Controlling Amphiphilic Functional Block Copolymers’ Self-Assembly: From Structure to Size

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Abstract
Nanostructure of self-assembled particles, such as micelles and polymersomes play an important role in drug delivery, especially in tumor therapy. Particles with various structures and proper sizes (20~500 nm) are regarded as perfect candidates for controlled drug delivery due to controllable size that benefits the extended permeation and retention (EPR) and high payload that increases drug delivery efficiency. In this review, we summarized recent representative studies in controlling the size and structure of Amphiphilic block copolymers self-assembled particles with pH- and temperature responsiveness.

Keywords: Nanoparticles; Self-assembly; Size; Structure

Introduction
Nanostructure of self-assembled particles, such as micelles and polymersomes plays an important role in drug delivery, especially in tumor therapy. Particles with various structures are regarded as perfect candidates for controlled drug delivery due to highly selective cellular uptake and exceptional payload that increases drug delivery efficiency [1-4]. Size, as another benefit that can be controlled precisely from self-assembly provided the possibilities of positive targeting. Controllable size (20 ~ 500 nm) benefits the extended permeation and retention (EPR) and enhances the tumor therapy as reported by several studies [5-8].

Recently, it becomes an attractive trend to enable specialized functionalities on the self-assembled particles due to the tumor tissues’ specific micro-environment, such as low pH, high temperature and re-dox potential [9]. Environment-dependent selective drug release of particles with various structure and sizes pioneers a novel platform in cancer therapy with minimized side-effect and heighten drug delivery efficiency. In this review, we will summary current methods that are utilized in functionalizing self-assembled particles with different structures and sizes.

Amphiphilic block copolymers
Amphiphilic block copolymers are consisted of more than two covalent bond connected blocks with different affinities to solvent. Variable hydrophobicity and packing number of the polymer chains among all the blocks initiate the polymers’ self-assembly and result in particles with diverse morphology and structures, such as micelles, rods and polymersomes. Recent studies have shown the possibility to precisely control the self-assembly structure of block copolymers by targeting at dimensionless packing parameter, p as defined below:

\[ p = \frac{v}{a_0 l_c} \]

Where v is the volume of the hydrophobic chains, a0 is the optimal head group area, and lc is the length of the hydrophobic
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Applications of RAFT were also reported by Charleux and Tam et al. Different self-assembled structure can be achieved by varying the molecular weight distribution of desired macromolecules can be well controlled by RAFT polymerization. Besides the structure control over the block copolymers' self-assembly, RAFT also provides the possibility to functionalize block copolymers and the related self-assembled particles due to the ease of tuning properties on molecular level with various stimuli-responsiveness, such as pH, redox potential, light and temperature. Muller et al. have previously synthesized pH-responsive Amphiphilic block copolymer poly (acrylic acid)-b-polystyrene (PAA-b-PS) with different hydrophobicity [14]. Different self-assembled structure can be achieved by varying block length, solvent and preparation route. It was reported that as the hydrophobic content of Polystyrene continues increasing, the morphology of self-organized particles transit from spherical micelles, to worm-like micelles and polymersomes when it reaches the highest content. In addition, the formed particles present size increase when the chain length of polystyrene increases along with the structure transition occurs. It shifts from micelles of 26 nm to large polymersomes with 1μm diameter. Similar applications of RAFT were also reported by Charleux and Tam et al. resulting in both size and structure adjustable pH-responsive particles [15-17].

Thermo-responsive self-assemblies

Other than pH-responsiveness, temperature response of drug delivery systems. Recently, PVCL has been utilized to fabricate temperature responsive micelles and polymersomes that have various size ranges and temperature responsiveness. poly(vinyl pyrrolidone)-b-poly(N-vinylcaprolactam) (PVCL) exhibits high cell viability and low cytotoxicity making it a strong candidate in biomaterial applications such as drug delivery systems. Recently, PVCL has been utilized to fabricate temperature responsive micelles and polymersomes which have inherent limitation in vivo due to the lack of biocompatibility and toxicity after hydrolysis. Compared to PNIPAM related polymersomes, polyvinyl caprolactam (PVCL-PDMS-PVCL) et al. have all been developed to form temperature responsive particles with different morphology, structure and sizes [18-20]. Youk et al. have applied RAFT polymerization to synthesize Amphiphilic block polymers PVCL related system which has inherent limitation in vivo due to the LCST. It was reported that the elevated temperature (40-42 °C) in tumors will cause the vehicle morphology changes and trigger the cargo release. However, only a few studies on temperature-responsive particles with various structures have been reported whereas the majority is poly (N-isopropylacrylamide) (PNIPAM) -related system which has inherent limitation in vivo due to the lack of biocompatibility and toxicity after hydrolysis. Compared to PNIPAM related polymersomes, polyvinyl caprolactam (PVCL) exhibits high cell viability and low cytotoxicity making it a strong candidate in biomaterial applications such as drug delivery systems. Recently, PVCL has been utilized to fabricate temperature responsive micelles and polymersomes that have various size ranges and temperature responsiveness.

Conclusion and Perspectives

We summarized the recent progress of functional particles' self-assemblies from Amphiphilic block-copolymers and the control over size and structure. The significant achievements recently people made in controlling functional Amphiphilic block copolymers self-assembly will pave a new way for targeting drug delivery and give strong inspirations to researchers in both academia and industry for exploring new systems in efficient drug delivery. Enhanced therapeutic effects of well-designed particles provide enormous possibilities for scientists to overcome diseases associated with traditional chemotherapy methods. On the other...
hand, the role of particles’ shape has attracted more attentions in cellular uptake and targeting drug delivery. People utilized inorganic particles in polymer’s self-assembly process and achieved versatile shapes particle. The hybrid particles showed great potential and provide more possibilities for researchers to regulate the properties in self-assembly.

References


