DELOS-SUSP PROCEDURE: PREPARATION OF STABLE AQUEOUS NANOSUSPENSIONS OF MOLECULAR MATERIALS

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The preparation of nanosuspensions of molecular materials have stimulated a great interest during the last years, at scientific and industrial level, since these systems could show different properties compared to the corresponding microstructured systems, and thus they could be used for new applications. For example, a surprisingly large proportion of new drug candidates emerging from drug discovery programmes are water insoluble, and therefore poorly bioavailable, leading to abandoned development efforts. These so-called "brick-dust" candidates can now be rescued by formulating them into crystalline nanosuspensions [1]. Nanosuspensions overcome delivery issues for these compounds by obviating the need to dissolve them, and maintaining the drug in a preferred crystalline state of size sufficiently small for pharmaceutical acceptability.

The DELOS process is an efficient high-pressure crystallization method, which uses compressed CO_2, for the straightforward production of crystalline micro- and nanosized particulate materials [2]. The driving force of a DELOS crystallization is the fast, large and extremely homogeneous temperature decrease (i.e.; 80°C in milliseconds) experienced by a CO_2-expanded solution when it is depressurized from a given working pressure to atmospheric pressure. This temperature decrease provokes a pronounced and homogeneous increase of the supersaturation ratio, at any point of the solution, and the phenomenon of catastrophic nucleation occurs causing the precipitation of nano- or micron-sized crystalline particles with a narrow particle size distribution.

Recently we have developed a new efficient procedure based on DELOS, for the preparation of molecular material nanoparticles stabilized in an aqueous phase [3], named DELOS-SUSP. In the preparation of colloidal systems by precipitation procedures, the size and size distribution of the dispersed nanoparticles are strongly dependent on the homogeneity of the supersaturation level, at any point of the liquid solution, at any time of the procedure. In the DELOS-SUSP method the cooling of the solution, which is the precipitation driving force, takes place with the same extent at any point of the solution, favoring the production of nanosuspensions with a narrow dispersed particles size distribution. As it can be observed in Figure 1, using this technique we have been able to prepare stable nanosuspensions with a mean particle size of 100nm.

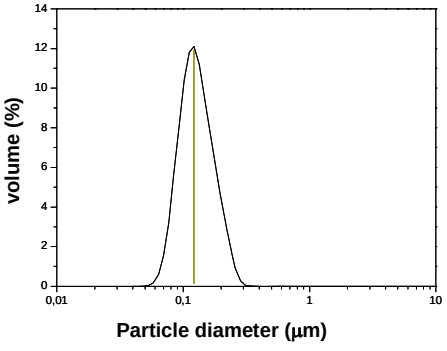

Figure 1. a) Photographs of cholesterol in water suspensions prepared by mixing methods (left two samples) and by the DELOS-SUSP procedure (right sample). b) Laser light diffraction analysis of a cholesterol nanosuspension in water, obtained through the DELOS-SUSP method.

In these work, we have analyzed the influence of different DELOS-SUSP operational parameters (the initial solution supersaturation (β_i), CO_2 content of the CO_2-expanded solution, stabilizer/solute molar ratio and stabilizer nature) over the structural characteristics of the nanosuspensions produced (particle size distribution of the dispersed nanoparticles, stability, rate of rupture, morphology). To perform this study, cholesterol and water were used as model materials for disperse and dispersant phase respectively, and CTAB (cetyl trimethyl ammonium bromide) and Tween 80 (Polyethylene glycol sorbitan monooleate) as model cationic and neuter surfactants respectively.

The results of this study show that the size distribution of the dispersed particles and the stability of the cholesterol nanosuspensions are mainly governed by the supersaturation of the initial cholesterol solution and the nature of the stabilizer
We also have observed that the long term stability and the propensity to aggregation of the suspended nanoparticles are intimately related to the nature, concentration and placement of the surface-active substances.

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