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Functional Zwitterionic Polymers on the Surface: Structures and Applications

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Abstract: Zwitterionic polymers are important in a wide range of industrial, biological and medical fields. Their chemical structures include an equal amount of anion and cation groups, and such structures give rise to many unique functionalities, such as temperature response, anti-polyelectrolyte effect, and strong hydration properties. In this review, we focus on the structures and applications of functional zwitterionic polymers on surfaces. We review three areas of applications according to the architecture of the polymeric systems: surface coating, complex solutions, and hydrogel. We review the simulation and theory work, and highlight some outlooks for further development.

1. Introduction

Zwitterionic polymers are characterized by the presence of zwitterionic groups, which is formed by an equal amount of anionic and cationic groups, on their molecular chains. These polymers contain strongly charged groups and high dipole moments, even though the sum of the charges is zero. The zwitterionic groups bind strongly to water molecules via electrostatically induced hydration.^[1] They show excellent lubrication and antifouling properties as well as very good biocompatibility, especially on surfaces.^[2] Therefore, zwitterionic polymers have many encouraging applications in a wide range of industrial, biological and medical fields.^[3]

Zwitterionic polymers can be classified into polybetaine and polyampholyte according to their chemical structure (Scheme 1). Polybetaine has the cationic and anionic groups located on the same monomer unit, such as poly(sulfobetaine methacrylate) (PSBMA),^[4] poly(carboxybetaine methacrylate) (PCBMA),^[5] and poly(2-methacryloyloxyethyl phosphorylcholine) (PMPC)^[6]. In contrast, polyampholyte has the opposite charge groups located on different monomer units. Examples of polyampholyte are 2-(dimethylamino)ethyl methacrylate, methyl methacrylate block copolymer (DMAEMA-MAA)^[7], and zwitterionic peptides.^[8]

The strong dipole and electrostatic interaction of the zwitterionic groups is the underlying cause that gives rise to many unique characteristics of zwitterionic polymers.^[9] One of the most distinctive properties of zwitterionic polymers is their relatively low solubility in pure water and that the solubility increases with the addition of salts. This effect is called the anti-polyelectrolyte effect, since non-zwitterionic polyelectrolytes exhibit the opposite solubility behavior with salt added.^[10] The essential reason causing the effect is a change in the zwitterionic polymer's conformation, from a collapsed state in the absence of salt to a

stretched state in the presence of salt. Another distinctive property of zwitterionic polymers is their super hydration ability,^[11] caused by the particularly strong electrostatic attraction between the polymer and the water molecules.

Zwitterionic polymers' properties are enriched by the multitude of available architectures. Among the different architectures, zwitterionic polymer-coated surfaces including membranes^[2] and brushes^[12] are the most prevailing. These surfaces exhibit adjustable conformational change and antifouling/anti-bacterial properties,^[13] which are particularly important to applications in membrane-based desalination. Another interesting architecture is the surface grafting of zwitterionic polymers onto nanoparticles. This makes adjustable

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((Author Portrait))

Scheme 1. Schematic representations of (a) polybetaine and (b) polyampholyte.

core-shell structures for metal ion detection.^[14] In recent years, zwitterionic polymers has also been incorporated into hydrogel materials, giving rise to temperature response and conductivity on skin surface.^[15]

Zwitterionic polymers' unique features have found wide applications, including antifouling, anti-ice,^[16] self-healing, water-oil separation,^[2a, 17] blood contacted sensor,^[18] and drug delivery.^[19] In particular, the application of zwitterionic polymers against fouling was inspired by the external surface of the mammalian cell phosphatidylcholine membrane.^[20] To create antifouling surfaces, various zwitterionic polymers, including PSBMA,^[21] PCBMA,^[5] and PMPC^[6] have been used. In addition, zwitterionic polymers can resist non-specific protein adsorption in blood serum^[22] and increase the stability of enzymes in urea without losing the bioactivity.^[23] Therefore, brushes of poly(carboxybetaine acrylamide) (PCBAA) and poly(3-caprolactone)-block-poly(diethylaminoethyl methacrylate)-block-poly(sulfobetaine methacrylate) (PCL-PDEA-PSBMA) with perfect biocompatibility can be used as blood contacted sensor and drug delivery.^[24]

There are many reviews have summarized various aspects of zwitterionic polymers.^[3, 25] Lowe and McCormick summarized the synthesis methods and solution properties of zwitterionic polymers of both the polyampholytes and the polybetaines.^[25a] Shao and Jiang reported the differences between zwitterionic and nonionic materials, as well as the differences among zwitterionic materials such as carboxybetaine (CB) and sulfobetaine (SB).^[25b] Zheng et al. reviewed the applications of zwitterionic polymers, including blood contacted sensor, drug delivery, and marine coating.^[3] Xiao et al. gave an overview of the salt-responsive zwitterionic polymer brushes with various functionalities including tunable surface lubrication, switchable fouling-antifouling property, salt-induced anti-microbial activity, and salt-responsive anti-polyelectrolyte effect.^[25c] Xu et al. reviewed the structure and functionality of polyelectrolyte brushes,^[25d] systematically

Figure 1. Chemical Structures of PSBMA, PCBMA and PMPC.

the basic properties of the polyelectrolyte and zwitterionic polymer brushes, including the chemical structures, substrates, film thickness, grafting density, and fouling properties.

Due to the significant efforts made on the design and application of zwitterionic polymers, much progress has been made in recent years on functional zwitterionic polymers. In this review, we provide a summary on the most recent progress of functional zwitterionic polymers on surfaces. We organize this review article in three aspects: (1) chemical structures, (2) applications, and (3) simulations and theories. Despite the great progress on the development of zwitterionic polymers with various functions, the development of theoretical methods for such polymers are lagging behind, such that modelling tools have not been fully exploited to aid the design and development of functional zwitterionic polymers. Therefore, we feel that it is imperative to provide an overview of the current progress on the theory and modeling of zwitterionic polymers. In this review, we first give a brief introduction on zwitterionic polymers, followed by the chemical structures and applications of zwitterionic polymers surfaces reported in recent years in Section 2 and Section 3. In Section 4, we offer our view on the future development of theory and simulation of zwitterionic polymers. Finally, we provide some outlooks. We hope that this review will stimulate more creative thinking and innovative ideas to advance research in functional zwitterionic polymer surfaces.

2. Chemical Structure

2.1. Polybetaine

The first example of polybetaine was reported in 1957.^[26] The polybetaine carries both cationic and anionic groups on the same monomer unit. In general, the cationic moiety is a quaternary ammonium, and the anionic moiety can be sulfonate, carboxylate, and phosphonate, etc. According to the anionic moieties, we can classify the zwitterionic polymers as sulfobetaine (SB),^[27] carboxybetaine (CB)^[28] and phosphorylcholine (PC).^[12a] Besides that, some new types of polybetaine like amino acid grafted to the

Figure 2. (a) Transport properties of TFC and TFC-PSBMA membranes, PDA stands for polydopamine. Adapted with permission from Ref. [13]. Copyright (2017) American Chemical Society. (b) Static water and oil (GS-1) contact angles of the membrane surfaces and cyclic oil/water separation tests for the pristine PES membrane and PES/P3 membrane, where P3 stands for P(CBMA-co-TFOA). Adapted with permission from Ref. [29]. Copyright (2016) the Royal Society of Chemistry. (c) Normal interaction forces between two PDA/P(DMA-co-MPC)-coated mica surfaces in PBS buffer. Adapted with permission from Ref. [12a]. Copyright (2018) American Chemical Society. (d) Chemical structure of PGLuDMA. pH-Responsiveness of the glutamic acid in the polymer side chains exposed to the polymer film/water interface. Adapted with permission from Ref. [30]. Copyright (2015) the Royal Society of Chemistry.

end of side chain units have been designed in recent years.^[30–31] Here, we list the chemical structures of the most commonly used polybetaine in Figure 1. Due to the positive and negative charges of the monomers, the polybetaines are highly hydrated and water soluble in solution.^[8] It makes them widely used in biomedicine. For example, Obstals et al. tested the recalcification times and adhesion of platelets of three polybetaines, PMPC, PSBMA and poly((3-methacryloylamino-propyl)-(2-carboxy-ethyl) dimethyl-ammonium carboxybetaine methacrylamide) (PCBMAA), grafted directly from poly(4-methyl-1-pentene) (TPX) membranes. There was a good improvement in the recalcification time (a proxy of initiation of coagulation) and hemocompatibility comparing with the non-modified counterpart.^[32] The authors found that polymer brushes based on PCMA resulted in the best hemocompatibility. In the following part of this section, we introduce the polybetaines based on the classifications shown in Figure 1 to highlight the properties of surface tethered polybetaines due to their unique chemical structures.

PSBMA is the most commonly studied zwitterionic polybetaine. PSBMA has an upper critical solubility temperature (UCST) and exhibits a temperature-controlled wetting performance.^[33] Niskanen et al. prepared a star shaped PSBMA and showed that the interactions between sodium dodecyl sulfate

(SDS) or cetyl trimethyl ammonium bromide (CTAB) and PSBMA has a significant effect on the thermal transition of the polymer.^[34] Increasing the molecular weight, polymer concentration, or local concentration of side chains all push the cloud point of PSBMA to higher temperatures. Further studies showed that SDS can form hydrophobic domains along the polymer chains, preventing the polymers from making a thermal phase transition. The hydrophobic domains of the PSBMA–SDS complexes can be used to stabilize curcumin in aqueous solutions and to increase the intensity of its fluorescent emission. Rodríguez-Hidalgo et al. built a coarse-grained model for poly(2-(N-morpholino) ethyl methacrylate)–PSBMA (PMEMA–PSBMA) copolymer by dissipative particle dynamics method.^[35] The simulation results showed that the PMEMA–PSBMA system developed two different micellar states with a well-defined core–corona structure due to the lower critical solubility temperature (LCST) and UCST. The adjustable critical solution temperatures induced a core–corona structure can be controlled and predicted depending on the intensity of the stimulus applied. As for the surface properties of PSBMA, Liu et al. grafted PSBMA on polyamide thin-film composite (TFC) membrane by controlled architecture of zwitterionic polymer brush layer.^[13] Fouling resistance was characterized by chemical force microscopy and adsorption

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propensity of proteins/bacteria. The microscopy results showed that the micrograph for the TFC-PSBMA membrane exhibited virtually no fluorescence, comparing with the TFC and TFC-PDA membrane. Corresponding quantitative adsorption propensity showed that the percentages of colony-forming of TFC and TFC-PDA membrane were nearly 20 times and 5 times that of TFC-PSBMA membrane, respectively. In addition to the excellent fouling resistance, the modified membrane exhibited significantly lower water flux decline comparing to the pristine TFC membrane. (Figure 2(a)) Such membranes have the potential for water treatment membranes without compromising intrinsic transport properties. However, we should also note that surface modification may not promise a better membrane performance in long term as shown in the study of Tirado et al.^[36] The results of long-time biofouling and flux recovery tests emphasized the importance of long-term filtration experiments as an ultimate test for assessing bio-fouling resistance of modified desalination membranes.

PCBMA is another commonly studied zwitterionic polybetaine. Wang et al. modified the aromatic polyamide reverse osmosis membrane (TE membrane) with PCBMA.^[37] The TE membrane was modified by the redox initiated graft polymerization of 2-(dimethylamino) ethyl methacrylate (DMAEMA), followed by the surface quaternization reaction with 3-bromopropionic acid to obtain the PCBMA chains on the membrane surface. The water flux tests shown that PCBMA-modified membrane had better resistance to nonspecific bovine serum albumin and lysozyme adsorption. The membrane also exhibited better anti-microbial property than the pristine TE membrane. The copolymers of PCBMA also have good surface properties such as oil-fouling resistant and oil/water separation. Zhang et al. synthesized poly(carboxyl betain methyl acrylamide-co-3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl acrylate) (P(CBMA-co-TFOA)) by obtaining the PCBMA block from poly(N-[3-(Dimethylamino) propyl] methacrylamide) (PDMAEMA) block.^[29] After adding P(CBMA-co-TFOA) as the additives into poly(ether sulfone) (PES) membranes, the membranes demonstrated excellent oil-fouling resistant capacity and remarkable antifouling stability in oil/water emulsion separation tests (Figure 2(b)).

PMPC contains a zwitterionic phosphorylcholine group composed of a positively charged trimethylammonium cation and a negatively charged phosphate anion. This structure also appears as the head group of phospholipids in the cell membrane. 2-methacryloyloxyethyl phosphorylcholine (MPC) and its copolymers are biocompatible, showing lower cytotoxicity compared to other polymers like polyethylene glycol (PEG).^[38] Münch et al. presented a multifunctional polymer coating with the zwitterionic MPC unit as the functional group and the photoreactive 4-benzophenyl methacrylate (BPO) using a fast one-step deposition and crosslinking process by UV-irradiation.^[39] The results indicate that an exactly balanced ratio between thickness of the dry films, degree of swelling, and water contact angle is necessary to create surface coatings with tailored properties. The study showed that films of MPC with a content of 1% BPO delivered optimal oil repellency and high antifouling capability tested by cell adsorption experiments of Gram-negative (*E. coli*) and Gram-positive (*B. subtilis*) bacteria as well as of the yeast fungus *S. cerevisiae*. Zhang et al. quantitatively investigated the responses of surface-grown biocompatible brushes of PMPC to different types of salt using ellipsometry.^[12b] Their results showed that the addition of salts did not change the

hydration state nor the structure of PMPC brushes at all concentration ranges. However, the addition of ions could change the balance of intra- and intermolecular forces as well as the stiffness of PMPC molecules. The addition of SO_4^{2-} also increased the friction coefficient of the PMPC brushes. The copolymers of polydopamine (PDA) and PMPC, poly(dopamine methacrylamide-co-2-methacryloyloxyethyl phosphorylcholine) (P(DMA-co-MPC)), also showed excellent antifouling and lubrication features.^[12a] The lubrication of the PDA/P(DMA-co-MPC) coating exhibited Amontons-like behaviors in phosphate-buffered saline: the friction was directly proportional to the applied load but independent of the shear velocity (Figure 2(c)).

Amino acids, having a carboxyl group ($-\text{COOH}$) and an amine group ($-\text{NH}_2$), are well-known natural zwitterions at the intermediate pH ($\text{pK}_a^{\text{COOH}} < \text{pH} < \text{pK}_a^{\text{NH}_3^+}$). Amino acid-based zwitterionic polymers have better biocompatibility than many synthetic zwitterionic polymers.^[30-31] Fujii et al. synthesized a zwitterionic polymer containing the side chains of glutamic acid grafted to the end of a dodecyl hydrocarbon chain PGLuDMA (Figure 2(d)).^[30] The polymer films made by PGLuDMA exhibited charge selective protein adsorption behavior due to the weak synergistic interaction between the α -amine and the γ -carboxylic acid. Furthermore, Liu et al. synthesized a group of amino acid-based zwitterionic polymers (pAAZ) derived from natural amino acids including serine, ornithine, lysine, aspartic acid, and glutamic acid.^[31] The pAAZ brushes showed excellent structural stability in phosphate-buffered saline for long term suppression to bacterial attachment, which makes up for the shortcomings of traditional zwitterionic polymers.

2.2. Polyampholyte

The polymer films made by synthetic polyampholytes were first reported in the 1950s via conventional free radical polymerization techniques.^[40] However, in recent years, the amino acid based polyampholytes are the most widely used.^[41] One example is the zwitterionic peptides, Ye et al. compared the antifouling performance of a peptide with alternating positive and negative residues (CRERERE) and neutral residues (CYSYSYS) as shown in Figure 3a.^[8] CRERERE attached onto gold substrates showed lower contact angles and surface height by atomic force microscopy (AFM) than CYSYSYS. In addition, nonspecific protein adsorption with single-protein solutions and natural complex media indicated that CRERERE has higher antifouling ability than CYSYSYS. For example, the contact angles of Au-CYSYSYS and Au-CRERERE were 39.7° and 19.6° , respectively. For CYSYSYS, The adsorptions of lysozyme and cow milk were nearly 6 times and 7.25 times than CRERERE. Further molecular dynamics (MD) simulations indicated that the strong surface hydration of peptide self-assembled monolayers contributes to its fouling resistance by impeding interactions with proteins. Cui et al. designed another zwitterionic peptides (sequence of EESKSESKSGGGGC) for the sensitive and selective detection of alpha-fetoprotein (AFP).^[42] The obtained biosensing interface responded to the target AFP with high selectivity and sensitivity. The fabricated aptamer-sensor exhibited promising feasibility for the quantification analysis of AFP in real human serum samples. As for the block polymer of amino acid based polyampholytes, Piatkovsky et al. prepared a polystyrene (PS)-based copolymer with an alternating lysine-glutamic acid peptide PS-*b*-(KE)₁₅.^[43]

Figure 3. (a) Molecular structures of an amphiphilic peptide with a sequence of CYSYSYS and CRERERE, schematic illustration of the attachment of peptide self-assembled monolayers on the Au surfaces. Adapted with permission from Ref. [8]. Copyright (2015) American Chemical Society. (b) Physicochemical characterization of ZIPPs. ZIPPs and ELPs by circular dichroism spectroscopy, dynamic light scattering (DLS), mobility, and biodistribution of ZIPPs. Adapted with permission from Ref. [44]. Copyright (2019) Elsevier. (c) Antifouling behaviors of the zwitterionic peptide monolayers. Adapted with permission from Ref. [45]. Copyright (2020) American Chemical Society.

After coating ultrafiltration (UF) and reverse-osmosis (RO) membranes with PS-*b*-(KE)₁₅, they found significantly reduced fouling on the membranes. The mechanism responsible for the reduced fouling of the modified membranes was found to be the reduction of the coating – attributed to the adsorption of the polyampholytes. The authors also found that the presence of calcium abolished the antifouling effects of the PS-*b*-(KE)₁₅ layer on both UF and RO membranes. Banskota et al. designed zwitterionic polypeptides (ZIPPs) with a repetitive (VPX₁X₂G)_n motif, where X₁ and X₂ are cationic and anionic amino acids (Figure 3b).^[44] After testing of pharmacokinetics, biodistribution and activity of (glucagon-like peptide-1) GLP1 fusions (Figure 3c), they demonstrated that a combination of lysine and glutamic acid in the ZIPP conferred superior pharmacokinetics for both intravenous and subcutaneous administration comparing to uncharged control polypeptides of the same molecular weight. Besides, Li et al. recently studied the chain length and the monovalent/divalent ions on the antifouling properties of zwitterionic peptides. The sequences are including C(KE)₅, CP₄S₁₀, CP₄(KE)₃, CP₄(KE)₅, CP₄(KE)₈, CP₄(KE)₁₀, CP₄(KE)₁₅, and CP₄(KE)₂₀.^[45] The results demonstrated that longer zwitterionic peptides exhibit better antifouling performance and divalent ions significantly reduce the antifouling performance (Figure 3c). The MD simulations indicated that the loss of antifouling performances are caused by inter-chain electrostatic crosslinks of divalent ions.

Despite of numerous studies on the functionality and applications of polybetaines and polyampholytes, there are relatively fewer studies on the fundamental mechanisms of the properties of these polymers. It is still not very clear how the lubrication and antibacterial performance are affected by the degree of polymerization, grafting density, as well as inter- and intrachain interactions. Additionally, the persistence of surface modification is another important factor for the applications that needs to be further investigated. For polyampholytes, there are not much researches in recent years even though many

polyampholytes were synthesized before 2000s.^[46] With the development of amino acid polymerization methods,^[47] we believe that there will be more related work to expand the family of poly(amino acids) and even polyampholyte. In addition, the comparative studies like hydration, antifouling and conformations etc. caused by chemical structures of polybetaine and polyampholyte will be a key research topic of zwitterionic polymers.

3. Application

3.1. Zwitterionic Polymers for Surface Coating

Surface coatings of zwitterionic polymers have gained great attention from both academia and industry because of their potential applications such as antifouling, lubrication, and anti-ice/frog, etc. Zwitterionic polymer-based surface coatings can be divided into two categories: surface brush and adhering membrane. The outstanding antifouling performance of zwitterionic polymer brushes was systematically proved by Higaki et al.^[48] Specifically, the anti-fouling character of polymer brushes against marine organisms was investigated by performing settlement tests with barnacle cypris larvae, mussel larvae, and marine bacteria. The testing zwitterionic polymer brushes, including PMPC, poly(3-[dimethyl (2-methacryloyloxyethyl) ammonio]ethanesulfonate)(PMAES), poly(3-[dimethyl(2-methacryloyloxyethyl) ammonio]propanesulfonate) (PMAPS) and poly(3-[dimethyl(2-methacryloyloxyethyl)ammonio]butanesulfonate) (PMABS) exhibited versatile anti-fouling characters for the marine organisms examined (Figure 4a). After a careful comparison, the authors gave a trend of efficiency of different types of polymer brushes at reducing bacterial colonization: zwitterionic polyelectrolytes > hydrophobic polymers

Figure 4. (a) Changes of friction coefficients of PVBIPS brushes of ~68 nm thickness in response to NaCl solutions with different concentrations. Schematic of chain conformation from a collapse state to an extended state induced by salt solutions. Adapted with permission from Ref. [49]. Copyright (2015) American Chemical Society. (b) Photos of water droplets before and after contacting on the gradient surface and uniform (with a 15 min BCS reaction time) PDMA/PS/KHI surfaces, respectively. Adapted with permission from Ref. [50]. Copyright (2015) Elsevier. (c) Digital photos of different samples: bare glass, PSBMA-SH and PSBVI-SH, after storage in a freezer at -20°C for 30 min (upper) and 24 h (bottom), taken immediately after transfer to ambient lab conditions (temperature $\sim 21^{\circ}\text{C}$, 88% relative humidity). Light transmission at the normal incident angle for various samples after 30 min and 24 h storage in a freezer at -20°C , immediately after transfer to ambient lab conditions (temperature $\sim 21^{\circ}\text{C}$, 88% relative humidity). Adapted with permission from Ref. [16b]. Copyright (2016) the Royal Society of Chemistry.

> unmodified Si wafer > cationic polyelectrolyte. Yang et al. synthesized and characterized zwitterionic poly(3-(1-(4-vinylbenzyl)-1*H*-imidazol-3-ium-3-yl) propane-1-sulfonate) (PVBIPS) brushes as ion-responsive smart surfaces via surface-initiated atom transfer radical polymerization (SI-ATRP).^[49] In addition to their lubrication and antifouling properties, PVBIPS brushes were also salt-responsive. When adding salt, the brushes exhibited “anti-polyelectrolyte effect” behaviors: brushes were extended and the corresponding lubrication performance was also improved (Figure 4b). This work provides a controllable antifouling and lubrication strategy for multifunctional applications. Beyond the properties of antifouling, Ren et al. fabricated a complementary density gradient of poly(3-dimethylmethacryloyloxyethyl ammonium propane sulfonate) (PDMA/PS) and KHIFSDSSE peptide (KHI, derived from neural cell adhesion molecule NCAM which mediates cell-cell adhesion).^[50] By combining fluorescent labeling, X-ray photoelectron spectrometry (XPS) and quartz crystal microbalance with dissipation (QCM-D) techniques, the authors showed that Schwann cells migrated directionally toward the gradient direction (higher KHI density) with significantly enhanced mobility (Figure 4c). The complementary gradient highlighted a perspective on designing complex biomaterials for desired tissue regeneration. Kim et al. studied the self-assembly of random copolymer brushes, PECH-DMAPS_m (where *m* is the mol% of DMAPS end group), at an air–water interface using surface pressure–area isotherms, infrared spectroscopy, and X-ray reflectivity analysis. This random copolymer always showed Langmuir monolayer structures at the air–water interface, which were basically

composed of a hydrophobic bristle phase in the air side and a hydrophilic backbone and bristle phase in the water side. The well-balanced hydrophilicity and hydrophobicity of the copolymer enables the self-assembly of the monolayer structure.^[51] Ezzat and Huang designed a zwitterionic polymer brush coatings with excellent anti-fog and anti-frost properties.^[16b] They prepared PSBMA and poly(sulfobetaine vinylimidazole) (PSBVI) brushes by precisely controlling the thicknesses of the polymer thin films. Tested by visually and UV-vis spectroscopy, the results indicated that the optical transmittance of substrates modified with superhydrophilic polymer coatings under both hot and cold fogging conditions was very high (Figure 4d). In addition, PSBMA coating was developed to endow substrates with superhydrophilicity and underwater superoleophobicity for use in oil/water and emulsion separation.^[52] These studies inspire further investigations towards the fabrication of zwitterionic polymer decorated surfaces with novel properties and applications.

Copolymers of zwitterionic polymers are widely used for making anti-fouling and anti-fogging coatings. Wang et al. prepared copolymer of PSBMA and poly(ethylene glycol)dimethacrylate (PEGDMA) coating on 3-aminopropyl triethoxysilane modified silicon.^[53] Besides the excellent anti-biofouling properties, the zwitterionic polymer network coatings can be repaired in water with repaired mechanical properties and the anti-biofouling characteristics. (Figure 5a). Polyamide membrane was synthesized via interfacial polymerization incorporating zwitterionic copolymers, poly(2-(dimethylamino) ethyl methacrylate)-co-poly(sulfobetaine methacrylate) (PDMAEMA-co-PSBMA).^[54] The membrane showed excellent

Figure 5. (a) Tapping mode AFM images ($25 \times 25 \text{ nm}^2$) in air of zwitterionic polymer network coatings. Mechanically damaged surface. Same surface after immersing into water for 1 min and drying by argon. Adapted with permission from Ref. [53]. Copyright (2017) the Royal Society of Chemistry. (b) Organic fouling on membranes prepared by interfacial polymerization using only MPD (left) and pure zwitterionic copolymer (right) as amine-containing monomers in the aqueous solutions, assessed by the filtration of a BSA solution in PBS buffer under 2 bar transmembrane pressure. Initial buffer flux: $20 \text{ L m}^{-2} \text{ h}^{-1}$. BSA rejection: $\sim 100\%$. Adapted with permission from Ref. [54]. Copyright (2019) American Chemical Society.

fouling resistance by comparing the protein adsorption and bacteria fouling to a pristine membrane without zwitterionic segments. With the increasing of zwitterionic polymer fraction, the modified membrane became more hydrophilic and achieved a 27-fold higher flux than that of the pristine membrane, along with good selectivity in the nanofiltration range (Figure 5b). zwitterionic copolymer coatings also showed good anti-fog and oil-fouling resistance properties, such as polyhedral oligomeric silsesquioxane-poly[2-(dimethylamino)-ethyl methacrylate]-*block*-poly(sulfobetaine methacrylate) (POSS-PDMAEMA-*b*-PSBMA).^[55]

3.2. Zwitterionic Polymers for Complex Solutions

Zwitterionic polymers can be dispersed in solution to stabilize hydrophobic compounds.^[34] Qian et al. reported a strategy for effective adsorption of cesium from aqueous solution by using a Prussian blue nanocrystal-crosslinked thermosensitive copolymer of PSBMA.^[56] Above the UCST, the adsorption efficiency of cesium ions was enhanced, because of the increasing of PSBMA dispersity. The adsorption showed high selectivity towards cesium ions and kinetically followed a pseudo-second-order model. PB-PSBMA could be efficiently regenerated and reused with a high adsorption efficiency after five cycles. Zwitterionic polymers dispersed in solution usually exhibit pH, temperature, or ions responsive effect. L-serine-based

zwitterionic polymers, poly(L-serinyl acrylate)s (PSAs), showed dual responsiveness toward pH and temperature in aqueous solution (Figure 6a).^[57] Near its isoelectric point pH 2.85, the PSA is in its zwitterionic form. In the pH range of 2.3–3.5, the aqueous PSA solution appeared as a two-phase system. In this pH range, the two-phase PSA solution also became one-phase upon heating, exhibiting UCST-type phase transition. The cloud point was found to increase with increasing molecular weights of the PSA. It was also observed that the addition of an electrolyte such as brine solution could affect the cloud point of PSA solution, following the anti-polyelectrolyte effect. Delgado et al. studied the Hofmeister salt series on the zwitterionic polymers.^[58] The light scattering results showed the conformations of zwitterionic polymers in solutions with different salt concentrations, salt types, and temperatures. Zwitterionic repeat units are dressed with counterions when they are dissolved by adding salt (Figure 6b). The transition between ion exclusion and inclusion is not as apparent for well-hydrated salt ions. In the high salt concentration region ($> 0.6 \text{ M}$), electrostatics plays little role in the conformations due to the overall charge neutrality of the zwitterionic units, even though the charge screening is still increasing.

Zwitterionic polymers can also form nanoparticles in solution. Adamiak et al. synthesized polymeric nanoparticles and soluble homopolymers encoded with multiple copies of a peptide substrate for proteases.^[59] They tested whether enzyme processing of peptide side chains of polymeric nanoparticles and soluble homopolymers could lead to enhanced macrophage cell uptake as a result of changes in morphology and charge of the materials. The results indicated that zwitterionic nanoparticles were able to undergo cellular internalization by RAW 264.7 cells after proteolytic cleavage. However, other nanoparticles analogues generally showed minimal changes. This phenomenon was confirmed by flow cytometry measurements and TEM images of nanoparticles treated with denatured enzyme or active enzyme (Figure 6c). It means that the charge switch of the material after proteolysis is not necessarily the prevailing factor for cell uptake but must also be coupled with the morphological change. Ibrahim et al. designed a copolymer of N, N'-methylene bis(acrylamide) (MBAAm) and PSBMA, poly(MBAAm-co-SBMA), which can form stable nanoparticles in aqueous solution.^[60] The nanoparticles were used to modified polysulfone hollow fiber membranes for dye removal after preparing by dry/wet phase inversion method. The membrane showed high water permeability and dye removal ability. This as-prepared membrane can be an attractive candidate for the treatment of industrial and textile wastewater treatment. Liu et al. designed a pH-responsive zwitterionic polypeptide to deliver doxorubicin.^[61] Both positively and negatively charged moieties were introduced onto the same side chain by grafting short-chain zwitterions via aminolysis reaction of polysuccinimide with L-lysine. This structure provided a nano-scale homogenous mixture of balanced charges, and showed excellent resistance to nonspecific protein adsorption. Further studies indicated that the stabilization and release of doxorubicin can be precisely controlled by changing the pH. The nanoparticles exhibited excellent stabilities in protein solutions at pH = 7.4 and significantly enhanced drug release characteristics under acidic conditions.

Zwitterionic polymers can also graft on nanoparticles, forming a core-shell structure. PSBMA brushes were grafted onto

Figure 6. (a) Effect of concentration on cloud point: transmittance curves of PSA100 in water at varying concentrations and temperature-concentration phase diagram of aqueous PSA100 solution at pH = 2.6. Effect of pH and NaCl concentrations on the cloud point of aqueous solutions of PSAs of different molecular weights. Adapted with permission from Ref. [57]. Copyright (2015) American Chemical Society. (b) Dependence of $R_{h,90} \pm 0.5$ nm of poly(3-[2-(acrylamido)ethyl]dimethylammonio]propanesulfonate) (PAEDAPS) on Hofmeister salt concentrations Na₂SO₄ (●), NaCl (◇), NaBr (△), NaNO₃ (▲), NaClO₄ (○), and NaSCN (□) at 25 °C and average of R_h plateau from 0.8 to 2.0 M. Adapted with permission from Ref. [58]. Copyright (2017) American Chemical Society. (c) Cell uptake of nanoparticles after thermolysin treatment for 15 h at 37 °C by RAW 264.7 cells. Adapted with permission from Ref. [59]. Copyright (2017) American Chemical Society. (d) Size of Ag nanoparticle end-capped using PSBMAm 2 in NaCl solutions of various concentrations as determined by DLS. Thermal reversibility of PSBMAm 2/Ag nanoparticle after storing under ambient conditions for 2 months in 0.5 M NaCl. Adapted with permission from Ref. [62]. Copyright (2015) American Chemical Society.

metal nanoparticles (Au, Ag and Pt).^[62] The brush layer of zwitterionic polymers make the nanoparticles stable dispersion in solution, which make them less sensitive to the environment like pH and ionic strength. The nanoparticles also exhibited a temperature response due to the presence of PSBMA as the size of the core-shell structure showed reversible response of salt concentration and temperature (Figure 6d). Chen et al. coated a poly(2-(methacryloyloxy)ethyl)-dimethyl-(3-sulfopropyl) ammonium hydroxide (PMSA) shell onto Fe₃O₄@SiO₂ nanoparticles.^[63] Glycopeptide enrichment experiments confirmed the resulting Fe₃O₄@SiO₂@PMSA showed high glycopeptide enrichment, detection sensitivity, and binding

capacity. In the selective enrichment of N-linked glycopeptides from tryptic digests of proteins extracted from a mouse liver, Fe₃O₄@SiO₂@PMSA showed the great potential of the detection and identification of low-abundance N-linked glycopeptides in biological samples. Parnsubsakul et al. used zwitterionic polypeptide, EKEKEKPPPPC(EK)₃, to cap gold nanoparticles (AuNP-(EK)₃).^[14] AuNP-(EK)₃ can be applied to sense Ni²⁺ as Ni²⁺ can trigger the aggregation of the AuNP-(EK)₃ nanoprobe and results in a red-to-purple color change of the solution. The modification of the N-terminus allowed the nanoprobe to retain its stability, even in a high ionic strength medium due to the “anti-polyelectrolyte effect”.

Figure 7. (a) The chemical structure of the polyzwitterion (PMAA-co-SBMA). Transmittance vs temperature for the LCST-type hydrogels with different monomer mass ratios (MAA/SBMA). Transmittance vs temperature for the UCST-type hydrogels with different monomer mass ratios (MAA/SBMA). Photos of a UCST (MAA/SBMA = 2:5) hydrogel before and after phase transitions. Photos of a LCST-type (MAA/SBMA = 5:2) hydrogel before and after phase transitions. Adapted with permission from Ref. [15]. Copyright (2018) American Chemical Society. (b) Photos of the biomimetic skin attached to a prosthetic finger with the assistance of VHB tapes, a biomimetic skin whose hydrogel layer is cut into half, and the biomimetic skin after self-healing. The resistance and capacitance of the biomimetic skin before fracture and after self-healing. Adapted with permission from Ref. [15, 64]. Copyright (2018) Springer Nature. (c) The scanning electron microscope (SEM) images of P(DMAEMA-SS-SBMA) hydrogel (S#50) at 5°C, 45°C and 65°C. Adapted with permission from Ref. [65]. Copyright (2018) Elsevier.

3.3. Zwitterionic Polymer Based Hydrogels

Hydrogels are hydrophilic polymers swollen by water that are insoluble owing to reversible cross-links, and exhibit rapid and autonomous self-healing and self-recovery with tunable structural, mechanical, and rheological properties, which are widely used in flexible electronics. Owing to the highly hydrophilic and conductivity properties, zwitterionic polymers based hydrogel is a hot topic in recent years, especially the hydrogels on surfaces.^[66] Lei et al. design a series of zwitterionic hydrogels from copolymer of poly(methacrylic acid) (PMAA) and PSBMA (PMAA-co-PSBMA).^[15, 64] The copolymer showed a switch of UCST and LCST upon changing the ratio of PMAA and PSBMA. Specifically, when PSBMA was the majority, PMAA-co-PSBMAs exhibited UCST type. Further increasing the MAA content, the zwitterionic hydrogels surprisingly transformed to be LCST type. (Figure 7a). Both the UCST and LCST hydrogels showed ultrastretchability (>10000% strain), high strength (~300 kPa), self-healability (at room temperature within 12 h), 3D printability, distinct stimuli-

responsibility, biocompatibility, and antibacterial activity. Meanwhile, the ionic conductivity of PMAA-co-PSBMAs allowed multiple sensory capabilities toward temperature, strain, and stress. For example, when the biomimetic skin was attached to a prosthetic finger with the assistance of an epidermis-like dielectric elastomer (VHB tape), it enabled the prosthetic finger to sense strain and temperature stimuli through different stimuli-receptors and recorded the finger's bending-straightening movement information based on capacitance changes during deformation. When the ionic-conductive hydrogel layer of the biomimetic skin was cut into half, it could autonomously repair the crack after being brought into contact (Figure 7b). Within 20 min, the ionic resistance and capacitance can be restored with only about 0.04 and 0.9% drift, respectively. The self-healing biomimetic skin was able to detect the finger's movement and showed similar capacitance changes before fracture and after self-healing (Figure 7b). Recently, a poly-carboxybetaine based hydrogel was designed for simultaneous optical monitoring of pH and glucose in diabetic wound treatment.^[67] Sun et al. designed a multi-

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responsive P(DMAEMA-SS-SBMA) copolymeric hydrogel.^[65] Similar to PMAA-co-PSBMA, P(DMAEMA-SS-SBMA) also showed both UCST and LCST modes, and different pore size and response sensitivity of shrunken structures below UCST and above LCST were visualized by scanning electron microscope (SEM) images (Figure 7c). The hydrogel exhibited a highly swollen state with a swelling ratio of 17.8 and a pore size of 106 μm at 45°C. They deswelled unequally at 5°C with a compact surface with pore size of 30 μm and a loose bulk with pore size of 83 μm , while deswelled uniformly at 65°C with a dense shrunken structure of small pore size of 12 μm . This copolymer can be used for controlled drug release. The gradient-release between 5 and 45°C can be achieved by the “on-off” switching for drug release. In two cycles with different starting temperatures, the hydrogels loaded with Rhodamine B were alternatively placed in 5 and 45°C. Sharp increase and slight increase were observed at 45°C and 5°C respectively, indicating rapid and sustained release respectively. Besides, redox-sensitive degradation of P(DMAEMA-SS-SBMA) hydrogels could achieve the entire release of the encapsulated molecules in a reducing environment. Kao et al. made a hydrogel by incorporating arginine–glycine–aspartate (RGD) sequence and/or vascular endothelial growth factor mimicking (QK) peptide to PSBMA.^[68] This newly designed hydrogel can improve cell adhesion and influence stem cell differentiation without loss of mechanical properties. Relative to RGD-grafted PSBMA hydrogels, the RGD/QK incorporation further improved human adipose-tissue derived stem cells differentiated into adipogenic lineage, while RGD or RGD/QK additions had no substantial effects on osteogenesis under osteogenic induction.

4. Simulation and Theory

The successful development of zwitterionic polymers for a variety of technological applications urges us to better understand these polymers. However, due to the complexity of electrostatic interactions and the multiscale nature of zwitterionic polymer architectures, the fundamentals of zwitterionic polymers is far from elucidated. This lack of understanding and the insufficiency in available theories and modeling tools are preventing us from tailoring specific zwitterionic polymer structures and architectures for particular applications. In this section, we highlight some of the current progress in simulation and theory for zwitterionic polymers and offer our perspectives in this area.

Behaviors of polymers can often be described qualitatively using scaling theories. These theories are often simple and allow us to get an intuitive understanding of the qualitative behavior of the polymeric systems. On this front, the pioneering work is by Edwards et al. on a polyampholyte solution.^[69] With a scaling argument, Edwards et al. predicted the phase changes from the extended to a condensed phase when the temperature drops below a critical temperature. Further explorations on scaling behaviors were presented by Higgs and Joanny,^[70] Gutin and Shakhnovich,^[71] and Dobrynin and Rubinstein,^[72] also on a single polyampholyte chain in solution. Higgs and Joanny considered the screening effects due to the salts and noted that the added salts screen the intrachain electrostatic interactions, making the chain more swollen.^[70] This is consistent with the experimentally observed antipolyelectrolyte effect. Gutin and Shakhnovich

considered the effect of random net charges and suggested that the collapsed state of the polyampholyte chain may be strongly elongated in shape.^[71] Dobrynin and Rubinstein developed a two-parameter theory for a polyampholyte chain and classified three temperature regimes for the chain conformations.^[72]

More sophisticated approaches for polyelectrolytes have also been presented in the literature, offering much greater details on the behavior of these polymer chains. Polyelectrolytes are polymers modeled as a chain of dipoles on a backbone and they can be considered as a special class of polyampholytes. Using a variational field-theoretic method, Kumar and Fredrickson described the statistics of a single polyelectrolyte chain in solution.^[9] It leads to analytical relations for the radius of gyration of the polymer chain as a function of the chain length, electrostatic interaction strength, added salt concentration, dipole moment, and degree of ionization of the zwitterionic monomers. The theory suggests that both charge-dipole and dipole-dipole interactions determine the conformation of the chain: while dipole-dipole interactions on the chain tend to collapse the chain, the added salts screen the electrostatic interaction and condense on the zwitterionic sites. In another work, using the self-consistent-field theory, Kumar, Sumpter, and Muthukumar presented a theory for the phase separation of polyelectrolyte blends, showing that the interfacial tension is strongly dependent on the mismatch in dipolar interactions.^[73] However, sophisticated theories on zwitterionic polymers are still a rarity. In recent years, we have made much progress in describing charge correlation in polyelectrolyte solutions^[74] and developed more sophisticated field-theoretic approaches for describing dipolar interactions.^[75] We hope that these theories may soon translate into greater understanding and better descriptions of zwitterionic polymers. Additionally, theories for polybetaines are almost nonexistent. Given the wide applications of polybetaines, effective phenomenological theories for polybetaines may bring great benefit.

The electrostatic interactions are the key that determines the properties of zwitterionic polymers. Due to the particulate nature of the charge, the electrostatic correlations in a zwitterionic polymer system may require simulation to fully describe. To this end, effective coarse-grained models for the polymers and efficient simulation methods are necessary. By devising a coarse-graining strategy and using Langevin dynamics, Mahalik and Muthukumar investigated the formation of vesicles by polybetaines in salt-free aqueous solutions.^[76] The study found that the competition between hydrophobic interactions and dipole-dipole interactions gives rise to a variety of self-assembled structures. Monte Carlo (MC) methods can also be an effective strategy for investigating charge correlations. An early work by Kantor et al. performed MC simulations on randomly-charged polyampholyte chains in the absence of salt and found that polyampholytes with overall charge neutrality collapse into the globular form.^[77] However, applications of MC methods on zwitterionic polymers are still scarce. With recent developments in more efficient MC methods for simulating electrostatic interactions,^[78] there have already been good tools for exploring zwitterionic polymer systems of greater complexity.

Molecular interactions also play an important role in determining specific interactions with zwitterionic polymers. Particularly, the strong hydration effect of zwitterionic polymers is due to the particularly favorable attraction between zwitterionic moieties and the surrounding water molecules. Such molecular

Figure 8. (a) Electrostatic potential surfaces of carboxybetaine (CB) molecules with different lengths of carbon spacers: CB0, CB1, CB2, CB3, and CB4. Relative hydration free energy ($\Delta\Delta G$) of CB molecules as a function of carbon spacer length. Association free energy of five CB molecules with Na^+ : CB0- Na^+ , CB2- Na^+ , and CB4- Na^+ . r_1 and r_2 are the distances between Na^+ and the two oxygen atoms of CB molecules. Adapted with permission from Ref. [79]. Copyright (2013) American Chemical Society. (b) Ion selectivity (S) of the nanopore as a function of the background salt concentration C_b for various pHs at grafting density $\sigma_m = 0.1$ chains per nm^2 and as a function of pH for two levels of C_b at $\sigma_m = 0.1$ chains per nm^2 . Lines and symbols denote the results for voltages $V_0 = 0.2$ V and 1 V, respectively. “□”, “○”, and “△” in denote the results for pH = 2.2, 5, and 9, respectively. Inset highlights the result of ion selectivity at pH = 2.2 for C_b in the range of 100–1000 mM. Adapted with permission from Ref. [80]. Copyright (2015) Royal Society of Chemistry.

interactions need to be investigated with molecular dynamics (MD) simulations, but the drawback is that the simulations are often limited to small systems. Jiang et al. is perhaps the most prolific in applying MD simulations to investigate the important physics and chemistry concerning zwitterionic polymers, albeit using smaller zwitterionic moieties.^[25b] On exploring the effect of molecular structure, Shao and Jiang considered varying carbon spacer length on zwitterionic carboxybetaines with carbon spacer length ranging from zero to four (CB0, CB1, CB2, CB3, CB4)^[79] and compared the charge distribution, hydration, and association with Na^+ (Figure 8a). For CB0, CB1 and CB2, the variation of carbon spacer length may affect the hydration and ionic association significantly. For CB3 and CB4, the variation of

carbon spacer length may just tune the number of methylene groups in the molecule and molecular flexibility, but hardly change the partial charges of the two charged groups. The hydration free energy of carboxybetaines tends to be smaller with increasing carbon spacer length. Additionally, the carboxybetaine molecules with longer carbon spacer length form associations with Na^+ more easily. The simulation results have been confirmed by the experimental work of Higaki et al.^[1a] On elucidating the molecular-level non-fouling mechanisms, Shao et al. compared the structure of a chymotrypsin inhibitor 2 in the zwitterionic carboxybetaine moieties and the non-zwitterionic oligo(ethylene glycol) solutions. They showed that the zwitterionic moieties do not accumulate around the protein and that the hydrophobic interactions are the

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key difference between zwitterionic and non-zwitterionic moieties.^[81] On applying MD simulations to the more complex zwitterionic systems, He et al. explored the mechanical properties of PCBMA hydrogels with additional hydroxyl groups (–OH) as physical cross-linkers.^[82] Results showed that the hydrogels have higher elastic modulus than PCBMA hydrogels because the hydroxyl groups primarily associate with the charged groups of PCBMA.

While most theories and simulations are limited to zwitterionic polymers in a solution, we note that there are a great number of applications of zwitterionic polymers on surfaces, and therefore, robust theories and simulations for interfacial properties of zwitterionic polymers must be developed. With interfaces involved, ion polarizability will become a key factor affecting the surface properties; it is, therefore, important to consider ion polarizability in these systems.^[83] For surface tension calculations, we note that Lin and Hong reviewed the wetting phenomena and models for oil–water separation.^[84] The theoretical basis may be applied to model the surface tension on zwitterionic polymer coating systems.

Beyond the charge-conformation correlation, transport properties in systems involving zwitterionic polymers are also important to technological applications. It is worth noting that Zeng et al. studied theoretically, for the first time, the ion transport and selectivity in short nanopores functionalized with pH tunable, zwitterionic polymer brushes.^[80] The influence of the presence of H⁺ and OH[−] ions along with the chemical reactions between functional groups on zwitterionic polymer chains and protons was also considered (Figure 8b). The results showed that the charge density of zwitterionic polymer layers is not homogeneously distributed and depends significantly on the background salt concentration, pH, grafting density of zwitterionic polymer chains, and applied voltage bias. Ion selectivity of the biomimetic nanopore can be regulated from anion-selective (cation-selective) to cation-selective (anion-selective) by diminishing (raising) the solution pH when a sufficiently small grafting density of PE chains, large voltage bias, and low background salt concentration are applied (Figure 8b).

Based on the consideration of the existing theoretical work, we believe that the future theory work on zwitterionic polymers may continue to deepen in the following three aspects: temperature effect, salt effect, and surface properties. A future direction in this area is to build more sophisticated systems with the improvement of computing power and new methods developed in recent years.^[85] Systems with longer chain lengths, zwitterionic polymers on surfaces, zwitterionic polymers with complex architecture or charge structure, dynamic effects, and bio-polymer integration will be of great importance to theory and simulation work in the near future.

5. Summary

Zwitterionic polymers are of great importance in a variety of applications, including antifouling, lubrication, drug delivery and oil–water separation. Many of the unique properties of zwitterionic polymers are owing to the specific chemical structures with totally equal anionic and cationic groups on the molecular chains, which give rise to temperature response, anti-polyelectrolyte effect and strong hydration. Understanding the related mechanism of the chemical structures and surface interactions of various

zwitterionic polymers is critical for many applications that involve functional zwitterionic polymers.

In this review, we have provided an overview of the surface functional zwitterionic polymers according to the outline of structures of the polymers and applications. Along with the creation of zwitterionic polymer surfaces for new applications, future work should also aim to work out the molecular mechanisms of the relationship between the conformation and properties of the polymers. Additionally, more efforts are needed for developing suitable techniques for the characterization of the structures and functionalities of the zwitterionic polymer modified surfaces on the molecular scale, in particular in real-time. More efficient and faster simulation methods are needed to predict the micro process like the interactions of inter-chain and ion-chain, etc. There are many zwitterionic polymers and each has its unique functions. If we develop a better understanding on the structure–function relationships of the zwitterionic polymers, we will be able to take advantages of their unique properties and develop new biomaterials in a way never achieved previously.

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Keywords: zwitterionic polymers • functional polymer surfaces • hydrogels.

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