Polymer-based materials with biocide activity for biomedical applications

Madalina ZANOAGA, Fulga TANASA
"Petru Poni" Institute of Macromolecular Chemistry, 41A Grigore Ghica Voda Alley, Iasi, Romania
zanoaga@icmpp.ro

***Abstract* — Polymer and material science has had a major impact on our day-to-day life. Telecommunications, automotive and aero-space industry, medicine and health care, agriculture and leisure are just a few domains significantly affected by the development of polymeric materials. An area of great current interest in terms of polymer R&D is that of polymers with biocide activity designed and produced for biomedical applications. For example, in the field of medicine and health care, biocide polymers may be incorporated, or even extruded, into fibers and used for contact materials (such as sterile bandages and clothing). The use of polymers with biocide activity is promising for enhancing the efficiency of some existing antimicrobial agents and for minimizing the environmental problems associated to conventional biocide agents by reducing their toxicity, increasing their activity and selectivity, prolonging their lifetime. In comparison with low molecular antimicrobials, these biocide polymeric materials have some advantages: they are nonvolatile, chemically stable and do not permeate through skin, they can contribute to the reduction of losses through volatilization, photolytic decomposition, transportation, etc. This paper offers an overview of some recent data concerning the synthesis and characteristics of some polymer-based materials with biocide activity designed for biomedical applications.**

***Index Terms* — biocide activity, biomedical applications, polymeric materials.**

I. INTRODUCTION

Microbial infection remains one of the most serious complications in medical devices, drugs, health care and hygienic applications, general and dental surgery equipment, as well as in water purification systems, textiles, food packaging and food storage [1-3]. Antimicrobials gain interest from both academic and industry due to their potential to provide quality and safety benefits to many materials. Low molecular weight antimicrobial agents have serious limitations and disadvantages, such as toxicity to the environment and short-term antimicrobial activity. To overcome these problems, polymer-based materials with biocide activity were employed. The use of such materials offers promise for enhancing the efficiency of some existing antimicrobials, designing and producing of new biocide materials, and minimizing the environmental problems by reducing the residual toxicity of these agents, increasing their efficiency and selectivity, and prolonging the lifetime. Research concerning the development of polymeric materials with biocide activity represents a great challenge for both the academic community and industry.

Therefore, there is a definite need for new materials to respond to specific challenges. In principle, the ideal solution is a method for rendering biomaterials resistance towards microorganisms. Antimicrobial polymers can provide a very convenient way for achieving this goal.

An area of polymer and material science research that presents great current interest, and yet has received insufficient attention, is that of the development of polymers with biocide activity. In the field of health care and hygienic applications, biocide polymers may be incorporated into fibers, or possibly extruded into fibers themselves, and used as contact disinfectants and sterile materials in many biomedical applications, such as septic dressings, bandages and clothing. For example, antimicrobial surgical gowns and antifungal polymeric coatings (cast on surfaces such as shower walls and various piping) can minimize the problems of bio-fouling and the release of pathogens into streaming fluids [4].

Polymeric materials with biocide activity have the advantage that they are non-volatile and chemically stable and do not permeate through skin. Therefore, they can reduce losses associated with volatilization, photolytic decomposition, and transportation [5-9]. In the field of polymers used for biomedical applications, infections associated with inserted biomaterials [10] are a significant challenge and the most common cause of the implant failure. The polymer-based materials with biocide activity will act towards reducing the rate of such incidents [11]. Even more, catheters made of polymers able to slowly release an antibiotic could save many patients subjected to post-implant infections. Antimicrobial polymers could also fight against infections around permanent implants, such as pacemakers. In the field of natural and polymer-based textiles for medical applications, research was aiming to develop new products with biocide finishes, such as materials sterilized by using dry/wet heat or radiation (UV, ionizing radiation) [12].

Significant progress has been made in the past few decades in the design, synthesis and characterization of polymers to be used for preventing microbial attack and decay in biomedical applications [13]. One very effective method of achieving biocide activity in polymer-based materials is to add an organic or inorganic biocide to the polymers during processing [4, 14]. Another option is to endow a biocide activity to the polymer after processing [4, 15, 16]. A different approach is the design of polymers bearing functional groups with biocide activity starting

from monomers containing reactive groups able to undergo (co)polymerization or (co)polycondensation processes [4, 17-22]. The grafting of antimicrobials onto natural or synthetic polymers is another pathway toward new biocide materials [23-25].

The basic requirements to design polymer-based materials with biocide activity, factors affecting their antimicrobial activity, synthetic strategies to obtain biocide polymeric materials and their prospects for future development are summarized in the present paper.

II. PRINCIPLES FOR THE DESIGN OF BIOCIDE POLYMERIC MATERIALS

1. Basic Requirements

The ideal antimicrobial polymeric material should have the following characteristics: (1) it is easily and inexpensively synthesized, (2) displays stability in long-term use, as well as for storage, at the temperature of its assigned application, (3) it is insoluble in water in the case of the water disinfection application, (4) it doesn`t decompose and it is not producing toxic by-products, (5) it shows no toxicity or irritating effect upon use, (6) it can be regenerated after depletion, (7) it has biocide activity toward a wide range of pathogens in short intervals [26].

2. Factors that Influence the Biocide Activity

The biocide activity of polymer-based materials designed for biomedical applications and their mechanism of activity are significantly influenced by structural and functional factors (such as molecular weight, distance between reactive moieties on the polymer chain, the hydrophilic/hydrophobic balance), as well as by vicinity (nature of counter ions) [27, 28].

2.1. Molecular Weight. Many research groups have studied the influence of the molecular weight on the biocide activity, due to its important role. The antimicrobial activity of acrylate monomers containing biguanide groups in the side-chain (Fig. 1) and their homopolymers and copolymers with acrylamide was investigated [29, 30] and conclusions indicated that biocide efficiency against *S. aureus* strongly depends on the molecular weight.

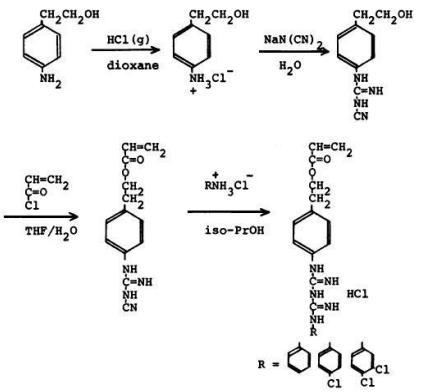

Fig. 1. Acrylic monomers with biguanide groups

The optimum was reached for molecular weights ranging between $5x10^4$ and $1.2x10^5$ Da. For values below $5x10^4$ Da, the biocide activity increased with molecular weight, but above $1.2x10^5$ Da it decreased sharply. Still, the evaluation of antibacterial activity of the polymeric biguanides is complicated by the fact that they interact with some constituents of culture media. In a clean system with no interfering materials (such as negatively charged macromolecules), the polymeric biguanides are much more active than the monomeric species. The higher activity of polymers may be accounted for by their stronger interactions with the cell wall and the bacteria cytoplasmic membrane, as the primary process of the biocide action.

In the case of poly(trialkyl-vinyl-benzylammonium chloride) (Fig. 2) [31], it was found that the antimicrobial properties toward *S. aureus* increased monotonically with the molecular weight up to $7.7x10^4$ Da.

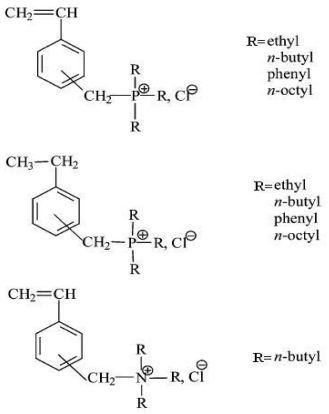

Fig. 2. Quaternary phosphonium and ammonium salts with biocide activity

By comparing the activity against various types of microorganisms (*S. aureus*, *B. subtilis*, *E. coli*, *A. aerogenes*, *P. aeruginosa*), the study revealed that it remotely depends on the molecular weight.

The dependency of biocide activity of poly(tributyl-4-vinylbenzyl phosphonium chloride) (Fig. 3) on molecular weight was also studied against *S. aureus* in saline solutions [32]. Thus, it was shown that the antibacterial properties increased with the molecular weight from $1.6x10^4$ to $9.4x10^4$ Da.

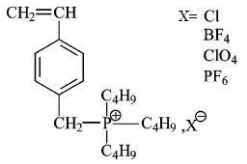

Fig. 3. Structure of the monomeric tributyl(4-vinylbenzyl)phosphonium salt

As a common feature of biocide activity of polycations already presented, a sequence of elementary processes can be described: adsorption of polymeric biocide onto the microbial cell surface, diffusion through the cell wall, adsorption onto the cytoplasmic membrane, disruption of the cytoplasmic membrane, leakage of the cytoplasmic constituents and, finally, the cell death. Since the bacterial cell surface is negatively charged (as evidenced by its susceptibility to electrophoresis), the polycations adsorption onto cell surface is expected to take place to a greater extent than the corresponding monomers [33-36].

Dendrimers of quaternary ammonium functionalized poly(propylene-imine)s (Fig. 4) were investigated [37, 38]

and their biocide activity vary with the molecular weight by a parabolic curve.

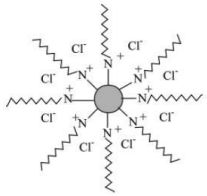

Fig. 4. Second generation of poly(propyleneimine) dendrimer quaternary ammonium biocides

In contrast with these results, it was reported that bacteriostatic activity of copolymers of vinylamine, methyl acrylate and *N*-vinyl pyrrolidone with pendant quaternary ammonium groups showed no dependency on their molecular weight [39]. In order to explain this opposite behaviour, it is necessary to consider the bacteria structure. It is well known that bacteria are divided into two groups, Gram-positive (such as *S. aureus*) and Gram-negative (such as *E. coli*), based on their cell wall properties. Gram-positive bacteria have a cell wall more susceptible to be penetrated, while Gram-negative bacteria have an additional barrier in the cell wall structure.

Most of the above-presented studies were dealing with *S. aureus* and indicated that polymers with molecular weight up to $5x10^4$ to $9x10^4$ Da diffused easily across the cell wall of this Gram-positive bacterium. For Gram-negative bacteria, such as *E. coli*, the diffusion through the cell membrane is more complicated due to the cell wall supplementary protection.

2.2. Length of the Macromolecular Chain (spacer length). The biocide activity of a polymeric material depends on the distance between reactive moieties (spacer length) through changes in both conformation and charge density of the polymer, which consequently affect the interaction with the cytoplasmic membrane [26].

For a polymeric quaternary ammonium chloride biocide, the hydrophilic-lipophilic balance influences the antimicrobial properties [27]. Same for poly(trialkyl-vinyl-benzyl ammonium chloride) for which the biocide activity was the highest for the longest chain (12 carbon atoms) studied [28]. Other materials, such as perfluoro-propylated and perfluoro-oxa-alkylated end-capped 2-(3-acrylamido-propyl-dimethyl ammonium) ethanoate (APDMAE) (Fig. 5) were synthesized and characterized in relation to *S. aureus* and *P. aeruginosa* and proved to be more effective toward both pathogens when the macromolecular chain was at the maximum extent [40].

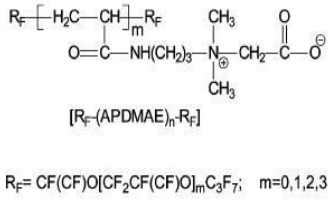

Fig. 5. Structure of APDMAE monomers

Copolymers of methacryloyl-ethyl trialkyl phosphonium chlorides/*N*-isopropylacrylamide (METR NIPA Am) (Fig. 6) showed increasing biocide activity against *E. coli* along with the increasing of the alkyl chain between two consecutive phosphonium groups [41, 42].

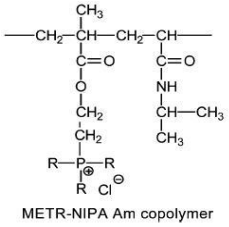

Fig. 6. Copolymer METR-NIPA Am

Therefore, it can be stated that the relationship between biocide activity and alkyl spacer length depends on the binding affinities of short *versus* long chains at the target site, as well as on the different aggregation behavior of these long/short spacers [26].

2.3. Effect of Counterion. Basically, the biocide activity of polymer-based materials depends on their vicinity in terms of counterions, due to their ability to form ion pairs of different strength and the capacity to generate free ions [26]. In the case of some polymeric phosphonium salts [21], the activity against *S. aureus* was proved to be low for a counterion which generates strong ion pairs. Thus, antimicrobial properties depend on various counterions in the following sequence: chloride > tetraflouride > perchlorate > hexafluorophosphate, and it can be related to the polymers solubility. Still, due to the conflicting results in the literature (*e. g.*, homopolymers of vinylamine and methyl methacrylate with pendent quaternary ammonium groups showed no effect of counter anions such as chloride, bromide and iodide on their antibacterial activity [37]), the mechanism of counterions influence is not yet completely lightened, but it can be assumed that they alter the polymers solubility [26].

III. SYNTHETIC STRATEGIES TO OBTAIN BIOCIDE POLYMERIC MATERIALS

Polymeric materials with biocide activity represent a serious alternate option in terms of biomedical applications, especially when it comes to expected benefits: enhancing the activity and lowering toxicity, increasing the selectivity and prolonging their active time. There are various strategies to obtain such materials, but the most used are: synthesis of biocide moieties bearing monomers able to undergo subsequent (co)polymerization; grafting antimicrobial units onto natural or synthetic polymers; synthesis of biocides as part of polymers able to be submitted to controlled degradation and gradual release of bioactive segments.

3.1. Synthesis of Monomers Bearing Biocide Moieties. Biocide agents that contain reactive functional groups, such as hydroxyl, carboxyl or amino groups [26], can be covalently linked to a wide variety of monomers able to undergo subsequently (co)polymerization processes. The most common monomers and their corresponding polymers are the acrylic type compounds. Their main advantages are: they can be easily (co)polymerized; they can bear different hydrophilic/hydrophobic segments useful for biomedical applications. Some of the recent advances in this field

[43-61], namely monomers containing biocide units, are presented in Fig. 7.

These (co)polymers may be used not only as antimicrobials, but as drug carriers as well, even for drugs controlled delivery. Different factors, such as structural (the nature of the α-heteroatom in the biocide unit – P, N, S), physical (crystalline character, solubility) or chemical (the nature of co-monomers, method of synthesis, reaction conditions), are significantly affecting the biocide activity of the final compound.

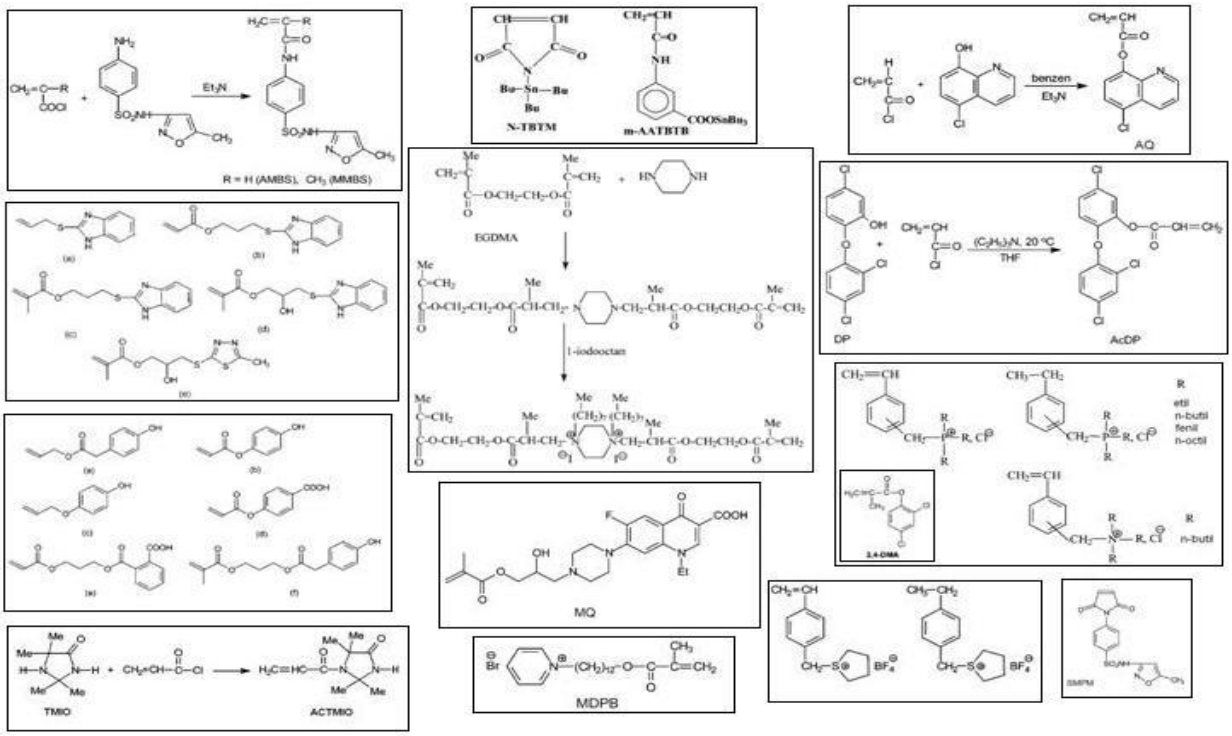

Fig. 7. Monomers bearing biocide units

An interesting feature of these materials is the biocide activity may be more intense in homopolymers than in the corresponding copolymers.

3.2. Grafting Antimicrobial Units onto Natural or Synthetic Polymers. Biocides can be immobilized onto a wide variety of pre-formed synthetic (co)polymers, even dendrimers or micelles.

Cross-linked copolymers based on copolymerization of vinylbenzyl chloride either with 2-chloroethyl vinyl ether or with methylmethacrylate, using divinylbenzene as a cross-linker, were reported [62]. The cross-linked copolymers were further modified by quaternization with triphenylphosphine and triethyl-amine. Other polymers having phenolic moieties were prepared by the reaction of amine-functionalized copolymers with *p*-hydroxybenzoic acid, 2,4-dihydroxy-benzoic acid and 3,4,5-trihydroxy-benzoic acid [63]. Poly(ethylene-co-vinylalcohol) containing a 2-benzimidazolecarbamoyl moiety was synthesized and its activity against pathogens was studied [2]. It was also reported the synthesis of poly (styrene-*co*-maleic anhydride) with surface-containing functional anhydride groups of different percentage by solution polymerization. The biocide compound, containing ampicilin, was obtained by a coupling reaction [64]. Poly(styrene-*co*-maleic anhydride) was used as a carrier for active agents containing amino- or hydroxyl groups [65].

Polymeric quaternary "onium" salts is the class of the antimicrobial polymers that has received, probably, the most attention. Water-soluble polymers having a phosphonium group were synthesized starting from methacryloyloxyethyl trialkyl phosphonium chloride and *N*-isopropylacrylamide [41]. The copolymer with octyl-containing substituents in phosphonium groups was found to have a high antibacterial activity against *E. coli*. However, there is no report about the antimicrobial properties of the monomer itself to compare with the copolymers.

A series of statistical copolymers derived from 2-(dimethylamino)ethyl methacrylate with four different hydrophobic monomers (ethyl, butyl, cyclohexyl and octyl
methacrylates) [66] were prepared via free radical copolymerization and then modified with 1,3-propanesulphone. The antimicrobial activity of the sulphopropylbetaine copolymers was tested against *S. aureus* and *E. coli*, it mainly depends on the copolymer composition and pathogen. Polymeric phosphonium salts with side-chains of different length between the main chain and the reactive group were prepared [26]. *E. g.*, poly[4-(2-tributylphosphonioethyl) styrene chloride-*co*-4-(2-chloro-ethyl)-styrene], poly[4-(3-tributyl-phosphoniopropyl)-styrene chloride-*co*-4-(3-chloropropyl)styrene. Glycidyl methacrylate (GMA)-based copolymers bearing quaternary ammonium groups were prepared by treating GMA-1,4-divinylbenzene copolymer beads with hydrogen chloride and then reacting with various amines, such as triethylamine, N,N-dimethyloctylamine, N,N-dimethyl-dodecylamine, and N,N-dimethylhexadecylamine) [67]. Similarly, a

copolymer system based on GMA and a divinylbenzene-bearing phosphonium group was prepared [68]. The synthesis of quaternary phosphonium salts grafted on an insoluble gel-type styrene-7% divinylbenzene copolymer was reported [69].

Recent advances in polymer chemistry provide new materials for biomedical applications. Dendrimers are novel highly branched three-dimensional [70]. They can be tailored as to possess uniform or discrete functionalities, tunable inner cavities, surface reactive moieties, different size and molecular weight and solvent interactions.

The fourth generation 4 poly(propyleneimine) dendrimer bearing -NH_2 end groups (Fig. 8) has attracted much attention as a potential biocide due to its compact structure and availability of many end groups.

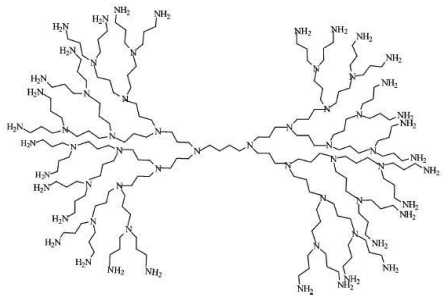

Fig. 8. The structure of the poly(propyleneimine) amine-terminated dendrimer (4-th generation)

Polymers with general structure of polystyrene triazinediones were synthesized from commercial polystyrene [71-73] and it was found they are highly effective against *S. aureus*.

Recently, a very interesting comparison between some polymeric materials containing quaternary ammonium moieties and N-chlorinated polymers has been reported [73]. The results showed that N-chlorinated polymeric beads were much more effective against *S. aureus* and *E. coli* than polymeric quaternary ammonium salts.

A series of hydantoinyl/quat siloxane biocide copolymers containing both N-halamine and quaternary salt groups simultaneously [74] were synthesized and it was proven copolymers are adequately soluble in water as to be used for coating cotton swatches.

Polyelectrolites were also considered for such applications. Thus, it was reported on the antimicrobial behaviour of polyelectrolyte multilayer films, based on polyethyleneimine (PEI), poly(acrylic acid) (PAA), containing cetrimide and silver (AgNO3) [75].

Other antimicrobial materials resulted from modified polyacrylamide by introducing an amino group in the side chain of the polymer through the reaction with ethylenediamine [76]. The corresponding polymer was reacted with two different classes of reagents: aromatic aldehydes containing active groups (such as *p*-hydroxy-benzaldehyde, vanillin, *p*-chlorobenzaldehyde, anisalde-hyde) and phenolic ester derivatives (such as *p*-hydroxy-methylbenzoate, 2,4-dihydroxymethylbenzoate, 2-hydroxy-methylbenzoate, 3,4,5-trihydroxypropylbenzoate).

Various copolymers were prepared by the copolymerization of 2-chloroethylvinyl ether with vinyl-benzyl chloride [77]. Subsequently, copolymers were quaternized by reaction with triethylamine, triphenyl-phosphine and tributylphosphine. The phosphonium-containing polycationic biocides were more effective than quaternary ammonium salts.

As for the naturally occurring polymers, chitosan, alginate, dextran were considered for biomedical applications, as well as natural fibers. Chitosan, a de-acetylated product of chitin, has many interesting properties, such as antimicrobial activity and nontoxicity. It contains an amine group at C2, which is important because amino groups are nucleophilic and readily react with electrophilic reagents. Chitosan modified under mild conditions is regioselective. Many attempts have been made to use chitosan in the alimentary, cosmetic, textile, medical and pharmaceutical industries [78].

Hydrogel membranes with biocide activity were obtained from a chitosan-alginate sponge with high stability and superabsorbent properties [79] able to be used to effectively suppress bacterial proliferation to protect wounds from bacterial invasion.

N-alkyl chitosan derivatives were prepared by introducing alkyl groups into the amine groups of chitosan, via a Schiff's base intermediate [80]. Quaternization of the *N*-alkyl chitosan derivatives with methyl iodide produced water-soluble cationic polyelectrolytes. The antimicrobial activities of the chitosan quaternary ammonium salts increased with the increase in the chain length of the alkyl substituent and this may be ascribed to the contribution of the increased lipophilic properties of these derivatives. Chitosan and quaternized chitosan were functionalized by grafting onto acrylic acid modified poly(ethylene terephthalate) [81]. Their high biocide efficiency against *S. aureus* is attributed to the possibility of the chitosan release from the PET surface, which also become a limit of these materials activity.

Two anionic monomers, mono(2-methacryloyloxy-ethyl)acid phosphate and vinylsulfonic acid sodium salt (VSS), were grafted onto chitosan to obtain copolymers with zwitterionic properties [82]. These polymers showed antimicrobial activity dependent on the pH: when the pH varied to 6.2, the biocide activity decreased to 10-15%.

Another modified chitosan, *N*-(2-hydroxy)propyl-3-trimethylammonium chitosan chloride, synthesized by the reaction of glycidyl trimethylammonium chloride and chitosan [83], showed excellent antimicrobial activity, higher than the unmodified chitosan, due to the quaternary ammonium groups.

New polymeric materials, derivatives of dipyridyl, were synthesized by the reaction of chloroacetylated cross-linked dextran microparticles with dipyridyl compounds (such as 4,4'-dipyridyl, *N*-*n*-octyldipyridinum chloride, *N*-benzyldipyridinum) [84].

Ion exchange fibers, containing quaternary ammonium, phosphonium or thiol groups, were prepared by graft copolymerization of vinyl monomers on loofah natural fibers [85]. They displayed high absorption capacity toward silver ions, so, silver modified loofah fibers were also obtained. The biocide activity of these materials was tested against *E. coli* and *S. aureus*. The effect is expected to be a combination of mechanisms due to the quaternary ions and silver ions adsorbed on fibers.

Biologically active moieties were reacted with the aminic groups of chitosan to yield antimicrobial chitosans. Specifically, vanillin, p-hydroxybenzaldehyde, p-chloro-benzaldehyde, anisaldehyde, methyl 4-hydroxybenzoate, methyl 2,4-dihydroxybenzoate, propyl 3,4,5-trihydroxy-benzoate and 2-hydroxymethylbenzoate were attached [86]. Their biocide activity may be due to the presence of phenolic hydroxyl groups.

3.3. Biocides as Products of Polymer Hydrolysis. Biocides can be included into polymers main chains using different synthetic approaches in order to obtain bonds able to be submitted to controlled hydrolysis and gradual discharge of fragments with antimicrobial activity. Polymers fit for such strategy are, as a general rule, the polycondensates (polyamides, polyesters, polyurethanes) [26, 87]. Still, polyketones, prepared by reacting benzene, chloroacetyl chloride, 1,2-dichloroethane and dichloro-methane [88], proved to be effective biocides. Drugs can also be incorporated into polymers backbone, as shown with a drug-polymer model compound [89] synthesized using 1,6-hexane diisocyanate (HDI), polycaprolactone diol (PCL) and a fluoroquinolone antibiotic, namely ciprofloxacin. The degradation products with ciprofloxacin bonded to fragments of PCL and HDI did not display biocide activity. Another known antimicrobial agent, bithionol [2,2'-thio-bis(2,4-dichlorophenol)] [90], reacted with phosgene and yielded in bischloroformate; then, it was used to synthesize alternating copolycarbonates, polyurethanes or copolycarbonate/polyurethane. There was no specific antimicrobial study reported for these polymers. Therefore, it is necessary to continue research in this field.

IV. PROSPECTS FOR FUTURE DEVELOPMENT

Polymeric disinfectants are ideal for water purification applications because they can be fabricated by various techniques and made insoluble in water. Antimicrobial polymers are powerful candidates for polymeric drugs with high activity. Quaternary ammonium compounds act like polycations and have high absorption and biocide properties. Implants of cross-linked amylase starch containing various ratios of ciprofloxacin were already used. Natural fibers or electrospun polymer-based fibers with biocides were prepared to be used as antimicrobial wound dressings (Fig. 9).

Fig. 9. Antimicrobial wound dressings

Textiles and fibrous materials are subjected to various finishing techniques to afford: (a) protection for the user of against bacteria, yeast, dermatophytic fungi, and other related microorganisms for aesthetic, hygienic or medical purposes; (b) protection of the textile itself from biodegra-dation caused by mold, mildew and rot-producing fungi; (c) protection for textiles from insects and other pests (Fig. 10).

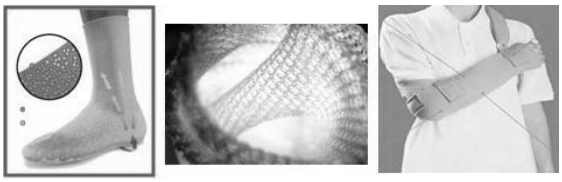

Fig. 10. Prophylactic biocide materials

Prophylactic medical shoes for diabetes and arthritis use biocids in order to avoid bacteria and fungi growth, control microorganisms contamination and proliferation, prevent infections and bad odours, protect shoes from degradation under microorganisms attack.Antimicrobial substances incorporated into packaging materials can control microbial contamination by: reducing the growth rate and maximum growth population, and/or extending the lag phase of the target pathogens, or by inactivating the microorganisms by direct contact.

Future work should focus on the development of new polymeric materials with biocide activity to be used not only for biomedical and health care applications, but for soil sterilization also, in order to replace the toxic materials currently in use, such as methyl bromide. Participation and collaboration of research institutes, industry and government regulatory agencies will be the key factor for the future success of these polymeric materials.

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