 13%, it was waited for about 1 minute and measurements were performed. Good repeatability of results was obtained. Sample was added into the tank by Pasteur pipette.

Figure B and C: Sample was taken directly from the tank (during stirring) immediately after measurements and was observed under the microscope. By looking at the figure B it can be said that good dispersion was achieved.

Please see figures A, B and C below:

Figure A



Figure B



Figure C



Observation of particles under the microscope should not be neglected, microscope is a very useful tool, helping in particle size analysis. First estimation of particle size and shape analyst/researcher can get by simple and direct observation of the particles under the microscope. Optical properties of particles (refractive index and absorption) can be estimated too, by observing particles under the microscope in different mediums with different refractive index values) - if the particles and medium have the same refractive index , then you won't see any particles by observing medium with particles under the microscope .

Several important stages of particle size analysis are:

- Observing the particles under the microscope
- Finding correct optical values: refractive index and absorption.
- Sample preparation method and sampling.
- Choosing the right dispersant (for wet dispersion)
- Achieving of good dispersion and performing measurements (Finding optimal conditions/ settings, research and method development)

When measurements are performed in a dry manner, measured particle size can depend on sample measurement time strongly because of particle shape. For example if small plate like particles or fragile particles are measured ,

many particles can be broken up in collisions easily before they reach measurement zone , and that is why the short measurement time should be chosen (in condition that good repeatability of results and good fit are obtained) in order to avoid fine fraction overestimation, caused by particles brake-up.

It should be noted that optimal conditions / settings for micronized and non micronized powders of the same raw material can differ strongly either in a wet method or in a dry method, - for example conditions/settings, chosen for particle size analysis of powder with particles bellow 20 μm can differ strongly from particle size analysis of the same powder (raw material) with particles between 30 - 280 μm . The reasons for that are: adhesion forces (attraction forces), chemical structure of raw material, etc... , - and generally while using PSD machines /analyzers (by laser diffraction) researchers and analysts can have a lot of difficulties while trying to find the "Universal " method (If it can be found at all) for particle size analysis of specific raw material, having the same measurements settings / conditions for micronized and not micronized powders.

Another important issue that is worth to mention is choosing secondary standards, - for example powders as Talc , Maize starch , Starch 1500 and Magnesium stearate can be used as secondary standards (in addition to Quality Audit Standards) to ensure system suitability. Talc, Magnesium Stearate, Starch 1500 and Maize Starch generally give a good reproducibility and repeatability (while using in wet dispersion units) of results.

In conclusion, different points represented in this article can be useful in method development of particle size analysis of different raw materials and in understanding processes, that may take place in pharmaceutical, chemical and many others branches of industries and fields of researches.

References:

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2. Wet method development for laser diffraction measurements. Malvern Application Note: MRK561-01