TITLE: Reversibly core-cross-linked micelles sensitive to reductive environment for the design of drug delivery systems

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INTRODUCTION: Over the last decade, polymer micelles attracted an increasing interest in drug pharmaceutical research because they could be used as efficient drug delivery systems. Micelles of amphiphilic block copolymers are supramolecular core-shell type assemblies of tens of nanometers in diameter. An accumulation of polymer nanocarriers to solid tumours is possible due to the EPR effect. Even if micelles get a high stability in aqueous media, the dissociation of micelles is not always preserved when they are injected in the blood compartment. This work aims at reporting on the design of reversibly cross-linked micelles by introducing disulfide bridges in the micelle core to provide higher stability.

EXPERIMENTAL: Polymer synthesis: Block copolymers are obtained by ROP of ε-CL and α-ClCL from monomethoxy poly(ethylene glycol) (MPEO) Mn =5000 g/mol and then substituted by NaN_3.
Micelles formation: A stock solution of copolymer and the cross-linking agent is prepared in DMF (1%). A solution of 20 mL of water was added to the organic solution (5mL) under vigorous stirring for one day. $CuSO_4$ and sodium ascorbic acid were added to click the cross-linking agent to the copolymer. The reaction was allowed to proceed for one day at room temperature and purified by dialysis against water.

RESULT AND DISCUSSION: These copolymers have been synthesized with a good yield and well-defined macromolecular parameters. Controlled composition of the azido copolymers was achieved. For each copolymer type, two different azide contents have been studied, i.e. about 25 and 35%. The azide has been chosen since it is easily introduced without polymer degradation and it reacts via a “click” reaction with alkyne derivatives by Huisgens 1,3 dipolar cycloaddition. This reaction can be performed in water will be applied here for the micelle cross-linking by a bis-alkyne molecule bearing disulfide bridges. The hydrodynamic diameters of the cross-linked and non-cross-linked micelles formed are reported and the spherical shape of the micelles was confirmed by TEM. In addition, the micelle cross-linking was confirmed by addition of a 10-fold excess of DMF, a good solvent for both PEO and PCL blocks. In case of cross-linked systems, the core of the micelles is able to swell giving objects of larger size than in water (about 400 nm diameter). Again, in case of non-cross-linking micelles, dissociation is observed due to the solubilization of the azido-copolymers. The stealthiness of the cross-linked micelles was evaluated by the study of the complement consumption (CH50). The cytotoxicity of the cross-linked micelles and uptake were performed and achieved.

CONCLUSIONS: These new functional copolymers were all successfully micellized, reversibly cross-linked and are stealthy, which shows the efficiency of the developed cross-linking process and offers a series of nanocarriers to be tested further as it is show on first biological tests.

REFERENCES: S. Cajot, et al., Design of reversibly core cross-linked micelles sensitive to reductive environment, J. Control. Release (2011), doi:10.1016/j.jconrel.2011.03.026

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