Polymer Vesicles

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Thermally Responsive Polymer Vesicles

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Since lipid vesicles or "liposomes" were first reported four decades ago,[1] vesicles composed of small surfactant and lipid molecules have been the focus of extensive research as they play an important role in several biological functions including the storage and transportation of small molecules.[2] Cationic liposome–DNA complexes are the most studied nonviral gene-delivery system in humans. However, despite this plethora of information, liposomes still have not attained their full potential as drug and gene carriers partly because of their poor chemical, thermal, and mechanical stability.

It is well known that amphiphilic block copolymers can self-assemble into a variety of different morphologies in solution. These morphologies include spheres, rods, lamellae, and vesicles. The control of these different morphologies is based on the ability to manipulate factors such as the nature of the hydrophilic group, the number and length of the hydrophobic segments, the type and concentration of the added salt, and the solution temperature. It is primarily the value of the critical packing density that determines the special structures of the aggregates.[3] Amphiphilic block copolymers can self-assemble into vesicular structures. A number of examples of polymer vesicles and their properties were discussed in a review by Discher and Eisenberg.[4] Polymer vesicles have several advantages over vesicles formed by small amphiphilic molecules. Architectures of vesicle-forming polymers can be designed to implement desired physical, chemical, and biological functions in the resultant vesicles. Moreover, the robustness of polymer vesicles, arising mainly from the fact that polymer molecular weights are orders of magnitude greater than those of lipids, allows numerous potential applications.

Among others, polymer vesicles formed from polystyrene-*block*-poly(ethylene oxide) and polystyrene-*block*-poly(acrylic acid) have been intensively studied by Eisenberg and co-workers[5] and reviewed by several authors.[4,6–8] A typical method of forming vesicles from amphiphilic block copolymers involves the use of an organic solvent, such as THF, *N*,*N*-dimethylformamide (DMF), or 1,4-dioxane, to prepare a polymer solution, followed by mixing of the organic solution with water.[6,7,9–11] In this method, the self-assembly process is highly dependent on the rate of solvent mixing, which is difficult to control. Also, further purification processes are required, which can be time-consuming and problematic. In addition, many factors such as the copolymer composition, initial polymer concentration, nature of the solvent, temperature, and other additives can affect the morphology of the vesicles.[3]

To overcome these shortcomings in preparing vesicles from amphiphilic block copolymers, stimuli-responsive block copolymers that self-assemble into vesicles in the absence of organic solvents were reported. For example, Lecommandoux and co-workers[12] reported that polybutadiene-*block*-poly(L-glutamic acid) can form well-defined vesicular morphologies after its direct dissolution in basic aqueous solution. The size of the aggregate can be manipulated reversibly by changing the pH value and ionic strength. It is possible to covalently "capture" the morphology of the system and transform a transient supramolecularly self-assembled aggregate into a permanent shape-persistent stimuli-responsive nanoparticle by using the 1,2-vinyl bonds present in the polybutadiene block. The formation of polymer vesicles from polybutadiene-*block*-poly(L-glutamate)s was also reported by Kukula et al.[13] They showed that the size of the vesicles was independent of the pH of the solution and that the solvating peptide units could undergo a helix–coil transition without serious changes in the morphology of the vesicle.

Also, Lecommandoux and Rodriguez-Hernandez[14] reported pH-responsive "schizophrenic" vesicles based on poly(L-glutamic acid)-*block*-poly(L-lysine). The schizophrenic vesicles can be reversibly produced in moderately acidic or basic aqueous solutions from polypeptide diblock copolymers. These pH-sensitive nanoparticles are expected to be a promising candidate in macromolecular nanobiotechnology. Armes and Du[15] also reported pH-responsive self-cross-linking vesicles formed from poly(ethylene oxide)-*block*-poly{[2-(diethylamino)ethyl methacrylate]-*stat*-[3-(trimethoxysilyl)propyl methacrylate]} (PEO-*b*-P(DEA-*stat*-TMSPMA)). This block copolymer can form vesicles spontaneously in aqueous THF solution, with the hydrophilic PEO chains forming the corona and the pH-sensitive P(DEA-*stat*-TMSPMA) blocks located in the membrane walls. Their results show that the permeability of the vesicle walls is pH-sensitive. Starting with a highly biocompatible monomer, 2-(methacryloyloxy)ethyl phosphorylcholine (MPC), and a pH-sensitive monomer, 2-(diisopropylamino)ethyl methacrylate

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(DPA), Armes and co-workers[16] showed that by changing the pH of the solution from pH 2 to above 6 the PMPC-*b*-PDPA diblock copolymer can form biocompatible vesicles spontaneously, with the hydrophobic PDPA chains forming the vesicle walls. These vesicles are authentic polymeric analogues of conventional surfactant-based liposomes and are expected to find biomedical applications as nanosized delivery vehicles.

Recognition-induced vesicle formation was reported by Rotello and co-workers.[17] Polystyrene functionalized with diamidopyridine (DAP; recognition unit) self-assembles into microspheres in nonpolar media. The microspheres can be transformed into vesicles by adding thymine-functionalized polymer; the resultant vesicles can be transformed back to microspheres by the addition of DAP-functionalized polymer. Stimuli-responsive polypeptide vesicles obtained through conformation-specific assembly were reported by Deming and co-workers.[18]

Thermally responsive materials are advantageous for biological applications compared to pH-responsive materials as a result of the stringent pH requirements in the mammalian system. The first example of temperature-induced vesicle formation from the self-assembly of amphiphilic block copolymers directly in water was recently reported by McCormick and co-workers.[19] They reported that poly[*N*-(3-aminopropyl)-methacrylamide hydrochloride]-*block*-(*N*-isopropylacrylamide) (PAMPA-*b*-PNIPAM) with a well-controlled structure, synthesized through reversible addition–fragmentation chain-transfer (RAFT) polymerization, exists as unimers in aqueous solution and self-assembles into vesicles when the solution temperature is raised above the lower critical solution temperature of the PNIPAM chain. The transition from the unimer to the vesicle occurs reversibly in a narrow temperature range (2–3 K). The transition temperature depends on the composition of the block copolymer, with those polymers that have longer NIPAM block lengths exhibiting lower transition temperatures ranging from about 30 to 40 °C. It was also shown that both the concentration of the solution and the heating rate influence the average size and size distribution of the vesicles. Another important feature is that the vesicles can be structurally "locked" by ionic cross-linking of the PAMPA block with poly(sodium 2-acrylamido-2-methylpropanesulfonate) (PAMPS), an oppositely charged polyelectrolyte (Figure 1). Compared to chemically cross-linked vesicles,[20] ionically cross-linked systems are advantageous because of the facile nature of the cross-linking reaction (the process can be completed within a few minutes) and the reversibility of the cross-linking with added salt, which will facilitate the removal of the vesicles after biological applications.

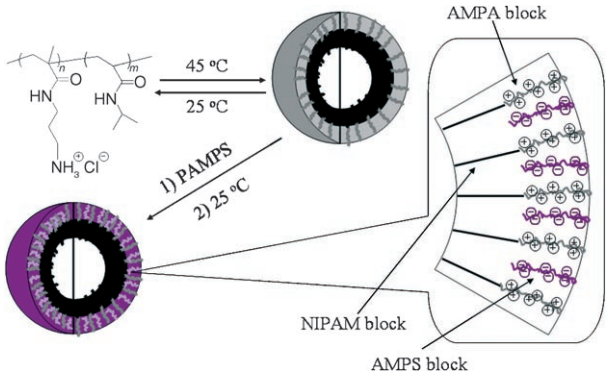

Figure 1. Schematic illustration of the formation of vesicles from PAMPA-*b*-PNIPAM diblock copolymers and their subsequent ionic cross-linking.[19]

The results from McCormick and co-workers[19] are an outgrowth of their earlier success in the synthesis of hydrophilic–hydrophobic block copolymers with well-defined architectures through RAFT polymerization. In the last few years, McCormick and co-workers have focused on the RAFT polymerization of hydrophilic (meth)acrylamide monomers[21] and the self-assembling behavior of these block copolymers in aqueous solution.[22] Following their finding that NIPAM, an important thermal responsive monomer, could easily be polymerized by RAFT in a controlled fashion,[23] they succeeded in synthesizing a series of NIPAM-containing block copolymers with well-defined block lengths. They found that these block copolymers could easily self-assemble into thermally responsive micelles in aqueous solution.[22,24] As reported by the groups of Wooley[25] and Liu,[26] polymer micelles can be stabilized by chemical cross-links of the micellar shell. These stabilized micelles are referred to as "shell-cross-linked" (SCL) micelles. McCormick and co-workers demonstrated that the incorporation of an active monomer unit (*N*-acryloxysuccinimide) into a NIPAM-containing block copolymer allowed for the facile formation of uniform SCL micelles by reaction with ethylenediamine in aqueous media.[22a] When cystamine is used as a cross-linking agent, these SCL micelles can be reversibly cleaved using either dithiothreitol or tris(2-carboxyethyl)phosphine; the degraded micelles can be re-cross-linked using cystamine as a thiol-exchange reagent. After thiol/disulfide exchange, the chemical structure of the re-formed SCL micelles remains the same as that before cleavage. Thus, the SCL micelles can be cleaved and re-cross-linked repeatedly in a fully reversible process. These SCL micelles may find an application as nanoscale drug-delivery vehicles, as the rate of drug release from the micelles and their surface properties (charge and stiffness) can be easily controlled.[27]

The significant breakthrough made by McCormick and co-workers in the research of polymer vesicles, especially that concerning the temperature-induced direct formation of polymer vesicles in water and SCL micelles based on polyelectrolyte complexes,[19] will give a strong impetus to researchers in both academia and industry to further explore the possibilities of practical applications of polymer vesicles in such areas

as coatings, drug-delivery systems, nanoparticles, nanoreactors, cosmetics, and pollution control.

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