# Reversibly cross-linked polymer micelle as smart drug delivery device

*Philippe Lecomte, Raphaël Riva, Sébastien Cajot, Christine Jérôme**

Centre for Education and Research on Macromolecules (CERM), University of Liège, Liège, Belgium
e-mail address c.jerome@ulg.ac.be

Since many years, the number of applications of polymers in the pharmaceutical field is steadily increasing, mostly for the elaboration of controlled drug delivery systems. For example, amphiphilic block copolymers present the remarkable property to self-assemble in water with formation, in most cases, of spherical micelles characterized by a hydrophobic core surrounded by a hydrophylic corona. Rapidly, the encapsulation of poorly soluble drugs in the micelle's core was investigated with the purpose to increase the solubility of the drug in aqueous media, prevent its degradation and decrease its toxicity.

This work aims at reporting the development of a smart drug delivery device based on new amphiphilic block copolymers made up of degradable aliphatic polyesters and bioeliminable poly(ethylene oxide). Typically, azide-functionalized amphiphilic block copolymers were synthesized allowing a post-modification of the micelle's core by the well-known copper azide-alkyne cycloaddition reaction (CuAAC), which is particularly adapted for the modification of aliphatic polyesters without any degradation[1,2]. Firstly, the reversible cross-linking of the micelle's core was investigated with the purpose to avoid a premature release of the drug due to a rapid dilution of the micellar solution below the critical micellar concentration (CMC) after injection in the bloodstream. For this purpose, a dialkyne bearing a disulfide bond was used as a cross-linking agent in order to allow thereafter the cleavage of the covalent bond in the presence of a reductive agent, such as glutathione, exclusively into the cytoplasm, so only after internalization of the vector.

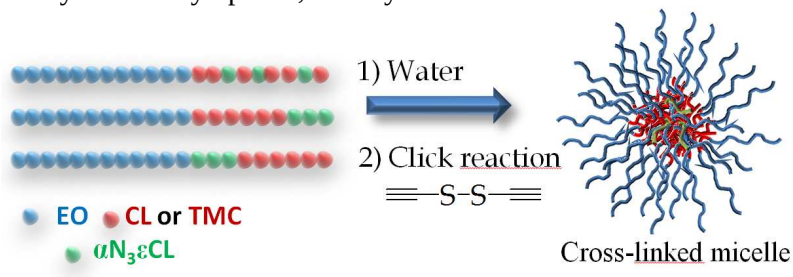


*Figure 1. Developed strategy for the synthesis of reversibly cross-linked micelle by CuAAC*

In parallel, the azide pendant groups were used to covalently graft a drug also by the CuAAC reaction. As model molecules, the grafting of alkyne bearing fluorescent dyes was investigated leading to the synthesis of fluorescent micelles. The effect of the architecture of the copolymer on the efficiency of the coupling reaction, realized directly inside the micelle's core, and the fate of the carrier after internalization were investigated.[3]

References

1) Riva, R.; Schmeits, S.; Stoffelbach, F.; Jérôme, C.; Jérôme, R.; Lecomte, P. *Chemical Communications* **2005**, 5334
2) Riva, R.; Schmeits, S.; Jérôme, C.; Jérôme, R.; Lecomte, P. *Macromolecules* **2007**, *40*, 796
3) Cajot, S.; Lecomte, P.; Jérôme, C.; Riva, R. *Polymer Chemistry* **2013**, *4*, 1025