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Divergent synthesis of dendrimer-like pH-responsive macromolecules through a combination of ATRP and ROP for controlled release of anti-cancer drug†

Roya Sedghi,[a] Hossein Abdi Oskooie,[a] Majid M. Heravi,[a] Mohammad Reza Nabid*[b] and Amir Hassan Zarnani[cd]

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This work is focused on the synthesis and controlled drug release behavior of 8-arm and 12-arm amphiphilic pH-responsive dendrimer-like block copolymers. To study the role of architecture and the number of arms at the critical micelle concentration (CMC) value, differential scanning calorimetry (DSC), micelle size and in vitro controlled release of drug, we investigated a series of 8-arm and 12-arm block copolymers. The poly(acrylic acid) (PAA)-carrying dendrimer-like block copolymers were synthesized in two main steps. First, a second-generation dendrimer-like poly(3-caprolactone) (PCL) was obtained by ring-opening polymerization (ROP) of 3-caprolactone (CL) from a bis and tris-hydroxylated core. For this goal, a conventional selective AB_2-type branching agent for the PCL chain ends was designed: the latter includes a carboxyl (A) group for its attachment to the PCL arm ends and two geminal hydroxyls (B_2) for the reiteration of the PCL growth as second generation using ROP. Subsequently, the hydroxyl-end groups quantitatively converted into bromoester groups as atom transfer radical polymerization (ATRP) initiating sites. The second step is the ATRP which thus served to grow poly(tBA) chains. After the hydrolysis of the t-butyl ester groups, amphiphilic, pH-responsive dendrimer-like block copolymers were obtained. Transmission electron microscopy (TEM) and dynamic light scattering (DLS) demonstrated that the micelles exhibit a spherical shape with a size range of 43–64 nm in diameter. As a model drug, quercetin was loaded into the obtained $2G_3(PAA)_8$ and $3G_3(PAA)_{12}$ micelles via a dialysis method for in vitro release studies and their response to pH variation was investigated. The in vitro cytotoxicity evaluation of the polymers clearly showed that both compounds are safe in a wide range of concentrations (several times above the CMC value).

Introduction

Amphiphilic block copolymers composed of hydrophilic and hydrophobic blocks have attracted significant attention in the past decade due to their ability to self-assemble into micelles with a core–shell structure in one of the block's selective solvents.[1–4] Beyond a particular polymer concentration, known as the CMC, micelles are formed from polymeric surfactant. Depending on some parameters, such as: the nature of the blocks, the length of the blocks, temperature and the architecture of the block copolymer, micelles might be formed in various shapes and show different aggregation behavior.[5–7] It was found

[a]Department of Chemistry, School of Science, Azzahra University, Vanak, Tehran, Iran
[b]Department of Chemistry, Shahid Beheshti University, G.C, 1983963113, Tehran, Iran. E-mail: m-nabid@sbu.ac.ir
[c]Nanobiotechnology Research Center, Avicenna Research Institute, ACECR, Tehran, Iran
[d]Immunology Research Center, Tehran University of Medical Sciences, Tehran, Iran

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