Antimicrobial Polymers

L. A. Camacho-Cruz, M. A. Velazco-Medel, A. Cruz-Gómez, and E. Bucio

Abstract The development of new antimicrobial substances has been a topic of prime importance in recent years because of the growing appearance of antimicrobial resistant pathogens, which have become one of the most worrying threats for public health in recent years. Polymeric antimicrobials are a good alternative for the development of new medicines since they have non-specific antimicrobial mechanisms and unique characteristics as materials which allow for the production of robust substrates for therapeutic uses. In recent years, many examples of antimicrobial polymeric materials have been produced with a great variety of morphologies, functionalities, and specific applications. Since this topic continues to be relevant, this chapter deals with the most fundamental aspects of antimicrobial polymeric materials as well as describing recent advances in the field to provide the reader with a reference on the most general aspects of this area.

Keywords Bacteria growth inhibition · Polymers · Antimicrobial polymers · Drug delivery systems · Cationic polymers · Peptide mimics · Zwitterionic polymers

1 Introduction

Antimicrobial substances have been one of the most influential advances in human development because of the substantial improvement in the quality of life that was derived from their uses. Currently, humans take for granted having a life which is devoid of any serious illness derived from pathogens such as bacteria, viruses, and fungi; however, life before the twentieth century was often plagued with mortality rates (due to infections) that would be unthinkable in the modern world. Due to this usefulness, antibiotics, antifungal substances, antivirals, and antiseptics have been

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widely overused by medical practitioners and by the public in general. This, combined with the persistence of these substances on medical waste, has caused the development of an increasing amount of antimicrobial resistant pathogens. These types of organisms would be uncurable with current medicines, fact that will inevitably cause a serious health problem if the current trends continue (World Health Organization n.d.). Therefore, the development of new antimicrobial substances is of prime importance, especially if these new substances contribute poorly to the increase of antimicrobial resistance. In this sense, antimicrobial polymeric materials are good alternatives to conventional molecular antimicrobial substances because of their unique characteristics.

Antimicrobial polymers may be advantageous in many ways compared to discrete molecular antibiotics. For instance, antimicrobial polymers have non-specific mechanisms to stop pathogen growth; for example, the lysis of bacteria by the disruption of cell membranes due to opposing charges (Muñoz-Bonilla and Fernández-García 2012). This is in stark contrast to molecular antibiotics which normally have very specific mechanisms of action; for example, the prevention of DNA synthesis by binding to determinate receptor sites (Neu 1989). Since the mechanisms of action of antimicrobial polymers are much more general, the development of antibiotic resistance against these polymers is harder. Although this may be regarded as one of the most relevant characteristics of antimicrobial polymers, some other advantages include the ability to form solid substrates for application on medical devices and implants and the combination with other polymeric materials to add properties such as pH or thermal responses. Additional to intrinsically antimicrobial materials, polymers which are not naturally antimicrobial (i.e. most polymers) may also be used for the controlled and localized release of discrete antimicrobial substances, which may also be beneficial in many scenarios. This not only allows for better treatment of certain diseases, but also allows for the fabrication of existing polymeric implants and medical devices which are also antibacterial (Pino-Ramos et al. 2016).

Because of the relevant characteristics of these systems and the growing interest to produce new antimicrobial substances, it is relevant to compile the most common characteristics of antimicrobial polymers and the advances this field has achieved. Therefore, this chapter will deal with the general characteristics of three major groups of antimicrobial polymers; polymeric materials with intrinsic bactericidal properties, antifouling or pathogen repellant polymers, and polymeric substrates enhanced with discrete antimicrobials. Since most of the advancements in this field have been achieved to produce antibacterial substrates, most of this chapter will deal with these materials; however, antifungal, antialgal, and antiviral materials will be also briefly considered.

2 Fundamentals

To better understand the relevance of antimicrobial substances, it is important to firstly correctly identify some terms which are often used interchangeably even when there are crucial differences between them: Antimicrobial, antibacterial, biocidal, bactericidal, and antifouling substances.

Firstly, an antimicrobial substance is a chemical compound that may inhibit the development of pathogens such as bacteria, fungi, yeasts, algae, etc. For an antimicrobial substance to be useful it also must be relatively biocompatible, namely by not being harmful to mammal cells. An antibacterial substance is, in contrast, only stops bacteria from developing. These lasts substances are sometimes also wrongly called bactericidal substances (which means that they kill bacteria). In addition, antimicrobial substances may also inhibit the development of bacteria by not allowing the formation of antibacterial colonies on their surfaces (antifouling behavior). Finally, biocidal substances not only kill pathogens, but also kill mammal cells; these substances are still useful for general disinfection; however they do not present the same biocompatibilities as true antimicrobial substances (Ergene et al. 2018). As a reference for the reader, Fig. 1 illustrates the differences between these kinds of behaviors.

The verification of antimicrobial properties is normally conducted by in vitro or in vivo assays that test the effectiveness of the material in either inhibiting the growth of a certain pathogen, or the effectiveness of the material in killing a certain pathogen. The most common quantification parameter for antimicrobial growth inhibition is the minimum inhibitory concentration (MIC) which is the concentration of an antimicrobial needed to inhibit visible growth of a pathogen. Another quantification parameter is the minimum bactericidal concentration (MBC) which is defined as the concentration needed to kill at least 99.9% of the pathogen in a culture medium (Andrews 2001).[1] Additional to these parameters, another way to quantify the antimicrobial effect is to measure the circular zone of inhibition when the material is placed on a petri dish culture containing ~10^6 CFU/mL of a given pathogen (Fig. 2), additionally, Petri dish cultures may be used to visually count the CFU that are formed in presence of the microorganism. This test is also known as the Kirby–Bauer method (Drew et al. 1972).

As mentioned above, another important characteristic of antibacterial substrates is that they are not toxic to mammal cells (or human cells if their applications are limited to human use); therefore, additional parameters exist to quantify the toxicity of these materials. HC_{50} is the most common parameter to compare the toxicities of different polymeric substrates, this parameter is defined as the concentration in

[1] Although these parameters were originally defined for bacterial assays, they have been used to describe the effects on growth and death of other pathogens.

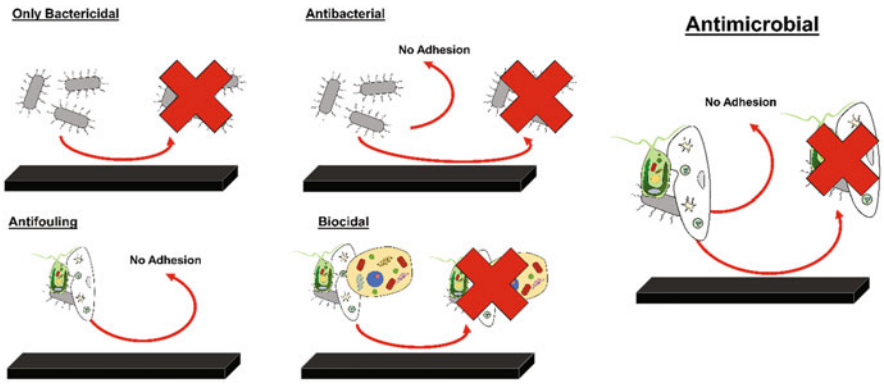


Fig. 1 Definition of various terms used to describe antimicrobial substances

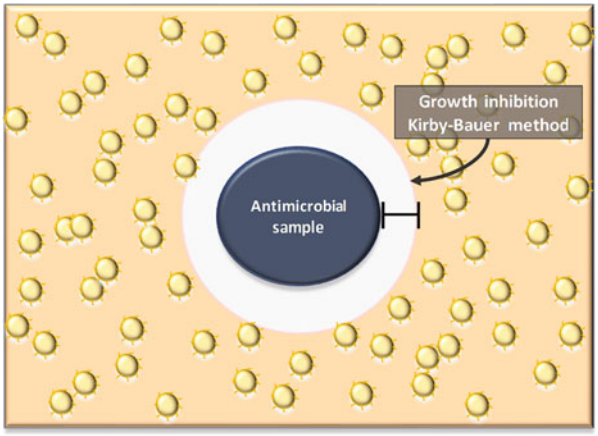


Fig. 2 Zone of inhibition test for antimicrobial performance

which a tested substance produces a release lysis on 50% of the red blood cells in buffer media given a certain incubation period (Punia et al. 2015).

3 Polymeric Materials with Intrinsic Antimicrobial Properties

Polymers and polymeric derivatives with intrinsic antimicrobial properties are of great interest for the development of novel antibiotics both to fight the growing trend of antimicrobial resistant organisms, and to find materials useful for the treatment of pathogenic infections with more specific characteristics. Derived from the fact that polymeric chains do not enter as easily within cells (in contrast to smaller molecules), many of the current antimicrobial polymers target the cell membranes (or cell

walls) of pathogens. In this sense, most polymeric antimicrobials destabilize the cell membranes by electrostatic interactions; specifically, since many bacteria and other pathogens have an overall negative charge in their cell membranes, many polymeric antimicrobials tend to be positively charged (Xue et al. 2015; Ergene et al. 2018). Even when this is the most common mechanism of antimicrobial behavior for polymers, many other polymers act through other mechanisms; therefore, there exist other antimicrobial polymeric systems without a net charge which even mimic other natural antimicrobial peptides (Brogden 2005). Due to this variety, in this section, an overview of the most common types of antimicrobial polymers with intrinsically activity will be presented and some representative and recent examples of each group will be discussed.

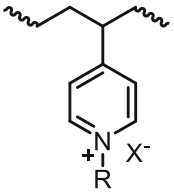
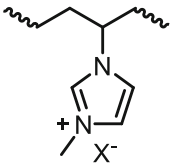
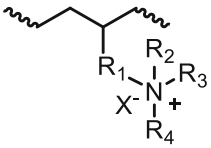
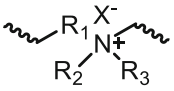
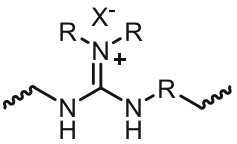
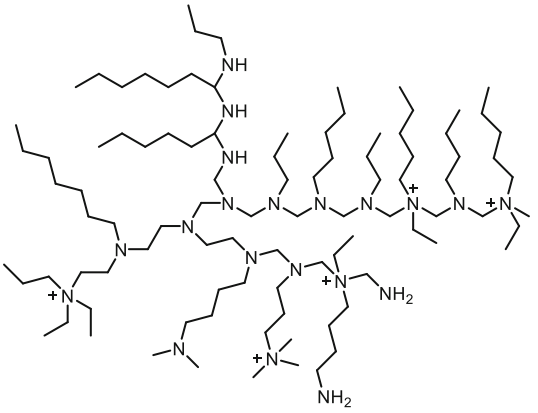
3.1 Polymers with Ammonium Groups

Arguably, polymers that contain quaternary ammonium ions are the most often researched variety of antimicrobial materials. This family of polymers is so interesting for the research community because it is relatively easy to produce poly(quaternary ammonium) salts through alkylation of polymers containing amine groups or by the polymerization of ammonium-containing monomers (Arora and Mishra 2018). Additional to this, there exist many biocompatible heterocycles containing amine groups that may be used as a basis for these kinds of polymers (Anderson and Long 2010; Almeida et al. 2012). Finally, this functional group is also important because monomers containing amines and ammonium salts may be synthesized from other monomeric bases such as acrylate and methacrylate monomers and these monomers may be further copolymerized to form materials with great assortment of characteristics (Muñoz-Bonilla and Fernández-García 2012; Xue et al. 2014). As a result of this range of features, antimicrobial polymers containing ammonium groups may be further subdivided into many categories which are shown in Table 1. This classification is by no means exhaustive, but it allows for an easier identification of antimicrobial polymers despite their different structures.

Although these kinds of polymers have clear differences, most studies have focused in finding the relationship between specific structural characteristics and the antimicrobial behavior of the polymers. Firstly, something that is definitive is that ammonium-containing polymers have an antibacterial behavior because of their positive charges; however, the potential of these polymers to be antibacterial depends on the density of this positive charge. In general, a greater density of positive charge promotes greater bacterial inhibition because of a greater potential to disrupt cell membranes. As a result, dendrimers and hyperbranched polymers containing many ammonium groups tend to have lower MIC for bacteria (Ergene et al. 2018).

Another important parameter is the length of an alkyl chain that is supported by an ammonium nitrogen because this is directly related to the hydrophobic/hydrophilic balance of the polymeric material. It has been shown that the optimal chain

Table 1 Classification of antimicrobial polymers containing quaternary ammonium ions

Polymer family	Base structure (R = alkyl/aryl, X^- = counterion)
Polymers containing pyridinium rings	
Polymers containing imidazolium rings	
Polymers with pendant ammonium groups	
Polymers with amines on the main chain (ammonium ionenes)	
Polymers derived from guanidine	
Hyperbranched and dendritic ammonium polymers	

size to fulfill this objective and decrease MIC for these substances are alkyl chains between 6 and 8 carbons which vary depending on the structure of the polymer. On the one hand, shorter chains (between 1 and 5 carbons) may not function optimally because proteins tend to adhere to hydrophilic substrates, covering the substrate and neutralizing its positive charge. On the other hand, longer chains (more than 8 carbons) may promote bacterial adhesion, they may be difficult to solubilize, and may be toxic to the host cells (Muñoz-Bonilla and Fernández-García 2012; Xue et al. 2014; Ergene et al. 2018).

A third parameter that affects the antimicrobial effect of many polymeric systems is the average molecular weight of the system. This parameter is important because it influences the capacity of the polymer to interact with the cell membranes of pathogens and also influences the net charge density (Kenawy et al. 2007).

Finally, the identity of the counterion may also be influential in the antibacterial activity. A very important factor for the effect of this counterion is it size which influences the hydrophobic/hydrophilic balance of a substrate; however, many other factors are involved when determining if a counterion will change the antimicrobial activity. Firstly, the dissociation of the polymeric salt is very important for the antimicrobial effect. Therefore, these polyelectrolytes should be preferably strong electrolytes, a factor which may be determined by the identity of the counterion. Additionally, some polymers may not only disrupt the cell walls, but also replace Ca^{2+} or Mg^{2+}, effectively disrupting the electrolytic balance within the cells. This is also dependent on the counterion's mobility within the cell environment. Since these factors may all influence the counterion's role on the antimicrobial activity, it is not as easy to find general trends, so the effect of a counterion is better evaluated for each antimicrobial substrate (Xue et al. 2014; Ergene et al. 2018). As a final note, Fig. 3 summarizes the characteristics that may define the antimicrobial characteristics of ammonium-containing polymers mentioned within this section.

As an additional consideration, although the mechanisms of microbial inhibition for these polymers are similar, the effectiveness of the growth inhibition depends on the type of pathogen involved. Since most of the pathogens which have negatively charged membranes are bacteria, ammonium-containing polymers are much more used as antibacterials rather than antimicrobials. The antibacterial behavior further depends on the type of bacteria involved. For instance, the outer layers of the cell walls of Gram-negative bacteria possess a membrane of lipopolysaccharide, which prevents the charged polymeric chains to interact with the negatively charged peptidoglycan cell wall; in contrast, Gram-positive bacteria have their loose peptidoglycan membranes exposed (Beeby et al. 2013). A diagram depicting the differences in membranes of these types of bacteria is presented in Fig. 4. Due to these differences, Gram-positive bacteria often need lower antibacterial concentrations to be inhibited.

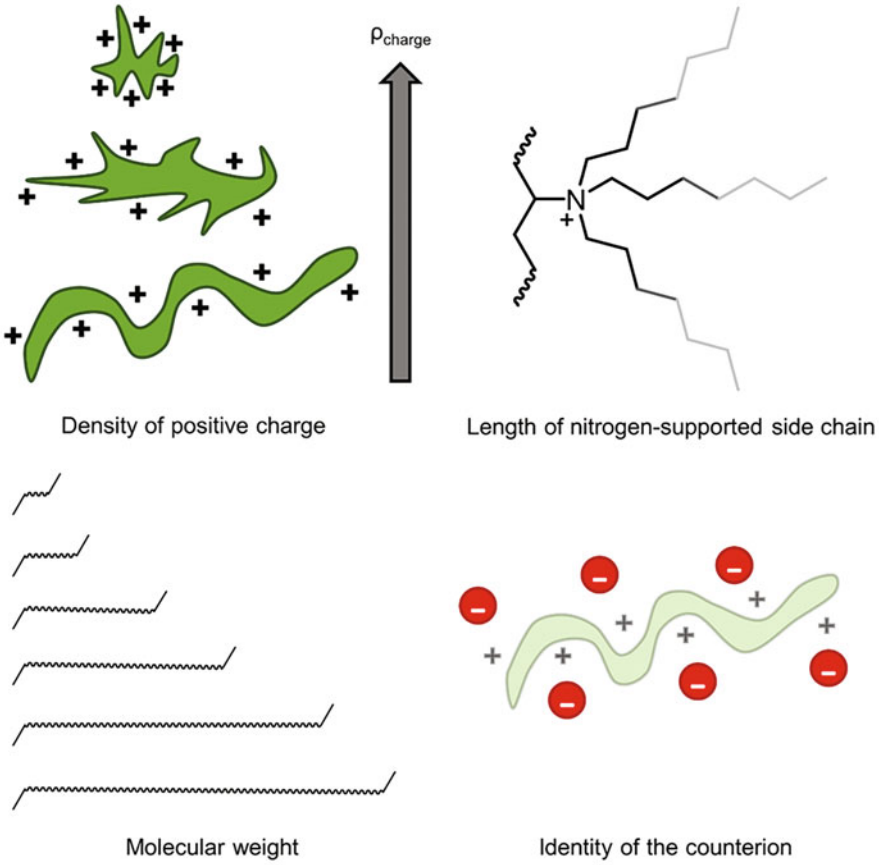


Fig. 3 Factors determining the antimicrobial characteristics of amine salts

3.1.1 Polymers Containing Pyridinium or Imidazolium Rings

Pyridine and imidazole rings are very resourceful bases for antimicrobial polymers since both heterocycles are biocompatible because they are present in compounds such as DNA bases and other biologically relevant substances such as histamine (Muñoz-Bonilla and Fernández-García 2012). The formation of polymers containing such heterocycles is achieved by the previous synthesis of vinyl containing heterocyclic monomers such as *N*-vinylimidazole, or 4-vinylpyridine (4VP). The corresponding vinylic monomer is then polymerized by a radical polymerization by any conventional method of initiation to form the antimicrobial polymers. This methodology, although simple, if combined with finer methods of polymer synthesis such as controlled living polymerizations, allows for the development of polymers and copolymers with very specific microstructures. Since these materials have been researched extensively, many reviews already cover many of the developments on

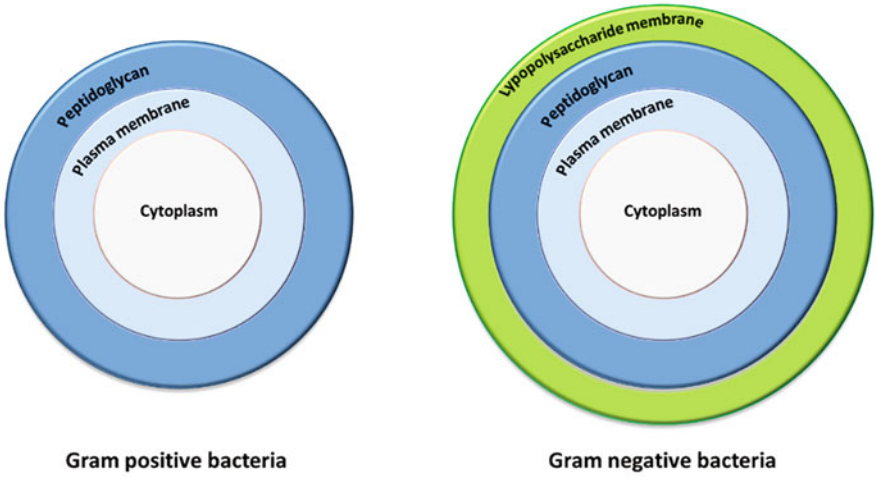


Fig. 4 Difference between Gram-positive and Gram-negative bacteria. Gram-negative bacteria possess an external extra lipopolysaccharide membrane

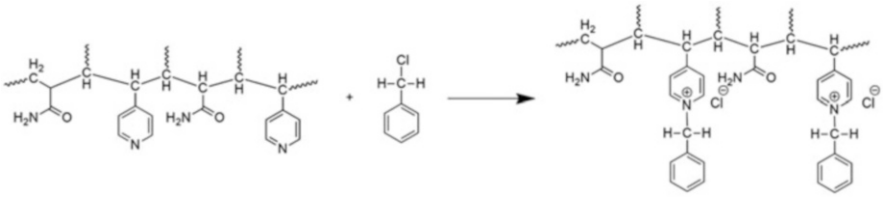


Fig. 5 Production of pyridinium-containing polymers quaternized with chloromethyl benzene

this area; therefore, in this chapter, only recent and relevant advances will be exemplified (Anderson and Long 2010; Jain et al. 2014; Xue et al. 2014; Arora and Mishra 2018; Ergene et al. 2018).

Pyridine may be readily quaternized because of the nucleophilicity of its nitrogen, even when the ring is already within a polymer; therefore, the most common route for obtaining pyridinium polymers is to first obtain a polymer with pyridine group and then performing the quaternization. One recent example of this is the formation of a copolymer of acrylamide (AAm) and 4VP initiated with γ-radiation for the development of cross-linked hydrogels which were later quaternized with chloromethyl benzene (Fig. 5). The MBC and pathogen killing kinetics of these substrates were tested against *S. aureus*, *E. coli*, *P. aeruginosa*, and *C. albicans*. It was found that this substrate was effective in inhibiting against the bacteria, but not the fungi, suggesting that the killing mechanism of the polymer is indeed the disruption of the charged membranes. Although no hemolysis data is reported, the material has potential to function as wound dressings (Arslan et al. 2017).

Ammonium-containing polymers have gained such importance that they have been combined with other substrates to include functionalities beyond pure

antibacterial activities. For example, by using ATRP poly(4-vinylpiridine) (P4VP) has been grafted onto graphene oxide (GO) for intrinsic antibacterial applications and drug delivery for therapeutic effects against cancer. In this work, Kavitha et al. (2015) measured the antibacterial effect in vitro of GO-*g*-P4VP, showing slight bacterial inhibition at concentrations at low as 100 μg/mL and a considerable growth inhibition effect (>80%) at 1000 μg/mL. Additional to the antibacterial properties, these materials were also verified to have low cytotoxicity (for NIH3T3 cells, MTT assay); for instance, the materials maintained high cell viability (~90%) at concentrations of 10 mg/mL after 5 day incubation, behavior which is similar to the one reported for GO. Finally, the load and release of camptothecin onto the materials allow for a considerable reduction on the cell viability of cancerous cells at concentrations as low as 10 nM (Kavitha et al. 2015).

As a final example, pyridinium polymers [poly(pyridinium-1,4-diyliminocarbonyl-1,4-phenylene-methylene chloride)] have also been combined with poly(3,4-ethylenedioxythiophene) (PEDOT) which allowed for the production of biocompatible and antibacterial n-doped conducting films for their use as electrochemical electrodes and sensors (Sánchez-Jiménez et al. 2019).

The imidazole group has also been thoroughly used as an antibacterial substrate because even when it is not quaternized, it shows antibacterial and antifungal properties (Anderson and Long 2010; López-Saucedo et al. 2017). Nevertheless, quaternized polymers tend to be more effective than their non-quaternized counterparts. Polymeric imidazolium compounds are also interesting because they commonly are ionic liquids; therefore, solubility issues are not as common. Recent advancements on the antibacterial activities of antibacterial imidazolium compounds include the synthesis of *N*-alkylated derivatives of many different *N*-vinylimidazole polymers, the grafting of quaternized *N*-vinylimidazole onto existing polymeric substrates, and the formation of different polymeric microstructures and morphologies of quaternized polyimidazoles. In 2016, for example, Zheng et al. synthesized a series of quaternized monomers of *N*-vinylimidazole (Fig. 6a), and their subsequent polymerization using AIBN, obtaining MICs as low as 0.009 μmol/mL for *S. aureus* and 0.018 μmol/mL for *E. coli.* In this work, the quaternized monomers were also copolymerized with styrene and acrylonitrile in presence of divinylbenzene as a crosslinking agent and benzoin ethyl ether as photoinitiator (Fig. 6b), these membranes not only were better substrates for solid polymeric membrane formation, but also retained good antibacterial activities (Zheng et al. 2016).

Another recent example of imidazolium-containing polymers was the formation of nanoparticles from *N*-alkylated poly(*N*-vinylimidazole) with bromine as a counterion. In this work, spherical nanoparticles of sizes below 100 nm were synthesized through radical polymerization initiated with AIBN. MICs were measured to be around 0.003 μmol/mL against *S. aureus* and 0.002 μmol/mL against *E. coli*, while also having relatively low cytotoxicity when cell viability was evaluated for mouse fibroblasts 3T3(A) and L929(B) (Fang et al. 2019).

Imidazolium polymers have also been grafted onto other polymeric substrates to produce antibacterial alternatives of these materials. For example, in 2016,

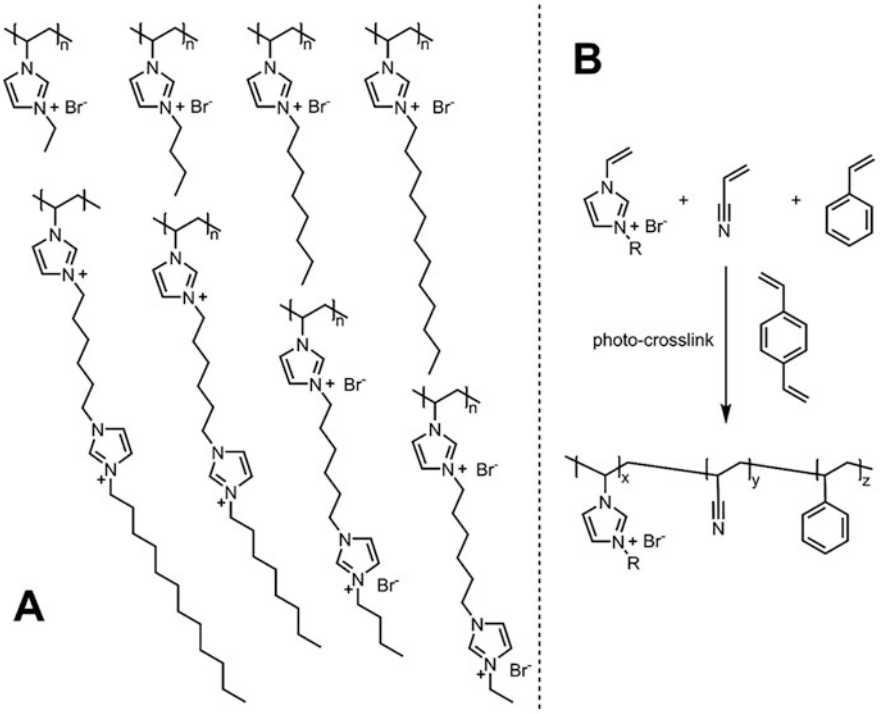


Fig. 6 Synthesis of derivatives of poly(*N*-vinylimidazole) for antibacterial purposes

N-vinylimidazole was grafted onto polyvinylchloride (PVC) using radiation as a clean initiator method. After the grafting procedure, the imidazole was quaternized with CH_3I through a nucleophilic substitution reaction. The synthesized materials were proven to be slightly antibacterial against *S. aureus* (Meléndez-Ortiz et al. 2016).

3.1.2 Polymers with Pendant Ammonium Chains

Polymers with ammonium chains are also a very common group of antimicrobial materials because they may be synthesized through many methods (Froidevaux et al. 2016). However, the most common examples of these polymers use amine containing vinyl monomers which are later polymerized through conventional methods. A recent example of this type of polymers was the UV-initiated synthesis of copolymers of 2-hydroxyethyl methacrylate and acryloyloxyalkyltriethylammonium bromides derivatives for the formation of antibacterial films, these polymeric materials were effective antibacterials against *E. coli* and *S. aureus* (Galiano et al. 2019). Another interesting example of polymeric materials containing pendant ammonium groups is the synthesis of amino acid-based polymers through RAFT polymerization (Fig. 7). These polymers were also verified

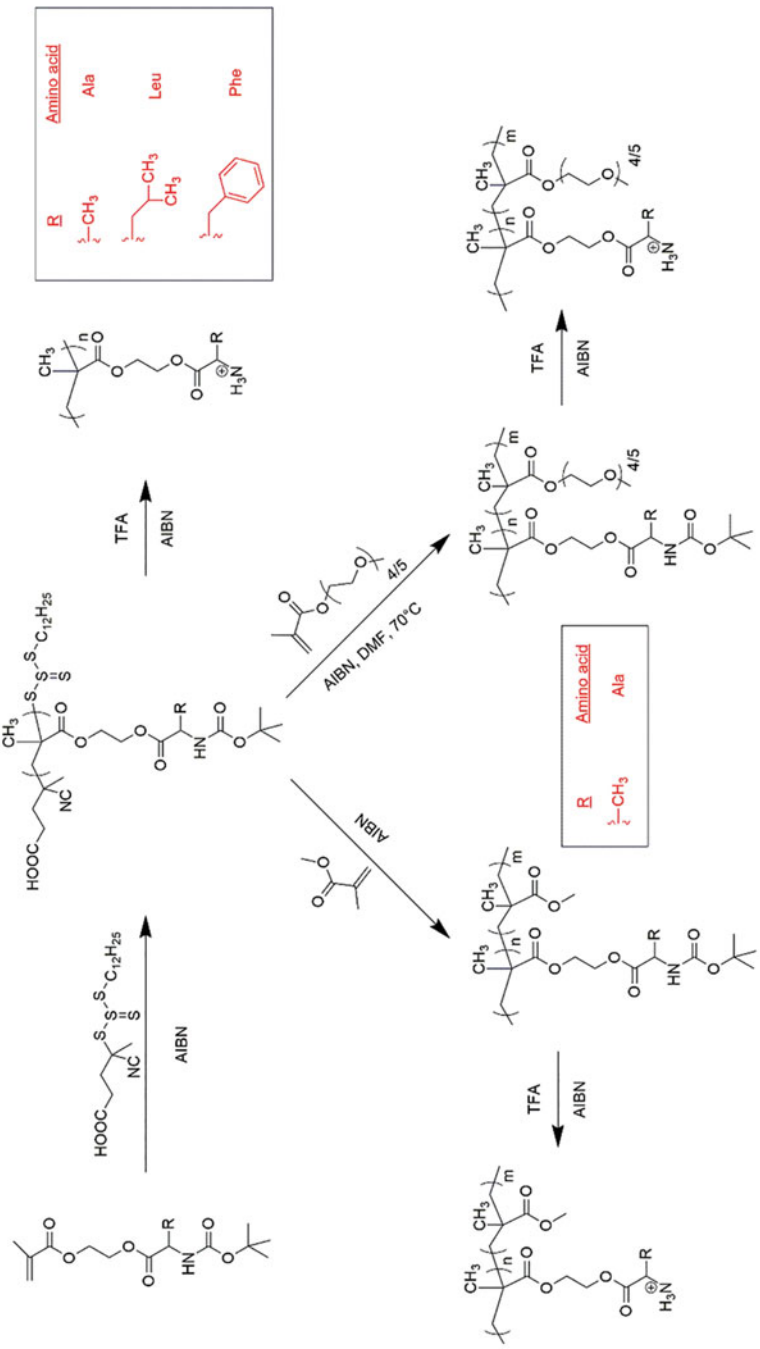


Fig. 7 Amino acid-containing polymers as an example of pendant ammonium groups

to be antibacterial against *E. coli* by measuring the zone of inhibition on Lysogeny broth (LB) agar after incubation for 12 h, and by quantifying the absorbance of LB culture medium containing *E. coli* and a polymeric sample against culture time (Mukherjee et al. 2017).

3.1.3 Polymers with Amines on the Main Chain

Another important variety of polymers which have been used as antimicrobial agents are polymers with ammonium groups on the main polymeric chain. These types of compounds are also called ammonium ionenes and are usually synthesized through polycondensation reactions, either by reaction of dicarbonyl groups and amines, or by the reaction of carbon dichlorides and amines (Fig. 8).

Some recent developments involve the formation of novel microstructures and composites of ionene materials with other solid substances. For example, Ding et al. (2015) synthesized a polyurethane (PU) derivative through the condensation of polyethylene glycol (PEG), butylene glycol, and an ammonium-containing diol with methylene diphenyl diisocyanate (MDI) as seen in Fig. 9. Afterward, $ZnCl_2$

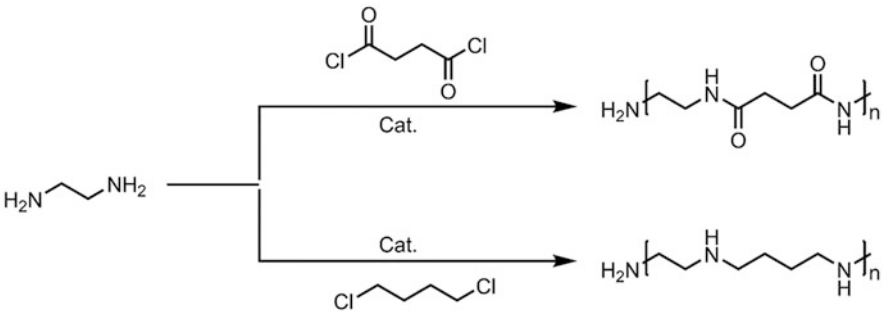


Fig. 8 Synthesis of polymers containing amine or amide groups on the main chain

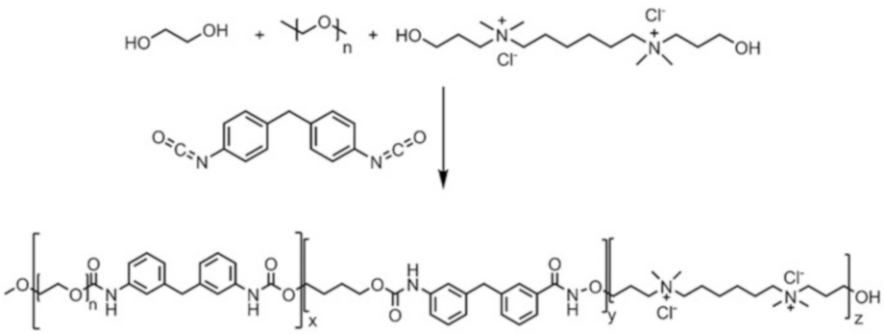


Fig. 9 Synthesis of PU ionenes

was added to the PU system to enhance the antimicrobial properties of the system against *E. coli*. Through this work it was found that the antibacterial effect of the ammonium ionene and $ZnCl_2$ caused a synergistic effect that provided the films with bacterial growth inhibition at least in vitro (zone of inhibition test) (Ding et al. 2015).

In another work, the effect of the topology of the ammonium ionenes in the antibacterial and hemolysis properties of the materials was investigated. For this, Mayr et al. (2017) synthesized a series of polyamide derivatives through a two steps procedure. First, they reacted one equivalent of either *o*-, *m*-, or *p*-phenylenediamine with 4-(Chloromethyl)benzoyl chloride to form dichloride derivatives which were later polycondensed with quaternized diamines. When evaluating MICs against *E. coli*, it was found that the *m*-derivative of the polyamides was not significatively antibacterial, while the other derivatives were (MICs ~2 μmol/mL). This indicated that the topology does affect in the interactions between the polymers and the bacteria. Additionally, these materials showed overall low cytotoxicity (hemolysis below 15%) at concentrations 2 μmol/mL of with no relevant trends found between topology and hemolysis caused by the ionenes (Mayr et al. 2017).

As a final example of ammonium-containing ionenes, in 2018 polymeric materials derived from lithocholic acid and tertiary amine linkers were synthesized by polycondensation reactions. In this work the MICs of the materials against *S. aureus* and *E. coli* was measured, showing that these materials are indeed effective in inhibiting the growth of this pathogens (Ganewatta et al. 2018).

3.1.4 Polymers Derived from Guanidine

Guanidine polymers are one of the most important groups among ammonium polymers because these substrates have been proven successful and have been readily used as antiseptics because of their antibacterial, antiviral, antifungal, and antiamoebic activities. The most common guanidine polymeric derivative is poly (hexamethylene biguanide) (PHMB) (Fig. 10) which has been already used commercially as antiseptic in wound dressings, topical agents for wound treatment, gloves, cleaning solutions for contact lenses, and general antiseptic solutions for both human and veterinary use (Lee et al. 2004; Lim et al. 2008; Kariduraganavar et al. 2014; Ali and Wilson 2017; Niu et al. 2017). This polymeric system has been demonstrated to be effective against many pathogens; however, it is important to mention that it may be slightly toxic to human cells at higher concentrations than it is normally used for therapeutic effects; therefore, its use must be taken with care (Asiedu-Gyekye et al. 2015).

Recently, even when most of the developments have focused on improving pharmaceutical formulations of PHMB, some other polymeric analogs have been

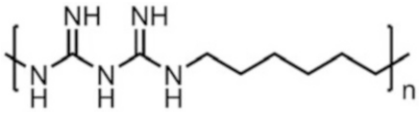


Fig. 10 Structure of poly (hexamethylene biguanide)

produced. For instance, in 2017, Grace and collaborators synthesized different varieties of acrylic polymers containing a guanidine pendant group through Cu (0) mediated polymerization of amide containing acrylate monomers with different chain lengths on the pendant groups followed with a guanylation with 1H-pyrazole-1-carboxamidine hydrochloride. The antibacterial effects of this polymer were tested against *P. aeruginosa*, *K. pneumonia*, *St. pneumoniae*, *S. aureus*, and *E. coli*, with low MICs (<8 g/mL) against *S. pneumoniae*, *S. aureus*, and *E. coli.* Additionally, hemolysis testing was performed within the concentrations around the MIC, showing low cytotoxicity for materials with longer alkyl chains, suggesting that the hydrophilic/hydrophobic balance importantly influences the hemolysis of the materials (Grace et al. 2017).

3.1.5 Hyperbranched and Dendritic Ammonium Polymers

The final classification of antimicrobial polymers is hyperbranched and dendritic ammonium polymers. This type of polymers has also shown to be very effective antibacterial substances because of their big positive charge densities. Even when they show very promising antibacterial application, the use of these polymers is often limited by their biocompatibilities, because they tend to interact more strongly with mammal cells. However, recent advances have achieved better biocompatibility.

One recent example of antimicrobial activity of dendritic polymers was the synthesis of silane dendrimers containing pendant amine groups which have been shown to be effective against ram-positive *S. aureus* and Gram-negative *E. coli*. In this study the MBCs and MICs for different dendritic systems and values as low as 1 ppm were found to be effective against both bacteria. Additionally, toxicity assays suggest that some of the dendritic materials represent useful systems with hemolysis below 20% at therapeutic concentrations (Fuentes-Paniagua et al. 2016). Another example in this area includes the formation of polyamide dendrimers with quaternized amine groups with antibacterial activity and low toxicity (Zainul Abid et al. 2016).

3.2 Polymers with Phosphonium Groups

Analogous to ammonium-containing polymers, phosphonium derived polymers are an important variety of antimicrobials which mainly function by destabilizing the cell walls or membranes of pathogens, especially those of bacteria. Therefore, many of the characteristics which are representative of ammonium-containing polymeric materials are also valid for phosphonium containing polymers, namely the effect of the charge density on polymer chains, the length of pendant alkyl chains, the effect of the average molecular weight, and the effect of counterions.

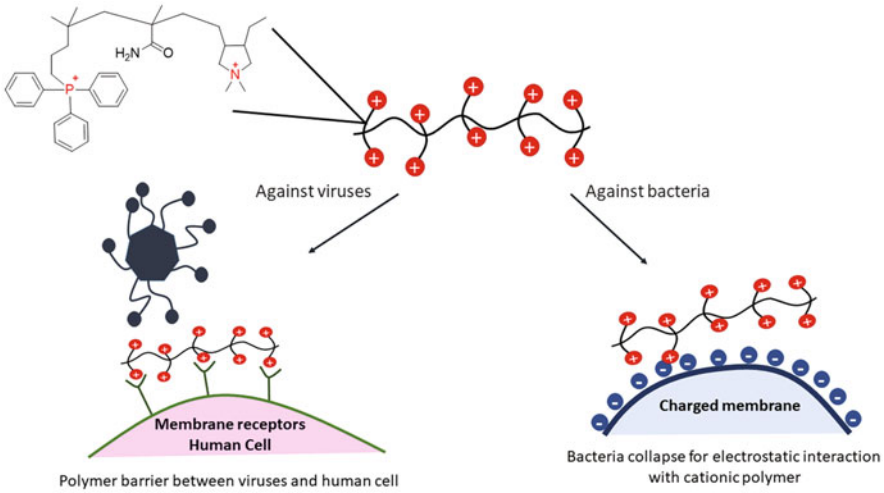


Fig. 11 Mechanisms of action of phosphonium and ammonium-containing polymers against bacteria and viruses (Xue et al. 2014)

Recent examples of phosphonium antimicrobial polymers are much more limited than those containing quaternary ammonium ions; therefore, in this section some representative examples of these systems will be presented briefly. It is important to note that these polymeric materials have historically been also very important, thus many reviews already cover many classical and important examples (Kenawy et al. 2007; Xue et al. 2015; Cuthbert et al. 2018).

As a first example of these types of systems, copolymers of acrylamide and (4-penten-1-yl)triphenylphosphonium bromide (PTPB) were produced by conventional radical polymerization with 2,2′-azobis(2-methylpropionamidine) dihydrochloride (AIBA) as an initiator. As an addition, they formed terpolymers of acrylamide, PTPB, and diallyldimethylammonium chloride (DADMAC) to form a system containing both ammonium and phosphonium groups. After obtaining the polymers the authors evaluated both the antibacterial and antiviral activities of the materials against *E. coli* and adenovirus through viability of infected HEK 293 cells. The antibacterial activity of the materials was directly correlated with the content of phosphonium groups, with the lowest MICs reported for the copolymer only containing phosphonium groups (~20 ppm). According to AFM imaging, the lysis of *E. coli* is achieved at around 30 min. At MIC concentrations, the compounds also showed good antiviral activities that were due to cytotoxicity on host cells for viruses. The authors theorized that the mechanism of action for antibacterial properties is due to bacterial membrane disruption, while antiviral properties are present due to blocking of the passage of viruses onto endocytosis receptors of host cells. An illustration of these mechanisms is present in Fig. 11 (Xue et al. 2014).

In another example, carbohydrate-containing polymers which also contained pendant phosphonium groups were produced. To get these polymers, first,

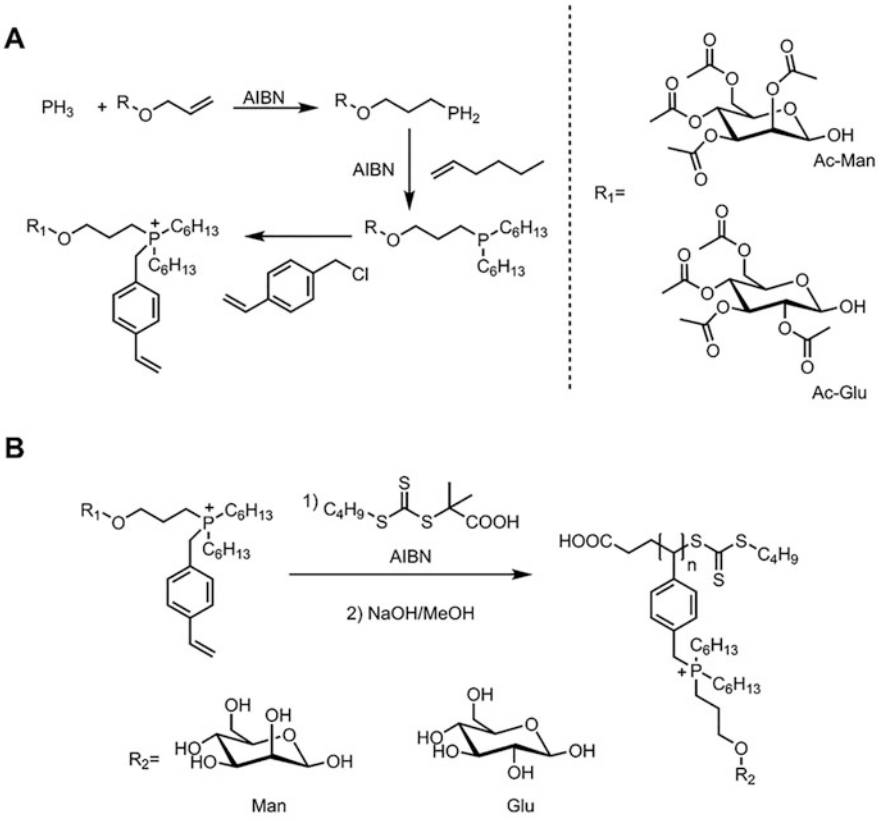


Fig. 12 Synthetic route for carbohydrate-containing phosphonium polymer

monomers containing phosphonium groups and hexoses were synthesized as shown in Fig. 12. This step was followed by the polymerization of said monomers through RAFT (Fig. 12). The inclusion of carbohydrates was intended as a mean for better absorption of the polymeric antibacterials onto bacterial pili with mannose receptors (*E. coli*); additionally, glucose was also used to compare the effect of this moieties. Counterintuitively, the MIC for the material containing mannose was not as low as others in the series, which indicates that charge is the prime factor which renders the materials antibacterials. Additionally, the antibacterial activity and hemolysis were correlated with the hydrophilicity of the substrates since the most hydrophilic polymer presented the lowest values MIC and the highest values for concentration at HC_{50} (Cuthbert et al. 2018).

As a final recent example of this material, temperature resistant polyphosphonium polymers were added to the extrusion process of common ABS as a mean to provide antibacterial properties to the final plastics. These materials were successfully extruded into the polymer without changing the mechanical properties of ABS polymer and without leaking when in solution. The polymers showed good

antibacterial activities against *E. coli* and *S. aureus* with MICs as low as 4 g/mL for *E. coli* and 1 g/mL for *S. aureus* (Zeng et al. 2019).

4 Halogen-Containing Antimicrobial Polymers: N-halamine Polymers

It is well-known that some antibiotics present halogens in their structure, which confer part of the antimicrobial properties. The antimicrobial activity of the halogen-containing polymers is mainly associated with their poor hydrophilicity. In some studies, it has been demonstrated that the halogen group is the leader in the growth inhibition process, and when the halogen is removed, the antimicrobial activity decreases considerably.

In 1996, Worley and Sun developed this functional group to stabilize the antimicrobial properties of free halogens. The chemical structure of *N*-halamines contains at least one nitrogen–halogen covalent bond which provides stability and slow release of free active halogen species into the environment. The general structure of these compounds is represented on structure 1 in Fig. 13. The main biocidal impact of the *N*-halamines is because they can be a protector group for active oxidative halogen species (Cl^+ or Br^+), which can be transferred to the cell

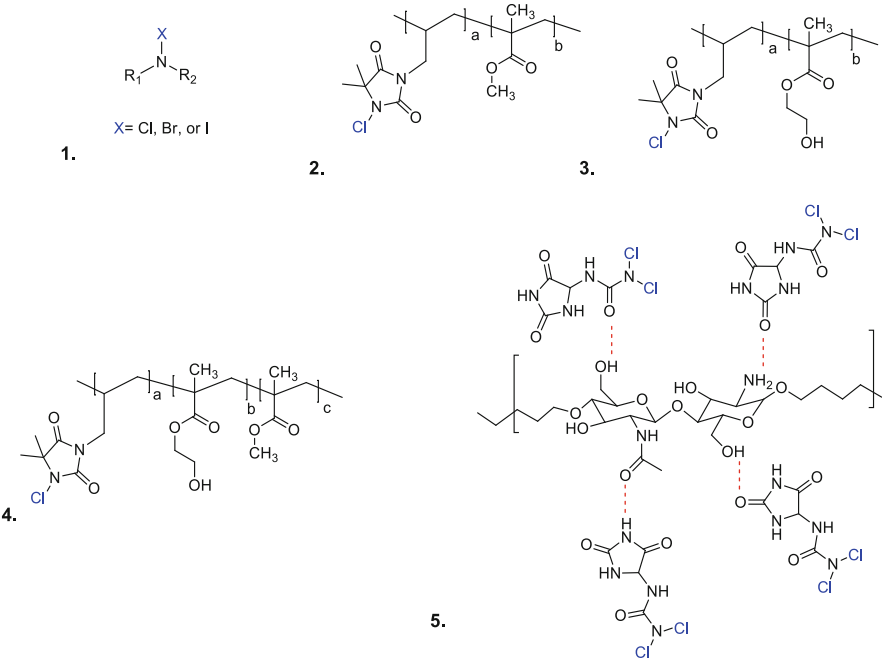


Fig. 13 *N*-halamine functional group and polymers containing it

membrane and have it oxidized. Thus, these types of polymers are considered as oxidant polymers. For that reason, these groups have been used in the elaboration of antimicrobial additives for polymers (Chen and Sun 2006). For instance, they have both been only loaded into polymeric matrixes and particles (Dong et al. 2015), and attached covalently to preformed polymers (Dong et al. 2014).

Gao's group in 2018 made copolymers and a terpolymer with pendant *N*-halamine group (see Fig. 13). With this work they demonstrated the impact of the morphology of the polymer in its antimicrobial properties. The terpolymer (structure 4 in Fig. 13) showed growth inhibition against *E. coli* and *S. aureus*, with better biocompatibility compared with that of the copolymers. They attributed this to the aggregation state of the polymers (Chang et al. 2018).

As another example, Chylinska et al. immobilized *N*-halamine groups in carboxymethyl chitosan films via hydrogen bonds (see structure 5 in Fig. 13). The resulting material showed good antimicrobial performance against *E. coli* and *S. aureus*. Besides, the modification with the *N*-halamine groups did not modify the thermal, mechanical, or chemical properties of the initial chitosan (Chylińska et al. 2019).

The incorporation of this functional group into the polymer structure has provided antimicrobial properties to polymers used for food packaging and drug excipients. Finally, it is of interest to mention some of the systems in which *N*-halamines have been incorporated; for instance, polyethylene terephthalate (PET) (Chien et al. 2019), polyurethane (Qiao et al. 2017; Xiu et al. 2017), and natural polysaccharides (Lan et al. 2019) have all been modified with these types of compounds.

5 Antimicrobial Peptides

Antimicrobial peptides (AMPs) are molecules composed, generally, from 12 up to 50 amino acids that are present in practically all kinds of living organisms, from prokaryotic cells to plants, animals, and humans which create a natural self-defense mechanism against pathogens (Brogden 2005). AMPs comprise a gamut of over 2000 compounds that act mostly contra bacteria but also have been useful as antifungal, antiparasitic, and antiviral agents (Lei et al. 2019). Besides, some studies have exposed that AMPs exhibit anticancer and antifouling activities (Wang 2010). The mentioned properties have aroused a special interest in the understanding and developing of these compounds as an alternative treatment versus multidrug-resistance bacteria (Waghu et al. 2018), since some studies have shown that the resistance developed to AMPs is lower compared to the usual prescribed antibiotics.

Regarding their structure, AMPs are amphipathic and, typically, have a polycationic character, though this does not exclude the existence of some neutral and polyanionic peptides (Lei et al. 2019). Thanks to these two main attributes, AMPs are attracted to the characteristic negative charged microbial membranes.

Lysozyme was the first AMP discovered in 1922 by Alexander Fleming, the same that a few years later would open the door to the golden era of antibiotics with the

discovery of penicillin in 1928 (Phoenix et al. 2013). The apparent supremacy and efficiency of antibiotics killing bacteria produced a momentary pause in researching of AMPs and their properties. Nonetheless; when bacteria were capable of evolving multidrug resistance, scientists turned back to AMPs as an alternative to fight the serious health problems arising from abuse and misuse of antibiotics.

Some studies in this respect were done between 1960s and 1970s; however, it was until 1980s that AMPs began to emerge again with the discovery of cecropins isolated from the moth (*Hyalophora cecropia*) (Hultmark et al. 1983), and the posterior identification of magainins from clawed frog *Xenopus laevis* (Zasloff 1987), which currently are still under consideration about their spermicidal and microbicidal activity (Zairi et al. 2009).

As a simple classification, it is possible to talk about four classes of AMPs: the first one is peptides with cationic character without cysteine residues. There compounds are characteristically disordered in water, but in presence of lipid compounds (for example, phospholipid vesicles and liposomes) they adopt a helical form (α-helix), which is presumably the responsible (and proportional to) for the activity against Gram-positive and Gram-negative bacteria. The second one is another group of cationic peptides with no presence of cysteine but instead having proline, phenylalanine, arginine, or tryptophan residues. The third group contains both cationic and anionic peptides, these AMPs possess cysteine residues and adapt to a β-sheet conformation with intramolecular disulfide bonds. An example of these is α-defensins from animals (including humans). Finally, a fourth group is formed by anionic peptides that require zinc to show antimicrobial activity.

5.1 Transmembrane Pore Formation as a Mechanism for Cellular Killing

To understand the mechanism with which AMPs kill bacteria, it is important to start considering the different stages where these peptides initiate to interact with pathogens (Matsuzaki 2019). This process begins with the electrostatic attraction between the bacteria's membrane surface, which is negatively charged, and the positive charge present in peptides. It is important to mention that AMPs do not produce a similar effect in plants' and animals' membranes because the negative electric charge is within the inner leaflet as well as the stability that cholesterol confers to the cells. To continue the process, an attachment to the cytoplasmic membrane must occur, which is commonly hindered by the layers that protect bacteria (polysaccharides in Gram-positive bacteria or pass over polysaccharides, teichoic, and lipoteichoic coat in Gram-negative bacteria). Once these barriers have been overcome and the interaction is established, the pathogen's death is carried out because of pore formation into the membrane that produces the membrane permeation. This pore formation depends on the relation between peptide and lipid composition relation. When there is enough peptide presence, a reorganization into the membrane

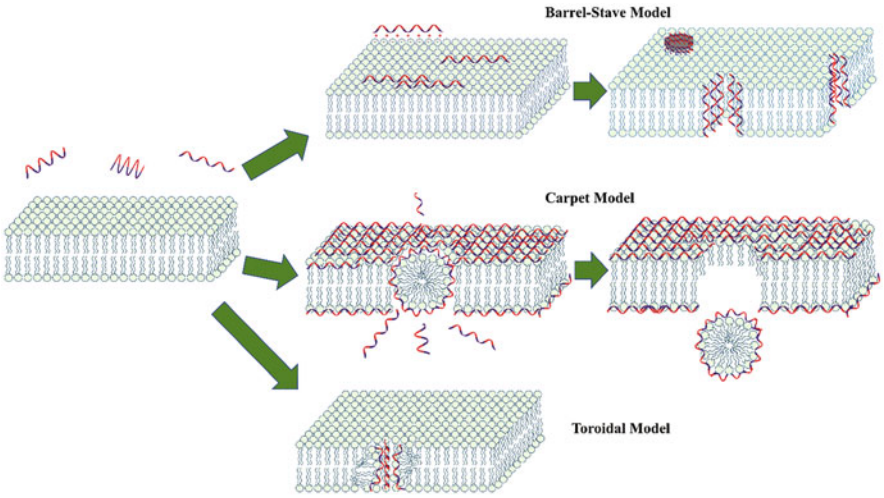


Fig. 14 Proposed models of action for AMPs

structure is accomplished, giving place to its permeabilization. There have been recognized three model lysis membrane mechanisms for α-helical structures: the barrel-stave, the carpet and the toroidal model (Fig. 1).

The "barrel-stave model" (Shai 1999) is proposed to explain the pore formation as a consequence of the shape that a group of α-helices adopts in the middle of the lipid membrane, this is, as the AMPs-lipid ratio increases, the hydrophobic parts of both components are aligned so that the peptides are transversal to the membrane plane forming a channel (pore). Alamethicin is a peptide that illustrates this model in a perfect way.

The "carpet model" (López-Meza and Aguilar 2011) describes the behavior of most of AMPs. In this model, as cationic peptides begin to be attracted to the anionic lipid layer, they stay oriented parallel to the pathogen membrane. When a critical concentration is reached, the peptides act as detergent and, instead of pores, formation of micelles is observed, causing the membrane disruption. This mechanism has been observed in peptides formed up to 23 amino acids, such as insect cecropin and dermaseptin from amphibian skin (biomedical engineering trends).

Finally the "toroidal model" is followed by molecules like magainins and melittins (Sengupta et al. 2008). Toroidal pores are formed when the peptide-lipid ratio is exceeded and instead of staying parallel to the membrane plane, the peptides are reoriented in transversal position so that the lipid head-groups of the membrane are always associated with the AMP hydrophobic moieties. In addition, and simultaneously, the polar faces of the peptides associate themselves with the polar part of the membrane. These two facts force the lysis of the membrane. As a reference for the reader, Fig. 14 shows a diagram of these mechanisms.

5.2 *Antimicrobial Resistance and Viability*

Even when AMPs have demonstrated to be potential candidates to face pathogens due to the wide range of activity and their fast response time versus microorganisms, it is important to considerate that there is a lack of successful and conclusive studies that support their use as commercial drugs. Moreover, for this to happen it is essential that the costs of synthesis and production are reduced and to find a way so that AMPs increase their stability as therapeutic agents (Gordon et al. 2005). Although AMPs have shown almost no resistance to pathogens, some bacteria have developed strategies to annul the peptides action. An illustration is the case of *Staphylococcus aureus* which has exhibited a reduction of its surface net negative charge as a mechanism of inhibition peptide attachment; *S. aureus* also produces a proteolytic enzyme (aureolysin) that gives place to the AMP degradation, nullifying the antimicrobial effect. Some Gram-negative bacteria (*Yersinia enterocolitica*) have transformed the composition of their outer membrane, resulting in resistance to AMPs.

6 Antimicrobial Peptide Mimics

Since AMPs have appeared as an alternative to common antibiotics, the power of emulate the properties of this compounds has attracted the attention of many researchers because it not only offers the possibility to better understand natural AMPs, but also because it offers the ability to more easily control structural their structural parameters (Thaker et al. 2012). The main characteristics to imitate in mimics of AMPs are cationic charge and amphiphilic structure, which, as previously discussed, are thought to be the attributes that grant AMPs their antimicrobial activity. In addition, the mimicked structures must show more resistance to proteases than current AMPs to be of interest in this field (Unubol et al. 2017).

Among the molecules proposed until today are poly-*N*-substituted glycines, where side chains are added to the nitrogen in their structure, thus reducing protease sensibility (Rotem and Mor 2009). Besides, when these groups are incorporated in periodical form, they confer a helical structure to the molecules just as the ones which are typical in α-helix AMPs conformation.

Other molecules that have exhibited some antibacterial activity are β-peptides mimics. These β-amino acid-derived polymers possess both helices and a β-sheet architecture, and have demonstrated the ability to form pores, promote phospholipid transbilayer diffusion (Epand et al. 2004), and have less response to protease activity.

As an additional system, aryl amide oligomers and phenylene ethynylenes studies display promising antimicrobial activity. The first ones present a membrane lysis mechanism with low toxicities, these compounds also resemble magainins and

cecropins (Liu et al. 2004). On the other hand, phenylene ethynylenes produce severe damage to the pathogen lipidic membrane (Wang et al. 2011).

In summary, the synthetic route to mimetic AMPs and its potential as agents with antimicrobial activity has already been explored by several scientists; however, the challenge to control the properties of these designed peptidomimetics is still present and several other studies must be carried out in order to offer new alternatives to present antibiotics.

7 Polymers with Added Antimicrobial Agents

The fabrication of polymers with intrinsic antimicrobial activity depends directly on the polymer structure, molecular weight, solubility, and forms. All of these parameters are very difficult to control if a reproducible and trustworthy synthetic procedure is needed, which has become an issue that has slowed down the development of intrinsic antimicrobial agents. Therefore, to mitigate this issue and to accelerate the development of these kinds of systems, another approach that is often used to provide antimicrobial activity to preformed polymers and polymeric devices is the addition of different well-known agents, such as bactericidal compounds, or AMPs.

The incorporation of these antibiotics inside the polymer chains conducts to a resulting polymer with high bacterial repellence or growth inhibition. These antimicrobial compounds can be coated onto surfaces for several applications such as medical devices, paint additives, water treatment, food packaging, among others (Kumar et al. 2008; Das et al. 2015). The compounds attached to polymers possess intrinsically antibacterial properties by themselves with a mechanism of action which is described in literature.

The nature of the antimicrobial agent can be organic or inorganic, with a notable example being the incorporation of peptides or proteins has been used for the same purpose. A broad number of antimicrobial compounds have been attached or mixed with polymers to avoid microbial growth or adhesion. The addition of these compounds can be achieved by two ways: On the one hand, using conventional synthetic chemistry reactions to covalently bind the active molecule to the substrate. On the other hand, the incorporation may be carried out by mixing the compound and the polymer to form a composite.

A wide range of medical devices (such as catheters, sutures, and valves), membranes, and food wraps are manufactured with polymers like polypropylene (PP), polyethylene (PE), poly(lactic acid) (PLA), poly(vinyl chloride) (PVC), polydimethylsiloxane (PDMS), polyurethane (PU), polyamide, poly (tetrafluoroethylene) (PTFE), etc. In the case of medical instruments and devices, these polymeric devices tend to become contaminated within a few days of contact with the patient, causing risky hospital-acquired infections (HAI). To mitigate this problem, the incorporation of antimicrobial compounds to polymeric materials is very useful even if the material is prone to pathogen contamination.

7.1 Metal-Loaded Polymers

In this section, the addition of inorganic compounds to polymeric matrixes will be studied. There are a lot of reviews that cover the incorporation of these type of compounds to polymeric matrixes to provide antimicrobial capacity to polymers (Muñoz-Bonilla and Fernández-García 2012; Siedenbiedel and Tiller 2012; Jain et al. 2014; Palza 2015). The most common approach is to use elemental metals which organize in nanoclusters or nanoparticles (NPs) since these systems are toxic to bacteria (Ren et al. 2009). Another way to add inorganic compounds is deposition of other inorganic compounds onto the polymeric surfaces. Silver, copper, or zinc NPs are probably the most widely used metal particles as an antimicrobial agent in polymeric composites; however, other compounds such as titanium dioxide (TiO_2) (Felice et al. 2017; Krehula et al. 2017), nitric oxide (NO) (Sadrearhami et al. 2018; Rong et al. 2019), and zinc oxide (ZnO) (Marra et al. 2016) have also been employed too for both biomedical and food applications (Hoseinnejad et al. 2018).

One advantage of these metals is that their MICs are commonly extremely low, but at the same time, they are typically expensive. Although the mechanism of action of these inorganic compounds is not completely described, at least for silver compounds (silver nanoparticles (AgNPs) and silver ions), one of the main pathways that stops bacterial growth is that silver ions (Ag^+) tend to bind to proteins, altering the pathogen cells. AgNPs also interfere with the microorganisms' growth due to the formation of complexes with nitrogenous bases in DNA and RNA (Morones et al. 2005; Petica et al. 2008; Woo et al. 2008; Aziz et al. 2014, 2015, 2016, 2019; Gudikandula and Charya Maringanti 2016; Burdușel et al. 2018).

In addition to the previous mechanisms, metals can participate in redox reactions and can act as a catalyst for some enzymatic reactions. The presence of external metals can increase these reactions, producing an excess of reactive oxygen species (ROS) derivatives which produce oxidative stress in the cell. The cytotoxicity of different metal have been reported against Gram-positive and Gram-negative bacteria such as *E. coli*, *P. aeruginosa*, *S. aureus*, *S. epidermis*, among others (Lemire et al. 2013).

Different metals (reduced and oxidized forms) have been deposited into hydrogels and polymers by different methods. Some of these methods are the following: electrochemistry (Domínguez-Domínguez et al. 2008; Jovanović et al. 2012; Fu et al. 2016; Karimzadeh et al. 2016; Tian et al. 2017), radiation (Son et al. 2006; Pant et al. 2011), or, most commonly, conventional chemistry, such as redox reactions (Payami et al. 2016). Typically for these substrates, antimicrobial activities of the resulting material are measured in many of these studies. The immobilization of these metallic particles and ions is favored by coordinating functional groups onto the polymeric structure (Tylkowski et al. 2017); for example, AgNPs and oxidized silver can coordinate with carboxylate groups of polymer chains, through electrostatic interactions, as seen in Fig. 15a. Additionally, they can interact with positive charged groups such as ammonium salts when the metallic nanoparticles are suspended in a surfactant, forming a micelle-type structure (Agnihotri et al. 2013)

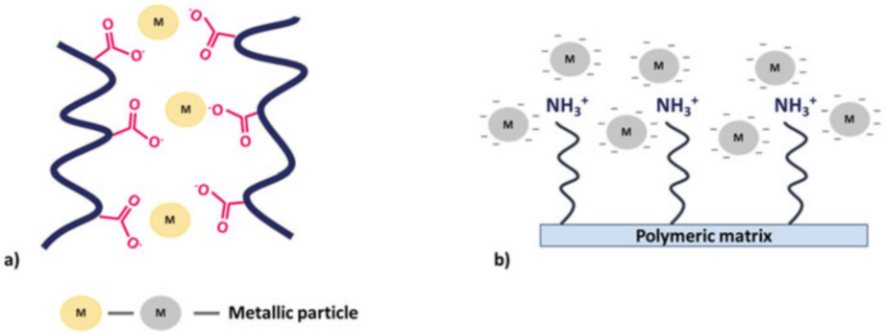


Fig. 15 Metallic particle immobilization via electrostatic interaction with (**a**) carboxylate groups and (**b**) ammonium salts

as it is represented in Fig. 15b. Nevertheless, there exist reports about direct covalent attachment of silver in polymer chains with significant results against *S. aureus* (Akhavan et al. 2018).

Although many metals have shown good antibacterial activities, silver is the most used and studied metal due to its broad-spectrum antimicrobial activity, since it presents high stability, low-cost, and ease of preparation. AgNPs have been embedded and immobilized onto different and relevant polymers used in food industry (Llorens et al. 2012) and biomedical applications (Zare and Shabani 2016), by a variety of methods. Some polymeric matrixes that have been modified with AgNPs are: PTFE (Reznickova et al. 2014; López-Saucedo et al. 2019), PLA (Busolo et al. 2010), PE (Song et al. 2011), PP (López-Saucedo et al. 2018), among others (Mei et al. 2014).

Extensively, there exist a lot of reports about hydrogel/AgNPs composites (Xu and Zhou 2008; Jovanović et al. 2012; Rhim et al. 2013; Fazly Bazzaz et al. 2014) which are vastly used as antimicrobial materials. The NPs deposition and immobilization can be reached by two pathways, one alternative is mixing both components (hydrogel and preformed AgNPs) to form a polymer/metal composite; the other option is in situ formation using any aforementioned method; both techniques result in materials with high capacity to killing bacteria (Cioffi et al. 2005; Araújo et al. 2018). Most reports employ the second way to obtain AgNPs inside a polymer or hydrogel, mainly by chemical reduction of $AgNO_3$ using conventional reducing agents (sodium borohydride ($NaBH_4$), monosaccharides, citrate, polyols, etc.) (Rodríguez Nuñez et al. 2019). For surface immobilization of metal NPs, brush-type polymer grafting is used, this allows for NPs retention when the nanoparticle gets embedded between polymer chains. As a greater enhancement, the use of stimuli-responsive polymers provides controlled retention and release of the metal nanoparticle (Gupta et al. 2008).

As an example, hydrogels used for contact lens manufacturing tend to contaminate easily by common bacteria, and the incorporation of antimicrobial compounds has reduced the risk for microbial-associated infections for lens users. Fazly Bazzaz

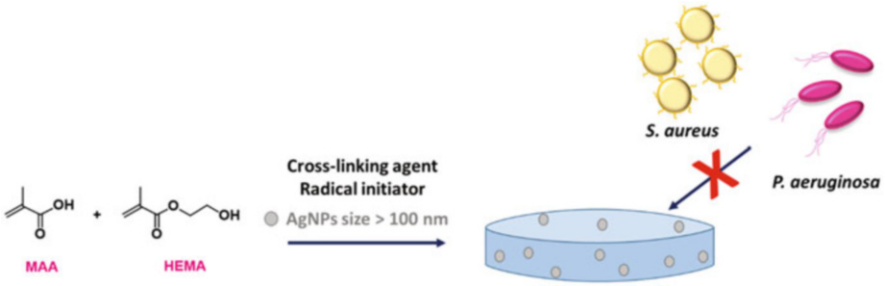


Fig. 16 Synthesis of MAA-*co*-HEMA 3D hydrogel impregnated with high size AgNPs for growth inhibition of bacteria

et al. (2014) added preformed AgNPs (size >100 nm) to a cross-linked hydrogel of methacrylic acid (MAA) and 2-hydroxyethyl methacrylate (HEMA) (similar material to that of soft contact lenses) to avoid bacterial adherence onto the hydrogel surface. They tested the impregnated material against *S. aureus* and *P. aeruginosa*. The hydrogels with different amount of AgNPs demonstrated high antibacterial properties which were not related to AgNPs content (Fazly Bazzaz et al. 2014). A schematic representation of this is shown in Fig. 16.

Since the addition of AgNPs has demonstrated good bactericidal capacity while mixed with some polymers, they have been used in injectable-hydrogel systems showing the same antibacterial activity and good biocompatibility. Niu and coworkers in 2018 achieved AgNPs stabilization with the encapsulation using a poly(ethylene glycol dimethacrylate)/Poly(acrylic acid) (PEGMA/PAAc) copolymer. The formation of silver nanoparticles was conducted by chemical reduction of $AgNO_3$ with $NaBH_4$, while the silver was reducing, the encapsulation with the polymer was occurring. The coating formation is driven by the electrostatic interactions between the carboxylic acids (or their conjugated carboxylate base) and the silver particle. The formation of the micelle-type particle prevents AgNPs aggregation during the reduction process (Ag^+ to Ag^0) as it is represented on Fig. 17a. The antibacterial test results against *S. aureus* and *E. coli* showed growth inhibition for both bacteria with minimal concentration of AgNPs. The biocompatibility studies with HeLa cells showed low cytotoxicity when silver concentrations were kept low (but still in therapeutical ranges for this study) (Niu et al. 2018).

Other hydrogels made of poly(vinyl alcohol) (PVA) (Alcântara et al. 2019), alginate (Ghasemzadeh and Ghanaat 2014; Martins et al. 2015), agar (Rhim et al. 2013), cellulose (El-Shishtawy et al. 2011; Yang et al. 2012; Rouabhia et al. 2014), chitosan (Agnihotri et al. 2012; Nguyen et al. 2019), and gelatin (Xu and Zhou 2008; Kanmani and Rhim 2014). These materials have either been impregnated or mixed with AgNPs and have exhibited good antibacterial capacity against common pathogenic bacteria.

Other hydrogels have been loaded with copper and gold following the same procedures (Ribeiro et al. 2017; Araújo et al. 2018). Some of the materials are useful for burn wound dressings and as wound healing agents (Boonkaew et al. 2014a, b;

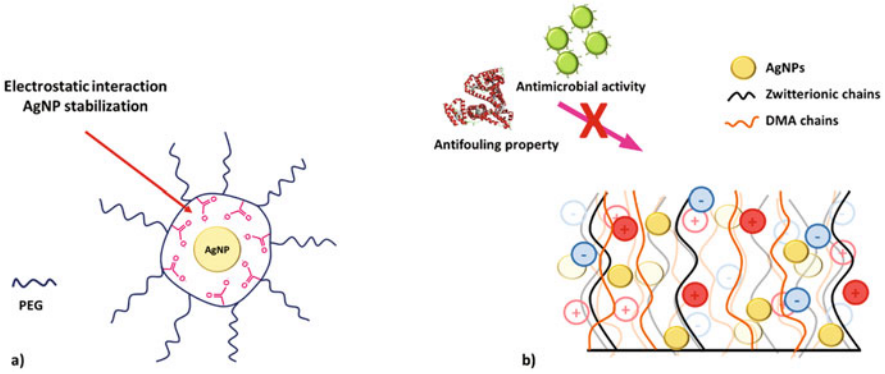


Fig. 17 AgNPs immobilization into a hydrogel structure by the (**a**) AgNPs stabilization by electrostatic interaction with carboxylic groups and by the (**b**) in situ formation with catechol groups as reducing agent with zwitterionic moieties for antifouling properties

Mohamed and Sabaa 2014). Moreover, zwitterionic hydrogels and AgNPs have been mixed to form bifunctional materials. In this case, the zwitterionic moiety provides antifouling properties (avoids protein adhesion and consequently bacterial adhesion) and the silver provides the antimicrobial properties. As it can be seen in Fig. 17b, a copolymer of dopamine methacrylate (DMA) and *N*-(3-Sulfopropyl)-*N*-(methacryloxyethyl)-*N*,*N*-dimethylammonium betaine (DMAPS) was synthesized to immobilize silver nanoparticles, the AgNP formation was conducted by reduction of $AgNO_3$ with the catechol group in the DMA, which is oxidized to the ortho-quinone form while the silver was reduced (GhavamiNejad et al. 2016).

7.2 Polymers with Organic Antimicrobials: Attachment and Immobilization

As we mentioned previously, the antimicrobial activity of a polymeric matrix or of a hydrogel can be attributed to the active molecules embedded on their chains, since not all the polymers present intrinsic antimicrobial properties. Some of them have application in the controlled release of drugs, and others only to avoid bacteria adherence to the surfaces.

The main content of this section is the addition of organic compounds to polymeric matrixes for antimicrobial and antifouling properties. These compounds can be biocides, antibiotics, or active molecules against any type of microorganisms, like fungi, viruses, or bacteria. Several drugs have been introduced to polymers and hydrogels, especially those with broad-spectrum antimicrobial activity, some of the most representative examples are shown in Fig. 18. These antimicrobial compounds have well-known bactericidal activity, and their mechanisms of action are

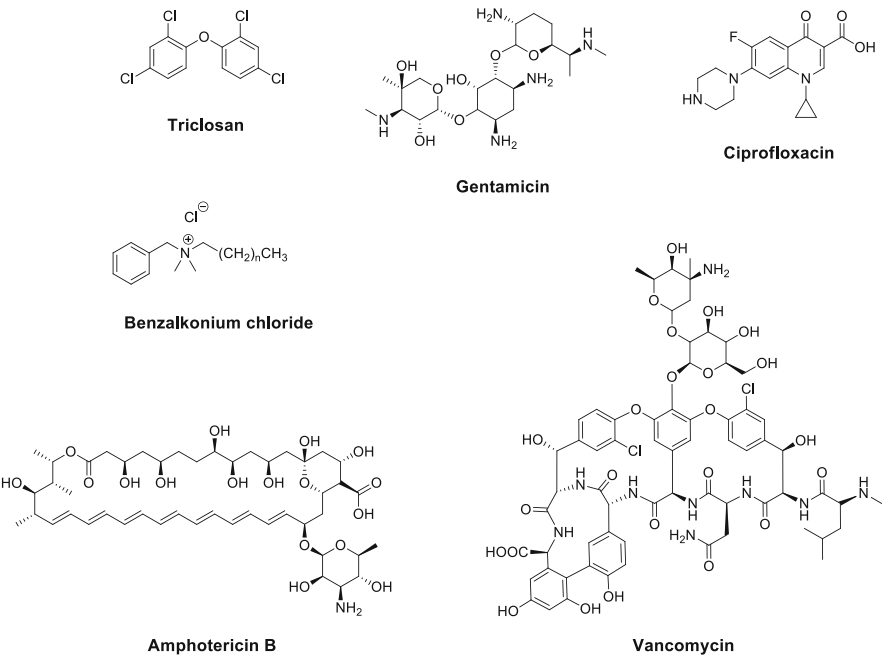


Fig. 18 Antimicrobial agents introduced in polymers

extensively described in the literature (Hancock 2005; Kohanski et al. 2010; Kapoor et al. 2017).

One important aspect is that some polymers used for biomedical applications have been directly modified with other macromolecules under the same purpose, mainly to avoid the bacteria biofilm formation and prevent HAIs. In contrast, some studies suggest that the addition of hydrophilic moieties onto the surfaces only stops bacterial adhesion, for that situation, it is necessary to add other antimicrobial compounds.

The incorporation of the bioactive organic compounds can be attained by two methods. On the one hand, by the immobilization via non-covalent bonds between polymer chains, and on the other hand by the covalent connection of the molecule to the polymer backbone, using different *grafting* techniques.

The first one is the loading of the drug inside the polymer, which allows the controlled retain/release of drugs. The grade of retention depends directly from the chemical structure of both drug and polymer, because they influence the supramolecular (non-covalent) interactions between their functional groups. Other important aspect to consider is the acid-base behavior of the groups and the thermostability of the components, since the usability of the material also depends on them, as well as the capacity of load drugs.

As mentioned before, the immobilization of the bioactive molecules can be reached using different *grafting* techniques, but the main approach used is the

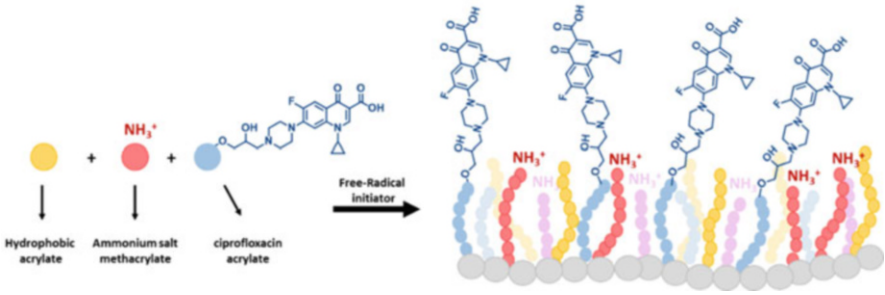


Fig. 19 Amphiphilic copolymer with ciprofloxacin as pendant

synthesis of a monomer containing the antimicrobial group. This strategy has been employed to covalently attach molecules with different properties. The synthesis of a monomer, specially, "drug"—acrylates or—methacrylates is the most used procedure. Ciprofloxacin, AMPs, gentamicin, and other antibiotics have been bound to polymers using this technique to provide or to improve antimicrobial properties (Permyakova et al. 2018; Xiao et al. 2018; Hu et al. 2019).

For example, ciprofloxacin has been loaded and introduced in polymers and hydrogels by the two methods. Some of these polymers have been, for example, cyclodextrin-agar hydrogels (Blanco-Fernandez et al. 2011), chitosan films and nanoparticles (García et al. 2017; Sobhani et al. 2017), alginate and alginate copolymers (Ahmed and Boateng 2018; Patel et al. 2019), PLA/gelatin mixture (Xia et al. 2019), poly(lactic-*co*-glycolic acid) (PLGA) (Liu et al. 2018), etc. The presence of ciprofloxacin confers antimicrobial properties, mainly, against a broad number of Gram-positive and Gram-negative bacteria (Campoli-Richards et al. 1988), such as *S. pneumoniae*, *P. aeruginosa*, *E. coli,* and *S. aureus*.

Although, in most cases, ciprofloxacin has been loaded in the polymer, there are reports about covalent immobilization in the polymer structure, as a pendant group (Xue et al. 2012; He et al. 2018), Man He et al. 2018 synthesized an amphiphilic copolymer with dual antimicrobial effect, first provided by the ammonium salts and second provided by ciprofloxacin covalent attached to the polymer. The polymerization was performed by a conventional free-radical polymerization of the three different components, see Fig. 19. Each component in the polymerization was selected with a specific purpose, the alkyl acrylate (yellow ball) provided hydrophobic character to the final polymer, as well as the amino methacrylate (red ball) fulfilled two functions: first, offering hydrophilicity and second to provide antimicrobial properties, the last component was the ciprofloxacin acrylate (blue ball in Fig. 19) with known antibiotic effect. This amphiphilic polymer showed growth inhibition against *E. coli* (He et al. 2018).

The grafting method has been employed to modify polymers with additional brush-type or stimuli-responsive polymers. In this graft, the drug loading and release can be reached by a stimulus and non-covalent interactions. For example, PVC catheters were modified with poly(methacrylic acid) (PMAA) using ionizing

radiation (PVC-*g*-MAA), loaded with ciprofloxacin and benzalkonium chloride, and their antimicrobial performance was tested (Zuñiga-Zamorano et al. 2018). The pH-sensitivity of the PMAA allowed the diffusion of ciprofloxacin and benzalkonium chloride inside the chains when the pH is above the pKa of the acidic groups. The antimicrobial effect was demonstrated with *P. aeruginosa*, *E. coli,* and *S. aureus*, the ciprofloxacin-loaded catheters showed good bacteria growth inhibition against the three pathogens and those with benzalkonium chloride only affected the *S. aureus*.

Vancomycin has been loaded onto hydrogels and polymeric matrixes, and due to its chemical structure, it can interact through hydrogen bond with the polymer. Drug delivery systems employ vancomycin for its broad-spectrum activity and for providing antifouling properties. This antibiotic has been loaded in chitosan nanoparticles and aerogels for wound dressing applications (Xu et al. 2015; López-Iglesias et al. 2019; Hassan et al. 2020), alginate (Kurczewska et al. 2017), polycarbonate (Zhang et al. 2017), gelatin (Aksoy et al. 2019), and commercial polymeric excipients such as Eudragit RL 100 (Santos Ferreira et al. 2018) and HPMC (Mahmoudian and Ganji 2017).

8 Zwitterionic Polymers as Antifouling Materials

Zwitterionic polymers (Poly(Zw)) are polymers with both positive (cations) and negative (anions) charges incorporated into their structure, these charges can be distributed randomly in all the macromolecule, but always maintaining the stoichiometry 1:1. This class of polymers includes polybetaines and polyampholytes, whose differences can be seen in Fig. 20.

Poly(Zw)s present excellent properties in solution (Blackman et al. 2019), due to the charges in their structure. They are also considered as stimuli-responsive polymers, because some of them respond to changes in temperature, electric field, and pH. Nevertheless, the most important and exploited property is that they can repel and stabilize proteins (Pelegri-O'Day et al. 2017) due to their multi-charges in their structure. This causes a decrease in the cell and bacteria deposition too. Their main application is as surface coatings since they prevent the biofilm formation or present

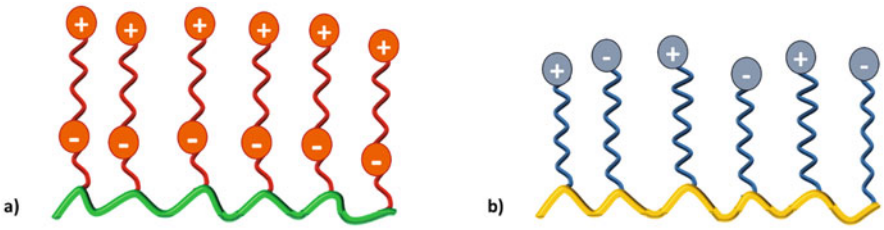


Fig. 20 General charge distribution of zwitterionic polymers, (**a**) polybetaines and (**b**) polyampholytes

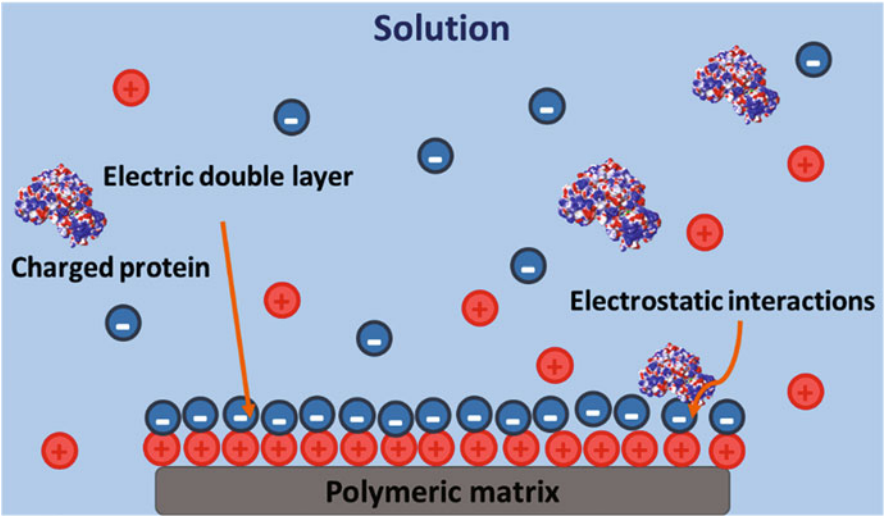


Fig. 21 Electrical double layer formed onto the pristine surfaces that promotes the protein attachment

antifouling properties (He et al. 2016; Zheng et al. 2017; Wang et al. 2018; Zeng et al. 2018; Zhang et al. 2018a, b, 2019a, b; Fu et al. 2019; Van Andel et al. 2019; Sun et al. 2020), but they are also used as polymeric drug delivery systems (Sun et al. 2017).

The difference between the unmodified polymeric matrixes and those modified with poly(Zw)s is that the former tend to form an electrical double layer (see Fig. 21) and this favors the attachment of charged proteins (Lubarsky et al. 2005), which trigger the migration and stabilization of microbes and cells onto the surface; while the modified surfaces for the well distributed charges do not polarize the charges, hence they do not allow the protein attachment.

Several polyampholytes and polybetaines have demonstrated high repellence to proteins, and have been employed to modified surfaces for marine and biomedical applications (Haag and Bernards 2017; Kardela et al. 2019), for the improvement of membranes (Zhang et al. 2018a, b; Yang et al. 2020), and even the synthesis of multi-charged containing hydrogels is also explored (Shen et al. 2019; Vales et al. 2020). The synthesis methods to obtain this kind of macromolecules involve controlled living radical polymerizations (CLRP), controlling living ionic polymerizations (CLIP), free-radical polymerizations (FRP), and ring-opening metathesis polymerizations (ROMP) (Kudaibergenov 1996; Bernards and He 2014; Laschewsky 2014; Tao et al. 2018; Morimoto et al. 2020). In addition, these polymers can be grafted onto surfaces by different techniques, such as grafting from and grafting to approaches (Wu et al. 2019a, b).

For example, Zhang et al. (2018a, b) made a functionalization of membranes with a polyampholyte polymer to provide it with antibacterial and antifouling properties. Additionally, they loaded graphene oxide sheets (GO) into the polymer chains using vacuum filtration (see Fig. 22). The immobilization of GO in the polymer was

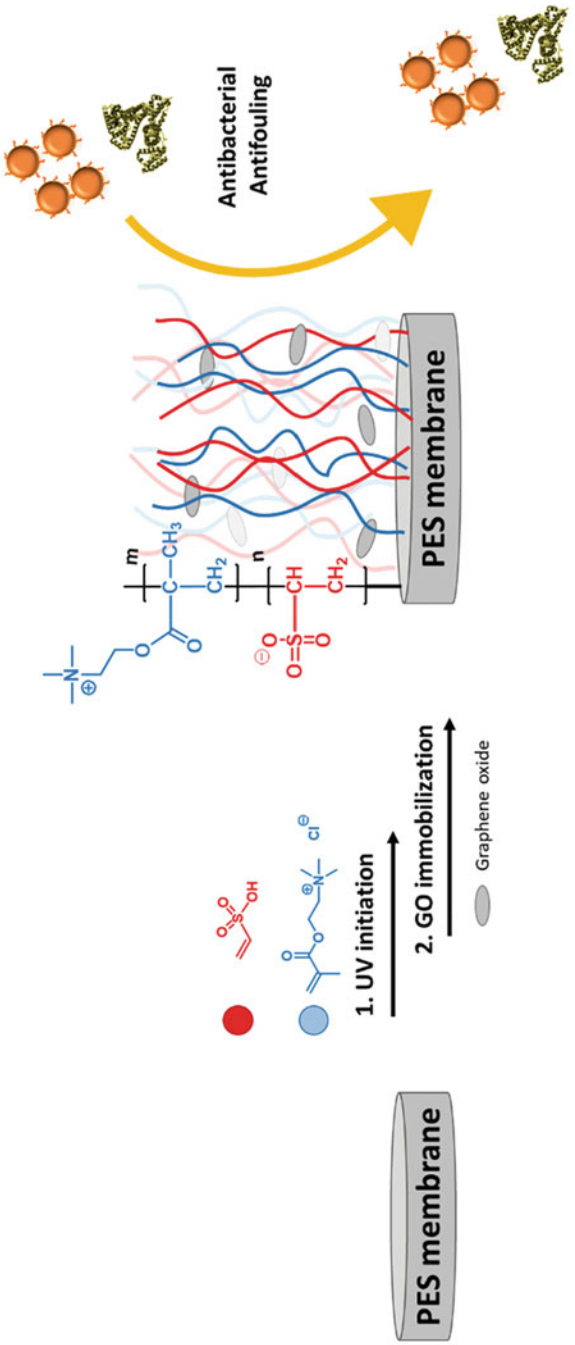


Fig. 22 UV-photoinitiated polyampholyte grafting onto PES membranes and GO for antifouling and antimicrobial properties

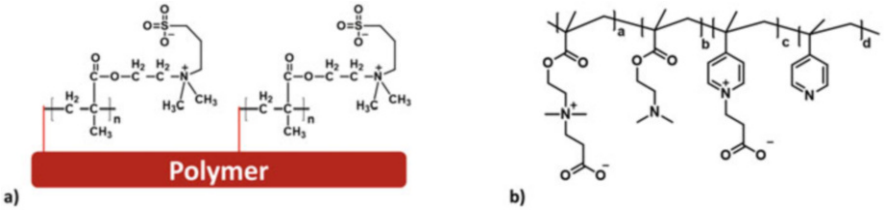


Fig. 23 (**a**) Modification of polymeric matrixes with DMAPS and (**b**) Synthesis of zwitterionic copolymers for antimicrobial and antifouling properties

because GO prevents the bacteria growth. The protein absorption and antimicrobial tests were performed to the final modified dual membrane, and they demonstrated that the functionalization with GO and zwitterion hydrogel is a promising strategy to prevent biofouling and protein adhesion in ultra-filtration membranes. Similar work was carried out by Zhang and Yang group in 2019 on graphene oxide carbon nanofibers for the development of aptasensors (Zhang et al. 2019a, b).

Another example is the modification and manufacturing of surface coatings with polybetaine-type polymers. In 2018, Lee et al. and Wu et al. grafted *N*-(3-Sulfopropyl)-*N*-(methacryloxyethyl)-*N*,*N*-dimethylammonium betaine (DMAPS) onto polyurethane (PU) and polydimethylsiloxane (PDMS), respectively, by different grafting techniques, obtaining good antifouling materials, Fig. 23a.

As a final example, polymers derived from 4-vinyl pyridine (4VP) and dimethyl amino ethyl methacrylate (DMAEMA) were *N*-substituted with an ethyl carboxylate to form the zwitterionic copolymer, see Fig. 23b. The resulting polymer was further characterized and tested for protein adsorption and cell adhesion. With these experiments, they found that the polymers displayed non-fouling activity against Bovine Serum Albumin (BSA), lysozyme proteins, and human kidney cells (Wu et al. 2019a, b).

9 Conclusions

As pictured in the sections above, antimicrobial polymers have many varieties and have been already shown effective for many applications. Although this field had huge advancements, better and more applicable polymeric materials are expected to appear in the following years. These materials present an alternative to classical molecular antibiotics and are expected to improve the odds against the rise of antimicrobial resistant pathogens in order to improve healthcare conditions and have alternative therapies for all types of pathogens.

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