# New pH-sensitive flower micelles for potential tumour targeting

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Over the last decade, polymeric 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. [1,2]

In principle, the micelle core is usually constructed with biodegradable hydrophobic polymers such as aliphatic polyesters, e.g. poly(ε-caprolactone) (PCL), which serves as a reservoir for the incorporation of various hydrophobic drugs. Water soluble poly(ethylene oxide) (PEO) is most frequently used to build the micelle corona because it is very efficient in preventing protein adsorption at surfaces and stabilizes the nanoparticles in blood compartment, giving rise to particles invisible to the body defence system called stealthy or long circulating particles.

Novel polymeric micellar drug delivery systems have been synthesized based on different macromolecular architectures that combine three different polymers, hydrophobic PCL, hydrophilic PEO and poly(2-vinylpyridine) (P2VP), a pH sensitive block, which is water-soluble upon protonation and hydrophobic at physiological pH.

By synthesizing appropriate macromolecular architectures, spherical micelles containing PCL-based core and PEO-based shell are expected to be formed in aqueous solution, while the P2VP block should belong to the core in neutral solution and to the shell in acidic solution. After intravenous injection, these small size (<100 nm) micelles should selectively accumulate in tumour tissues due to the EPR effect. Because of the acidic pH at the proximity of the tumours, the P2VP block is going to swell and to reach the corona, involving a decrease of the hydrophobic core so triggering the release of the drug.

The developed strategy to combine these polymers consists in the synthesis of an ABC linear triblock copolymer: P2VP-*b*-PEO-*b*-PCL. This new copolymer presents a pH response due to the presence of the P2VP sequence and forms spherical micelles in aqueous solvent which look like flowers when the P2VP block is unprotonated and causes the curvature of the PEO block (Figure 1).

This new architecture allows a potential tumour targeting. When the micelles are accumulated in the tumour tissues due to the EPR effect, the P2VP, the pH sensitive block, is protonated and present on the surface of the micelles. If a non-specific ligand (biotin) is fixed on the P2VP block, its exposition will be modulated by the pH decrease typical of tumour tissues. Therefore, when the micelles are present in the bloodstream and near healthy cells, the P2VP block is unprotonated and does not expose the biotin which also interacts with healthy cells. However, under acid conditions met in solid tumours, the P2VP is protonated and exposes the cell-interacting ligand on the surface of the micelles and so enables their internalization by biotin receptor-mediated endocytosis [3].

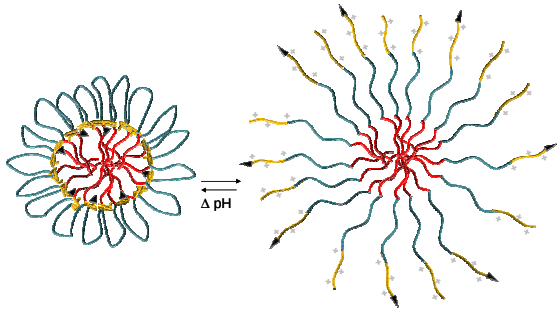


**Figure 1: micellar architecture vs. pH**

The self-assembly and the supramolecular architecture of the triblock copolymer in aqueous solution was studied by light scattering, TEM imaging and fluorescence techniques. Spherical micelles are obtained and exhibit the expected pH response thanks to the P2VP block. The potential targeting was also studied by Surface Plasmon Resonance which gives evidence to the shielding/deshielding of biotin in presence of an Au film covered by avidine.

With the aim of building up novel simple, stealthy and tumor selective drug delivery systems, a block of pH-responsive P2VP polymer has been added to commonly used PCL/PEO amphiphilic systems. Novel copolymer architecture has been synthesized and their micellization vs. pH has been carefully investigated. The potential targeting activity of this new architecture has been tested by Surface Plasmon Resonance.

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