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Preparation of multifunctional micelles from two different amphiphilic block copolymers

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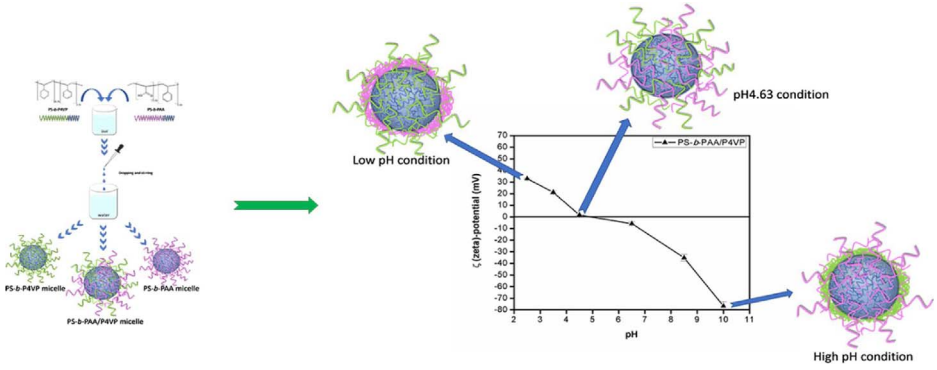
GRAPHICAL ABSTRACT



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ABSTRACT

Micelles are widely used in drug delivery owing to their attractive properties such as controllable drug release rates and the ability to target certain locations by conjugating with specific molecules. However, with the current state of understanding, only the core–shell and corona sites of micelles can be utilized. To form a micelle, each block copolymer was dissolved in DMF and then dropped into a polar solvent. Polymer micelles were formed through the agglomeration of the hydrophobic part that constituted a non-polar core and a hydrophilic corona. In this study, poly(styrene)-*block*-poly(4-vinylpyridine) (PS-*b*-P4VP) and poly(styrene)-*block*-poly(acrylic acid) (PS-*b*-PAA) formed micelles with a PS core in water. The hydrophobic PS domains were insoluble in the aqueous phase, which led to aggregation. Furthermore, from the pH-sensitive characteristic of weak polyelectrolyte, the changing of pH condition has an affected to the degree of ionization. Due to their characteristics, we prepared micelles from block copolymers at various pH values to increase the functionality of the micelles.

1. Introduction

Block copolymer micelles (BCMs) are popular therapeutic delivering molecules due to their ability to assemble and disassemble under certain conditions, allowing encapsulation and release of therapeutic molecules in specific environments [1–3]. Using the self-assembling ability of block copolymers in certain solvents, multicomponent nanostructures can be fabricated by incorporating particles in the core of BCMs [4,5]. Furthermore, BCMs combined with the layer-by-layer (LbL) assembly technique could allow the construction of layered structures of conjugates of BCMs and other molecules [6,7]. Usually, a variety of components such as therapeutic proteins, magnetic particles,

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and drugs are encapsulated and conjugated within BCMs through electrostatic interactions [8–11]. The BCM drug carriers effectively combine with other compounds to form multilayered films, enabling a well-controlled drug release [6,12]. By using external stimuli such as pH, temperature, and light, release and encapsulation of drugs with BCMs can be controlled [13–15]. For example, polymer micelles from poly(2-(diisopropylamino)ethyl methacrylate) and poly(2-(dibutylamino)ethyl methacrylate) were used in the gastrointestinal (GI) tract, since both the polymers dissolve in acidic solution and flocculate in alkaline solution, thereby responding to pH changes in the GI tract [16]. Polyethylene glycol (PEG) conjugated with 20% chlorin e6 (Ce 6) was used to prepare nanomicelles; the outer part of the micelles chelated with Cu^{2+} and used as an optical imaging agent in organic photodynamic therapy (PDT) [9]. Furthermore, a combination of monophosphoryl lipid A encapsulated within a poly(ethylene glycol)-*block*-poly(propylenesulfide) (PEG-*b*-PPS) block copolymer exhibited a role in cellular and humoral response [17].

Nowadays, the research on BCMs not only focuses on developing new methods and applications, but also on improving the properties of micelles, such as their drug loading efficiency, to achieve better therapeutic results. For example, cancer treatment was improved using poly (ethylene glycol)-*block*-poly(ε-caprolactone) (PEG-*b*-PCL) micelles loaded with multiple anticancer agents [18]. To deliver sparingly water-soluble anticancer agents and decrease the release rate of paclitaxel (PTX), the latter was conjugated with oligo(L-lactic acid) (o(LA)) and loaded into the PEG-*b*-PLA micelles, which displayed enhanced compatibility compared to that of unconjugated PTX. Further, on o(LA) conjugation, the amount of PTX loading increased from 11 to 54% [19]. Through the encapsulation and conjugation of BCM with other molecules, one can utilize the corona and core sites to improve the chemical and/or physical properties of the therapeutic micelle carriers. For the past ten years, micelles have been used as containers for delivering many kinds of molecules. Their loading, release, and targeting properties have steadily been improved. However, micelles prepared from a single block copolymer might limit the range of molecules that can be encapsulated. Hence, researchers have tried using multiple block copolymer-based, multifunctional micelles to incorporate different components [20,21].

In this study, highly functional micelles were formed from two different block copolymers with different charges, poly(styrene)-*block*-poly(acrylic acid) (PS-*b*-PAA) and poly(styrene)-*block*-poly(4-vinylpyridine) (PS-*b*-P4VP), as schematically shown in Fig. 1. The block copolymer solution was prepared by completely dissolving PS-*b*-PAA and PS-*b*-P4VP in DMF. Then, the solution was dropped into water (polar solvent) to form a mixed micelle. The micelle prepared at pH 4.63 is expected to consist of a PS core with PAA and P4VP corona. Using the pH-

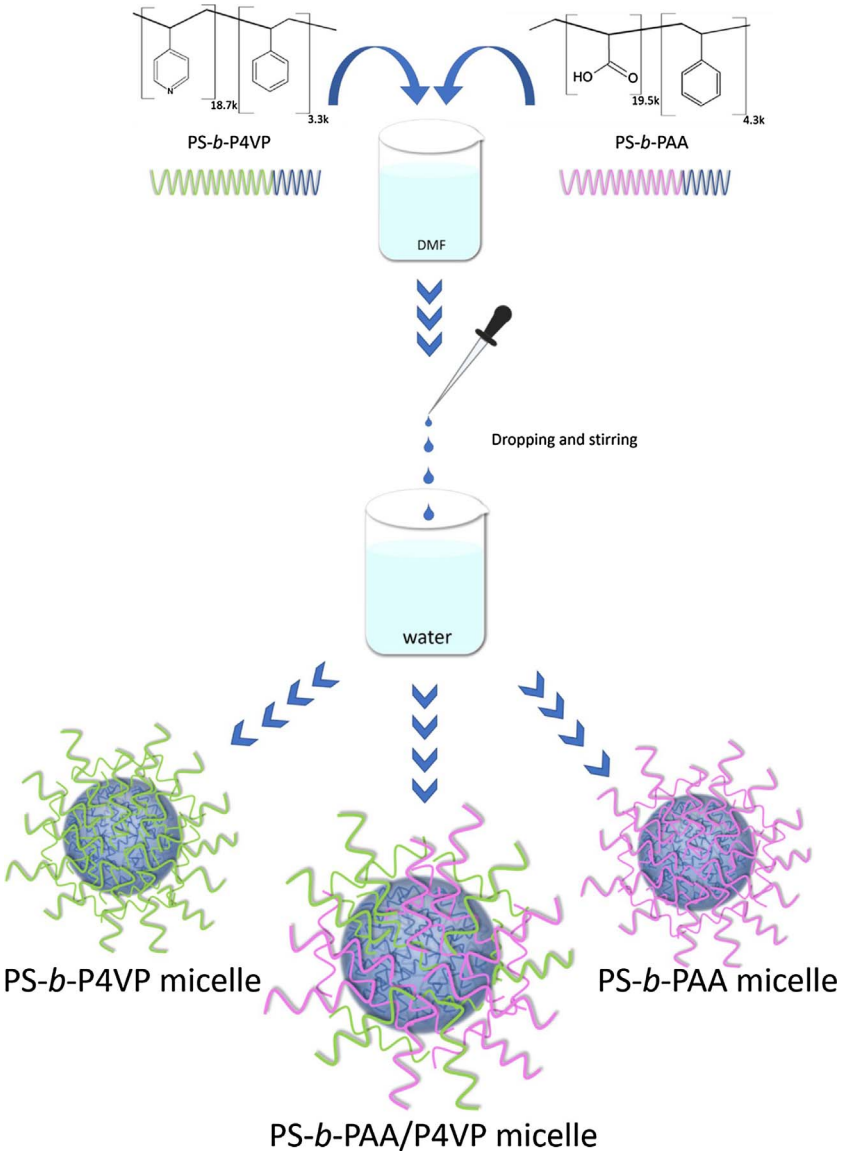

Fig 1. Scheme of micelle formation with two different block copolymers. PS-*b*-PAA and PS-*b*-P4VP were dissolved in DMF and assembled into micelles in DI water at pH 4.63.