P1.16: Microfluidics for precise tuning of cubosome nanoparticle size

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Introduction

Cubosomes are nano-sized dispersions of bicontinuous cubic phases in water, ideal to deliver bioactive molecules in therapeutic applications [1]. Typically they are prepared either by fragmenting the cubic phase in excess water using high energy input, or using solvent-shifting approaches [2]. In both cases, poor experimental control at the micron-scale (e.g. poor control on concentration gradients), limits the fine tuning of the particle properties and results in cubosomes with broad size distributions.

Microfluidics enables the control and manipulation of fluids at the micron-scale. Its micron-sized channels lead to laminar flow regimes and enhanced experimental control. In this regime, hydrodynamic focusing can be used to decrease the mixing time between different components by decreasing the distances that molecules must travel for total mixing.

In this work, in order to achieve rapid and controlled mixing at the micron-scale, we employ the solvent-shifting method in a microfluidic device [3]. The ultimate goal is to obtain cubosomes of tunable narrow size distributions.

Materials and Methods

Using a COC microfluidic device composed by a cross-junction where 3 inlets and one outlet meet, an ethanol-lipid solution is flowed in the central inlet, which is squeezed by two side streams of water with stabilizer (F127). As the lipid-ethanol solution narrows, ethanol and water are mixed in a controlled way by diffusion, leading to the formation of cubosomes.
The obtained cubosomes were compared with the ones obtained following a solvent-shifting approach using a bulk methodology. To do so, the concentration of all components was adjusted to the same as in the microfluidic methodology.
Particles size was determined by Dynamic Light Scattering, and the structure by Small Angle X-ray Scattering.

Results and Discussion

The flow rate ratio (Q_R) is defined by the ratio between the centre inlet to the side inlets. By manipulating the Q_R between the lipid solution to the stabilizer solution, we manipulate the width in which the hydrodynamic focusing occurs, influencing the assembly time in a homogeneous way. As a result, an increase in Q_R results in a decrease of the particle size. This is contrast with particles assembled with the bulk methodology, where the size is kept constant, except for higher dilution ratios where it increases. This reinforces that by manipulating the flow conditions (especially Q_R), we can tune the cubosome size.
SAXS measurements show that the particles obtained using this microfluidic methodology have a Pn3m crystallographic spacegroup, as expected for this concentration and temperature range [4].

Conclusions

We showed that by the use of microfluidics, the sizes of cubosomes can be manipulated in the 130-210 nm range. Since nanoparticle size is a key parameter in drug delivery, this constitutes a relevant step towards the design of new and more efficient formulations.

Acknowledgments

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