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Review

Polyelectrolytes and Polyelectrolyte Complexes as Future Antibacterial Agents

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Abstract: Antibiotic-resistance (ABR) poses a critical public health challenge within the broader antimicrobial resistance crisis. This review evaluates the potential of polyelectrolytes (PEs) and polyelectrolyte complexes (PECs) for controlled antibiotic delivery as a strategy to combat ABR and biofilm-related infections. PECs, particularly those incorporating chitosan and other polycations, enhance antibacterial efficacy by disrupting bacterial cell walls and obstructing their nutrient flow. They are also effective in penetrating biofilms and providing sustained drug release. Despite these advantages, there is a need for further in vivo research and clinical trials to validate these findings. This review provides a comprehensive overview of PECs' potential to advance antibacterial therapies and outlines future research directions to further explore their applications.

Keywords: antibiotic resistance; polyelectrolyte complexes; controlled drug delivery; chitosan; antibacterial resistance; biofilm-related infections; antibacterial efficacy; biofilm penetration; sustained drug release; in vivo research

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1. Introduction

Antibiotic-resistance (ABR), a critical aspect of the broader antimicrobial resistance (AMR) crisis, poses a severe global public health challenge. The World Health Organization (WHO) reported that ABR caused approximately 1.27 million deaths in 2019 and contributed to an additional 5 million deaths worldwide [1,2]. Projections suggest that by 2050, AMR-related diseases could lead to 10 million deaths each year, with an estimated economic impact of USD 100 trillion [3]. Moreover, experts estimate that ABR will result in 390,000 annual deaths in Europe [4].

Worsening these challenges, the Centers for Disease Control and Prevention (CDC) reports that up to 50% of antibiotic prescriptions in the US are either inappropriate or ineffective [3], a problem that is similarly prevalent in Europe. In the European Union and European Economic Area (EU/EEA), healthcare-associated infections (HAIs) affect over 3.5 million people annually, resulting in more than 90,000 deaths and approximately 2.5 million disability-adjusted life years lost. Notably, 71% of these infections are caused by ABR, including those resistant to last-resort treatments such as carbapenem-resistant Enterobacterales [5].

Recent global data indicate a growing prevalence of ABR, mainly in biofilm forming bacteria, where the horizontal transfer of resistance genes is facilitated [4]. Poor medical practices and irrational prescriptions are major contributors to many resistances. Stewart et al. highlight that it is not hard to turn microbes resistant to penicillin with subtherapeutic concentrations [3]. This underscores the critical need for proper antibiotic stewardship [1,6]. Inadequate concentrations of antibiotics can lead to metabolic changes in bacteria cells. These can result in the deactivation of drug molecules, cell expulsion, or entry prevention of antibiotics [2,4].

Bacterial biofilms—complex bacterial structures with strong intercellular communication and extracellular matrices—reduce exposure and facilitate resistance to antibiotics [7]. Biofilms are common in chronic wounds as well as in implanted medical devices like catheters and prosthetics [8]. Sometimes, they can lead to sepsis if the infection is not managed correctly [9]. Therefore, appropriate coating of implants and wound dressings with antibacterial agents might limit and prevent biofilms formation. This can also diminish the risk of resistances, since it reduces antibiotics usage [10,11].

Staphylococcus aureus and *Pseudomonas aeruginosa* are two principal biofilm-forming bacteria. Patients of chronic obstructive pulmonary disease (COPD) and cystic fibrosis are at high risk of infection with *P. aeruginosa* and biofilm formation in the lung [12,13]. Similarly, *P. aeruginosa*, *S. aureus*, *Staphylococcus epidermidis*, and *Streptococcus pyogenes*, as well as opportunistic pathogens like *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Enterococcus faecalis* are significant contributors to implant-related infections. These infections pose substantial health and economic burdens, often requiring prolonged antibiotic therapy and surgical intervention [14–16]. Also, *S. aureus*, *P. aeruginosa*, and *E. coli* are commonly found in infected wound environments.

As traditional antibiotics have become increasingly ineffective, there is an urgent need for new therapeutic and prevention strategies [1,5]. One promising approach involves polyelectrolytes (PEs) and polyelectrolyte complexes (PECs) from natural or synthetic sources as potential antibacterial agents. PEs, which are charged polymers obtained from nature or by chemical synthesis, with opposite charges interact in an appropriate polar environment to form PECs. PEs and PECs were reported to have promising applications in the field of infectious diseases [17–21]. These materials not only offer innovative drug delivery systems, such as with nanoparticles (NPs), but may also possess internal antibacterial properties, making them valuable antibacterial agents [22–25].

In biomedicine, PEs and PECs are pivotal in advancing new approaches, particularly by enabling the development of more efficient, less invasive, and cost-effective medical practices [20–26]. Their application in targeted drug delivery systems is particularly significant as it enhances drug bioavailability and minimizes toxicity. The adaptability of PEs extends to controlled release formulations and their use in bioadhesive materials, particularly for oral, nasal, and buccal applications [27,28]. This highlights their broad utility in pharmaceutical formulations [25,27–29]. Applications involve tissue regeneration therapy, surface modification and functionalization of implants, construction of artificial organs, gene therapy, cancer treatment, and the injectable delivery of pharmaceuticals to specific sites—an advantage in antibiotic administration [30–33].

In addition, PECs offer diverse functionalities in various domains. For instance, they can serve as matrices for encapsulating probiotics, protecting them from harsh gastric environments [34–36], and exhibit antibacterial and antioxidant properties that enhance food preservation [37]. Additionally, PECs are utilized as foundational materials in food storage and packaging, further expanding their practical applications [38].

Given the increasing prevalence of ABR, the potential of PEs and PECs in biomedical applications and advanced technologies is particularly significant. This review will examine the role of PEs and PECs as prospective antibacterial agents, focusing on their formation and antibacterial properties, especially in wound healing, medical devices, oral cavity infections, cutaneous infections, and lung infections. Additionally, we will highlight their role in pharmaceutical development, particularly in the controlled release of antibacterials and biofilm disruption.

2. Classification and Physicochemical Properties of PEs

PEs, also called polyions, combine polymers and ions in one molecule. Polyions are considered ancient molecules, given that life entails the replication of charged polymers to pass genetic information in the form of RNA or DNA. Interestingly, PEs might have formed even before the beginning of life [16].

A PE is defined as any macromolecule consisting of repeating units that dissociate into a charged polymeric molecule when placed in ionizing solvents such as water, leading to the formation of polyanions or polycations. PEs are always found associated with small counter-ions that lead to neutrality; positive counter-ions in the case of polyanions and negative in the case of polycations [33,39].

Their properties depend on several factors such as molecular weight (Mw), charge density and distribution, and branching. These can also depend on the medium, such as pH and ionic force [40].

PEs can be classified according to their charge into polycations and polyanions or to their origin into natural and synthetic. Examples of PEs are stated below.

2.1. Natural Polyelectrolytes

Natural PEs (Table 1) are derived from biological sources, such as plants, animals, and fungi. In most cases they are polysaccharides. A brief description of the most commonly used PEs in biomedical applications is as follows:

- Chitosan (CS) is a polysaccharide derived from chitin by deacetylation reactions, and thus, some authors consider it pseudo-natural. It consists of N-acetyl-D-glucosamine and D-glucosamine. It is the second most abundant natural polymer after cellulose. It is found in several marine creatures but is mainly extracted from shrimp and crabs, since it is found in their exoskeleton. It is also found in the cell walls of yeast and fungi, imparting strength to their structures [41–43].
- CS is characterized by its positive charge and is used in wound healing and drug delivery systems thanks to its excellent pharmaceutical properties, such as mucoadhesion, biocompatibility, biodegradability, and antimicrobial efficacy [44,45]. CS turns into a PE only in acidic conditions due to the protonation of amino groups; thus, it is very sensitive to pH [43]. In addition, its properties vary accordingly to the degree of acetylation and charge distribution, as well as the Mw [43].
- Alginate (Alg) is a linear polysaccharide derived mainly from brown seaweeds, such as *Laminaria* species, *Macrocystis pyrifera*, *Saccharina japonica*, and *Ascophyllum nodosum*. It is a polyacid that consists of alternating β-D-mannuronic acid and α-L-guluronic acid residues linked by 1,4-glycosidic bonds [46,47]. Alginate is well-known for its gelling properties (mainly in the presence of divalent cations), which, coupled with its remarkable biodegradability and biocompatibility, makes it a cornerstone in pharmaceutical technology and biotechnology [48,49]. Importantly, alginate also possesses antimicrobial properties, minimal immunogenicity, and both hygroscopic and humectant qualities [49]. These features not only enhance its role in drug delivery, tissue engineering, and wound healing, but also highlight its transformative impact on the pharmaceutical industry and its potential for pioneering research applications [50].
- Carboxymethylcellulose (CMC) is a cellulose-derived PE found in plant cell walls, such as those in wood pulp and cotton. Recent research has explored alternative, sustainable sources of cellulose, including sago palm, corn husk, rice husk, rice stubble, and waste materials like paper sludge and cotton gin waste [48,51]. CMC is produced by chemically modifying cellulose with carboxymethyl groups, enhancing its functionality. CMC is known for its water solubility and hemostatic properties; it has applications in wound dressings and drug delivery systems. Furthermore, its strong hydrophilicity, bioadhesive properties, and low toxicity make it an excellent candidate for various applications [52,53].
- Chondroitin Sulfate (ChS), is an anionic glycosaminoglycan, widely found in vertebrates, invertebrates, and bacteria. Structurally, ChS consists of repeating disaccharide units of D-glucuronic acid and N-acetyl galactosamine, with sulfate groups at various carbon positions. It is categorized into subgroups like ChS-A, ChS-B, ChS-C, ChS-D, and ChS-E, based on the sulfate group's position [54]. ChS has valued biomedical applications thanks to its chondroprotective and anti-atherogenic effects [10,55]. Antibacterial activity was also reported [11].

- Hyaluronic Acid (HA) is a natural, linear glycosaminoglycan and an important component of the extracellular matrix. Structurally, HA comprises repeating disaccharide units of D-glucuronic acid and N-acetyl-D-glucosamine, linked by alternating β-1,3 and β-1,4 glycosidic bonds [56]. This biopolymer exists predominantly as high Mw, typically over 1000 kDa, in healthy tissues, where it exhibits antiangiogenic and immunosuppressive properties. Conversely, low Mw HA fragments, resulting from degradation, are linked to inflammatory responses and angiogenesis [57]. Due to its superior biodegradability, biocompatibility, and "hydration capacity" HA is widely utilized in tissue engineering and wound healing applications [56,58].
- Carrageenans (CRGs) are naturally occurring anionic polysaccharides, being extracted from red algae (Rhodophyta); their corresponding to sulfated esters of polygalactose of high Mw. β-carrageen is an exception, since it is deprived of sulfate ester moieties [59]. Depending on the degree of sulfation and the positions of the sulfate groups, CRGs are classified into five main groups: λ, κ, ι, ε, and μ. κ-CRG, the most common in pharmaceutical technology, is composed of alternating units of 1,3-linked β-D-galactose where a sulfate group is bound to C4, and 1,4 linked anhydogalactose units [60,61]. It has several biological activities, including those antiviral against herpes simplex virus (HSV) and human papilloma virus (HPV) [62]. Studies have proven that i-CRG is effective against a strain of influenza virus, and its effect is similar to that of oseltamivir. Furthermore, CRGs have shown antioxidant, antitumor, and immunomodulatory properties [62–64].
- Fucoidan (Fuc) is a sulfated polyanion and polysaccharide derived from brown seaweeds, such as *Fucus vesiculosus*. It is composed primarily of L-fucose and sulfated ester groups, with minor components including D-xylose, glucuronic acid, D-galactose, and D-mannose [65,66]. Its biological activities—anticoagulant, anti-inflammatory, antibacterial, antiviral, and anticancer properties—are influenced by Mw, sulfation levels, and monosaccharides composition [66]. Fuc typically features two types of chains: Type I, consisting of α (1→3) linked fucose, and Type II, characterized by alternating α (1→3) and α (1→4) linked fucose [65,66].
- Heparin (Hep) is a highly sulfated, heterogeneous linear glycosaminoglycan predominantly sourced from animal tissues, such as porcine intestinal mucosa and bovine lung. It consists of 1,4-glycosidically linked D-glucosamine and uronic acid. Uronic acid units can either be α-L-iduronic acid or β-D-glucuronic acid, which can be sulfated at several positions [67,68]. Beyond its well-documented anticoagulant and anti-inflammatory properties, Hep has demonstrated significant efficacy in combating bacterial infections. It also showed activity against malaria and Lyme disease [68–70].
- Pectin is a complex, weak polyanionic heteropolysaccharide found in plant cell walls, widely used for its gelling and thickening properties. It consists mainly of (1 → 4)-α-D-galacturonic acid (Gal A) residues, branched with neutral sugars [71]. Pectin is known for its ability to form stable complexes with positively charged molecules. This property makes it valuable in electrochemistry and biocompatible film formation [49,72].
- Poly-amino acids are increasingly valued in drug delivery systems [73]. Among these, γ-poly (glutamic acid) (γ-PGA) stands out as a biodegradable, non-toxic, and water-soluble biopolymer, synthesized through bacterial fermentation. Interestingly, its resistance to proteolytic degradation makes it a strong contender for a variety of biomedical applications, as it can be used in drug carriers or as an antibacterial agent. High Mw γ-PGA (800–1000 kDa) is particularly notable for its exceptional water retention capability, absorbing up to 5000 times its weight, although its water solubility diminishes with increased Mw [73,74].
- Gelatin, a denatured collagen derivative used in food, pharmaceuticals, and biomedical fields for its ability to form thermoreversible gels. It is zwitterionic, has a positive or negative charge according to pH, and is produced through partial hydrolysis of collagen. Gelatin has a Mw ranging from 15 to 250 kDa. Gelatin's gelation occurs as

the denatured polypeptides partially reform collagen-like triple helices upon cooling, stabilized by hydrogen bonds, electrostatic, and hydrophobic interactions [75,76].

- Others such as cyclodextrin-based macrocyclic oligosaccharides are derived from starch. Cyclodextrins are categorized into α-, β-, or γ-cyclodextrins based on the number of glucopyranose units in their cyclic structure, but their derivatives may be synthesized. The hydrophobic cavity within cyclodextrins facilitates the formation of inclusion complexes with a variety of compounds, thereby enhancing drug solubility, stability, and permeability through biological barriers [77,78]. Additionally, xanthan gum, a polysaccharide produced through the fermentation of *Xanthomonas campestris*, is widely used in pharmaceutical formulations. Its high Mw and anionic nature enable it to significantly increase viscosity, stabilize emulsions, and form protective films around active ingredients, thereby enhancing the bioavailability and controlled release of drugs [79].

Table 1. Natural Polyelectrolytes and their key Properties.

Polyelectrolyte	Functional Group [1]	Properties	Source	Refs.
Alginate	-COOH	Gel-forming with divalent cations	▪ Brown seaweeds	[48,51]
Carboxymethylcellulose	-COOH	High hydrophilicity, biodegradable	▪ Plant cell walls	[51,52]
Carrageenan	$-SO_4^{2-}$	Gel-forming, thickening properties	▪ Red algae	[64,80]
Chondroitin sulfate	$-SO_4^{2-}$	Biocompatible, chondroprotective	▪ Animal cartilage	[10,55]
Chitosan	$-NH_2$	pH-sensitive, biodegradable	▪ Exoskeletons of crustaceans	[44,45]
Fucoidan	$-SO_4^{2-}$	Interacts with proteins and cells	▪ Brown seaweeds	[65,81]
Gelatins	$-NH_2$	Thermoreversible gels	▪ Animal connective tissues	[75,76]
Heparin	$-SO_4^{2-}$	Interacts selectively with multiple proteins	▪ Animal tissues	[67,68]
Hyaluronic acid	-COOH	Biodegradable, enhances drug specificity	▪ Connective tissues	[56,57]
Pectin	-COOH	Anionic, forms stable complexes	▪ Plant cell walls	[49,71]
Poly-amino acids	$-NH_2$	Biodegradable, hydrophilic	▪ Bacterial fermentation	[73,74]
Xanthan Gum	-COOH	High viscosity, gel-forming	▪ Bacterial fermentation	[79]

[1] Functional Group: (COOH)—Carboxyl groups; (NH_2)—Amino groups; (SO_4^{2-})—Sulfate groups.

2.2. Synthetic Polyelectrolytes

Synthetic PEs (Table 2) are chemically engineered to provide specific properties and functionalities tailored for various applications. Notable examples include:

- Dextran sulfate (DS) is an anionic PE derived from dextran, a complex polysaccharide composed of α-1,6-linked glucose units. It is widely employed in biomedical applications, notably for its anticoagulant properties, due to its ability to inhibit blood

clotting by interacting with specific biological proteins. Additionally, DS has demonstrated potential as an antibacterial agent, contributing to its versatility in therapeutic applications [82,83].

- Polyacrylic acid (PAA) is an anionic polyelectrolyte characterized by its remarkable water solubility and high-water absorption capacity. Synthesized from acrylic acid monomers, PAA features ionizable carboxyl groups that facilitate its gelation and thickening properties [84,85]. These attributes make PAA valuable in pharmaceutical applications, particularly in controlled drug release systems and gel formulations. Its capacity to form cross-linked networks, achieved through radiation or chemical cross-linking, enhances its stability and versatility. It is biodegradable and recent studies indicate that it also exhibits antibacterial properties [85].
- Polymalic acid (PMA) is a biopolymer synthesized from L-malic acid, with its polymerization achieved using the yeast-like fungus *Aureobasidium pullulans*. It is biodegradable and a safe excipient in drug delivery systems such as polymeric micelles, and with nanoparticles [86,87].
- Polyvinylsulfonic acid sodium salt (PVSNa) is a sulfonic acid-based polyanion with remarkable physicochemical properties, including high water solubility and the ability to form complexes with cations, due to its sulfonic acid functional groups. It is synthesized through the polymerization of vinyl sulfonic acid, resulting in a strong aliphatic sulfonic acid polymer that is soluble in water and lower alcohols [88,89].
- Polystyrene carboxylic acid (PSA) is an anionic PE synthesized by introducing carboxylic acid groups onto polystyrene chains [90,91]. This polymer is recognized for its high water solubility and ability to form complexes with various cations. PSA is utilized in drug delivery systems and industrial formulations due to its capacity to modulate solution viscosity and enhance formulation stability [90,91].
- Polyacrylamide acid (PAM) is a polyanion with key physicochemical properties, including the formation of three-dimensional networks with high water retention. Its structure can be tailored through co-polymerization with anionic monomers like acrylate or 2-acrylamido-2-methylpropane sulfonate (AMPS), affecting its solubility and viscoelastic properties. These modifications enhance PAM's effectiveness in drug delivery systems by improving drug encapsulation and controlled release [92,93].

Table 2. Synthetic Polyelectrolytes and their key Physicochemical Properties.

Polyelectrolyte	Functional Group [1]	Properties	Source	Refs.
Dextran sulfate	-SO_4^{2-}	Highly soluble in water; forms gels with counterions	▪ Derived from dextran, a polysaccharide from bacterial fermentation of sucrose.	[82,83]
Polyacrylic acid	-COOH	Water solubility; high-water absorption; gel formation	▪ Produced by polymerization of acrylic acid, derived from petroleum-based propylene.	[84,85]
Polymalic acid	-COOH	Soluble in water; forms gels in aqueous environments	▪ Synthesized from malic acid, derived from fruits or chemically produced.	[86,87]
Polyvinylsulfonic acid sodium salt	-SO_3Na	High water solubility; complex formation with cations	▪ Produced by polymerizing vinyl sulfonic chloride, derived from vinyl compounds.	[88,89]
Polystyrene carboxylic acid	-COOH	Complex formation; viscosity adjustment	▪ Made from carboxylated polystyrene; styrene derived from petroleum.	[90,91]

Table 2. *Cont.*

Polyelectrolyte	Functional Group [1]	Properties	Source	Refs.
Polyacrylamide acid	-CO_2NH_2	Gel-forming; high-water retention	▪ Created by polymerizing acrylamide, derived from acrylonitrile (propylene and ammonia)	[92,93]

[1] Functional Group: (COOH)—Carboxyl groups; (NH_2)—Amino groups; (SO_3H)—Sulfonic acid group.

3. Polyelectrolyte Complexes (PECs)

3.1. Formation of PECs

PECs result from the electrostatic interaction between two oppositely charged PEs. If one of the PEs is a drug molecule, complexes are called nanoplexes [92–94]. In an appropriate aqueous medium, PEs react, releasing their counterions, which results in the formation of PECs and phase separation: the results are a concentrated phase as a coacervate, precipitate, or gel and diluted phase. Also, PECs can remain soluble [31,95].

There are other methods used in the synthesis of PECs. For example, layer by layer (LbL) deposition is a technique used to cover medical devices with several layers of PEs in order to increase their biocompatibility. For that, films are functionalized, then inserted into a solution of PEs, and afterwards with another solution with opposing charged PEs. The cycle is repeated according to the desired number of layers. PECs form in the junction between layers (interfacial complexation) [56,96,97]. It is shown that besides benefiting from the properties of each PE in the complexed layers, the complexation provides mechanical stability in swelling [98]. In addition, electrospinning is a method used in the fabrication of nanofibers from PEs; this method saves a great deal of time, since it dispenses cycle repetition [99].

3.2. Antibacterial Application

The rapid growth of ABR is driving research to develop new antibacterial agents that can serve as alternatives or be used in combination with current antibiotics, thus mitigating the risk of resistances. PEs and their complexes have been a point of attraction for researchers to develop new systems with antibacterial potential. Interestingly, quercetin/CS complexes increased bacterial inhibition from 17% (quercetin alone) to 41% of *P. aeruginosa* and evidenced concentration-dependent biofilm inhibition [7]. This synergism was also found in lyzosym/ulvan nanoplexes against *S. aureus* as the complex more than tripled the antibacterial effect [100].

The antibacterial properties of PEs depend on several factors such as the Mw of the polymer, complex stoichiometry, pH and ionic strength of the medium, and polymer concentration [101]. A study found that lower Mw CS in CS/γ-PGA PECs showed stronger antibacterial activity than higher Mw CS [102]. Interestingly, this effect was more pronounced against Gram-positive bacteria [102,103]. Notwithstanding, another study demonstrated that no significant difference in antibacterial activity resulted from different Mw of CS. Furthermore, PECs based on high Mw quaternary ammonium salts of CS showed higher antibacterial activity than lower Mw CS [104]. Regarding PECs stoichiometry, stoichiometric PECs are devoid of charge, which implies fewer antimicrobial properties. Concerning the pH and ionic strength of the medium, most PECs are prepared from weak acids and bases; thus, pH changes can lead to the neutralization of some charges, and consequently less interaction with bacterial cell structures. Ionic strength can lead to structural changes such as polymer folding; thus, charge might be embedded in the center of the polymer [20,94,96,105–107]. In addition, a study demonstrated that salts promoted the rapid release of PEs, specifically CS and CD, from their complexes [97]. Finally, it depends on the concentration of the PEs [102,108].

Having that in mind, many biomedical applications of PECs were reported in the literature, mainly in the field of medical devices such as in wound dressings and implants, in addition to applications in skin products, and other applications in the field of infectious diseases have been studied (Table 3).

Table 3. Key PECs Investigated, their Applications and Antibacterial Effects.

PEC	Tested Bacteria	Application	Refs.
CS/Alg	*E. coli*, *S. aureus*, *K. pneumoniae*, and *P. aeruginosa*	▪ Wound healing ▪ Implants ▪ Coating contact lenses	[69,109–112]
CS/ChS	*B. subtilis* and *E. coli*	▪ Wound healing ▪ Implants ▪ Controlled release	[10,11,69]
CS/HA	*P. gingivalis*	▪ Oral cavity infections ▪ Controlled release	[11,113]
CS/PCD	*S. aureus* and *E. coli*	▪ Implants ▪ Controlled release	[101,114–116]
CMC/HACC	*E. coli* and *S. aureus*	▪ Wound healing	[98]
CS/Dex-P	*S. aureus* and *E. coli*	▪ Controlled release	[101]
CS/γ-PGA	*S. aureus* and *E. coli*	▪ Implants	[45,117]
Alg/QHEC-Et	*M. luteus* and *P. aeruginosa*	▪ Skin products	[118]
Xanthan/CS	*S. aureus* and *E. coli*	▪ Oral cavity infections	[119]
PPy/PA	*S. aureus* and *E. coli*	▪ Implants	[120]
PEI/Alg	*S. aureus* and *E. coli*	▪ Implants	[121]
PEI/DS	*S. mutans*, *S. sanguinis*, and *P. gingivalis*	▪ Oral cavity infections	[122]

PEC_Polyelectrolyte Complex; Alg: Alginate; CMC: Carboxymethylcellulose; CS: Chitosan; ChS: Chondroitin Sulfate; Dex-P: Dextran Phosphate; DS: Dextran Sulfate; HA: Hyaluronic Acid; HACC: 2-Hydroxypropylmethyl Ammonium Chloride Chitosan; PA: Polyanion; PCD: poly(betacyclodextrin citrate); PEI: Polyethylenimine; PPy: Polypyrrole; QHEC-Et: Quaternized Hydroxyethyl Cellulose Ethoxylate; γ-PGA: γ-Poly(glutamic acid).

3.2.1. Wound Healing

Wound healing is a complex process that requires a specific and appropriate environment to proceed free of complications. It consists of four main phases (Figure 1): The coagulation phase, also known as hemostasis, is characterized by clot formation. Clots are composed of fibrin fibers trapping cells and preventing further bleeding. The inflammatory phase follows, involving chemotaxis and the activation of inflammatory cells such as macrophages and neutrophils, which play a crucial role in eliminating infectious agents and inducing angiogenesis. The proliferative phase is marked by epithelialization and angiogenesis, leading to the formation of granulation tissue and the extracellular matrix by fibroblasts. This matrix is primarily composed of collagen, glycosaminoglycans, and fibronectin. The final phase, remodeling, consists of the maturation and reorganization of the collagen fibers. This last phase can last for months, depending on the wound's nature and the individual's healing capacity [123].

It is important to keep in mind that for wound infection to occur, there are several factors that come into play. Those factors can be related to the host, such as diabetes, malnutrition, hypoxia, peripheral arterial diseases, obesity, older age, and immune suppression. Interestingly, 70% of lower limb amputations result from diabetic foot complications [124]. Factors can also be related to microbial virulence, incontinence, anaerobic conditions, re-

sistance, biofilm formation, polymicrobial interactions, synergism, cross-contamination, and quantity, all of which contribute to microbial bioburden associated with microbial load, phenotype, and species. Other factors can be related to wound environment such as the presence of necrotic tissue, delayed granulation or epithelial migration, the presence of foreign bodies, and differences in pH and the inflammation matrix [3,123,125].

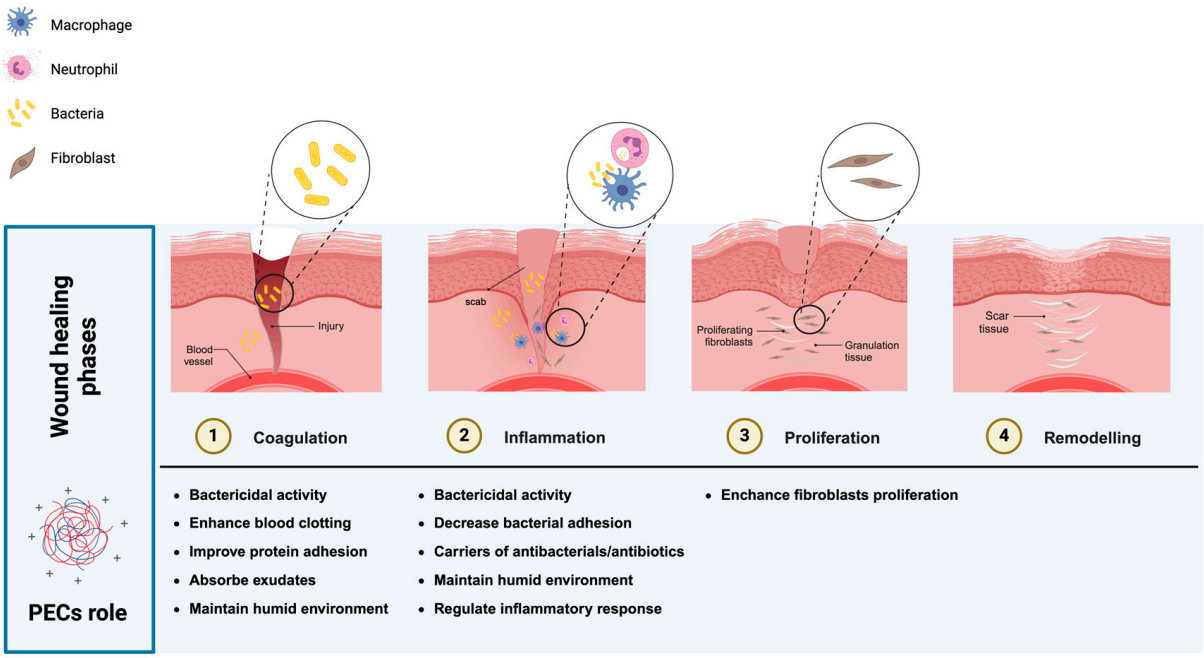

Figure 1. The four phases of wound healing and the role of PECs in each phase.

Wound infections significantly retard wound healing; when bacterial count exceeds 10^5 organisms/g of tissue, or when β-hemolytic *Streptococcus* is present, healing becomes impossible. Infections prolong the inflammatory phase and interfere with the proliferative phase, as they lead to the release of collagenases—enzymes that break down collagen which are crucial for maintaining the structural integrity of the wound matrix. Collagen degradation can weaken the wound site and delay tissue repair [3,123,125]. Furthermore, some bacteria have the potential to perturb the functioning of the immune system. For example, *S. pyogenes* and *S. pneumoniae* affect chemoattraction. Others such as *Streptococcus* spp., *N. meningitidis*, *Klebsiella* spp., *E. coli*, *P. aeruginosa*, and *H. influenzae* can mask surface antigens. Some bacterial species like *N. gonorrhoea* alter functional properties of neutrophils such as the production of reactive oxygen species. Also, *E. coli*, *P. aeruginosa*, and *S. aureus* induce neutrophil apoptosis following phagocytosis. Interestingly, *E. coli* can alter, either by increasing or decreasing, neutrophil apoptosis or necrosis [125].

ABR is a major risk for wound management. These resistances result mainly from incorrect practices in wound management, which can sometimes be caused by misleading symptoms, as signs of inflammation may or may not indicate an infection. This frequently leads to the irrational use of antibiotics [3,125,126]. For instance, acute wounds require a systematic course of antibiotics; meanwhile, chronic ones do not. Instead, in the latter, the key step is biofilm removal and a repetitive topical multimodal course of antibiotics [3]. Despite this, a survey in Norway demonstrated that 53% of patients with chronic wounds had been prescribed a course of systematic antibiotics [3]. Furthermore, a post hoc study on 350 chronic wounds across 20 clinicians and 14 wound care centers found that antibiotherapy prescriptions did not correlate with "bacterial load (CFU/g)" and that in 33.3% of patients on systematic antibiotics, no clinical signs and symptoms were found [126].

Having said that, successful wound management consists of two main parts: eliminating bacterial load, and tissue repair. This implies correct control of the wound environment, such as exudate and microbial bioburden. Also, the presence of some minerals, such as

Ca^{2+}, can accelerate the process, since it is a procoagulant. Wound dressings can help create this environment and accelerate the healing process by creating a humid environment and a physical barrier [3,98,125,127]. Importantly, PEs and PECs help create this environment thanks to their hydrophilic nature and swelling and absorption properties, as they absorb the exudate while maintaining a humid environment, leading to more concentrated blood cells and solid components. This, in addition to the antimicrobial properties of PEs, can accelerate the healing process [10,53,128].

Many efforts are put towards finding solutions to the irrational use of antibiotics and current resistances. Using antimicrobials like silver ions is considered a viable solution. Silver NPs have strong and broad-spectrum antibacterial effects. Many silver-based dressings have been approved such as Acticoat™, Actisorb®, Silverlon™, Acticoat®, Aquacel Ag®, and Silvasorb®. However, due to silver's toxicity, the need for high application frequencies, and fibroblast inhibition, it is important to find alternatives [128,129]. Therefore, the new trend in research is generating PECs loaded with or without antibiotics to control the bacterial load and treat infected wounds.

PECs can either be applied as antimicrobials or drug delivery systems in wound dressings to prevent and mitigate the chance of resistances. Films of PECs of CMC/Hydroxypropyltrimethyl ammonium chloride chitosan (HACC) and Ca2+ showed antibacterial activity against E. coli and S. aureus. Interestingly, despite films formed from HACC alone showing higher antibacterial properties, more comprehensive healing was verified in vivo in the case of CMC/HACC thanks to improved gelling properties [98]. Complexes of CS/ChS were found to decrease cell viability of *B. subtilus* and *E. coli* to 40% and 45%, respectively. In addition, CS/ChS accelerated wound healing by enhancing blood clotting and protein adhesion. This can be attributed to the hydrophilic property of the complex and to the fact that ChS is a part of the extracellular matrix, and CS induced fibroblasts proliferation and differentiation [10]. In addition, an in vivo study found that PECs of CS/Hep had many advantages in wound healing. This is due to its antimicrobial properties, accelerated coagulation and the inflammatory phase and regulated the inflammatory response. Interestingly, the presence of heparin was thought to increase the blood circulation in the wound area [107]. Other in vivo and in vitro experiences showed a hemostatic effect of CS/carboxymethyl starch. In addition, antibacterial activity against *S. aureus* was verified. Hemostasis was inversely proportional to CS content, while the increase in anti-*S. aureus* activity was directly proportional to the content of CS [108]. PAA/TMCh-covered nanofibers have been found to inhibit bacterial adhesion and have a bactericidal effect due to TMCh [130]. Aerogels are considered ideal matrixes for wound dressing as they allow wound-airing thanks to porosity. CS/Alg aerogels showed significant *S. aureus* and *K. pneumoniae* reduction [112]. Dual-layer PEC films can be used as wound dressing materials, where the under layer of gellan gum containing TiO_2_NPs promotes fibroblast proliferation, while the outer layer of CS/Levofloxacin exhibits antibacterial activity [131].

PECs can be used as drug delivery platforms that control the topical release of antibiotics, replacing repetitive antibiotic exposure, and mitigating, therefore, the risk of resistance, namely in the case of biofilm infected wounds. Nanofibers composed of nanohydroxyapatite and CS/gelatine PECs loaded with tetracycline showed a controlled release of the antibiotic with the following diameters of inhibition zone (DIZ): (DIZ day_1 = 14 nm, DIZ day_9 = 13 nm) and (DIZday_1 = 20 nm, DIZday_9 = 18 nm) in the case of *E. coli* and *S. aureus*, respectively. In addition, good mechanical and swelling properties were verified, implying maintenance in a wet wound environment [128]. Furthermore, LbL coating of polyethylene terephthalate dressing with PCD and CS loaded with silver in the first layer and ibuprofen in the last layer composes a promising platform for the healing of chronic and painful wounds. These patches provide sustained release of Ag^+, and this release was inversely proportional to the number of layers. The same study found that ibuprofen was released over 6 h [111]. Sponges, thanks to their porosity, improve wound drainage. Sponges of silver Sulfadiazine (AgSD) encapsulated in CS/Alg PECs can maintain a humid

environment for wounds and provide sustained release of the antimicrobial agent. More complex formation leads to a less bactericidal effect due to attenuated penetration [110].

3.2.2. Implants

Medical devices and implants are indispensable assets in medical practice. Examples are catheters, stents, and prosthetics. Joint replacement surgery is one of the most important, as more than 3.1 million total hip and 2.5 million total knee arthroplasties are conducted per year in Europe [132]. The most important cause of implants failure is the detachment of the prosthesis from the bone, bone fracture, and infection [8]. Removal of the infected medical device is essential in 63–72% of catheter associated bacteremia cases, and antibiotics only are not successful most of the time [8]. Infectious bacteria grouping up in biofilm is the most dangerous stage of infection due to high resistances. This is more worrying in the case of prosthetics, due to reduced blood supply, and consequently, exposure to the immune response. Bacterial species most found in biofilms are *S. epidermis*, *S. aureus*, and *P. aeruginosa*. These make up approximately 75% medical devices' biofilms. In infected implants, bacteria are either found on the implant surface or in the subjacent tissue, which allows them to avoid antibiotics and natural host defense. They can also be present in planktonic form, as biofilms on the hardware, or intracellularly [8]. The origin of infection can be the host's or a contaminated environment [8].

Having that in mind, for implants to be safe, a series of conditions should be satisfied. Biocompatibility, antimicrobial, and antibiofilm characteristics are on the top of the list. Antibacterial properties are substantial in the few hours following the surgery because the immune response is still not active [117].

Medical devices are commonly made of hydrophobic polymer such as Poly (ethylene terephthalate) (PET) [56,121], polyesters like 3-hydroxybutyric acid-co-3-hydroxyvaleric acid (PHBV) and Poly (ethylene terephthalate) [55,56], polylactic acid [11], and Poly-dimethylsiloxane [114]. Titanium, germanium, common in bone implants, and stainless steel, common in orthopedics, are also used, thanks to their excellent physicochemical characteristics [114,120,133]. Hydrophobic materials enhance bacterial adhesion; therefore, appropriate coating is essential to reduce bacterial adhesion, obtain bactericidal effects and reduce ABR. Interestingly, PECs have a set of properties that make them excellent candidates for implants' coatings, to turn more biocompatible and give less propensity for biofilm formation. These properties will be discussed in this section.

There are many methods which have been investigated and applied to combat bacterial infection or prevent biofilm formation on implants. The most common is a course of systematic antibiotics to eradicate or suppress microorganisms. However, long term and frequent use of systematic antibiotics is strongly related to resistances, superinfections, and toxicity since very high doses are required to achieve therapeutic concentrations [45].

Coating with silver NPs is a viable option; however, again due to its toxicity, research is shedding the light on the potential antibacterial effect of PECs [8]. In fact, many coating materials found in the literature depend on CS [55,110]. PEC-based coatings are biocompatible, hydrophilic, and have internal antimicrobial properties. The most common PECs are those formed from Alg/CS [109,110,133].

The antibiofilm activity of PECs is due to their repellent activity against bacteria and biological components [11,56,69,109,110]; especially in that blood protein adhesion is the primary step in biofilm formation that opens the way for bacterial agglomeration [134]. Ultracentrifuged compact (uc)CS/Alg PECs form cell- and bacteria-repellent surfaces, avoid bacterial and biological components adhesion. These ucPECs are selection materials for catheter fabrication [69,109]. SNO-CS/heparin, SNO-CS/HA, and SNO-CS/ChS reduced bacterial, platelet, and inflammatory factor adhesion [69]. CS/lysine-based surfactant showed blood protein repellent activity (mixed protein solution > albumin > fibrinogen > gamma-albumin). Being delivery materials of amoxicillin, activity against *S. aureus* and *E. coli* was evidenced [134].

Coating with PECs showed antibacterial properties. Interestingly, significant reduction in *P. aeruginosa* and *S. aureus* was verified after 24 h of heparin/ChS PECs application compared to glass control [69]. Dental implants made of γPGA/CMC/CS PECs scaffolds showed inhibition zones (17 mm and 14 mm) lower than those that CS alone scaffolds (22 nm and 17 nm) against *S. aureus* and *E. coli*, respectively. Nevertheless, PECs are preferred over CS due to optimized gelling properties [45]. Notwithstanding, other studies demonstrated that PECs had higher antibacterial activity compared to CS alone [10,11]. A porous poly(ε-caprolactone) (PCL)-based scaffold immersed in a hydrogel of PECs of CS/γ-PGA can help in tissue regeneration and have antimicrobial characteristics with 15-fold decreases in *S. aureus* and 4-fold decreases in *E. coli* count after 8 h and 6 h of incubation [117].

Encapsulating antibacterial agents and antibiotics helps deliver therapeutic concentrations [8]. Sponge-like CS/Alg hydrogels, prepared by ionic crosslinking of PECs, and encapsulating AgSD, showed activity against *P. aeruginosa* and less against *S. aureus* [110]. Silver encapsulated in polypyrrole/polyanion was tested as a coating material for orthopedic implants. This provided antibacterial activity against *S. aureus*, a major pathogen in implant infections, and *E. coli*. Interestingly, *E. coli* was killed within 120 min of exposure. This effect was attributed to the penetration of silver ions [120]. Non-vascular stents are used to relieve obstruction caused by tumors. Covering stents with a multilayer film of PEI-CA-doxorubicin/O-Alg-doxorubicin provided local delivery of doxorubicin and reduced survival rates to 11.5% and 10.9% against *S. aureus* and *E. coli*, respectively, thus preventing stent-related infections [121]. Inguinal hernia can be either congenital or result from the weakening of the abdominal wall [135]. Worldwide, 20 million hernias are repaired annually. Meshes are normally used to treat and repair hernias. A mesh coated with Alg/ciprofloxacin complex reduced the MIC of *S. aureus* and *P. aeruginosa* by half [136]. Controlled release of gentamycin, commonly used in orthopedics for post-surgery prevention, from CS/PCD-coated titanium scaffolds, provided sustained release, comparative to titanium-coated Gentamicin. When the film comprised 15 layers, antibacterial activity was observed for up to 6 days of incubation [114]. Vancomycin was also encapsulated in CS/gelatin PECs within a bone-mimicking scaffold. A biphasic release of the antibiotic was verified, first by diffusion, and later by liberation following polymer degradation [137]. Streptomycin, a cationic antibiotic commonly used in the treatment of osteomyelitis, was encapsulated in a PE multilayer on a germanium substrate for bone transplantation using the LBL technique. The release depended on the number of layers, with a slower release associated with an increased number of layers and antibiotic/PE ratio, as well the type of PE, where the natural Alg showed a slower release rate compared to the synthetic PAA [133]. Coating PET with Rifampicin encapsulated in CS/HA evidenced controlled release of the antibiotic; interestingly, the film itself showed a bactericidal effect and reduced bacterial adhesion [56]. Lomefloxacin-loaded CS/ChS PECs were found biocompatible and exhibited high antibacterial activity against *S. aureus* and *E. coli*. Interestingly, this method [11] reduced the use of antibiotics by 99.99%, while simultaneously demonstrating controlled release of Levofloxacin.

Incorporating bisphosphonate drugs and antibiotics into bone implants for fracture treatment can mitigate many of the detrimental effects associated with these drugs, particularly in bone surgeries. Coating the implant scaffold Ti40Nb with PECs of poly(L-lysine)/cellulose sulfonate demonstrated sustained release of rifampicin and risedronate. This release depended on pH and ionic strength [138].

3.2.3. Skin and Ocular Products

There are several other applications of PECs, for example, in skin products. 4-hexylresorcinol is a hydrophobic biocide used as an antimicrobial in many skin products. A study found that incorporating it in non-stoichiometric PECs of Alg/(quaternized hydroxyethyl cellulose ethoxylate) demonstrated increased hydrophilicity without impacting its antimicrobial properties. The whole complex showed antibacterial effect against *M. luteus* and to a less ex-

tent against *P. aeruginosa* with MIC values of 0.00070 ± 0.00004 wt% and 0.035 ± 0.003 wt%, respectively [118]. In addition, skin flora in dermatological products provide many advantages in cases of Eczema or other skin affections. A study showed that encapsulating *S. epidermidis* in PECs can be a good drug carrier that limits the excessive proliferation and invasion of the bacteria. The bactericidal effect was stronger when synthetic polyions were used compared to natural (CS/Alg) ones. Also, more aggregation was verified in the case of the natural ones; thus, there was a lower bactericidal effect. In this case, natural PEs are more desired as a bactericidal effect is not desired here [35]. Diabetic foot is still a public health challenge. Infections are more serious in this case due to reduced vascularization and, consequently, less effective delivery of systemic antibiotics. A study developed a sponge by lyophilizing a hydrogel of CS/PCD that carries ciprofloxacin in inclusion complexes and ionic interactions, thanks to its zwitterionic characteristics. This sponge demonstrated in vitro sustained antibacterial activity against *S. aureus* and *E. coli* [116]. LBL PECs were also found to control the growth of beneficial bacteria thanks to their bacteriostatic effects.

Corneal ulcer is an important infection resulting from contact lenses. A study found that coating contact lenses with CS/Alg PECs might reduce the risk of infection. They found that the PECs, as well as their separate polymers, had a significant inhibitory effect on *S. aureus*, and *E. coli*, and that this effect was very close to the one of vancomycin on the first, and ampicillin on the last. The same study found that CS did not prove to have any inhibitory effect against *P. aeruginosa*, but PECs and alginate did. Furthermore, Alg had a concentration independent effect on *P. aeruginosa* and *E. coli*. DIZ varied between 11 and 15 nm. In addition, swelling properties of these polymers help with maintaining wetness of the surface of the contact lenses, leading, thus, to less microbial adhesion [139].

3.2.4. Oral Cavity and Lung Infections

According to Ribeiro et al., there are several lesions that affect the oral cavity. Oral cavity lesions are an important cause of health issues given that they affect half of the world's population. These include infections such as gingivitis and periodontitis, among others [29]. The most commonly prescribed antibiotics for these situations are amoxicillin, ampicillin, clindamycin, azithromycin, tetracyclic, doxycycline, and metronidazole [1]. Systems of PECs and antimicrobials encapsulated in PECs demonstrated promising activity against these infections. A computational method was developed to study the dynamics of PECs and ampicillin in a film of ampicillin loaded CS/HA. This film is to be applied in periodontal pockets to treat periodontitis—an infection commonly caused by *Porphyromonas gingivalis* [113]. Chlorohexidine is an antimicrobial commonly used in mouthwashes and dental gels, and when encapsulated in PECs of CS/xanthan gum, it showed enhanced adhesiveness, indicating its potential in forming injectable hydrogels [140]. *S. mutans*, *S. sanguinis*, and *P. gingivalis* are involved in many periodontitis problems. *Punica granatum* peel extract has antibacterial activity against these strains. This activity is preserved in cases of complexation in PEI/DS NPs, providing rapid release in 5 min followed by prolonged release. Moreover, mucoadhesion leads to residence on the oral mucosa for 2 h. All of this might be a solution to the detrimental side effects of chlorohexidine, especially tooth pigmentation [122].

In addition, hydrogels made from tragacanth and xanthan gum, and CS encapsulating secnidazole, demonstrated greater mucoadhesive properties ex vivo compared to commercial formulations. Compared to using antimicrobials alone, the complex showed higher activity against pathogenic bacteria like *S. aureus* and *E. coli* while being more compatible with *L. brevis*. Surprisingly, CS addition lad to less mucoadhesion, however increased antibacterial activity [119].

P. aeruginosa is quite common in lung infections such as COPD and cystic fibrosis. Many times, it results in biofilm formation, which is a dangerous complication in bacterial lung infections. Nanoplexes of antibiotics/PE can achieve 100% encapsulation efficiency and 60–80% loading efficiency of ofloxacin and levofloxacin—two quinolones important in treating *P. aeruginosa* infections. NPs are more efficient in the delivery of antibiotics as they

penetrate the sputum, and since nanoplexes are NPs, this method can be promising for COPD patients. Additionally, nanoplexes of HA/gentamicin provided controlled release and increased antibiotic half-life [58].

3.2.5. Controlled Release

PECs are considered important platforms for the controlled delivery of antibiotics, which contributes significantly to the mitigation of antibiotic resistance [56,101,141–143]. PECs' NPs can have an important impact on the pharmacokinetics of antibiotics, as exposure to subtherapeutic concentrations of antibiotics, common in biofilms, multiplicates the risk of resistances [8]. For instance, PECs encapsulating ofloxacin provided sustained release of the quinolone as 50% was released in the first 24 h [141]. Sustained release depends on several factors, such as the Mw of the PEs. For example, controlled released of cefazolin from CS/Dextran phosphate hydrogel was achieved and found to be associated with the Mw of dextran phosphate maintained on the antibacterial activity against *S. aureus* and *E. coli* with inhibition diameters of 30 and 20 nm, respectively [101]. Drug release also depends on the PE content or concentration. Ampicillin released from CS/HA increased with decreasing HA content: 33% versus 87% from formulations with 6%, or 3% versus 12% of HA [113]. Moreover, Alg in pectin/Alg implied lesser release of ciprofloxacin, an antibiotic commonly used in urinary tract infections and absorbed in acidic medium [144], but the opposite was verified regarding pectin as the higher the concentration is, the higher the drug release is [145]. In addition, the antibacterial activity of triclosan was extended from 3 and 4 days (CS/triclosan) to 9 days (PCD (triclosan)/CS) against of *E. coli* and *S. aureus*, respectively [115].

Peptide antibiotics are not stable in vivo; therefore, encapsulation in PECs can increase their availability and, therefore, efficacy. Encapsulating JM72, a peptide with antimicrobial properties, in CS-N-arginine/Alg microparticles provided more stability, preserving its effectiveness against *Aeromonas diakinesis*, an endemic bacterium in Pakistan that can cause serious infections [105].

4. PECs Mechanism of Action

4.1. Against Procaryotic Bacteria

Antibacterial activity of PECs results mainly from the positive charge of polycations. Studies demonstrate that the antibacterial activity of PECs increases as the stoichiometric ratio of polyelectrolytes becomes less balanced, which correlates sometimes with a greater number of the exposed positive charges responsible for antibacterial activity [45]. Although the mechanisms of action of polycations are not completely elucidated, there are several suggestions regarding how polycation, namely CS, mechanisms of action depend inherently on the interaction between the positive charge of CS and the negative charge of bacterial components. Due to its high Mw, CS polymers cannot penetrate the bacterial cell wall and show bactericidal activities by disrupting the cell membrane and causing cytoplasmic leakage.

Additionally, quaternary ammonium salts of CS, such as HACC, have stronger activity than CS, due to its stronger positive charge which is pH independent. Their activity originates from their strong positive charge, which interacts with the negative charge of the bacterial membrane leading to its disruption [20,98,129]. Adhesion to the negatively charged bacterial surface results in blocking pores on the surface and impeding nutrient flow and exchange through the bacterial cell wall and membrane, and then metabolism suppression (Figure 2) [45,130]. Moreover, CS has the ability to chelate essential metals required for cell wall stability, compromising bacterial survival [11]. CS is adsorbed on the cytoplasmic membrane, leading to the leakage of cytoplasmic components and the loss of organelles [38,130]. Furthermore, CS oligomers inhibit transcription from DNA [70].

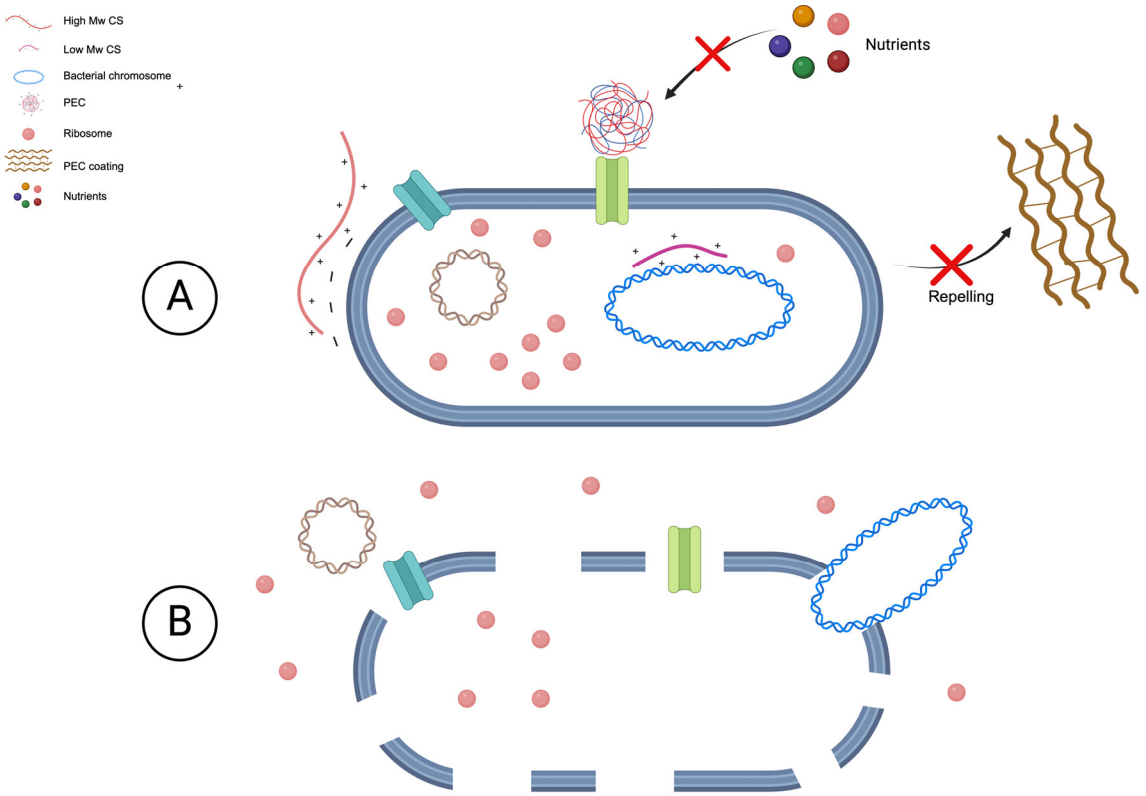

Figure 2. Antibacterial mechanism of PECs and PEs: (**A**) intact bacteria, (**B**) bacterial cell lysis.

It is worth noting that the efficacy of CS can vary among different types of bacteria; for example, studies suggest that the inhibitory effect on Gram-positive bacteria is generally stronger than that on Gram-negative bacteria due to the composition of the cell wall. The outer layer in Gram-positive bacteria has higher negative charge on the cell wall due to the presence of teichoic acid [11,45]. In Gram-negative bacteria, CS's positive charge binds to O-specific antigenic oligosaccharide repeating units, leading to the blockage of nutrient flow, ending with bacterial death, meanwhile in Gram-positive bacteria, cell membrane is coated with the cell wall that has GlcNAc and N-acetylmuramic acid, as well as isoglutamate and teichoic acid. This leads to cells wall disruption and cytoplasmic content voiding [45]. Also, sticking on the bacterial cell wall leads to pore blockage and metabolism inhibition, thus suppressing the exchanges across the wall and bacterial death [55].

Sulfated PEs like CRG, DS, fucoidan, and heparin can also demonstrate antibacterial activity, as thanks to their negative charge, they prevent the access to some aliments, like cationic metals, to the bacteria [11]. In addition, heparin was found to reduce adhesion of *S. aureus* and *E. coli* [85]. Interestingly, a study found that polystyrene sulfonate/ polyallylamine hydrochloride (PAH/PSS) PECs had stronger bactericidal activity compared to CHI/Alg PECs. This is due to the higher number of amino groups [35].

It is very worrying that some forms of resistances might render bacteria less responsive even to PEs. For example, methicillin resistant staphylococcus aureus (MRSA)'s extracellular capsule renders the bacteria more hydrophobic and reduces the exposed negative charge. This results in less interaction with hydrophilic PECs compared to *S. aureus*. It was found that PECs are less active against mobile bacteria like *P. aeruginosa* in comparison to non-moving ones [55].

Bacterial activity of PEs can be controlled according to the formulation. For instance, NPs of CS have higher surface comparing to volume, thus higher antibacterial effect. A study found that preparing those particles by ionic gelation or PEComplexation lead to higher activity than with precipitation. In the case of the last, precipitation is obtained by the addition of alkaline solution leading to neutralizing positive charges of CS and, thus, its

activity. However, in the two other cases, crosslinking results from the addition of a small molecule such as TPP (ionic gelation) or a macromolecule (PEComplexation). Importantly, this method yielded the smallest particles, and higher antibacterial activity results from the combination of increased ZP and smaller particle size [146].

The repellent activity of PECs results from the hydrophilic surface and the negative zeta potential given that the charge of most bacteria is negative [134]. A recent report found that positively charged biomaterial surfaces were successful in slowing the adhering of Gram-negative but not Gram-positive bacteria [8]. In addition to coating prosthetic surfaces with charged molecules, the use of macromolecules (e.g., heparin and polypeptides) to form a hydrated layer on the artificial surface was also shown to be promising in reducing bacterial colonization and biofilm formation by interfering with the binding of bacteria to various substrates [8].

4.2. Against Biofilms

Biofilm formation is one of the challenges associated with medical devices such as catheters, leading sometimes to complications and sepsis [3,125,132]. Biofilm formation occurs in several stages, including the following: (i) Attachment: In this phase, bacteria adhere to surfaces through van der Waals forces and electrostatic interactions. PECs can modify surface properties, influencing bacterial adhesion. For instance, cationic PEs can alter the surface charge of materials, inhibiting initial attachment [35]; (ii) Proliferation: Following attachment, bacterial cells proliferate, forming microcolonies. PECs may inhibit this proliferation by restricting nutrient access or directly affecting bacterial metabolic pathways [147]; (iii) Maturation: As the biofilm develops, it forms a complex structure with channels for nutrient flow and waste removal. The penetration of PEs and PECs into mature biofilms can facilitate the penetration of antibiotics, enhancing bacterial susceptibility. Research indicates that PECs composed of alginate and chitosan can effectively penetrate biofilms formed by Staphylococcus aureus, improving the efficacy of antibiotics [45,130]; (iv) Post-maturation: In this stage, biofilms can disperse, allowing bacterial cells to colonize new surfaces. PEs and PECs may influence this dispersal process, depending on their formulation and interaction with specific bacterial species [140].

The capacity for biofilm formation varies significantly among microbial species and isolates. For example, *P. aeruginosa* is well known for its robust biofilm-forming ability, especially in chronic infections, while *E. coli* exhibit variable biofilm-forming capabilities depending on the strain and environmental conditions [148]. Research shows that PEs and PECs can demonstrate varying levels of effectiveness against different species and isolates. For instance, a specific PEC formulation was effective against biofilms formed by *Acinetobacter baumannii*, while another formulation was more effective against *Enterococcus faecium*. This diversity underscores the importance of tailoring PEs and PECs formulations based on the target pathogen and its specific biofilm characteristics [11].

In addition, biofilm formation is characteristic of chronic wounds, which slows down the healing process. Ischemia, and the presence of foreign bodies in wounds, leads to bacterial aggregation in communities and the formation of biofilms. Aggregated bacteria produce an extracellular polymeric substance (EPS) that consists of polysaccharides, proteins, glycolipids, and bacterial DNA. This matrix significantly reduces antibacterial penetration, and thus, efficacy. In addition, biofilm bacteria induce a constant inflammatory state and rhamnolipid state that leads to fast necrosis of neutrophils. Biofilms are more tolerant to host defense, and to systemic as well as topical antibacterial therapy. They also extend the inflammatory phase of wound healing, provoking a damaging immune response once bacteria are protected by biofilm from the immune systems. Moreover, tissue debris generated by this detriment immune response and necrosis serve as nutrients for biofilm bacteria, leading to a vicious cycle, resulting in more damage [3,125,132]. Additionally, bacteria in biofilm modify the physiological environment, turning it more suitable for its growth and proliferation. For instance, dental biofilm-forming bacteria turn the

environment more acidic and anaerobic, thereby promoting the growth and proliferation of additional bacterial species [148].

In addition to the traditional resistance mechanisms to antibiotics, such as beta lactamase production and efflux pumps expression, there are several more mechanisms for biofilm bacteria. Biofilm is considered a physical barrier that hinders the penetration of antibiotics. In addition, the acidic and anoxic conditions within biofilms contribute to the degradation of antibiotics. Polymers in the extracellular matrix can trap and inactivate antibiotics. Most important is the gradient's exposure to antibiotics, as not all biofilm bacteria are exposed to same concentration. Bacteria residing in the most internal parts are exposed to sublethal concentrations that induce bacterial tolerance. All these factors combined resulted in an increase in the MIC of antibiotics to more than 1000-fold in the case of *P. aeruginosa*, which is one of the most important bacteria in biofilm formation. Worryingly, the same effect was observed in methicillin-sensitive *S. aureus* [8].

Thanks to its positive charges, CS disrupts negatively charged EPS components through ionic interactions with DNA, proteins, and the cellular membrane, increasing the permeability of the biofilm and altering gene expression [147]. Furthermore, CS chelates some primordial metals for transcription and translation, such as Mg^{2+}, Ca^{2+}, and Zn^{+}. PECs' NPs have higher penetration through the biofilm structure and higher contact surface, and therefore, improved antibacterial activity. As such, antibiotic encapsulation in CS-based PECs can be a resource for limiting resistances. Thanks to higher diffusion, small Mw CS has higher antibiofilm characteristics compared to medium then to high Mw[11].

Interestingly, bacteria in the inner parts of the biofilm enter a dormant state due to a lack of nutrients and harsh conditions. In this state, bacteria are significantly more resistant to antibiotics due to their low to nonexistent metabolic activity [8].

QS is a communication language among biofilm bacteria. It is a regulatory mechanism of gene expression in response to alterations in cell populations. This results from the secretion of signaling proteins, such as autoinducing peptides that induce the expression of virulence factor genes. In addition, high cell density accelerates horizontal transfer of resistance genes [8]. Quercetin/CS nanoplates resulted in more suppression of QS of *P. aeruginosa* biofilm compared to quercetin alone. In addition to increasing the penetration and availability of quercetin, CS itself has antibiofilm properties [7]. CS can interrupt QS by interfering with gene expression of biofilm bacteria. This can lead to a reduced production of EPS polymers in a dose-dependent manner, and virulence factors, which make bacteria more susceptible to antibiotics. This highlights the importance of the delivery of CS-based PECs [147]. PEs and PECs offer promising avenues for combating AMR, particularly in the fight against ESKAPE pathogens (*E. faecium*, *S. aureus*, *K. pneumoniae*, *A. baumannii*, *P. aeruginosa*, and *Enterobacter* spp.). Their multifaceted mechanisms of action can disrupt biofilm formation at multiple stages, enhancing the effectiveness of traditional antibiotics. Future research should focus on optimizing the formulations of PEs and PECs to target specific AMR strains and explore their potential in clinical applications.

5. Conclusions and Outlook

Chitosan (CS) has emerged as the most widely used polycation in PECs due to its significant antibacterial activity. This activity, however, is influenced by environmental factors, namely pH, which can limit its efficacy. To overcome this, quaternary salts of CS were developed, offering improved stability and antibacterial effectiveness across a broader pH range, and providing more versatility. PECs provide a new hope for antibiotics' stewardship; especially that those based on CS have, themselves, antibacterial properties or serve as drug delivery systems. PECs provide improved controllable gelling and adhesiveness properties, which turn them a point of attraction for the controlled delivery of antibiotics, especially local delivery in chronic wounds and coatings of medical devices. This indicates potentially curbing the rise in antibiotic resistance, which is particularly important in the context of growing concerns about the efficacy of conventional antibiotics. Persistent cells and viable but non-culturable (VBNC) cells present additional challenges in this context. Their

presence in biofilms, where they evade conventional antimicrobial treatments, complicates infection management. Therefore, the integration of PECs, especially those derived from CS, could provide a dual benefit by targeting both vegetative and persistent or VBNC forms of bacteria. Although most PEs are known to be biocompatible, very few articles studied the efficacy and safety of PECs in vivo, as most studies reported only in vitro results. No clinical trials were found either. This indicates the need for more in vivo testing since the reported in vitro studies are encouraging. Furthermore, most studies were concentrated on *S. aureus* and *E. coli* as models for Gram-positive and negative bacteria. This indicates a need for broader testing against other bacterial species, particularly those implicated in nosocomial infections such as *Klebsiella* and Enterobacter species, especially that the risk of resistance is higher in a hospital environment. Moreover, *P. acnes*, a commensal microorganism residing in sebaceous follicles, is increasingly recognized as a contributor to prosthetic surgery-related infections, was underestimated in the literature. In conclusion, while PECs present a promising strategy for antibacterial therapy, particularly in the management of chronic wound infections, further research is required. This includes expanding the scope of studies to encompass a broader range of bacterial species, conducting more in vivo research, and initiating clinical trials. Such efforts are essential to fully understand the potential of PECs in medical applications and improving patient outcomes.

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