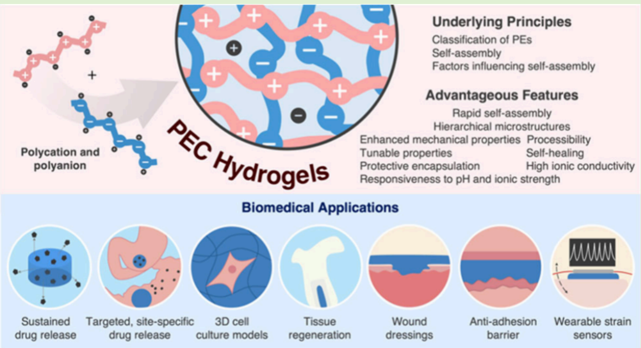
pubs.acs.org/Biomac
Review

Hydrogels Based on Polyelectrolyte Complexes: Underlying Principles and Biomedical Applications

Belynn Sim, Jun Jie Chang, Qianyu Lin, Joey Hui Min Wong, Valerie Ow, Yihao Leow, Yi Jing Wong, Yi Jian Boo, Rubayn Goh,* and Xian Jun Loh*

Cite This: *Biomacromolecules* 2024, 25, 7563−7580

ABSTRACT: Ionic complexes of electrostatically charged biomacromolecules are key players in various biological processes like nucleotide transportation, organelle formation, and protein folding. These complexes, abundant in biological systems, contribute to the function, responsiveness, and mechanical properties of organisms. Coherent with these natural phenomena, hydrogels formed through the complexation of oppositely charged polymers exhibit unique attributes, such as rapid self-assembly, hierarchical microstructures, tunable properties, and protective encapsulation. Consequently, polyelectrolyte complex (PEC) hydrogels have garnered considerable interest, emerging as an up-and-coming platform for various biomedical applications. This review outlines the underlying principles governing PEC hydrogels. The classification of polyelectrolytes and the self-assembly of PEC hydrogels are discussed, including the factors influencing their self-assembly process. Recent developments of PEC hydrogels for biomedical applications, including drug delivery, tissue engineering, wound healing and management, and wearable sensors, are summarized. This review concludes with the prospective directions for the next generation of PEC hydrogel research.

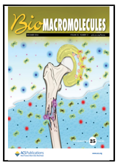


1. INTRODUCTION

Supramolecular hydrogels represent a propitious class of materials with unique properties which arise from their intricate self-assembly driven by noncovalent interactions. Unlike conventional hydrogels that rely on chemically cross-linking polymer chains through covalent bonds, supramolecular hydrogels form three-dimensional networks via reversible interactions, such as hydrophobic interactions, hydrogen bonding, host−guest interactions, ligand coordination, ionic interactions, $\pi-\pi$ bonding, and van der Waals forces.[1] This reversible and dynamic nature of these interactions enables supramolecular hydrogels to impart viscoelastic behavior, injectability, reversibility, repairability, and responsiveness to external stimuli (e.g., temperature and pH), making them a popular choice for biomedical applications.[2−4]

In particular, electrostatic hydrogels, which are supramolecular hydrogels formed from electrostatic interactions, have drawn considerable interest in recent years, as their long-range electrostatic associations promote quicker self-assembly and offer enhanced tunability.[5] This associative behavior is pertinent to numerous biological processes and synthetic applications.[6] In natural systems, ionic complexes of electrostatically charged biomacromolecules play crucial roles in various biological processes, including nucleotide transportation,[7,8] organelle formation,[9] and protein folding.[10−12] The distribution of charges, presence of hydrophobic moieties, and steric effects govern their structural shapes and conformation, ultimately contributing to their function, responsiveness, and tunable mechanical properties within organisms.[6,13] In synthetic applications, oppositely charged polymers can form polyelectrolyte complexes (PECs), which can be engineered into hydrogels.[5,6] Likewise, these dynamic ionic bonds that are formed within PEC hydrogels dictate their resultant responsiveness and properties, bestowing them with a diverse range of unique attributes, such as rapid self-assembly, hierarchical microstructures, responsiveness to stimuli (e.g., pH and ionic strength), tunable mechanical properties, and protective encapsulation.[5,6] These inherent characteristics position them as an enticing materials platform for an array of biomedical applications.[5]

Received: September 10, 2024
Revised: November 8, 2024
Accepted: November 13, 2024
Published: November 18, 2024



https://doi.org/10.1021/acs.biomac.4c01240

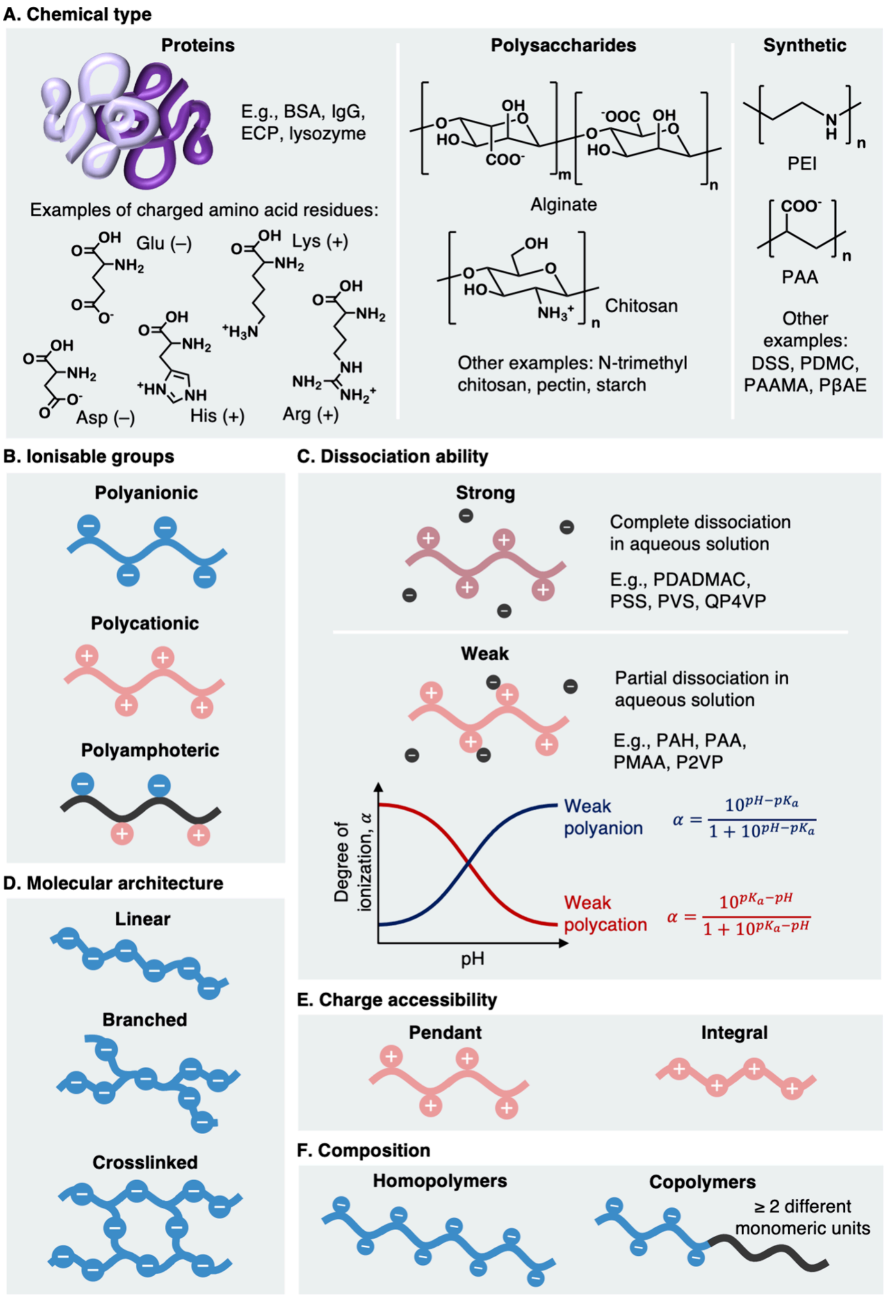


Figure 1. Classification of polyelectrolytes based on various aspects. (A) Chemical types: proteins, polysaccharides, and synthetic polymers. (B) Ionizable groups: polyanionic, polycationic, and polyamphoteric. (C) Dissociation ability: Strong and weak. The degree of ionization is illustrated as a function of pH along with the Henderson–Hasselbalch equations. (D) Molecular architecture: linear, branched, or cross-linked. (E) Charge accessibility: Pendant and integral. (F) Composition: homopolymers with identical monomeric units or copolymers with 2 or more different monomers.

For many biomedical applications, material failure can compromise treatment outcomes. Thus, ensuring the mechanical stability of gels throughout their intended function is paramount to maintaining the efficacy of therapeutic interventions.[14] PEC hydrogels are particularly advantageous in this regard, as they are relatively strong and stable owing to the high binding strengths of electrostatic associations above 5 $\varepsilon k_B T$.[2,15,16] In contrast, most of the other classes of supramolecular gels often demonstrate weak mechanical strength, which is expected due to their relatively lower binding energies.[16−18] While electrostatic interactions can be weakened in aqueous media due to screening effects from mobile counterions, PEC hydrogels can be dialyzed with large amounts of water for the removal of these ions from the hydrogel. This process enhances the mechanical properties of the PEC hydrogels by bringing opposite charges of the polymers closer together, thereby increasing the binding strength and lifetime of these electrostatic interactions.[19,20]

The facile preparation of PECs under mild conditions avoids undesirable consequences such as toxicity related to organic solvents and protein denaturation, especially in the delivery of therapeutic proteins.[21] Furthermore, PEC hydrogels are capable of associating with therapeutic drugs and releasing the payload in response to pH.[21] Most notably, PEC hydrogels

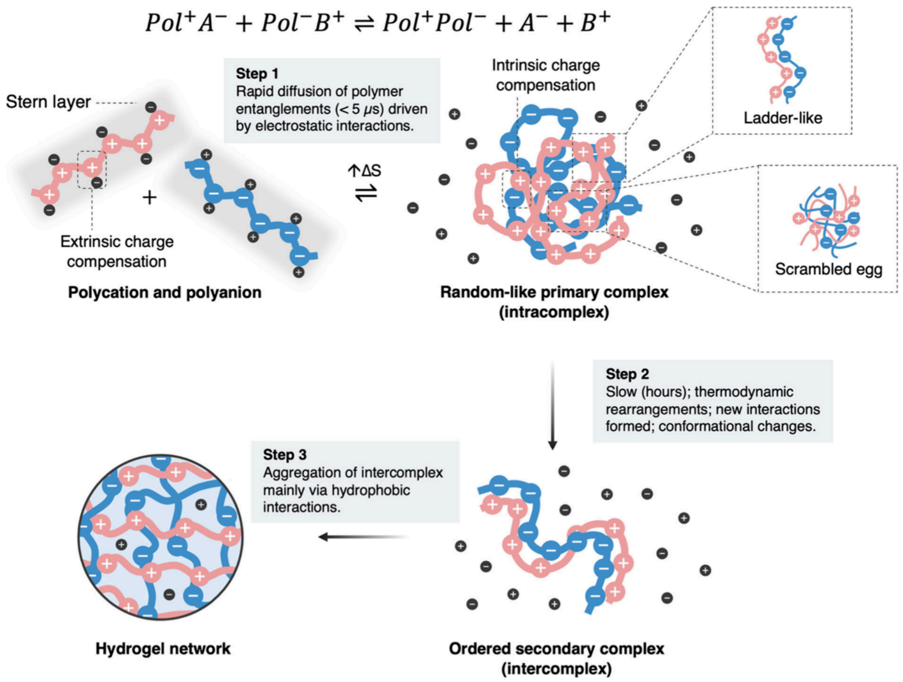


Figure 2. Polyelectrolyte complexation and the self-assembly of PEC hydrogels.

demonstrate the unique ability to selectively partition charged macromolecules, such as proteins, enzymes and nucleotides, within their PEC domains, thereby shielding them from enzymatic degradation and enabling successful transfection into cells,[22,23] a feature absent in other classes of supramolecular gels.

While the terms "coacervate hydrogels" and "PEC hydrogels" are sometimes used interchangeably in literatures, it is important to be clear on the difference between coacervates and PEC hydrogels. Coacervates result from liquid−liquid phase separation, whereas PEC hydrogels form viscoelastic solids. In this review, we aim to provide a holistic overview of the underlying principles governing hydrogels based on PECs. In the following sections, we first introduce the various ways polyelectrolytes can be classified and the self-assembly of PEC hydrogels. We then delve into the extrinsic and intrinsic factors that influence their self-assembly process. Thereafter, we discuss the most recent developments of PEC hydrogels in biomedical applications, which include drug delivery, tissue engineering, wound healing and management, and wearable sensors. Whenever possible, we specifically highlight how electrostatic interactions can endow the hydrogel with the desired properties for the specific biomedical application. Finally, we conclude by outlining prospective directions for the next generation of PEC hydrogel research and the critical knowledge gaps to be addressed. This review stands as the first to uniquely serve as a guide on PEC hydrogels for biomedical applications, setting the stage for future advancements in this emerging field.

2. CLASSIFICATION OF POLYELECTROLYTES

As defined by the International Union of Pure and Applied Chemistry (IUPAC), polyelectrolytes (PEs) are macromolecules bearing a significant proportion of constitutional units with ionic groups that dissociate in polar solvents, such as water.[24] PEs are largely soluble in water and demonstrate unique properties owing to their flexibility and electrostatic interactions.[21,25,26] As such, PEs hold considerable promise for various applications in drug delivery, tissue engineering, wound care, wound management, and wearable sensors.[25,27,28]

As illustrated in Figure 1, PEs can be classified based on several aspects. Depending on their chemical type, PEs can be categorized into proteins, polysaccharides and synthetic polymers. Proteins are composed of amino acids, some of which carry charges, such as aspartic acid, glutamic acid, arginine, histidine and lysine. These charged amino acids allow proteins to adopt an overall net charge depending on the pH of the surrounding environment. Examples include bovine serum albumin (BSA), immunoglobin (IgG), eosinophil cationic protein (ECP) and lysozyme. Polysaccharides, such as alginate and chitosan, as well as synthetic polymers like polyehyleneimine (PEI) and poly(acrylic acid) (PAA), also fall under this classification.[13,29] Another way to classify PEs is by their ionizable groups. PEs can be either polyanionic or polycationic. Polyanions carry acidic groups, such as carboxyls, sulfates or phosphate, whereas polycations possess basic groups, like amines and phosphonium. Polyampholytes constitute a special class of PEs that bear both basic and acidic groups.[27] Peptides and proteins have been recognized as the most common examples of polyampholytes.[25]

PEs can also be classified by their dissociation ability. Strong PEs undergo complete dissociation in aqueous solutions, maintaining a constant charge regardless of pH. Inversely, weak PEs partially dissociate, and their charge is greatly influenced by the pH of the surrounding medium.[21] The ionization degree (α) of weak PEs can be calculated using the Henderson−Hasselbalch eq (Figure 1C). This relationship allows for the estimation of α based on the pK_a of the ionizable groups and the surrounding pH.[30] Experimentally, the degree of ionization can be determined through potentiometric titration, where the pH of the solution is systematically varied while measuring the charge,[31] or by zeta potential measurements, which assess the surface charge of PEs in solution.[32]

Additionally, PEs can be categorized based on their molecular architectures (e.g., linear, branched, and cross-linked).[21] Depending on the accessibility of the charged groups, PEs can be either of pendant type, where charged groups are affixed as side groups, or integral type, where charged groups are incorporated into the backbone chain.[33] Finally, PEs may be further classified as homopolymers or copolymers with two or more different monomeric units.[21]

Understanding the classification of PEs is fundamentally important for selecting appropriate PEs when designing PEC hydrogels for specific biomedical applications. For example, the choice of molecular architecture—whether linear, branched, or cross-linked—can affect the swelling behavior and mechanical integrity of the PEC hydrogel, which is crucial for applications like tissue regeneration or wearable sensors. Additionally, weak PEs that exhibit pH-dependent charge behavior would be ideal for formulating hydrogels that can release drugs in response to specific pH conditions, such as in acidic tumor microenvironments. By strategically selecting PEs based on these classifications, the properties of PEC hydrogels can be tailored to meet the specific demands of diverse biomedical applications.

3. SELF-ASSEMBLY OF HYDROGELS BASED ON POLYELECTROLYTE COMPLEXES

Polyelectrolyte complexes (PECs) are formed due to the electrostatic interactions between oppositely charged PEs in solution accompanied by a concurrent release of low molecular weight counterions.[13,34] This expulsion of counterions drives the complexation process and can be described by the simple reaction of a polyanion (Pol^-) and polycation (Pol^+), resulting in the formation of a PEC ($\mathrm{Pol}^-\mathrm{Pol}^+$). Prior to complexation, the ionic charge groups of PEs are extrinsically compensated with a Stern layer of counterions that are spatially confined (Figure 2). When oppositely charged PEs are mixed together, including but not limited to a stoichiometric ratio of 1:1, Coulombic attraction manifests and persists to a point where charge neutralization occurs between the charged groups of both PEs. Consequently, counterions are no longer required for charge compensation and are expelled into the bulk solution.[21,35,36] This expulsion of charge contributes to an increase in entropy of the system, conferring PE complexation as an entropically driven process.[37,38] As a result, an interpolymer ion pair, referred to as a PEC, is formed, where ionic charges between PEs are intrinsically compensated by each other.[38]

The self-assembly of a PEC hydrogel incorporates three main steps (Figure 2). In the first step, there is rapid diffusion ($<5\ \mu$s) of mutual entanglements between polymer chains driven by electrostatic interactions, resulting in the assembly of a random-like primary complex immediately upon mixing the oppositely charged PE solutions.[25,39] The second step proceeds slower in the order of hours, in which thermodynamic arrangements happen within the intracomplex to obtain an ordered secondary complex. During this process, new interactions (e.g., ionic bonds and hydrogen bonds) are formed and distorted PE chains are redistributed to attain a new conformation that is closer to equilibrium.[25,29,39] In the final step, intercomplex aggregation occurs as the secondary complexes accumulate together primarily via hydrophobic interactions, resulting in the formation of a hydrogel network.[29]

Over the years, researchers have proposed two models, namely the ladder-like model and the scrambled-egg model, based on the supramolecular order of polymer chains in a stoichiometric PEC to facilitate the understanding of PEC formation and their structures (Figure 2).[29,39] Typically, a low concentration of PEs results in a ladder-like structure with ordered chain packing. Conversely, a scrambled-egg structure with disordered packing is attained when the concentration of PEs is high.[37] Nevertheless, these two models only represent limiting cases. The appropriate model that better aligns most PEC systems often lies somewhere between these two models but leans more toward the scrambled-egg model than the ladder-like model.[40] Importantly, the self-assembly process and final morphology of PEC hydrogels are influenced by a range of factors, which will be discussed further in Section 4.

4. FACTORS INFLUENCING SELF-ASSEMBLY OF PEC HYDROGELS

The self-assembly and formation of PEC hydrogels is strongly influenced by both intrinsic factors and extrinsic factors. Intrinsic factors pertain to the characteristics that are associated with the polymers themselves, whereas extrinsic factors are associated with the external aqueous environment.[41] These factors also have profound influence on the stability and mechanical properties of PEC hydrogels. A fundamental understanding of these factors is necessary for tailoring PEC hydrogels with optimized properties for specific biomedical applications.

4.1. Intrinsic Factors.

The molecular weight (M_w) of oppositely charged polymers is among the intrinsic factors that influence the gelation and mechanical properties of the PEC hydrogels.[42,43] In general, high M_w PEs tend to result in stiffer and more stable PEC hydrogels due to their greater capacity for chain entanglement and stronger electrostatic interactions, thereby forming a denser and more interconnected network. For instance, one study demonstrated that complexing chitosan and sodium alginate of similarly high M_w ($\sim 10^5$ Da) formed PEC hydrogels with high tensile strength of 12.3 MPa. In contrast, PEC hydrogels that were formed by complexing chitosan ($M_w \approx 10^5$ Da) with lower M_w polysaccharides (e.g., carrageenan, chondroitin, and heparin sodium) exhibited much lower tensile strength.[44] However, it is also important to note that while high M_w often enhances the mechanical properties of the gel, M_w similarity between PEs influences the primary complexes formed. When the M_w of PEs is similar, a ladder-like structure is typically observed. In this scenario, the tight internal binding of the PEs limits solvent penetration and hinders gel network formation. On the other hand, when the M_w of the PEs differs significantly, a scrambled egg structure is formed, where the polymers can rearrange themselves and aggregate more effectively into a gel network. For example, in PEC hydrogels composed of chitosan and *Mesona chinensis* polysaccharide, the gels with different M_w PEs had higher viscosity, water-holding capacity and storage modulus as compared to the gels prepared from similar M_w PEs.[42]

Charge density, which refers to the number of charged groups per unit length of polymer chain, also plays an important role in influencing both the gelation and mechanical properties of PEC hydrogels. PEs with higher charge densities form stronger electrostatic interactions between the oppositely charged polymers, leading to the formation of tighter and more compact PEC domains. This results in enhanced mechanical

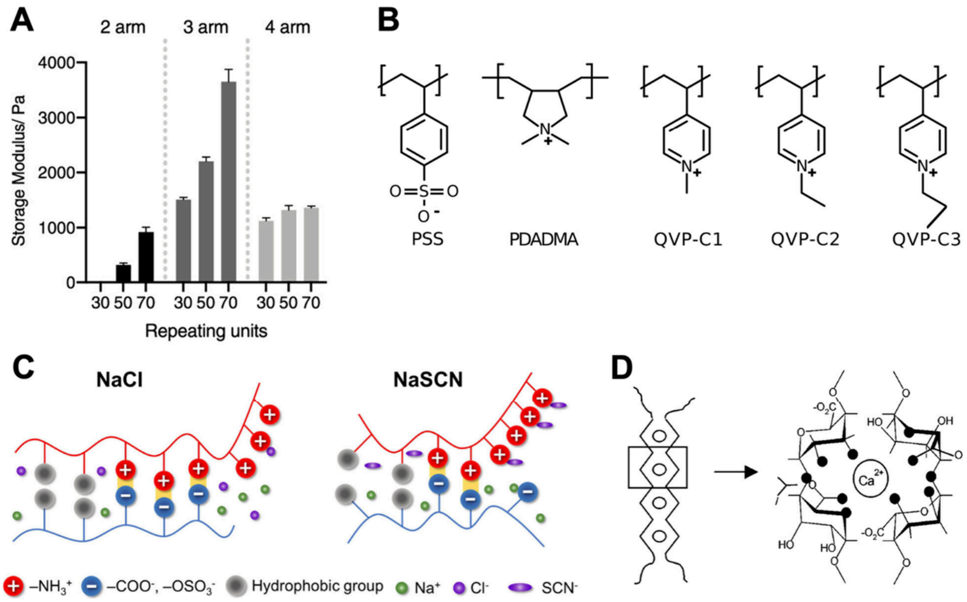


Figure 3. (A) Correlation between the number of arms in PEs and the storage modulus of the resultant PEC hydrogel. Reproduced with permission from ref.[43] Copyright 2023 American Chemical Society. (B) From left to right: anionic poly(styrenesulfonate) (PSS) and cationic poly(4-vinylpyridine) (P4VP) with increasing hydrophobic substituents (methyl, ethyl, and propyl groups). Reproduced with permission from ref.[6] Copyright 2017 American Chemical Society. (C) The effect of kosmotropic ions (e.g., Cl^-) and chaotropic ions (e.g., SCN^-) on the electrostatic interactions within PECs. Reproduced with permission from ref.[46] Copyright 2023 Elsevier. (D) Illustration of an "egg-box" structure attained when Ca^{2+} is chelated by two guluronic acid blocks of sodium alginate. Reproduced with permission from ref.[47] Copyright 2001 American Chemical Society.

stiffness and stability of the hydrogel. In a study done by You et al., quarternization was performed on chitosan to increase its charge density and solubility. The quarternized chitosan (QCh) exhibited stronger electrostatic interactions with PAA within the QCh/PAA hydrogel matrix. As a result, the QCh/PAA hydrogel demonstrated improved mechanical strength and self-recovery properties as compared to the PEC hydrogels composed of PAA and unmodified chitosan, which had a lower charge density.[45]

The molecular architecture of the PEs is another intrinsic factor that impacts the formation and mechanical properties of PEC hydrogels. PEs with multiple charged side chains or complex architectures tend to form more robust gel networks due to the availability of additional sites for ionic interactions. A notable study by Nguyen et al. revealed that polymer architecture, particularly the number of arms in the PEs, directly influences the stiffness of the resultant PEC hydrogel. The study demonstrated that increasing the number of arms leads to the formation of more PEC domains, thereby stiffening the gel and decreasing its pore size (Figure 3A). However, excessive increase in the number of arms may cause the oppositely charged arms to become too distant to form effective ionic interactions, consequently lowering stiffness.[43]

The hydrophobicity of PEs influences the stability and resistance of PEC hydrogels against salt doping, which in turn affects the formation and mechanical properties of the hydrogels. Hydrophobic interactions reduce swelling in response to salt, thereby preserving the hydrogel's structural integrity and stiffness. For instance, Sadman et al. quaternized cationic poly(4-vinylpyridine) (P4VP) with increasing hydrophobic substituents (methyl, ethyl, and propyl groups) and complexed with anionic poly(styrenesulfonate) (PSS) (Figure 3B). As the hydrophobicity of the complexes increased with longer substituent chains, the PECs had greater resistance to swelling in saline environments, resulting in a lower swelling ratio and greater stiffness.[6] This illustrates how hydrophobic modifications can improve the stability and mechanical strength of PEC hydrogels, particularly in high-salinity conditions.

Lastly, the stiffness of PEs is a determining factor of the structure of PECs, which may affect the formation and resulting properties of PEC hydrogels. Simulations indicate that rigid PE chains tend to organize into ladder-like PEC structures, whereas flexible PEs form scrambled egg PEC structures.[48] However, the effect of PE stiffness specifically on PEC hydrogel formation remains less understood. Based on the simulations, it can be postulated that rigid PEs, forming ladder-like PECs, might hinder hydrogel network formation. In contrast, flexible PEs forming scrambled-egg PECs may enable more effective chain aggregation and gel network development. Investigating PE stiffness within hydrogel systems could be invaluable, potentially revealing how chain rigidity affects properties like network density, swelling behavior, and mechanical resilience.

4.2. Extrinsic Factors.

Besides intrinsic factors, multiple extrinsic factors ranging from polymer stoichiometric ratios,[49] to pH,[50] to type of salt and ion concentration[51] in the aqueous environment significantly influence the self-assembly process of PEC hydrogels. Stoichiometry of positively to negatively charged groups is of essence to the self-assembly of PEC hydrogels. An excess of either positively or negatively charged groups lowers the degree of complexation. This imbalance introduces electrostatic repulsion within the polymeric matrix, which reduces the amount of physical cross-links formed and consequently inhibits the formation of PEC hydrogel.[51] By achieving an approximately equimolar ratio of opposite charges, optimal cross-linking density can be achieved, thereby promoting the formation of PEC hydrogels.

Table 1. Summary of the Key Benefits of PEC Hydrogels in Comparison to the Challenges Faced by Other Classes of Hydrogels for Specific Biomedical Applications

Biomedical application	Key benefits of PEC hydrogels	Challenges faced by other classes of hydrogels
Drug delivery	• Sustained drug release • pH-triggered release for targeted, site-specific delivery • Loading efficiency of up to 100%	• Lack of ionic interactions • Limited encapsulation of hydrophilic, charged proteins • Frequent initial burst release • Lack of pH-responsiveness
Tissue engineering	• Processable, yet mechanically stable • Tunable viscoelasticity • Better resemblance to ECM • Encapsulation of ionically charged therapeutics	• Lack of ionic interactions and counterions • Lack of balance between processability and mechanical stability
Wound healing and wound management	• *In situ* gelation • Responsive to wound conditions such as pH and ionic strength • Self-healable • Anti-adhesion properties	• Limited responsiveness to wound environment • Typically softer and lack mechanical strength
Wearable sensors	• High ionic conductivity • Self-healable • Mechanically resilient • Anti-freezing when embedded with salts	• Often lack ionic conductivity • Lack of balance between self-healing and mechanical performance

PEC hydrogels composed of weak PEs are highly sensitive to the pH of the bulk aqueous environment as pH dictates the degree of protonation and thus the ratio of charged groups within the hydrogel.[52] Chitosan and its derivatives are commonly employed in PEC hydrogels where an acidic environment would protonate their amine groups to generate the positive charges for complexation to occur.[53] Chitosan is frequently paired with carboxylic acid bearing polymers such as salecan and sodium alginate, as their carboxylic groups are deprotonated into anionically charged carboxylates in an alkaline environment. However, an alkaline environment would also deprotonate the amine groups in chitosan into its electroneutral state, which disrupts the charge balance and inhibits the formation of PEC hydrogels.[53] To overcome this, strategies such as incorporating buffering systems or adjusting the pH of the aqueous media are employed to balance the necessary charge states for PEC hydrogel formation.[54−56]

In addition to the charge ratio, which can be tuned by varying polymer stoichiometry or pH, the type and concentration of salts significantly influence the self-assembly behavior of PEC hydrogel.[5,42] Salts can interfere with the self-assembly of PEC hydrogels through electrostatic shielding[51] or promote gel formation by forming strong ion bridges via chelation.[42,51,57,58] Aside from these mechanisms, the specific ion effects of kosmotropic and chaotropic salts also affect the complexation and stability of PEC hydrogels by modulating interactions between the PEs and hydrophobicity.[46] Kosmotropic ions, which are hydrated and less polarizable ions (e.g., Cl^-), generally do not interact with PEs and behave as co-ions in solution (Figure 3C). In contrast, chaotropic ions (e.g., SCN^-), which are dehydrated and highly polarizable, tend to break the intrinsic ion pairs between PEs and form extrinsic ion pairs with the PEs instead. This substitution increases the PEC's hydrophobicity, thereby encouraging aggregation and facilitating the formation of a PEC hydrogel network. At higher ion concentration, both kosmotropic and chaotropic ions can disrupt the intrinsic PE ion pairs, resulting in electrostatic screening effect.[46] This screening effect reduces electrostatic interactions between the oppositely charged PEs, weakening the cross-links essential to the formation of PEC hydrogels.[51] This effect is more pronounced for ions that are small and highly charged, such as the monovalent ions Na^+ and K^+, which bind more effectively to the PEs and increase the extent of charge screening.[42] While high salt concentration generally hinders the formation of PEC hydrogels, low salt concentrations can introduce slight electrostatic shielding, which paradoxically promotes PEC hydrogel formation. This reduces the strength of the Coulombic attraction between PEs, enhancing the matrix flexibility and in turn enabling the formation of PEC hydrogels with improved water uptake ability.[42]

In contrast to the inhibitory effect of salts, specific ions such as Ag^+ and Ca^{2+} have been shown to strengthen PEC hydrogels as they can be chelated by the polymer matrixes.[51] Ag^+ forms bidentate complexes with both the carboxylic acid and amine groups in a chitosan/sodium alginate PEC hydrogel.[51] On the other hand, it is well-known that Ca^{2+} can be chelated by two guluronic acid blocks of sodium alginate,[51] thus forming a reversible and strong cross-linked network with an "egg-box" structure (Figure 3D).[47,59] These act as additional cross-links to promote PEC hydrogel formation and thus an increase in concentration of these ions is associated with increased hydrogel stiffness.[42] Besides ions involved in chelation, oxoanions[60] are also found to aid PEC hydrogel self-assembly as they tune the positive−negative charge ratio by promoting the protonation of amine groups (usually on chitosan) in acidic aqueous environments.[42] This results in enhanced electrostatic interaction, which together with hydrogen bonding between the polymers, leads to synergistic improvement in PEC hydrogel formation.[42]

Temperature also influences the formation and mechanical properties of PEC hydrogels by altering the stability of ionic bonds between oppositely charged PEs. Ionic bonds within PEC hydrogels exhibit temperature dependence, where an increase in temperature initiates thermally activated bond dissociation. As temperature rises, ionic bond breakage occurs at a faster rate, weakening the ionic bond strength and reducing bond lifetime. This impairs the gel's structural integrity, forming a softer gel with lower modulus.[61] Despite this temperature-induced softening, it has been shown that prolonged exposure to elevated temperatures through thermal annealing promotes the reconfiguration and reformation of

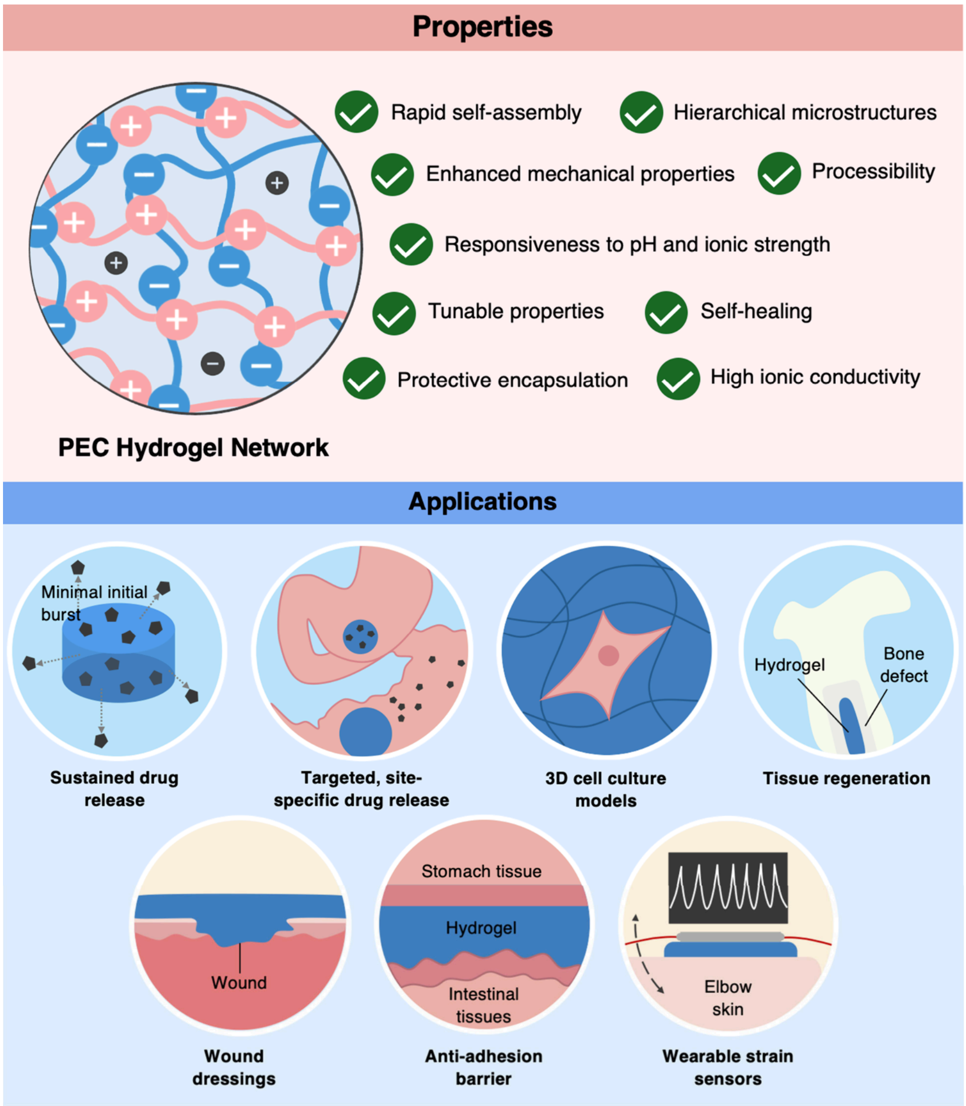


Figure 4. Unique properties that PEC hydrogels exhibit and their biomedical applications.

ionic bonds, increasing the ionic bond density over time. With a greater number of ionic associations within the PEC hydrogel, a denser network with larger modulus but lower breaking strength is achieved.[62]

5. BIOMEDICAL APPLICATIONS

As a fascinating class of supramolecular hydrogels, PEC hydrogels offer a broader range of unique opportunities for biomedical applications as compared to those of other classes (Table 1). To be utilized as biomaterials, hydrogels must be composed of biocompatible materials to ensure they do not yield cytotoxic or immunogenic byproducts upon degradation.[63] As such, PEC hydrogels formulated from naturally occurring peptides, polysaccharides, and well-established biocompatible polymers like polyethylenimine, poly(acrylic acid) , alginate and chitosan are widely favored. Over the past 9 years, PEC hydrogels have mainly gained traction in areas of therapeutic delivery (Section 5.1), tissue engineering (Section 5.2), wound healing and wound management (Section 5.3), as well as wearable sensors (Section 5.3). In this section, we explore these applications of PEC hydrogels in greater detail while highlighting the unique properties conferred by the electrostatic associations within the PECs (Figure 4).

5.1. Drug Delivery. Conventional therapeutic delivery methods are limited by a plethora of disadvantages such as the need for repeated administration due to the short half-lives of drugs, poor patient compliance, compromised efficacy, systemic toxicity and adverse side effects associated with high dosages.[64−66] To overcome these hurdles, research efforts are steered toward developing drug delivery systems that are able to localize and control the delivery of drugs.[64] Injectable stimuli-responsive hydrogels composed of hydrophobic−hydrophilic−hydrophobic copolymers have been extremely popular for their ability to undergo sol−gel transition when injected *in vivo* without surgery, thus enhancing patient compliance.[67−69] These copolymers form micelles that aggregate into a gel network via hydrophobic interactions. While these hydrogels effectively encapsulate hydrophobic drugs within the micellar cores, encapsulating hydrophilic compounds such as charged proteins remain challenging.[68] Even when successful, these compounds frequently experience burst release during the hydrogel's initial swelling, especially if their size is smaller than the hydrogel's pore size.[69]

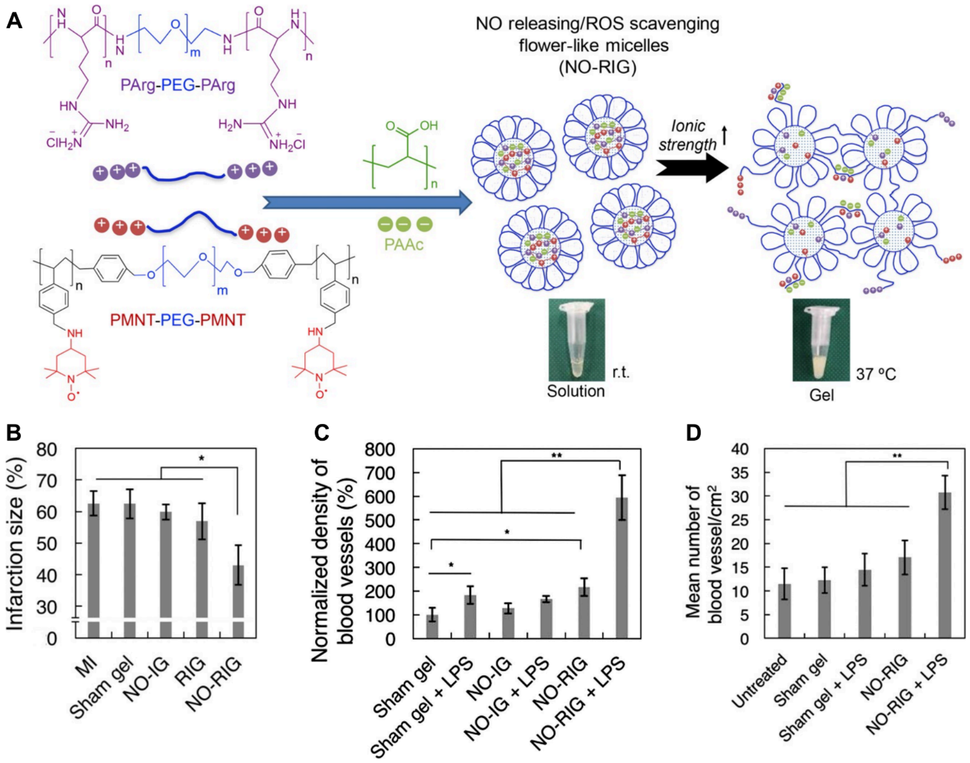


Figure 5. (A) Schematic of NO-releasing and ROS-scavenging PEC hydrogel (NO-RIG). (B) Infarction size of mice models (*, $P < 0.05$, $n = 6-7$). (C) Quantification of angiogenesis at the injected areas (*, $P < 0.05$; **, $P < 0.01$, $n = 3-4$). (D) Mean number of blood vessels at the vicinity of the areas injected with gel (**, $P < 0.01$, $n = 3-4$). Reproduced with permission from ref.[72] Copyright 2018 Elsevier.

In recent years, advancements in PEC hydrogels have shown promising results in efficiently encapsulating hydrophilic compounds, minimizing burst release, and extending sustained release profiles. For instance, Nagasaki and his research group developed a redox-active, injectable hydrogel (RIG) based on PECs, which is composed of anionic poly(acrylic acid) (PAAc) and a cationic polyamine-poly(ethylene glycol)-polyamine (PMNT−PEG-PMNT) copolymer with reactive oxygen species (ROS)-scavenging moieties, for local protein therapeutics.[68] Aside from gelating in response to an increase in temperature, the protein-loaded PEC micellar formulation also underwent gelation in response to an increase in ionic strength under physiological conditions when injected *in vivo*. This unique gelation response involves the partial disintegration of the PEC core due to the electrostatic shielding effect as ionic strength increases, followed by the cross-linking of collapsed PE segments via electrostatic interactions. Consequently, the PEC hydrogel exhibits high mechanical strength and stability, which results in prolonged retention time *in vivo*. Irrespective of the protein drug type, *in vitro* studies have demonstrated sustained release profiles of proteins over 2 weeks with minimal initial burst. This ideal release behavior is not only attributed to the hydrophobic interactions between the protein and the triblock copolymer but also electrostatic interactions between the charged proteins and the PEC hydrogel network, thus enabling stable encapsulation and suppression of rapid diffusion. When loaded with interleukin-12 (IL-12) for antitumor immunotherapy, subcutaneous injection of the PEC hydrogel effectively inhibited tumor growth in tumor-bearing mice compared to pristine IL-12.[68] Leveraging on these benefits, the research group employed the same PEC hydrogel system to deliver lidocaine for postoperative pain management.[70] Lidocaine, with its short half-life and hydrophilic nature, presents challenges for cellular internalization, resulting in compromised efficacy as a local anesthetic.[70,71] However, the injectable and mechanically resilient PMNT−PEG-PMNT/PAAc PEC hydrogel system, which has a significantly higher storage modulus than conventional amphiphilic gels, stably encapsulated cationic lidocaine within the gel network and demonstrated continuous release of lidocaine for over 3 days without any obvious burst release. *In vivo* evaluation in a carrageenan-induced arthritis mouse model unveiled that the lidocaine-loaded RIG elicited a prolonged and potent analgesic effect compared to pristine lidocaine.[70] Subsequently, Nagasaki and his research group incorporated cationic poly(L-arginine)-PEG-poly(L-arginine) (PArg−PEG-PArg) into the redox-active PMNT−PEG-PMNT/PAAc PEC hydrogel formulation to generate nitric oxide (NO) via local enzymatic reactions of PArg, while also scavenging overproduced ROS, thereby regulating local NO levels for effective cardiovascular treatment (Figure 5A).[72] NO, a bioactive gas that is endogenously generated, is essential to protect and regulate cardiovascular functions.[73,74] However, its therapeutic utility is hampered by its short half-life and limited bioavailability, especially in inflamed tissues where excessive ROS generated instantaneously react with endogenous NO.[72] The newly formulated PArg−PEG-PArg/PMNT−PEG-PMNT/PAAc PEC hydrogel system exhibited prolonged retention time and achieved uniform distribution of the gel in myocardial tissue for more than 10 days, which in turn extended the therapeutic effect in mice with myocardial infarction (MI). Treatment of MI with the PArg−PEG-PArg/PMNT−PEG-PMNT/PAAc PEC hydrogel *in vivo* resulted in a considerable reduction in infarction size and improved heart function (Figure 5B). In addition, improved angiogenesis and new blood vessel formation was achieved, indicating the effectiveness of the PEC hydrogel in regulating the release of NO (Figure 5C,D).[72]

PEC hydrogels have also emerged as a novel carrier for targeted site-specific delivery of therapeutics owing to the synergistic interactions between oppositely charged PEs. Several PEC hydrogels with the ability to release their therapeutic payloads in response to pH variations have been developed.[50,75−77] This property is exploited by Hujaya et al., who employed a PEC hydrogel prepared by physically mixing anionic and cationic cellulose nanofibrils derivatives at a low concentration of 0.5% w/w in acetate buffer.[77] Through this approach, they achieved a controlled and pH-responsive release of doxorubicin (DOX). At physiological pH 7.4, DOX release from the hydrogel was restricted because of the interactions between the protonated amine groups in DOX and carboxylates in the anionic cellulose nanofibrils. Conversely, DOX release was enhanced at pH 4 because of the protonation of the carboxylic groups, which reduces the Coulombic interactions with DOX and facilitates its diffusion from the gel network. This pH-dependent release profile of DOX from the PEC hydrogel enables selective inhibition of drug release in healthy tissues, thereby mitigating the potential adverse effects from the cytotoxic drug, while facilitating targeted delivery in acidic pathophysiological environments, such as tumor tissues, which exhibit slightly lower pH than healthy tissues.[77,78]

The versatility of PEC hydrogels in providing pH-triggered and sustained release profiles can be extended to other therapeutic agents for site-specific delivery. In the context of the gastrointestinal (GI) tract, this property of PEC hydrogels is valuable for protecting drugs that are prone to decomposition or degradation in the acidic environment of the stomach, thus facilitating their intact delivery to the intestines for absorption and subsequent therapeutic effect.[50,75,76] Hu et al. formulated a PEC hydrogel using oppositely charged polysaccharides, chitosan and salecan, as a sophisticated nutrient delivery platform for the targeted release of vitamin C (VC) in intestines.[50] The PEC hydrogel exhibited a compact and rigid network structure with a high storage modulus, demonstrating mechanically stability owing to the strong electrostatic interactions between the cationic amino groups of chitosan and the anionic carboxyl groups of salecan. *In vitro* studies revealed inhibited release of VC in simulated gastric fluid (SGF, pH 1.2), primarily ascribed to the protonation of carboxyl groups within the PEC gels in SGF, which resulted in the formation of strong hydrogen bonding, thereby densifying the gel network, and impeding the release of VC. In contrast, a substantially higher release of VC was observed in simulated intestinal fluid (SIF, pH 7.4) in a swelling-controlled manner due to the deprotonation of carboxyl groups within the PEC hydrogel. This mechanism allowed for a much higher concentration of VC to be maintained in the bloodstream as compared to pristine VC. These findings highlighted the notable potential of PEC hydrogels for site-specific nutrient delivery in the intestine.[50] In another similar example, Lv et al. further elucidated the swelling behavior of PEC hydrogels in this pH-triggered release mechanism. They prepared a PEC hydrogel from cationic carboxymethyl chitosan (CMCS) and anionic alginate for the oral delivery of protein drugs via the GI tract.[76] The hydrogel prepared with a CMCS/alginate weight ratio of 1/2 exhibited impressive pH response, with the swelling ratio in SIF being 34 times higher compared to that in SGF. The low swelling ratio of the CMCS/alginate hydrogel in SGF minimizes the release of a protein model drug, Bovine Serum Albumin (BSA), whereas a high swelling ratio of the CMCS/alginate hydrogel in SIF enhances its release.[76] Therefore, the pH-triggered site-specific sustained release achieved by using PEC hydrogels represents a promising advancement in oral delivery of drugs, offering a noninvasive alternative to other methods and thus making a substantial stride in pharmaceutical advancements.

As drug delivery carriers, PEC hydrogels are typically prepared in a facile manner by mixing the therapeutic agent with the oppositely charged PEs.[69] This method often achieves near-complete loading efficiency of up to 100% and allows for easy adjustment of the loaded therapeutic agent according to patient-specific requirements.[77] Despite this, researchers have attempted to further enhance drug loading capacities of PEC hydrogels by incorporating additional chemical cross-linkers. For instance, Hoang et al. chemically cross-linked a pH-responsive PEC hydrogel composed of PAAc and norbornene-functionalized chitosan with bistetrazine-poly(*N*-isopropylacrylamide) (bisTz-PNIPAM) via inverse electron demand Diels−Alder click reaction (iED-DA) for colon-targeted drug delivery.[75] Through this approach, additional chemical cross-links were introduced within the PEC hydrogel, which enhanced the porosity of the gel for drugs to diffuse into and reside within the matrix. Consequently, this enabled high drug loading and subsequent release of 5-ASA in a simulated colon environment.[75] In addition to the versatility and tunability of PEC hydrogels in encapsulating therapeutic agents, this example underscores the ease in which their drug loading capacities can be further enhanced. However, the introduction of chemical cross-links transforms the hydrogel into a covalently cross-linked gel, losing its supramolecular and reversible properties.

5.2. Tissue Engineering. Hydrogels are highly appealing as three-dimensional (3D) scaffolds owing to their resemblance, both structurally and functionally, to cellular microenvironments.[79] Alginate hydrogels ionically cross-linked with divalent ions exhibit commendable strength and stability due to their strong electrostatic associations. As such, they are highly favored for cell encapsulation and as matrices for cellular growth.[80,81] These hydrogels have been explored for various biomedical applications as they possess porosity that enables efficient nutrient exchange and sustains cell viability over extended durations, both *in vitro* and *in vivo*.[2] However, over time, the presence of Ca^{2+}−alginate bonds within the gel diminishes due to gradual release of Ca^{2+}. It has been shown that the release of Ca^{2+} can undesirably trigger the upregulation of inflammatory cytokines and chemokines upon subcutaneous injection of the hydrogels into mice.[82]

In contrast, PEC hydrogels formed through electrostatic interactions between oppositely charged PEs offer superior mechanical stability. For instance, Nurlidar et al. fabricated a PEC hydrogel using polycationic arginylated poly(Pro-Hyp-Gly) and polyanionic succinylated poly(Pro-Hyp-Gly) as a three-demensional (3D) scaffold for tissue regeneration[83] This PEC hydrogel exhibited remarkable stability for more than 2 weeks under physiological conditions. In addition, rat bone marrow stromal cells were successfully encapsulated within the hydrogel during gel formation, which maintained their viability, proliferated, and formed multicellular aggregates *in vitro*. Beyond their mechanical stability, PEC hydrogels are well-

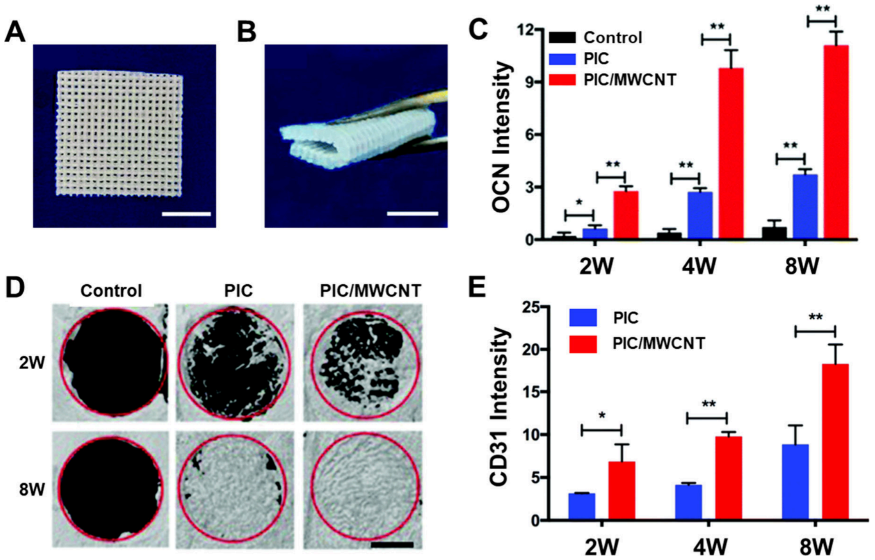


Figure 6. (A) PIC/MWCNT with interconnected grid structures (scale bar = 5 mm). (B) Twisting PIC/MWCNT scaffold. (C) Quantitative analysis of osteogenic-specific gene, osteocalcin (OCN) positive staining postimplantation. (D) Sagittal section of microcomputed tomography images showing bone regeneration postimplantation (scale bar = 2 mm). (E) Quantitative evaluation of CD31 immunohistochemical staining for vascularization at the bone repair site postimplantation (*, $p < 0.05$; **, $p < 0.01$). Reproduced with permission from ref.[89] Copyright 2019 The Royal Society of Chemistry.

established as advantageous for tissue engineering applications as they exhibit tunable modulus and similar structures with the native extracellular matrix.[5,27] Unlike conventional hydrogels, PEC hydrogels are composed of counterions within the gel network, which allow them to respond to electrical stimuli. These counterions enable the PEC hydrogel to undergo electro-chemomechanical contraction, a process in which the hydrogel mechanically deforms or contracts in response to an electric field, similar to biological tissues responding to electrical impulses.[84] This ability to mimic biological responses makes PEC hydrogels ideal matrices or scaffolds that promote cellular growth and tissue regeneration.[27]

In tissue engineering applications, achieving a balance between mechanical performance and processability is crucial for scaffold design. However, tough hydrogels often encounter challenges related to processability. PEC hydrogels emerge as a promising solution to this issue, as evident in several studies. For example, Zhu et al. showcased that PEC hydrogels can possess both toughness and easy processability by adjusting their mechanical properties with salt. By introducing saline water to plasticize a PNaSS/PMPTC PEC hydrogel, they created weak yet highly viscoelastic gels capable of adapting and maintaining their shape when processed via compression molding and extrusion. This behavior arises from the electrostatic screening of charge groups on the PEs by the salt, which weakens the ionic associations between them. Subsequent dialysis removes the salts and counterions, facilitating ionic bond recovery to ultimately yield tough hydrogels with favorable mechanical properties. In fact, the mechanical properties of the final hydrogel can be finely tuned by modulating the ratio of charge groups in the PEC hydrogel. Consequently, the convenient tunability of PEC hydrogels' mechanical properties allows the gels to achieve both toughness and processability, rendering them versatile and ideal for constructing tissue engineering scaffolds. Taking advantage of the processability and good mechanical properties inherent in PEC hydrogels, Chiellini et al. employed a computer-aided wetspinning (CAWS) technique to fabricate layered microstructured PEC hydrogels.[85] These intricately layered hydrogels, composed of poly(γ-glutamic acid) and chitosan, facilitate the construction of a long-term 3D *in vitro* culture model of pancreatic ductal adenocarcinoma with human pancreatic cancer cell line BxPC-3. Through this innovative approach, BxPC-3 cells were uniformly colonised within the 3D scaffold and exhibited a duct-like structure differentiation—a hallmark of pancreatic cancer. Furthermore, the cultured BxPC-3 cells on the 3D PEC hydrogel formed multicellular spheroids and overexpressed specific tumor markers such as fascin and cytokines *in vitro*. Thus, the easy processability and good mechanical properties of PEC hydrogels enables the creation of 3D microstructured hydrogels that more accurately mimic the tumor microenvironment compared to conventional 2D cell cultures, thereby offering significant potential for the screening of anticancer drugs.[85] In 3D cell cultures, the hydrogel's viscoelastic properties play a crucial role in providing mechanical cues to adherent cells, thus influencing their behaviors and creating physiologically relevant *in vitro* models.[86,87] While other supramolecular hydrogels also exhibit viscoelasticity, PEC hydrogels offer a distinctive advantage in terms of their highly tunable viscoelastic properties. This allows tissue cultures to be constructed with stiffness that closely resembles the biological tissue being studied.[43]

Beyond serving as scaffolds for constructing 3D cell models, the benefits discussed thus far also position PEC hydrogels as ideal scaffolds for tissue engineering. Successful tissue regeneration relies on the interfacial scaffold-cell interactions, which guide the restructuring of cell architecture to achieve diverse tissue characteristics. Recently, Rao et al. prepared PEC hydrogel scaffolds with xanthan gum and chitosan in the presence of D-(+)-glucuronic acid δ-lactone.[88] This addition enhanced chitosan solubility and produced cationic amino groups for *in situ* complexation with polyanionic xanthan gum. Fe_3O_4 magnetic nanoparticles (MNPs) were incorporated into these hydrogel scaffolds to enhance tissue regeneration. These MNPs stimulate cellular interactions under a magnetic field, thereby improving cell adhesion, proliferation, and differentiation. Complexation of oppositely charged PEs ensures homogeneous distribution and stabilization of Fe_3O_4 MNPs within the matrix via electrostatic interactions and hydrogen bonding. In addition to improved elasticity and mechanical properties, *in vitro* culture of NIH3T3 fibroblasts on MNPs-incorporated PEC hydrogels demonstrated increased adhesion and proliferation in an external magnetic field compared to the pristine PEC gels, as the MNPs could be internalized by the cells. These findings underscore the capability of PEC hydrogels to serve as favorable hosts for MNPs, enabling better control over cellular behavior in the presence of a magnetic field and potentially promoting regeneration of skin, cartilage, muscle, and connective tissues.[88] Leveraging on this capability, Cui et al. introduced multiwalled carbon nanotubes (MWCNT) into PNaSS/PMPTC PEC hydrogels to imbue the 3D-printed scaffold with bioactivity for bone regeneration (Figure 6A).[89] CNTs are renowned for their osteoconductive and inductive properties, which accelerate bone regeneration by promoting the osteogenic differentiation of stem cells, enhancing osteoblast activity, improving biocompatibility, and exhibiting antimicrobial activity. The nanocomposite scaffold exhibited a Young's modulus of 4.47 MPa and could withstand large deformations (Figure 6B). Incorporating a low concentration of MWCNT (3% w/w) to the hydrogel scaffold significantly improved bone marrow-derived mesenchymal stem cell (BMSCs) proliferation, increased the calcium deposition and upregulated the expression of osteogenesis-related genes *in vitro*. Upon implantation in rats, the MWCNT-incorporated PEC hydrogel promoted bone regeneration and neovascularisation *in vivo* (Figure 6C−E).[89] This further accentuates the advantageous capability of PEC hydrogels to serve as favorable hosts for various agents, thus offering significant potential to enhance the repair efficiency of bone tissues and other tissues.

While the incorporation of MWCNTs into PNaSS/PMPTC PEC hydrogels showcases their promising role in promoting bone regeneration and tissue repair, it is important to acknowledge that the inherent strength and stability of PEC hydrogels may fall short in meeting the mechanical demands of bone tissue engineering. To ensure effective bone regeneration, hydrogel scaffolds must possess mechanical properties that is similar to the native bone extracellular matrix. As such, researchers have explored various strategies to bolster the mechanical strength of PEC hydrogels for bone tissue engineering applications. One such strategy, as demonstrated by Belluzo et al., involves the application of ultrasound to compatibilize a PEC hydrogel composed of chitosan and carboxymethyl cellulose.[90] This sonochemical reaction induces interpolymer microradical coupling, resulting in a highly porous scaffold with a more uniform pore distribution and greater compressive strength and elastic modulus compared to their uncompatibilized counterpart. Notably, the elastic modulus of the compatibiliszed PEC hydrogel closely resemble the Young's modulus of cartilage, highlighting its potential for cartilage tissue engineering.[90] In another approach, chitosan/sodium alginate PEC hydrogels were intercalated within a poly(acrylamide)-cross-linked network, which enhanced the mechanical strength but compromised the gel's injectability and reversibility.[57] The intercalated PEC hydrogel exhibits ladder-like fibrous surfaces and highly interconnected macroporous networks with pore sizes of 150 to 300 nm, appropriate for bone regeneration. Furthermore, the ammonium and carboxylate groups within the PEC hydrogel can chelate with calcium and phosphate ions in simulated body fluid (SBF) to form bone-like apatite. The fibrous topology of the hydrogel improved the proliferation and adhesiveness of hFOB1.19 osteoblasts, demonstrating its potential in bone tissue engineering.[57] These two examples underscore the versatility of PEC hydrogels in terms of their mechanical properties, demonstrating that they are not only highly tunable but can also be effectively strengthened.

5.3. Wound Healing and Wound Management.

Ensuring adequate moisture levels at wound sites is an important requirement for wound dressing materials.[91] Unlike traditional ones such as cotton wool, gauze or bandages, hydrogels have been widely utilized as wound dressings because of their high water content, hydrophilic nature and versatile chemical, mechanical and biological properties.[92] However, conventional hydrogels lack specific functionality in their design for wound healing and primarily function by passively retaining moisture around the wound, thus limiting the efficiency of wound healing.[92] PEC hydrogels represent a budding class of advanced dressing materials for wound healing applications, offering advantages such as easy and tunable formulation, *in situ* gelation, and encapsulating capabilities.[5] As mentioned in the section 5.2, the easy processability and favorable mechanical properties of PEC hydrogels position them to be highly suitable for tissue engineering applications. Likewise, these attributes are particularly advantageous in wound healing applications. This is because the moldable gel can effectively fill tissue defects of intricate shapes or serve as conformable patches in topical dermal wound treatments.[93] For example, Oliveira et al. reported that alginate/chitosan PEC hydrogels were moldable and self-healable, potentially applicable as compliant wound healing patches with cell-encapsulation capabilities.[93] By combining positively charged chitosan and negatively charged alginate at pH 4, PECs were formed through favorable electrostatic interactions. Subsequently, the pH was raised to generate PEC precipitates, followed by compaction and dehydration cycles with encapsulated cells. The prepared PEC hydrogel demonstrated exceptional adaptability, enabling it to undergo abstract sequential shape changes while maintaining its mechanical properties. Various segments of these gels could bind into a single piece with shape-morphing structures. *In vitro* studies with the PEC hydrogel revealed promising results, in which high viability of L929 rat fibroblasts was attained and viability of human adipose stem cells (hASC) cells remained unchanged.[93]

In general, hydrogel wound dressings should ideally possess sufficient mechanical strength to support tissue repair and effectively absorb of wound exudates after conforming to the tissue defect. Moreover, the development of wound healing materials with both antibacterial and tissue regenerating capabilities would be highly beneficial. PEC hydrogels have demonstrated the potential to meet these requirements. Recently, Sharma et al. developed a PEC hydrogel made from polyanionic chondroitin sulfate (CS) and polycationic chitosan (CH) for chronic wound management.[94] Compared to pristine CH or CS, the *in situ* formed PEC hydrogel scaffold exhibited enhanced toughness due to the favorable electrostatic associations between cationic groups ($-NH_3^+$) on CH and anionic groups ($-COO^-$ and $-SO_4^-$) on CS when CS solution penetrates through CH. These interactions led to increased swelling and porosity, facilitating wound exudate

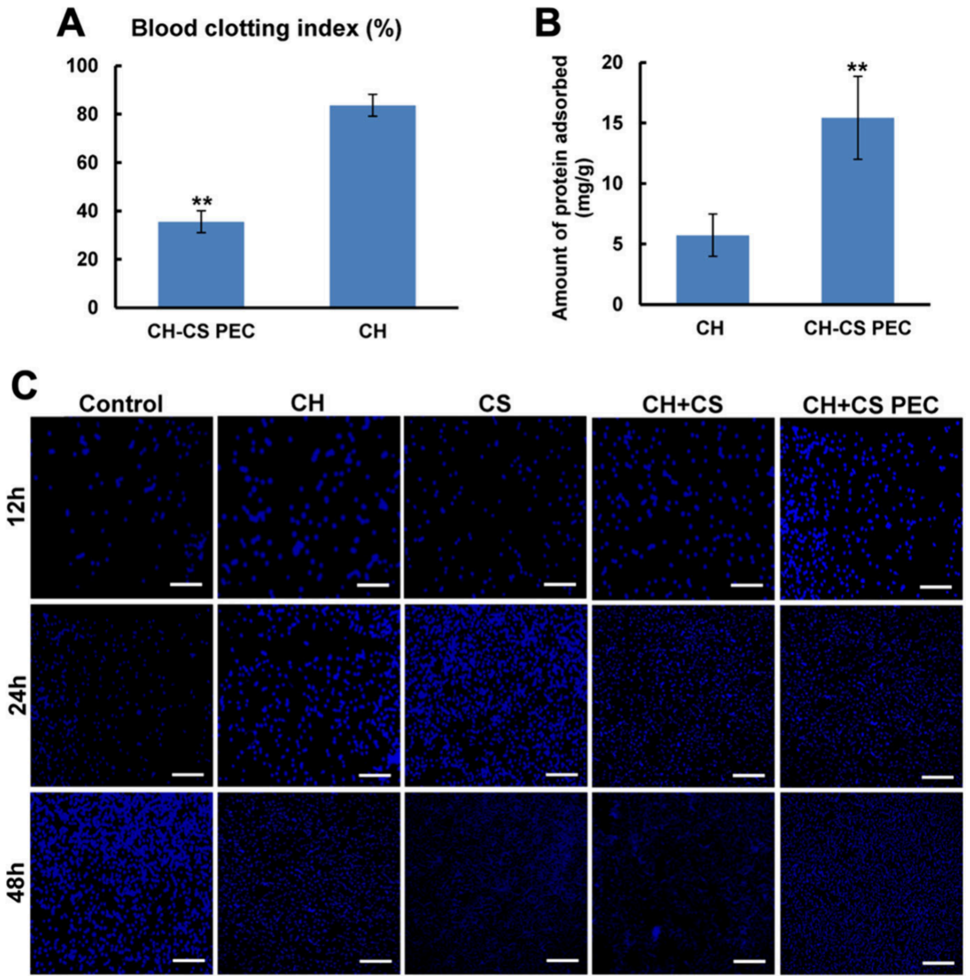


Figure 7. (A) Blood clotting index and (B) the amount of proteins adsorbed onto scaffolds based on CH−CS PEC and CH. ** ($p < 0.05$). (C) Images (scale bar = 100 μm) taken via fluorescence microscopy of mouse fibroblast proliferation. Reproduced with permission from ref.[94] Copyright 2019 Elsevier.

absorption and wound healing. CH possess antibacterial and hemostatic properties, while CS promotes tissue regeneration, intracellular signaling, cell adhesion, and proliferation. By harnessing the unique attributes of both PEs, the CS/CH PEC hydrogels demonstrated antibacterial and tissue-regenerating potential. Results unveiled that the lyophilized CH−CS PEC scaffold was hemocompatible and demonstrated improved protein absorption and blood clotting capabilities (Figure 7A and 7B). Moreover, it also exhibited antibacterial efficacy against both Gram-negative and Gram-positive bacteria. Cytotoxicity studies on L929 fibroblasts indicated that the CH−CS PEC scaffold was cytocompatible and promoted cellular growth, making it a suitable scaffold for wound healing and tissue regeneration (Figure 7C).[94] In particular, hydrogel wound dressings that are robust yet easily detachable from wet tissues hold significant value for wound healing applications. Studies have shown that PEC hydrogels possess this capability. In a recent study by Wang et al., an adhesive PEC hydrogel (mTA-PAA/PEI) for wound healing was achieved by mixing anionic AA and cationic PEI with modified tannic acid (mTA), followed by photo-cross-linking with ultraviolet light.[95] The mTA-PAA/PEI hydrogel demonstrated strong adhesion to wet tissues (~1552 J/m^3) and robust mechanical properties arising from the strong electrostatic interactions between anionic $-COO^-$ groups and cationic $-NH_3^+$ groups, as well as the presence of phenyl and catechol groups on mTA with the hydrophobic extended alkyl chains interacting with PAA and PEI. Upon exposure to urea solution, the adhesion strength drastically lowered to ~191 J/m^3, which made it readily removable. Additionally, the PEC hydrogel was highly conformable to tissues, rendering it suitable for wound healing applications.[95]

In postsurgical wounds, the formation of tissue adhesions is an inevitable complication often caused by oxidative stress incurred from surgical procedures.[96] Tissue injuries as a result of foreign body reactions, infections or mechanical trauma during surgery lead to generation of ROS, which inflict oxidative damage to cellular components such as DNA, proteins and cell membranes. At the same time, oxidative stress promotes inflammation, which increases vascular permeability and in turn releases inflammatory mediators like interleukin 6 (IL-6), tumor necrosis factor a (TNF-a), and myeloperoxidase (MPO). This inflammation cascade promotes coagulation or fibrin formation.[96,97] Consequently, tissues that are usually separated can adhere to one another, leading to unwanted adhesions.[98] PEC hydrogels, known for their high mechanical stability, strength and prolonged retention *in vivo*, function as effective physical barriers against adhesion formation. Designed by Nagasaki and team, the previously mentioned PMNT−PEG-PMNT/PAAc PEC hydrogel has demonstrated effectiveness in preventing adhesions and oxidative stress.[97] *In vivo* experiments on talc-induced adhesion mice models revealed prolonged localization of the gel in the abdominal cavity, acting as a barrier between tissues for up to 7 days to prevent tissue adhesion. In addition, the PEC gel, incorporating grafted nitroxide radicals with antioxidative properties, scavenges ROS and inhibits inflammatory cytokines and neutrophil infiltration, effectively impeding inflammation spread to further prevent adhesion formation. This PEC gelation system, applicable in both open and delicate surgical procedures including endoscopic, catheter, and robotic surgeries, highlights its potential as a high-performance antiadhesion agent.[97]

Given the versatile nature of PEC hydrogels as favorable hosts, various compounds can be incorporated to enhance wound healing. For instance, CH was blended with sodium alginate and aloe vera gel (AV) by Gallardo-Rivera et al. to form PEC infused with bioactive AV for wound healing purposes.[99] The PEC hydrogel was formed through electrostatic attraction between CH and alginate with the aid of Ca^{2+} as a cross-linker. AV is widely known to be immunomodulatory, anti-inflammatory and promote wound healing. Indeed, results revealed that encapsulating AV in the PEC hydrogel enhances the viability and migration of fibroblasts and lymphocytes, which are crucial components of the wound healing process.[99] Beyond the critical emphasis on wound healing, the importance of wound care is equally crucial. The emergence of biosensors plays a pivotal role in elevating and monitoring wound care procedures, thus contributing to more effective and personalized treatment strategies. One such example is WoundSense, a commercially available moisture biosensor that can be placed on wounds to evaluate moisture levels without the need to disturb or remove the dressing.[100] In a similar pursuit, Muhammed Adnan et al. developed wound biosensor using a PEC hydrogel prepared with ampholytic gelatin, anionic sodium alginate and Ca^{2+}.[101] By leveraging on the host capabilities of PEC hydrogels, the authors encapsulated gallic acid, an active sensory compound with antioxidant properties, offering visual cues on wound status. At the infected site where pH is generally acidic, the hydrogel preserved its initial off-white color and then gained color under basic conditions. The strong complexation granted the gel with optimal mechanical strength and stability, which ultimately facilitates easy handling of the diagnostic device. Interestingly, an increase in cross-linking time was observed to result in higher cross-linking density, leading to increased rupture force and gel strength. This unexplored phenomenon suggests potential advantageous properties of PEC hydrogels that have yet to be unveiled, hinting at numerous undiscovered applications. Overall, this PEC hydrogel provides promise as a visual biosensor for wound management.[101]

5.4. Wearable Sensors. PEC hydrogels have emerged as desirable ion-conductive materials for the development of wearable sensors in biomedical applications. Their unique combination of properties, like high ionic conductivity, dynamically reversible electrostatic interactions, processability, toughness, and high biocompatibility, positions PEC hydrogels to be well-suited as stretchable ionic conductors for ionic sensors.[102,103] In general, PEC hydrogels have been explored for their potential as ionic electronic skins (e-skins) with strain-sensing capabilities. These e-skins serve as valuable tools that can monitor human motions, contributing to advancements in healthcare and ultimately improve health outcomes.[104] For example, Zhu et al. developed a PEC/polyaniline (PAni) hybrid hydrogel that can be facilely patterned with multichannel sensor arrays to enable monitoring of large deformations in real time.[103] The hybrid gel was prepared by incorporating conductive PAni into a tough and processable PEC matrix of anionic poly(sodium p-styrenesulfonate) (PNaSS) and cationic poly(3-(methacryloylamino)propyltrimethylammonium chloride) (PMPTC) through phytic acid. 1 M (9.3 wt %) of Ani endowed the hydrogel with superior breaking strain (395%), fracture stress (1.15 MPa), tensile modulus (5.31 MPa) and conductivity (0.7 S/m) as compared to most existing conductive hydrogels. As inherited from the PEC matrix, the PEC/PAni hydrogels demonstrated distinct rate-dependent and self-recovery behaviors. The relatively strong electrostatic associations within the PEC matrix contribute to its structural integrity when subjected to loading, while the relatively weak electrostatic interactions acted as dynamic reversible bonds that broke and reformed over time. Accordingly, the hydrogel demonstrated applicability as strain sensors that were able to effectively detect subtle human motions, like finger movements and swallowing.[103] In certain cases where achieving robust mechanical performance in tandem with self-healing abilities of PEC hydrogels can be challenging, Sahoo et al. outlined the possibility of using chemical−physical and physical−physical cocrosslinking methods to attain double-networked hydrogels capable of dissipating energy synergistically.[105] Using a PEC matrix of cationic chitosan, anionic PAA, and tetraethylene glycol (TEG), three types of double-networked hydrogels were obtained by incorporating different cross-linkers. Convenient tunability of the hydrogels' mechanical properties was achieved, allowing tensile strength and strain to be adjusted to up to 1170 kPa and 1175%, respectively. In addition, the hydrogels exhibited high self-healing efficiency owing to their dynamic cross-linked network. Attributed to the abundant hydroxyl groups present in the monomers, these hydrogels were also self-adhesive on various materials, such as skin, glass, metal, wood, copper, coin, plastic, aluminum, and polytetrafluoroethylene. Notably, high stretchability of up to 1500% coupled with underwater adhesion for strain sensing of finger movements was achieved by the hydrogels, rendering them useful as soft sensors to monitor human motion in real time. This example highlights that in cases where PEC hydrogels fall short in terms of the balance between mechanical performance and self-healing, PEC hydrogels can easily attain this equilibrium through innovative cross-linking strategies.

While self-healing is important in hydrogel-based e-skins, the integration of anti-freezing properties is imperative to prolong their durability, improve their reliability and broaden their application range.[106] The majority of previously developed e-skins experience poor sensitivity, brittleness and significantly reduced elasticity when exposed to subzero temperatures, limiting their utility in extremely cold environments. Recognizing the potential of PEC hydrogels as favorable hosts, Li et al. fabricated anti-freezing ionic skins based on PEC hydrogels composed of PAAm and Fe^{3+}-chelated PAA (PAA-Fe^{3+}), with the incorporation of NaCl.[106] The PAAm/PAA−Fe^{3+}/NaCl hydrogels exhibited high tensile strength (1.18 MPa), tissue-like Young's modulus (0.33 MPa), mechanical resilience and fatigue resistance due to the synergistic effect between hydrogen bonding, hydrophobic and coordination interactions within the hydrogel matrix. The incorporation of NaCl into the PEC gel enhanced the mechanical performance

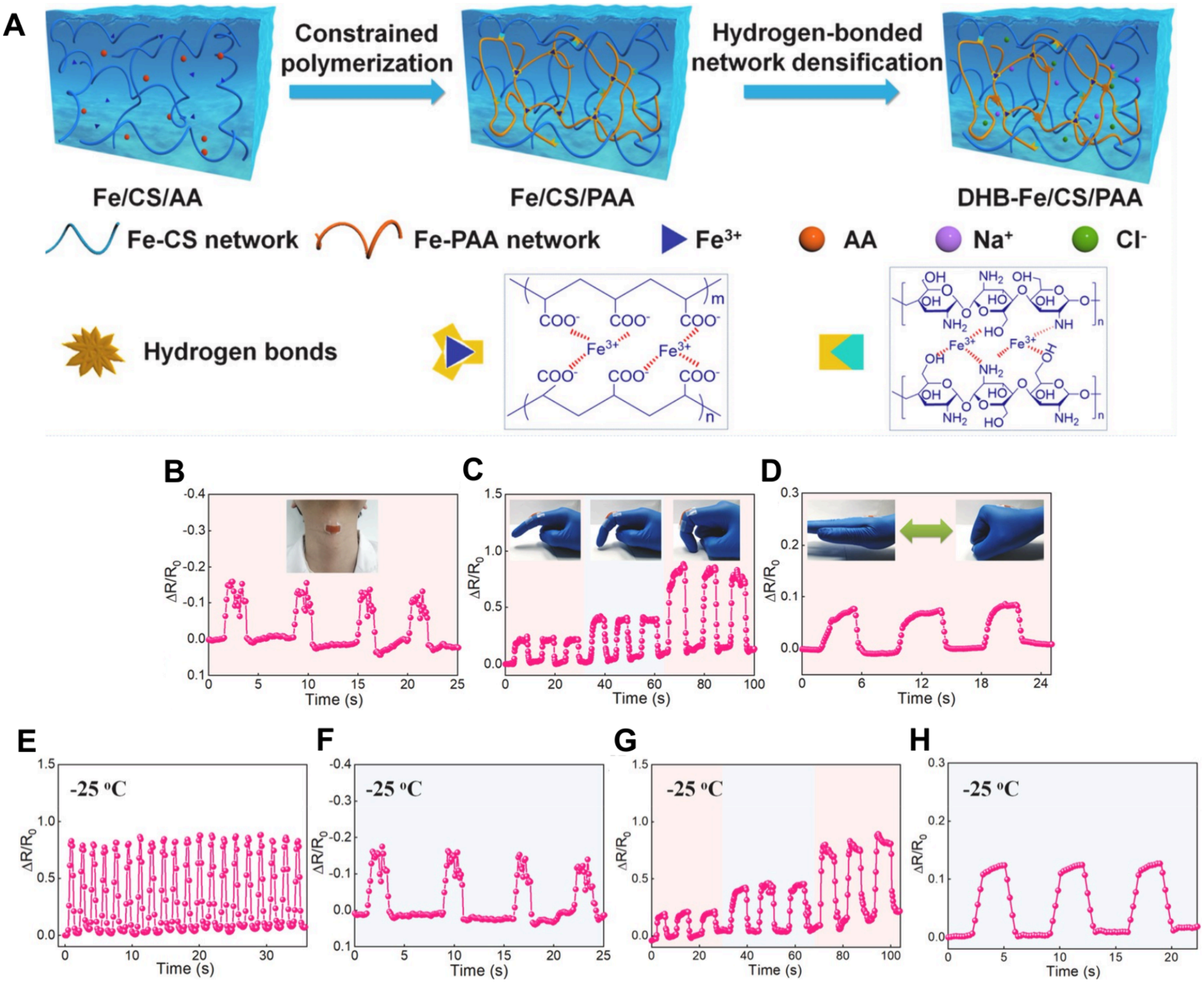


Figure 8. (A) The preparation of DHB-Fe/CS/PAA hydrogels. Variations in relative resistance for monitoring human motions, such as (B) swallowing, (C) finger and (D) opisthenar bending in real time. (E) Variations in relative resistance when subjected to repeated cycles of stretching and releasing at −25 °C under 50% strain. Variations in relative resistance when monitoring (F) swallowing, (G) finger and (H) opisthenar bending at −25 °C.[58] Reproduced with permission from ref.[58] Copyright 2021 Elsevier.

of the ionic skins, which achieved high pressure (0.1−10 kPa) and strain (0.2−500%) sensitivity over a broad range. In addition, NaCl imparted the hydrogel with anti-freezing properties such that it can function under low temperatures of up to −24.7 °C. the incorporation of inorganic salts into the hydrogel matrix disrupts the hydrogen bonds between water molecules to inhibit their freezing. Meanwhile, the reversibility of the hydrogen bonds and coordination interactions between PAA, PAAm and Fe^{3+} endowed the ionic skins to be self-healable, thereby reinforcing the reliability and extending the lifespan of the ionic skins.[106] Using a similar approach, Song et al. designed another anti-freezing ionic skin sensor based on PEC hydrogels.[58] A double-networked hydrogel (Fe/CH/PAA) was first assembled via hydrogel network-constrained polymerization. In this process, an anionic PAA network chelated with Fe^{3+} (Fe-PAA) was formed within a cationic chitosan network chelated with Fe^{3+} (Fe-CS) through Coulombic interactions (Figure 8A). Thereafter, salts were embedded to achieve a densified hydrogen-bonded Fe/CS/PAA (DHB-Fe/CS/PAA) gel, which was self-healable with high tensile strength (~0.34 MPa), extensive stretchability (>1370%), and exemplary fatigue resistance for 1000 cycles. Due to the abundance of charged groups and embedded salts, the hydrogel was highly conductive (0.24 S m^{-1}) and mechanically flexible at subzero temperatures as low as −25 °C. As an ionic sensor, the DHB-Fe/CS/PAA hydrogel demonstrated consistent resistance signals across a broad range of 0.5% to 500%, quick response time (<180 ms) and remarkable durability when subjected to 500 cycles of 100% strain. By assembling a wearable ionic sensor with the DHB-Fe/CS/PAA hydrogel, monitoring of complex human movements in real time, such as swallowing, wrist bending, and finger bending, was achieved (Figure 8B−H).[58]

6. CONCLUSION AND FUTURE PERSPECTIVES

Highly abundant and essential in biological systems, ionic complexes of electrostatically charged biomacromolecules play a key role in the function, responsiveness, and tunable mechanical properties of organisms. Inspired by these natural phenomena, materials can be designed to capitalize on the array of noncovalent interactions between macromolecules. Just like their natural counterparts, hydrogels formed through the complexation of oppositely charged polymers exhibit unique attributes, including rapid self-assembly, hierarchical microstructures, tunable properties, and protective encapsulation. Accordingly, PEC hydrogels have emerged as a versatile platform for various biomedical applications. However, research efforts in this field are in their infancy.

Most research initiatives over the past few years have focused on the dynamic and static properties of PEC hydrogels, like stimuli-responsiveness, the ability to encapsulate charged therapeutic modalities and biomedical applications. However, the molecular understanding that governs these properties is often overlooked by innovators and thus remains far less explored. Despite significant foundational research establishing the structure−property relationship of PEC hydrogels for various applications,[5] a critical question arises: are these findings adequate for researchers to consider when designing such platforms for biomedical applications with complex requirements?

Based on the current research on PEC hydrogels for drug delivery applications, there seems to be insufficient understanding on how the encapsulation of therapeutic modalities with diverse physicochemical properties may alter molecular interactions within the PEC hydrogel matrix, leading to deviations in self-assembly, structures, and properties. Likewise, in utilizing PEC hydrogels for wearable sensors, there is limited understanding on how additives intended to enhance conductivity or impart anti-freezing properties interact with the PEC hydrogel matrix at a molecular level and thus influence their structures and properties. On that account, a deeper molecular understanding of PEC hydrogels is necessary to ensure each system is well-designed with optimal properties for specific biomedical applications, each carrying distinct material requirements. This depth of understanding becomes even more critical for PEC hydrogels designed for tissue engineering applications, where researchers must unravel how electrostatics in PEC hydrogels interact with cells and ultimately influence their growth, morphology, and function.

In summary, PEC hydrogels represent a fascinating class of electrostatic hydrogels with unique properties that render them promising for various biomedical applications. By delving deeper into the molecular and cellular interactions that PEC hydrogel systems can offer, a more comprehensive understanding of the platform can be distilled. This knowledge can be applied in designing the next generation PEC hydrogel systems for specific applications, potentially unveiling new attributes that were previously undiscovered and widening their use in many more applications than we can currently anticipate.

AUTHOR INFORMATION

Corresponding Authors

Xian Jun Loh − *Institute of Materials Research and Engineering (IMRE), Agency for Science, Technology and Research (A*STAR), Singapore 138634, Republic of Singapore; School of Materials Science and Engineering, Nanyang Technological University (NTU), Singapore 639798, Republic of Singapore; Department of Materials Science and Engineering, National University of Singapore (NUS), Singapore 117576, Singapore;* orcid.org/0000-0001-8118-6502; Email: lohxj@imre.a-star.edu.sg

Rubayn Goh − *Institute of Materials Research and Engineering (IMRE), Agency for Science, Technology and Research (A*STAR), Singapore 138634, Republic of Singapore;* orcid.org/0000-0001-8333-8143; Email: rubayn_goh@imre.a-star.edu.sg

Authors

Belynn Sim − *Institute of Materials Research and Engineering (IMRE), Agency for Science, Technology and Research (A*STAR), Singapore 138634, Republic of Singapore; School of Materials Science and Engineering, Nanyang Technological University (NTU), Singapore 639798, Republic of Singapore;* orcid.org/0009-0005-8301-150X

Jun Jie Chang − *Institute of Materials Research and Engineering (IMRE), Agency for Science, Technology and Research (A*STAR), Singapore 138634, Republic of Singapore;* orcid.org/0000-0003-3072-2832

Qianyu Lin − *Institute of Materials Research and Engineering (IMRE), Agency for Science, Technology and Research (A*STAR), Singapore 138634, Republic of Singapore*

Joey Hui Min Wong − *Institute of Materials Research and Engineering (IMRE), Agency for Science, Technology and Research (A*STAR), Singapore 138634, Republic of Singapore*

Valerie Ow − *Institute of Materials Research and Engineering (IMRE), Agency for Science, Technology and Research (A*STAR), Singapore 138634, Republic of Singapore; Department of Biomedical Engineering, National University of Singapore (NUS), Singapore 117583, Singapore*

Yihao Leow − *Institute of Materials Research and Engineering (IMRE), Agency for Science, Technology and Research (A*STAR), Singapore 138634, Republic of Singapore; School of Materials Science and Engineering, Nanyang Technological University (NTU), Singapore 639798, Republic of Singapore*

Yi Jing Wong − *Institute of Materials Research and Engineering (IMRE), Agency for Science, Technology and Research (A*STAR), Singapore 138634, Republic of Singapore; School of Materials Science and Engineering, Nanyang Technological University (NTU), Singapore 639798, Republic of Singapore*

Yi Jian Boo − *Institute of Materials Research and Engineering (IMRE), Agency for Science, Technology and Research (A*STAR), Singapore 138634, Republic of Singapore*

Complete contact information is available at:
https://pubs.acs.org/10.1021/acs.biomac.4c01240

Author Contributions

Belynn Sim: conceptualization, writing (main), editing. Jun Jie Chang: writing. Qianyu Lin: writing. Joey H. M. Wong: writing. Valerie Ow: writing. Yihao Leow: writing. Yi Jing Wong: writing. Yi Jian Boo: writing. Xian Jun Loh: conceptualization, supervision. Rubayn Goh: conceptualization, editing.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This research was supported by the following grants: IAF-PP (A*STAR, HMBS Domain) H20C6a0033 (OrBiTAl): OculaR Biomaterials for Vitreoretinal Therapeutic Applications and National Research Foundation Investigatorship grant NRFI07−2021−0021 Thermogels for Therapeutic Applications (THETA).

REFERENCES

(1) Omar, J.; Ponsford, D.; Dreiss, C. A.; Lee, T.-C.; Loh, X. J. Supramolecular Hydrogels: Design Strategies and Contemporary Biomedical Applications. *Chem.-Asian J.* **2022**, *17* (9), No. e202200081.

(2) Lim, J. Y. C.; Lin, Q.; Xue, K.; Loh, X. J. Recent advances in supramolecular hydrogels for biomedical applications. *Mater. Today Adv.* **2019**, *3*, 100021.

(3) Dong, R.; Pang, Y.; Su, Y.; Zhu, X. Supramolecular hydrogels: synthesis, properties and their biomedical applications. *Biomater. Sci.* **2015**, *3* (7), 937−954.

(4) Appel, E. A.; del Barrio, J.; Loh, X. J.; Scherman, O. A. Supramolecular polymeric hydrogels. *Chem. Soc. Rev.* **2012**, *41* (18), 6195−6214.

(5) Senebandith, H.; Li, D.; Srivastava, S. Advances, Applications, and Emerging Opportunities in Electrostatic Hydrogels. *Langmuir* **2023**, *39* (48), 16965−16974.

(6) Sadman, K.; Wang, Q.; Chen, Y.; Keshavarz, B.; Jiang, Z.; Shull, K. R. Influence of Hydrophobicity on Polyelectrolyte Complexation. *Macromolecules* **2017**, *50* (23), 9417−9426.

(7) Vieregg, J. R.; Lueckheide, M.; Marciel, A. B.; Leon, L.; Bologna, A. J.; Rivera, J. R.; Tirrell, M. V. Oligonucleotide-Peptide Complexes: Phase Control by Hybridization. *J. Am. Chem. Soc.* **2018**, *140* (5), 1632−1638.

(8) Kanasty, R.; Dorkin, J. R.; Vegas, A.; Anderson, D. Delivery materials for siRNA therapeutics. *Nat. Mater.* **2013**, *12* (11), 967−977.

(9) Brangwynne, C. P.; Tompa, P.; Pappu, R. V. Polymer physics of intracellular phase transitions. *Nat. Phys.* **2015**, *11* (11), 899−904.

(10) Perutz, M. F. Electrostatic Effects in Proteins. *Science* **1978**, *201* (4362), 1187−1191.

(11) Sheinerman, F. B.; Norel, R.; Honig, B. Electrostatic aspects of protein-protein interactions. *Curr. Opin. Struct. Biol.* **2000**, *10* (2), 153−159.

(12) Walther, T. H.; Ulrich, A. S. Transmembrane helix assembly and the role of salt bridges. *Curr. Opin. Struct. Biol.* **2014**, *27*, 63−68.

(13) Neitzel, A. E.; De Hoe, G. X.; Tirrell, M. V. Expanding the structural diversity of polyelectrolyte complexes and polyzwitterions. *Curr. Opin. Solid State Mater. Sci.* **2021**, *25* (2), 100897.

(14) dos Santos, V.; Brandalise, R. N.; Savaris, M., Biomaterials: Characteristics and Properties. In *Engineering of Biomaterials*, dos Santos, V.; Brandalise, R. N.; Savaris, M., Eds. Springer: Cham, 2017; pp 5−15.

(15) Wanasingha, N.; Dorishetty, P.; Dutta, N. K.; Choudhury, N. R. Polyelectrolyte Gels: Fundamentals, Fabrication and Applications. *Gels* **2021**, *7* (3), 148.

(16) Danielsen, S. P. O.; Semenov, A. N.; Rubinstein, M. Phase Separation and Gelation in Solutions and Blends of Heteroassociative Polymers. *Macromolecules* **2023**, *56* (14), 5661−5677.

(17) Xu, J.; Zhu, X.; Zhao, J.; Ling, G.; Zhang, P. Biomedical applications of supramolecular hydrogels with enhanced mechanical properties. *Adv. Colloid Interface Sci.* **2023**, *321*, 103000.

(18) Zhou, J.; Li, J.; Du, X.; Xu, B. Supramolecular biofunctional materials. *Biomaterials* **2017**, *129*, 1−27.

(19) Luo, F.; Sun, T. L.; Nakajima, T.; King, D. R.; Kurokawa, T.; Zhao, Y.; Ihsan, A. B.; Li, X.; Guo, H.; Gong, J. P. Strong and Tough Polyion-Complex Hydrogels from Oppositely Charged Polyelectrolytes: A Comparative Study with Polyampholyte Hydrogels. *Macromolecules* **2016**, *49* (7), 2750−2760.

(20) Luo, F.; Sun, T. L.; Nakajima, T.; Kurokawa, T.; Zhao, Y.; Sato, K.; Ihsan, A. B.; Li, X.; Guo, H.; Gong, J. P. Oppositely Charged Polyelectrolytes Form Tough, Self-Healing, and Rebuildable Hydrogels. *Adv. Mater.* **2015**, *27* (17), 2722−2727.

(21) Bourganis, V.; Karamanidou, T.; Kammona, O.; Kiparissides, C. Polyelectrolyte complexes as prospective carriers for the oral delivery of protein therapeutics. *Eur. J. Pharm. Biopharm.* **2017**, *111*, 44−60.

(22) Wu, H.; Ting, J. M.; Tirrell, M. V. Mechanism of Dissociation Kinetics in Polyelectrolyte Complex Micelles. *Macromolecules* **2020**, *53* (1), 102−111.

(23) Srivastava, S.; Levi, A. E.; Goldfeld, D. J.; Tirrell, M. V. Structure, Morphology, and Rheology of Polyelectrolyte Complex Hydrogels Formed by Self-Assembly of Oppositely Charged Triblock Polyelectrolytes. *Macromolecules* **2020**, *53* (14), 5763−5774.

(24) *Compendium of Polymer Terminology and Nomenclature: IUPAC RECOMMENDATIONS 2008*. R. Soc. Chem.: 2009.

(25) Zhao, L.; Skwarczynski, M.; Toth, I. Polyelectrolyte-Based Platforms for the Delivery of Peptides and Proteins. *ACS Biomater. Sci. Eng.* **2019**, *5* (10), 4937−4950.

(26) Winkler, R. G.; Cherstvy, A. G., Strong and Weak Polyelectrolyte Adsorption onto Oppositely Charged Curved Surfaces. In *Polyelectrolyte Complexes in the Dispersed and Solid State I: Principles and Theory*, Müller, M., Ed. Springer: Berlin, Heidelberg, 2014; pp 1−56.

(27) Wang, C.-G.; Surat'man, N. E. B.; Chang, J. J.; Ong, Z. L.; Li, B.; Fan, X.; Loh, X. J.; Li, Z. Polyelectrolyte Hydrogels for Tissue Engineering and Regenerative Medicine. *Chem.-Asian J.* **2022**, *17* (18), No. e202200604.

(28) Zhang, J.; Zhang, Q.; Liu, X.; Xia, S.; Gao, Y.; Gao, G. Flexible and wearable strain sensors based on conductive hydrogels. *J. Polym. Sci.* **2022**, *60* (18), 2663−2678.

(29) Meka, V. S.; Sing, M. K. G.; Pichika, M. R.; Nali, S. R.; Kolapalli, V. R. M.; Kesharwani, P. A comprehensive review on polyelectrolyte complexes. *Drug Discovery Today* **2017**, *22* (11), 1697−1706.

(30) Rud, O. V.; Landsgesell, J.; Holm, C.; Košovan, P. Modeling of weak polyelectrolyte hydrogels under compression - Implications for water desalination. *Desalination* **2021**, *506*, 114995.

(31) Nagasawa, M. Ionization Equilibrium and Potentiometric Titration of Weak Polyelectrolytes. *Physical Chemistry of Polyelectrolyte Solutions* **2015**, *158*, 67−114.

(32) Barbosa, J. A. C.; Abdelsadig, M. S. E.; Conway, B. R.; Merchant, H. A. Using zeta potential to study the ionisation behaviour of polymers employed in modified-release dosage forms and estimating their pKa. *Int. J. Pharm.: X* **2019**, *1*, 100024.

(33) Polyelectrolytes. In *Polyelectrolytes and Nanoparticles*, Koetz, J.; Kosmella, S., Eds. Springer: Berlin, Heidelberg, 2007; pp 5−46.

(34) Manoj Lalwani, S.; Eneh, C. I.; Lutkenhaus, J. L. Emerging trends in the dynamics of polyelectrolyte complexes. *Phys. Chem. Chem. Phys.* **2020**, *22* (42), 24157−24177.

(35) Bordi, F.; Sennato, S.; Truzzolillo, D. Polyelectrolyte-induced aggregation of liposomes: a new cluster phase with interesting applications. *J. Phys.: Condens. Matter* **2009**, *21* (20), 203102.

(36) Wang, Q.; Schlenoff, J. B. The Polyelectrolyte Complex/Coacervate Continuum. *Macromolecules* **2014**, *47* (9), 3108−3116.

(37) Pergushov, D. V.; Müller, A. H. E.; Schacher, F. H. Micellar interpolyelectrolyte complexes. *Chem. Soc. Rev.* **2012**, *41* (21), 6888−6901.

(38) Fu, J.; Schlenoff, J. B. Driving Forces for Oppositely Charged Polyion Association in Aqueous Solutions: Enthalpic, Entropic, but Not Electrostatic. *J. Am. Chem. Soc.* **2016**, *138* (3), 980−990.

(39) Kulkarni, A. D.; Vanjari, Y. H.; Sancheti, K. H.; Patel, H. M.; Belgamwar, V. S.; Surana, S. J.; Pardeshi, C. V. Polyelectrolyte complexes: mechanisms, critical experimental aspects, and applications. *Artif. Cells, Nanomed., Biotechnol.* **2016**, *44* (7), 1615−1625.

(40) Philipp, B.; Dautzenberg, H.; Linow, K.-J.; Kötz, J.; Dawydoff, W. Polyelectrolyte complexes — recent developments and open problems. *Prog. Polym. Sci.* **1989**, *14* (1), 91−172.

(41) Sungoradee, T.; Srikulkit, K. Preparation and Characterizations of PSS/PDADMAC Polyelectrolyte Complex Hydrogel. *Polymers* **2022**, *14* (9), 1699.

(42) Yang, J.; Shen, M.; Wu, T.; Luo, Y.; Li, M.; Wen, H.; Xie, J. Role of salt ions and molecular weights on the formation of Mesona chinensis polysaccharide-chitosan polyelectrolyte complex hydrogel. *Food Chem.* **2020**, *333*, 127493.

(43) Nguyen, D. H. T.; Utama, R. H.; Tjandra, K. C.; Suwannakot, P.; Du, E. Y.; Kavallaris, M.; Tilley, R. D.; Gooding, J. J. Tuning the Mechanical Properties of Multiarm RAFT-Based Block Copolyelectrolyte Hydrogels via Ionic Cross-Linking for 3D Cell Cultures. *Biomacromolecules* **2023**, *24* (1), 57−68.

(44) Li, X.; Shang, L.; Li, D.; Wang, W.; Chen, S.; Zhong, H.; Huang, Y.; Long, S. High-strength, strong-adhesion, and antibacterial

polyelectrolyte complex hydrogel films from natural polysaccharides. *Polym. Test.* **2022**, *109*, 107547.

(45) You, J.; Xie, S.; Cao, J.; Ge, H.; Xu, M.; Zhang, L.; Zhou, J. Quaternized Chitosan/Poly(acrylic acid) Polyelectrolyte Complex Hydrogels with Tough, Self-Recovery, and Tunable Mechanical Properties. *Macromolecules* **2016**, *49* (3), 1049−1059.

(46) Yamazaki, M.; Yabe, M.; Iijima, K. Specific ion effects on the aggregation of polysaccharide-based polyelectrolyte complex particles induced by monovalent ions within Hofmeister series. *J. Colloid Interface Sci.* **2023**, *643*, 305−317.

(47) Braccini, I.; Pérez, S. Molecular Basis of Ca2+-Induced Gelation in Alginates and Pectins: The Egg-Box Model Revisited. *Biomacromolecules* **2001**, *2* (4), 1089−1096.

(48) Lazutin, A. A.; Semenov, A. N.; Vasilevskaya, V. V. Polyelectrolyte Complexes Consisting of Macromolecules With Varied Stiffness: Computer Simulation. *Macromol. Theory Simul.* **2012**, *21* (5), 328−339.

(49) Tsao, C. T.; Chang, C. H.; Lin, Y. Y.; Wu, M. F.; Wang, J.-L.; Han, J. L.; Hsieh, K. H. Antibacterial activity and biocompatibility of a chitosan-*γ*-poly(glutamic acid) polyelectrolyte complex hydrogel. *Carbohydr. Res.* **2010**, *345* (12), 1774−1780.

(50) Hu, X.; Wang, Y.; Zhang, L.; Xu, M. Formation of self-assembled polyelectrolyte complex hydrogel derived from salecan and chitosan for sustained release of Vitamin C. *Carbohydr. Polym.* **2020**, *234*, 115920.

(51) Li, X.; Shang, L.; Li, D.; Wang, W.; Chen, S.; Zhong, H.; Huang, Y.; Long, S. High-strength, strong-adhesion, and antibacterial polyelectrolyte complex hydrogel films from natural polysaccharides. *Polym. Test.* **2022**, *109*, 107547.

(52) Hu, X.; Wang, Y.; Zhang, L.; Xu, M. Construction of self-assembled polyelectrolyte complex hydrogel based on oppositely charged polysaccharides for sustained delivery of green tea polyphenols. *Food Chem.* **2020**, *306*, 125632.

(53) Hu, X.; Yan, L.; Wang, Y.; Xu, M. Self-assembly of binary oppositely charged polysaccharides into polyelectrolyte complex hydrogel film for facile and efficient Pb2+ removal. *Chem. Eng. J.* **2020**, *388*, 124189.

(54) Kargaki, M.-E.; Arfara, F.; Iatrou, H.; Tsitsilianis, C. pH-Sensitive Poly(acrylic acid)-g-poly(L-lysine) Charge-Driven Self-Assembling Hydrogels with 3D-Printability and Self-Healing Properties. *Gels* **2023**, *9* (7), 512.

(55) Sanchez-Ballester, N. M.; Sciortino, F.; Mir, S. H.; Rydzek, G. Weak Polyelectrolytes as Nanoarchitectonic Design Tools for Functional Materials: A Review of Recent Achievements. *Molecules* **2022**, *27* (10), 3263.

(56) Li, G.; Zhang, G.; Sun, R.; Wong, C.-P. Dually pH-responsive polyelectrolyte complex hydrogel composed of polyacrylic acid and poly (2-(dimthylamino) ethyl methacrylate). *Polymer* **2016**, *107*, 332−340.

(57) Suneetha, M.; Rao, K. M.; Han, S. S. Mechanically improved porous hydrogels with polysaccharides via polyelectrolyte complexation for bone tissue engineering. *Int. J. Biol. Macromol.* **2020**, *144*, 160−169.

(58) Song, H.; Sun, Y.; Zhu, J.; Xu, J.; Zhang, C.; Liu, T. Hydrogen-bonded network enables polyelectrolyte complex hydrogels with high stretchability, excellent fatigue resistance and self-healability for human motion detection. *Composites, Part B* **2021**, *217*, 108901.

(59) Lee, H.-R.; Jung, S. M.; Yoon, S.; Yoon, W. H.; Park, T. H.; Kim, S.; Shin, H. W.; Hwang, D. S.; Jung, S. Immobilization of planktonic algal spores by inkjet printing. *Sci. Rep.* **2019**, *9* (1), 12357.

(60) Shen, J.-S.; Cai, Q.-G.; Jiang, Y.-B.; Zhang, H.-W. Anion-triggered melamine based self-assembly and hydrogel. *Chem. Commun.* **2010**, *46* (36), 6786−6788.

(61) Liu, Y.; Hu, J.; Xiao, Z.; Jin, X.; Jiang, C.; Yin, P.; Tang, L.; Sun, T. Dynamic behavior of tough polyelectrolyte complex hydrogels from chitosan and sodium hyaluronate. *Carbohydr. Polym.* **2022**, *288*, 119403.

(62) Wu, S.; Zhu, M.; Lu, D.; Milani, A. H.; Lian, Q.; Fielding, L. A.; Saunders, B. R.; Derry, M. J.; Armes, S. P.; Adlam, D.; Hoyland, J. A. Self-curing super-stretchable polymer/microgel complex coacervate gels without covalent bond formation. *Chem. Sci.* **2019**, *10* (38), 8832−8839.

(63) Bernard, M.; Jubeli, E.; Pungente, M. D.; Yagoubi, N. Biocompatibility of polymer-based biomaterials and medical devices - regulations, in vitro screening and risk-management. *Biomater. Sci.* **2018**, *6* (8), 2025−2053.

(64) Dreiss, C. A. Hydrogel design strategies for drug delivery. *Curr. Opin. Colloid Interface Sci.* **2020**, *48*, 1−17.

(65) Yun, Y. H.; Lee, B. K.; Park, K. Controlled Drug Delivery: Historical perspective for the next generation. *J. Controlled Release* **2015**, *219*, 2−7.

(66) Senapati, S.; Mahanta, A. K.; Kumar, S.; Maiti, P. Controlled drug delivery vehicles for cancer treatment and their performance. *Signal Transduction Targeted Ther.* **2018**, *3* (1), 7.

(67) Singh, N. K.; Lee, D. S. In situ gelling pH- and temperature-sensitive biodegradable block copolymer hydrogels for drug delivery. *J. Controlled Release* **2014**, *193*, 214−227.

(68) Ishii, S.; Kaneko, J.; Nagasaki, Y. Development of a long-acting, protein-loaded, redox-active, injectable gel formed by a polyion complex for local protein therapeutics. *Biomaterials* **2016**, *84*, 210−218.

(69) Park, M.-R.; Seo, B.-B.; Song, S.-C. Dual ionic interaction system based on polyelectrolyte complex and ionic, injectable, and thermosensitive hydrogel for sustained release of human growth hormone. *Biomaterials* **2013**, *34* (4), 1327−1336.

(70) Nagasaki, Y.; Mizukoshi, Y.; Gao, Z.; Feliciano, C. P.; Chang, K.; Sekiyama, H.; Kimura, H. Development of a local anesthetic lidocaine-loaded redox-active injectable gel for postoperative pain management. *Acta Biomater.* **2017**, *57*, 127−135.

(71) Møiniche, S.; Mikkelsen, S.; Wetterslev, J.; Dahl, J. B. A qualitative systematic review of incisional local anaesthesia for postoperative pain relief after abdominal operations. *Br. J. Anaesth.* **1998**, *81* (3), 377−383.

(72) Vong, L. B.; Bui, T. Q.; Tomita, T.; Sakamoto, H.; Hiramatsu, Y.; Nagasaki, Y. Novel angiogenesis therapeutics by redox injectable hydrogel - Regulation of local nitric oxide generation for effective cardiovascular therapy. *Biomaterials* **2018**, *167*, 143−152.

(73) Lundberg, J. O.; Weitzberg, E.; Gladwin, M. T. The nitrate-nitrite-nitric oxide pathway in physiology and therapeutics. *Nat. Rev. Drug Discovery* **2008**, *7* (2), 156−167.

(74) Massion, P. B.; Feron, O.; Dessy, C.; Balligand, J.-L. Nitric Oxide and Cardiac Function. *Circ. Res.* **2003**, *93* (5), 388−398.

(75) Hoang, H. T.; Jo, S.-H.; Phan, Q.-T.; Park, H.; Park, S.-H.; Oh, C.-W.; Lim, K. T. Dual pH-/thermo-responsive chitosan-based hydrogels prepared using "click" chemistry for colon-targeted drug delivery applications. *Carbohydr. Polym.* **2021**, *260*, 117812.

(76) Lv, X.; Zhang, W.; Liu, Y.; Zhao, Y.; Zhang, J.; Hou, M. Hygroscopicity modulation of hydrogels based on carboxymethyl chitosan/Alginate polyelectrolyte complexes and its application as pH-sensitive delivery system. *Carbohydr. Polym.* **2018**, *198*, 86−93.

(77) Hujaya, S. D.; Lorite, G. S.; Vainio, S. J.; Liimatainen, H. Polyion complex hydrogels from chemically modified cellulose nanofibrils: Structure-function relationship and potential for controlled and pH-responsive release of doxorubicin. *Acta Biomater.* **2018**, *75*, 346−357.

(78) Boedtkjer, E.; Pedersen, S. F. The Acidic Tumor Microenvironment as a Driver of Cancer. *Annu. Rev. Physiol.* **2020**, *82* (1), 103−126.

(79) Li, X.; Sun, Q.; Li, Q.; Kawazoe, N.; Chen, G. Functional Hydrogels With Tunable Structures and Properties for Tissue Engineering Applications. *Front. Chem.* **2018**, *6*. DOI: 10.3389/fchem.2018.00499

(80) Ghidoni, I.; Chlapanidas, T.; Bucco, M.; Crovato, F.; Marazzi, M.; Vigo, D.; Torre, M. L.; Faustini, M. Alginate cell encapsulation: new advances in reproduction and cartilage regenerative medicine. *Cytotechnology* **2008**, *58* (1), 49−56.

(81) Pérez-Luna, V. H.; González-Reynoso, O. Encapsulation of Biological Agents in Hydrogels for Therapeutic Applications. *Gels* **2018**, *4* (3), 61.

(82) Chan, G.; Mooney, D. J. Ca2+ released from calcium alginate gels can promote inflammatory responses in vitro and in vivo. *Acta Biomater.* **2013**, *9* (12), 9281−9291.

(83) Nurlidar, F.; Kobayashi, M.; Terada, K.; Ando, T.; Tanihara, M. Cytocompatible polyion complex gel of poly(Pro-Hyp-Gly) for simultaneous rat bone marrow stromal cell encapsulation. *J. Biomater. Sci., Polym. Ed.* **2017**, *28* (14), 1480−1496.

(84) Shang, J.; Shao, Z.; Chen, X. Electrical Behavior of a Natural Polyelectrolyte Hydrogel: Chitosan/Carboxymethylcellulose Hydrogel. *Biomacromolecules* **2008**, *9* (4), 1208−1213.

(85) Chiellini, F.; Puppi, D.; Piras, A. M.; Morelli, A.; Bartoli, C.; Migone, C. Modelling of pancreatic ductal adenocarcinoma in vitro with three-dimensional microstructured hydrogels. *RSC Adv.* **2016**, *6* (59), 54226−54235.

(86) Engler, A. J.; Sen, S.; Sweeney, H. L.; Discher, D. E. Matrix Elasticity Directs Stem Cell Lineage Specification. *Cell* **2006**, *126* (4), 677−689.

(87) Chaudhuri, O.; Koshy, S. T.; Branco da Cunha, C.; Shin, J.-W.; Verbeke, C. S.; Allison, K. H.; Mooney, D. J. Extracellular matrix stiffness and composition jointly regulate the induction of malignant phenotypes in mammary epithelium. *Nat. Mater.* **2014**, *13* (10), 970−978.

(88) Rao, K. M.; Kumar, A.; Han, S. S. Polysaccharide-based magnetically responsive polyelectrolyte hydrogels for tissue engineering applications. *J. Mater. Sci. Technol.* **2018**, *34* (8), 1371−1377.

(89) Cui, H.; Yu, Y.; Li, X.; Sun, Z.; Ruan, J.; Wu, Z.; Qian, J.; Yin, J. Direct 3D printing of a tough hydrogel incorporated with carbon nanotubes for bone regeneration. *J. Mater. Chem. B* **2019**, *7* (45), 7207−7217.

(90) Belluzo, M. S.; Medina, L. F.; Cortizo, A. M.; Cortizo, M. S. Ultrasonic compatibilization of polyelectrolyte complex based on polysaccharides for biomedical applications. *Ultrason. Sonochem.* **2016**, *30*, 1−8.

(91) Liang, Y.; He, J.; Guo, B. Functional Hydrogels as Wound Dressing to Enhance Wound Healing. *ACS Nano* **2021**, *15* (8), 12687−12722.

(92) Wang, W.; Ummartyotin, S.; Narain, R. Advances and challenges on hydrogels for wound dressing. *Curr. Opin. Biomed. Eng.* **2023**, *26*, 100443.

(93) Oliveira, M. B.; Bastos, H. X. S.; Mano, J. F. Sequentially Moldable and Bondable Four-Dimensional Hydrogels Compatible with Cell Encapsulation. *Biomacromolecules* **2018**, *19* (7), 2742−2749.

(94) Sharma, S.; Swetha, K. L.; Roy, A. Chitosan-Chondroitin sulfate based polyelectrolyte complex for effective management of chronic wounds. *Int. J. Biol. Macromol.* **2019**, *132*, 97−108.

(95) Wang, X.; Huang, H.; Xu, R.; Fang, Y.; Weng, Y.; Wang, Z.; Xiong, X.; Liu, H. Robust but On-Demand Detachable Wet Tissue Adhesive Hydrogel Enhanced with Modified Tannic Acid. *ACS Appl. Mater. Interfaces* **2023**, *15* (39), 45676−45688.

(96) Braun, K. M.; Diamond, M. P. The biology of adhesion formation in the peritoneal cavity. *Semin. Pediatr. Surg.* **2014**, *23* (6), 336−343.

(97) Nakagawa, H.; Matsumoto, Y.; Matsumoto, Y.; Miwa, Y.; Nagasaki, Y. Design of high-performance anti-adhesion agent using injectable gel with an anti-oxidative stress function. *Biomaterials* **2015**, *69*, 165−173.

(98) Cheong, Y. C.; Laird, S. M.; Li, T. C.; Shelton, J. B.; Ledger, W. L.; Cooke, I. D. Peritoneal healing and adhesion formation/reformation. *Hum. Reprod. Update* **2001**, *7* (6), 556−566.

(99) Gallardo-Rivera, R.; de los Ángeles Aguilar-Santamaría, M.; Silva-Bermúdez, P.; García-López, J.; Tecante, A.; Velasquillo, C.; Román-Guerrero, A.; Pérez-Alonso, C.; Vázquez-Torres, H.; Shirai, K. Polyelectrolyte complex of Aloe vera, chitosan, and alginate produced fibroblast and lymphocyte viabilities and migration. *Carbohydr. Polym.* **2018**, *192*, 84−94.

(100) Milne, S. D.; Seoudi, I.; Al Hamad, H.; Talal, T. K.; Anoop, A. A.; Allahverdi, N.; Zakaria, Z.; Menzies, R.; Connolly, P. A wearable wound moisture sensor as an indicator for wound dressing change: an observational study of wound moisture and status. *Int. Wound J.* **2016**, *13* (6), 1309−1314.

(101) Adnan, P. K. M.; Sreejith, L. Compact poly-electrolyte complex hydrogels of gelatin and sodium alginate for sensing wound status. *Mater. Lett.* **2022**, *313*, 131705.

(102) Zhao, J.; Chen, Y.; Yao, Y.; Tong, Z.-R.; Li, P.-W.; Yang, Z.-M.; Jin, S.-H. Preparation of the polyelectrolyte complex hydrogel of biopolymers via a semi-dissolution acidification sol-gel transition method and its application in solid-state supercapacitors. *J. Power Sources* **2018**, *378*, 603−609.

(103) Zhu, F.; Lin, J.; Wu, Z. L.; Qu, S.; Yin, J.; Qian, J.; Zheng, Q. Tough and Conductive Hybrid Hydrogels Enabling Facile Patterning. *ACS Appl. Mater. Interfaces* **2018**, *10* (16), 13685−13692.

(104) Liza, L.; Kabir, M. H.; Jiang, L.; Jerrams, S.; Chen, S. The technology of wearable flexible textile-based strain sensors for monitoring multiple human motions: construction, patterning and performance. *Sens. Diagn.* **2023**, *2* (6), 1414−1436.

(105) Sahoo, S. D.; Vasudha, T. K.; Muthuvijayan, V.; Prasad, E. Chitosan-Based Self-Healable and Adhesive Hydrogels for Flexible Strain Sensor Application. *ACS Appl. Polym. Mater.* **2022**, *4* (12), 9176−9185.

(106) Li, S.; Pan, H.; Wang, Y.; Sun, J. Polyelectrolyte complex-based self-healing, fatigue-resistant and anti-freezing hydrogels as highly sensitive ionic skins. *J. Mater. Chem. A* **2020**, *8* (7), 3667−3675.

■ NOTE ADDED AFTER ASAP PUBLICATION

This review published ASAP on November 18, 2024. The caption to Figure 1 has been updated and the corrected version reposted on November 22, 2024.