**Microfluidic generation of curcumin-loaded albumin nanoparticles by solvent-shifting precipitation in core-sheath flows**

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Curcumin (CCM) is a natural polyphenol traditionally used as spice and food coloring. It is also considered a nutraceutical with many demonstrated properties: antioxidant, anti-inflammatory, anticancer, antiprotozoal, antiviral and antibacterial. However, despite these beneficial properties, the extreme low solubility of CCM in water limits its bioavailability and, at the same time, impedes its inclusion in functional foods and beverages. Therefore, the encapsulation of CCM in hydrophilic carriers is highly desirable. In particular, the binding of CCM to soluble proteins is a promising alternative for better bioavailability. Microfluidic techniques enable the implementation of low energy and continuum processes, with fast mass transfer and homogeneous mixing at the microscale. Here, we describe the microfluidic generation of CCM-loaded albumin nanoparticles (NPs) using devices designed to produce solvent-shifting nanoprecipitation by hydrodynamic focusing in cylindrical capillaries (core-sheath flows). Two coaxial fluid streams were forced to co-flow as core and sheath fluids along the capillary tube. The ethanol stream containing CCM (inner fluid) was squeezed by the aqueous protein solution (outer fluid). Interdiffusion across the core-sheath interface enabled rapid mixing and the consequent solvent shifting, which triggered the nucleation of precursors and the growth of nanoparticles. Microfluidic devices were fabricated by assembling the following components: stainless steel dispensing needles, transparent tee connectors, Teflon tubing, and silicon tubing for fittings. An alpha-lactalbumin (α-LA) solution (0.2% w/v) was prepared in 50mM and pH 7 phosphate buffer saline (PBS). Also, CCM (0.05%w/v) was prepared in ethanol 96% v/v. The inner fluid was the organic solution of CCM, injected at the flow rate *QCCM*, which was hydrodynamically focused by the outer fluid, the aqueous solution of α-LA, injected at the flow rate *Qα-LA*. Both fluids were injected using a hydrostatic pumping system. The flow regime was completely defined by two controlling parameters: the flow rate ratio (*Qα-LA* /*QCCM*) and the total flow rate (*QCCM* +*Qα-LA*). The independent effects of these fluid dynamic variables on NPs size was evaluated by DLS. It was observed that NPs size decreased with both, the flow rate ratio and the total flow rate. These results showed that the microfluidic technique allows one to adjust the diameter of NPs by controlling the flow rates of the precursor fluids. Then, the optimal operation conditions selected to CCM-α-LA NPs production were: *Q α-LA* /*QCCM* =10 and *QCCM* +*Q α-LA*= 20 mL/h. The obtained NPs with an average diameter of 181±3nm resulted highly monodisperse and presented an encapsulation efficiency of 43±1.4% quantified by UV−visible spectrophotometry. Scanning electron and transmission electron microscopy images showed that NPs where spherical, uniformly dispersed and presented well-defined borders. In vitro CCM release study was evaluated in PBS (pH 6.8) during 4 h and it was observed that the 74% of the encapsulated CCM was released. It is concluded that the proposed methodology is a promising route to scale up the microfluidic elaboration of nanoparticles for the encapsulation of active ingredients.

Keywords: microfluidics, curcumin encapsulation, nanoprecipitation.