Advanced Antimicrobial Materials and Applications: Maleic Anhydride Antimicrobial Polymers

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Abstract Care for human life should be a priority for all the people on Earth. The number of elements jeopardizing human life, including pathogenic microbes, has been increasing. Many microbial infections are often challenging to treat and result in the patient's death. Moreover, the currently applied decontamination methods are often not effective. Therefore, research around the world has been focused on developing new solutions to fight against harmful microbes. An interesting and promising concept in this field are polymers exhibiting antimicrobial activity. Among such polymers, much attention has been paid to maleic anhydride-derived materials. Maleic anhydride is a well-known raw material used in a wide spectrum of industries. Due to its specific structure it finds its applications in many polymerization and copolymerization processes. Some of the products possess antimicrobial properties and can be used as protective coatings or drug carriers. This chapter presents the examples of the scientists achievements in the field of antimicrobial maleic anhydride polymers.

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1 Introduction

The term microbes depicts a large group of microorganisms, the oldest forms of life on Earth, whose existence traces date back more than 3.5 billion years (Kumar and Chordia 2017). It is estimated that the number of microbe types can reach up to 10^{30} with bacteria, fungi, viruses, protozoa, microalgae, and archaea being the most important representatives (Bisen et al. 2012a; Lustgarten 2016; Dodds and Whiles 2020). Vast majority of them inhabit the human body constituting its natural microbiome. The digestive gut, mouth, skin, and nose are the places where most of the microorganisms can be found. Their occurrence is essential for proper functioning of the human organism (Grice and Segre 2012; National Academies of Sciences Engineering and Medicine 2017; Smith 2020). Some, like the probiotics, help to keep the intestinal microbial balance (Hatti-Kaul et al. 2016; Rani et al. 2019), others, inhabiting the human reproduction system, are essential for the reproduction (Sun and Chang 2014; Atanasova and Yilmaz 2015; Kumar and Chordia 2017).

Despite all the positive aspects, some microbes, the pathogens, cause infections (Singh et al. 2014; Chatterjee and Raval 2019). Microbes and the diseases they cause are a serious threat to human life (Institute of Medicine 2003). Death as a result of microorganisms infections is such a frequent phenomenon, that the amount of the fatal cases is much higher than the number caused by any other factors (Huang et al. 2016). Harmful microorganisms can be transferred to organisms through food, air, or water (Chatterjee and Raval 2019; Pigłowski 2019). In recent years the outbreaks of severe acute respiratory syndrome (SARS) (2002–2003), Ebola virus (2014–2016), or Zika virus (2016) posed a serious threat for the global population (Groneberg et al. 2005; Schlagenhauf et al. 2017; Den Boon et al. 2019; Noorbakhsh et al. 2019). Moreover, the world has been facing a severe problem of the increasing antimicrobial resistance (AMR) restricting the human ability to fight against bacterial infections (Nicolle 2011; Brinkac et al. 2017; Mcewen and Collignon 2017; Septimus 2018). Once bacterium is defeated by a certain class of drugs, it can acquire resistance and further usage of the drug will be ineffective (Mcewen and Collignon 2017; Smith 2020). First reports of AMR date back to 1942 when *Staphylococcus aureus* strains showed resistance to penicillin (Ben Maamar et al. 2020). Nowadays, microbial infections require the development of new drug types that have the ability to combat multi-drug resistant pathogens (Hacker and Dobrindt 2006; Brown 2015; Andersson et al. 2016; Miró-Canturri et al. 2019).

Among other areas, health care and food packaging and storage are the most exposed ones to harmful microorganisms (Kenawy et al. 2007). Nowadays, most common microbial pathogens causing dangerous infections belong to the bacteria group (Nicolle 2011; Chatterjee and Raval 2019). *Escherichia coli* is one of their most common representatives. The first reports on its occurrence are dated to 1885

when Theodor Escherich isolated this bacterium strain (Croxen et al. 2013). It is responsible for diarrhea and extraintestinal diseases such as blood stream and urinary tract infections (Nicolle 2011; Croxen et al. 2013; Gomes et al. 2016). Another quite common bacteria is *Salmonella* which is transmitted to human mainly through infected foods such as eggs (Chlebicz and Śliżewska 2018). In most cases, *Salmonella* causes diarrhea; however, almost 5% of the patients can develop bacteremia, a state in which bacteria is present in the bloodstream (Pegues et al. 2006). Bacteria from the *Shigella* species are known for causing shigellosis, a disease which manifests mostly through diarrhea and can be dangerous for both children and adults. In 2010 almost 40,000 people in the age above five died from it, while in 2013 it caused deaths of 34,400 children below that age (Mani et al. 2016; Chatterjee and Raval 2019). Another microbe, *S. aureus*, affects mostly the human skin. It causes wounds creation and skin diseases; however, it is also responsible for the majority of post-surgery infections and problems with blood stream (Nicolle 2011; Chatterjee and Raval 2019). *Listeria monocytogenes* is a common bacteria causing listeriosis. The disease manifests mostly through fever, headache, diarrhea, vomiting, and nausea; in pregnant women it can result in miscarriage (Hernandez-Milian and Payeras-Cifre 2014; Chlebicz and Śliżewska 2018).

2 Prevention, Control, and Treatment Methods Against Microbes

The growing awareness of the threat has led to stronger emphasis on hygiene, education on antimicrobial resistance, and effective sanitation (World Health Organization 2015). Hygiene is strongly related to antiseptics, which are widely used in the health care. Sterilization is probably the oldest approach to microorganisms control. This method, based on application of steam, hydrogen peroxide gas plasma, UV irradiation, gamma irradiation, ethylene oxide, vaporized hydrogen peroxide, kills all the microbes (Hogg 2005; Rutala and Weber 2019). Antiseptic agents such as chlorhexidine, alcohol, or iodophor reduce the number of microorganisms on the skin surface (Williamson et al. 2017; Rutala and Weber 2019). Surgery has a high risk of infection, therefore the strongest antiseptics agents such as ethylene oxide and hydrogen peroxide are used in this case. All the medical equipment used during surgery is subjected to a high-level disinfection before the contact with patient. The procedure kills almost all the microbes; however, some bacterial spores are resistant to this method. Other hospital equipment such as wheelchairs, blood pressure cuffs, bed rails, bedpans, bedside tables are treated with low-level disinfection method. This approach is milder and successful in elimination of some viruses, fungi, and vegetative bacteria species. However, it is not strong enough for spores and mycobacteria (Rutala and Weber 2019).

Disinfection methods are also used against airborne microbes, especially in ventilation systems (Wang et al. 2019a). Special particulate filters in heating systems, air conditioning (HVAC) systems, and ventilation are used to a limited number of pathogens (Möritz et al. 2001; González et al. 2016; Stockwell et al. 2019).

Another tool for air disinfection is UV germicidal irradiation successfully applied in many systems (Tseng and Li 2005; Memarzadeh et al. 2010; Reed 2010; National Academies of Sciences Engineering and Medicine 2017).

The preventive approach to microbes is very important in the area of the food industry for food preservation. Reducing the microbes growth extends the product shelf-life. The most common techniques applied for that purpose are drying, boiling, oxidation, freezing, smoking, UV irradiation, ultrahigh water pressure, and usage of chemical preservatives (Bisen et al. 2012b; Chatterjee and Abraham 2018).

The methods described above, unfortunately, cannot be applied universally in everyday life due to technical and/or economic barriers and the possible insufficiency. Alarming is the fact that there are not many ways to efficiently eliminate pathogens from our surroundings. Despite the constant development in medicine and technology, there are still limitations in controlling and preventing infections. However, there are other ways to fight the microorganisms. One of them is the employment of antimicrobial polymers that can act as surface coatings and drug carriers hindering the microorganisms growth (Siedenbiedel and Tiller 2012; Musumeci and Puglisi 2013; Zhang and Wagner 2017; Tiwari and Chaturvedi 2018; Kamaruzzaman et al. 2019; Nagaraja et al. 2019).

3 Antimicrobial Polymers

Antimicrobial agents are substances developed for two purposes: reducing the growth or killing microorganisms. They are divided into groups based on their action mechanism or their chemical structure (Musumeci and Puglisi 2013).

Antimicrobial polymers are the agents that became the subject of intensive academic research during the last few years (Kenawy et al. 2007; Rodríguez-Hernández 2017; Yang et al. 2018). Polymers classified as antimicrobial either exhibit their own antimicrobial activity or are conjugated to other antimicrobial compounds such as antibiotics (Kamaruzzaman et al. 2019). The antimicrobial activity is strictly related to several factors such as the molecular weight, counterions type, length of spacer located between polymer and the active site, or hydrophilic–hydrophobic balance. There are three types of antimicrobial polymers (Siedenbiedel and Tiller 2012; Huang et al. 2016; Benčina et al. 2018):

- polymeric biocides—polymers linked with covalent bonds to bioactive antimicrobial repeating units such as the carboxyl, hydroxyl, or amino groups,
- biocidal polymers that possess antibacterial activity in their whole chain. They contain biocides such as quaternary ammonium, tertiary sulfonium, guanidinium, or phosphonium,
- biocide-releasing polymers with two subgroups:
  - the biocide-releasing compounds are attached to the polymeric backbone,
  - composites consisting of polymer and biocide-releasing molecules.

The usage of antimicrobial polymers has multiple advantages compared to the conventional solutions. First of all, they are long-term-activity materials; second, they are non-toxic, chemically stable, nonvolatile; third, they can act selectively; fourth, the skin is an impassable barrier for them. Moreover, in some cases, they exhibit greater operational efficiency than the conventional antimicrobial agents (Kenawy et al. 2007). The great application potential of antimicrobial polymers is exploited in the food, medical, and textile industries. Primarily they are used as antimicrobial surfaces and coatings on medical devices, implants, as antimicrobial packing films and textile fibers (Bastarrachea and Goddard 2015; Huang et al. 2016; Zhang and Wagner 2017; Ergene et al. 2018; Zhong et al. 2020; Prasad et al. 2020). Maleic anhydride-based polymers are one of the examples of such materials.

4 Maleic Anhydride

Maleic anhydride, also known as 2-5-furandione or maleic acid anhydride, was synthesized for the first time around 1830 (Gooch 2007; Hernández-Moreno et al. 2014). This material is a solid in room temperature; it is colorless or slightly white and has irritating odor. Its chemical structure bases on heterocyclic ring containing oxygen and four carbon atoms; two carbonyl groups are present at the C_2 and C_5 positions and a double bond between the third and fourth carbon atom (Fig. 1) (Musa 2016).

Maleic anhydride is produced at industrial scale from butane gas or benzene, in fixed or fluidized-bed processes, or in oxidation in the presence of vanadium oxide catalysts (Higgins and Hutchings 1980; Edwards 1985; Dente et al. 2003; Gascón et al. 2005). Maleic anhydride is also obtained as a by-product in production of phthalic anhydride (Hernández-Moreno et al. 2014).

The occurrence of the double bond renders the compound highly reactive. Additionally, the electron withdrawing forces from the two electron-deficient C=O substituent groups are responsible for strong electron-accepting properties. These features make maleic anhydride widely used as an intermediate product in reactions based on electrophilicity, in the Michael reactions, alkylation, acylation, halogenations, sulfonation, formation of Diels–Alder adducts, photodimerization, or free radical polymerization (Parker et al. 2001; Musa 2016). It is used for production of unsaturated polyester resin, copolymers, food additives, agricultural chemicals, alkyl succinic anhydrides, cosmetics, oil additives, detergents, malic and fumaric acid (Hernández-Moreno et al. 2014; Ashland 2017).

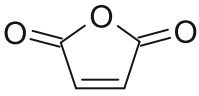

Fig. 1 The structure of maleic anhydride

4.1 Maleic Anhydride Polymers

As a monomer, maleic anhydride exhibits very low tendency to homopolymerize. However, copolymerization reactions with donor monomers are its main field application (Nasirtabrizi et al. 2013).

Free radical polymerization of maleic anhydride and alkyl vinyl ether leads to development of high molecular weight alternating copolymers. Their modification by exchange of α-olefins in the place of alkyl vinyl ether monomer results in synthesis of terpolymers (Musa 2016).

Unsaturated polyester resins can be synthesized in condensation reaction of dibasic organic acids such as maleic and phthalic anhydride with dihydric alcohols, for example propylene glycol (Bodnar et al. 1990; Ahamad et al. 2001). They can also be obtained in a more sustainable way from polyethylene terephthalate (PET) waste and maleic anhydride (Vaydya and Nadkarni 1987). Maleic anhydride can also be used for modification of alkyd resins as its presence in the structure impacts the color and water resistance of the resin (Boruah et al. 2012).

Polyolefins modified with maleic anhydride are an interesting class of copolymers from the industrial point of view. They can be obtained in free radical processes. However, this type of production leads to degradation and troublesome changes in the products' rheological properties. To overcome these obstacles, a process based on pericyclic mechanism such as the Alder-Ene reactions may be employed. The product is characterized by high adhesion, paintability, and compatibility (Vicente et al. 2008).

The maleic anhydride polymers group includes also acrylic and N-vinyl amide/maleic anhydride copolymers. Synthesis of the first is based on conventional free radical mechanism, whereas, complex radical copolymerization is responsible for the synthesis of the second. Both groups are effective corrosion inhibitors and antifouling agents (Veron et al. 2001; Temiz et al. 2006; Musa 2016).

One of the most known alternating maleic anhydride copolymers is styrene-maleic anhydride copolymer. It has unique thermal and mechanical properties; it is transparent and can be modified for example with hydroxyl or amino groups. It finds the application in many fields including the packaging, and the automotive and construction industries. It can be produced in several ways such as conventional free radical copolymerization and controlled polymerization processes: the nitroxide mediated polymerization (NMP) and the reversible addition-fragmentation chain transfer (RAFT) (Huang and Turner 2017).

Ring-opening metathesis polymerization (ROMP) is a method for olefin metathesis reactions. It has been known since the 1950s as a living polymerization technique for polymers chain growth. The mechanism of this method consists of the conversion of cyclic olefins to a polymeric material. The ROMP reactions are catalyzed by transition metal compounds such as tungsten, tantalum, molybdenum, ruthenium, and titanium (Bielawski and Grubbs 2007). Some of the monomers applied in the ROMP are maleic anhydride derivatives. The obtained products are used for development of functionalized unsaturated polymers (Musa 2016).

4.2 Antimicrobial Maleic Anhydride Polymers

4.2.1 Poly(Styrene-Maleic Anhydride)

Poly(styrene-maleic anhydride) is the most common material from antimicrobial maleic anhydride polymers group (Fig. 2).

One of first reports on evaluation of its antimicrobial activity was made by Jeong et al. (2001). The antimicrobial properties were acquired upon introduction of antimicrobial groups to the polymer structure. The unmodified copolymer was synthesized in reaction of styrene and maleic anhydride in anhydrous N, N-dimethylformamide solution with azobisisobutyronitrile as the free radical polymerization initiator. The modification was based on the interaction of the copolymer with 4-aminobenzoic or 4-hydroxybenzoic acid in the presence of triethylamine. Both occurred as a result of the ring opening between the succinic anhydride unit and the active agent. The reactions caused the formation of the amide and ester bond between 4-aminobenzoic and 4-hydroxybenzoic acid, respectively.

The materials were subjected to antifungal tests with *Aspergillus niger* and antibacterial studies with *Escherichia coli* and *Staphylococcus aureus*. The results showed that the pure 4-aminobenzoic acid and 4-hydroxybenzoic acid had higher antifungal activity than the modified copolymers. At the same time, the copolymer sample modified with 4-aminobenzoic acid exhibited 10% fungal growth, while modification with 4-hydroxybenzoic acid resulted in 30% fungal growth. The collected data indicated that the antimicrobial agents release rate driven by hydrolysis was too slow, as the pristine active agents gave better results. The problem could be solved by changing one of the factors such as temperature, pH, or the solution ionic strength.

Outcomes from the antibacterial measurements were more promising. The modified copolymers exhibited excellent antibacterial properties. The *S. aureus* growth reduction was almost 100% for both modifications. The antibacterial action of the 4-hydroxybenzoic acid modified copolymer against *E. coli* was also good; however, the 4-aminobenzoic acid sample caused only 45% reduction. The antimicrobial agents alone eliminated the bacteria with efficiency of 93%.

Jeong et al. (2002) conducted a modification of poly(styrene-*alt*-maleic anhydride) copolymer with 4-aminophenol. The conjugation of the copolymer and the active agents occurred due to the ring-opening reaction.

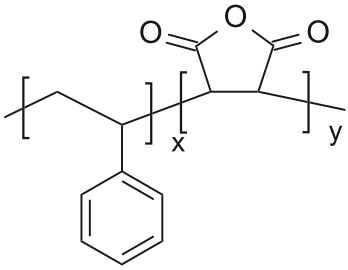

Fig. 2 Poly(styrene-*alt*-maleic anhydride)

Antibacterial experiments were performed with *Staphylococcus aureus* and *Escherichia coli.* In both cases, the pristine 4-aminophenol exhibited a 100% effective antibacterial action. The modified copolymer had a higher activity against *S. aureus* strains (99.9%) than against *E. coli* (95.3%). This was attributed to the longer time needed for the conjugate to diffuse through the pathogen's cellular membrane—in comparison to the time required by the pristine active agent. Furthermore, the copolymer contained only 35% of 4-aminophenol in its structure. Additional tests indicated that 4-aminophenol was not released from the polymer matrix. This suggests that the modified copolymer exhibited its own bactericidal activity related to the presence of phenylic hydroxyl group.

Fang et al. (2009) examined poly(styrene-*alt*-maleic anhydride) derivatives obtained by amidation or hydrolysis in different conditions as anti-HIV agents. All the tests were carried out in in vitro conditions, in accordance with the cellular model. The products showed positive outcomes against the virus. The most promising material was poly[styrene-*alt*-(maleic acid, sodium salt)] which was developed on the way of hydrolysis of poly(styrene-*alt*-maleic anhydride) in the presence of sodium hydroxide.

Cloete et al. (2013) modified poly(styrene-*co*-maleic anhydride) by partial imidization in the presence of 3-dimethylamino-1-propylamine and used it as a waterborne coating component. The product was additionally ammonolyzed to make it soluble in water. The copolymer was then used as a surfactant in emulsion polymerization of styrene and n-butyl acrylate. The final product, latex modified with the copolymer, acquired antibacterial and antifungal properties that were tested in composite bacterial and yeast suspension.

Copolymer of styrene and maleic anhydride is also a potential choice as a carrier for antimicrobial substances. It does not exhibit any teratogenic or toxic effects; it can additionally improve the pharmaceuticals' circulatory half-life as well as their solubility in lipids (Huang and Turner 2017).

Patel et al. (1998) examined the copolymer synthesized in the solution copolymerization as a carrier for covalently bonded acriflavine. The coupling of the active substance was carried out in N,N-dimethylformamide in the presence of triethylamine catalyst. The antimicrobial tests conducted against *Bacillus subtilis* indicated inhibition of the microbes growth due to slow release of the drug from the polymer matrix.

Patel et al. (1999) applied this copolymer as the ampicillin carrier. Poly(styrene-*co*-maleic anhydride) was synthetized in the solution copolymerization in the presence of benzoyl peroxide catalyst. The antimicrobial compound was bounded to the polymer's anhydride groups by amide bond formation in the presence of triethyl amine catalyst. The ampicillin release rate was evaluated in 37 °C during 8 days. The impact of maleic anhydride content in the copolymer on the growth of *E. coli*, *B. subtilis,* and *S. aureus* was determined. The content of maleic anhydride in the polymer had a major influence on the drug release rate and it could be used to control the release; the bacteria growth was inhibited within 8–16 h.

Moghadam et al. (2010) examined the release of ceftriaxone antibiotic from poly (styrene-*alt*-maleic anhydride) and the impact of the bonding type on the release.

Two types of copolymers were prepared: the first one on the way of chemical grafting of ceftriaxone by the amidation reaction between the copolymer's anhydride groups and the antibiotic; the second one by the modification of the copolymer with isopropyl amine what led to formation of poly(styrene-*alt*-maleic anhydride)-isopropyl amide to which the antibiotic was physically loaded. The chemical grafting allowed to achieve higher ceftriaxone release than the physical forces-driven modification.

Khazaei et al. (2013) investigated the release of antiviral amantadine from poly (styrene-*alt*-maleic anhydride). The active component was linked to the copolymer's surface by reaction between its amino groups and the polymer's anhydride groups. The grafting resulted in the formation of the amide bond. The product was suitable for the drug delivery system.

4.2.2 Poly(Methyl Methacrylate-*Co*-Maleic Anhydride)

Patel et al. (1997) used poly(methyl methacrylate-*co*-maleic anhydride) (Fig. 3) as a carrier for antimicrobial acriflavine. The material's synthesis was based on the solution copolymerization of maleic anhydride with methyl methacrylate. The coupling reaction was carried out in dry dimethylformamide in the presence of triethylamine. The performed tests confirmed the active agent release from the polymer matrix and the growth inhibition of *E. coli*, *B. subtilis,* and *S. aureus* after 8–16 h.

Antimicrobial properties of several methyl methacrylate and maleic anhydride copolymers were examined by Abd El-Rehim et al. (2004). The syntheses were carried out under gamma rays irradiation. The copolymers were modified with sulfa drugs, hydroxylamine hydrochloride, and 4-amino salicylic acid, what resulted in the introduction of amino groups into the copolymer's anhydride rings. Antimicrobial tests revealed that the raw copolymer exhibited its own antimicrobial activity against *S. aureus*. The material modified with sulfa drugs, such as sulfanilamide, sulfaguanidine, and sulfaquinoxaline, showed the most significant growth inhibition of *E. coli* and *Candida albicans*.

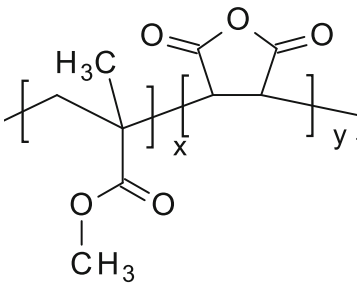

Fig. 3 Poly(methyl methacrylate-*co*-maleic anhydride)

4.2.3 Poly(Maleic Anhydride-*Alt*-Acrylic Acid)

Can et al. (2014) examined the possibility of using poly(maleic anhydride-*alt*-acrylic acid) (Fig. 4) as acriflavine carrier. The water soluble copolymer was obtained through the free radical polymerization process. The reaction was performed in the solution of 1,4-dioxane, and benzoyl peroxide as the radical initiator. Modification of the obtained product with acriflavine was conducted in dimethylformamide in the presence of triethylamine catalyst. The conjugate showed antibacterial properties against enterohemorrhagic *Escherichia coli* (EHEC) and *S. aureus*. However, the results from the antimicrobial tests against *Enterococcus faecium* and *Listeria monocytogenes* indicated unrestricted growth of these bacteria.

4.2.4 Poly(Maleic Anhydride-*Co*-Vinyl Acetate)

Another polymer evaluated for the role of a polymeric carrier for antiexternal fungal acriflavine was poly(maleic anhydride-*co*-vinyl acetate) (Fig. 5). The free radical copolymerization process was applied as the copolymer development method. The reaction between the maleic anhydride and the vinyl acetate took place in methyl ethyl ketone solvent and benzoyl peroxide initiator. Acriflavine was covalently bonded to the copolymer as a result of the amidization reaction. The substrates of the copolymer/acriflavine conjugate were mixed in the ratio of 1:1 and 1:2 for the polymer and the active agent, respectively. The better outcomes were achieved for sample prepared in the 1:1 ratio (Karakuş 2016).

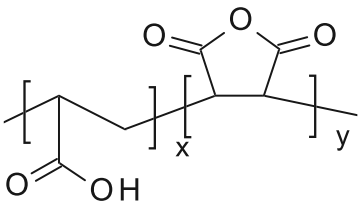

Fig. 4 Poly(maleic anhydride-*alt*-acrylic acid)

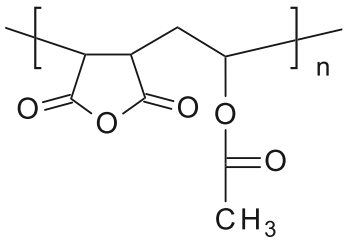

Fig. 5 Poly(maleic anhydride-*co*-vinyl acetate)

4.2.5 N-vinyl Amide/Maleic Anhydride Copolymers

The most widely used antimicrobial polymer from this group is the poly(N-vinyl pyrrolidone-maleic anhydride) (Fig. 6) and its derivatives.

Temiz et al. (2006) investigated N-vinyl pyrrolidone-maleic anhydride copolymers modified with poly(ethylene imine). The raw copolymer was synthesized in the free radical solution copolymerization in 1,4-dioxane with azobisisobutyronitrile as the free radical initiator. The material was hydrolyzed and subjected to the complexation reaction with poly(ethylene imine). Two samples containing different ratios of the copolymer and poly(ethylene imine) were prepared for the tests: the first one consisted of the copolymer and poly(ethylene imine) in 1:1 ratio (COOH/N molar ratio 1:1.5), the ratio in the second one was 1:0.67 (COOH/N molar ratio 1:1). Gram-positive bacteria (*Listeria monocytogenes* and *S. aureus*) and Gram-negative bacteria (*E. coli* and *Salmonella enteritidis*) were chosen for the tests. The materials were unable to inhibit the Gram-negative bacteria growth. However, both modified copolymers possessed antimicrobial activity against the Gram-negative *L. monocytogenes*; in the case of *Staphylococcus aureus*, only the first material, with increased concentration of carboxylic groups, exhibited the desired effect. Hence, the greater the amount of –COOH groups in the polymer structure, the better the antibacterial activity against *S. aureus* strains.

Talu et al. (2010) synthesized a terpolymer consisting of N-vinyl-2-pyrrolidone, maleic anhydride, and N-isopropyl acrylamide. The monomers were mixed during the free radical polymerization in 1:2:1 ratio, respectively. Several terpolymerization reactions were carried out in various reaction time of 6, 12, 24, and 36 h. Evaluation of their antimicrobial activity against six bacterial species: Gram-positive—*S. aureus*, *Streptococcus faecalis* and Gram-negative—*Salmonella enteritidis*, *E. coli*, *Klebsiella pneumoniae,* and *Pseudomonas aeruginosa* showed that all the terpolymers exhibited antimicrobial properties. However, the antibacterial action against the Gram-negative bacteria was weaker compared to the Gram-positive ones. The highest growth reduction was for *S. aureus* strains; the reaction time had an impact on the antimicrobial properties and the materials obtained after 36 h exhibited the highest activity. This phenomenon was attributed to the larger number of carboxylic group in the structure as a result of a longer development process time.

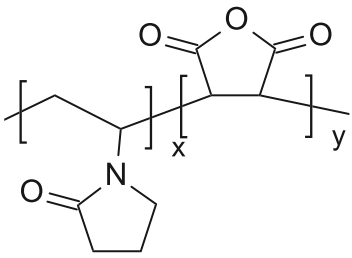

Fig. 6 Poly(N-vinyl pyrrolidone-maleic anhydride)

Hemalatha et al. (2014) modified N-vinylpyrrolidone and maleic anhydride copolymer with N,N-diethylaminoethanol and subjected it to antibacterial tests against four Gram-negative strains: *Klebsiella aerogenes*, *E. coli*, *Pseudomonas aeruginosa*, *Pseudomonas desmolyticum* and one Gram-positive bacteria: *S. aureus*. All the materials exhibited antimicrobial properties for the Gram-negative bacteria, however not for the Gram-positive ones, which was due to a different bacterias' surface response mechanisms.

4.2.6 N-halamine Polymeric Compounds

N-halamine compounds constitute a group of substances with at least one covalent bond between the nitrogen and a halogen such as chlorine or bromine. Their interaction with microbes causes the bond break. As a consequence, the halogen is released causing disruption of the cell and oxidation of the thiol groups in the microbe's cell membrane. Moreover, the N-halamines may be "recharged" which results in their unending antimicrobial activity. Their significance in the antimicrobial field has been growing over the years (Cerkez 2018).

An antimicrobial coating made of branched poly(ethylene imine) and styrene-maleic anhydride copolymer was used to cover the surface of polypropylene pellets (Bastarrachea and Goddard 2015). The antimicrobial tests on *Listeria monocytogenes* were conducted using chlorinated and unchlorinated pallets. The chlorination was necessary as N-halamines-derived coatings possess weak microbe growth inhibition efficiency in their unchlorinated state. Both pellet forms inactivated *L. monocytogenes*. The antibacterial driving force was the unique chemical system consisting of the cationic amine groups and N-halamine forming groups arising from chlorination (Bastarrachea and Goddard 2015). The outcome is in agreement with the conclusions drawn from studies of antimicrobial properties of cationic polymers (Yang et al. 2018). In addition, it was possible to "recharge" the material by means of rechlorination (Bastarrachea and Goddard 2015). Similar results were presented for the coating made of poly(ethylene imine) and styrene-maleic anhydride copolymer against *Escherichia coli* O157:H7 (Bastarrachea and Goddard 2016).

A copolymer of acrylamide and maleic anhydride was chlorinated to convert its amide groups to acyclic N-halamine and was applied as a coating for cotton fabrics (Wang et al. 2019c). The modified copolymer, unlike its unchlorinated version, displayed antimicrobial properties against *S. aureus* and *E. coli.*

4.2.7 Maleic Anhydride Polymers with Quaternary Ammonium Salts

Quaternary ammonium compounds are well-known cationic surfactants which exhibit strong antibacterial and antifungal activity. They consist of a positively charged, quaternary nitrogen atom connected to a hydrophobic tail. In addition,

most of them have four carbon-nitrogen bonds that allow them to carry an indefinite positive charge (Morrison et al. 2019). The quaternary ammonium compounds usually belong to the chloride or bromide salts group, less often iodide salts group (Jiao et al. 2017).

Their antimicrobial properties are connected to the ionic and hydrophobic interactions between the quaternary ammonium compounds, which are positively charged, and the components of the bacteria cell membrane, mostly the heads of the phospholipid bilayers, which are negatively charged. The interactions lead to damage of the membranes and cells' death (Majumdar et al. 2009; Gliścińska et al. 2013; Jiao et al. 2017; Noh et al. 2017; Morrison et al. 2019; Zeng et al. 2020). Due to the efficiency against various pathogens, quaternary ammonium compounds have been widely used as disinfectants and detergents in commercial products (Kenawy et al. 2002; Sauvet et al. 2003; Xue et al. 2015). Nevertheless, the salts are volatile and highly toxic to the environment (Wang et al. 2019b).

It is believed that quaternary ammonium functional polymers are less harmful to mammalian cells and have an increased action selectivity and efficiency. This originates from their higher positive charge density that yields greater affinity for the negatively charged microorganisms' cell membranes (Majumdar et al. 2009). Moreover, the polymeric compounds may be modified with cationic and hydrophobic side chains and therefore display amphiphilicity. It has been reported that amphiphilicity affects the activity of polymers containing quaternary ammonium salts against pathogens (Timofeeva and Kleshcheva 2011). Because of all these properties, quaternary ammonium polymeric compounds have become the research scope for many scientists (Dizman et al. 2004; Majumdar et al. 2009; Wang et al. 2019b).

Conventionally, polymeric materials containing quaternary ammonium compounds can be synthesized by two approaches. In the first one, the post-polymerization, the quaternization of the reactive polymer precursors is conducted. The products may vary in the cationization degree. In the second approach, the monomers containing quaternary ammonium functional groups are copolymerized within the polymer network. The final product has the most functionality; however, its molecular characterization may be a challenging task (Jiao et al. 2017).

Many different antimicrobial polymers with quaternary ammonium salts have been reported and described in the literature, including pyridine quaternary ammonium salt polymer nanocapsules (Zeng et al. 2020), poly(ethylene-*co*-acrylic acid) copolymers grafted with aliphatic quaternary ammonium salts (Noh et al. 2017), polysiloxane copolymers (Sauvet et al. 2003), polyurethane coatings with quaternary ammonium salts (Nurdin et al. 1993), various acrylamide homopolymers and copolymers (Zhang et al. 2015), acrylate homopolymers (Zhong et al. 2017), polystyrenes grafted with different quaternary ammonium groups (Jiang et al. 2006), modified polyvinylpyridines (Tiller et al. 2001), and cationic polycarboxybetaine esters (Zhang et al. 2008).

However, the number of studies and literature reports on maleic anhydride polymers with incorporating quaternary ammonium salts is limited. Wang et al. (2012) developed antimicrobial compounds containing quaternary ammonium salts and

their polymers using natural resin acids which acted as active hydrophobic components. The resin acids were mainly composed of diterpene resin acids. The analysis of the products' bactericidal activity was performed using the disk-diffusion method and tested against various Gram-negative bacteria: *Pseudomonas aeruginosa*, *E. coli*, *Klebsiella pneumoniae*, *Proteus vulgaris*, *Enterobacter agglomerans*, *Salmonella typhimurium*, *Alcaligenes faecalis* and Gram-positive bacteria: *Staphylococcus aureus*, *Bacillus cereus*, *Streptococcus pyogenes*, *Micrococcus luteus*, *Mycobacterium smegmatis*, *Corynebacterium xerosis*. The viability of the bacteria strains has decreased significantly due to the hydrophobicity and the distinctive structure of the materials.

Dominic et al. (2016) presented a novel route for the synthesis of quaternary ammonium dialkyl maleates and their copolymerization with methyl methacrylate. The activity against modified *E. coli*, which showed a resistant behavior against ampicillin, was tested. The atomic force microscopy technique revealed the mechanism behind the activity against the bacteria. The activity was connected to the electrostatic interactions between the bacteria and cationic quaternary ammonium group, and also to the long alkyl chain poking the cell and breaching its membrane. The process resulted in breaking the bacterial cells into pieces. Moreover, the obtained copolymer was degradable.

Ganewatta et al. (2014, 2015) reported the antibacterial properties of surfaces grafted with resin acid derived cationic compounds containing immobilized quaternary ammonium. The surfaces were prepared by the copper-catalyzed azide−alkyne 1,3-dipolar cycloaddition and surface-initiated atom transfer radical polymerization. The antibacterial assay was conducted against Gram-negative *E. coli* and Gram-positive *S. aureus* bacteria strains. A significant change in the cells viability was observed. There was a variation between the biocidal activity against *E. coli* and *S. aureus* which was due to the structural differences—an additional outer cell wall in Gram-negative bacteria. Additionally, the prevention of the biofilm formation was observed, and the minimal cytotoxicity was noted.

Uppu and Haldar (2016) reported the syntheses of antibacterial amphiphilic polymers derived from poly(isobutylene-*alt*-maleic anhydride). First, the polymeric derivative, the poly(isobutylene-*alt*-N-(N′,N′- dimethylaminopropyl)-maleimide) was prepared, then it was modified to obtain alkyl chain quaternized polymers and amide- or ester-quaternized polymers. The final products differed in the structure, molecular weight, as well as the quaternization degree. The goal of the modifications was to form a polymer with a specific function. Its purpose was to imitate the behavior of peptides displaying the antibacterial activity against bacterial endotoxins. Lipopolysaccharide, a major component of the outer wall of Gram-negative bacteria, is one of these endotoxins. The antibacterial activity was tested against *E. coli*, *S. aureus*, and pathogens of increased resistance—Vancomycin-resistant *Enterococci* and Methicillin-resistant *Staphylococcus aureus*. It was revealed that the polymeric derivative alone, when dissolved in water, does not exhibit antibacterial activity and thus the addition of the quaternary compound was

necessary. The results of the biocidal tests have shown that highly hydrophobic polymer was lethal not only to bacteria but also toxic to mammalian cells. On the other hand, highly hydrophilic polymer did not exhibit strong antibacterial properties but was not harmful to mammalian cells. Two compounds with adequate hydrophobicity and hydrogen bonding interactions exhibited effective antibacterial properties without any adverse effects to mammalian cells.

Uppu et al. (2016) presented an easy post-functionalization approach to develop maleic anhydride-based amphiphilic polymers. The synthesis allowed to adjust the amphiphilic properties of the resulting compounds by changing the side chains hydrophobicity. The substrate polymer and the synthesis steps were similar to the Author's previous work (Uppu and Haldar 2016). The four developed polymeric materials showed antibacterial activity against multi-drug resistant *Acinetobacter baumannii* biofilms on surfaces. Moreover, the bacteria did not gain any resistance to the polymeric materials, contrarily as to antibiotics.

Barman et al. (2019a) reported the studies about the activity of amino-acid conjugated polymers against drug-resistant *Acinetobacter baumannii*. Poly(isobutylene-*alt*-maleic anhydride) was used as the starting compound, similar as in the studies conducted by Uppu et al. (2016) and Uppu and Haldar (2016). The resulting materials had diverse activity against the pathogen due to the variation of the amino acid in the polymers. After optimization, the product demonstrated excellent properties against *A. baumannii* and caused the cell death in less than 2 min. Moreover, it showed the ability to remove the previously formed biofilm. No resistance towards the antimicrobial polymer after repeating the passage 14 times was displayed.

In other study, Barman et al. (2019b) developed membrane-active, amino-acid (glycine and L-alanine) conjugated polymers and combined them with a hydrophobic antibiotic—rifampicin. The material was tested against Gram-negative bacteria: *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *E. coli*. The products were similar to the ones obtained in the previous research and based on poly(isobutylene-*alt*-maleic anhydride) and various amino acids. When combined with the antibiotic, the materials exhibited a promising activity against drug-resistant bacteria strains. Also, they did not display any harmful nature towards mammalian cells.

4.3 Concerns About Using Maleic Anhydride Antimicrobial Polymers

The employment of maleic anhydride antimicrobial polymers delivers a great chance of fighting various pathogens including drug-resistant, deadly strains. The need for these materials grows increasingly, hence the amount of research has been and will be thriving as well. It must not be forgotten that the product applicability depends not only on its antibacterial activity but also on other properties that must be considered and evaluated. That includes toxicity against mammalian cells and possible

accumulation in the human body when it comes to drug-carriers systems. Along with that, the biodegradability and stability should be born in mind. In case of surfaces grafted or covered with protective layers of maleic anhydride antimicrobial polymers their abrasive properties need to be analyzed together with UV radiation resistance. The toxicity of these systems is also crucial. Moreover, the optimal adhesive properties of the layers are vital. One of the most important aspects of the material applicability and functionality is its processing technology which should be workable and the price of the final product which cannot be too high.

5 Conclusions

Despite the development of new technologies and the constant progress in medicine, antimicrobial infections are still one of the major threats to the human life. Usage of polymeric materials containing maleic anhydride could be one of the solutions of the problems related to pathogenic microbes and their interactions with people. The group of antimicrobial polymers based on maleic anhydride consists of:

- poly(styrene-maleic anhydride),
- poly(methyl methacrylate-*co*-maleic anhydride),
- poly(maleic anhydride-*alt*-acrylic acid),
- poly(maleic anhydride-*co*-vinyl acetate),
- N-vinyl amide/maleic anhydride copolymers,
- N-halamine polymeric compounds,
- polymers containing quaternary ammonium salts,
- derivatives of the abovementioned materials such as: poly[styrene-*alt*-(maleic acid, sodium salt)], poly(N-vinyl pyrrolidone-maleic anhydride), branched poly (ethylene imine) and styrene-maleic anhydride copolymer, poly(isobutylene-*alt*-N-(N′,N′-dimethylaminopropyl)-maleimide), poly(isobutylene-*alt*-maleic anhydride).

The polymers have been tested as antimicrobial coatings and drug delivery systems. They gave good results with potential applications in health care and in the food packaging industry. Most of the research however, was focused on the antibacterial action and only a few cases examined their antifungal and antiviral activity. Maleic anhydride polymers are promising antimicrobial agents and it can be assumed that the interest in their application will grow in the next years. Nonetheless, there are certain issues that still have to be addressed related to their mechanical properties and the adverse effects they can have in human.

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