Synthesis of functional amphiphilic copolymers for elaboration of third generation drug carrier

Synthetic and natural biodegrabable polymers have been an active topic of research in organic synthesis, as confirmed by the high number of publications and pattens in this field of research. During the last decade, a great effort was devoted to synthesis of polymers with well-defined composition and architecture for drug delivery in order to overcome the major drawbacks of traditionnal drug delivery systems such as diffusion limitation of the drug through the cell membrane, recognition of the drug as foreigner body.

In this work, it was proposed to prepare a new nanometric system able to encapsulated the drug inside the nanoparticule and release it in specific body region. The size of these new drug carriers has to be typically lower than 100 nm. They should be surrunded by a flexible hydrophilic crown, typically poly(ethylene oxide) which major role is to push back plasmatics proteins from recognition and thus to increase the lifetime of the particles in the circulatory system. It is also possible to induce a targeting by functionalization of the surface of a vector by a ligand officiating like agent of recognition.

The proposed strategy consists of the synthesis of amphiphilic copolymers for the formation of micellar systems for carrying molecules of biological interest. The hydrophobic sequence used is a poly-ε-caprolacton (PCL), a biodegradable and biocompatible aliphatic polyester. The hydrophilic sequence consists of end-functionnalized poly(ethylene oxide) (PEO), in order to obtain a third generation vector. The originality of this work lays in the architecture of amphiphilic and functional copolymers used. The PCL chains are grafted with end-functionnalized PEO segments.

The synthesis of these original amphiphilic copolymers is based on the grafting of PEO α,ω-telechelic under a functional PCL. In a second step, the micelles formed by this amphiphilic copolymer were functionalized, in aqueous medium, by the agent of targeting by a reductive amination.

First, the hydrophobic backbone of copolymer was obtained by copolymerization of the ε-caprolacton with the α-chloro-ε-caprolacton. Statistical copolymers of various compositions then underwent a nucleophilic substitution of the chlorides by azides functions to form the poly(αN_3εCL-co-εCL). In Parallel, some PEO α,ω heterobifunctionnals were prepared. The amphiphilic copolymers were then obtained by a reaction of cycloaddition 1,3 of Huisgen between alkynes of the PEO and the azides of the PCL chains. The fonctionnalization of this copolymers by the aminofluorescein, used like model molecule, by a reductive amination. These grafts copolymers forms spherical micelles with a diameter of 40 nm and larger aggregates (120 nm).

In this work, several amphiphilic graft copolymers (PCL-g-PEO) have been successfully synthesized by “click” chemistry. These polymers were then reacted with a hydrophilic molecule, the fluorescein, according to reductive amination reaction. In the future, this strategy will be extended to the functionalisation of the PEO grafts by a bioactive molecule, e.g. mannose, with the purpose to prepare third generation drug carrier.