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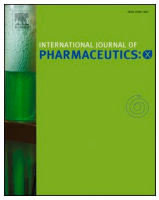

Polycarboxybetaine in advanced drug delivery systems: From structure-function relationship to therapeutic applications

Zhuang Liu [1], Yanan Zhai [1], Shunye Wang, Jiahui Bai, Dan Wang, Ziyang Wang, Xiang Gao [*], Jing Gao [*]

State Key Laboratory of National Security Specially Needed Medicines, Beijing Institute of Pharmacology and Toxicology, 27 Taiping Road, Haidian District, Beijing 100850, PR China

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ABSTRACT

Zwitterionic polycarboxybetaines (PCBs), combining quaternary ammonium cations and carboxylate anions in their repeating units, have emerged as promising materials for drug delivery applications. Their exceptional hydration, biocompatibility, and antifouling properties make them attractive alternatives to polyethylene glycol (PEG), particularly given growing concerns about immunogenicity of PEG. PCBs can be functionalized through various methods, including modification of side-chain moieties, adjustment of spacer length between charged groups, and incorporation of responsive elements. When applied to delivery drug, PCBs have been successfully developed into multiple formats including micelles, hydrogels, liposomes, and nanoparticles. Notably, in protein drug delivery, PCBs demonstrate significant advantages such as enhancing protein stability, extending circulation time, improving penetration through biological barriers, and reducing immunogenicity. Despite these promising features, several challenges remain, including complex synthesis requirements, limited mechanical properties, and pending FDA approval as pharmaceutical excipients. This review provides a comprehensive analysis of PCBs from the structure-function relationship, synthesis methods, and applications in drug delivery systems, while examining current limitations and future prospects.

1. Introduction

With further demands for efficacy and safety, drug delivery technology is garnering increasing attention and driving the development of the global pharmaceutical industry. A drug delivery system (DDS) can be defined as the most efficient method to maximize a drug's therapeutic effect while minimizing adverse effects. Some scholars have succinctly summarized this as "making drugs work better" (Bae and Park, 2020). Over the past decades, various nanodrug carriers such as dendrimers, nanogels, polymeric micelles, liposomes, and polymeric nanoparticles have been widely used for the efficient delivery of drugs. The continuous development of new materials is driving advances in drug delivery vehicles, as materials science and nanomedicine are subjects of intensive research.

Polyethylene glycol (PEG) is considered one of the most effective materials for prolonging the circulation time of nanomedicines by reducing non-specific protein adsorption in blood (Bukowski et al., 2002; Caliceti and Veronese, 2003; Leung et al., 2000; Molineux, 2002; Reddy et al., 2002; Safra et al., 2000; Szebeni et al., 2000a; Szebeni et al., 2000b). Significant preclinical research has been accumulated in this field, and many related products have been successfully marketed and used in clinical treatments (Giardiello et al., 2016; Margolis et al., 2017). The first PEG-based protein formulation, Adagen®, introduced in 1990, marked the beginning of the PEGylation era and opened a new frontier in delivery technology (Park et al., 2022). However, despite its widespread success, growing evidence suggests that PEG may elicit immunogenic responses, particularly when used in conjunction with proteins or advanced DDS such as liposomes (Harashima et al., 1996; Yamaoka et al., 1995). This limitation has led researchers to explore alternative materials that could replicate the benefits of PEG while minimizing its drawbacks.

One promising alternative is polycarboxybetaine (PCB), has garnered significant attention (Ali et al., 2023; Anthi et al., 2023; Chen et al., 2023; Choi et al., 2022; Ding et al., 2019; Du et al., 2017; Elsabahy

* Corresponding authors.
E-mail addresses: gaoxiang609@126.com (X. Gao), gjsmmu@126.com (J. Gao).
[1] These authors contributed equally to this work.

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et al., 2013; Horne et al., 2023; Hu et al., 2023; Ruseva et al., 2023; Shen et al., 2023; Wang et al., 2023a; Wang et al., 2022; Wang et al., 2023b; Yagasaki and Matubayasi, 2023; Yao et al., 2022; Zhang et al., 2022). Negatively charged carboxylated polybetaines constitute the PCB family. The first synthetic PCB analog, poly (4-vinylpyridine betaine), was reported by Ladenheim et al. in 1957 (Shi et al., 2022), and since then, various structures of different properties and functions have been derived. The common characteristics of the PCB family include its biocompatibility, non-toxicity, high hydrophilicity, exceptional resistance to protein and cellular adsorption, and tunability. Therefore, PCB is a superior choice for medical applications, including biosensors, medical devices, cell encapsulation, and drug delivery (Ibrahim et al., 2022; Shao et al., 2014; Zhu et al., 2016b; Zhu et al., 2021).

In particular, PCBs are widely used in various advanced drug delivery systems to modulate drug release, optimize pharmacokinetic and pharmacodynamic properties, and increase drug bioavailability (Ward et al., 2006; Yang et al., 2015; Zhang et al., 2015; Zhang et al., 2006). PCB excels in protein drug modification by enhancing protein stability and activity, prolonging drug circulation in the bloodstream, promoting drug absorption across physiological barriers, reducing immune responses, and improving in vivo safety. Despite PCB's benefits in drug delivery systems, it has not yet received FDA approval as a pharmaceutical excipient (Cheng et al., 2010). Several excellent reviews introduce the basics of zwitterionic materials, including their synthesis, solution behavior, surface hydration, early applications, and interactions with biomolecules (Li et al., 2022). However, reviews specifically focusing on PCBs are scarce, and those available often provide scattered and haphazard descriptions of PCB's role in advanced drug delivery systems. A unified governance framework is needed to synthesize key research insights and reveal major research trends. In this review, we describe the synthesis, structure and function of PCBs, and then highlight the application of PCBs in advanced drug delivery systems, especially their role in protein-based drugs. The challenges for further applications of PCBs are emphasized to present a scientific basis for PCB as a valuable polymeric matrix for therapeutic delivery.

2. Overview of PCB

2.1. Chemical structure and structure-function relationship

Zwitterionic polymers, characterized by their pairs of oppositely charged ions while maintaining overall neutral charge, have emerged as extremely hydrophilic materials with unique properties (Higaki et al., 2022; Racovita et al., 2021; Semak et al., 2022; Shimizu et al., 2021; Sun et al., 2021). Among them, PCB has been one of the most extensively studied. The structure of PCB mimics glycine betaine, an osmoprotectant widely found in biological systems. The structural formula of betaine, $(CH_3)_3NCH_2COO^-$, was first extracted from sugar beets by Scheibler (Racovita et al., 2021). Modern PCBs typically consist of a quaternary amine and a carboxyl group on the same monomer unit, separated by an alkyl chain of variable length (Fig. 1). These oppositely charged ions can fully dissociate in media with sufficient dielectric constant across various physicochemical conditions, including different pH levels and ionic strengths (Blackman et al., 2019).

PCBs exhibit three key functional properties that make them ideal for biomedical applications: exceptional hydration capability, outstanding antifouling properties, and low immunogenicity. These properties are directly linked to their molecular structure and can be understood through a clear structure-function relationship.

The exceptional hydration capability of PCB stems from its unique molecular structure. The simultaneous presence of positively charged quaternary ammonium groups and negatively charged carboxylate groups creates a strong ionic solvation effect. Unlike conventional hydrophilic materials that rely primarily on hydrogen bonding, PCBs interact with water molecules through stronger electrostatic interactions. This distinction in water interaction mechanism represents a fundamental advantage of zwitterionic materials over traditional hydrophilic polymers like PEG (Kitano et al., 2005a; Tada et al., 2009).

Molecular dynamics simulations have revealed that water molecules surrounding PCB surfaces exhibit a highly structured hydration layer with significantly longer residence time and lower mobility compared to those near conventional hydrophilic materials. Chen's experimental studies using surface plasmon resonance (SPR) and molecular simulations demonstrated that PCB surfaces bind water more strongly through ionic solvation than PEG surfaces that use hydrogen bonding (Chen et al., 2005). This tight binding of water molecules is further evidenced by differential scanning calorimetry (DSC) measurements by Morisaku and colleagues (Morisaku et al., 2008), which showed a higher proportion of non-freezable water in PCB hydrogels. And due to the uniform distribution of positive and negative charges at the molecular level, the dipole moment on the surface of the amphiphilic material is significantly reduced. Using SFG spectroscopy, C. Leng demonstrated that hydration peaks around 3200 cm^{-1} are mainly formed on the PCB surface and strong hydrogen bonds are crucial for establishing the protective hydration layers (Fig. 2) (Encinas et al., 2019; Leng et al., 2016; Tsao et al., 2020a). In summary, when the PCB is exposed to water, a first-stage hydration layer is formed through this ion-dipole interaction. The secondary hydration layer is formed by the extension of the hydrogen bonding network (Kitano et al., 2002), which introduces additional hydration forces (Ball, 2008).

The hydration structure of PCB polymers exhibits both physical and chemical advantages over traditional hydrophilic polymers. Choi et al. described how zwitterionic polymers show unique "antipolyelectrolyte" behavior (Choi et al., 2021; Wang et al., 2018), where their solubility

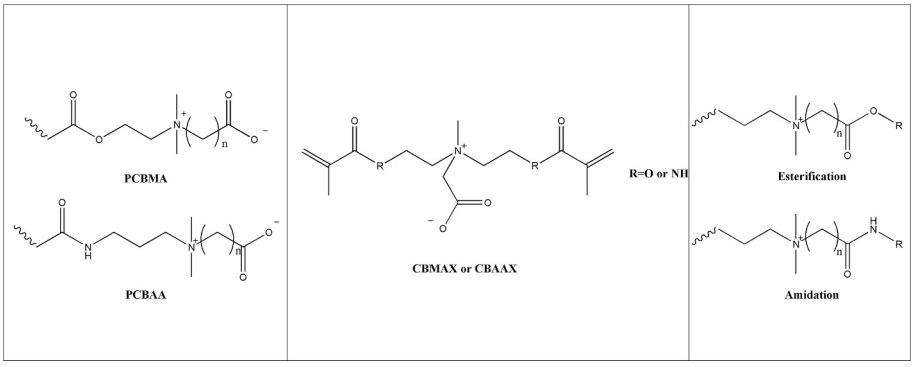

Fig. 1. Chemical structure of CBs. Left: Two most common forms of PCBs: poly(carboxybetaine methacrylate) (PCBMA)and poly(carboxybetaine acrylamide) (PCBAA). The spacer between amine and the methacrylate group of carboxybetaine methacrylate can be functionalized to derive PCB analogs. Middle: CBs cross-linker including CBMA cross-linker (CBMAX) and CBAA cross-linker (CBAAX) is used for the preparation of zwitterionic hydrogel. Right: Further functionalization can be realized through esterification or amidation of the carboxyl group.

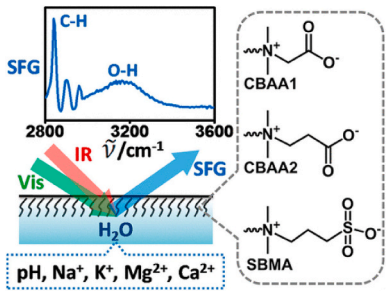

Fig. 2. SFG spectra of pCBAA1, pCBAA2, and pSBMA in water (Leng et al., 2016). Copyright 2016, adapted with permission from Leng et al. under the Creative Commons Attribution-Non Commercial License.

increases with salt concentration (unlike polyelectrolytes), further demonstrating their distinct hydration mechanism. This superior hydration capability directly contributes to PCB's antifouling properties and biological stability.

This exceptional hydration capability directly leads to PCB's another key property: outstanding antifouling performance. Protein adsorption is a critical initial step triggering clinical bio-contamination events, such as poor hemocompatibility, induced inflammation, and thrombosis. While many hydrophilic surfaces can reduce non-specific protein adsorption, PCB's performance stands out due to its strong hydration barrier mechanism.

The tightly bound water layer forms both a physical barrier preventing proteins from approaching the surface and an energetic barrier, as protein adsorption would require displacing strongly bound water molecules—a thermodynamically unfavorable process (Li et al., 2022). Computational studies by Y.L. Liu, employing multiple simulation techniques (molecular mechanics, Monte Carlo, molecular dynamics, and steered MD), revealed that PCB brushes had superior water molecule interactions and protein resistance compared to PEG brushes. Surface plasmon resonance measurements validated these findings, showing undetectable nonspecific protein adsorption (<0.3 ng/cm^2) from undiluted human serum or plasma, which is close to the detection limit of SPR sensors (~3 pg/mm^2). (Jiang and Cao, 2010; Ladd et al., 2008; Naito et al., 2021; Shao et al., 2012). Contact angle is a key parameter for measuring surface wettability; low contact angles (<90°) indicate hydrophilic surfaces with easy spreading of water molecules and are usually associated with resistance to protein adsorption. PCBs form low contact angles due to the presence of strong hydrophilicity in a "non-conjugated" conformation (Yang et al., 2009).

The charge-balanced nature of PCB also contributes to its antifouling properties by reducing specific electrostatic interactions with charged regions of proteins. Research has identified several critical factors affecting antifouling efficiency, including modified surface (polymerization degree >100 with grafting density > 0.29 chains/nm^2 for protein adsorption <10 ng/cm^2) (Feng et al., 2005), and balanced charge ratio (1:1 positively and negatively charged head groups) (Holmlin et al., 2001).

Importantly, unlike PEG, PCB does not interfere with hydrophobic interactions in aqueous solutions, which is crucial for maintaining the natural function of biomolecules. Studies by Shao and colleagues demonstrated that PCB causes minimal exposure of protein hydrophobic regions (approximately 1/10 reduction in hydrophobic SASA), while PEG causes about 1/3 reduction (Shao and Jiang, 2015). The result highlight PCB's ability to provide antifouling protection without disrupting essential biomolecular functions.

Building on these fundamental properties, the low immunogenicity of PCB represents its third key advantage, especially for long-term biological applications (He et al., 2022; Tischer et al., 2014; Yang et al., 2022). This property emerges naturally from the previous two characteristics but is further enhanced by PCB's biomimetic structure, which resembles glycine betaine, a natural solute in living organisms for osmotic regulation (Zhu et al., 2016a). This structural similarity allows the body to recognize PCB as a 'self' component rather than a foreign material, thereby enhancing biocompatibility. With minimal protein adsorption (<5 ng/cm^2 in 100 % plasma), it prevents immune responses and outperforms other materials (e.g., oligoethylene glycol), which adsorb 200 ng/cm^2 (Ladd et al., 2008; Larsson et al., 2007; Zhang et al., 2008). And PCB-modified nanoparticles maintain stable sizes in undiluted human serum, indicating effective evasion of immune system recognition (Fig. 3). Long-term stability studies by Zhang and colleagues confirmed that PCB materials can maintain in vivo stability for three months without capsule formation, demonstrating prolonged low immunogenicity (Zhang et al., 2013).

Using Raman and ATR-IR spectroscopy, Hiromi Kitano's research revealed that PCB maintains the natural water structure in solution, with O—H stretching patterns closely resembling pure water. This characteristic contributes to minimal protein and cell adsorption on CMB copolymers (Kitano et al., 2005b; Tada et al., 2009). These findings align with Ostuni's identified essential properties for non-fouling materials: hydrophilicity, electroneutrality, and specific hydrogen-bonding characteristics (Ostuni et al., 2001).

The remarkable functional properties of PCB—hydration, antifouling, and low immunogenicity—can be precisely tailored through structural modifications. This tunability is a key advantage of PCB materials and provides a foundation for their diverse applications. The structural diversity of PCBs stems from several key variables: (1) the choice of (meth)acrylate or (meth)acrylamide forming the polymer backbone, (2) functionalization of side-chain moieties, (3) the length of the alkyl spacer separating the anionic and cationic groups, and (4) various substituent groups of the quaternary ammonium. For instance, Shao-Yi Jiang's group at the University of Washington developed carboxybetaine methacrylate (CBMA) and later carboxybetaine acrylamide (CBAA), with the latter showing improved hydrolytic stability due to its acrylamide backbone, making it more suitable for long-term applications in complex environments (Cao et al., 2014).

These structural modifications directly influence functional performance. While increasing the chain length between positive and negative charges can enhance hydrophilicity, studies have shown that only PCBs with one- and two-carbon spacers effectively resist non-specific protein adsorption. S. Bhattacharjee and colleagues demonstrated that poly (carboxybetaine methacrylate) (PCBMA) with a 1-carbon spacer (C1) exhibited significantly longer plasma circulation compared to conjugates containing mixed 1-carbon and 2-carbon spacers, highlighting the critical role of charge separation distance in vivo (Bhattacharjee et al., 2015; Du and Qian, 2016; Sinclair et al., 2018; Wang et al., 2018).

Beyond these core structural elements, PCB can be further functionalized as a bifunctional material enabling diverse applications through strategic modifications (Liu et al., 2020a; Ostuni et al., 2001; Wang et al., 2014). Its abundant functional groups allow coupling with targeted ligands or active biomolecules, enhancing the properties of various materials through conjugation. For instance, Xu et al. developed poly(carboxybetaine thiophene) (PCBTh), a linear zwitterionic conductive polymer combining carboxybetaine with thiophene, which significantly reduced protein, bacterial, and cellular attachment while maintaining conductivity (Pasquina-Lemonche et al., 2020; Tanaka and Sackmann, 2005; Xu and Lee, 2020). Advanced structural modifications have enabled the development of responsive or 'smart' PCBs. By esterifying the anionic carboxyl group and introducing tertiary amines instead of quaternary ammonium groups, pH-responsive polymers with tunable buffering capacity can be created. Such modifications have led to charge-switchable, targeted, pH-responsive, and photo-responsive PCB variants, expanding their potential applications in drug delivery and other biomedical fields (Banerjee et al., 2021; Li et al., 2021; Sinclair et al., 2013; Wang et al., 2019; Ward et al., 2006; Wei et al., 2017).

Advanced material science techniques have further expanded PCB's potential through innovative processing methods (Huang et al., 2012).

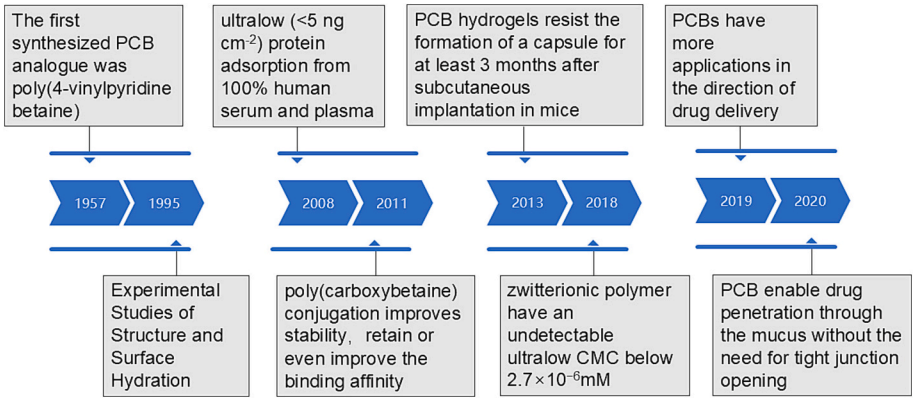

Fig. 3. Milestones for the study of PCBs.

Notable developments include Nana Cai's PCB hydrogel-powered activated carbon composite (Cai et al., 2017), which demonstrated excellent stability and hemocompatibility, and Chou's spin-coatable zwitterionic hydrogel (PCBAA). The latter innovation achieved precise thickness control (15–150 nm) through crosslinker concentration adjustment, with coatings exceeding 25 nm thickness showing ultra-low fouling levels (<5 ng/cm^2) against undiluted human blood serum, highlighting the superior resistance of zwitterionic PCB surfaces to non-specific protein adsorption. The material's abundant carboxylate functional groups enable straightforward EDC/NHS chemistry-based functionalization while maintaining antifouling properties through hydrolysis of unreacted groups (Chou et al., 2016; Yu et al., 2021).

In summary, PCBs fulfill different functions and exhibit varied properties precisely by altering their structure, including molecular weight, degree of polymerization, and functional group types. This structural tunability allows for the custom design of PCBs to meet specific requirements in drug delivery and other biomedical applications, thereby optimizing therapeutic outcomes while maintaining the core benefits of hydration, antifouling, and low immunogenicity. This structure-function relationship provides the foundation for PCB's diverse applications in advanced drug delivery systems.

2.2. Synthesis of PCB-derived products

PCB synthesis primarily follows two strategic approaches: direct polymerization of zwitterionic monomers or post-polymerization modification of precursor polymers to incorporate zwitterionic moieties. Each method offers distinct advantages and faces specific challenges (Table 1) (Lowe and McCormick, 2002; Racovita et al., 2021).

The direct polymerization of zwitterionic monomers can proceed through either chain growth or step growth mechanisms. Modern polymerization techniques including atom transfer radical polymerization (ATRP) (Fig. 4) (Gao et al., 2010), controlled radical polymerization (CRP), and reversible addition-fragmentation chain transfer (RAFT) have significantly advanced this field. However, the simultaneous presence of electrophilic and nucleophilic groups in these monomers can complicate the synthesis process and polymer characterization (Laschewsky, 2014).

Table 1
Synthetic routes of PCBs.

Synthetic routes	Advantages	Disadvantages
The polymerization of zwitterionic monomers	Reaction can occur with a yield of nearly 100 %.	The molecular characterization is difficult.
The polymerization of precursor monomers	The polymerization process is easy and subsequent characterization is convenient.	Due to the neighboring groups' effects and the complex reactions during the chemical functionalization, the reaction cannot occur with a yield of 100 %.

Post-polymerization modification offers greater synthetic control and easier polymer characterization. This approach encompasses three main strategies: (1) addition reactions between tertiary amines and α, β-unsaturated acids, (2) substitution reactions between tertiary amines and haloalkyl carboxylates, and (3) ring-opening reactions of carboxylic acid lactones with tertiary amines. While this method facilitates diverse chemical structures, complete conversion can be challenging due to neighboring group effects (Kudaibergenov et al., 2006).

Emerging synthetic technologies, including ring-opening metathesis polymerization (ROMP) and click chemistry, have expanded the PCB synthesis toolkit. These methods enable further functionalization through esterification or amidation of carboxyl groups. For example, H. C. Hung's group developed a novel approach combining mechanical strength with surface fouling resistance. They achieved that by preparing hydrophobic precursors through coupling tertiary amines with carboxylic acid esters, which can later be hydrolyzed to form an amphiphilic ionic layer (Hung et al., 2017).

3. Applications of PCBs in drug delivery systems

DDS exhibit significant advantages over traditional drug formulations in terms of bioavailability, targeting capability, and therapeutic efficacy. These systems can enhance drug bioavailability by protecting drugs from adverse environmental influences through encapsulation in nanoparticles, microspheres, micelles, and liposomes. The controlled release mechanisms prevent concentration fluctuations common in traditional formulations, thereby reducing side effects while maintaining therapeutic effects over extended periods. This is particularly beneficial for diseases requiring long-term treatment.

A crucial advancement in DDS is the improved targeting capability (Wilson, 2014). Unlike traditional formulations that affect both diseased and healthy tissues, modern delivery systems can be designed to target specific lesions through surface modifications. Liposomes, for instance, have demonstrated remarkable effectiveness in cancer treatment by enhancing tumor penetration and retention. Furthermore, these carriers protect drugs from degradation, particularly beneficial for sensitive biopharmaceuticals like proteins and vaccines (Lin et al., 2020a).

The performance of delivery systems largely depend on material selection. Traditional materials like PLGA and PEG create degradable carriers for controlled release, while liposomes utilize phospholipid bilayers for steady drug release. PCBs, with their unique properties discussed earlier, have emerged as promising candidates for material-based DDS. In this section, we first introduce recent advances for processing PCB into different functional material formats such as micelles, nanoparticles, and hydrogels. We then discuss how PCB materials are used in protein drug delivery systems to significantly extend drug half-life,

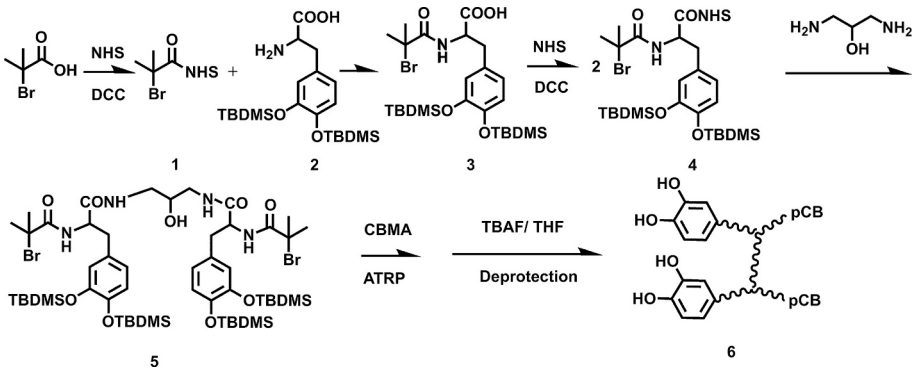

Fig. 4. Two PCB arms were grown from an initiator with two catechol groups via atom transfer radical polymerization (Gao et al., 2010). Copyright 2010, adapted with permission from Gao et al. under the Creative Commons Attribution-Non Commercial License.

reduce immunogenicity and toxicity, and enhance drug penetration through mucous membranes and barriers (Tsao et al., 2020a).

3.1. PCB-based drug delivery systems

3.1.1. Bottlebrush or star polymers

Just as branched PEGs result in unique modification effects, certain PCBs with distinctive spatial structures also provide numerous advantages for drugs. W. F. Lin et al. synthesized a *star*-shaped carboxybetaine polymer using ATRP from a β-CD initiator. In vivo experiments showed that this polymer remained in circulation for an extended period in mice, and even with repeated injections, it did not cause significant damage or inflammation in major organ tissues, nor did it lead to a notable increase in antibodies in the blood. In vitro experiments confirmed the in vivo results, suggesting that the star-shaped carboxybetaine polymer has significant potential for drug delivery systems (Lin et al., 2015). Notably, while star-shaped carboxybetaine polymers (PCBs) demonstrate promising drug delivery potential through their unique spatial architecture, the impact of molecular weight on modification efficacy remains underexplored in this field. Drawing parallels from PEGylation studies, higher molecular weights (e.g., 40 kDa branched PEG) can significantly extend drug half-lives and reduce immunogenicity (Harris et al., 2001), yet excessive modification often leads to substantial bioactivity attenuation or loss. For instance, 40 kDa branched PEGylated interferon-α-2a exhibits 18-fold enhanced in vivo antiviral activity but reduced in vitro receptor binding due to steric hindrance. Current PCB research lacks systematic investigation into this critical parameter. Blindly increasing molecular weight may replicate PEGylation's inherent trade-offs: larger sizes could further prolong circulation times but exacerbate active site masking or induce aberrant tissue accumulation (e.g., reversible renal tubular vacuolization observed with 40 kDa PEGylated tumor necrosis factor in animal models). Additionally, synthetic challenges and batch-to-batch consistency issues for high-molecular-weight PCBs remain significant hurdles. Future studies should therefore establish quantitative relationships between PCB molecular weight and modification outcomes, balancing pharmacokinetic optimization with bioactivity preservation. This could involve adapting PEGylation's "molecular weight threshold effect" theory (Harris et al., 2001) to identify optimal PCB size windows or developing biodegradable PCB conjugates to achieve spatiotemporal bioactivity release.

The ability to cross the blood-brain barrier (BBB) represents another critical application. R. N. Wang et al. found that cylindrical polymer brushes (CPBs) with PCB side chains exhibited superior tissue permeability compared to spherical nanomaterials and PEG-based analogs. Their research with different CPB variants (BCPB-F, BCPB-H, BCPB, and ECPB) demonstrated that fluorination and betaine modification significantly enhanced BBB-crossing capability (Fig. 5) (Wang et al., 2022).

3.1.2. Micelles

Micelles are 5–50 nm colloids self-assembled from amphiphilic copolymers or lipid polymer conjugates. When the concentration of polymers exceeds the critical micelle concentration (CMC), these amphiphilic polymers self-assemble in aqueous solution through hydrophobic interactions, forming structures with drugs encapsulated in a hydrophobic core and surrounded by a hydrophilic shell for stability. Their small size enables passive targeting of solid tumors, while their

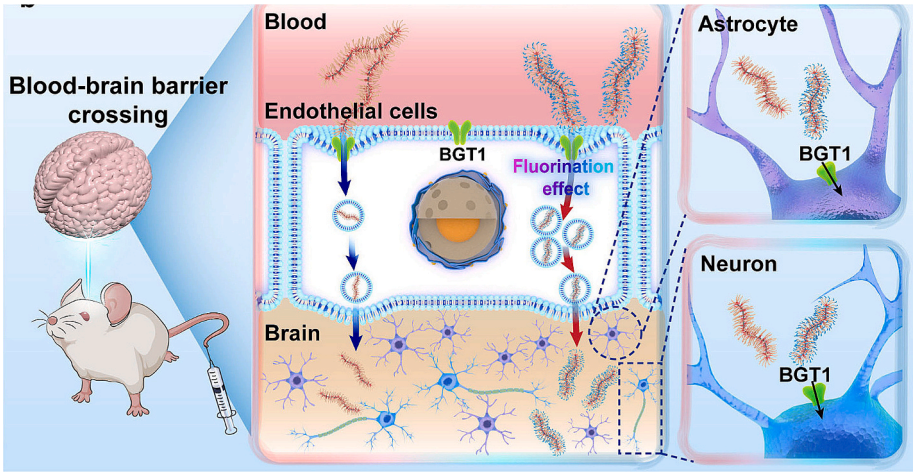

Fig. 5. Schematic diagram of the BBB penetration of BCPB-F and BCPB (Wang et al., 2022). Copyright 2022, adapted with permission from Wang et al. under the Creative Commons Attribution-Non Commercial License.

core-shell structure makes them ideal for drug delivery.

A major limitation of conventional micellar carriers is their tendency to disassemble below the CMC, compromising drug bioavailability in vivo. Y. Lu et al. demonstrated that micelles comprising superhydrophilic PCB polymer and superhydrophobic lipid domains can achieve an undetectable CMC below 10^{-6} mM—orders of magnitude lower than typical micellar systems ($>10^{-3}$ mM). In a mouse melanoma model, these ultralow-CMC micelles completely eradicated tumors when delivering docetaxel, while conventional formulations failed to reverse tumor growth (Fig. 6) (Lu et al., 2018).

Polymer micelles are easy to prepare, easy to load, and easy to deliver to the lesion site. Several studies of intelligent micelles have led to the promise of a wider clinical application of this delivery system. W. F. Lin developed a degradable cross-linked micellar system based on an amphiphilic ion (carboxybetaine) for active tumor-targeted drug delivery. The synergistic optimization of long cycle stability, tumor-specific delivery and responsive drug release was achieved by the anti-pollution property of PCBMA, intelligent cross-linking of disulfide bonds, biodegradability of poly(ε-caprolactone), and incorporation of targeting ligands (Lin et al., 2016). Similarly, G. F. Zhao et al. created a redox-sensitive micellar system for co-delivering doxorubicin and curcumin to combat multidrug resistance, utilizing PCB's unique properties for controlled drug release in the tumor microenvironment (Zhao et al., 2020).

3.1.3. Hydrogel

Hydrogels are crosslinked polymers capable of retaining large amounts of water while maintaining their structure. Their high water content, soft texture, and porous nature closely resemble living tissue, making them excellent candidates for drug delivery (Bai et al., 2019; Zhu et al., 2020). Hydrogels offer sustained drug release through various mechanisms including diffusion, swelling, and environmental stimuli response. The polymers give the hydrogels low toxicity, low side effects and low blood substance adhesion, which slows down the opsonization and reduces phagocytic clearance. In addition, the polymers form a reticulated cross-linked structure, and the drug can be almost completely masked from all of its own signals when it is individually encapsulated in the superhydrophilic gel (Asadi et al., 2021; Fu et al., 2021).

The integration of zwitterionic materials like PCB into hydrogels has shown remarkable benefits. Jiang and colleagues demonstrated that PCBMA hydrogels implanted subcutaneously in mice exhibited minimal inflammatory response and foreign body reaction compared to conventional materials, with reduced protein adsorption and increased blood vessel density around the implant (Grainger, 2013; Veiseh and Vegas, 2019; Zhang et al., 2013). For injectable drug delivery systems, hydrogel-encapsulated therapeutic agents also exhibit excellent stability and extended circulating half-life in vivo (Richter and Akerblom, 1983; Tsao et al., 2020a; Zhang et al., 2015).

A key challenge with zwitterionic hydrogels has been their weak mechanical properties due to super hydrophilicity. Two innovative approaches have emerged to address this limitation: The development of triazole-zwitterionic (TR-ZW) hydrogels by Q.S. Liu et al., which incorporate π-π stacking for enhanced mechanical properties while maintaining excellent antifouling characteristics (Liu et al., 2020b); The creation of zwitterionic-elastomeric-networked (ZEN) hydrogels combining PCB and poly(sulfobetaine) networks, achieving high mechanical strength through complementary cross-linking densities and strong electrostatic interactions (Gong et al., 2003; Shao et al., 2014). Compared to the first approach, the second reduces protein adsorption and fiber sac formation (Dong et al., 2021). Additionally, L. R. Carr and colleagues developed CBMAX, a CBMA-based dimethacrylate cross-linker that enables the formation of hydrogels with both excellent non-fouling properties and high mechanical strength (Carr et al., 2011).

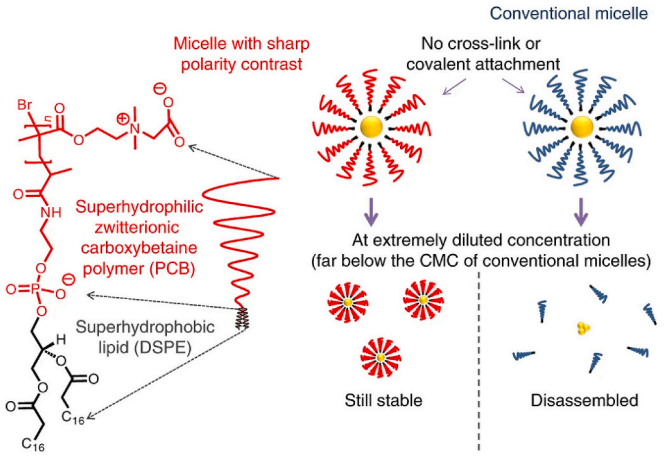

Fig. 6. Ultra-low-CMC micelles and their unusual ability to stabilize cargoes in extremely diluted conditions with micelle concentrations far below the CMC of common micelles (Lu et al., 2018). Copyright 2018, adapted with permission from Lu et al. under the Creative Commons Attribution-Non Commercial License.

3.1.4. Liposomes and nanoparticles

Liposomes are nanoscale spherical structures consisting of a phospholipid bilayer (4–5 nm thick) surrounding an aqueous core, with particle sizes ranging from 30 nm to the micrometer scale. The basic components - amphiphilic phospholipids and cholesterol - form a bilayer structure that closely mimics cell membranes, conferring high biocompatibility and biodegradability. This structural similarity enables liposomes to serve as an efficient, multi-functional drug delivery platform by protecting drugs from enzymatic degradation, improving drug stability, reducing toxicity, and enabling higher dosing for enhanced therapeutic effects.

PEG modification has been widely adopted to prolong liposome circulation time; however, its amphiphilic nature introduces destabilizing effects on lipid bilayers, necessitating cholesterol supplementation to counteract membrane rigidity and drug leakage. In contrast, PCB modification leverages superhydrophilicity driven by electrostatic hydration to stabilize liposomes without auxiliary additives. The charged moieties of PCB enhance aqueous phase polarity and induce robust hydration of lipid polar headgroups, thereby preserving bilayer fluidity and structural integrity. This mechanism enables PCB-modified liposomes to achieve circulation half-lives comparable to or exceeding those of cholesterol-stabilized PEGylated systems (Cao et al., 2012).

Besides, PCB modification particularly excels in nucleic acid delivery applications. While PEGylation of cationic liposomes extends circulation time, it significantly compromises siRNA encapsulation efficiency, cellular uptake, and endosomal/lysosomal escape. In contrast, DSPE-PCB modification not only enhances siRNA silencing efficiency by approximately 20 % compared to DSPE-PEG lipoplexes in vitro but also improves siRNA encapsulation efficiency (92 % at an N/P ratio of 20/1, whereas DSPE-PEG achieves 73 %) and cellular uptake (78 %, in contrast to 32 % for DSPE-PEG). This improvement is attributed to PCB's pH-responsive behavior, which enables a dynamic increase in surface charge under acidic conditions (e.g., from $+8.19 \pm 0.53$ mV at pH 7.4 to $+24.6 \pm 0.87$ mV at pH 4.5), thereby promoting endosomal membrane fusion and facilitating the cytoplasmic release of siRNA. Unlike PEG, which forms a steric barrier, DSPE-PCB provides stability without hindering intracellular delivery or siRNA release, making it particularly effective for systemic siRNA delivery. Furthermore, in vivo studies demonstrated a 62 % reduction in ApoB mRNA expression following DSPE-PCB treatment, whereas DSPE-PEG resulted in only a 7 % reduction, along with a significant decrease in serum cholesterol levels, suggesting its potential in hypercholesterolemia therapy (Fig. 7) (Li et al., 2014; Qiao et al., 2018).

Beyond liposomes, polymeric nanoparticles represent another

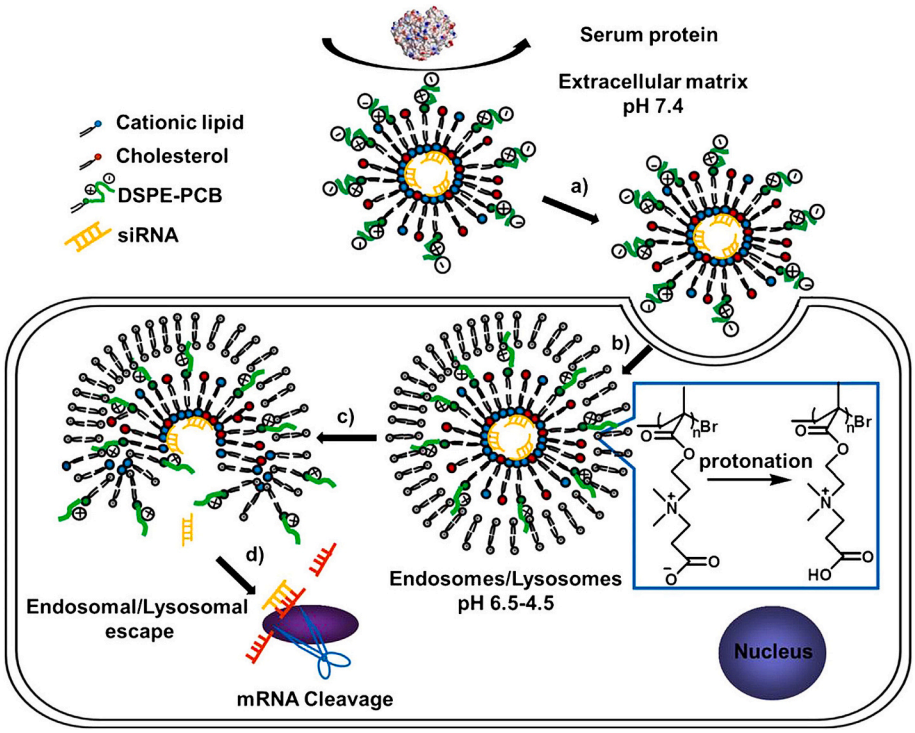

Fig. 7. Schematic diagram of DSPE-PCB lipoplexes for siRNA delivery with enhanced siRNA endosomal/lysosomal escape ability. (a) Resistant nonspecific protein adsorption. (b) Cellular endocytosis. (c) Protonation of DSPE-PCB in endosomes/lysosomes. (d) mRNA Cleavage (Li et al., 2014). Copyright 2014, adapted with permission from Li et al. under the Creative Commons Attribution-Non Commercial License.

promising vehicle for drug delivery. Their customizable structures and properties allow precise tuning of formulations, enabling control over stability, surface charge, loading efficiency, and release kinetics. Drugs can be encapsulated in the nanoparticle core, entrapped in the polymer matrix, or bound to the surface, offering diverse application possibilities. PCB-modified nanoparticles have shown particular promise in tumor therapy through several innovative approaches.

The enhanced permeability and retention (EPR) effect and leaky tumor vessels enable nanoparticle carriers to improve drug accumulation in tumors while reducing side effects on normal tissues. While both PEG and zwitterionic modifications can extend circulation time, PEGylation often compromises nanoparticle internalization due to its inert molecular structure. To address this limitation, S. Wang et al. developed nanomedicine with zwitterionic-to-cationic charge conversion ability (ZTC-NMs), comprising a glutathione-responsive camptothecin prodrug segment and a pH-responsive PCB-like zwitterionic segment. This system achieves surface charge conversion in the tumor microenvironment, improving cellular internalization efficiency (Shao and Jiang, 2015; Wang et al., 2016; Wang et al., 2020).

Building on this concept, M. Bernards and colleagues developed an instant affinity-switchable NDV based on pH-sensitive surface protonation. This system features an ultra-resistant poly(carboxybetaine) (PCB) shell and strategically placed sulfo groups near a hydrophobic DOX-loaded core. The NDV demonstrates rapid transition from strong resistance at physiological pH to high tumor cell membrane affinity in slightly acidic tumor environments. The pH sensitivity can be fine-tuned through the quantity of strong acidic sulfo groups acting as zeta potential adjustors. This design resulted in more efficient tumor tissue capture and improved tumor growth inhibition compared to PEGylated systems, while minimizing effects on healthy tissues (Wang et al., 2015).

3.2. PCBs in protein drugs modification

Despite the remarkable success of protein drugs in recent decades, they face several significant challenges. These include limited bioavailability due to large molecular weights, structural instability under varying environmental conditions, potential immunogenicity (particularly for non-human or recombinant proteins), and short blood circulation half-lives. These limitations often necessitate frequent injections or infusions, increasing patient burden and potentially reducing compliance (Sugahara et al., 2010).

To significantly improve the efficacy and bioavailability of protein/peptide drugs, polymeric carriers are commonly used. Polymer carriers have the unique advantage that they are able to remain stable in biological fluids and avoid rapid degradation of the drug. With different formulation forms, polymeric carriers can support sustained release of drugs, reducing the need for frequent dosing and effectively protecting protein/peptide drugs from enzymatic breakdown. In addition, these polymeric carriers are usually well biocompatible, harmless to humans and safe to use. (Mahmoudi et al., 2016). Generally, the “gold standard” for protein drug modification and protection is PEGylation. PEGylation improves the circulation properties of nanoparticles and protein drugs by preventing adsorption of plasma proteins and recognition by the cells of the mononuclear phagocyte system. However, the use of PEGylated drugs is severely hampered by the semi-antigenic nature of PEG. PCB is one of the best alternatives to PEG due to its superior superhydrophilicity and ultra-low immunogenicity.

3.2.1. Enhancing protein stability and maintaining activity

PCB conjugation has demonstrated remarkable advantages in maintaining protein stability and activity. Shaoyi Jiang’s research showed that zwitterionic PCB polymers maintain protein stability without sacrificing binding affinity. Their work with organophosphate hydrolase (OPH) demonstrated a dramatic increase in bioavailability from 5 % to 53 % through PCB conjugation (Fig. 8) (Keefe and Jiang, 2012).

Conventional polymer modifications often result in significant activity loss due to non-selective attachment near protein active sites, especially with dense modifications and multiple binding sites. (Xie et al., 2017). For instance, Pegasys (PEGylated interferon alpha-2a)

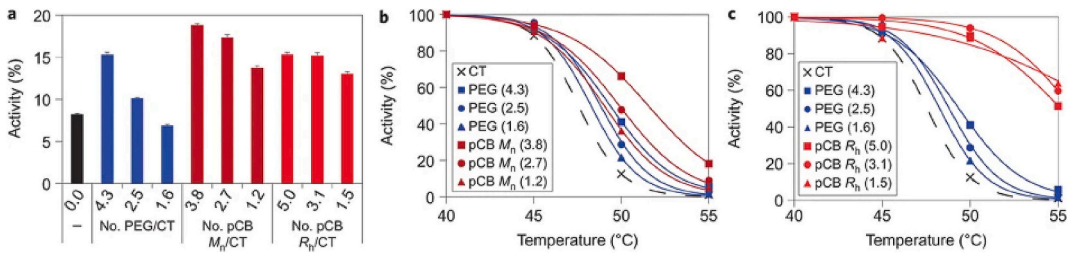

Fig. 8. Stability of PEG, PCB M_n (similar molecular weight) and PCB R_h (similar hydrodynamic size) conjugated with enzyme CT. (a) Activity of conjugates after 8 h incubation in 5 M urea. (b,c) Relative activity of PEG and PCB Mn conjugates (b) and PEG and PCB R_h conjugates (c) after 10 min incubation at different temperatures (Keefe and Jiang, 2012). Copyright 2012, adapted with permission from Keefe and Jiang under the Creative Commons Attribution-Non Commercial License.

retains only 7 % of unmodified IFN-a2a activity. In contrast, PCB-modified IFN-a2a maintains 4.4-fold higher antiproliferative activity compared to PEGylated versions of similar molecular weight, and 3-fold higher than those of comparable hydrodynamic size (Fig. 9) (Han et al., 2018). Similar benefits have been observed with insulin modifications. While PEGylated insulin Lispro (LY2605541) requires high molar concentrations to achieve comparable glucose-lowering effects, J. Xie reported that PCB-conjugated insulin maintains in vitro bioactivity while improving pharmacokinetics. Notably, this modification increased in vivo glucose-lowering activity by approximately 24 % compared to native insulin at equal molar doses (Xie et al., 2017).

The molecular basis for these differences lies in the polymers' interaction with proteins. PEG can act as a crowding agent, reducing protein solubility and increasing surface hydrophobicity through steric repulsion. Conversely, PCB maintains protein activity through its tightly bound aqueous layer, minimizing interference with protein-receptor interactions.

3.2.2. *Prolonging blood circulation and enabling drug penetration through mucus*

A formulation providing longer durations of release is theoretically as effective as an immediate release formulation, as long as the drug concentration in the blood remains below the maximum safe concentration (C_{max}) and above the minimum effective concentration (C_{min}). Thus, the direction of development of almost all current formulations is to prolong the duration of drug action, thereby reducing the number of doses and minimizing side effects and periods of ineffectiveness. PCB modifications effectively extend drug circulation time, which is achieved through multiple mechanisms, including increased particle size to reduce glomerular filtration and decreased interactions with MPS cells (Wang et al., 2016).

The effectiveness of this approach is demonstrated in various applications, including both large proteins and small peptides. For example, PCB-modified bioscavengers achieved circulation half-lives of up to a week (Zhang et al., 2016; Zhang et al., 2019), while PCB-conjugated GLP-1 maintained activity for six days after a single subcutaneous injection (Tsao et al., 2020b; Yin et al., 2021).

Beyond enhancing circulation time, PCB demonstrates superior mucus penetration capabilities. Studies show that PCB-based particles achieve 6.7 times greater diffusion than PEG particles and over 100 times that of charged particles in mucus barriers (Han et al., 2020), significantly enhancing drug bioavailability (Zhang et al., 2016).

3.2.3. *Decreasing immunity and increasing in vivo safety*

Many biological treatments, such as enzyme replacement therapy, require multiple doses to fully cure diseases. However, repeated injections of protein drugs with high immunogenicity increase the risk of immune reactions in patients, making treatment less effective and potentially leading to fatal adverse reactions. One major cause of the loss of efficacy of protein drugs is the production of antigen-specific antibodies (Ab). Once Ab binds to protein drugs, it can directly neutralize their pharmacological activity (neutralizing) or reduce their therapeutic exposure (non-neutralizing) via accelerated blood clearance (ABC). Antibodies can be categorized into two types based on their sources: antibodies against the protein itself, often called anti-drug antibodies (ADA), and antibodies against substances attached to the protein, including PEG (Hershfield et al., 2014).

A critical advantage of PCB modification is its ability to reduce immunogenicity of protein while avoiding the generation of anti-polymer antibodies, a common issue with PEG. Systematic studies

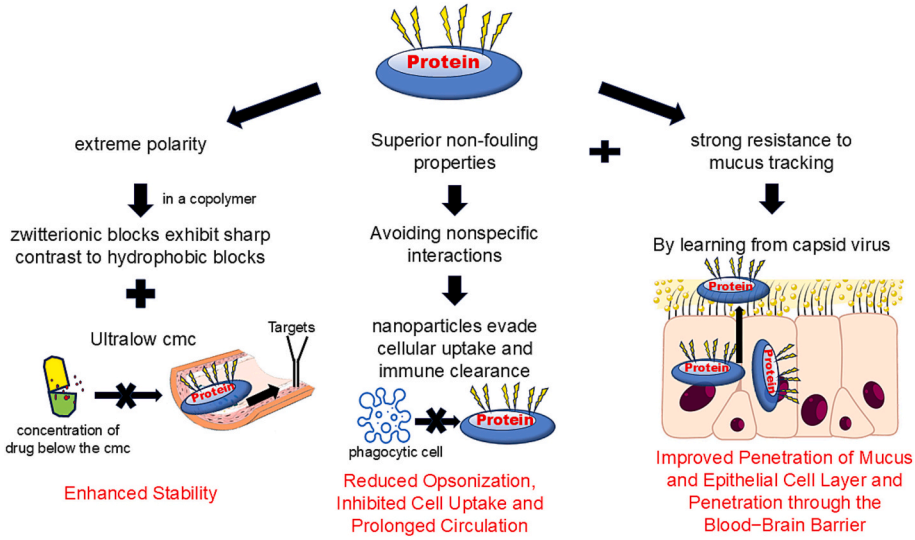

Fig. 9. The effect of PCB on the protein drugs.

comparing PCB and PEG conjugation across proteins with varying immunogenicity levels revealed that PCB-specific antibody generation remained minimal regardless of carrier protein immunogenicity, while PEG showed increasing immunogenicity with more immunogenic carriers (Liu and Jiang, 2016; Pelegri-O'Day et al., 2017; Richter and Akerblom, 1983; Zhang et al., 2018).

The superior immunological profile of PCB extends to both administration routes and repeated dosing scenarios. In subcutaneous administration, B. W. Li's investigation demonstrated that PCB-modified L-asparaginase showed improved lymphatic diffusion while maintaining reduced immunogenicity, enabling safer and more efficient drug delivery through this challenging route (Li et al., 2018a; Li et al., 2020; Li et al., 2018b). For repeated treatments, PCB-encapsulated proteins avoid the accelerated blood clearance observed with PEGylated alternatives (Higaki et al., 2017; Leng et al., 2018). Recent innovations in PCB application include nanosized zwitterionic networks (PCB NCs) that protect proteins while maintaining their structure. These systems have shown particular promise in clinical models, maintaining therapeutic efficacy even after multiple administrations without triggering immune responses (Fig. 10) (Li et al., 2018c).

4. Challenges of PCBs in drug delivery

The continuous attempts of PCBs in drug delivery show a promising future, suggesting that PCBs may be FDA-approved for human consumption. However, there are still many drawbacks to consider before they become a drug. Rewrite a passage from William Shakespeare's famous play "Hamlet" as the theme of this section-"to use PCB or not to use PCB, that is a question".

Complex preparation methods, such as ATRP or RAFT, and harsh reaction conditions (e.g., strict oxygen removal or the use of metal catalysts) limit its further application. We also need to consider cost-effectiveness. Zwitterionic compounds are often assembled via complex multi-step synthesis. Multiple pathways are used to control the critical step of coupling anionic and cationic groups, inevitably leading to various side effects. In practice, such multistep synthesis implies complex purification operations for the final product. Leaching of acrylics, which may be used in experiments, can pose serious problems, especially in the biomedical field. Many of the difficulties in PCB synthesis arise from the sensitivity and incompatibility of most chemical reactions to the simultaneous presence of electrophilic and nucleophilic reagents (Laschewsky, 2014).

Zwitterionic materials exhibit weak mechanical properties due to their highly hydrophilic nature. When used for their antifouling capabilities, PCBs are typically conjugated as brush-like structures, albeit with a thickness rarely exceeding 100 nm. This limited thickness adversely affects their hydrophilicity, mechanical strength, and lubricity, falling short of desired performance expectations. Moreover, the inadequate mechanical properties of PCB hydrogels developed to date severely restrict their practical application, posing a significant challenge for further PCB advancement. Introducing non-zwitterionic components has been explored to enhance mechanical strength. For instance, Haraguchi et al. demonstrated that sulfobetaine polyacrylamide/inorganic clay nanocomposite hydrogels increased tensile strength from 19.0 kPa to 71.3 kPa. However, their long-term mechanical stability and excellent antifouling properties appear compromised when combined. Thus, improving stability without compromising antifouling efficacy remains a critical goal (Yao et al., 2022). Functionalizing PCB side chains, such as esterification or amidation of carboxylic acid groups, introduces groups susceptible to hydrolysis, further impacting structural stability (Banerjee et al., 2011).

Additionally, firmly conjugating highly hydrophilic CB polymers to hydrophobic surfaces presents challenges due to (I) mutual exclusion between hydrophilic CB groups and hydrophobic surfaces in aqueous media, and (II) potential detachment of CB polymers from hydrophobic surfaces in aqueous environments due to the higher affinity of hydrophilic CB groups for water molecules (Lin et al., 2020b). Zwitterionic hydrogels, characterized by their high swelling ratio from super-hydrophilic properties, often exhibit inconsistent behavior with hydrophobic surfaces, resulting in hydrogel coatings detaching from these surfaces. Bridging molecules like silane coupling agents and dopamine can enhance hydrogel adhesion to substrates through covalent bonding. However, the effectiveness of these bridging molecules is hindered by the complex microenvironment (e.g., pH and solubility), limiting long-term application.

Understanding how drugs interact with the immune system is crucial for assessing material immunogenicity and advancing clinical applications. However, the detailed molecular and cellular mechanisms remain incompletely understood. While PCBs can shield substances from their modified active pharmaceutical ingredient (API), such as proteins, the precise processing and presentation of these materials by antigen-presenting cells (APCs), and subsequent interactions with T cells and B cells upon drug entry, particularly in minute quantities, require further investigation. Besides, in contrast to PEG, PCBs demonstrate superior resistance to non-specific protein adsorption, multi-functionalization, and oxidative environments. However, these attributes have

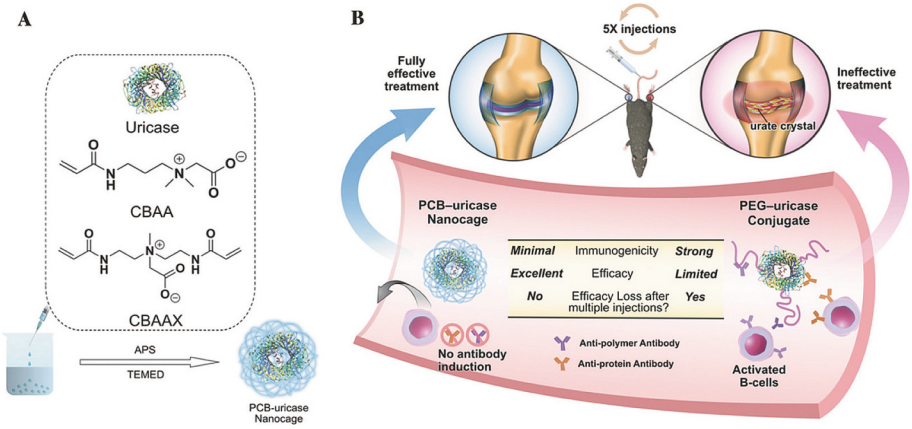

Fig. 10. Encapsulation of Uricase in Zwitterionic PCB Nanocages for Enhanced Immunologic Protection and Gout Treatment Efficacy. (A) Encapsulation of uricase with zwitterionic PCB NC. (B) Schematic illustration of the sequence of events after native uricase, PEGylated uricase, and uricase encapsulated by PCB NC enter the blood stream. Both antiuricase and anti-PEG antibodies are produced after multiple injections of PEG-uricase conjugate, leading to the loss of efficacy in gout treatment. PCB NC shields uricase from immune recognition and produces no antipolymer or antiuricase antibodies, leading to enhanced pharmacokinetics and improved efficacy in gout treatment (Li et al., 2018c). Copyright 2018, adapted with permission from Li et al. under the Creative Commons Attribution-Non Commercial License.

somewhat constrained the widespread application of PCBs. Their lack of biodegradability via natural metabolism leads to polymer accumulation in cells, potentially disrupting normal cellular functions and posing risks in gene or nanomedicine therapies (Yang et al., 2014). Therefore, it is necessary to conduct a long-term investigation into its safety.

5. Conclusions and Perspectives

The discovery of more insoluble drugs and the emergence of advanced therapies, such as cell and gene therapies, have rendered traditional formulation methods often inadequate. Thus, innovative formulation technologies are essential for effective drug delivery. Open-minded approaches and novel designs are critical for the development of new delivery systems. Continuous progress in basic research and interdisciplinary collaboration forms the foundation for these advancements, while the integration of medical and industrial sectors is key to their commercialization. Consequently, utilizing new and superior materials for drug research and development is vital for the ongoing evolution of delivery systems.

One such promising material is PCB. Besides the high hydrophilicity inherent to zwitterionic materials, PCB polymers possess unique characteristics. They are dual-functional, being both functionalized and non-fouling, allowing the attachment of ligands directly to PCB polymers via NHS/EDC chemistry for targeted drug delivery applications. Additionally, the positively and negatively charged sites can be selectively regulated, which is significant for smart, responsive drug development. Due to these advantages, PCBs show substantial potential in medical and pharmaceutical fields. However, much work remains to realize the full potential of zwitterionic materials.

Designing and optimizing the structure of PCBs—such as dendrimers, nanogels, polymeric micelles, liposomes, and polymeric nanoparticles—is urgently needed to enhance drug performance. The studies reviewed suggest that PCBs are strong candidates for various advanced drug delivery systems due to properties like superhydrophilicity and resistance to protein adsorption. Zwitterionic polymers also offer advantages such as good biocompatibility, minimal immune system stimulation, and low antibody production. Compared to PEG, they perform better in enhancing drug solubility, prolonging in vivo circulation time, improving drug efficacy, and reducing side effects.

A review of past literature shows that researchers predominantly focus on PCB-modified protein drugs. PCB offers three main benefits for protein drugs: enhancing stability and maintaining activity, prolonging blood circulation, and promoting absorption across physiological barriers, and preventing immune reactions, thus improving in vivo safety. However, it is surprising that there are fewer studies on nucleic acid-based drugs.

PCBs display intriguing properties, including pH sensitivity, temperature sensitivity, ionic conductivity, and optical characteristics. However, research on smart drugs, particularly temperature-sensitive drug delivery systems, remains limited. Additionally, studies examining the physicochemical properties of PCBs and their compatibility with other materials are scarce. The potential of PCBs in bionic drug delivery systems, bio-metal organic frameworks, and other innovative delivery mechanisms has yet to be explored. Systematic investigations are required to understand long-term biological responses, including in vivo degradation pathways, chronic toxicity, and biosystem stability.

Although the number of articles on PCBs in biomedical applications is limited, it suggests that this research direction is still in its infancy. The unique properties of polybetaine offer compelling evidence for optimism regarding the future of PCBs in advanced drug delivery systems. A promising direction for future research in the field of PCB-based advanced drug delivery systems includes the development of stimuli-responsive systems, which could offer dynamic control over drug release in response to specific environmental triggers. Additionally, integrating PCB with emerging therapeutic modalities could enhance the versatility and efficacy of drug delivery platforms. Advanced targeting strategies, such as the development of more precise and selective targeting mechanisms, would further improve the specificity of PCB-based systems in reaching desired tissues or cells. Moreover, novel synthesis and fabrication methods are essential for Scale-up and manufacturing. While challenges remain, we believe that continued research and development in PCB are likely to lead to innovative therapeutic solutions and improved patient outcomes.

CRediT authorship contribution statement

Zhuang Liu: Writing – original draft, Visualization, Conceptualization. **Yanan Zhai:** Writing – original draft, Visualization, Conceptualization. **Shunye Wang:** Writing – review & editing. **Jiahui Bai:** Writing – review & editing. **Dan Wang:** Writing – review & editing. **Ziyang Wang:** Writing – review & editing. **Xiang Gao:** Writing – review & editing, Supervision. **Jing Gao:** Supervision, Project administration, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

References

Ali, S.A., Al-Muallem, H.A., Mazumder, M.A.J., 2023. Stimuli-Responsive Macromolecular Architecture by Butler Cyclopolymerizations: Synthesis and applications. Chem. Rec. 23, e202200235.

Anthi, J., Vaněčková, E., Spasovová, M., Houska, M., Vrabcová, M., Vogelová, E., Holubová, B., Vaisocherová-Lísalová, H., Kolivoška, V., 2023. Probing charge transfer through antifouling polymer brushes by electrochemical methods: the impact of supporting self-assembled monolayer chain length. Anal. Chim. Acta 1276, 341640.

Asadi, N., Pazoki-Toroudi, H., Del Bakhshayesh, A.R., Akbarzadeh, A., Davaran, S., Annabi, N., 2021. Multifunctional hydrogels for wound healing: special focus on biomacromolecular based hydrogels. Int. J. Biol. Macromol. 170, 728–750.

Bae, Y.H., Park, K., 2020. Advanced drug delivery 2020 and beyond: Perspectives on the future. Adv. Drug Deliv. Rev. 158, 4–16.

Bai, T., Li, J.Q., Sinclair, A., Imren, S., Merriam, F., Sun, F., O'Kelly, M.B., Nourigat, C., Jain, P., Delrow, J.J., Basom, R.S., Hung, H.C., Zhang, P., Li, B.W., Heimfeld, S., Jiang, S.Y., Delaney, C., 2019. Expansion of primitive human hematopoietic stem cells by culture in a zwitterionic hydrogel. Nat. Med. 25, 1566–+.

Ball, P., 2008. Water as an active constituent in cell biology. Chem. Rev. 108, 74–108.

Banerjee, I., Pangule, R.C., Kane, R.S., 2011. Antifouling Coatings: recent Developments in the Design of Surfaces that Prevent Fouling by Proteins, Bacteria, and Marine Organisms. Adv. Mater. 23, 690–718.

Banerjee, S.L., Saha, P., Ganguly, R., Bhattacharya, K., Kalita, U., Pich, A., Singha, N.K., 2021. A dual thermoresponsive and antifouling zwitterionic microgel with pH triggered fluorescent "on-off" core. J. Colloid Interface Sci. 589, 110–126.

Bhattacharjee, S., Liu, W.G., Wang, W.H., Weitzhandler, I., Li, X.H., Qi, Y.Z., Liu, J.Y., Pang, Y., Hunt, D.F., Chilkoti, A., 2015. Site-specific Zwitterionic Polymer Conjugates of a Protein have Long Plasma Circulation. Chembiochem 16, 2451–2455.

Blackman, L.D., Gunatillake, P.A., Cass, P., Locock, K.E.S., 2019. An introduction to zwitterionic polymer behavior and applications in solution and at surfaces. Chem. Soc. Rev. 48, 757–770.

Bukowski, R.M., Tendler, C., Cutler, D., Rose, E., Laughlin, M.M., Statkevich, P., 2002. Treating cancer with PEG intron - Pharmacokinetic profile and dosing guidelines for an improved interferon-alpha-2b formulation. Cancer 95, 389–396.

Cai, N.N., Li, Q.S., Zhang, J.M., Xu, T., Zhao, W.Q., Yang, J., Zhang, L., 2017. Antifouling zwitterionic hydrogel coating improves hemocompatibility of activated carbon hemoadsorbent. J. Colloid Interface Sci. 503, 168–177.

Caliceti, P., Veronese, F.M., 2003. Pharmacokinetic and biodistribution properties of poly(ethylene glycol)-protein conjugates. Adv. Drug Deliv. Rev. 55, 1261–1277.

Cao, Z.Q., Zhang, L., Jiang, S.Y., 2012. Superhydrophilic Zwitterionic Polymers Stabilize Liposomes. Langmuir 28, 11625–11632.

Cao, B., Tang, Q., Cheng, G., 2014. Recent advances of zwitterionic carboxybetaine materials and their derivatives. J. Biomater. Sci. Polym. Ed. 25, 1502–1513.
Carr, L.R., Xue, H., Jiang, S.Y., 2011. Functionalizable and nonfouling zwitterionic carboxybetaine hydrogels with a carboxybetaine dimethacrylate crosslinker. Biomaterials 32, 961–968.
Chen, S., Zheng, J., Li, L., Jiang, S., 2005. Strong resistance of phosphorylcholine self-assembled monolayers to protein adsorption: insights into nonfouling properties of zwitterionic materials. J. Am. Chem. Soc. 127, 14473–14478.
Chen, Y., Sui, X., Zhang, T., Yang, J., Zhang, L., Han, Y., 2023. Ice recrystallization inhibition mechanism of zwitterionic poly(carboxybetaine methacrylate). Phys. Chem. Chem. Phys. 25, 2752–2757.
Cheng, G., Mi, L., Cao, Z.Q., Xue, H., Yu, Q.M., Carr, L., Jiang, S.Y., 2010. Functionalizable and Ultrastable Zwitterionic Nanogels. Langmuir 26, 6883–6886.
Choi, W., Park, S., Kwon, J.S., Jang, E.Y., Kim, J.Y., Heo, J., Hwang, Y., Kim, B.S., Moon, J.H., Jung, S., Choi, S.H., Lee, H., Ahn, H.W., Hong, J., 2021. Reverse Actuation of Polyelectrolyte effect for in Vivo Antifouling. ACS Nano 15, 6811–6828.
Choi, J., Kim, S., Mun, H.J., Yoo, J., Choi, S.H., Char, K., 2022. Antifreeze and Rheological Properties of Injectable Triblock Copolymer Hydrogels with Supramolecular Junctions. Macromol. Rapid Commun. 43, e2100618.
Chou, Y.N., Sun, F., Hung, H.C., Jain, P., Sinclair, A., Zhang, P., Bai, T., Chang, Y., Wen, T.C., Yu, Q., Jiang, S., 2016. Ultra-low fouling and high antibody loading zwitterionic hydrogel coatings for sensing and detection in complex media. Acta Biomater. 40, 31–37.
Ding, F., Yang, S., Gao, Z., Guo, J., Zhang, P., Qiu, X., Li, Q., Dong, M., Hao, J., Yu, Q., Cui, J., 2019. Antifouling and pH-responsive Poly(Carboxybetaine)-based Nanoparticles for Tumor Cell Targeting. Front. Chem. 7, 770.
Dong, D.Y., Tsao, C., Hung, H.C., Yao, F.L., Tang, C.J., Niu, L.Q., Ma, J.R., MacArthur, J., Sinclair, A., Wu, K., Jain, P., Hansen, M.R., Ly, D., Tang, S.G.H., Luu, T.M., Jain, P., Jiang, S.Y., 2021. High-strength and fibrous capsule-resistant zwitterionic elastomers. Sci. Adv. 7.
Du, H.B., Qian, X.H., 2016. The Hydration Properties of Carboxybetaine Zwitterion Brushes. J. Comput. Chem. 37, 877–885.
Du, Y., Gao, J., Chen, T., Zhang, C., Ji, J., Xu, Z.K., 2017. Understanding the Oxidative Stability of Antifouling Polymer Brushes. Langmuir 33, 7298–7304.
Elsabahy, M., Li, A., Zhang, F., Sultan, D., Liu, Y., Wooley, K.L., 2013. Differential immunotoxicities of poly(ethylene glycol)- vs. poly(carboxybetaine)-coated nanoparticles. J. Control. Release 172, 641–652.
Encinas, N., Angulo, M., Astorga, C., Colilla, M., Izquierdo-Barba, I., Vallet-Regi, M., 2019. Mixed-charge pseudo-zwitterionic mesoporous silica nanoparticles with low-fouling and reduced cell uptake properties. Acta Biomater. 84, 317–327.
Feng, W., Zhu, S., Ishihara, K., Brash, J.L., 2005. Adsorption of fibrinogen and lysozyme on silicon grafted with poly(2-methacryloyloxyethyl phosphorylcholine) via surface-initiated atom transfer radical polymerization. Langmuir 21, 5980–5987.
Fu, M.J., Liang, Y.J., Lv, X., Li, C.N., Yang, Y.Y., Yuan, P.Y., Ding, X., 2021. Recent advances in hydrogel-based anti-infective coatings. J. Mater. Sci. Technol. 85, 169–183.
Gao, C.L., Li, G.Z., Xue, H., Yang, W., Zhang, F.B., Jiang, S.Y., 2010. Functionalizable and ultra-low fouling zwitterionic surfaces via adhesive mussel mimetic linkages. Biomaterials 31, 1486–1492.
Giardiello, M., Liptrott, N.J., McDonald, T.O., Moss, D., Siccardi, M., Martin, P., Smith, D., Gurjar, R., Rannard, S.P., Owen, A., 2016. Accelerated oral nanomedicine discovery from miniaturized screening to clinical production exemplified by paediatric HIV nanotherapies. Nat. Commun. 7, 13184.
Gong, J.P., Katsuyama, Y., Kurokawa, T., Osada, Y., 2003. Double-network hydrogels with extremely high mechanical strength. Adv. Mater. 15, 1155-+.
Grainger, D.W., 2013. All charged up about implanted biomaterials. Nat. Biotechnol. 31, 507–509.
Han, Y.J., Yuan, Z.F., Zhang, P., Jiang, S.Y., 2018. Zwitterlation mitigates protein bioactivity loss in vitro over PEGylation. Chem. Sci. 9, 8561–8566.
Han, X.F., Lu, Y., Xie, J.B., Zhang, E.S., Zhu, H., Du, H., Wang, K., Song, B.Y., Yang, C.B., Shi, Y.J., Cao, Z.Q., 2020. Zwitterionic micelles efficiently deliver oral insulin without opening tight junctions. Nat. Nanotechnol. 15, 605–+.
Harashima, H., Huong, T.M., Ishida, T., Manabe, Y., Matsuo, H., Kiwada, H., 1996. Synergistic effect between size and cholesterol content in the enhanced hepatic uptake clearance of liposomes through complement activation in rats. Pharm. Res. 13, 1704–1709.
Harris, J.M., Martin, N.E., Modi, M., 2001. Pegylation: a novel process for modifying pharmacokinetics. Clin. Pharmacokinet. 40, 539–551.
He, J., Yang, J., Li, M., Li, Y., Pang, Y., Deng, J., Zhang, X., Liu, W., 2022. Polyzwitterion Manipulates Remineralization and Antibiofilm Functions against Dental Demineralization. ACS Nano 16, 3119–3134.
Hershfield, M.S., Ganson, N.J., Kelly, S.J., Scarlett, E.L., Jaggers, D.A., Sundy, J.S., 2014. Induced and pre-existing anti-polyethylene glycol antibody in a trial of every 3-week dosing of pegloticase for refractory gout, including in organ transplant recipients. Arthritis Res. Ther. 16, R63.
Higaki, Y., Inutsuka, Y., Sakamak, T., Terayama, Y., Takenaka, A., Higaki, K., Yamada, N. L., Moriwaki, T., Ikemoto, Y., Takahara, A., 2017. Effect of Charged Group Spacer Length on Hydration State in Zwitterionic Poly(sulfobetaine) Brushes. Langmuir 33, 8404–8412.
Higaki, Y., Furusawa, R., Otsu, T., Yamada, N.L., 2022. Zwitterionic Poly (carboxybetaine) Brush/Albumin Conjugate Films: Structure and Lubricity. Langmuir 38, 9278–9284.
Holmlin, R.E., Chen, X., Chapman, R.G., Takayama, S., Whitesides, G.M., 2001. Zwitterionic SAMs that resist Nonspecific Adsorption of Protein from Aqueous Buffer. Langmuir 17, 2841–2850.
Horne, R., Ben-Shlomo, N., Jensen, M., Ellerman, M., Escudero, C., Hua, R., Bennion, D., Guymon, C.A., Hansen, M.R., 2023. Reducing the foreign body response on human cochlear implants and their materials in vivo with photografted zwitterionic hydrogel coatings. Acta Biomater. 166, 212–223.
Hu, S., Cheng, Q., Shang, Y., Wang, Z., Zhu, R., Zhang, L., Wu, W., Zhang, S., Li, J., 2023. Synthesis of pH-responsive polyzwitterions for activated cellular uptake and tumor accumulation of gold nanoparticles at tumorous acidity. Biomed. Mater. 18.
Huang, C.J., Brault, N.D., Li, Y.T., Yu, Q.M., Jiang, S.Y., 2012. Controlled Hierarchical Architecture in Surface-initiated Zwitterionic Polymer Brushes with Structurally Regulated Functionalities. Adv. Mater. 24, 1834–1837.
Hung, H.C., Jain, P., Zhang, P., Sun, F., Sinclair, A., Bai, T., Li, B.W., Wu, K., Tsao, C., Liu, E.J., Sundaram, H.S., Lin, X.J., Farahani, P., Fujihara, T., Jiang, S.Y., 2017. A Coating-Free Nonfouling Polymeric Elastomer. Adv. Mater. 29.
Ibrahim, M., Ramadan, E., Elsadek, N.E., Emam, S.E., Shimizu, T., Ando, H., Ishima, Y., Elgarhy, O.H., Sarhan, H.A., Hussein, A.K., Ishida, T., 2022. Polyethylene glycol (PEG): the nature, immunogenicity, and role in the hypersensitivity of PEGylated products. J. Control. Release 351, 215–230.
Jiang, S.Y., Cao, Z.Q., 2010. Ultralow-Fouling, Functionalizable, and Hydrolyzable Zwitterionic Materials and their Derivatives for Biological applications. Adv. Mater. 22, 920–932.
Keefe, A.J., Jiang, S.Y., 2012. Poly(zwitterionic)protein conjugates offer increased stability without sacrificing binding affinity or bioactivity. Nat. Chem. 4, 60–64.
Kitano, H., Imai, M., Sudo, K., Ide, M., 2002. Hydrogen-Bonded Network Structure of Water in Aqueous solution of Sulfobetaine Polymers. J. Phys. Chem. B 106, 11391–11396.
Kitano, H., Mori, T., Takeuchi, Y., Tada, S., Gemmei-Ide, M., Yokoyama, Y., Tanaka, M., 2005a. Structure of water incorporated in sulfobetaine polymer films as studied by ATR-FTIR. Macromol. Biosci. 5, 314–321.
Kitano, H., Tada, S., Mori, T., Takaha, K., Gemmei-Ide, M., Tanaka, M., Fukuda, M., Yokoyama, Y., 2005b. Correlation between the structure of water in the vicinity of carboxybetaine polymers and their blood-compatibility. Langmuir 21, 11932–11940.
Kudaibergenov, S., Jaeger, W., Laschewsky, A., 2006. Polymeric betaines: Synthesis, characterization, and application. In: Donnio, B., Guillon, D., Harada, A., Hashidzume, A., Jaeger, W., Janowski, B., Kudaibergenov, S., Laschewsky, A., Njuguna, J., Pielichowski, J., Pielichowski, K., Takashima, Y. (Eds.), Supramolecular Polymers Polymeric Betains Oligomers, pp. 157–224.
Ladd, J., Zhang, Z., Chen, S., Hower, J.C., Jiang, S., 2008a. Zwitterionic polymers exhibiting high resistance to nonspecific protein adsorption from human serum and plasma. Biomacromolecules 9, 1357–1361.
Larsson, A., Ekblad, T., Andersson, O., Liedberg, B., 2007. Photografted Poly(ethylene glycol) Matrix for Affinity Interaction Studies. Biomacromolecules 8, 287–295.
Laschewsky, A., 2014. Structures and Synthesis of Zwitterionic Polymers. Polymers 6, 1544–1601.
Leng, C., Sun, S.W., Zhang, K.X., Jiang, S.Y., Chen, Z., 2016. Molecular level studies on interfacial hydration of zwitterionic and other antifouling polymers in situ. Acta Biomater. 40, 6–15.
Leng, C., Huang, H., Zhang, K.X., Hung, H.C., Xu, Y., Li, Y.X., Jiang, S.Y., Chen, Z., 2018. Effect of Surface Hydration on Antifouling Properties of mixed Charged Polymers. Langmuir 34, 6538–6545.
Leung, H.W., Ballantyne, B., Hermansky, S.J., Frantz, S.W., 2000. Peroral subchronic, chronic toxicity, and pharmacokinetic studies of a 100-kilodalton polymer of ethylene oxide (Polyox N-10) in the Fischer 344 rat. Int. J. Toxicol. 19, 305–312.
Li, Y., Cheng, Q., Jiang, Q., Huang, Y.Y., Liu, H.M., Zhao, Y.L., Cao, W.P., Ma, G.H., Dai, F.Y., Liang, X.J., Liang, Z.C., Zhang, X., 2014. Enhanced endosomal/lysosomal escape by distearoyl phosphoethanolamine-polycarboxybetaine lipid for systemic delivery of siRNA. J. Control. Release 176, 104–114.
Li, B.W., Xie, J.Y., Yuan, Z.F., Jain, P., Lin, X.J., Wu, K., Jiang, S.Y., 2018a. Mitigation of Inflammatory Immune responses with Hydrophilic Nanoparticles. Angewandte Chem.-Int. Ed. 57, 4527–4531.
Li, B.W., Yuan, Z.F., Hung, H.C., Ma, J.R., Jain, P., Tsao, C., Xie, J.Y., Zhang, P., Lin, X.J., Wu, K., Jiang, S.Y., 2018b. Revealing the Immunogenic risk of Polymers. Angewandte Chem.-Int. Ed. 57, 13873–13876.
Li, B.W., Yuan, Z.F., Zhang, P., Sinclair, A., Jain, P., Wu, K., Tsao, C., Xie, J.Y., Hung, H. C., Lin, X.J., Bai, T., Jiang, S.Y., 2018c. Zwitterionic Nanocages Overcome the Efficacy loss of Biologic Drugs. Adv. Mater. 30.
Li, B.W., Yuan, Z.F., He, Y.W., Hung, H.C., Jiang, S.Y., 2020. Zwitterionic Nanoconjugate Enables Safe and Efficient Lymphatic Drug delivery. Nano Lett. 20, 4693–4699.
Li, Y., Ji, W.H., Peng, H., Zhao, R.C., Zhang, T.L., Lu, Z.G., Yang, J., Liu, R.Y., Zhang, X., 2021. Charge-switchable zwitterionic polycarboxybetaine particle as an intestinal permeation enhancer for efficient oral insulin delivery. Theranostics 11, 4452–4466.
Li, Q., Wen, C., Yang, J., Zhou, X., Zhu, Y., Zheng, J., Cheng, G., Bai, J., Xu, T., Ji, J., Jiang, S., Zhang, L., Zhang, P., 2022. Zwitterionic Biomaterials. Chem. Rev. 122, 17073–17154.
Lin, W.F., Ma, G.L., Ji, F.Q., Zhang, J., Wang, L.G., Sun, H.T., Chen, S.F., 2015. Biocompatible long-circulating star carboxybetaine polymers. J. Mater. Chem. B 3, 440–448.
Lin, W.F., Ma, G.L., Kampf, N., Yuan, Z.F., Chen, S.F., 2016. Development of Long-Circulating Zwitterionic Cross-Linked Micelles for Active-Targeted Drug delivery. Biomacromolecules 17, 2010–2018.
Lin, X.J., Boit, M.O., Wu, K., Jain, P., Liu, E.J., Hsieh, Y.F., Zhou, Q., Li, B.W., Hung, H.C., Jiang, S.Y., 2020a. Zwitterionic carboxybetaine polymers extend the shelf-life of human platelets. Acta Biomater. 109, 51–60.
Lin, X.J., Wu, K., Zhou, Q., Jain, P., Boit, M.O., Li, B.W., Hung, H.C., Creason, S.A., Himmelfarb, J., Ratner, B.D., Jiang, S.Y., 2020b. Photoreactive Carboxybetaine

Copolymers Impart Biocompatibility and Inhibit Plasticizer Leaching on polyvinyl Chloride. ACS Appl. Mater. Interfaces 12, 41026–41037.
Liu, S., Jiang, S., 2016. Zwitterionic polymer-protein conjugates reduce polymer-specific antibody response. Nano Today 11, 285–291.
Liu, G.Y., Li, K.J., Wang, H.B., Ma, L., Yu, L., Nie, Y., 2020a. Stable Fabrication of Zwitterionic Coating based on Copper-Phenolic Networks on Contact Lens with improved Surface Wettability and Broad-Spectrum Antimicrobial activity. ACS Appl. Mater. Interfaces 12, 16125–16136.
Liu, Q., Chiu, A., Wang, L., An, D., Li, W., Chen, E.Y., Zhang, Y., Pardo, Y., McDonough, S.P., Liu, L., Liu, W.F., Chen, J., Ma, M., 2020b. Developing mechanically robust, triazole-zwitterionic hydrogels to mitigate foreign body response (FBR) for islet encapsulation. Biomaterials 230, 119640.
Lowe, A.B., McCormick, C.L., 2002. Synthesis and solution properties of zwitterionic polymers. Chem. Rev. 102, 4177–4189.
Lu, Y., Yue, Z.G., Xie, J.B., Wang, W., Zhu, H., Zhang, E.S., Cao, Z.Q., 2018. Micelles with ultralow critical micelle concentration as carriers for drug delivery. Nat. Biomed. Eng. 2, 318–325.
Mahmoudi, M., Bertrand, N., Zope, H., Farokhzad, O.C., 2016. Emerging understanding of the protein corona at the nano-bio interfaces. Nano Today 11, 817–832.
Margolis, D.A., Gonzalez-Garcia, J., Stellbrink, H.J., Eron, J.J., Yazdanpanah, Y., Podzamczer, D., Lutz, T., Angel, J.B., Richmond, G.J., Clotet, B., Gutierrez, F., Sloan, L., Clair, M.S., Murray, M., Ford, S.L., Mrus, J., Patel, P., Crauwels, H., Griffith, S.K., Sutton, K.C., Dorey, D., Smith, K.Y., Williams, P.E., Spreen, W.R., 2017. Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial. Lancet 390, 1499–1510.
Molineux, G., 2002. Pegylation: engineering improved pharmaceuticals for enhanced therapy. Cancer Treat. Rev. 28, 13–16.
Morisaku, T., Watanabe, J., Konno, T., Takai, M., Ishihara, K., 2008. Hydration of phosphorylcholine groups attached to highly swollen polymer hydrogels studied by thermal analysis. Polymer 49, 4652–4657.
Naito, N., Ukita, R., Wilbs, J., Wu, K., Lin, X.J., Carleton, N.M., Roberts, K., Jiang, S.Y., Heinis, C., Cook, K.E., 2021. Combination of polycarboxybetaine coating and factor XII inhibitor reduces clot formation while preserving normal tissue coagulation during extracorporeal life support. Biomaterials 272.
Ostuni, E., Chapman, R.G., Holmlin, R.E., Takayama, S., Whitesides, G.M., 2001. A survey of structure-property relationships of surfaces that resist the adsorption of protein. Langmuir 17, 5605–5620.
Park, H., Otte, A., Park, K., 2022. Evolution of drug delivery systems: from 1950 to 2020 and beyond. J. Control. Release 342, 53–65.
Pasquina-Lemonche, L., Burns, J., Turner, R.D., Kumar, S., Tank, R., Mullin, N., Wilson, J.S., Chakrabarti, B., Bullough, P.A., Foster, S.J., Hobbs, J.K., 2020. The architecture of the Gram-positive bacterial cell wall. Nature 582, 294-+.
Pelegri-O'Day, E.M., Paluck, S.J., Maynard, H.D., 2017. Substituted Polyesters by Thiol-Ene Modification: Rapid diversification for Therapeutic Protein Stabilization. J. Am. Chem. Soc. 139, 1145–1154.
Qiao, C., Yang, J., Shen, Q., Liu, R., Li, Y., Shi, Y., Chen, J., Shen, Y., Xiao, Z., Weng, J., Zhang, X., 2018. Traceable Nanoparticles with dual Targeting and ROS Response for RNAi-Based Immunochemotherapy of Intracranial Glioblastoma Treatment. Adv. Mater. 30, e1705054.
Racovita, S., Trofin, M.A., Loghin, D.F., Zaharia, M.M., Bucatariu, F., Mihai, M., Vasiliu, S., 2021. Polybetaines in Biomedical applications. Int. J. Mol. Sci. 22.
Reddy, K.R., Modi, M.W., Pedder, S., 2002. Use of peginterferon a1fa-2a (40 KD) (Pegasys (R)) for the treatment of hepatitis C. Adv. Drug Deliv. Rev. 54, 571–586.
Richter, A.W., Akerblom, E., 1983. Antibodies against polyethylene glycol produced in animals by immunization with monomethoxy polyethylene glycol modified proteins. Int. Arch. Allergy Appl. Immunol. 70, 124–131.
Ruseva, K., Todorova, K., Zhivkova, T., Milcheva, R., Ivanov, D., Dimitrov, P., Alexandrova, R., Vassileva, E., 2023. Novel Triple Stimuli Responsive Interpenetrating Poly(Carboxybetaine Methacrylate)/Poly(Sulfobetaine Methacrylate) Network. Gels 9.
Safra, T., Muggia, F., Jeffers, S., Tsao-Wei, D.D., Groshen, S., Lyass, O., Henderson, R., Berry, G., Gabizon, A., 2000. Pegylated liposomal doxorubicin (doxil): Reduced clinical cardiotoxicity in patients reaching or exceeding cumulative doses of 500 mg/m(2). Ann. Oncol. 11, 1029–1033.
Semak, V., Eichhorn, T., Weiss, R., Weber, V., 2022. Polyzwitterionic Coating of Porous Adsorbents for Therapeutic Apheresis. J. Funct. Biomater. 13.
Shao, Q., Jiang, S., 2015a. Molecular understanding and design of zwitterionic materials. Adv. Mater. 27, 15–26.
Shao, Q., He, Y., White, A.D., Jiang, S.Y., 2012. Different effects of zwitterion and ethylene glycol on proteins. J. Chem. Phys. 136.
Shao, Q., Mi, L., Han, X., Bai, T., Liu, S., Li, Y., Jiang, S., 2014. Differences in cationic and anionic charge densities dictate zwitterionic associations and stimuli responses. J. Phys. Chem. B 118, 6956–6962.
Shen, X., Dirisala, A., Toyoda, M., Xiao, Y., Guo, H., Honda, Y., Nomoto, T., Takemoto, H., Miura, Y., Nishiyama, N., 2023. pH-responsive polyzwitterion covered nanocarriers for DNA delivery. J. Control. Release 360, 928–939.
Shi, D., Beasock, D., Fessler, A., Szebeni, J., Ljubimova, J.Y., Afonin, K.A., Dobrovolskaia, M.A., 2022. To PEGylate or not to PEGylate: Immunological properties of nanomedicine's most popular component, polyethylene glycol and its alternatives. Adv. Drug Deliv. Rev. 180, 114079.
Shimizu, A., Hifumi, E., Kojio, K., Takahara, A., Higaki, Y., 2021. Modulation of double Zwitterionic Block Copolymer Aggregates by Zwitterion-specific Interactions. Langmuir 37, 14760–14766.
Sinclair, A., Bai, T., Carr, L.R., Ella-Menye, J.R., Zhang, L., Jiang, S.Y., 2013. Engineering Buffering and Hydrolytic or Photolabile Charge Shifting in a Polycarboxybetaine Ester Gene delivery Platform. Biomacromolecules 14, 1587–1593.
Sinclair, A., O'Kelly, M.B., Bai, T., Hung, H.C., Jain, P., Jiang, S., 2018. Self-Healing Zwitterionic Microgels as a Versatile Platform for Malleable Cell Constructs and Injectable Therapies. Adv. Mater. 30, e1803087.
Sugahara, K.N., Teesalu, T., Karmali, P.P., Kotamraju, V.R., Agemy, L., Greenwald, D.R., Ruoslahti, E., 2010. Coadministration of a Tumor-Penetrating Peptide Enhances the Efficacy of Cancer Drugs. Science 328, 1031–1035.
Sun, F., Hung, H.C., Yan, W.S., Wu, K., Shimchuk, A.A., Gray, S.D., He, W., Huang, X.L., Zhang, H., 2021. Inhibition of oral biofilm formation by zwitterionic nonfouling coating. J. Biomed. Mater. Res. Part B-Appl. Biomater. 109, 1418–1425.
Szebeni, J., Baranyi, L., Savay, S., Bodo, M., Morse, D.S., Basta, M., Stahl, G.L., Bunger, R., Alving, C.R., 2000a. Liposome-induced pulmonary hypertension: properties and mechanism of a complement-mediated pseudoallergic reaction. Am. J. Phys. Heart Circ. Phys. 279, H1319–H1328.
Szebeni, J., Baranyi, L., Savay, S., Lutz, H.U., Jelezarova, E., Bunger, R., Alving, C.R., 2000b. The role of complement activation in hypersensitivity to pegylated liposomal doxorubicin (DOXIL (R)). J. Liposome Res. 10, 467–481.
Tada, S., Inaba, C., Mizukami, K., Fujishita, S., Gemmei-Ide, M., Kitano, H., Mochizuki, A., Tanaka, M., Matsunaga, T., 2009a. Anti-biofouling properties of polymers with a carboxybetaine moiety. Macromol. Biosci. 9, 63–70.
Tanaka, M., Sackmann, E., 2005. Polymer-supported membranes as models of the cell surface. Nature 437, 656–663.
Tischer, T., Rodriguez-Emmenegger, C., Trouillet, V., Welle, A., Schueler, V., Mueller, J. O., Goldmann, A.S., Brynda, E., Barner-Kowollik, C., 2014. Photo-patterning of non-fouling polymers and biomolecules on paper. Adv. Mater. 26, 4087–4092.
Tsao, C., Yuan, Z.F., Zhang, P., Liu, E., McMullen, P., Wu, K., Hung, H.C., Jiang, S.Y., 2020a. Enhanced pulmonary systemic delivery of protein drugs via zwitterionic polymer conjugation. J. Control. Release 322, 170–176.
Tsao, C., Zhang, P., Yuan, Z.F., Dong, D.Y., Wu, K., Niu, L.Q., McMullen, P., Luozhong, S. J., Hung, H.C., Cheng, Y.H., Jiang, S.Y., 2020b. Zwitterionic Polymer Conjugated Glucagon-like Peptide-1 for Prolonged Glycemic Control. Bioconjug. Chem. 31, 1812–1819.
Veiseh, O., Vegas, A.J., 2019. Domesticating the foreign body response: recent advances and applications. Adv. Drug Deliv. Rev. 144, 148–161.
Wang, Z., Ma, G.L., Zhang, J., Lin, W.F., Ji, F.Q., Bernards, M.T., Chen, S.F., 2014. Development of Zwitterionic Polymer-based Doxorubicin Conjugates: Tuning the Surface Charge to Prolong the Circulation and Reduce Toxicity. Langmuir 30, 3764–3774.
Wang, Z., Ma, G.L., Zhang, J., Yuan, Z.F., Wang, L.G., Bernards, M., Chen, S.F., 2015. Surface protonation/deprotonation controlled instant affinity switch of nano drug vehicle (NDV) for pH triggered tumor cell targeting. Biomaterials 62, 116–127.
Wang, J., Yuan, S.M., Zhang, Y.J., Wu, W., Hu, Y., Jiang, X.Q., 2016. The effects of poly (zwitterions)s versus poly(ethylene glycol) surface coatings on the biodistribution of protein nanoparticles. Biomater. Sci. 4, 1351–1360.
Wang, H.F., Hu, Y., Lynch, D., Young, M., Li, S.X., Cong, H.B., Xu, F.J., Cheng, G., 2018. Zwitterionic Polyurethanes with Tunable Surface and Bulk Properties. ACS Appl. Mater. Interfaces 10, 37609–37617.
Wang, Y.Q., Huang, D., Wang, X., Yang, F., Shen, H., Wu, D.C., 2019. Fabrication of zwitterionic and pH-responsive polyacetal dendrimers for anticancer drug delivery. Biomater. Sci. 7, 3238–3248.
Wang, S., Zhang, F.W., Yu, G.C., Wang, Z.T., Jacobson, O., Ma, Y., Tian, R., Deng, H.Z., Yang, W.J., Chen, Z.Y., Chen, X.Y., 2020. Zwitterionic-to-cationic charge conversion polyprodrug nanomedicine for enhanced drug delivery. Theranostics 10, 6629–6637.
Wang, R.N., Yang, S., Xiao, P.P., Sun, Y., Li, J., Jiang, X.Q., Wu, W., 2022. Fluorination and Betaine Modification Augment the Blood-Brain Barrier-Crossing Ability of Cylindrical Polymer Brushes. Angewandte Chem.-Int. Ed. 61.
Wang, Q., Fu, H., Qi, X., Zhang, L., Ma, H., 2023a. Immobilization of horseradish peroxidase with zwitterionic polymer material for industrial phenolic removal. Biointerphases 18.
Wang, Y., Liu, W., Dong, X., Sun, Y., 2023b. Design of Self-Assembled Nanoparticles as a Potent Inhibitor and Fluorescent Probe for β-Amyloid Fibrillization. Langmuir 39, 12576–12589.
Ward, M., Sanchez, M., Elasri, M.O., Lowe, A.B., 2006. Antimicrobial activity of statistical polymethacrylic sulfopropylbetaines against gram-positive and gram-negative bacteria. J. Appl. Polym. Sci. 101, 1036–1041.
Wei, T., Tang, Z.C., Yu, Q., Chen, H., 2017. Smart Antibacterial Surfaces with Switchable Bacteria-Killing and Bacteria-Releasing Capabilities. ACS Appl. Mater. Interfaces 9, 37511–37523.
Wilson, D.N., 2014. Ribosome-targeting antibiotics and mechanisms of bacterial resistance. Nat. Rev. Microbiol. 12, 35–48.
Xie, J., Lu, Y., Wang, W., Zhu, H., Wang, Z., Cao, Z., 2017. Simple Protein Modification using Zwitterionic Polymer to Mitigate the Bioactivity loss of Conjugated Insulin. Adv. Healthc. Mater. 6.
Xu, J., Lee, H., 2020. Anti-Biofouling strategies for Long-Term Continuous use of Implantable Biosensors. Chemosensors 8.
Yagasaki, T., Matubayasi, N., 2023. Molecular Dynamics Study of the Antifouling Mechanism of Hydrophilic Polymer Brushes. Langmuir 39, 13158–13168.
Yamaoka, T., Tabata, Y., Ikada, Y., 1995. Fate of water-soluble polymers administered via different routes. J. Pharm. Sci. 84, 349–354.
Yang, W., Xue, H., Li, W., Zhang, J., Jiang, S., 2009. Pursuing "Zero" Protein Adsorption of Poly(carboxybetaine) from Undiluted Blood Serum and Plasma. Langmuir 25, 11911–11916.

Yang, Q.H., Wang, L.G., Lin, W.F., Ma, G.L., Yuan, J., Chen, S.F., 2014. Development of nonfouling polypeptides with uniform alternating charges by polycondensation of the covalently bonded dimer of glutamic acid and lysine. J. Mater. Chem. B 2, 577–584.
Yang, J.T., Chen, H., Xiao, S.W., Shen, M.X., Chen, F., Fan, P., Zhong, M.Q., Zheng, J., 2015. Salt-Responsive Zwitterionic Polymer Brushes with Tunable Friction and Antifouling Properties. Langmuir 31, 9125–9133.
Yang, L., Wu, H.S., Liu, Y.Q., Xia, Q.F., Yang, Y., Chen, N.Y., Yang, M., Luo, R.F., Liu, G. Y., Wang, Y.B., 2022. A robust mussel-inspired zwitterionic coating on biodegradable poly (L-lactide) stent with enhanced anticoagulant, anti-inflammatory, and anti-hyperplasia properties. Chem. Eng. J. 427.
Yao, M., Wei, Z., Li, J., Guo, Z., Yan, Z., Sun, X., Yu, Q., Wu, X., Yu, C., Yao, F., Feng, S., Zhang, H., Li, J., 2022. Microgel reinforced zwitterionic hydrogel coating for blood-contacting biomedical devices. Nat. Commun. 13, 5339.
Yin, X.Y., Liang, W.C., Wang, Y.C., Xiao, Y., Zhou, Y., Lang, M.D., 2021. A zwitterionic terpolymer based coating potentially for antibacterial and antifouling applications. Mater. Chem. Phys. 261.
Yu, R., Zhu, R., Jiang, J., Liang, R., Liu, X., Liu, G., 2021. Mussel-inspired surface functionalization of polyamide microfiltration membrane with zwitterionic silver nanoparticles for efficient anti-biofouling water disinfection. J. Colloid Interface Sci. 598, 302–313.
Zhang, Z., Chen, S.F., Jiang, S.Y., 2006. Dual-functional biomimetic materials: Nonfouling poly(carboxybetaine) with active functional groups for protein immobilization. Biomacromolecules 7, 3311–3315.
Zhang, Z., Zhang, M., Chen, S., Horbett, T.A., Ratner, B.D., Jiang, S., 2008. Blood compatibility of surfaces with superlow protein adsorption. Biomaterials 29, 4285–4291.
Zhang, L., Cao, Z.Q., Bai, T., Carr, L., Ella-Menye, J.R., Irvin, C., Ratner, B.D., Jiang, S.Y., 2013. Zwitterionic hydrogels implanted in mice resist the foreign-body reaction. Nat. Biotechnol. 31, 553-+.
Zhang, P., Sun, F., Tsao, C., Liu, S.J., Jain, P., Sinclair, A., Hung, H.C., Bai, T., Wu, K., Jiang, S.Y., 2015. Zwitterionic gel encapsulation promotes protein stability, enhances pharmacokinetics, and reduces immunogenicity. Proc. Natl. Acad. Sci. USA 112, 12046–12051.
Zhang, P., Jain, P., Tsao, C., Sinclair, A., Sun, F., Hung, H.C., Bai, T., Wu, K., Jiang, S.Y., 2016. Butyrylcholinesterase nanocapsule as a long circulating bioscavenger with reduced immune response. J. Control. Release 230, 73–78.
Zhang, P., Jain, P., Tsao, C., Yuan, Z.F., Li, W.C., Li, B.W., Wu, K., Hung, H.C., Lin, X.J., Jiang, S.Y., 2018. Polypeptides with High Zwitterion Density for Safe and Effective Therapeutics. Angewandte Chem.-Int. Ed. 57, 7743–7747.
Zhang, P., Liu, E.J., Tsao, C., Kasten, S.A., Boeri, M.V., Dao, T.L., Debus, S.J., Cadieux, C. L., Baker, C.A., Otto, T.C., Cerasoli, D.M., Chen, Y.T., Jain, P., Sun, F., Li, W.C., Hung, H.C., Yuan, Z.F., Ma, J.R., Bigley, A.N., Raushel, F.M., Jiang, S.Y., 2019. Nanoscavenger provides long-term prophylactic protection against nerve agents in rodents. Sci. Transl. Med. 11.
Zhang, J., Qian, S.X., Chen, L.D., Wu, M.M., Cai, Y.Q., Mou, X.Z., Feng, J., 2022. Antifouling and antibacterial zwitterionic hydrogels as soft contact lens against ocular bacterial infections. Eur. Polym. J. 167.
Zhao, G.F., Sun, Y., Dong, X.Y., 2020. Zwitterionic Polymer Micelles with dual Conjugation of Doxorubicin and Curcumin: Synergistically Enhanced Efficacy against Multidrug-Resistant Tumor Cells. Langmuir 36, 2383–2395.
Zhu, Y., Zhang, J., Yang, J., Pan, C., Xu, T., Zhang, L., 2016a. Zwitterionic hydrogels promote skin wound healing. J. Mater. Chem. B 4, 5105–5111.
Zhu, Y.N., Zhang, J.M., Yang, J., Pan, C., Xu, T., Zhang, L., 2016b. Zwitterionic hydrogels promote skin wound healing. J. Mater. Chem. B 4, 5105–5111.
Zhu, Y.N., Zhang, J.M., Song, J.Y., Yang, J., Du, Z., Zhao, W.Q., Guo, H.S., Wen, C.Y., Li, Q.S., Sui, X.J., Zhang, L., 2020. A multifunctional pro-healing Zwitterionic hydrogel for simultaneous optical monitoring of pH and glucose in diabetic wound treatment. Adv. Funct. Mater. 30.
Zhu, Z.Q., Gao, Q., Long, Z.Y., Huo, Q.Y., Ge, Y.F., Vianney, N., Daliko, N.A., Meng, Y.C., Qu, J., Chen, H., Wang, B.L., 2021. Polydopamine/poly(sulfobetaine methacrylate) Co-deposition coatings triggered by CuSO4/H2O2 on implants for improved surface hemocompatibility and antibacterial activity. Bioactive Materials 6, 2546–2556.