Tuning physico-chemical and biological properties of lipid cubosomes with a polyphosphoester stabilizer

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Non-lamellar lyotropic liquid crystalline nanoparticles (LNPs) have been highlighted as possible alternatives to vesicles,[1] due to the higher drug content they can encapsulate per nanoparticle and to their colloidal stability. To avoid nanoparticles coalescence, LNPs often require a steric stabilizer, which can exert a certain degree of cytotoxicity and affect the inner structure of the nanoparticles, influencing the interactions with cells. Aiming to address these issues, we studied the applicability of a novel biodegradable polyphosphoester (PPE) analog of Pluronic F127 (PF127) as a stabilizer for monoolein-based cubosomes, nanometric aqueous dispersion of the bicontinuous cubic phase.[2] Commonly, PF127 affects monoolein self-assembly giving a mixture of two bicontinuous cubic phases (space groups Pn3m and Im3m), due to the interactions between the hydrophobic moiety of the polymer and the lipid bilayer.[3] When PPE is used in place of PF127, only the Pn3m phase could be observed by SAXS investigations. PPE-cubosomes exhibited a thermo-responsive behavior in the temperature range 25 – 50 °C, with a reversible bicontinuous cubic-to-hexagonal phase transition. The morphology and the hydrodynamic size, evaluated by cryo-TEM and DLS, respectively, are in line with the those reported in the literature for these kinds of LNPs.[1] The surface characterization of nanoparticles stabilized either with PPE or PF127 was conducted *via* QCM-D on both hydrophilic and hydrophobic surfaces over a broad range of biologically relevant pH (4.5 – 7.4), showing a different surface behavior among the two formulations. Finally, the biocompatibility of the two formulations was investigated against two different cell lines (HUVEC and HEK) and for their hemolytic properties. Overall, the novel PPE formulation was less cytotoxic over the whole cubosome concentration range considered (25 – 100 μg/mL). with a greater hemocompatibility with respect to PF127-stabilized cubosomes. Imaging *in vitro* tests with the formulations loaded with a fluorescent dye showed also that regardless of the stabilizer, the two kinds of cubosomes are internalized by Raji cells in the same manner. These results proved the efficacy of PPE-stabilized cubosomes and the possibility to achieve greater biocompatibility and colloidal stability with respect to conventional formulations.

References

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