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Submission: May 25, 2016; Published: June 17, 2016

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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

Abbreviations: EPR: Extended Permeation and Retention; RAFT: Reversible Addition-Fragmentation Chain Transfer; PAA-b-PSt: Poly (Acrylic Acid)-b-Polystyrene; PNIPAM: Poly (N-isopropylacrylamide); PVCL: Caprolactam; PVVON-PVCL: Poly (Vinyl Pyrrolidone)-b-poly (N-vinylcaprolactam); PEO-b-PVCL: Polyethylene Oxide-b-Poly(N-vinylcaprolactam); PVCL-PDMS-PVCL: Poly(N-vinylcaprolactam)-Poly(dimethylsiloxane)-Poly(N-vinylcaprolactam); PCL-b-PVCL: Poly (ε-caprolactone)-b-Poly (N-vinylcaprolactam)

Introduction

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 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, $a_0$ is the optimal head group area, and $l_c$ is the length of the hydrophobic
tail. The structure of particles can be predicted from the value of $p$. Spherical micelles are favored when $p$ is below 1/3, micellar rods can form when $p$ is between 1/3 and 1/2 whereas polymersomes are favored when $p$ is greater than 1/2 and less than 1 [10].

More recently, Discher and Eisenberg have attempted to unify the experimental results obtained from different Amphiphilic block copolymers [11-13]. Reasoning from a series of examples drawn from the literature, they proposed a unifying rule for the formation of polymersomes (polymer-based vesicles) in water: i.e. a ratio of the mass of the hydrophilic part to the total mass 35±10%. An asymmetric molecule with a cylindrical shape and $f$=50% presumably reflects a certain balance between its hydrated part and a disproportionately large hydrophobic fraction. Finally, molecules with $f$=45% are expected to form micelles and those with $f$<23% are expected to self-assemble into inverted structures. Base on this theory, the morphologies of assemblies from Amphiphilic block copolymers can also be expected.

Functionalization of amphiphilic block-copolymers and self-assemblies

It is always challenging to achieve Amphiphilic block copolymers with accurate controlled hydrophobic chain length and the self-assembly behavior. Reversible addition-fragmentation chain transfer (RAFT) polymerization is one of the most powerful and versatile methods among the existing controlled polymerizations that provide the possibility to precisely construct the PVCL based block copolymers with well controlled block chain length and composition. Both molecular weight and molecular weight distribution of desired macromolecules can be well controlled by RAFT polymerization.

PH-responsive self-assemblies

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-poly (styrene) (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 warm-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 vehicles self-assembled from block copolymers is also an appealing property that can be utilized to advance anti-cancer drug delivery. Temperature sensitivity is one of the most interesting properties in stimuli-responsive polymers. In addition, temperature is one of the safest, the most controllable and achievable external stimuli. Since the temperature responsive polymer segments can be incorporated to either micelle shells or cores, the polymeric micelles can be classified into two categories, i.e. micelles with temperature responsive polymers as hydrophilic shell-forming segments below the LCST and micelles with temperature responsive polymers as hydrophobic core-forming segments above 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. poly(N-vinyl pyrrolidone)-b-poly(N-vinylcaprolactam) (PVOPON-PVCL), polylethylene oxide-b-poly(N-vinylcaprolactam) (PEO-b-PVCL) and poly(N-vinylcaprolactam)-poly(dimethylsiloxane)-poly(N-vinylcaprolactam) (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 poly ($\varepsilon$-caprolactone)-b-poly (N-vinylcaprolactam) (PCL-b-PVCL) with controlled thermo-sensitiveness. Repetitive aggregation and dispersion were observed between heating and cooling cycles from 20 to 40 °C with formation of micelles at 55±25 nm. It was also reported that increasing hydrophilic component PVCL dominates the self-assembly process by decreasing the self-assembled particles’ size and shifts the responsiveness toward lower temperature range.

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.

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