Biomacromolecules

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# Reviews

## The Chemistry and Applications of Antimicrobial Polymers: A State-of-the-Art Review

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Microbial infection remains one of the most serious complications in several areas, particularly in medical devices, drugs, health care and hygienic applications, water purification systems, hospital and dental surgery equipment, textiles, food packaging, and food storage. Antimicrobials gain interest from both academic research and industry due to their potential to provide quality and safety benefits to many materials. However, low molecular weight antimicrobial agents suffer from many disadvantages, such as toxicity to the environment and short-term antimicrobial ability. To overcome problems associated with the low molecular weight antimicrobial agents, antimicrobial functional groups can be introduced into polymer molecules. The use of antimicrobial polymers offers promise for enhancing the efficacy of some existing antimicrobial agents and minimizing the environmental problems accompanying conventional antimicrobial agents by reducing the residual toxicity of the agents, increasing their efficiency and selectivity, and prolonging the lifetime of the antimicrobial agents. Research concerning the development of antimicrobial polymers represents a great a challenge for both the academic world and industry. This article reviews the state of the art of antimicrobial polymers primarily since the last comprehensive review by one of the authors in 1996. In particular, it discusses the requirements of antimicrobial polymers, factors affecting the antimicrobial activities, methods of synthesizing antimicrobial polymers, major fields of applications, and future and perspectives in the field of antimicrobial polymers.

### 1. Introduction

Contamination by microorganisms is of great concern in a variety of areas, such as medical devices, healthcare products, water purification systems, hospitals, dental office equipment, food packaging, food storage, household sanitation, etc.[1,2] Bacterial contamination of biomedical devices, for example, permanent catheters or implants, is a major problem in those medical disciplines employing biomaterials.[3]

The use of long-term catheters can lead to serious implant-associated infections.[4] In fact, medical implants account for nearly one-half of all nosocomial infections. These infections are especially serious because bacteria that are often resistant to multiple antibiotics usually cause them. Resolution of these infections usually requires removal of the implant. Because the success of treatment in these cases is poor, emphasis has been placed on ways to prevent catheter-related infections. Infection in sites such as the brain or cerebrospinal fluid (CSF) can be more serious, because many antibiotics cannot effectively cross the blood−brain barrier to achieve therapeutic concentrations.

Antimicrobial agents are those materials capable of killing pathogenic microorganisms.[5] Antimicrobial agents of low molecular weight are used for the sterilization of water, as antimicrobial drugs, as food preservatives, and for soil sterilization.[6] However, they can have the limitation of residual toxicity even when suitable amounts of the agent are added.[7,8]

Various kinds of plastics are usually sterilized by means of either dry/wet heat, or ionizing radiation.[9] However, these polymers can be contaminated or infected by microorganisms such as bacteria if they are exposed to the atmosphere. Therefore, there is a definite need for new materials with

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antimicrobial activities. It is apparent that, in principle, the ideal solution of this problem is a method for rendering biomaterials resistant to microbial colonization. Antimicrobial polymers can provide a very convenient way for achieving this goal.

An area of polymer research that presents great current interest, yet has received insufficient attention, is that of the development of polymers with antimicrobial activities, generally known as polymeric biocides. In the area of health care and hygienic applications, biocidal polymers may be incorporated into fibers, or possibly extruded into fibers themselves, and used for contact disinfectants in many biomedical applications such as sterile bandages and clothing. For example, antimicrobial surgical gowns and antifungal polymeric coatings on surfaces such as shower walls and many kinds of tubing minimize the problems of biofouling and the release of pathogenic microorganisms into streams of flowing fluids.[10]

The use of antimicrobial polymers offers promise for enhancing the efficacy of some existing antimicrobial agents and minimizing the environmental problems accompanying conventional antimicrobial agents by reducing the residual toxicity of the agents, increasing their efficiency and selectivity, and prolonging the lifetime of the antimicrobial agents. Also, polymeric antimicrobial agents have the advantage that they are nonvolatile and chemically stable and do not permeate through skin. Therefore, they can reduce losses associated with volatilization, photolytic decomposition, and transportation. In the field of biomedical polymers, infections associated with biomaterials represent a significant challenge to the more widespread application of medical implants.[11−15] Infection is the most common cause of biomaterial implant failure in modern medicine. Antimicrobial polymers play an important role in reducing the incidences of such failures. Catheters made from a polymer that slowly releases an antibiotic could save the lives of many hospital patients who are subjected to infections every year. Antimicrobial polymers could also thwart infections around more permanent implants, such as pacemakers. In the field of textiles, work has been performed with the aim of developing new textile products with antimicrobial finishes for medical applications. Significant advances in the past three decades have been made in the synthesis and applications of polymers to prevent microbial attack and degradation for diverse end uses.[16]

One method of achieving antimicrobial polymers is to add an organic or inorganic biocide to the polymers during processing of the material.[10,17]

Another method is to endow a biocidal function to the polymer after processing.[10,18,19] A different approach for the preparation of polymers bearing groups with antimicrobial activity is the preparation of polymerizable monomer-containing biocide moieties and then polymerizing subsequently or copolymerizing with another monomer.[10,20−26] The grafting of antimicrobial agents into natural occurring or synthetic polymers is yet another approach to the problem of the preparation of bioactive materials with a potential use in various applications.

The current review is focused on the recent developments in the field of antimicrobial polymers primarily over the past 10 years and subsequent to the previous review of Worley and Sun.[10] The review is organized into sections discussing the basic requirements, factors affecting the antimicrobial activity of the polymer, and the various approaches and major applications of the antimicrobial polymers.

## 2. Basic Requirements for Antimicrobial Polymers

The ideal antimicrobial polymer should possess the following characteristics: (1) easily and inexpensively synthesized, (2) stable in long-term usage and storage at the temperature of its intended application, (3) not soluble in water for a water-disinfection application, (4) does not decompose to and/or emit toxic products, (5) should not be toxic or irritating to those who are handling it, (6) can be regenerated upon loss of activity, and (7) biocidal to a broad spectrum of pathogenic microorganisms in brief times of contact.

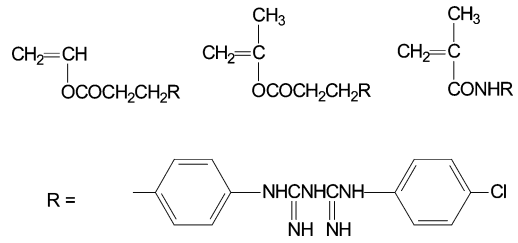



**Figure 1.**

## 3. Factors Affecting the Antimicrobial Activity

There are many factors for antimicrobial polymers that can affect their antimicrobial activity and mechanism of activity such as molecular weight, spacer length between active site and polymer, hydrophilic−hydrophobic balance, and nature of counterions.[27,28]

**3.1. Effect of Molecular Weight.** The molecular weight plays an important role in determining the antimicrobial properties. Therefore, many research groups have studied the molecular weight dependence. Ikeda and his co-workers investigated the antimicrobial activity of homopolymers of polyacrylates and polymethyl acrylates with side-chain biguanide groups and their copolymers with acrylamide (Figure 1).[29,30]

They found that the biocidal action of the polymethyl acrylate with pendent biguanide groups against *S. aureus* was markedly dependent on the molecular weight.

A molecular weight region between $5 \times 10^4$ and $1.2 \times 10^5$ Da was optimal for the required action. When the molecular weight was lower than $5 \times 10^4$ Da, the antimicrobial property increased with molecular weight, while the antibacterial activity decreased sharply with the increase of the molecular weight of the polymer over $1.2 \times 10^5$ Da. The dependence of antimicrobial properties was explained on the basis of the permeability through the cell wall. The molecular weight dependence of poly(trialkylvinylbenzylammonium chloride) (Figure 2) against *S. aureus* was also evaluated.[31]

The bactericidal properties were found to increase monotonically with molecular weight up to $7.7 \times 10^4$ Da, the highest molecular weight tested during the study. However, bacteriostatic activities of the fractionated polymeric quaternary ammonium salts against *S. aureus*, *B. subtilis*, *E. coli*, *A. aerogenes*, and *P. aeruginosa* were shown to have little molecular weight dependence.

Kanazawa and co-workers[32] investigated the molecular weight dependence of poly(tributyl 4-vinylbenzyl phosphonium chloride) (Figure 3) against *S. aureus* in saline solution and discovered that the antibacterial properties increased with the increase of molecular weight from $1.6 \times 10^4$ to $9.4 \times 10^4$ Da.

The higher antimicrobial activity of the polymers may be accounted for by the contribution of the polymers to each elementary process in the cidal action. For example, the sequence of elementary events in the lethal action of the cationic biocides may be considered as follows:[29] (1) adsorption onto the bacterial cell surface, (2) diffusion through the cell wall, (3) adsorption onto the cytoplasmic membrane, (4) disruption

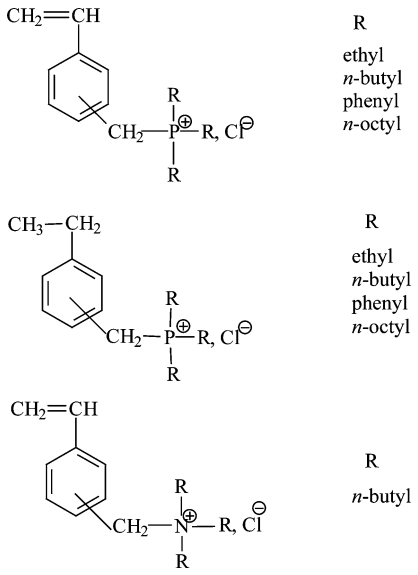



**Figure 2.** Structures of some quaternary ammonium and phosphonium salts with bioactivity.

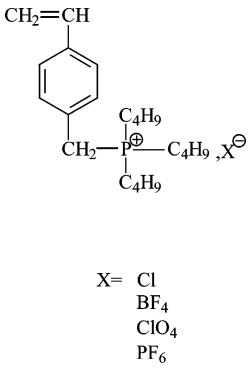



**Figure 3.** Tributyl(4-vinylbenzyl)phosphonium salt monomer.

of the cytoplasmic membrane, (5) leakage of the cytoplasmic constituents, and (6) death of the cell.

It is well known that the bacterial cell surface is usually negatively charged as evidenced by its susceptibility to electrophoresis. Adsorption of polycations onto the negatively charged colloidal surface is expected to take place to a greater extent than that of monomeric cations. Therefore, it is reasonable to assume that in the elementary process step (1) is enhanced for polymers as compared to that for monomers.

Ikeda and co-workers synthesized polycationic biocides with pendent phosphonium salts and compared their antibacterial activity with the corresponding monomers (Figure 2). They also demonstrated that the activity is increased in the order of increasing molecular weight.[25,29,33−36]

Chen and co-workers synthesized quaternary ammonium-functionalized poly(propyleneimine) dendrimers (Figure 4).[37]

They found that the antimicrobial properties of these dendrimer biocides have parabolic dependence on molecular weight. Tokura and co-workers[38] found similar results.

A very interesting comparison of small molecule biocides, polymer biocides, and dendrimer biocides with regard to their interactions with bacteria is quantitatively summarized in Table 1.[37]

However, Panarin and co-workers reported that the bacteriostatic properties had no molecular weight dependence for their copolymers of vinylamine, methyl acrylate, and *N*-vinyl pyrrolidone with pendent quaternary ammonium groups.[39] To explain properly the discrepancy of the trends in these data,

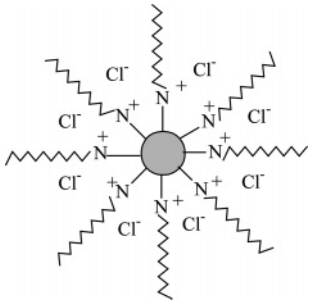


**Figure 4.** Generation 2 poly(propyleneimine) dendrimer quaternary ammonium biocides with eight QAC groups on the surface.

**Table 1.** Comparison among Molecules Biocides, via Their Interaction with Bacteria

| step | small molecule biocides | polymer biocides | dendrimer biocides |
|---|---|---|---|
| (1) initial adsorption | weak | strong | strong |
| (2) diffusion to the cytoplasmic membrane | high | low | medium |
| (3) binding to the membrane | low | medium | high |
| (4) disruption and disintegration of the membrane | low | medium | high |

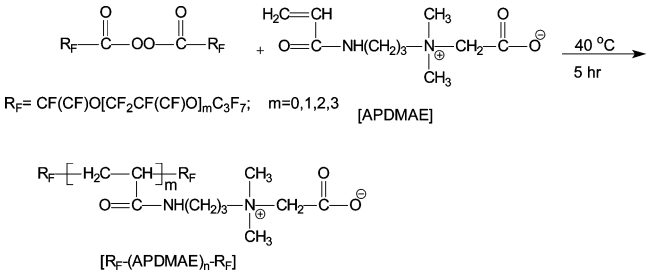
one needs to take into consideration the bacteria structure. Depending on the sophistication of the cell wall structure, bacteria can be divided into two classes, Gram-positive (e.g., *S. aureus*) and Gram-negative (e.g., *E. coli*). Gram-positive bacteria tend to have a loose cell wall, while Gram-negative bacteria have an outer membrane structure in the cell wall forming an additional barrier for foreign molecules. Most of the investigations that were summarized above deal with the molecular weight dependence on *S. aureus* eradication. Studies indicated that molecules with molecular weight up to $5 \times 10^4$ to $9 \times 10^4$ Da do not seem to have problems diffusing across the cell wall of the Gram-positive bacterium *S. aureus*. For Gram-negative bacteria, such as *E. coli*, the question of diffusion to the cell membrane is even more complicated due to the existence of an outer membrane.

**3.2. Effect of Counterion.** Kanazawa and co-workers investigated the counteranion dependence of poly[tributyl(4-vinylbenzyl)phosphonium] salts (Figure 3) against *S. aureus*. The antibacterial activity was found to be affected by the structure of the counter anions.[20] The activity was low for a counteranion, which tends to form a tight ion-pair with phosphonium ion, while it was high for those facilitating ionic dissociation to free ions. The antimicrobial properties were in the order of chloride > tetraflouride > perchlorate > hexafluorophosphate, which could be correlated with the solubility products of the polymers.

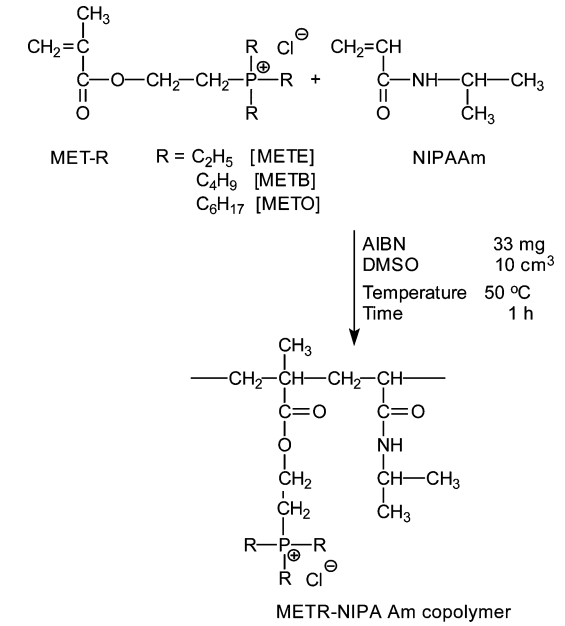
The antimicrobial activity of the quaternary ammonium dendrimers synthesized by Chen et al. showed dependence on the counterion. They found that the biocides with bromide anions are more potent than those with chloride anions.[37] However, the work carried out by Panarin and co-workers on the synthesis of homopolymers of vinylamine and methyl methacrylate with pendent quaternary ammonium groups showed no effect for counter anions on the antibacterial activities among chloride, bromide, and iodide.[39] It is not clear why counterions should have an effect on antimicrobial activity except where they alter solubilities of their host polymers.

**3.3. Effect of Spacer Length and Alkyl Chain.** It is quite reasonable that the antimicrobial activity is dependent on the

**Scheme 1.** Reaction of 2-(3-Acrylamidopropyldimethylammonio) Ethanoate [APDMAE] with Fluoroalkanoyl Peroxides




**Scheme 2.** Synthesis of METR-NIPAAm Copolymer




spacer length due to the change in both conformation and charge density of the polymer, which consequently affect the mode of interaction with the cytoplasmic membrane.[27] For a polymeric quaternary ammonium chloride biocide, the hydrophilic−lipophilic balance influences the antimicrobial properties. Although Panarin et al.[39] discovered that the antimicrobial activities of their polymers did not show differences with different chain lengths, Ikeda et al. studied poly(trialkylvinylbenzylammonium chloride) and discovered that the antimicrobial activity was the highest with the longest chain ($C_{12}$) that they investigated.[28]

Sawada and co-workers prepared perfluoro-propylated and perfluoro-oxaalkylated end-capped 2-(3-acrylamidopropyldimethylammonio)ethanoate (APDMAE) (Scheme 1).[40]

These fluorinated APDMAE polymers have been evaluated for their antibacterial activities against *S. aureus* and *P. aeruginosa*. It was found that prefluoro-oxaalkylated APDMAE polymer, because of its longer chain, was more active against both *S. aureus* and *P. aeruginosa*.

Recently, Nonaka and co-workers synthesized methacryloylethyl trialkyl phosphonium chlorides/*N*-isopropylacrylamide copolymers (Scheme 2).

They found that the antibacterial activity of the copolymers against *E. coli* was increased with increasing the alkyl chain length in the phosphonium groups in the copolymer.[41,42] Rationalization of the parabolic relationship between antibacterial properties and alkyl chain lengths has been debated. It has been attributed to (1) dual binding sites on the surface for which the relative binding affinities at each site differ for long and

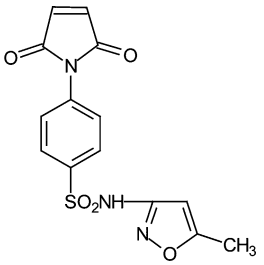
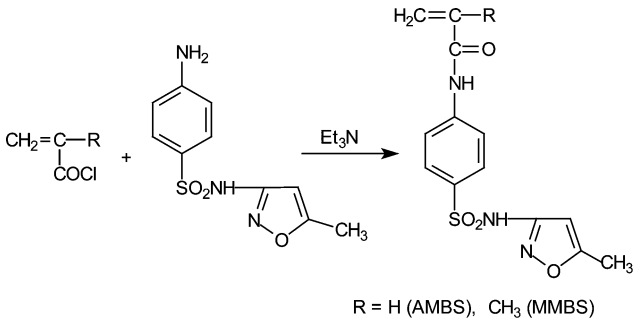


**Figure 5.** Structure of monomer SMPM.

**Scheme 3**




short alkyl substituents or (2) different aggregational behavior for long and short hydrophobes.[37]

## 4. Preparation and Activities of Antimicrobial Polymers

By attaching bioactive substrates to synthetic or naturally occurring macromolecules, it is expected to increase their therapeutic efficiencies while lowering their potential toxicities. Various approaches, which can achieve this attachment, are discussed as follows.

**4.1. Preparation of Polymerizable Monomer-Bearing Groups with Antimicrobial Activity.** Antimicrobial agents that contain reactive functional groups such as hydroxyl, carboxyl, or amino groups can be covalently linked to a wide variety of polymerizable derivatives. Most of the synthesized drug monomers and their polymers are acrylic types of pharmaceutically active compounds. The advantages of acrylic-type drug conjugate monomers are that these can be copolymerized to vary the drug concentration and that they can be used to prepare different hydrophilic/hydrophobic functionalities in the polymer drug conjugates for different purposes in the pharmaceutical industry.

In this context, Reddy et al.[43] synthesized antimicrobial drugs containing monomers (AMBS, MMBS) by reacting acryloyl chloride and methacryloyl chloride with 4-amino-*N*-(5-methyl-3-isoxazolyl)benzenesulfonamide in the presence of triethyl amine, Scheme 3.

Another monomer, *N*-[4-sulfamido-*N*-(5-methyl-3-isoxazolyl)-phenyl]maleimide (SMPM) (Figure 5), was prepared by reacting maleic anhydride with 4-amino-*N*-(5-methyl-3-isoxazolyl)benzenesulfonamide.

The three monomers were polymerized using benzoyl peroxide as a free radical initiator under nitrogen atmosphere at 70 °C. The polymers were soluble in DMSO, DMF, and THF and insoluble in nonpolar solvents. The antifungal screenings of these monomers and their polymers were achieved for two fungi, *A. niger* and *C. albicans*. The authors used a method to measure the zone of inhibition of monomers and polymers. Zone of inhibition is generally a circular zone around the antimicrobial polymer or the antibiotic, for example, in which growth of the microorganism susceptible to the tested material is inhibited.

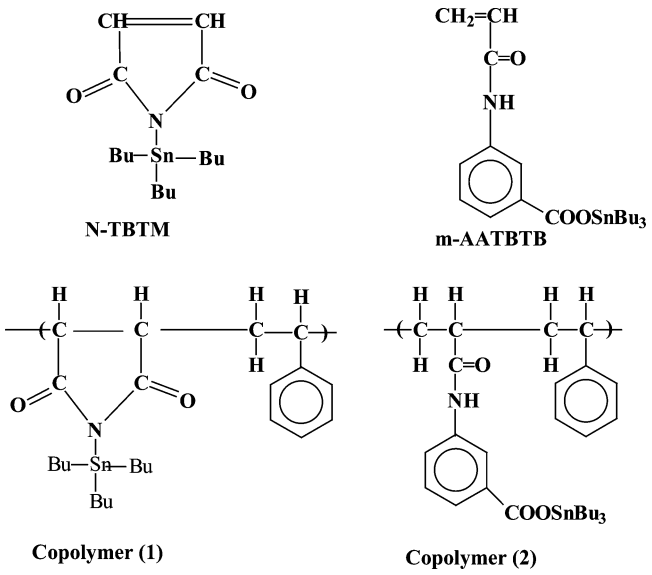



**Figure 6.** Monomers and copolymers based on N-TBTM and m-TBTM.

The zone of inhibition of different concentrations of monomers and polymer conjugates reveals that SMPM and its polymer poly(SMPM) have significant antifungal activities with both *C. albicans* and *A. niger*. The polymer−drug conjugate showed superior anti-microbial activity over the monomer at all concentrations. There are no data concerning the mode of actions of these polymers reported by the authors; however, they may function as a drug delivery system by slowly releasing the drug to the media.

Al-Diab and co-workers[44] have recently reported the synthesis of two novel organotin monomers, (*N*-tri-*n*-butyltin)maleimide (N-TBTM) and *m*-acryloylamino-(tri-*n*-butyltinbenzoate) (m-AATBTB) (Figure 6).

Copolymerization of these two monomers with styrene was carried out in bulk at 65 °C in sealed tubes under nitrogen atmosphere using azobisisobutyronitrile as the free radical initiator (Figure 6). The antibacterial activities of the synthesized organotin monomers and copolymers toward various types of Gram-positive and Gram-negative bacteria were investigated after 24 h contact time. The results showed that Gram-positive bacteria were more sensitive to the two monomers (m-AATBTB and N-TBTM) and their styrene copolymers than were the Gram-negative bacteria. They also reported that copolymerization of monomers with styrene decreased the potency of the monomers (m-AATBTB and N-TBTM) against Gram-positive and Gram-negative bacteria. This is expected due to the decrease of active functional groups in the polymer chain by introducing styrene, which has no antimicrobial activity in the chain. The authors did not discuss the mode of actions of these materials, but it could be due to the presence of the tin moiety on the polymer surface, which may interact with the cell wall leading to the death of the microorganism.

Moon and co-workers synthesized vinyl acryl monomers with azole moieties (Figure 7).[45]

Polymerization of monomers a−e (Figure 7) was attempted. However, only polymerization of 2-hydroxy-3-(5-methyl-1,3,4-thiadiazol-2-yl)thiopropyl methacrylate (Figure 7e) was successful in giving the corresponding polymer (Figure 8). It is interesting to observe that the polymer was a more effective antibacterial agent than was the monomer after 24 h contact. No report on the mode of action of these materials is described, but it might be due to the presence of the bezimidazole

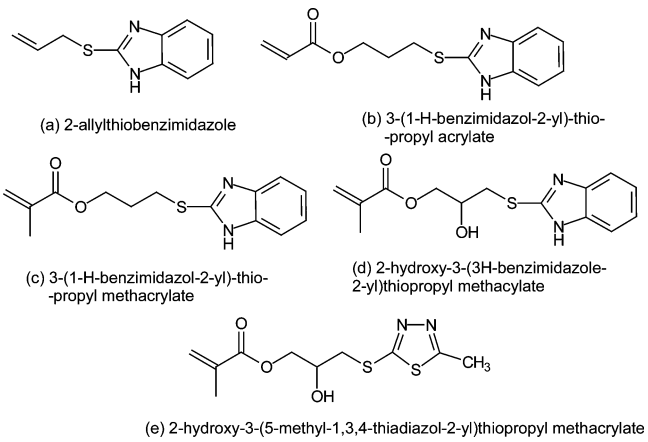



**Figure 7.** Structure of monomeric biocides.

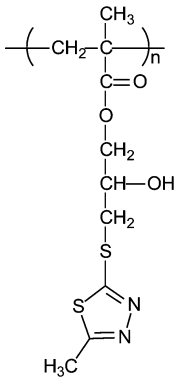


**Figure 8.** Structure of the polymeric biocide synthesized from 2-hydroxy-3-(5-methyl-1,3,4-thiadiazol-2-yl)thiopropyl methacrylate.

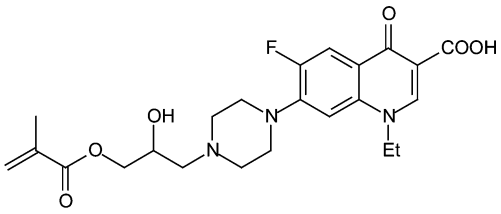


**Figure 9.** Structure of MQ.

derivatives, which are proposed to inhibit the cytochrome P-450 monooxygenase.

Recently, the same group reported the synthesis of monomers containing the quinoline moiety, 1-ethyl-6-fluoro-7-{4-[2-hydroxy-3-)2-methylacryloyloxy)propyl] piperazin-1-yl}-4-oxo-1,4-dihydroquinolin-3-carboxylic acid (MQ) (Figure 9).[46] The quinoline-containing monomer was polymerized by a free radical polymerization technique with azobisisobutyronitrile (AIBN) as an initiator in dimethylformamide solution.

The antibacterial activity of the monomer MQ against Gram-positive as well as Gram-negative bacteria was explored by the shake-flask method,[46] which is one of the testing methods commonly used for evaluating the biocidal activity of materials. The results indicated that it was antibacterial after 24 h contact time. The antimicrobial activity of the polymer PQ, synthesized by the polymerization of MQ, was determined, and the results indicated that it was a reasonably potent antimicrobial agent. This polymer could be functioning as a drug delivery system, releasing the norfloxacin, which is known to inhibit bacterial DNA gyrase and cell growth.

Cho et al.[23,47] reported the synthesis of the bactericidal monomer 2,4,4′-trichloro-2′-acryloyloxydiphenyl ether (AcDP) from acryloyl chloride and 2,4,4′-trichloro-2′-hydroxydiphenyl

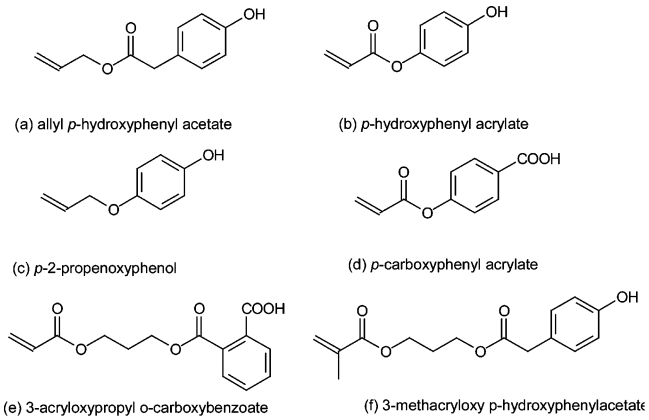



**Figure 10.**

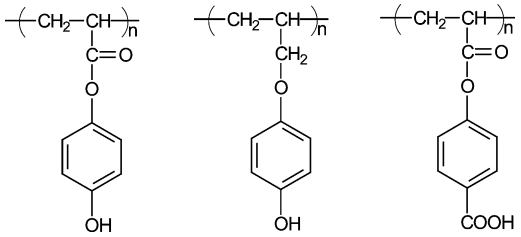


**Figure 11.**

ether (DP) in the presence of triethylamine in dry tetrahydrofuran (THF) at 20 °C (Scheme 4).

The AcDP monomer was either homopolymerized or copolymerized with methylmethacrylate (MMA), styrene (St.), or acrylic acid (AA).[23,47,48] The antimicrobial activities of the monomer AcDP and the prepared copolymers were tested against *Pseudomonas aeruginosa* and *Staphylococcus aureus*. The results showed a general trend that the monomer was more active toward the test organisms than were the homopolymer and copolymers. The results of these studies indicated clearly that the hydrophilicity of the copolymer affects the antibacterial activity.

Vinyl monomers with phenol and benzoic acid as pendent groups were synthesized by Park and co-workers (Figure 10).[49]

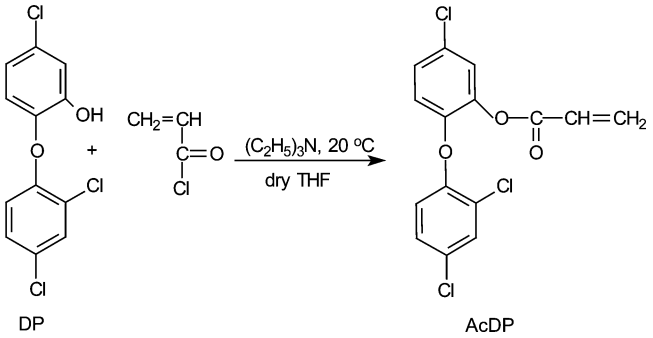
Some of these monomers were polymerized (Figure 11). The antimicrobial activities of the polymers were explored using the halo zone test after a contact time of 72 h at 28 °C. Surprisingly, the polymerization of the monomers decreased their antimicrobial activities significantly.

The above-mentioned authors stated that, even though the antimicrobial activity of the polymers is much lower than that of the corresponding monomers, they could be coated on glassy polymers. The concentration of antimicrobial agent on the coated polymeric material surface could be higher than that on the surface of the polymer compound with low molecular weight antimicrobial agent showing identical or even superior antimicrobial activity.

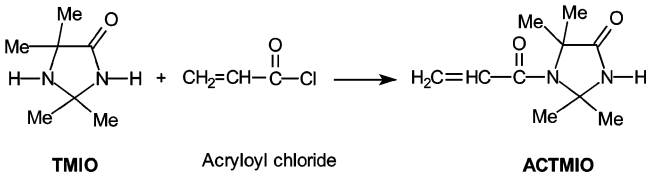
Recently, a relatively new class of biocidal polymers known as cyclic *N*-halamines demonstrated superior properties including biocidal efficacy, long-term stability, and rechargeability once the efficacy had been consumed during use. Several such materials have been prepared and tested for antimicrobial properties.[50−53]

Sun and co-workers reported the synthesis of cyclic amine monomer, 1-acryloyl-2,2,5,5-tetramethylimidazolidin-4-one (ACTMIO) (Scheme 5), by the reaction of acryloyl chloride with 2,2,5,5-tetramethylimidazolidin-4-one (TMIO).[54]

**Scheme 4.** Synthesis of AcDP




**Scheme 5**

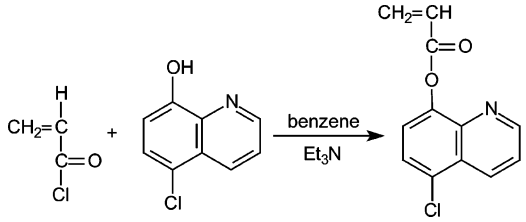



The monomer (ACTMIO) was copolymerized with several monomers such as acrylonitrile (AN), methyl methacrylate (MMA), and vinyl acetate (VAC). After regular chlorine bleach treatment, *N*-halamine derivatives of the corresponding polymeric materials exhibited antimicrobial properties against *Escherichia coli*, and these properties were durable and refreshable with chlorine bleaching. The results of biocidal efficacy for the halogenated polymers showed that PVAC-*co*-ACTMIO provided 99.9% reduction of *E. coli* after 30 min of contact, whereas for PMMA-*co*-ACTMIO and PAN-*co*-ACTMIO, the reduction provided was 99% and 90%, respectively, for the same time of contact. The halogenated polymers were tested for biocidal efficacy against *E. coli* in forms of films or powders. The results showed that the powdered halogenated copolymers demonstrated a total kill against *E. coli* at a flow rate of 0.2−0.6 mL/min, while the polymer films needed a contact time of less than 30 min to perform the total kill. No significant differences could be noticed in the antibacterial properties for the copolymers, indicating the similar functions possessed by the *N*-halamine structures.[55] It was reported that if the halogenated polymers were stored at 25 °C for 3 months, the antibacterial properties of the samples did not essentially change. This indicated that the polymers possessed proper stability in the dry state and that the *N*-halamine structures in all of the polymer samples were very stable. The mode of action of the *N*-halamine polymers is described as direct transfer of oxidative halogen ($Cl^+$ or $Br^+$) from the *N*-halamine nitrogen to the cell wall of the organism by direct contact followed by oxidation, rather than dissociation of $X^+$ into water followed by diffusion over to a cell.

It is known that 8-hydroxyquinoline derivatives have antimicrobial activity.[56] Bankova and co-workers reported the synthesis of 5-chloro-8-quinolinyl acrylate (AQ) by reacting 5-chloro-8-hydroxyquinoline with the acid chloride of acrylic acid (Scheme 6).[21,22]

The monomer AQ was polymerized (PAQ) and copolymerized with acrylic acid (PAA-*co*-AQ). The antimicrobial activities of AQ, PAQ, and P(AA-*co*-AQ) were tested against *E. coli*, and the results showed that AQ is more active than the homopolymer and the copolymer.[21] The antimicrobial activities here are displayed by the release of 8-hydroxyquinoline (HQ) moieties; the release studies showed correlation between the copolymer microstructure and hydrolysis behavior. The lower

**Scheme 6.** Synthesis of 5-Chloro-8-quinolinyl Acrylate (AQ)



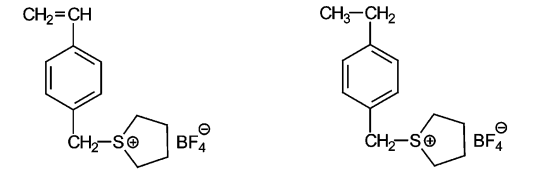

is the content of the HQ, the higher is the release rate, and the higher are the antimicrobial activities. In these kinds of antimicrobial polymers, the antimicrobial activities should increase with time due to the release of more active agent; however, after a certain time, they may become inactive because of releasing the entire active ingredient. In a subsequent publication, the same group reported the synthesis of other copolymers based on the monomer AQ.[24] They reported the synthesis of copolymers of monomer AQ with acrylamide P(AM-*co*-AQ) and *N*-vinyl-2-pyrrolidone P(VP-*co*-AQ). The antimicrobial activities of the monomer AQ, the homopolymer PAQ, and the prepared copolymers P(VP-*co*-AQ), P(AM-*co*-AQ), and P(AA-*co*-AQ) were tested against *S. aureus* and *S. tiphimurium*. In general, the antimicrobial activities of the tested materials increased in the order: P(VP-AQ) < P(AM-*co*-AQ) < P(AA-*co*-AQ). Increasing the acrylic acid content of the copolymer P(AA-*co*-AQ) to 95% caused an increase in the antibacterial activity of the copolymer to be almost similar to that of the monomer AQ.

Endo and co-workers reported the synthesis and the antibacterial activity of polymeric sulfonium salts to explore the effect of α-heteroatoms on the antibacterial activity of polymeric onium salts.[25] The polymeric sulfonium salt was obtained by polymerization of *p*-vinylbenzyltetramethylenesulfonium tetrafluoroborate (Figure 12) at 60−80 °C in acetonitrile with AIBN as an initiator.

Polymeric sulfonium salts exhibited a high antibacterial activity against Gram-positive bacteria. It was found that the activity of the polymeric sulfonium salts was much higher than that of the model compound, *p*-ethylbenzyl tetramethylene sulfonium tetrafluoroborate. However, the use of the sulfonium salts as disinfectants may be rather limited because of their low thermal stability.

Imazato et al.[57,58] prepared a new monomer, methacryloyloxydodecyl pyrimidinium bromide (MDPB) (Figure 13). A water-soluble homopolymer of MDPB and copolymer of MDPB with acrylamide were prepared (Figure 14). The bactericidal activity against oral *Streptococci* was investigated. However, cured resin incorporating MDPB, which is a water-insoluble form, had little bactericidal activity. Higher concentrations of the MDPB were more effective; for example, a concentration of 500 $\mu$g mL$^{-1}$ killed 99.999% within 1 min, while at 100 $\mu$g mL$^{-1}$, even after 480 min, the killing was slow. The mechanism of action for these quaternary compounds is believed to be due to the direct cationic binding to cell wall components, which leads to disruption of the cell wall membrane, and subsequently leads to leakage of critical cell contents and cell death.

Mathias et al.[35] synthesized new methacrylate monomers containing pendent bi-quaternary ammonium moieties based on (DABCO) [1,4-diazabicyclo-[2.2.2]-octane] (Figure 15).[35] The monomer was prepared by reacting DABCO with bromoalkanes such as with butyl and hexyl chains to be attached to one nitrogen of DABCO. The other nitrogen of DABCO was treated with 11-bromoundecanoic acid. The carboxylic group of the produced product was transferred to sodium salt by reacting it




*p*-Vinylbenzyl tetramethylene sulfonium tetrafluoroborate

*p*-Ethylbenzyl tetramethylene sulfonium tetrafluoroborate

**Figure 12.** Structure of some sulfonium salts.

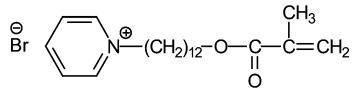
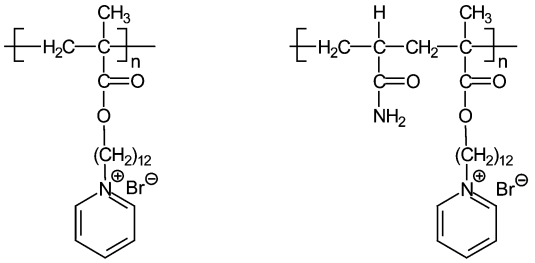


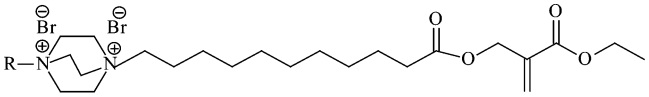

**Figure 13.** Structure of MDPB.




Homopolymer of MDPB

Co-po lymer of MDPB with acrylamide

**Figure 14.** Homo-polymer of MDPB, and copolymer of MDPB with acrylamide.



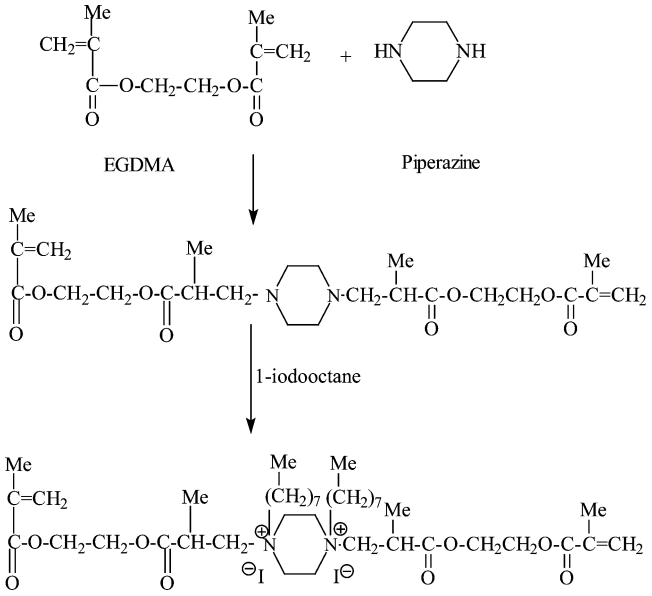

R= -$CH_2(CH_2)_2CH_3$ or -$CH_2(CH_2)_4CH_3$

**Figure 15.** Methacrylate monomers containing pendent quaternary ammonium moieties based on 1,4-diazabicyclo-[2.2.2]-octane (DABCO).

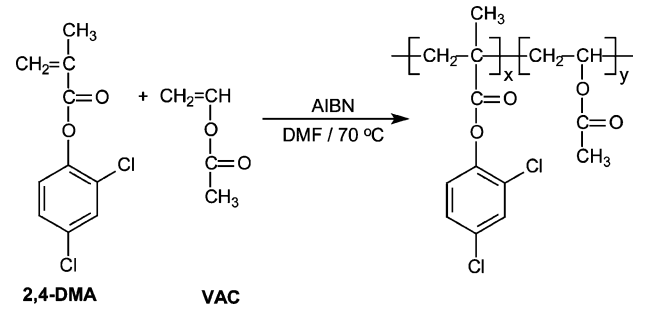
with $K_2CO_3$. The salt was reacted with ECMA (ethyl α-chloromethyl acrylate) to yield the methacrylate monomer with two quaternary ammonium groups (Figure 15). The monomer was polymerized by free radical polymerization. The antimicrobial activities of the prepared polymers were screened against *S. aureus* and *E. coli* as test organisms. The results showed that the monomers were not active against the test organisms, while the polymers showed moderate activities against the test organisms in polymer concentrations ranging from 1 mg/mL to 3.9 $\mu$g/mL. The minimum inhibitory concentration (MIC) value for the polymer with the butyl group was 250 $\mu$g/mL, while this value was reduced to 62.5 $\mu$g/mL with increasing the alkyl chain length to 6 carbons as in the case of the hexyl group. The lethal actions of these biocides are believed to follow the mode of action of cationic biocides, as they target the cytoplasmic membranes. It is believed that the incorporation of the DABCO group into the polymer might enhance its diffusion into the cell wall due to similarities of the polymer pendent group and the lipid layer. As a result, there is a combination of both ionic and van der Waals interactions, which should increase the binding of the polymers to the cytoplasmic membrane of the bacteria.

Singh et al.[59] described the synthesis of iodine containing quaternary amine methacrylate copolymers. The monomers were synthesized via a two-step reaction: the first step was the reaction of ethylene glycol dimethacrylate (EGDMA) with piperazine in methanol at 35 °C for 6 h. The second step was

**Scheme 7.** Synthesis of Quaternary Amine Methacrylate (QAMA)




**Scheme 8.** Synthesis of Poly(2,4-dichlorophenylmethacrylate-*co*-vinyl Acetate)




the quaternization of the synthesized monomer with 1-iodooctane (Scheme 7). The quaternized monomer was copolymerized with 2-hydroxyethyl methacrylate (HEMA) by free radical polymerization using ammonium persulfate and *N*,*N*,*N*′,*N*′-tetramethyl ethylenediamine as a redox initiator. Copolymers with various ratios of the quaternized monomers (QAMA) were synthesized. The antimicrobial activities of the QAMA containing copolymers were evaluated against *E. coli* and *S. aureus*. The results showed that all of the bacteria were killed by the next day after the incubation. In case of 40% content of QAMA in the copolymer, only a contact time of 10 min was required to show 100% kill. It was observed that increasing the QAMA content in the copolymer reduced the contact time required for killing *E. coli*.

Endo and co-workers described the synthesis and polymerization of trialkyl-3-[(and 4-)vinylbenzyl]phosphonium chloride (Figure 2) by reaction of 3- (and 4-) chloromethylstyrene with trialkylphosphine. The polymerization was carried out in toluene at room temperature under an atmosphere of nitrogen.[33,60] Low molecular weight model compounds of similar structure were synthesized (Figure 2). The results of the antibacterial activity study showed that the polymers, in general, were more active than the corresponding model compounds.

Patel and co-workers synthesized homo- and copolymers from 2,4-dichlorophenyl acrylate (2,4-DMA).[1] The monomer 2,4-DMA was prepared by reacting methacryloyl chloride and 2,4-dichlorophenol. Homo- and copolymers of 2,4-DMA and vinyl acetate (VAC) were prepared in DMF using 2,2′-azobisisobutyronitrile (AIBN) as an initiator (Scheme 8).

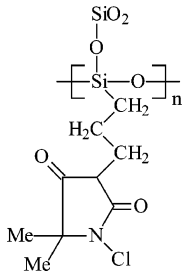


**Figure 16.**

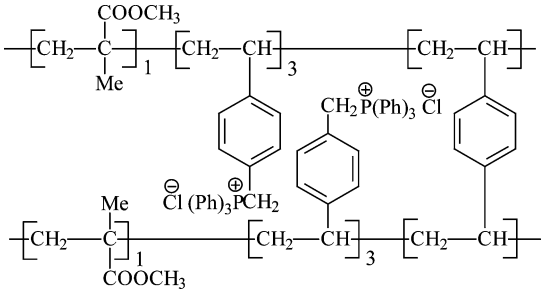


**Figure 17.**

The antimicrobial activities of the homopolymer and copolymers were evaluated against bacterial strains (*B. subtilis*, *E. coli*, and *S. citreus*), fungi (*A. niger*, *S. pulverulrmtum*, and *T. lignorum*), and yeasts (*C. utilis*, *S. cerevisiae*, and *P. stipitis*). The results showed that the antibacterial activity of the homopolymer corresponded to the lowest growth (20%), and the other copolymers exhibited 20−38% growth. The antifungal and the anti-yeast activities of the homopolymer showed 18−38% growth. The authors did not report antimicrobial activity for the monomer.

The monomer 3-triethoxysilylpropyl-5,5-dimethylhydantoin has been described and polymerized by the Worley group.[61]

It was polymerized on the surfaces of sand particles to produce an adhered film that, upon chlorination with dilute sodium hypochlorite bleach, became biocidal (Figure 16). The biocidal efficacy of this coated sand has been demonstrated in a cartridge filter experiment against the bacterial pathogens *Staphylococcus aureus* and *Escherichia coli*. Complete inactivation was observed within 1 min of contact for the former bacterium and in the interval of 1−5 min for the latter. Upon a loss of biocidal activity due to the depletion of bound chlorine, the coated sand particles could be recharged by further exposure to dilute bleach. Potential uses of biocidal sand include disinfection and odor control in water treatment facilities and recirculating baths.

**4.2. Immobilized Antimicrobial Agent on Synthetic Preformed Polymers.** The synthesis of cross-linked copolymers based on copolymerization of vinylbenzyl chloride (VBC) either with 2-chloroethyl vinyl ether (CEVE) or with methylmethacrylate (MMA), using divinylbenzene (DVB) as a cross-linker, was reported.[62] The cross-linked copolymers were further modified by quaternization with triphenylphosphine (Figure 17) and triethylamine.

The antimicrobial activities of the modified copolymers were evaluated against various microorganisms (*Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis*, *Aspergillus flavus*, *Fusarium oxysporum*, and *Candida albicans*). The antimicrobial activities of the modified copolymers were also evaluated against *C. albicans* SC5314, *A. flavus*, and *F. oxysporum* as fungal organisms. It was found that the diameter of the inhibition zone varied according to the active group in the copolymer and also

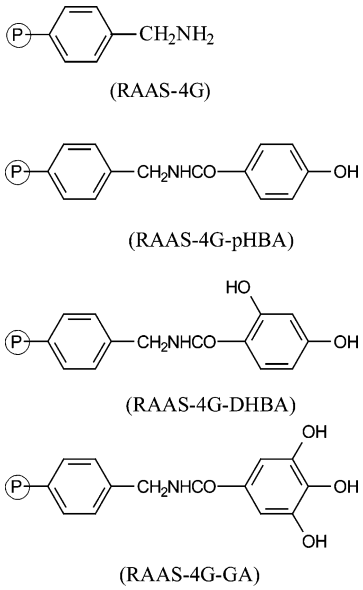



**Figure 18.**

the examined microorganism. In general, the copolymers showed antimicrobial activity against the tested microorganisms. However, the compound with the triphenylphosphonium salt of the modified copolymer was the most effective against bacteria and fungi species. A concentration of 20 mg/mL of triphenylphosphonium salt of the modified copolymer killed 100% of *C. albicans*. However, this polymer activity toward *A. flavus* was lower and gave 44% of the organism surviving at 20 mg/mL. Although the polymer shown in Figure 17 has very interesting structural features and a facile synthesis, the test method described was not the best way to evaluate these polymers. It would be preferable to pump the inocula through a column filter containing the polymer to ensure maximum contact and accurate contact time measurements.

Some polymers containing an antimicrobial pharmacophore can be prepared by the chemical anchoring of the pharmacophore to the polymers. The polymers having phenolic hydroxyl moieties were prepared by the reaction of amine-functionalized copolymers (RAAS-4G) with *p*-hydroxybenzoic acid, 2,4-dihydroxybenzoic acid, and 3,4,5-trihydroxybenzoic acid (Figure 18).[63]

The antibacterial activities of the polymers were evaluated against *E. coli* and *S. aureus* during 15−24 h contact time, and they increased in the order of the increasing number of the hydroxyl groups.[63] The activities were attributed to the phenolic hydroxyl groups in the resin. However, the exact mechanism of destruction of the surface of the cells due to the contact with these polymers has not been investigated by the authors.

Park et al. introduced a 2-benzimidazolecarbamoyl moiety (CBZ) to poly(ethylene-*co*-vinyl alcohol) (Figure 19).

The antifungal activity of the synthesized EVOH-CBZ was evaluated after incubation for 72 h at 28 °C against *Aspergillus fumigatus* and *Penicillium pinophilum* and showed antifungal activity. The inhibition zone diameter increased with increasing CBZ concentration.[2] The effect here was mainly from CBZ moieties. The authors mentioned when they complexed the polymer, EVOH-CBZ, with isophoronediamine, the cured DGEBA-CBZ complex sheet did not show any appreciable antifungal activity, indicating that release of CBZ units is needed to exhibit antifungal activity. Therefore, CBZ supported polymers will be of little potential use because large weight percentages are required for activity and because they could

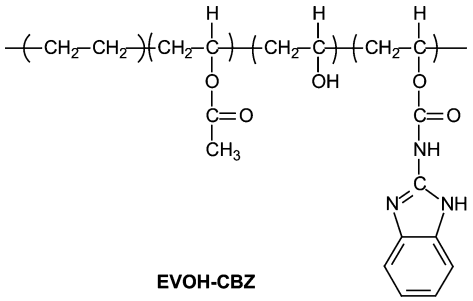
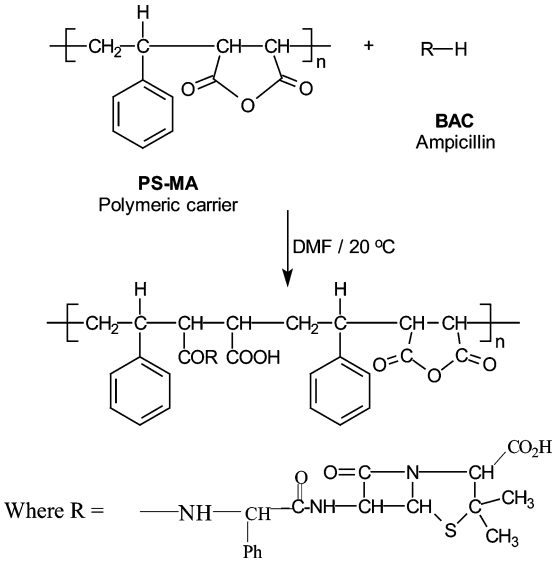



**Figure 19.**

**Scheme 9.** Coupling Reaction between Ampicillin and a Polymeric Carrier




not be used for long-term applications where water exposure would occur.

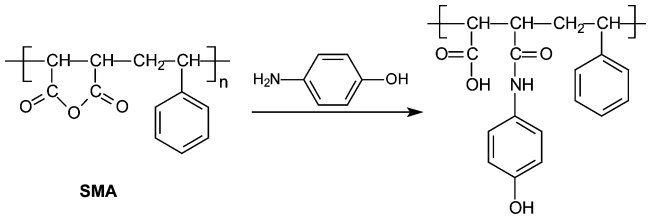
Patel et al.[64] reported the synthesis of poly (styrene-*co*-maleic anhydride) (PS-MA) with surface-containing functional anhydride groups of different percentages by solution polymerization. The biologically active compound (BAC), ampicillin, was bound on the surface of this matrix by a coupling reaction (Scheme 9).

The amount of ampicillin chemically bound to the matrix was spectroscopically characterized. The in vitro release rate of ampicillin in weak basic medium was studied along with the determination of its antimicrobial activity. The study indicated that the rate of drug release could be controlled by the amount of the incorporated anhydride. To study the antimicrobial activity of the prepared polymers, Patel et al. ran a control experiment, that is, only culture without the drug, which showed a higher growth rate than the experiment in the presence of the drug. The presence of the drug alone reduced the growth rate from the beginning. Bound drug was unable to show an effect in the beginning. However, after a delay of 8−16 h, bacterial growth was inhibited. This could be due to the release of the drug, which means that this system works as a controlled release system for the drug, and, once released, the ampicillin released begins to function according to the known mode of action of this class of antibiotics.

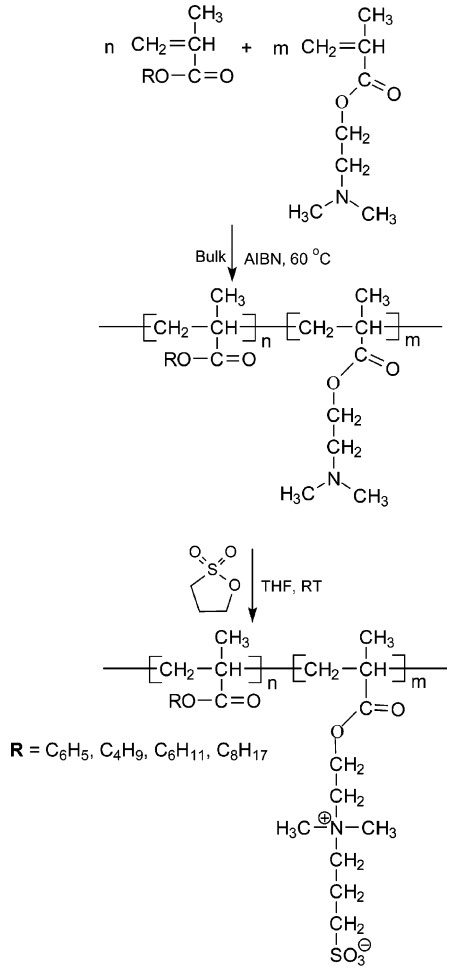
Poly(styrene-*co*-maleic anhydride) (PS-MA) was used by Lee and co-workers as a carrier for active agents containing amino or hydroxyl groups.[65]

In this context, 4-aminophenol (AP) was reacted with PS-MA to obtain SMA−AP conjugate (Scheme 10). SMA−AP

**Scheme 10.** A Route of Chemical Synthesis for SMA−AP




**Scheme 11.** Reaction Pathway Outlining the Preparation of the Target Sulfopropylbetaine Copolymers




exhibited bacterial activity against *E. coli* and *S. aureus*. The reduction in the number of the cells of *E. coli* was 95.3%, while it was 99.9% for *S. aureus*. The relatively lower activity of SMA−AP toward *E. coli* as compared to *S. aureus* is due to the outer membrane barrier in *E. coli*. No free AP was detected from the polymer incubated under similar conditions. Therefore, it was concluded that SMA−AP may be bactericidal by itself, and its bactericidal activity may last for a fairly long period of time under neutral conditions. However, there was no bactericidal mechanism suggested for SMA−AP, but it is possible that it was due to the phenolic hydroxyl group, which may attack the cell membrane, which leads to cell death. One advantage of this kind of antimicrobial system is that there is no release of active agent into the environment; it has bactericidal activity itself.

Probably the class of the antimicrobial polymers that has received the most attention over the years has been that of the polymeric quaternary "onium" salts.

Nonaka and co-workers synthesized water-soluble polymers having a phosphonium group from methacryloyloxyethyl trialkyl

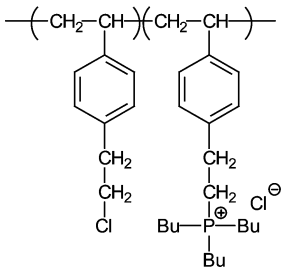


**Figure 20.**

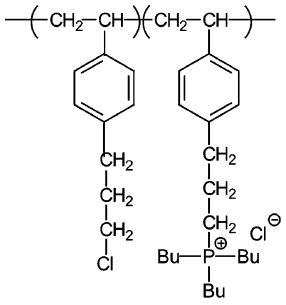


**Figure 21.**

phosphonium chloride (MET-R) (Scheme 2) and *N*-isopropylacrylamide (NIPAAm).[41] The copolymer [METO-NIPAAm], with octyl substituents in phosphonium groups (R = $C_8H_{17}$ [METO]), 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.

Lowe et al.[66] prepared a series of statistical copolymers derived from 2-(dimethylamino)ethyl methacrylate with four different hydrophobic monomers (ethyl, butyl, cyclohexyl, and octyl methacrylates) via free radical copolymerization under bulk conditions using AIBN as an initiator at 60 °C. The synthesized copolymers were modified with 1,3-propanesultone (Scheme 11) to yield polysulfopropylbetaine derivatives. The antimicrobial activities of the sulfopropylbetaine copolymers were tested against *S. aureus* and *E. coli* using the broth dilution method. The results showed that all of the copolymers showed bacteriostatic activity against the test organisms. However, the activities were mainly dependent on the copolymer composition and the test organism. The MIC values for *S. aureus* and *E. coli* were in the range of 1125−2000 $\mu$g/mL, which is about 2 orders of magnitude higher than those of the antibiotics ampicillin and erythromycin.

Polymeric phosphonium salts with different side-chain lengths between the main chain and the reactive group, poly[4-(2-tributylphosphonioethyl) styrene chloride-*co*-4-(2-chloroethyl)-styrene], Figure 20, and poly[4-(3-tributylphosphoniopropyl)-styrene chloride-*co*-4-(3-chloropropyl)styrene], Figure 21, were prepared by Kanazawa and Endo.[26]

The polymeric phosphonium salts were prepared by reacting tributylphosphine with the copolymers in toluene at room temperature under nitrogen atmosphere for 20 h. The antimicrobial activity of the polymer phosphonium salts was tested against *S. aureus* and *E. coli*, and the results showed high activity of the synthesized polymers.

They found that the antibacterial activity decreased as the side-chain length increased. However, in the two examples studied, there is only a difference of one carbon between the lengths of the two chains. Therefore, this difference in activity is probably due to other factors.

Nonaka and co-workers prepared copolymer beads bearing quaternary ammonium groups (Figure 22).[67]

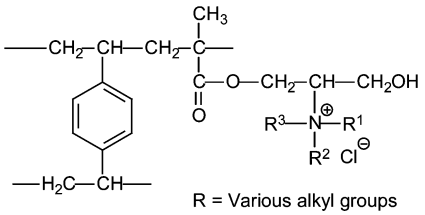



**Figure 22.** Resins containing quaternary ammonium groups.

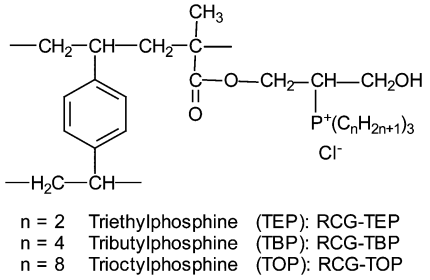
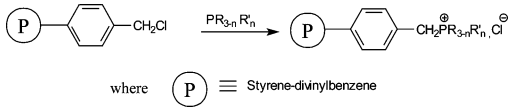



**Figure 23.**

**Scheme 12.** Preparation of Polymer-Grafted Phosphonium Salts by Quaternization of Styrene−7% Divinylbenzene



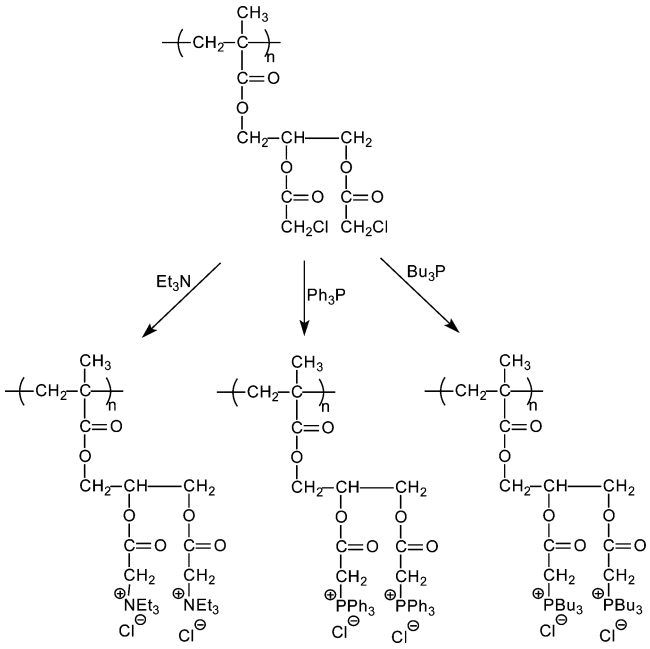

The beads were prepared by the treatment of glycidyl methacrylate (GMA)-1,4-divinylbenzene copolymer beads with hydrogen chloride and then were treated with various amines such as triethylamine, *N*,*N*-dimethyloctylamine, *N*,*N*-dimethyldodecylamine, and *N*,*N*-dimethylhexadecylamine. The antibacterial activities of the resins were examined against *E. coli* and *S. aureus*. The results showed that the antibacterial activity increased with the increase of the amount of quaternary ammonium groups in the resins. The activity of the resins was not affected by the chain length of the alkyl groups.

Another similar copolymer system based on glycidyl methacrylate and a divinylbenzene-bearing phosphonium group was prepared by Nonaka and co-workers (Figure 23).[68]

The copolymer beads, having 2-chloro-3-hydroxypropyl, were prepared by treating glycidyl methacrylate-1,4-divinylbenzene copolymer beads with hydrogen chloride. The produced modified beads were further treated with triethylphosphine, tributylphosphine, and trioctylphosphine. The antibacterial activities were examined against *E. coli* and *S. aureus* by measuring the decrease in the number of viable cells in bacteria suspension after contact with the resin for a prescribed time. The beads with trioctylphosphine exhibited high antibacterial activity against *E. coli* and *S. aureus* in water; however, the beads with triethylphosphine and tributylphosphine did not.

Nonaka and his co-workers noticed that there is a relationship between the adsorption ability of the resins for the anionic compounds such as dodecylbenzenesulfonic acid and the antibacterial activity. They found that the resin with high adsorption ability has high antibacterial activity. Therefore, in their subsequent work, they studied the interaction between the resins and bacteria by preparing resins having various phosphonium groups.[42] Uemura et al. studied the adsorption and elution behavior of the resins toward anionic surfactants as a model of the interaction between the resins and bacteria. It was found that the resin showing the highest antibacterial activity had the highest adsorption ability for anionic surfactants; therefore, the higher activity of copolymer beads having

**Scheme 13.** Antimicrobial Polymers Prepared by the Immobilization of Ammonium and Phosphonium Groups onto the Chloroacetylated Poly(glycidyl methacrylate)




trioctylphosphine is attributed to the strong interaction between the resins and bacteria.

Popa and co-workers synthesized quaternary phosphonium salts grafted on an insoluble "gel-type" styrene−7% divinylbenzene copolymer (Scheme 12).[69] The quaternary phosphonium salts were prepared from chloromethylstyrene−divinylbenzene copolymer and the corresponding phosphine in *N*,*N*-dimethylformamide by reacting for 2 h under stirring at room temperature to allow the copolymer beads to swell, and then refluxing at 110 °C for 72 h (Scheme 12).

The antibacterial activities of the products were tested against *S. aureus*, *E. coli*, and *P. aeruginosa*. The copolymers were minimally active against the test organisms after incubation for 18 h at 37 °C. They may have bacteriostatic properties because the best copolymer showed 40% reduction of the colony units after 18 h of exposure.

Modified glycidyl methacrylate polymers having quaternary ammonium and phosphonium groups were prepared.[18] Three different antimicrobial polymers were prepared (Scheme 13), and the antimicrobial activities of these polymers were tested against Gram-negative bacteria (*E. coli*, *P. aeruginosa*, *Shigella* sp., and *Salmonella typhae*), Gram-positive bacteria (*Bacillus subtilis* and *B. cereus*), as well as the fungus *Trichophytun rubrum*. The tested polymers showed significant antimicrobial activity against Gram-negative bacteria and the fungus after 24 h contact time, whereas these polymers were less active against Gram-positive bacteria. It was reported that the tributyl phoshonium salt was able to kill 100% of the fungus *Trichophytun rubrum* at a concentration of 10 mg/mL and a contact time of 24 h. Polymer with triphenylphosphonium salt was able to kill 100% *P. aeruginosa* at a lower concentration of 5 mg/mL; the same concentration of polymer with ammonium salt was able to kill 100% *P. aeruginosa* at the same contact time. Generally, it was found that the diameter of the inhibition zone varied according to the active group in the polymer and the test bacteria. The polymer with tributylphoshonium salt is the most effective against both Gram-positive and Gram-negative bacteria as compared to salts of triethylamine and triphenylphosphine.[18]

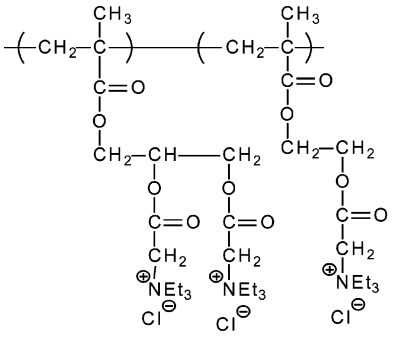


**Figure 24.**

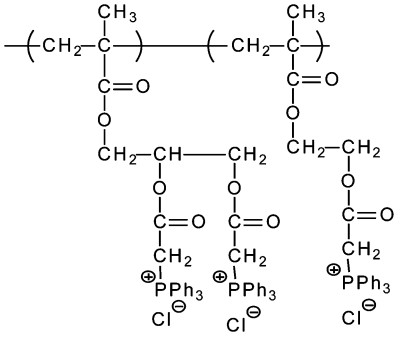


**Figure 25.**

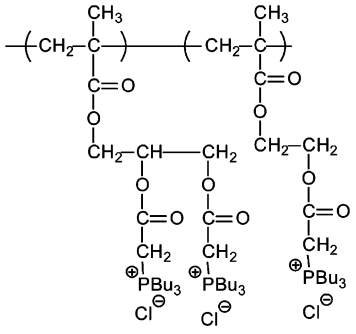


**Figure 26.**

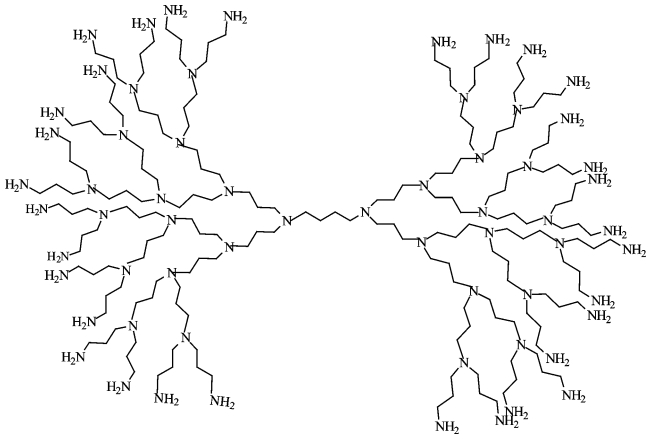
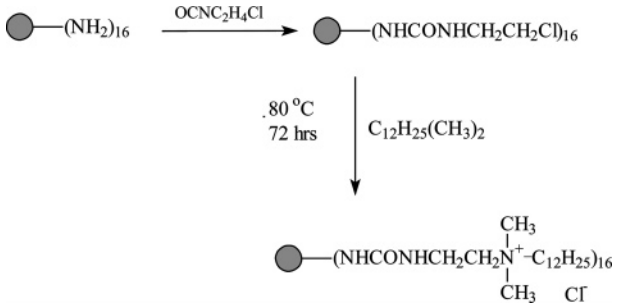


**Figure 27.** Commercially available generation 4 poly(propyleneimine) primary amine-terminated dendrimers.

Recently, quaternary ammonium and phosphonium salts were immobilized on a modified copolymer of glycidyl methacrylate and 2-hydroxyethyl methacrylate (Figures 24−26).[6]

Three copolymers were prepared by reacting the modified poly(glycidyl methacrylate-*co*-2-hydroxyethyl methacrylate) with triethylamine, triphenylphosphine, and tributylphosphine, respectively (Figures 24−26). The antimicrobial activities of the copolymers were studied against Gram-negative bacteria (*E. coli*, *P. aeruginosa*, *Shigella* sp., and *Salmonella typhae*), Gram-positive bacteria (*B. subtilus* and *B. cereus*), and the fungus *trichophyton rubrum*. The results showed that the three copolymers were highly active against the test organisms after incubation for 24 h at 30 °C. The copolymer with tributylphosphonium salt was the most effective one against the test organisms. Generally polymers with phosphonium salts showed excellent antimicrobial activity after 24 h incubation at 30 °C against *T. rubrum*; they killed 100% of *T. rubrum* at a concentration of 2.5 mg/mL. However, *T. rubrum* required a concentration of 10 mg/mL polymer with ammonium salt to kill 100% of *T. rubrum*. To kill 100% of *E. coli*, it required a concentration of 10 mg/mL polymer with triphenylphosphine or 5 mg/mL polymer with tributylphoshine. Polymer with triphenylphosphine proved to be able to kill 100% of *E. coli*, 97% of *P. aeruginosa*, and 48% of *B. subtilis* at a concentration of 10 mg/mL at the same contact time. The modes of actions of these polymers are similar to the mode of action of polyquats previously explained. In conclusion, it seems that these materials could be promising candidates for preventing biomaterial-related infections. The latter results are in agreement with the previously reported results.[6,18]

**Scheme 14.** Synthesis Scheme for the Generation 3 Quaternary Ammonium Dendrimers with C12 Hydrophobe



Recent advances in polymer chemistry seem to provide an ideal system for bioactive materials. Dendrimers are novel highly branched three-dimensional macromolecules that emanate from a central core.[70] They can be tailored to generate uniform or discrete functionalities and possess tunable inner cavities, surface moieties, sizes, molecular weight, and solvent interactions. Generation 4 poly (propyleneimine) dendrimer has attracted much attention as a potential antimicrobial agent because of its compact structure and the availability of many end groups.

Cooper and co-workers[37] modified the commercially available poly(propylene imine) dendrimers with 32 surface primary amine groups (Figure 27) to introduce the quaternary ammonium function on the dendrimers. The amine-funtionalized dendrimers were modified in two steps (Scheme 14). The first step was by reacting the primary amine group either with 2-chloroethyl isocyanate or with 2-bromoethyl isocyanate. The second step involved the reaction of halogen-containing dendrimers produced from the first step with tertiary amines to form the quaternary ammonium-functionalized poly(propylene imine) dendrimers. The antimicrobial properties of the modified dendrimers were evaluated using a bioluminescence method. They extensively studied the effect of the other factors such as the size of the dendrimers, length of the hydrophobic chain in the quaternary groups, and the effect of counterion.[37] The results showed that the higher generations of the dendrimer showed higher antibacterial activities. The results also showed that the antimicrobial activity is proportionally dependent on the molecular weight. Also, the counterion studies showed that the dendrimers with bromine as counterion were more potent than

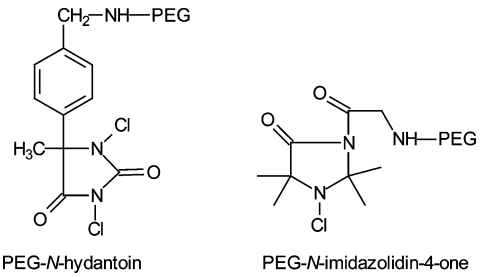



**Figure 28.**

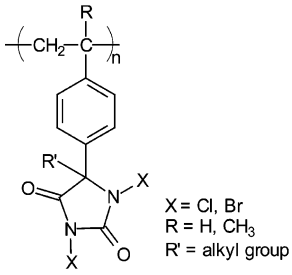



**Figure 29.**

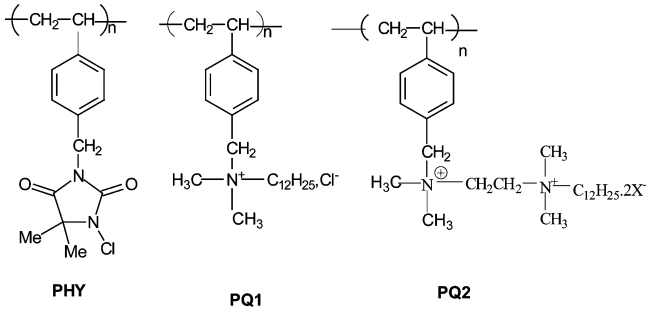



**Figure 30.**

those with chloride, although the reason for this observation is not clear. The dependence on the hydrophobic chain of the quaternary ammonium structure is similar to conventional polymer biocides, and shows a parabolic relationship, with dendrimer biocides carrying the C10 hydrophobe being the most potent. These results are consistent with our previous discussion about the effect of the counterion on the antimicrobial properties. The mode of actions of these dendrimer biocides was explained to be similar to the mode of action of cationic biocides. In this case, the dendrimers' initial adsorption onto the negatively charged bacterial cell surfaces is more rapid than the small molecule biocides due to their polycationic nature. Also, due to the compact structure of these dendrimers, their permeability into the cell is higher than that for the polymeric biocides. Therefore, the dendrimers can disrupt and disintegrate the cell wall to a higher extent than do the small molecules.

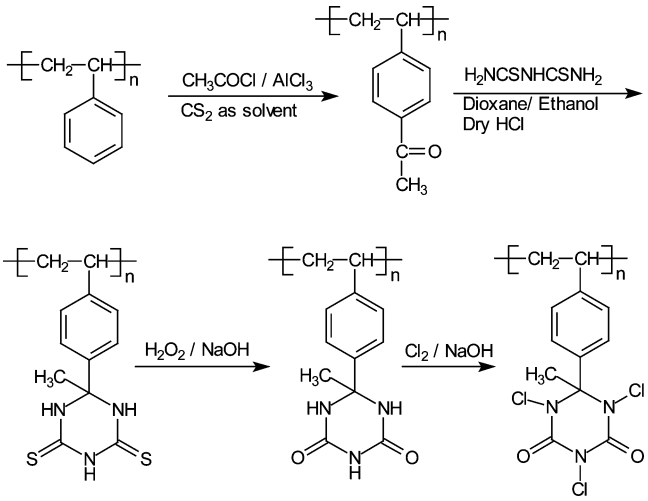
Worley and co-workers synthesized two poly(ethyleneglycol-*N*-halamine) polymers (Figure 28).[19] Dichlorohydantoins and chloroimidazolidin-4-ones were attached to a methoxy-poly-(ethylene glycol)-terminated amine.

The resulting water-soluble polymers have inactivated bacteria (*S. aureus*) over a prolonged period of time after 10 min contact time. The polymer containing the hydantion moiety showed better activity and stability than did the chloroimidazolidin-4-one polymer.

Materials of general structure (Figure 29), polystyrene hydantoin, were synthesized by Worley and co-workers.[71]

The biocidal activities of these polymers were tested against *S. aureus*. These polymers were capable of killing *S. aureus* in contact times of 1 s or less, most with one pass through the polymer filter. After a long period of storage at ambient temperature, their activity continued, and none were ineffective.

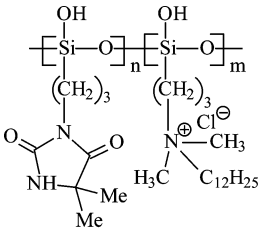
**Scheme 15.** Preparation of Polymer Poly[1,3,5-trichloro-6-methyl-6-(4′-vinylphenyl)-1,3,5-triazine-2,4-dione]




The polymers with general structure shown in Scheme 15 are polystyrene triazinediones synthesized by Sun, Worley, and co-workers.[73−75] These polymers are synthesized from commercial polystyrene; the first step was a Friedel−Crafts acylation using an acid chloride such as acetyl chloride in the presence of aluminum chloride. The formed polystyrene ketone was then reacted with dithiobiuret in the presence of HCl to form a polystyrene triazinethione. The thione was oxidized to the ketone using hydrogen peroxide in base, and halogenation was performed by exposure to aqueous free halogen (chlorine and bromine) in a reaction flask or in a packed column.[10,72]

The antimicrobial activity of the polymer described in Scheme 15 was tested against the bacterium *Staphylococcus aureus* in a water-filter application by packing a small column with the polymer and passing through it an aqueous solution of *S. aureus* bacterial suspension. The contact time of flow was 30 s, and the aliquots of effluent were plated on nutrient agar. The plates were incubated at 37 °C for 48 h before examination for viable organisms. It was found that no bacteria survived.

Recently, Worley et al. have reported a very interesting and important comparison between the polymeric quaternary ammonium materials and *N*-chlorinated polymers.[75] They described the synthesis of three systems based on poly(styrene) derivatives; that is, the three systems have the same polymer backbone, but only differed in their biocidal derivative moieties (Figure 30). The first system was based on the chlorinated methylated polystyrene hydantoin beads. It was prepared by reacting the potassium salt of 5,5-dimethylhydantoin with chloromethylated polystyrene beads in DMF at 100 °C for 12 h. The functionalized beads were suspended in a flask containing 5.25% sodium hypochlorite to produce the chlorinated beads (PHY). The other two systems were quaternary ammonium salts that were produced on the same chloromethylated polystyrene, which was made to react either with dimethyldodecylamine to yield PQ1 or with *N*,*N*,*N*′,*N*′-tetramethylethylenediamine in ethanol at reflux temperature for 12 h followed by reaction with dodecyl bromide to yield PQ2. The antimicrobial efficacies of the three systems were tested, and the results showed that the N-chlorinated polymeric beads were much more efficacious in an aqueous disinfection application against the bacteria *S. aureus* and *E. coli* than was that of the structurally similar polymeric quaternary ammonium salts (PQ1 and PQ2).



PHQS

**Figure 31.**

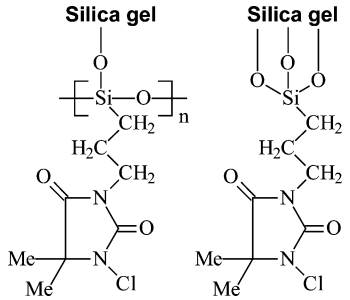



**Figure 32.**

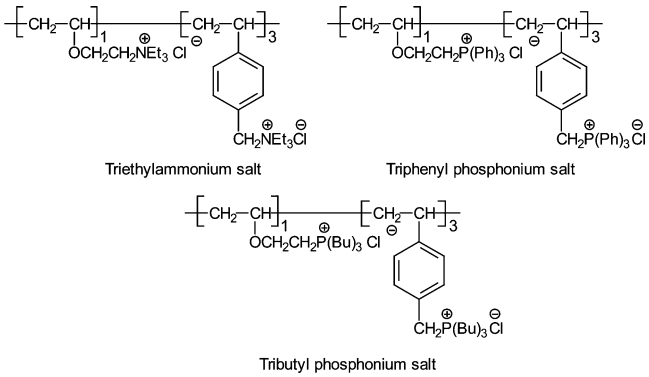


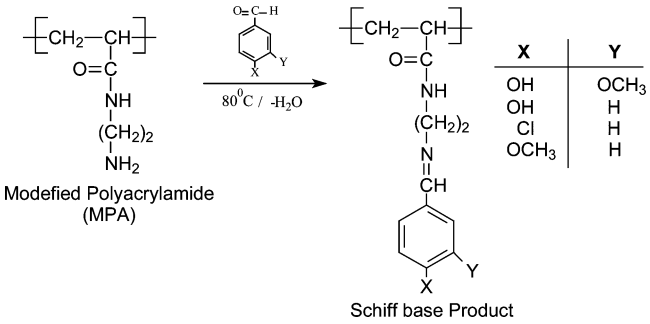

**Figure 33.** Ammonium and phosphonium groups immobilized on the copolymer of CEVE and VBC.

Worley et al. synthesized a very intriguing series of hydantoinyl/quat siloxane copolymers containing both *N*-halamine and quaternary salt functionalities simultaneously (Figure 31).[76] The copolymers are adequately soluble in water to be used for coating cotton swatches.

All of the biocidal polymer coatings were effective against *E. coli* O157:H7 and *Staphylococcus aureus*. However, it is evident that the coatings containing hydantoinyl siloxane functional groups (PHS and PHQS (1:1)) were much more effective against Gram-negative *E. coli* O157:H7 than was PQS.

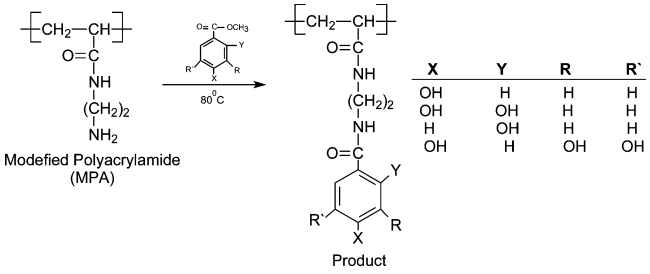
The monomer 5,5-dimethyl-3-(3-triethoxysilylpropyl) hydantoin and its hydrolysis product polymer poly[3-(5,5-dimethylhydantoinylpropyl)hydroxysiloxane were employed by the same group to functionalize the surfaces of silica gel particles to produce an adhered film that became biocidal upon chlorination with dilute sodium hypochlorite bleach (Figure 32).[77] The biocidal efficacy of the functionalized silica gel was demonstrated in a cartridge filter experiment against the bacterial pathogens *Staphylococcus aureus* and *Escherichia coli* O157:H7. Complete 6 log inactivations of the two bacterial species were observed within 30 s of contact. Moreover, upon loss of biocidal activity due to depletion of bound chlorine, the coated silica gel particles could be recharged by further exposure to dilute bleach. Potential uses of the biocidal silica gel include disinfection and odor control in water treatment facilities and recirculating baths.

**Scheme 16.** Schiff Base Formation between MPA and Various Aldehydes




| X | Y |
|---|---|
| OH | $OCH_3$ |
| OH | H |
| Cl | H |
| $OCH_3$ | H |

**Scheme 17.** Modification of MPA with Various Esters




| X | Y | R | R` |
|---|---|---|---|
| OH | H | H | H |
| OH | OH | H | H |
| H | OH | H | H |
| OH | H | OH | OH |

Grunlan et al. reported on the antimicrobial behavior of polyelectrolyte multilayer films containing cetrimide and silver.[78] They described six antimicrobial thin film systems, based upon polyethyleneimine (PEI), poly(acrylic acid) (PAA), silver nitrate ($AgNO_3$), and containing cetrimide. Film deposition was carried out on poly(ethylene terephthalate) (PET) film, with a thickness of 175 $\mu$m; the antimicrobial thin films were highly effective. Corona treatment of PET substrates prior to thin film deposition yielded a more effective film than did those with no surface treatment. It is believed that the strong negative surface charge imparted by the corona led to a more concentrated deposition of the positively charged antimicrobial agents. Another useful discovery was an enhanced antimicrobial efficacy in films made with cetrimide, an organic quaternary ammonium molecule, relative to films containing only silver.

Shyu et al. prepared hydrogel membranes with a polyelectrolyte method, based on homogenizing an interpolyelectrolyte complex, a chitosan−alginate sponge with high stability.[79] The spongelike chitosan−alginate hydrogels exhibited superabsorbent properties. The result of the antimicrobial activities after 24 h contact suggests that the PEC sponges containing antimicrobial agents should effectively suppress bacterial proliferation to protect wounds from bacterial invasion.

Recently, Kenawy's group modified polyacrylamide by introducing an amino group in the side chain of the polymer by reacting it with ethylenediamine.[80] The amine-modified polymer was reacted with two classes of active compounds. The first group was aromatic aldehydes containing active groups such as *p*-hydroxybenzaldehyde, vanillin, *p*-chlorobenzaldehyde, and anisaldehyde. The second group was phenolic ester derivatives such as *p*-hydroxymethylbenzoate, 2,4-dihydroxymethylbenzoate, 2-hydroxymethylbenzoate, and 3,4,5-trihydroxypropylbenzoate.

The modified polymers (Schemes 16 and 17) showed antimicrobial activity against *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis*, *Aspergillus flavus*, *Fusarium oxysporum*, and *Candida albicans*. The tests were carried out by the cut plug method after incubation for 36 h. The polymer derivative of *p*-chlorobenzaldehyde was the most effective against bacteria and fungi species. Also, the phenol-modified

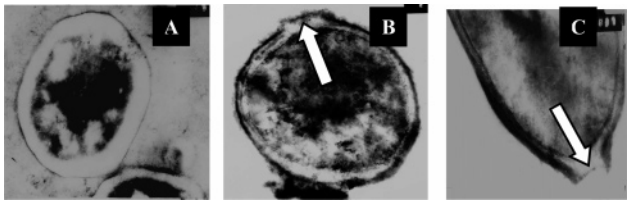



**Figure 34.** Electron scanning micrograph of (A) normal-control *Staphylococcus aureus*, and (B) and (C) treated *Staphylococcus aureus* cell (ref 81).

polymers showed high antimicrobial activities at the same contact time and concentration of 20 mg/mL. The mode of action here is related to the phenolic moieties. This may be due to the fact that phenols damage cell membranes and cause release of intracellular constituents. Phenols also cause intracellular coagulation of cytoplasmic constituents, leading to cell death or inhibition of cell growth.

Various copolymers were prepared by the copolymerization of 2-chloroethylvinyl ether (CEVE) with vinylbenzyl chloride (VBC).[81] The copolymers were quaternized by reaction of the copolymers with triethylamine, triphenylphosphine, and tributylphosphine (Figure 33).

The antimicrobial activities of the quaternized copolymers were tested against fungal organisms (*C. albicans, Aspergillus flavus*) and bacterial organisms (*B. subtilis, E. coli*, and *S. aureus*). The results showed that the phosphonium-containing polycationic biocides were more effective than were the quaternary ammonium salts. The antimicrobial activity of polymer with triphenylphosphonium salt against the selected microorganisms was high. It killed 71−98% of the microorganisms at a concentration of 5 mg/mL. However, a concentration of 10 mg/mL killed 98−100% of the tested fungi. Decreasing the polymer concentration to 2.5 mg/mL decreased the inhibition potency of the polymer to 50% inhibition for *Staphylococcus aureus*. It is quite clear that this polymer is a potent inhibitor for *C. albicans* where it performed 100% inhibition of growth for that organism at 10 mg/mL concentration and 98%, 96%, and 71% of organism growth inhibition at concentrations of 5, 2.5, and 1.25 mg/mL of the polymer, respectively. This selectivity of growth inhibition of polymer for *C. albicans* might be due to the interaction between this poly(cationic) biocide with the charged organism membrane. Examination of the *S. aureus* polymer-treated cells by electron microscopy indicated disruption for the cytoplasmic membrane (Figure 34), causing a release of potassium ions as shown by the assay of potassium leakage.

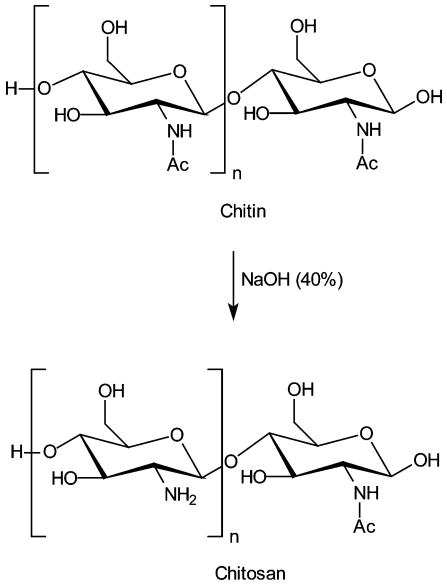
**4.3. Immobilized Antimicrobial Agent on Naturally Occurring Polymers.** Chitin is the second-most abundant biopolymer in nature. It is found in the shells of crustaceans, the cuticles of insects, and the cell wall of fungi.[82] Chitosan, a deacetylated product of chitin, has many interesting properties, such as antimicrobial activity and nontoxicity. It is obtained from shrimp and crab shell chitin by alkaline deacetylation (Scheme 18).[83]

Many attempts have been made to use chitosan in several fields such as the food, medical, cosmetic, and textile industries.[84]

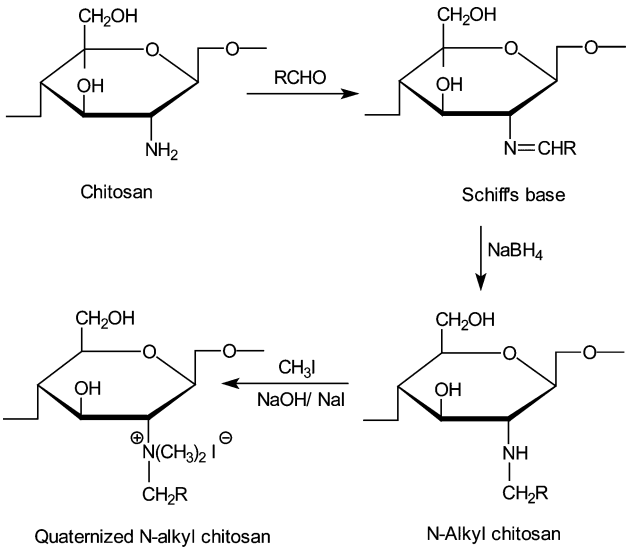
*N*-Alkyl chitosan derivatives were prepared by introducing alkyl groups into the amine groups of chitosan via a Schiff's base intermediate.[85] Quaternization of the *N*-alkyl chitosan derivatives with methyl iodide produced water-soluble cationic polyelectrolytes (Scheme 19).

The antimicrobial activities of the chitosan quaternary ammonium salts increased with the increase in the chain length of

**Scheme 18.** Preparation of Chitosan from Chitin




**Scheme 19.** Preparation Route to *N*-Alkyl Chitosan Derivatives

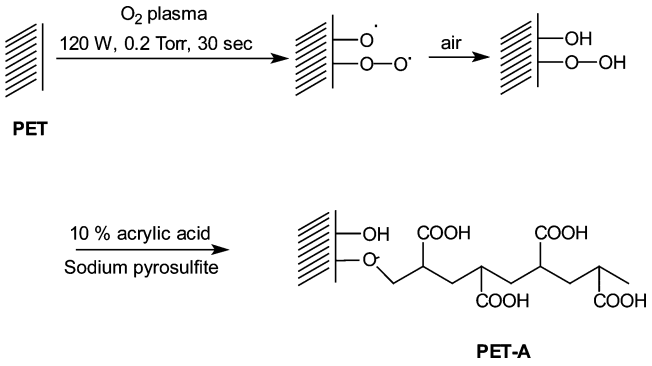



the alkyl substituent; this increased activity was ascribed to the contribution of the increased lipophilic properties of the derivatives.

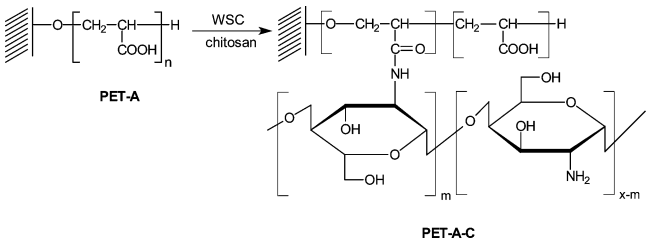
Huh et al. modified poly(ethylene terephthalate) (PET) texture by exposing it to an oxygen plasma glow discharge to produce peroxides on its surface.[86] These peroxides were then used as catalysts for the polymerization of acrylic acid (AA) to prepare a PET with a carboxylic acid group (PET-A) (Scheme 20). Chitosan and quaternized chitosan (QC) were then coupled with the carboxyl groups on the PET-A to obtain chitosan-grafted PET (PET-A-C) and QC-grafted PET (PET-A-QC), respectively (Schemes 21 and 22). The PET-A was dipped in 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (WSC) aqueous solution to activate the carboxyl groups on the surface, and it was subsequently transferred into the chistosan solution to obtain chitosan-grafted PET (PET-A-C) (Scheme 21).

QC-Grafted PET (PET-A-QC) was prepared by dipping the activated PET-A in QC solution (Scheme 20). The antibacterial activity of the chitosan-grafted PTEs was high against *S. aureus* and showed a high growth inhibition after laundering. The antimicrobial activity is attributed to the possibility of the release of the chitosan from the PET surface during shaking in the flask

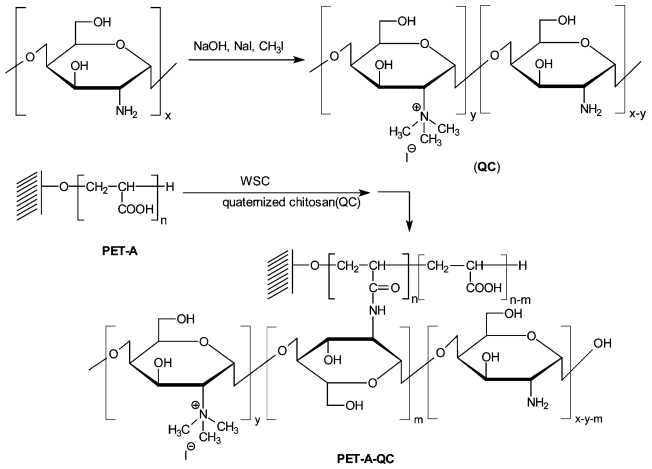
**Scheme 20.** Oxygen Plasma Treatment of PET and Graft Polymerization of Acrylic Acid (AA) on PET




**Scheme 21.** Formation of Chitosan-Grafted PET (PET-A-C)



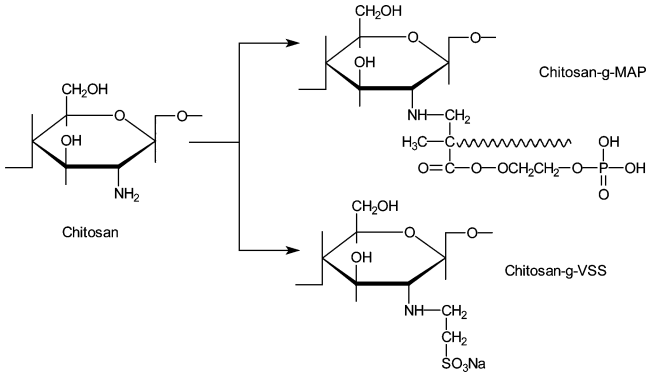

**Scheme 22.** Quaternization of Chitosan and Its Immobilization onto PET-A



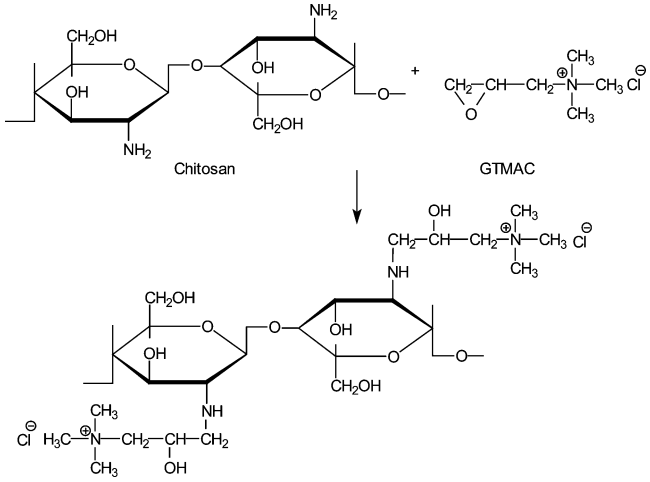

and to the presence of the quaternary ammonium ions of the grafted chitosan. Therefore, the mode of action could be due to disruption of cell membrane function, which consequently leads to the cell death. Even though these systems showed reasonable antimicrobial activity, the possibility that they lose the antimicrobial activity after time is high due to the release of grafted chitosan. It is always preferable to find self-sterilized materials (SSM), which remain active for longer periods of time and which do not release the active agent at high rate.

Two anionic monomers, mono (2-methacryloyloxyethyl) acid phosphate (MAP) and vinylsulfonic acid sodium salt (VSS), were grafted onto chitosan to obtain copolymers with zwitterionic properties (Scheme 23).[87] Results of the antimicrobial activities of the modified chitosan samples against *Candida albicans*, Trichophyton rubrum, and *Trichophyton violaceum* showed that optimum antimicrobial activities result at pH = 5.75 against *Candida albicans*. The antimicrobial activities of chitosan-*g*-MAP and chitosan-*g*-VSS were 95% and 75%, respectively, over 48−72 h contact time. The polymers showed the dependence of the antimicrobial activities on the pH; when the pH was changed to 6.2, the activities dropped to 10−15%.

**Scheme 23.** Preparation of Grafted Chitosan Copolymers




**Scheme 24.** Reaction Scheme for the Synthesis of HTCC




However, this is expected because it is known that high acidic and high basic media have effect on the microorganisms, and the studies showed pH variations up to 6.2 only.

*N*-(2-Hydroxy)propyl-3-trimethylammonium chitosan chloride (HTCC) was synthesized by the reaction of glycidyltrimethylammonium chloride (GTMAC) and chitosan (Scheme 24).[88]

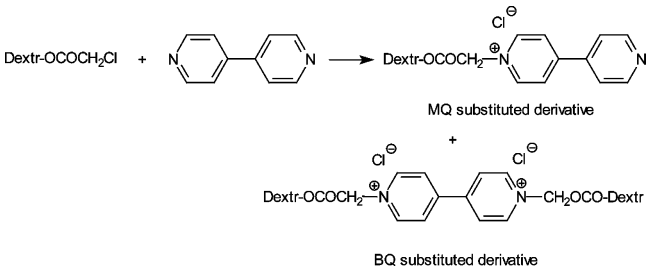
The modified chitosan (HTCC) showed excellent antimicrobial activity; it was stronger than the unmodified chitosan due to the quaternary ammonium groups. HTCC was blended with polyacrylonitrile (PAN) using NaSCN aqueous solution as a common solvent. The PAN/HTCC blend fibers were prepared via a wet spinning and drawing process. Addition of 0.5% HTCC to the blend fiber showed nearly 100% reductions in bacteria.

New polymeric derivatives of dipyridyl were synthesized by Avram and co-workers.[89] These compounds were synthesized by reaction of chloroacetylated cross-linked dextran microparticles with dipyridyl compounds as 4,4′-dipyridyl, *N*-*n*-octyldipyridinum chloride, and *N*-benzyldipyridinum chloride (Schemes 25 and 26).

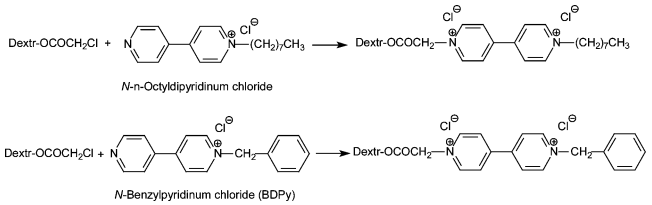
Preliminary studies concerning the antimicrobial activities of these polymeric dipyridyl compounds were performed, and the results showed that the polymeric dipyridyl conjugates have improved antimicrobial activity over the small molecular compounds.

Ion exchange fibers, with quaternary ammonium, phosphonium, or thiol groups, were prepared by graft copolymerization of vinyl monomers on loofah fiber, which is one of the natural fibers.[90] Methacryloyloxyethyl trimethyl ammonium chloride (METAC), tributyl-4-vinylbenzyl phosphonium chloride (TRVB), and 2,3-epithiopropyl methacrylate (ETMA) were used as vinyl

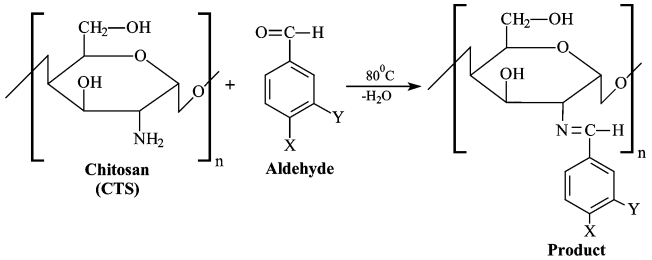
**Scheme 25.** Reaction of Chloroacetylated Cross-linked Dextran with Dipyridyl (MQ, Monoquaternized; BQ, Biquaternized)




**Scheme 26.** Reaction of Chloroacetylated Cross-linked Dextran with *N*-*n*-Octyldipyridinium Chloride and *N*-Benzyldipyridinium Chloride

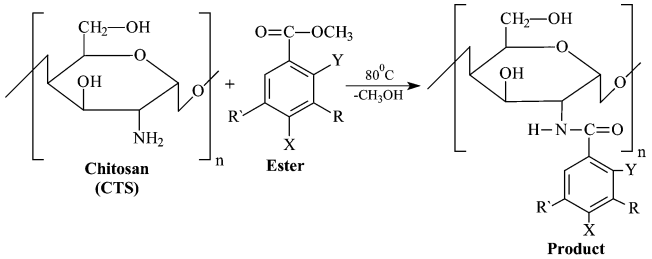



**Scheme 27.** Schiff Base Formation between Chitosan (CTS) and Different Aldehydes




| X | Y |
|---|---|
| OH | $OCH_3$ |
| OH | H |
| Cl | H |
| $OCH_3$ | H |

**Scheme 28.** Schiff Base Formation between Chitosan (CTS) and Different Esters




| X | Y | R | R` |
|---|---|---|---|
| OH | H | H | H |
| OH | OH | H | H |
| H | OH | H | H |
| OH | H | OH | OH |

monomers. Methacryloyloxyethyl trimethyl ammonium chloride (METAC) was grafted on loofah fiber by reacting it in deionized water using ammonium cerium nitrate as an initiator to yield loofah-grafted METAC (L-*g*-METAC). A similar method was used to prepare TBVB and ETMA grafted on loofah fibers to yield L-*g*-TBVB and L-*g*-ETMA (LE) (Figure 35). Further modification for the ETMA grafted on loofah fiber L-*g*-ETMA (LE) was carried out by reacting it with triethylenetetramine (TTA) to yield an ion exchange fiber LE-TTA (Figure 35).

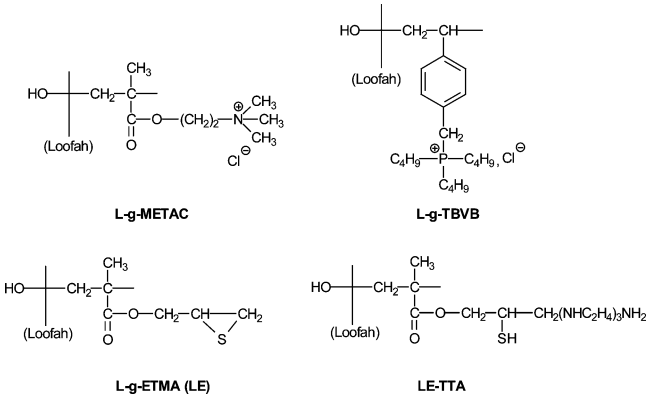



**Figure 35.** Structure of grafted loofah fibers.

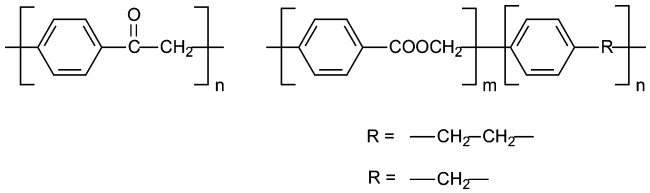


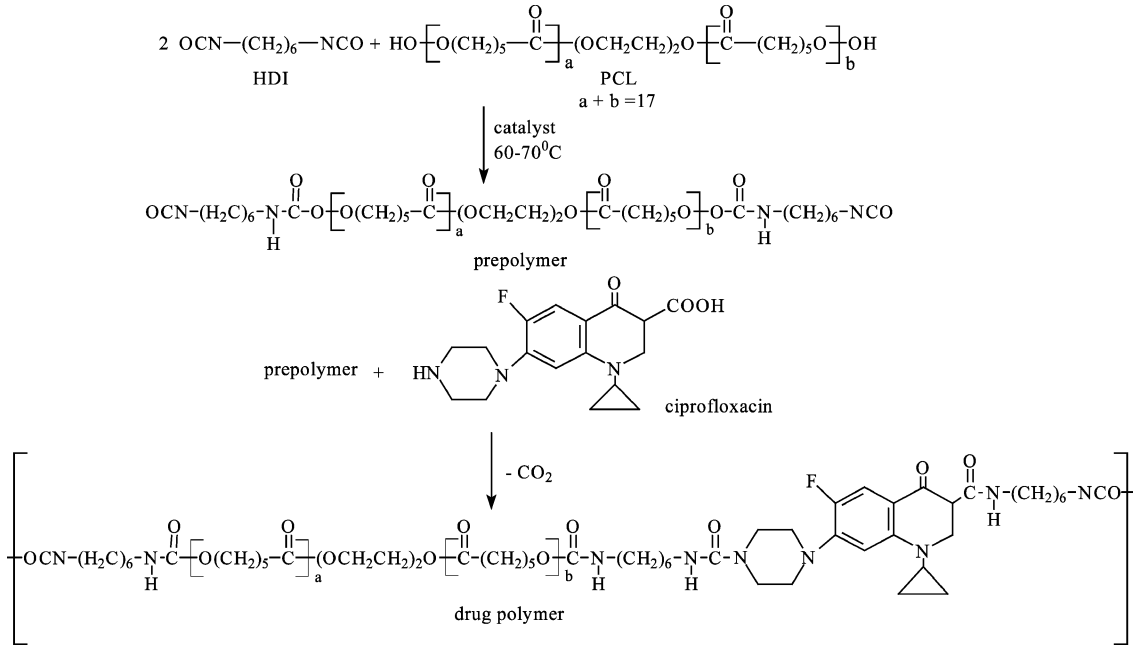

**Figure 36.** Polyketones.

Ion exchange fibers LE and LE-TTA had high adsorption ability for silver ions. Fibers LE and LE-TTA were stirred with $AgNO_3$ solution to produce silver ions adsorbed on both fibers (LE-Ag and LE-TTA-Ag). The antibacterial activity of the fibers was tested against *E. coli* and *S. aureus*. LE-TTA-Ag exhibited high antibacterial activity against *E. coli* and *S. aureus*, but LE-Ag did not. On the other hand, L-*g*-METAC and L-*g*-TRVB also exhibited high antibacterial activity against *E. coli* and *S. aureus*. However, the best results in this work were shown by the fiber L-*g*-TBVB, which has a tributylphosphonium group in the side chain. The fiber L-*g*-TBVB showed the highest activity against *S. aureus*, with a total kill after less than 2 h. The mechanism here is expected to be due to the quaternary ion and its known mode of action. Also, the silver adsorbed on fiber (LE-TTA-Ag) showed antimicrobial activity against *S. aureus*. The clear mode of action for this system was not clarified by the authors, but it could be due to the interaction of $Ag^+$ with cell enzymes after penetration of the cell wall, which leads to the cell death.

Chitosan has an amino group at C-2, which is important because amino groups are nucleophilic and readily react with electrophilic reagents. Chitosan modified under mild conditions often results in regioselectivity. In our laboratory, biologically active moieties were introduced into the amino groups of chitosan to yield antimicrobial chitosans. Specifically, vanillin, *p*-hydroxybenzaldehyde, *p*-chlorobenzaldehyde, anisaldehyde (Scheme 27), methyl 4-hydroxybenzoate, methyl 2,4-dihydroxybenzoate, propyl 3,4,5-trihydroxybenzoate, and 2-hydroxymethylbenzoate (Scheme 28) were attached.[91]

The anti-microbial activities of these modified chitosans were explored against fungi such as *Candida albicans* SC5314, *Aspergillus flavus*, and *Fusarium oxysporium*. Also, they were tested against bacteria such as *Bacillus subtilis*, *Escherichia coli*, and *Staphylococcus aureus* after 24 h contact time. These modified chitosans were found to be generally highly active toward fungi species (more than bacterial species). However, for polymer CTS1 (Scheme 27), concentrations of 20 mg/mL were able to kill 100% of *Bacillus subtilis*, *Escherichia coli*, and *Staphylococcus aureus*. A lower concentration of 10 mg/mL was able to kill 100% of *Staphylococcus aureus*. Also, polymer CTS2 showed total kill of 100% for *Aspergillus flavu*

**Scheme 29.** Synthesis of Drug Polymer




and *Fusarium oxysporium* at a concentration of 20 mg/mL; a lower concentration of 10 mg/mL killed 98% of *Staphylococcus aureus* at the same contact time. The mode of action could be due to the phenolic hydroxyl groups.

**4.4. Preparation of Hydrolyzable Antimicrobial Agents as Part of the Polymer Main Chain.** A number of chemical reactions can be employed to incorporate antimicrobial agents into polymeric backbones. Polymers with biologically active groups in the main chain are considered desirable as they may be hydrolyzed to active drugs and small innocuous molecules. Prime candidates for polymer structures in these categories are polyamides, polyesters, and polyurethanes.[92] Polyketones have been prepared by reacting benzene, chloroacetyl chloride, 1,2-dichloroethane, and dichloromethane using anhydrous aluminum chloride as a catalyst and nitrobenzene as a solvent (Figure 36).[93]

All of the samples of the polyketones showed inhibitory effects on the growth of *Bacillus substilis* and *Pseudomonas fluorescens*. They also showed antifungal activity against *Aspergillus niger* and *Trichoderma viride*.

A model drug polymer was synthesized using 1,6-hexane diisocyanate (HDI), polycaprolactone diol (PCL), and a fluoroquinolone antibiotic, ciprofloxacin (Scheme 29). The study showed that an antibiotic could be polymerized into the backbone of a polymer and that the polymer could be degraded by an inflammatory cell-derived enzyme cholesterol esterase.[94] Analysis of the solutions showed that ciprofloxacin was released, and it was able to inhibit the growth of *P. aeruginosa*. The degradation products containing ciprofloxacin bonded to fragments of PCL and HDI and did not display antimicrobial activity. The mechanism of action is similar to quinolones, which inhibit the activity of the bacterial DNA gyrase, which leads to bacterial cell death. However, for these systems, the complete degradation of the polymer backbone is necessary to release the known active formula of the drug.

Albertsson and co-workers described the incorporation of the known antimicrobial agent, bithionol[2,2′-thiobis(2,4-dichlorophenol)], in the polymer main chain.[95] Bithionol was found to react with phosgene to give the bischloroformate, and the latter was used for the preparation of alternating copolycarbonates, polyurethanes, or copolycarbonate/polyurethane (Figure 37).

The authors studied the hydrolysis rate of bithionol-containing polymers at 37 °C in buffer solution at pH 7.4. It releases bithionol at about 1% per day. There was no specific antimicrobial study for the prepared polymers reported.

## 5. Major Fields of Applications of Antimicrobial Polymers

**5.1. Water Treatment.** Chlorine or water-soluble disinfectants are used for sterilizing water. However, soluble disinfectants have the problems of residual toxicity of the agents, even if suitable amounts of the agents are used.[63] With the use of these disinfectants or antimicrobial agents, the problem of residues cannot be avoided, bringing about more serious consequences. Their residues can become concentrated in the food chain in the environment. In addition, because free chlorine and other related chemicals can react with organic substances in the water to yield trihalomethane analogues that are suspected of being carcinogenic, their use should be avoided. These drawbacks can be solved by the removal of microorganisms from water with insoluble substances.[8,96] One approach is the use of insoluble contact disinfectants that can inactivate, kill, or remove target microorganisms by mere contact without releasing any reactive agents to the bulk phase to be disinfected.

Polymeric disinfectants are ideal for applications in hand-held water filters, surface coatings, and fibrous disinfectants, because they can be fabricated by various techniques and can be made insoluble in water. Several workers in the past few decades have attempted to produce insoluble polymeric disinfectants for use in water treatment. A water-insoluble matrix based on iodinated poly(methyl methacrylate-*co*-*N*-vinyl-2-pyrrolidone) was synthesized by Tyagi et al.[97] The copolymer was synthesized from methyl methacrylate (MMA) and *N*-vinyl-2-pyrrolidone with a 1:1 (w/w) ratio and using 0.5% AIBN (w/w) as an initiator. The copolymer was sieved in particle size range 250−500 $\mu$m and was treated with molecular resublimed iodine at 37 °C for 24 h to yield the iodinated copolymer. This copolymer was used in the specially designed cartilage for testing the antimicrobial activity of the iodinated copolymer (Figure 38). As shown in Figure 38, the system was connected to a water tap via a water flow regulator. A known concentration

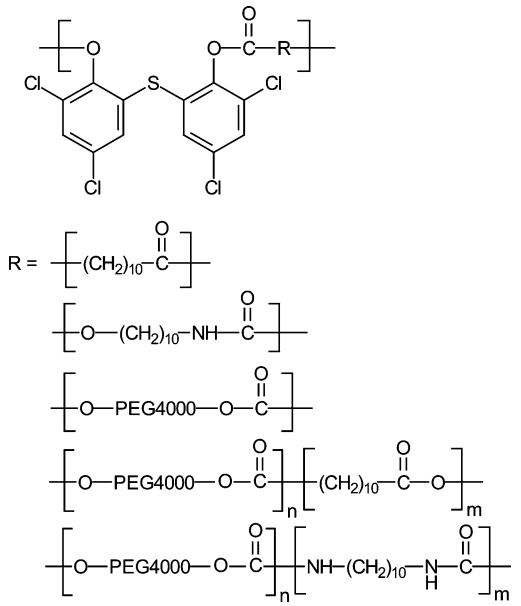


**Figure 37.**

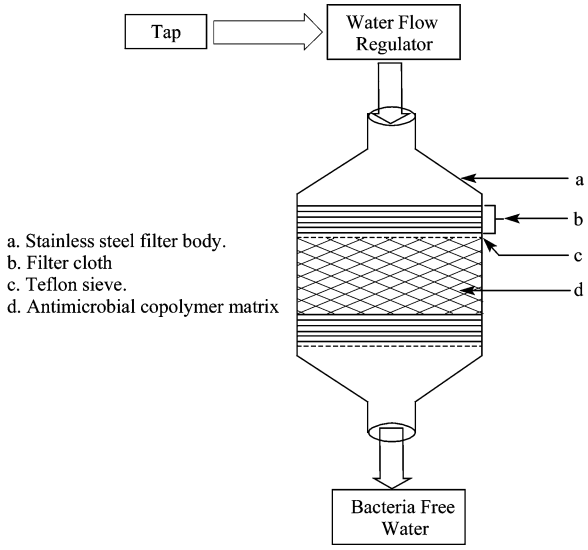



**Figure 38.** Diagram of the refill cartridge (ref 97).

of microbial cells composed of *E. coli*, *S. aureus*, and *Candida* spp. was inoculated into the water reservoir. The eluting water was tested at regular interval for the microbes. A volume of 8000 L of contaminated water was used. The microbial count with water flow was as shown in Table 2. The results indicated that the iodinated polymer remained effective against the test microorganisms until 5000 L of water had passed.

Tan and co-workers prepared modified polypropylene (PP) nonwoven cloths by radiation-induced grafting of 4-vinylpyridine (4-VP) onto PP nonwoven cloths and followed by quaternization with a halohydrocarbon such as benzyl bromide, benzyl chloride, ethyl bromide, butyl bromide, or hexadecyl bromide.[98] The activity results showed that the modified PP nonwoven cloths possessed the ability to capture the bacterial cell alive. It was found that the quaternization with benzyl bromide was the highest in the extent of removal of *E. coli*. There were no morphological changes of the adhered cells observed by SEM; thus, the surface of the modified PP nonwoven cloths may not be bactericidal, but bacteriostatic.

Cyclic *N*-halamines have superior properties including biocidal efficacy, long-term stability, and recharge ability, once

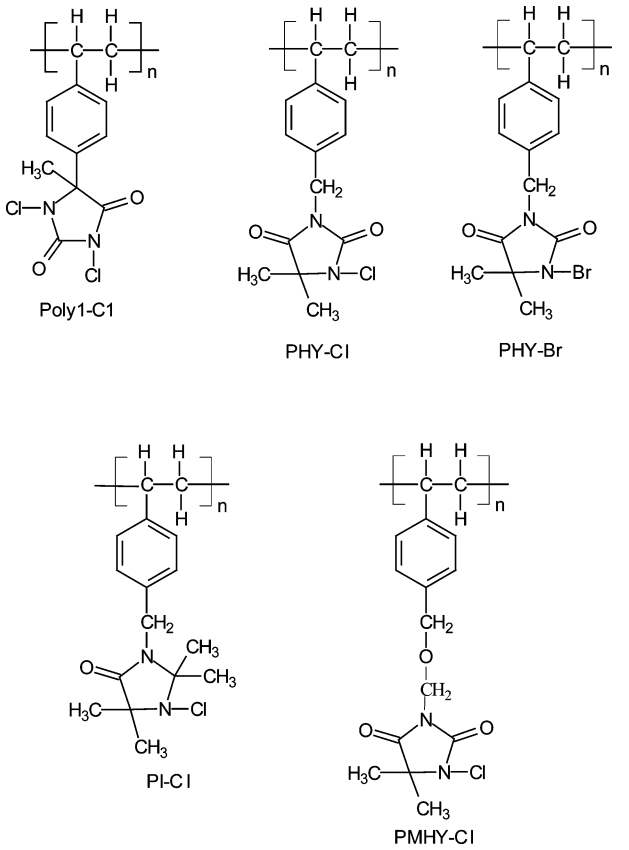



**Figure 39.**

**Table 2.** Microbial Counts with Respect to Water Flow through the Column

| | microbial density/100 L of water passed | | |
|---|---|---|---|
| species | initial | up to 5000 L | 5000−8000 L |
| *S. aureus* | $2 \times 10^5$ | nil | $1 \pm 1$ |
| *E. coli* | $2 \times 10^5$ | nil | $5 \pm 2$ |
| *Candida* | $1.5 \times 10^5$ | nil | $1 \pm 1$ |

the efficacy has been consumed during use.[50] Worley et al. at Auburn University have prepared several of such materials.[50,99,100] Of particular value for water and air disinfection applications are the *N*-halamine polymers that are prepared in the form of highly cross-linked porous beads. Functionalization of methylated polystyrene by halogenated hydantoin and imidazolidinone derivatives was reported. The structures of the several types of functionalized polymeric beads are shown in Figure 39.

Column filter biocidal efficacy tests were conducted for aqueous suspensions of the Gram-positive bacterium *S. aureus* and Gram-negative bacterium *E. coli* for four types of beads in this study (Figure 39). Glass columns were packed with beads of PHY-Cl, PHY-Br, PMHY-Cl, and PI-Cl. The suspensions of pathogenic bacteria were pumped through the columns. The results showed the efficacies of the bead columns for inactivation of *S. aureus* and *E. coli*. The PHY-Cl and PHY-Br polymer beads were able to exhibit complete inactivation of both species in the contact time interval of 1−2 s. In contrast, the polymer labeled Poly1-Cl in Figure 42 has been shown to accomplish the same task in less than 1 s. The PMHY-Cl polymer also completely inactivated both species of bacteria in a contact time of less than or equal to 1 s. The PI-Cl polymer beads inactivated *S. aureus* in a contact time between 2 and 3 s. The various polymeric beads will be particularly useful in the disinfection

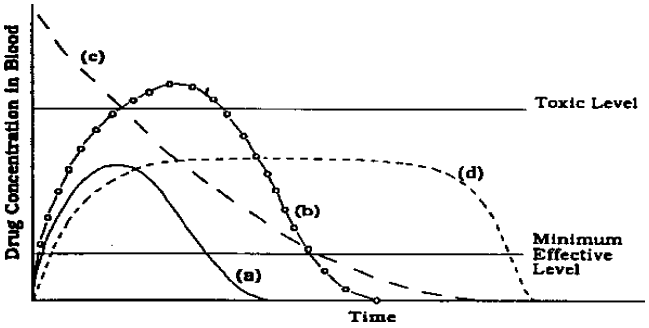



**Figure 40.** Theoretical plasma drug concentration after administration of various dosage forms: (a) standard oral dose; (b) oral overdose; (c) intravenous injection; and (d) controlled release system.

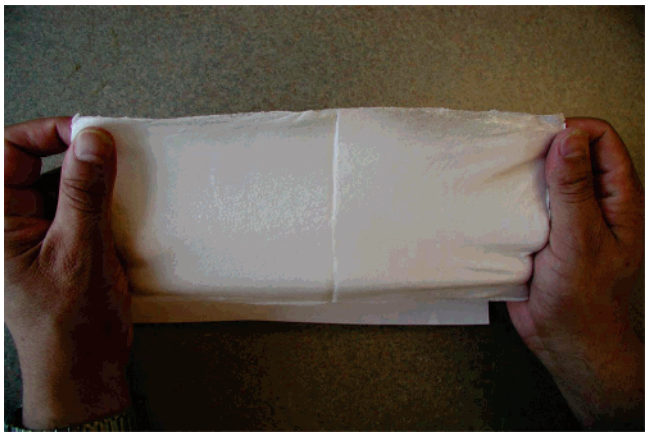


**Figure 41.** Antimicrobial electrospun sheet (ref 102).

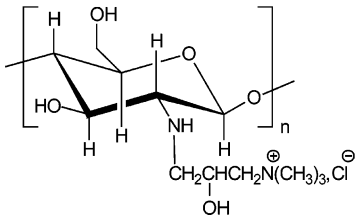


**Figure 42.** Hydroxypropyl trimethylammonium chitosan chloride.

of potable water and moist air flowing through cartridge fillers containing them.

**5.2. Medicine and Healthcare Products.** Most pharmacologically active agents are low molecular weight compounds, which readily penetrate into all cell types and are often rapidly excreted from the body. Consequently, large and repeated doses must be given to maintain a therapeutic effect, and, in addition, when specificity is limited, drugs invariably display a range of deleterious side effects. Attachment of drugs such as antimicrobial agents to macromolecular carriers alters their rate of excretion from the body and provides the possibility for controlled release over a prolonged period.[101] Controlled delivery systems are used to improve therapeutic efficacy and safety of drugs by delivering them at a rate dictated by the need of the physiological environment.[102]

The most attractive approach is the synthesis of new polymeric drugs based on well-known pharmacons or drugs bound covalently to a macromolecular biodegradable or soluble support.[103] The advantage of this kind of system over the traditional delivery system, which is based on physical combination, is mainly that the "polymeric drug" may display pharmacological activity by itself, but at the same time may be used as a carrier for the pharmaceutical agent.

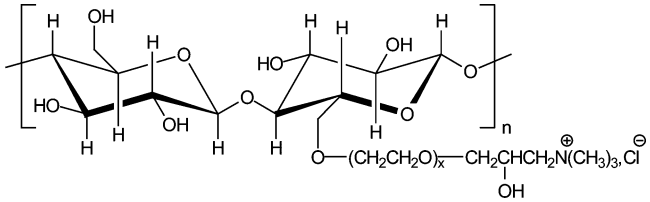


**Figure 43.** Quaternized hydroxyethyl cellulose polymer.

As schematically illustrated in Figure 40, the expected drug concentration profiles vary drastically according to the different methods of drug administration. Briefly, the drug concentration in blood reaches a maximum very rapidly after administration of a standard dosage (curve a), and then decreases to a minimum. At this point, repeated administration becomes necessary. Often the initial maximum concentration is above the therapeutically desirable level, increasing the risk of side effects, as it may reach the toxic level (curve b). On the other hand, the minimum concentration may be below the therapeutically effective level. In this way, standard dosage forms can result in a drug regimen in which the patient oscillates between alternating periods of drug overdose and drug inefficacy (curve c). Controlled release systems ideally smooth the peaks and valleys in the drug concentration in blood, providing a more effective drug regimen (curve d).

Antimicrobial polymers are powerful candidates for polymeric drugs with high activities, which can be ascribed to their characteristic nature of carrying the high local charge density of the active groups in the vicinity of the polymer chains.

Electrospun fibers containing tetracycline hydrochloride based on poly(ethylene-*co*-vinyl acetate), poly(lactic acid), and blending were prepared to use as an antimicrobial wound dressing.[102,104] Figure 41 shows the antimicrobial electrospun sheet.

The release of tetracycline hydrochloride from the electrospun mats was studied and showed a smooth release of the drug over 5 d.

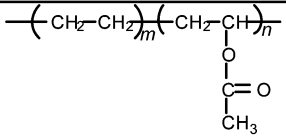
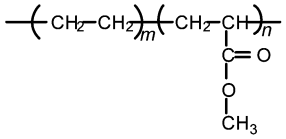
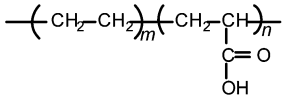
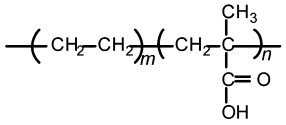
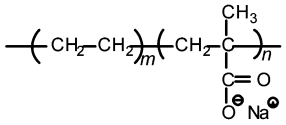
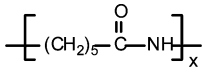
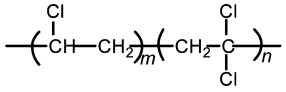
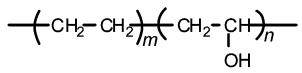
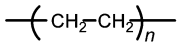
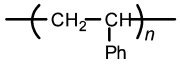
Chitosan and its derivatives have been reportedly used as film formers in hair products, setting agents, hair conditioners, and shampoos.[105] Recently, hydroxypropyl trimethylammonium chitosan chloride was synthesized for evaluation in a cosmetic application (Figure 42).[105]

Cellulose derivatives are commonly used in cosmetics as skin and hair conditioners. Quaternary ammonium cellulose derivatives are of particular interest as conditioners in hair and skin products (Figure 43).

Gentamicin-loaded poly(methyl methacrylate) beads constitute an effective drug delivery system for local antibiotic therapy in bone and soft tissue infections, as they enable gentamicin concentrations at the site of the infection to become much higher than can be achieved with systemic application.[106] The beads were implanted in a patient in infected joint arthroplasty, and it was found that a high level of antibiotics was achieved through the implant. The beads were left in situ for 5 years. Gentamicine-release testing revealed residual antibiotic release after being 5 years in situ. Gentamicin implants were impregnated in sheep and showed that the system is promising for the treatment of local infections in veterinary patients.[107]

Implants of cross-linked high amylase starch containing various ratios of ciprofloxacin antibiotic were prepared.[108] The implants were applied to rabbits along the femur between the quadriceps and biceps femoris muscles. The results showed that the implants having ciprofloxacin have a considerable potential as a drug delivery system for local prevention and treatment of bone and soft tissue infections.

**Table 3.** Functional Groups in Polymers Commonly Used for Food Packaging Material (Reference 114)

| polymer | formula |
|---|---|
| ethylene vinyl acetate (EVA) |  |
| ethylene methyl acrylate (EMA) |  |
| ethylene acrylic acid (EAA) |  |
| ethylene methacrylic acid (EMAA) |  |
| ionomer |  |
| nylon |  |
| polyvinylidene chloride (PVdC)-polyvinyl chloride (PVC) copolymer |  |
| ethylene vinyl alcohol (EVOH) |  |
| polyethylene (PE) |  |
| polystyrene (PS) |  |

Antimicrobial sutures were prepared by the radiation grafting of 2-hydroxyethyl methacrylate monomer (HEMA) on polypropylene monofilament.[109] The poly(HEMA) hydrogel grafted sutures were used for the immobilization of 8-hydroxy quinoline as an antimicrobial drug. It was found that the modified sutures exerted an antimicrobial activity against *S. aureus*.

Recently, concerns have been raised regarding the therapeutic effects exhibited by dental restorative materials.[110] Several attempts at modification of the resin matrix phase or filler to provide antimicrobial effects have been reported by Imazato and co-workers.[111] They reported the synthesis of an antibacterial monomer, 12-methacryloyloxydodecylpyridinium bromide (MDPB) (Figure 13). The monomer (MDPB) was synthesized by combining quaternary ammonium dodecylpyridinium with a methacryloyl group, so that the bactericide was immobilized in the resin matrix by copolymerization of MDPB with other monomers. The resin composites incorporating MDPB demonstrated inhibition of dental plaque formation on the surface, and no reduction in mechanical properties occurred even after storage for a long period in a wet environment.[58,112]

**5.3. Food Applications.** Microbial contamination reduces the shelf life of foods and increases the risk of food-born illness. The demand for minimally processed, easily prepared, and ready to eat "fresh" food products, as well as globalization of food trade, and distribution from centralized processing, pose major challenges for food safety and quality.[113] The interested reader is also referred to the review by Appendini and Hotchkiss, which represents a very interesting discussion of the need for antimicrobial food packaging.[113]

The food-borne microbial outbreaks are driving a search for innovative ways to inhibit microbial growth in the foods while maintaining quality, freshness, and safety. Traditional methods of preserving foods from the effect of microbial growth include thermal processing, dry freezing, refrigeration, irradiation, and adding antimicrobial agents or salts. Unfortunately, some of these techniques cannot be applied to some food products, such

as fresh meats and ready-to-eat products.[114] Also, there is a growing demand for foods without chemical preservatives.[115] Antimicrobial packing is a form of active packing in which the package interacts with the product or the head space between the package and food system to obtain a desired outcome.[116]

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 microorganisms or by inactivating the microorganisms by contact.[117] Antimicrobial polymers can be used in several food-related applications including packaging.[118] One of these applications is to extend the shelf life and promote safety by reducing the rate of growth of specific microorganisms by direct contact of the package with the surface of solid foods, for example, meat, cheese, etc., or in the bulk of the liquid, for example, milk or meat exudates. Second, antimicrobial packaging materials greatly reduce the potential for recontamination of processed products and simplify the treatment of materials to eliminate product contamination. For example, self-sterilizing packaging might eliminate the need for peroxide treatment in aseptic packaging. Third, at least in concept, this could result in self-sterilizing foods, especially liquids. This might be particularly useful for high acid products such as fruit juices. Antimicrobial polymers might also be used to cover surfaces of food processing equipment so that they self-sanitize during use. Examples include filler gaskets, conveyers, gloves, garments, and other personal hygiene equipment. The target microorganism and the food composition must be considered in antimicrobial packaging.

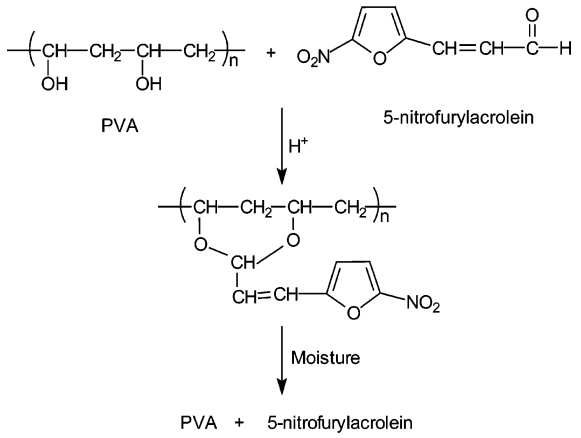
As with any antimicrobial agent, those to be incorporated into polymers have to be selected on the basis of their spectrum of activity, mode of action, chemical composition, and the rate of growth and physiological state of the targeted microorganisms.[119] Antimicrobial moieties attached to the polymer, however, need to be active while attached to the polymer. This activity is related to the mode of action. If, for example, the mode of action is on the cell membrane or wall of the microorganism, it is possible that the attached antimicrobial agent will act on the cells. This is likely not to be the case if it needs to enter the cytoplasm.

Examples of polymers with high antimicrobial activity in growth media and low activity in foods include triclosan in plastics.[120] Further considerations in antimicrobial packaging choice are the concentration of antimicrobials in the polymer film, the effect of film thickness on activity, and the physical and mechanical properties of the polymers after conversion to the final product. For example, antimicrobial activity of compounds coated or immobilized on the surface of polymer films may be independent of film thickness. However, if the antimicrobial is entrapped into the bulk of the material, the film thickness will play a role in the diffusion and concentration at the surface of the film.[121]

Some polymers are inherently antimicrobial and have been used in films and coatings. Cationic polymers such as chitosan promote cell adhesion.[122] Because charged amines interact with negative charges on the cell membrane, they can cause leakage of intracellular constituents. Chitosan has been used as a coating and appears to protect fresh vegetables and fruits from fungal degradation. Although the antimicrobial effect is attributed to antifungal properties of chitosan, it may be possible that the chitosan acts as a barrier between the nutrients contained in the produce and microorganisms.[123]

Bacterial acrylic polymers made by copolymerizing acrylic protonated amine co-monomers have been proposed as packaging materials for increased fruit and vegetable shelf life.[124] Examples of ionic and covalent immobilization of antimicrobials onto polymers or other materials have been reviewed in this work. This type of immobilization requires the presence of functional groups both on the antimicrobial agent as well as on the polymer. Examples[114] of polymers used for food packaging that have functional groups are shown in Table 3. Application of antimicrobial polymers in food is gaining interest from researchers due to its potential to provide quality and safety benefits. Currently, development is limited due to the availability of antimicrobials, new polymeric materials, and testing methods. With the advent of new materials and more information, this may change.

**Scheme 30.** Preparation of the Broad-Spectrum Antimicrobial Fiber Based on PVA

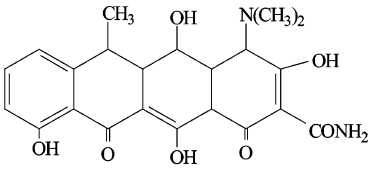



Future work in this field will focus on the use of biologically active derived antimicrobial compounds bound to polymers. The need for the new antimicrobials with a wide spectrum of activity and low toxicity will increase. Also, antimicrobial dendrimers may play an important role in this field of application. It is possible that research and development of "intelligent" or smart antimicrobial food packages will follow. These will be materials that sense the presence of microorganisms in the food. It may be also interesting to use the idea of pro-drugs in the antimicrobial polymeric food preservatives and packaging.

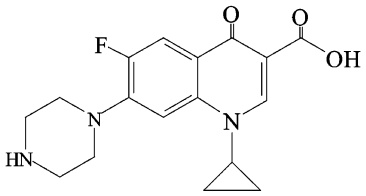
**5.4. Textile Products.** Antimicrobial treatment is rapidly becoming a standard finish for some categories of textile products such as for medical, institutional, and hygienic uses. Recently, it became popular in sportswear, women's wear, and aesthetic clothing to impart anti-odor or biostatic properties.[125,126]

Textiles and fibrous materials are subjected to various finishing techniques to afford (a) protection for the user of textile materials against bacteria, yeast, dermatophytic fungi, and other related microorganisms for aesthetic, hygienic, or medical purposes; (b) protection of the textile itself from biodeterioration caused by mold, mildew, and rot-producing fungi; and (c) protection for textiles from insects and other pests.[119,120] Basically, there are three mechanisms by which antimicrobial agents provide protection to textiles and the wearer. The majority of antimicrobial protective finishes function by the controlled-release mechanism. An excellent example of a controlled-release mechanism is the fiber with broad-spectrum antimicrobial properties based on poly(vinyl alcohol) (PVA) (Scheme 30). The fiber was prepared by reaction of 5-nitrofurylacrolein with poly(vinyl alcohol) in the presence of an acid catalyst.[16] The antimicrobial activity was produced by slow release of the nitro compound in the presence of moisture.

Shin and co-workers investigated the effect of the molecular weight on antimicrobial activity of chitosan-treated cotton



**Doxycycline**



**Ciprofloxacin**

**Figure 44.**

fabrics.[125] Three different molecular weights for chitosan were used. The results of the antibacterial activity of the chitosan-treated fabrics showed that the reduction rate increased as the molecular weight increased. However, the antimicrobial activity of chitosan-treated fabrics seems to be more affected by the treatment concentration than by molecular weight.

Polyamide fibers (PA6) with antibacterial properties were prepared by the graft polymerization of the acrylic acid on PA6 yarn.[129] The resultant fibers, containing carboxylic groups in their structure, were additionally modified with penicillin, neomycin, and gentamycin to obtain antimicrobial fibers. The activity was tested against *S. aureus*, *E. coli*, and *P. aeruginosa*, and the modified fibers showed strong biocidal effects on the Gram-positive microorganism *S. aureus* and the Gram-negative *E. coli*.

Choi and co-workers reported the dyeing of wool with antibiotic to develop novel infection-resistant materials for external biological end uses.[130] They were prepared by using a "dyelike" interaction of two antibiotics, Doxycycline (Doxy) and ciprofloxacin (Cipro), which are highly active against Gram-negative and Gram-positive bacteria and the only antibiotics approved for treatment of anthrax (*Bacillus anthracis*) infection by the Center for Disease Control and Prevention (Atlanta, GA).[130] The chemical structures of the two selected antibiotics are as shown in Figure 44.

Nylon was used as a synthetic control. The results showed that the sorption of Doxy was much higher in wool than in nylon, whereas sorption of Cipro was similar in both fibers. To investigate the effect of hydrolysis on sorption of antibiotics by wool, wool was hydrolyzed at 40 °C for different times. The fabric strength decreased only slightly, and the hydrolysis of wool considerably increased the sorption of both Doxy and Cipro. For comparison, Nylon also was hydrolyzed, and the studies showed that the sorption of Doxy was slightly greater on hydrolyzed nylon, whereas sorption of Cipro had substantially increased by hydrolysis for 1 h. Nevertheless, sorption of Cipro was always lower in hydrolyzed nylon than in hydrolyzed wool. The zone of inhibition (ZOI) test revealed the infection characteristics of antibiotic-dyed substances. Interestingly, wool fabrics dyed by Doxy at lower temperature, for example, 45 and 65 °C, showed greater ZOI than the fabric dyed at high temperatures. Measurement of Doxy release from wool indicated that low-temperature-dyed wool resulted in better-sustained release of Doxy than high-temperature-dyed wool. Low release of the antibiotic for wool dyed at high temperature was attributed to greater penetration of Doxy into the wool at high temperature, making Doxy difficult to release from the fiber interior. The sorption of antibiotics on nylon may be comparable to that on wool, but the resulting infection-resistant properties were much lower than those of wool and did not provide a sustained release. Also, the ZOI of hydrolyzed wool dyed with Doxy was greater than that of unhydrolyzed wool.

Polyurethane−chitosan blended polymer was used to improve shrinkage and antimicrobial properties of woolen fabrics.[131] The blended polymers were used to treat woolen fabric. The experimental results indicated an improvement in both the shrink-proof and the antimicrobial properties of the fabric. However, the yellowing and softness tendency of the fabric shifted toward an unfavorable outcome. Much more effort should be done in this field because it represents a very important area of application for antimicrobial polymers. The innovative work of Sun and co-workers concerning attaching *N*-halamine functional groups to cellulose to render textile materials biocidal has been discussed in earlier sections of this review.[52−55,73,74,126]

## 6. Future and Perspectives

Undoubtedly, the use of polymers in the medical field has reduced the suffering of humans and offered them a better hope for a better life. The range of application has been extended to include many fields such as artificial organs, drugs, health care products, implants, bone replacement and other prostheses, wound-healing, food, textile industry, and water treatment, etc.

The field of antimicrobial polymers, which has progressed steadily, but slowly, over the past years, appears to be on the verge of rapid expansion, as evidenced by a broad variety of new classes of compounds that have been prepared and studied in the past few years. For example, a very novel approach to isolating biocidal moieties on the surfaces of polymers has recently been reported by Wynne and co-workers.[132] This may be due to the current awareness about the spread of viruses such as HIV and hepatitis and by contact with contaminated surfaces that lead to more stringent health and medical regulation to treat most material with microbiocides. Modification of polymers and fibrous surfaces, and changing the porosity, wettability, and other characteristics of the polymeric substrates, should produce implants and biomedical devices with greater resistance to microbial adhesion and biofilm formation. A number of polymers have been developed that can be incorporated into cellulose and other materials, which should provide significant advances in many fields such as food packaging, textiles, wound dressing, coating of catheter tubes, and necessarily sterile surfaces. The greater need for materials that fight infection will give incentive for discovery and use of antimicrobial polymers. Of course, it should be kept in mind that newly developed biocidal polymers must strive to possess the attributes suggested in section 2 of this review. For example, biocidal polymers requiring contact times of the order of hours to provide substantial reductions in viable pathogens, such as some of those referenced in this review, really have no practical value; seconds, or minutes at most, should be the contact time goal for a real application. Furthermore, if the structural modification to the polymer caused by biocidal functionalization adversely affects the intended use pattern, the polymer will be of no importance. For example, if a fiber that must be exposed to aqueous bleach to render it antimicrobial (an *N*-halamine polymer) is weakened by that exposure, or its dye is bleached, it will have limited use.

Future work should focus on the development of new polymeric antimicrobial materials to be used for soil sterilization to replace the toxic materials currently in use such as methyl bromide. Many interesting ideas were formulated through writing this review. Of particular interest were the use of dendrimers as antimicrobial polymers and the use of *N*-halamine polymers as biocides. If one could combine both ideas by preparation of the dendrimer on an insoluble support and then modification of it to form *N*-halamines, this could be a very promising development.

Participation and collaboration of research institutes, industry, and government regulatory agencies will be the key for the success of antimicrobial polymeric materials.

## Abbreviations

APDMAE = perfluoro-oxaalkylated end-capped 2-(acrylamidopropyldimethylammonio)ethanoate
NIPAAm = *N*-isopropylacrylamide
AMBS = 4-acrylamido-*N*-(5-methyl-3-isoxazolyl)benzenesulfonamide
MMBS = 4-mehacrylamido-*N*-(5-methyl-3-isoxazolyl)-benzenesulfonamide
SMPM = *N*-[4-sulfamido-*N*-(5-methyl-3-isoxazolyl)phenyl] maleimide
N-TBTM = *N*-tri-*n*-butyltin maleimide
m-AATBTB = *m*-acryloylamino-(tri-*n*-butyltinbenzoate)
MQ = 1-ethyl-6-fluoro-7-{4-[2-hydroxy-3-)2-methylacryloyloxy)propyl]piperazin-1-yl}-4-oxo-1,4-dihydroquinolin-3-carboxylic acid
AIBN = azobisisobutyronitrile
AcDP = 2,4,4′-trichloro-2′-acryloyloxydiphenyl ether
DP = 2,4,4′-trichloro-2′-hydroxydiphenyl ether
MMA = methylmethacrylate
St. = styrene
AA = acrylic acid
ACTMIO = 1-acryloyl-2,2,5,5-tetramethylimidazolidin-4-one
TMIO = 2,2,5,5-tetramethylimidazolidin-4-one
AN = acrylonitrile
MMA = methyl methacrylate
Vac = vinyl acetate
AQ = 5-chloro-8-quinolinyl acrylate
VP = *N*-vinyl-2-pyrrolidone
MDPB = methacryloyloxydodecyl pyrimidinium bromide
MBA = methacryloyloxyethyl-*p*-hydroxybenzoate
VB16 = vinylbenzylcetyldimethylammonium chloride
DMF = dimethylformamide
PANVB16 = polyacrylonitrile-*co*-vinylbenzylcetyldimethylammonium chloride
CBZ = 2-benzimidazolecarbamoyl
BAC = biologically active compound
PS-MA = poly(styrene-*co*-maleic anhydride)
AP = 4-aminophenol
SMA−AP = styrene-*co*-maleic anhydride 4-aminophenol conjugate
MET-R = methacryloyloxyethyl trialkyl phosphonium chloride
METO = methacryloyloxyethyl trioctyl phosphonium chloride
GMA = glycidyl methacrylate
CEVE = 2-chloroethylvinyl ether
VBC = vinylbenzyl chloride
PET = poly(ethylene terephthalate)
MAP = 2-methacryloyloxyethyl acid phosphate
VSS = vinyl sulfonic acid sodium salt
HTCC = *N*-(2-hydroxy) propyl-3-trimethylammonium chitosaan chloride
GTMAC = glycidyltrimethylammonium chloride
METAC = methacryloyloxyethyl trimethyl ammonium chloride
TRVB = tributyl-4-vinylbenzyl phosphonium chloride
ETMA = 2,3-epithiopropyl methacrylate
HDI = 1,6-hexane diisocyanate
PCL = polycaprolactone diol
4-VP = 4-vinylpyridine
PP = polypropylene
HEMA = 2-hydroxyethyl methacrylate
PVA = poly(vinyl alcohol)
ZOI = zone of inhibition
MIC = minimum inhibitory concentration

## References and Notes

(1) Patel, M. B.; Patel, S. A.; Ray, A.; Patel, R. M. *J. Appl. Polym. Sci.* **2003**, *89*, 895−900.
(2) Park, E.-S.; Lee, H.-J.; Park, H.-Y.; Kim, M.-N.; Chung, K.-H.; Yoon, J.-S. *J. Appl. Polym. Sci.* **2001**, *80*, 728−736.
(3) Ranucci, E.; Ferruti, P. *Polymer* **1991**, *32*, 2876−2879.
(4) Bowersock, T. L.; Woodyard, L.; Hamilton A. J.; Deford, J. A. *J. Controlled Release* **1994**, *31*, 237−243.
(5) Kenawy, E.-R. *J. Appl. Polym. Sci.* **2001**, *82*, 1364−1374.
(6) Kenawy, E.-R.; Abdel-Hay, F. I.; El-Shanshoury, A. E.-R.; El-Newehy, M. H. *J. Polym. Sci., Part A: Polym. Chem.* **2002**, *40*, 2384−2393.
(7) Tan, S.; Li, G.; Shen, J.; Liu, Y.; Zong, M. *J. Appl. Polym. Sci.* **2000**, *77*, 1869−1876.
(8) Li, G.; Shen, J. *J. Appl. Polym. Sci.* **2000**, *78*, 676−684.
(9) Kamel, G. D.; Pfaller, M. A.; Rempe, L. E.; Jebson, P. J. R. *J. Am. Med. Assoc.* **1991**, *265*, 2364−2368.
(10) Worley, S. D.; Sun, G. *Trends Polym. Sci.* **1996**, *4* , 364−370.
(11) Woo, G. L. Y.; Yang, M. L.; Yin, H. Q.; Jaffer, F.; Mittelman, M. W.; Santerre, J. P. *J. Biomed. Mater. Res.* **2002**, *59*, 35−45.
(12) Acharya, V.; Prabha, C. R.; Narayanamurthy, C. *Biomaterials* **2004**, *25*, 4555−4562.
(13) Jiang, H.; Manolache, S.; Lee Wong, A. C.; Denes, F. S. *J. Appl. Polym. Sci.* **2004**, *93*, 1411−1422.
(14) Hume, E. B. H.; Baveja, J.; Muir, B.; Schubert, T. L.; Kumar, N.; Kjelleberg, S.; Griesser, H. J.; Thissen, H.; Read, R.; Poole-Warren, L. A.; Schindhelm, K.; Willcoxy, M. D. P. *Biomaterials* **2004**, *25*, 5023−5030.
(15) Baveja, J. K.; Li, G.; Nordon, R. E.; Hume, E. B. H.; Kumar, N.; Willcox, M. D. P.; Poole-Warren, L. A. *Biomaterials* **2004**, *25*, 5013−5021.
(16) Vigo, T. L. In *Biotechnol. Bioact. Polym. [Proc. Am. Chem. Soc. Symp.]*; Gebelein, C., Carraher, C., Eds.; Plenum Press: New York, 1994; pp 225−237.
(17) Yamamoto, T.; Uchida, S.; Kurihara, Y.; Nakayama, I. Jpn. Patent 94-204681, 1994.
(18) Kenawy, E.-R.; Abdel-Hay, F. I.; El-Shanshoury, A. R.; El-Newehy, M. H. *J. Controlled Release* **1998**, *50*, 145−152.
(19) Eknoian, M. W.; Worley, S. D.; Harris, J. M. *J. Bioact. Compat. Polym.* **1998**, *13*, 136−145.
(20) Kanazawa, A.; Ikeda, T.; Endo, T. *J. Polym. Sci., Part A: Polym. Chem.* **1993**, *31*, 1467−1472.
(21) Bankova, M.; Manolova, N.; Markova, N.; Radoucheva, T.; Dilova, K.; Rashkov, I. *J. Bioact. Compat. Polym.* **1997**, *12*, 294−307.
(22) Bankova, M.; Petrova, Ts.; Manolova, N.; Rashkov, I. *Eur. Polym. J.* **1996**, *32*, 569−578.
(23) Oh, S. T.; Han, S. H.; Ha, C. S.; Cho, W. J. *J. Appl. Polym. Sci.* **1996**, *59*, 1871−1878.
(24) Bankova, M.; Petrova, Ts.; Manolova, N.; Rashkov, I. *Eur. Polym. J.* **1996**, *32*, 325−330.
(25) Kanazawa, A.; Ikeda, T.; Endo, T. *J. Polym. Sci., Part A: Polym. Chem.* **1993**, *31*, 2873−2876.
(26) Kanazawa, A.; Ikeda, T.; Endo, T. *J. Polym. Sci., Part A: Polym. Chem.* **1994**, *32*, 1997−2001.
(27) Ikeda, T.; Hirayama, H.; Suzuki, K.; Yamaguchi, H.; Tazuke, S. *Makromol. Chem.* **1986**, *187*, 333−340.
(28) Ikeda, T.; Tazuke, S. *Makromol. Chem.* **1984**, *185*, 869−867.
(29) Ikeda, T.; Yamaguchi, H.; Tazuke, S. *Antimicrob. Agents Chemother.* **1984**, *26*, 139−144.
(30) Ikeda, T.; Hirayama, H.; Yamaguchi, H.; Tazuke, S.; Watanabe, M. *Antimicrob. Agents Chemother.* **1986**, *30*, 132−136.

(31) Ikeda, T.; Tazuke, S. *Polym. Prepr. (Am. Chem. Soc., Div. Polym. Chem.)* **1985**, *26*, 226−227.
(32) Kanazawa, A.; Ikeda, T.; Endo, T. *J. Polym. Sci., Part A: Polym. Chem.* **1993**, *31*, 1441−1447.
(33) Kanazawa, A.; Ikeda, T.; Endo, T. *J. Polym. Sci., Part A: Polym. Chem.* **1993**, *31*, 335−343.
(34) Ikeda, T.; Yamaguchi, H.; Tazuke, S. *J. Bioact. Compact. Polym.* **1990**, *5*, 31−41.
(35) Dizman, B.; Elasri, M. O.; Mathias, L. J. *J. Appl. Polym. Sci.* **2004**, *94*, 635−642.
(36) Kanazawa, A.; Ikeda, T.; Endo, T. *J. Polym. Sci., Part A: Polym. Chem.* **1993**, *31*, 3031−3038.
(37) Chen, C. Z.; Beck-Tan, N. C.; Dhurjati, P.; Van Dyk, T. K.; LaRossa, R. A; Cooper, S. L. *Biomacromolecules* **2000**, *1*, 473−480.
(38) Tokura, S.; Ueno, K.; Miyazaki, S.; Nishi, N. *Makromol. Symp.* **1997**, *120*, 1−9.
(39) Panarin, E. F.; Solovaskii, M. V.; Zaikina, N. A.; Afinogenov, G. E. *Makromol. Chem. Suppl.* **1985**, *9*, 25−33.
(40) Sawada, H.; Umedo, M.; Kawase, T.; Tomita, T.; Baba, M. *Eur. Polym. J.* **1999**, *35*, 1611−1617.
(41) Nonaka, T.; Hua, L.; Ogata, T.; Kurihara, S. *J. Appl. Polym. Sci.* **2003**, *87*, 386−393.
(42) Uemura, Y.; Moritake, I.; Kurihara, S.; Nonaka, T. *J. Appl. Polym. Sci.* **1999**, *72*, 371−378.
(43) Thamizharasi, S.; Vasantha, J.; Reddy, B. S. R. *Eur. Polym. J.* **2002**, *38*, 551−559.
(44) Al-Muaikel, N. S.; Al-Diab, S. S.; Salamah, A. A.; Zaid, A. M. A. *J. Appl. Polym. Sci.* **2000**, *77*, 740−745.
(45) Moon, W.-S.; Chung, K.-H.; Seol, D. J.; Park, E.-S.; Shim, J.-H.; Kim, M.-N.; Yoon, J.-S. *J. Appl. Polym. Sci.* **2003**, *90*, 2933−2937.
(46) Moon, W.-S.; Kim, J. C.; Chung, K.-H.; Park, E.-S.; Kim, M.-N.; Yoon, J.-S. *J. Appl. Polym. Sci.* **2003**, *90*, 1797−1801.
(47) Oh, S. T.; Ha, C. S.; Cho, W. J. *J. Appl. Polym. Sci.* **1994**, *54*, 859−866.
(48) Cho, W. J.; Ha, C. S. *J. Macromol. Sci., Pure Appl. Chem.* **1995**, *A32*, 479−495.
(49) Park, E.-S.; Moon, W.-S.; Song, M.-J.; Kim, M.-N.; Chung, K.-H.; Yoon, J.-S. *Int. Biodeterior. Biodegrad.* **2001**, *47*, 209−214.
(50) Chen, Y.; Worley, S. D.; Huang, T. S.; Weese, J.; Kim, J.; Wei, C.-I.; Williams, J. F. *J. Appl. Polym. Sci.* **2004**, *92*, 368−372.
(51) Qian, L.; Sun, G. *J. Appl. Polym. Sci.* **2004**, *91*, 2588−2593.
(52) Sun, Y.; Sun, G. *J. Appl. Polym. Sci.* **2001**, *81*, 617−624.
(53) Sun, Y.; Sun, G. *J. Appl. Polym. Sci.* **2003**, *88*, 1032−1039.
(54) Sun, Y.; Chen, T.-Y.; Worley, S. D.; Sun, G. *J. Polym. Sci., Part A: Polym. Chem.* **2001**, *39*, 3073−3084.
(55) Sun, Y.; Sun, G. *J. Appl. Polym. Sci.* **2001**, *80*, 2460−2467.
(56) Bankova, M.; Petrova, T.; Manolova, N.; Rashkov, I. *Eur. Polym. J.* **1998**, *34*, 247−253.
(57) Imazato, S.; Russell, R. R. B.; McCabe, J. F. *J. Dent.* **1995**, *23*, 177−81.
(58) Imazato, S.; Ebi, N.; Tarumi, H.; Russell, R. B.; Kaneko, T.; Ebisu, S. *Biomaterials* **1999**, *20*, 899−903.
(59) Punyani, S.; Singh, H. *J. Appl. Polym. Sci.* **2006**, *102*, 1038−1044.
(60) Kanazawa, A.; Ikeda, T.; Endo, T. *J. Polym. Sci., Part A: Polym. Chem.* **1993**, *31*, 3003−3011.
(61) Liang, J.; Wu, R.; Huang, T. S.; Worley, S. D. *J. Appl. Polym. Sci.* **2005**, *97*, 1161−1166.
(62) Kenawy, E.-R.; Abdel-Hay, F. I.; Abou El-Magd, A.; Mahmoud, Y. *React. Funct. Polym.* **2006**, *66*, 419−429.
(63) Nonaka, T.; Uemura, Y.; Ohse, K.; Jyono, K.; Kurihara, S. *J. Appl. Polym. Sci.* **1997**, *66*, 1621−1630.
(64) Patel, J. S.; Patel, S. V.; Talpada, N. P.; Patel, H. A. *Angew. Makromol. Chem.* **1999**, *271*, 24−27.
(65) Jeong, J.-H.; Byoun, Y.-S.; Lee, Y.-S. *React. Funct. Polym.* **2002**, *50*, 257−263.
(66) Ward, M.; Sanchez, M.; Elasri, M. O.; Lowe, A. B. *J. Appl. Polym. Sci.* **2006**, *101*, 1036−1041.
(67) Nonaka, T.; Uemura, Y.; Kurihara, S. *Nippon Kagaku Kaishi* **1994**, *12*, 1097−1106.
(68) Nonaka, T.; Ohtsuka, T.; Uemura, Y.; Kurihara, S. *Nippon Kagaku Kaishi* **1995**, *7*, 529−540.
(69) Popa, A.; Davidescu, C. M.; Trif, R.; Ilia, G.; Iliescu, S.; Dehelean, Gh. *React. Funct. Polym.* **2003**, *55*, 151−158.
(70) Frechet, J. M. J. *Science* **1994**, *263*, 1710−1715.
(71) Sun, G.; Chen, T. Y.; Sun, W.; Wheatley, W. B.; Worley, S. D. *J. Bioact. Compat. Polym.* **1995**, *10*, 135−144.
(72) Sun, G.; Chen, T. Y.; Worley, S. D. *Polymer* **1996**, *37*, 3753−3756.
(73) Sun, Y.; Sun, G. *Macromolecules* **2002**, *35*, 8909−8912.
(74) Sun, Y.; Sun, G. *J. Appl. Polym. Sci.* **2001**, *81*, 1517−1525.
(75) Chen, Y.; Worley, S. D.; Huang, T. S.; Weese, J.; Kim, J.; Wei, C.-I.; Williams, J. F. *J. Appl. Polym. Sci.* **2004**, *92*, 363−367.
(76) Liang, J.; Chen, Y.; Barnes, K.; Wu, R.; Worley, S. D.; Huang, T.-S. *Biomaterials* **2006**, *27*, 2495−2501.
(77) Liang, J.; Owens, J. R.; Huang, T. S.; Worley, S. D. *J. Appl. Polym. Sci.* **2006**, *101*, 3448−3454.
(78) Grunlan, J. C.; Choi, J. K.; Lin, A. *Biomacromolecules* **2005**, *6*, 1149−1153.
(79) Yu, S.-H.; Mi, F.-L.; Wu, Y.-B.; Peng, C.-K.; Shyu, S.-S.; Huang, R.-N. *J. Appl. Polym. Sci.* **2005**, *98*, 538−549.
(80) Kenawy, E.-R.; Abdel-Hay, F. I.; Abou El-Magd, A.; Mahmoud, Y. *J. Appl. Polym. Sci.* **2006**, *99*, 2428−2437.
(81) Kenawy, E.-R.; Mahmoud, Y. A.-G. *Macromol. Biosci.* **2003**, *3*, 107−116.
(82) Cho, Y.-W.; Cho, Y.-N.; Chung, S.-H.; Yoo, G.; Ko, S.-N. *Biomaterials* **1999**, *20*, 2139−2145.
(83) Rabea, E. I.; Badawy, M. E.-T.; Stevens, C. V.; Smagghe, G.; Steurbaut, W. *Biomacromolecules* **2003**, *4*, 1457−1465.
(84) Lim, S.-H.; Hudson, S. M. *Carbohydr. Res.* **2004**, *339*, 313−319.
(85) Kim, C. H.; Choi, J. W.; Chun, H. J.; Choi, K. S. *Polym. Bull.* **1997**, *38*, 387−393.
(86) Huh, M. W.; Kang, I.-K.; Lee, D. H.; Kim, W. S.; Lee, D. H.; Park, L. S.; Min, K. E.; Seo, K. H. *J. Appl. Polym. Sci.* **2001**, *81*, 2769−2778.
(87) Jung, B.-O.; Kim, C.-H.; Choi, K.-S.; Lee, Y. M.; Kim, J.-J. *J. Appl. Polym. Sci.* **1999**, *72*, 1713−1719.
(88) Nam, C.-W.; Kim, Y.-H.; Ko, S.-W. *J. Appl. Polym. Sci.* **1999**, *74*, 2258−2265.
(89) Avram, E.; Lacatus, C.; Mocanu, G. *Eur. Polym. J.* **2001**, *37*, 1901−1906.
(90) Nonaka, T.; Noda, E.; Kurihara, S. *J. Appl. Polym. Sci.* **2000**, *77*, 1077−1086.
(91) Kenawy, E.-R.; Abdel-Hay, F. I.; Abou El-Magd, A.; Mahmoud, Y. *J. Bioact. Compat. Polym.* **2005**, *20*, No. 1, 95−111.
(92) Vogl, O.; Tirrel, D. *J. Macromol. Sci., Chem.* **1979**, *A13*, 415−439.
(93) Patel, N. Z.; Patel, J. N.; Ray, R. M.; Patel, R. M. *Polym. Int.* **1992**, *28*, 163−167.
(94) Woo, G. L. Y.; Mittelman, M. W.; Santerre, J. P. *Biomaterials* **2000**, *21*, 1235−1246.
(95) Albertsson, A. C.; Donaruma, L. G.; Vogel, O. *Ann. N.Y. Acad. Sci.* **1985**, *446*, 105−115.
(96) Eknoian, M. W.; Worley, S. D. *J. Bioact. Compact. Polym.* **1998**, *13*, 303−314.
(97) Tyag, M.; Singh, H. *J. Appl. Polym. Sci.* **2000**, *76*, 1109−1116.
(98) Tan, S.; Li, G.; Shen, J.; Liu, Y.; Zong, M. *J. Appl. Polym. Sci.* **2000**, *77*, 1869−1876.
(99) Sun, Y.; Sun, G. *J. Polym. Sci., Part A: Polym. Chem.* **2001**, *39*, 3348−3355.
(100) Chen, Y.; Worley, S. D.; Kim, J.; Wei, C.-I.; Chen, T.-Y.; Santiago, J. I.; Williams, J. F.; Sun, G. *Ind. Eng. Chem. Res.* **2003**, *42*, 280−284.
(101) Duncan, R.; Kopeck, J. *Adv. Polym. Sci.* **1984**, *57*, 51−101.
(102) Kenawy, E.-R.; Bowlin, G. L.; Mansfield, K.; Layman, J.; Simpson, D. G. Sanders, E. H.; Wnek, G. *J. Controlled Release* **2002**, *81*, 57−64.
(103) Kulkarni, P. V.; Rajur, S. B.; Antich, P. P.; Aminabhvi, T. M.; Aralaguppi, M. I. *J. Macromol. Sci., Rev. Macromol. Chem. Phys.* **1990**, *C30*, 441−490.
(104) Kenawy, E.-R.; Abdel-Fattah, Y. R. *Macromol. Biosci.* **2002**, *2*, 261−266.
(105) Daly, W. H.; Guerrini, M. M.; Culberson, D.; Macossay, J. In *Science and Technology of Polymers and Advanced Materials*; Prasad, P. N., James, E., Kandil, S., Kafafi, Z., Eds.; Plenum Press: New York, 1998; p 493.
(106) Neut, D.; van de Belt, H.; van Horn, J. R.; van der Mei, H. C.; Busscher, H. J. *Biomaterials* **2003**, *24*, 1829−1831.
(107) Dernell, W. S.; Withrow, S. J.; Kuntz, C. A.; Dewll, R.; Garry, F. B.; Powers, B. E.; Shively, J. E.; Meyer, J. D.; Manning, M. C.; Fal, R. F.; Randolph, T. W. *J. Bioact. Compat. Polym.* **2001**, *16*, 119−135.
(108) Desevaux, C.; Lenaerts, V.; Girard, C.; Dubreuil, P. *J. Controlled Release* **2002**, *82*, 95−103.
(109) Tyagi, P. K.; Gupta, B.; Singh, H. *J. Macromol. Sci., Pure Appl. Chem.* **1993**, *A30*, 303−313.
(110) Imazato, S.; Ebi, N.; Takahashi, Y.; Kaneko, T.; Ebisu, S.; Russell, R.R.B. *Biomaterials* **2003**, *24*, 3605−3609.
(111) Imazato, S.; Torii, M.; Tsuchitani, Y.; McCabe, J. F.; Russell, R. R. B. *J. Dent. Res.* **1994**, *73*, 1437−1443.
(112) Imazato, S.; McCabe, J. F. *J. Dent. Res.* **1994**, *73*, 1641−1645.

(113) Appendini, P.; Hotckiss, J. H. *Innovative Food Sci. Emerging Technol.* **2002**, *3*, 113−126.
(114) Quintavalla, S.; Vicini, L. *Meat Sci.* **2002**, *62*, 373−380.
(115) Begin, A.; Van Calsteren, M.-R. *Int. J. Biol. Macromol.* **1999**, *26*, 63−67.
(116) Brody, A.; Strupinsky, E.; Kline, L. *Active Packaging for Food Applications*; Technomic Publishing Co.: Lancaster, PA, 2001.
(117) Plascencia-Jatomea, M.; Viniegra, G.; Olaya, R.; Castillo-Ortega, M. M.; Shirai, K. *Macromol. Biosci.* **2003**, *3*, 582−586.
(118) Hotckiss, J. *Food Addit. Contam.* **1997**, *14*, 601−607.
(119) Han, J. H. Antimicrobial food packaging. In *Novel Food Packaging Techniques*; Ahvenainen, R., Ed.; CRC Press LLC: Boca Raton, FL, 2003; pp 50−70.
(120) Cutter, C. *J. Food Prot.* **1999**, *62*, 474−479.
(121) Paik, J. S.; Dhanasekharan, M.; Kelly, M. J. *Packag. Technol. Sci.* **1998**, *11*, 179−187.
(122) Goldberg, S.; Doyle, R.; Rosenberg, M. *J. Bacteriol.* **1990**, *172*, 5650−5654.
(123) Cuq, B.; Gontard, N.; Guilbert, S. Edible films and coating as active layers. In *Active Food Packaging*; Rooney, M. L., Ed.; Blackie Academic and Professional: Glasgow, U.K., 1995; pp 111−142.
(124) Pardini, S. Imparting antimicrobial activity to acrylics. U.S. Patent 4,708,870, 1986; [CAN 106: 138910].
(125) Shin, Y.; Yoo, D. I.; Jang, J. *J. Appl. Polym. Sci.* **2001**, *80*, 2495−2501.
(126) Son, Y.-A.; Sun, G. *J. Appl. Polym. Sci.* **2003**, *90*, 2194−2199.
(127) Bajaj, P. *J. Appl. Polym. Sci.* **2002**, *83*, 631−659.
(128) Zhu, P.; Sun, G. *J. Appl. Polym. Sci.* **2004**, *93*, 1037−1041.
(129) Buchenska, J. *J. Appl. Polym. Sci.* **1996**, *61*, 567−576.
(130) Choi, H.-M.; Bide, M.; Phaneuf, M.; Quist, W.; Logerfo, F. *J. Appl. Polym. Sci.* **2004**, *92*, 3343−3354.
(131) Shih, C.-Y.; Huang, K.-S. *J. Appl. Polym. Sci.* **2003**, *88*, 2356−2363.
(132) Makal, U.; Wood, L.; Ohman, D. E.; Wynne, K. J. *Biomaterials* **2006**, *27*, 1316−1326.

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