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Microfluidics for controlled self-assembly of cubosome nanoparticles of tunable size

Celso J. O. Ferreira[1,2], Margarida Barros[1,2], Cláudia Botelho[1,2], M. Elisabete C. D. Real Oliveira[2], Bruno F. B. Silva[1,*]

[1] *INL-International Iberian Nanotechnology Laboratory, Av. Mestre José Veiga, Braga, Portugal;* [2] *University of Minho, Campus de Gualtar, Braga, Portugal;*

* *bruno.silva@inl.int*

Cubosomes are nano-sized dispersions of bicontinuous cubic liquid-crystalline phases. Typically they are composed of lipid and water and stabilized with a hydrophilic polymer. Compared to liposomes, these particles have a nanostructured interior with a higher fraction of lipid, being ideal to deliver bioactive hydrophobic molecules in health and food applications[1]. Cubosomes are typically prepared either by fragmenting the cubic liquid crystal in excess water using high energy input (e.g. ultra-sonication), or using solvent-shifting approaches, in which the lipid is first dissolved in a water-miscible solvent (typically ethanol), and later mixed with water and polymer stabilizer[2]. In both cases, poor experimental control at the micron- and nanoscales (e.g. poor control on concentration and heat gradients), limits the fine tuning of the particle properties and results in cubosomes with broad size distributions. In this work, we employ the solvent-exchange method using a microfluidic device[3], achieving rapid and controlled mixing at the micron-scale and obtaining cubosomes of tunable size and low polydispersity. The micron-sized channels in microfluidics lead to laminar flow regimes and enhanced experimental control. In this regime, hydrodynamic focusing can be used to decrease the mixing time between the different components, by decreasing the distances that molecules must travel for total mixing. An ethanol-lipid solution is flowed in a central inlet, which is squeezed by two side streams of water with stabilizer. As the lipid-ethanol solution narrows, ethanol and water are mixed in a controlled way by diffusion, leading to formation of cubosomes (figure 1). By manipulating the flow rate ratio (Q_R) between the two solutions we manipulate the width in which the hydrodynamic focusing occurs, influencing the assembly time in a homogeneous way. This way, by manipulating the Q_R, we are able to tune the size of the cubosome nanoparticles. Nanoparticle size is a key parameter in drug delivery, and being able to control it is therefore a relevant step towards the design of new and more efficient formulations.

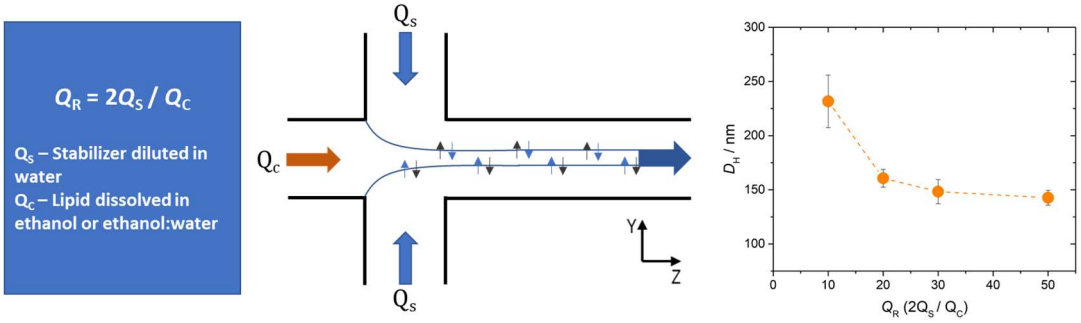

Figure 1: Schematic representation of the experiment setup. The calculated Q_R is used to manipulate the ratio in which the side solutions (Q_S) and centre solution (Q_C) are injected inside the microfluidic device. As the Q_R is changed inside the device, the centre solution has its width decreased which results in a shorter mixing time between the solvents. The change in time is translated in different particle sizes. The obtained samples from the device are later characterized using Dynamic Light Scattering (DLS).

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