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Smart nanocarriers for pH-triggered targeting and release of hydrophobic drugs ☆

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ABSTRACT

The use of hybrid pH-sensitive micelles based mainly on the $(PEO)_{129}(P2VP)_{43}(PCL)_{17}$ ABC miktoarm star copolymer as potential triggered drug delivery systems was investigated. Co-micellization of this star copolymer with a second copolymer labeled by a targeting ligand, i.e. biotin, on the pH sensitive block (poly-2-vinylpyridine) is considered here in order to impart possible active targeting of the tumor cells. Two architectures were studied for these labeled copolymers, i.e. a miktoarm star or a linear ABC terpolymer, and the respective hybrid micelles are compared in terms of cytotoxicity (cells viability) and cellular uptake (using fluorescent dye loaded micelles). Finally, the triggered drug release in the cytosol of tumor cells was investigated by studying, on the one hand, the lysosomal integrity after internalization and, on the other hand, the release profile in function of the pH.

1. Introduction

Tumor targeting of cytotoxic agent refers to the passive accumulation of drug nanocarriers to solid tumors, followed by active internalization into tumor cells. Passive targeting is achieved by the so-called "enhanced permeability and retention effect" when nanocarriers are formulated with a poly(ethylene oxide) (PEO) coating [1,2] to evade the reticuloendothelial system and subsequently accumulate in areas with characteristic leaky vasculature, such as tumor sites of injury, where the drainage is typically limited [3,4]. Most cytotoxic drugs act intracellularly and involve the internalization of the drug nanocarriers after passive accumulation. PEO coating may hinder cell interaction and, therefore, to increase the efficacy of nanocarriers, active targeting is explored by the incorporation of targeting moieties such as monoclonal antibodies [5] or ligands [6] at the surface of the nanocarriers [7,8]. Active targeting offers many benefits, including decreased side effects, owing to reduced accumulation in non-targeted organs, but they also present some sizeable drawbacks. First, a high density of ligands leads to accelerated removal of the targeted nanocarriers from the circulation and decreases the plasma residence time [1,9,10]. Second, some moieties, such as penetrating peptides [11] or biotin, lead to intracellular delivery into cytoplasm, but are not specific to tumor cells. Third, positive charges can enhance cellular interaction if they are present at the surface of the nanocarriers [12], but can also bring high toxicity due to non-specific binding [13–15].

In summary, an ideal nanocarrier to achieve the highest drug accumulation at the targeted site with limited uptake by non-targeted organs would combine both passive and active targeting. Recently, nanocarriers with a pH-sensitive shell [11,16–18] that can loose the most outer layer of the shell of the nanocarrier after arrival at the targeted site have been investigated. This removable corona offers the advantage of shielding the targeting ligands during circulation in the blood and exposing them once the nanocarrier has reached the tumor, making them available for receptor interaction. In these systems, the passive targeting can be achieved by the long circulation properties of the nanocarriers due to the PEO shell, and the active targeting is triggered by the loss of the PEO shedding corona through hydrolysis in an acidic environment, which exposes the targeting moieties and therefore increases the cellular uptake. Other reports also focus on the pH-triggered release of a drug once the carrier has reached the endosome by designing pH-sensitive nanoparticles able to destabilize and release their content in the acidic conditions of late endosomes [19–21].

Recently, researchers have reported on the synthesis [22] of novel star-shaped and pH-sensitive copolymers and on their micellization into pH-sensitive hybrid micelles [23]. These self-assembled micelles in aqueous media are based mainly on the pH-sensitive non-targeted $(PEO)_{129}(P2VP)_{43}(PCL)_{17}$ ABC star copolymer, which represents 90 wt.% of the hybrid micelle content, and which was co-micellized with 10 wt.% of a second pH-sensitive but targeted copolymer. As previously demonstrated [23], these spherical hybrid micelles have the peculiar ability to increase their diameter

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