Zwitterionic Polymer Surfactants for Drug Delivery

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ABSTRACT

Zwitterionic polymers have found a wide range of applications, e.g., as surface coatings and to modify nanoparticles, based on excellent non-fouling properties. These excellent properties were attributed to the unique superhydrophilicity of these polymers providing strong hydration effects. Here we introduced a so-called sharp contrast zwitterionic polymer surfactants. Each surfactant molecule composes a superhydrophilic zwitterionic polymer domain and a superhydrophobic domain. The polarity contrast between the two domains is drastically "sharper" than most conventional surfactant molecules. The synthetic route was discussed that led to the reaction between the two polarity distinct blocks to form the sharp contrast surfactant. The unique behavior of this sharp contrast surfactant and its use for drug delivery purposes was demonstrated. Compared with conventional stabilizing technologies, technologies based on zwitterionic polymer surfactant result novel colloid systems with unprecedented stability for drug delivery.

Keywords: zwitterion, drug delivery, nanomedicine

1 INTRODUCTION

Zwitterionic polymers have attracted increasing attention in the antifouling areas and biomedical applications. The use of zwitterionic polymers has been demonstrated in the form of surface coatings to effectively resist non-specific binding from proteins, cells, and full blood [1]. Such superior non-fouling property has been further demonstrated by immobilizing zwitterionic polymer networks on nearly any commonly used substrates through a glue-aided binding process [2]. The resulted zwitterionic coating was found to be ultra tough and durable by retaining non-fouling property after long-term immersion in water, long-term shearing in a buffer solution, long-term water flushing, repeated knife scratch and sandpaper abrasion [2]. The resulted coating further achieved long-term biofilm resistance to both Gram-positive and Gram-negative bacteria and fungi, which has rarely been reported in similar studies on antifouling surfaces [2].

Zwitterionic polymers have been further utilized to modify a nanoparticle. The non-fouling nature of the polymer has been expected to render a nanoparticle with excellent colloid stability and improve pharmacokinetics (PK) in blood for drug delivery. In one study where the zwitterionic polymer formed the surface of carbon-based nanoparticles, the protected nanoparticles maintained ultra high colloid stability in a protein solution, high salt solution, and after long-term incubation in phosphate buffered solution, while un-protected carbon-based nanoparticles severely aggregated in these conditions despite their surfaces were covered with small molecules of zwitterionic nature [3]. The ability for zwitterionic polymer protected nanoparticle to maintain colloid stability has been further extended to their stability upon a freeze-drying process. Nanoparticles protected with zwitterionic polymers maintained the size even without the presence of cryoprotectant during lyophilization, whereas other particle-protecting technologies including using polyethylene glycol (PEGylation) have to rely on cryoprotectant (e.g., 10%sucrose) to prevent particle aggregation [3, 4].

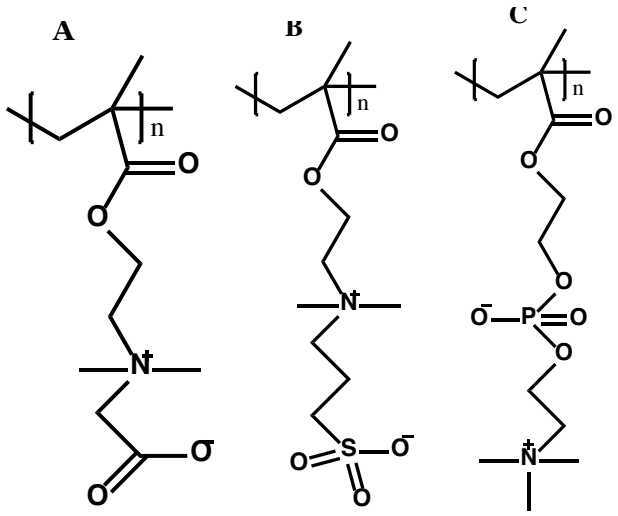

Figure 1: Representative molecular structures for zwitterionic polymers: (A) polymer(carboxybetaine), (B) poly(sulfobetaine), and (C) poly(phosphobetaine).

In another study where the zwitterionic polymer was used to conjugate with a protein drug, such as insulin, improved PK was observed compared with native insulin in a mouse model after intravenously injecting the modified and un-modified proteins [5]. This PK improvement was similar to a PEGylated insulin control whereas the molecular weight of PEG was the same as the zwitterionic polymer. Nevertheless, the intravenously injected PEGylated insulin had barely any improvement of pharmacological activity of lowering blood glucose

compared with native insulin, while the zwitterionic polymer conjugated insulin showed a 24% increase of the in vivo pharmacological activity. The superior performance of zwitterionic polymer has been attributed to both the improved pharmacokinetics and retained bioactivity of the modified insulin. Using PEG or other polymers for protein conjugation have been known for sacrificing the protein's bioactivity, likely due to the blocked protein activity center through hydrophobic-hydrophobic interaction and/or imposed steric hindrance [6]. The superhydrophilic nature of zwitterionic polymer circumvented these un-wanted interactions and significantly retained the protein bioactivity.

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Superhydrophilicity has been considered to contribute to the outstanding non-fouling property of zwitterionic polymers, as well as their unique capability to stabilize a nanoparticle. Then it is of particular interest to covalently link superhydrophilic zwitterionic polymers to hydrophobic molecules to form surfactant-like molecules. The resulting zwitterionic polymer surfactants are expected to self-assemble or to modify other types of colloid systems to achieve excellent colloid stability for drug delivery purposes.

2 SYNTHESIS OF ZWITTERIONIC POLYMER SURFACTANT

There has been a significant challenge in finding a common solvent to covalently linking a superhydrophilic zwitterionic polymer to a hydrophobic molecule or domain. A mixed solvent system may partially address this issue. For a controlled synthesis of zwitterionic polymer surfactant, a hydrophobic precursor for superhydrophilic zwitterionic polymer has been used (i.e., CB-tBu in Fig. 2A). CB-tBu monomer and its polymerized version, PCB-tBu (Fig. 2B) showed good solubility in organic solvents (e.g., acetonitrile and dimethylformamide). In these organic solvents, PCB-tBu was able to conjugate to hydrophobic blocks via its functional group R, followed by hydrolysis of the tBu ester groups by trifluoroacetic acid to regenerate zwitterionic carboxybetaine (CB) and obtain zwitterionic polymer surfactants, such as PLGA-PCB (Fig. 2C) [4] and DSPE-PCB (Fig. 2D) [7], where zwitterionic PCB was covalently linked to PLGA polymer and lipid DSPE, respectively.

The obtained zwitterionic polymer surfactants have a sharp polarity contrast between the superhydrophilic zwitterionic polymer domain and the hydrophobic domain. The polarity contrast is drastically "sharper" than most conventional surfactant molecules, so that the hydrophobic precursor method has to be involved.

3 ENHANCED STABILITY OF ZWITTERIONIC POLYMER SURFACTANT SYSTEMS

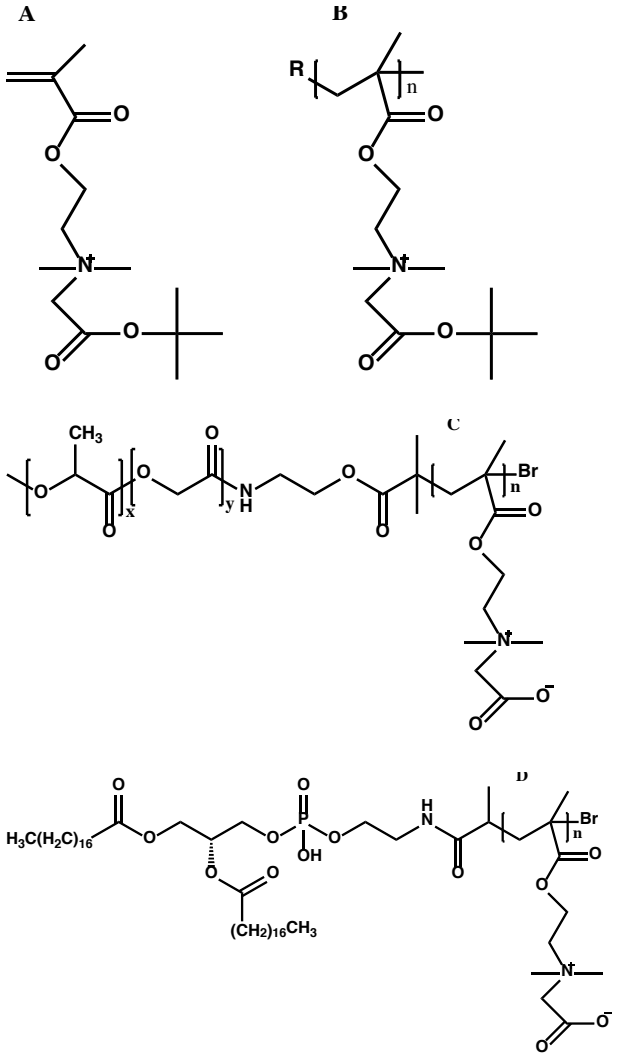

Figure 2: Molecular structures for (A) hydrophobic zwitterionic precursor monomer, CB-tBu, (B) hydrophobic zwitterionic precursor polymer, PCB-tBu, where R represents a reactive functional group for conjugation reaction, (C) obtained conjugation product with poly(lactic acid-co-glycolic acid) (PLGA), and (D) obtained conjugation product with 1,2-distearoyl-sn-glycero-3-phosphoethanolamine (DSPE).

The obtained PLGA-PCB self-assembled into nanoparticles of uniform size of ~150 nm through an appropriate nano-precipitation method [4]. The superhydrophilic PCB was expected to form the shell of the nanoparticle while the hydrophobic PLGA formed the core. The obtained nanoparticles were capable to encapsulate drugs, such as docetaxel, to achieve retention and sustained release of the drug (attributed to the function of PLGA). The obtained nanoparticles both with and without drug encapsulated showed great colloid stability after long-term incubated in bovine serum albumin solution and 100% fetal bovine serum, and through multiple cycled high-speed

centrifugation. More importantly, the nanoparticles with and without drug showed excellent stability through freeze-drying without the need for cryoprotectants. It should be noted that freeze-drying is required to prevent nanoparticle degradation, due to PLGA, or drug leakage in a solution form. The ultra protection of the nanoparticle based on the zwitterionic polymers has significant implications for this drug carrier platform for potential clinical and commercial applications.

The obtained DSPE-PCB has been used to modify a liposome assembly whereas the aqueous core of the vesicle was used to contain drugs such as doxorubicin [7]. This is a similar modification strategy to PEGylated liposome, where DSPE-PEG was used as a modifying component. PEGylated liposome has resulted in a series of drug formulations clinically used, such as DOXIL, which has doxorubicin encapsulated. In a side-by-side comparison between the DSPE-PCB modified liposome and the DSPE-PEG modified liposome, it was found that DSPE-PCB can uniquely stabilize the lipid membrane structure while DSPE-PEG tended to de-stabilize it. This stabilizing difference resulted in enhanced drug retention by DSPE-PCB modified liposome while drug leakage was found with DSPE-PEG modified liposome. Membrane stabilization and prevention of drug leakage can be generally achieved by using a large amount of cholesterol in the liposome composition, however, the DSPE-PCB modified liposome did not require any presence of cholesterol to achieve the stabilization and drug retention.

4 IMPROVED DRUG DELIVERY OF ZWITTERIONIC POLYMER SURFACTANT SYSTEMS

The DSPE-PCB modified liposomes and their drug formulations have been examined in rat and mouse models for their performance relating to drug delivery. For PK, DSPE-PCB modified liposomes achieved prolonged blood circulation time compared with un-modified liposomes. The circulation half-life was even longer than PEGylated counterpart. With doxorubicin encapsulated, the DSPE-PCB liposome (non-cholesterol containing) was compared with DOXIL, a cholesterol-containing PEGylated liposomal doxorubicin, in a C26 murine adenocarcinoma model. DSPE-PCB version achieved an identical survival curve to DOXIL, but showed a faster regression of tumors and thus a much earlier cure of the mice (~6 days earlier when all survived mice were cured).

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5 CONCLUSIONS

Superhydrophilicity of the zwitterionic polymer is an attractive feature enabling non-fouling and superior stabilization effect of nanoparticles. By synthesizing “sharp contrast” zwitterionic polymer surfactants, a variety of assembled nano-systems have been developed with enhanced stability and in vivo drug delivery advantage. Future zwitterionic polymer surfactant systems and their drug formulations are expected to outperform PEGylated systems and result in new generation nanomedicine to address a variety of disease diagnose and treatment challenge.

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