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Laser diffractometry size analysis of nanoparticles: the ignored pitfall of refractive indices!

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Laser diffraction (LD) is one of the most frequently used methods for particle size analysis of nanomaterials. The measuring range is 20 nm-2000 µm, i.e. it allows also detection of aggregates in the µm size range besides the nano bulk population. In the range 20 nm to about 4 µm the size needs to be calculated using the Mie theory which requires input of the real refractive index (RI) and imaginary refractive index (IRI). Both indices are material specific. Often the indices are not known, especially the RI, and values were estimated or the set value in the program was used. This leads to an article stating that 90% of the published measurements are false [1].

In this study, lipid nanoparticles (SLN, NLC) were used to assess the extent of error which can occur. They are ideal for such a study because of ease of exchange of core material, stabilizer layer and modification of size. For the last 10 years, the published nanoemulsions RI value of 1.456 combined with IRI of 0.01 were used for LD size calculation of many differently composed solid lipid nanoparticles. This can potentially lead to wrong calculation of size results. In this study it was systematically analyzed to which extent the chemical nature of the nanoparticle core material and the stabilizer layer, but also the particle size affect the RI, and consequently the calculated size in LD analysis.

Lipid nanoparticles were produced using three different core lipids (Cutina CP, Compritol 888 ATO and Dynasan 116), stabilized by three surfactants (Tween 80, TegoCare 450 and SDS), yielding a total of 9 different formulations (= solid lipid nanoparticles = SLN). Another 9 formulations were produced by loading these lipid particles with argan oil as cosmetic active (= nanostructured lipid carriers = NLC). The RI was measured by analysis of variously diluted lipid particle suspensions (e.g. 1-10%) using an Abbé refractometer at 200C [2], and extrapolating the RI to a solid content of 100%. The IRI was determined by fitting the originally detected scattered light data with the scattering curve analyzed by the software of the instrument (i.e. equal values at channel 100). All LD measurements were performed by a Mastersizer 2000 (Malvern Instruments Ltd., UK).

Both the core lipids and the stabilizers in the formulations were found to distinctly affect the RI. For example: RI values of 1.493, 1.514 and 1.488 were obtained, when using aragan-oil loaded Cutina CP NLC stabilized with 3 different surfactants (Tween 80, TegoCare 450 and SDS). Similar effects were observed for the other two lipids, confirming the strong influence of the stabilizer layer. Changing the lipid core composition to SLN (no argan oil) lead to a

decrease in the RI values for all nanoparticles. For example, for the Cutina CP-TegoCare 450 formulation the RI decreased from 1.514 to 1.464. Totally different particle diameters and size distributions are calculated with the wrong RI, e.g. the wrong RI of 1.456 yielded a diameter D99% of 0.892 µm and a monomodal size distribution, versus with the correct RI a diameter D99% of 3.106 µm and a bimodal size distribution were obtained. The large peak representing the relatively large particles (aggregates) in the sample. The RI is mainly affected by the chemical nature of the components. In contrast, the IRI showed no or little dependence on component but on particle size. For nanoparticle samples studied, IRI in the range 0-0.01 yielded no big differences in calculated size and size distributions.

For all nanomaterials it can be concluded, that chemical composition of core material but also composition of the stabilizer layers affects strongly the RI. Measurement of the RI is therefore an essential prerequisite for correct size analysis. Differences in RI of about 0.01 and larger can have a significant effect on the calculated size (rule of thumb). The diameters 90%-99% are much more affected than the diameters 50% in case a wrong RI is used. For the determination of IRI, the instrument software appears suitable.

References:

[1] Keck, C. M., Müller, R. H., Size analysis of submicron particles by laser diffractometry – 90 % of the published measurements are false, Int. J. Pharm. 355, 150-163, 2008
[2] Cornelia M. Keck, Cyclosporine Nanosuspensions: Optimized Size Characterization & Oral Formulations, Berlin, Free University of Berlin, 2006
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