Chapter 9
Polymer Macromolecules to Polymeric Nanostructures: Efficient Antibacterial Candidates

J. Lakshmipraba, Rupesh N. Prabhu, and V. Sivasankar

Contents

J. Lakshmipraba (✉) · R. N. Prabhu
Post Graduate and Research Department of Chemistry, Bishop Heber College, Tiruchirappalli, Tamil Nadu, India

V. Sivasankar
Department of Civil Engineering, School of Engineering, Nagasaki University, Nagasaki, Japan

Post Graduate and Research Department of Chemistry, Pachaiyappa's College, Chennai, Tamil Nadu, India

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Abstract Microbes pose a serious threat to life among human beings due to numerous infectious diseases. Though there is significant progress in the development of effective antimicrobial drugs, many infectious diseases are still difficult to treat. Polymers render a potential antimicrobial strategy to combat pathogens and gained a considerable attention in the recent past. Polyamine compounds are familiar about their vitality in many biological processes. Conspicuously, polyethyleneimine (PEI) as a polymeric chelating agent draws advantages such as high water solubility, modulation of functional groups, reliable molecular weight and physico-chemical stabilities. As reactive amino groups are abundant, a wide range of chemically modified cations with desirable properties make PEI remarkable. PEI offers an effective antimicrobial property, thanks to the hydrophobicity and positive charge density potentiated by alkylation. N-alkyl-substituted PEI immobilized over various knitted textiles showed evidence of strong bactericidal activity against a variety of airborne bacteria. It has also been realized that the molecular weight of polyethyleneimine and the antimicrobial activity are directly proportional to each other. The structure-activity relationship (SAR) plays a compelling role in comprehending the enhanced antimicrobial activity of linear and branched PEIs. In accordance with the above details, the present chapter focuses on the synthesis, characterization and antimicrobial applications of certain polymers, polymer metal complexes and nanopolymer materials.

Keywords Polyethyleneimine (PEI) · Antimicrobial property · Nanopolymer · Structure-activity relationship

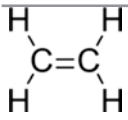
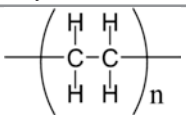
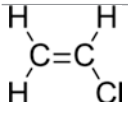
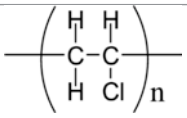
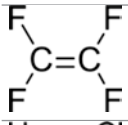
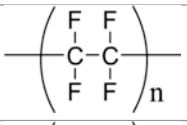
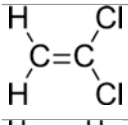
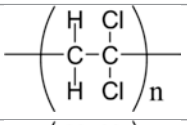
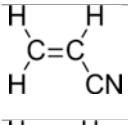
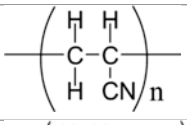
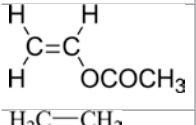
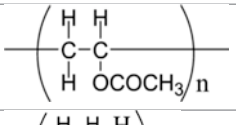
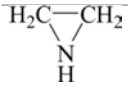
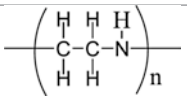
9.1 Introduction about Polymer

A polymer can be a rationalized chemical compound with large molecules made up of copious repeating units. In other words, polymer is a long-chain macromolecule that consists of multiple small repeating units that are linked together to form an array. The small repeating units are known as monomers. In the early 1920s, chemists suggested that most of the molecules have molecular weights of a few thousands, and molecules with higher molecular weight cannot be prepared. Further, it was suggested that macromolecules are aggregates of small molecules. Hermann Staudinger, a German chemist working in organic chemistry, initially questioned this point of view. He studied various compounds existing in nature such as rubber, proteins, cellulose and starch. He proposed that they were macromolecules composed of more than 10,000 atoms. He came up with a polymeric structure for rubber where copious numbers of isoprene units were held together by strong covalent bonds (Staudinger 1920). In 1953, for "his discoveries in the field of macromolecular chemistry", he was awarded the Nobel Prize in Chemistry. The terms

"monomer" and "polymer" were derived from Greek words, "mono (one)", "poly (many, numerous)" and "meros (part)".

Polymers are an integral part of the modern world. Many objects that we use in our day-to-day life have polymeric origin. Polymers can be characterized by uneven molecular weight (depending on its source or synthetic strategy or method of extraction). They have low specific gravity and generally resist corrosion. A polymer, based on the nature and number of functional groups present in the backbone, can form one-, two- or three-dimensional networks. Each repeating unit present in the polymer is known as -mer (or the basic unit); where the term "polymer" means a large number of repeating units. These repeating units contain mainly carbon and hydrogen, though sometimes other atoms such as oxygen, nitrogen, sulphur, chlorine, fluorine, silicon or phosphorous can also be present. A long chain is formed when many -mers are chemically attached together. Polymers differ from other molecules for the reason that due to their long-chain nature, the chains are intertwined in solution or in solid state or, for specific macromolecular structures, to become lined up as regular arrays in solid state. These molecular characteristics result in properties similar to those of solids, such as fibre-forming qualities, elasticity, strength and film-forming properties, which are normally not seen in small molecules. Many objects in daily life are composed of polymers; some of which are listed in Table 9.1.

Table 9.1 Polymers and applications

Monomer structure	Polymer structure	Name of the polymer	Applications/uses
		Polyethylene	Plastic bags, bottles, toys, electrical insulation
		Polyvinyl chloride (PVC)	Pipes, bags for intravenous solutions, tubing, floor coverings, non-food packaging
		Polytetrafluoro-ethylene (PTFE)	Non-stick coatings, electrical insulation
		Polyvinylidene chloride (saran)	Food wrap
		Polyacrylonitrile (Orlon or PAN)	Fibres for textiles, carpets, upholstery
		Polyvinyl acetate	Carpenter's glue, paper adhesive
		Polyethylenimine (PEI)	Detergents, CO_2 removal in space craft, adhesives, water treatment agents, cosmetics

9.2 Classification of Polymers

The following are some of the basic ways in which polymers can be classified (Young and Lovell 1991; Carreher Jr. 2003; Gupta 2010).

9.2.1 Classification of Polymers Based on Source

Depending on the source of origin, polymers can be grouped into three types.

1. ***Natural Polymers***: Natural polymers are the polymeric materials which are found in nature in plants, animals and other natural sources. Some common examples of natural polymers include cellulose and starch (polymers of glucose, which are found in plants), proteins (polymers of amino acids, which are found in humans and animals) or natural rubber (polymer of isoprene, which is obtained from the latex of rubber trees).
2. ***Synthetic Polymers***: These polymers can be synthesized in laboratories. They are produced commercially by industries for the day-to-day needs of mankind. Some commonly used polymers in our daily life include polyethylene (used in plastic for packaging), bakelite (used as electrical switches and many other electrical appliances), nylon (used in fishing nets, dress materials, etc.), polyvinyl chloride ([PVC] used in pipes, as insulation on electrical cables), Teflon (used as coating in non-stick pans), etc.
3. ***Semi-Synthetic Polymers***: Semi-synthetic polymers are polymers procured from natural sources and then making further modification by physical or chemical treatment in a laboratory before obtaining their final form of commercial and practical importance. Vulcanized rubber, cellulose acetate, etc. belong to this category.

9.2.2 Classification of Polymers Based on Structure

Polymers can be classified into three different types based on their structure as shown in Fig. 9.1.

1. ***Linear Polymers***: The monomer units in these are covalently attached together to form long continuous carbon-carbon chains, the remaining two valencies being satisfied by hydrogen or other small atoms or functional groups. They have high densities and high melting points due to greater packing efficiency. One example for linear polymers is polyvinyl chloride (PVC) which is largely used for the manufacture of electric cables, pipes, etc.

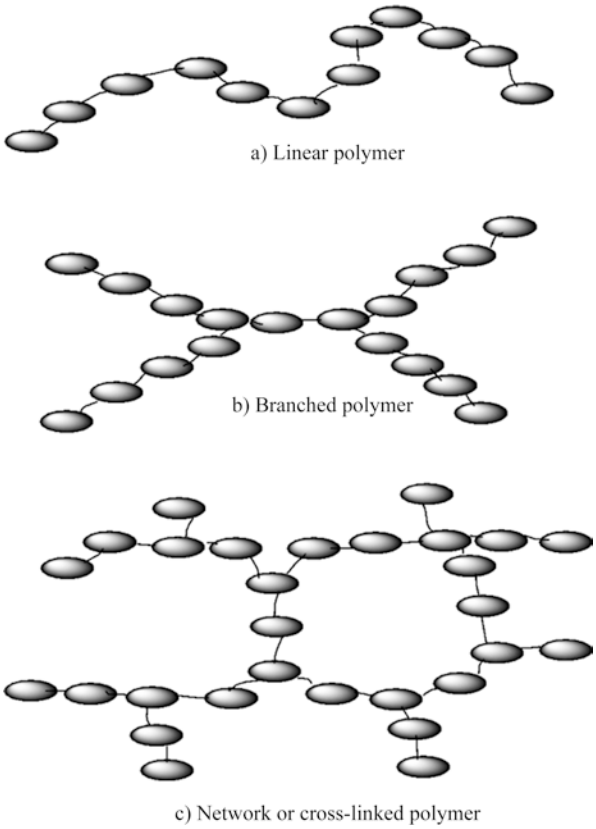


Fig. 9.1 Classification of polymers accroding to their structure

2. ***Branched Chain Polymers***: The structure of these polymers can be considered as branches emerging from random points on a single linear backbone. A small chain is generally covalently attached to the main linear backbone. As a result of branching, the polymers are less dense with low melting points. This is because, the polymers are not closely packed. Low-density polyethylene (LDPE) is generally used in manufacture of plastic bags and multipurpose containers. In addition, brush polymers, graft polymers, star-shaped polymers, comb polymers and dendrimers fall into this category.
3. ***Cross-linked or Network Polymers***: Here, the monomer units are linked together, resulting in the formation of a three-dimensional network. The monomers can have multiple functional groups and are connected randomly by covalent bonds between two or more linear chains. They are, however, brittle and hard. Common examples are bakelite (used as electrical insulators), vulcanized rubber (used in tyres), etc.

9.2.3 Classification of Polymers Based on Mode of Polymerization

Based on the manner of polymerization, polymers can be stratified into two as follows.

1. ***Addition Polymers***: Addition polymers are obtained by the recurring addition of the monomer units. The monomer units generally possess unsaturated bonds (double bonds or triple bonds). In this type of polymerization, small molecules like water or alcohol, etc., are not expelled (i.e., no by-product is obtained). The empirical formulae of addition polymers are the same as their monomers. They are generally initiated by the presence of free radical (Free-radical addition polymerization), proton, or Lewis acid (cationic addition polymerization), anions such as amide or alkoxide (anionic addition polymerization). Polymerization of ethane to form polyethene or styrene to polystyrene are some examples (Fig. 9.2).
2. ***Condensation Polymers***: The condensation reaction of monomers, accompanied by the elimination of small molecules such as water, HCl, ammonia, alcohol, etc., results in the fabrication of condensation polymers. Two or more functional groups are generally present in the monomers. The empirical formulae of condensation polymers and their monomers are different. A common example is the formation of nylon-66 (a polyamide) by the polymerization of adipic acid and hexamethylenediamine along with elimination of water molecules (Fig. 9.3).

9.2.4 Classification of Polymers Based on Molecular Forces

The properties manifested by polymers are a function of the extent of the force of attraction between the polymer molecules. Polymers can be categorized into four, based on the nature of the forces of attraction between them.

1. ***Elastomers***: Elastomers have elasticity with high viscosity. They are rubbery-like solid polymeric materials. When a small force is applied, they are easily expandable. When the force is removed, they, generally, recover their original shape. These kinds of polymers are held together by weak intermolecular forces. They are examples of amorphous polymers. The most common examples of these are rubber bands, hair bands and vulcanized rubber.

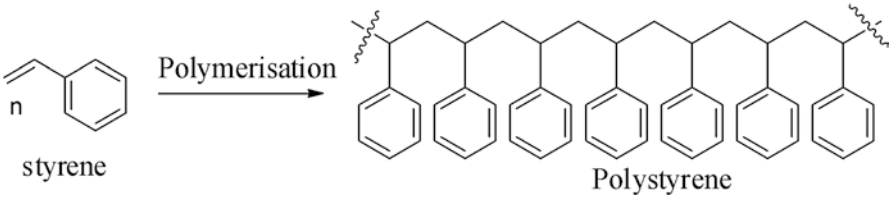


Fig. 9.2 Polymerization of styrene to polystyrene

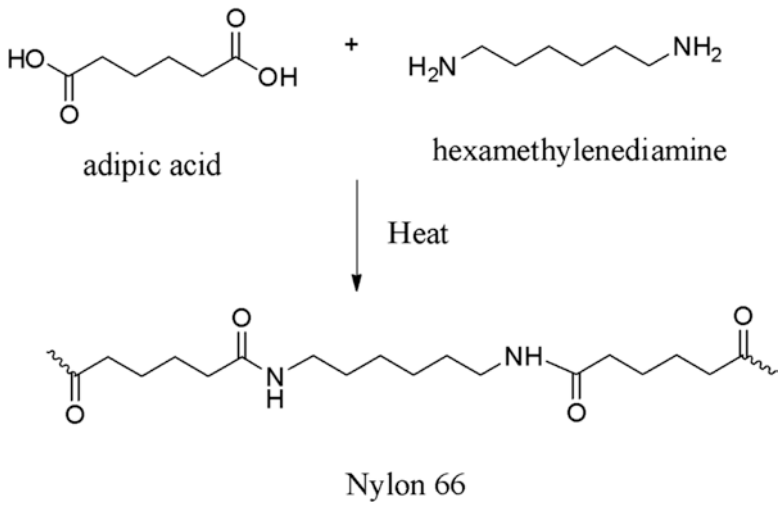


Fig. 9.3 Formation of nylon-66 by the polymerization reaction

2. ***Fibres***: These polymers are long and very thin in diameter. They can be easily entwined in fabric. They resemble a thread. The intermolecular forces between the chains are strong, which may be either dipole-dipole interaction or hydrogen bonds. The chains are thus closely packed and are inelastic with high tensile strength. Fibres are known to have abrupt and high melting points. Fibres can be natural or synthetic. Common examples are nylon-66, silk and dacron.
3. ***Thermoplastics***: Thermoplastics are long-chain polymers. The chains in the polymer are usually held together by van der Waal's forces. On the application of heat, these polymers become soft and upon cooling, they form a hard mass. They can be reheated, reshaped and frozen repeatedly and are thus mechanically recyclable. They do not possess any cross-linking bonds. Common examples are polyethylene, polystyrene, polycarbonate or polypropylene.
4. ***Thermosetting Plastics***: Thermosetting plastics are polymers with low molecular masses. Upon heating, cross-links are formed between the polymer chains; thereby, the polymers become hard and infusible. This reaction is irreversible, and once set, it is not possible to modify their shape. They are a three-dimensional network. They are resistant to consecutive mechanical deformation or softening due to heat or attack of solvents. Example: bakelite (a phenol-formaldehyde resin).

9.2.5 Classification of Polymers Based on the Type of Monomer Involved in the Structure

A polymer may possess identical or different monomers and can then be classified as homopolymers or copolymers as shown in Fig. 9.4 (Singh and Dubey 2009).

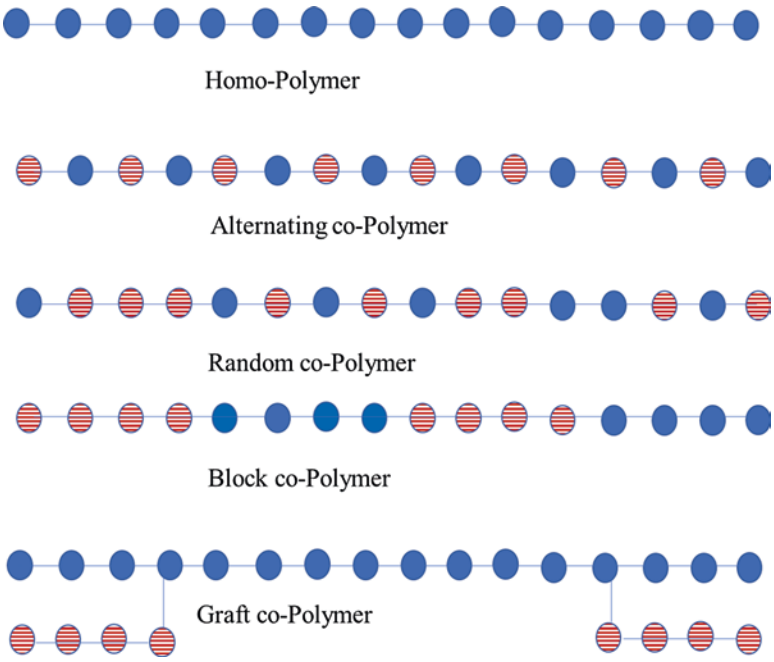


Fig. 9.4 Classification of polymer base on the monomer type

1. ***Homopolymers***: When identical monomer is repeated throughout the chain of the polymer, it is known as homopolymer. Or in other words, they have same monomeric units. Polyvinyl chloride, polyethylene, polystyrene and are some common examples.
2. ***Copolymers***: When monomers forming the polymers are different along the entire chain, it is known as copolymer. Copolymers resulted by the polymerization of two, three and four different monomeric species are also called bipolymers, terpolymers and quaterpolymers, respectively. Copolymers can be further divided into multiple types:

   (a) ***Alternating Copolymers***: In this type of copolymers, two monomeric units are arranged in an alternating fashion. The two monomers combine in 1:1 ratio. An example is copolymer of is nylon-66, which is synthesized by the polymerization of adipic acid and hexamethylenediamine.
   (b) ***Random Copolymers***: In this, the two monomers combine with each other in any order. The ratio of the monomers incorporated into the copolymer depends on variety of factors such as the properties of the individual monomers, the conditions in which the polymerization takes place, the conversion of the polymerization, etc.
   (c) ***Block Copolymers***: In this type of copolymer, all of similar types of monomer are assimilated in one part of the chain, and then all of the other is reacted in somehow. A block copolymer can be considered to be two homopolymers fused together at one of the ends.

(d) ***Graft Copolymers***: These polymers are obtained, when a polymeric chain of one type of monomer gets grafted onto a polymeric chain of another monomer.

9.2.6 Classification of Polymers Based on Tacticity

Tacticity may be defined as the geometrical arrangement (orientation) of the pendant groups of the monomer units with respect to the polymeric backbone (main chain). In other words, it is the relative stereochemistry of adjacent chiral carbon atoms within a polymer. On this basis, polymers may be classified into three types as shown in Fig. 9.5.

1. ***Isotactic Polymers***: In isotactic polymers, all the pendant groups or substituents are situated on the same side of the polymeric backbone. Isotactic polymers are generally semi-crystalline and often form a helical configuration. Polypropylene formed by Ziegler-Natta catalysis is an example of isotactic polymer.
2. ***Syndiotactic Polymers***: In syndiotactic polymers, the substituents have alternate positions along the polymeric backbone. Syndiotactic polystyrene, which is prepared by metallocene catalysis polymerization, is crystalline with a melting point of 161 °C. Gutta percha, which is chemically same as natural rubber, is also an example for syndiotactic polymer.
3. ***Atactic Polymers***: In atactic polymers, the substituent groups are randomly positioned along the polymeric backbone. Atactic polymers are usually amorphous, due to the random nature. Polyvinyl chloride, a polymer that is formed by free-radical mechanism, is usually atactic.

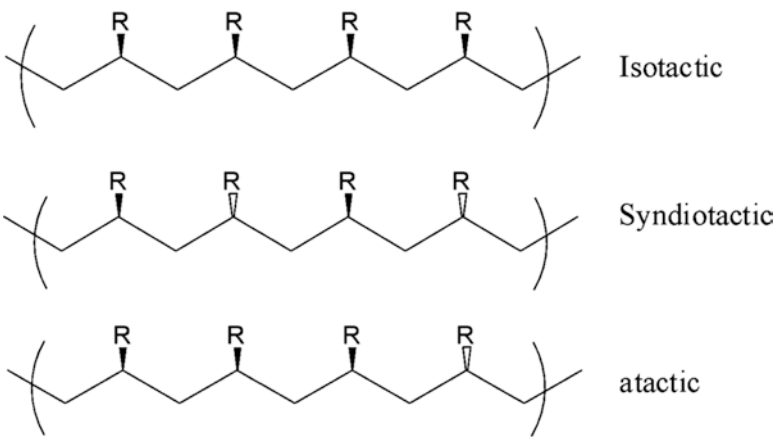


Fig. 9.5 Classification of polymer based on geometrical arragement

9.2.7 Biopolymers

Biopolymers are polymers that occur within living organisms. Some biopolymers can also be chemically synthesized these days from biological materials. Biological macromolecules or biopolymers can be grouped into four. They are lipids, carbohydrates, nucleic acids and proteins. These polymers are made up of different monomeric units and serve different functions.

1. ***Lipids***: They are biomolecules that do not interact appreciably with water molecules, that is, they are insoluble in water. They can be further classified as waxes, fats, phospholipids, saccharolipids and sterol lipids. Fatty acids are lipid monomers with a carboxyl group attached to one end of a long-chain hydrocarbon. Fatty acids form complex polymers such as triglycerides, phospholipids and waxes. Steroids or sterol lipids are made up of four fused carbon ring-like structures. They behave as hormones and signalling molecules. In saccharolipids, the carboxylate group of the fatty acids are attached to the sugar backbone. Lipids form cell membranes and protect the organs. Further, they insulate the body and help to store energy.
2. ***Carbohydrates***: They are biopolymers that are consisting of sugar monomers. They are prime requisite for the storage of energy. Carbohydrates are also known as saccharides or sugars and, their monomeric units are known as monosaccharides. Carbohydrates are obtained by the condensation polymerization of same or different monosaccharide units. The monomeric units are held together by glycosidic bonds. Some carbohydrates are linear (as in amylase) whereas some can be branched (as in amylopectin). Glucose is an important monosaccharide. It acts as the energy source during cellular respiration by breaking down into smaller molecules. Cellulose and starch are other examples of polysaccharide made up of glucose monomers.
3. ***Nucleic Acids***: They contain polynucleotide chain made up of nucleotide monomers. Deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) are examples. For the protein synthesis, nucleic acids contain instructions. They are carriers of genetic information from one generation to the next.
4. ***Proteins***: They are large biomolecules which form complex structures. Amino acid monomers are fused together to form proteins. They play a vital role in many biological functions such as muscle movement, transportation of molecules, etc. Haemoglobin, collagen, antibodies and enzymes are examples.

9.2.8 Inorganic Polymers

There are four main classifications of inorganic polymers as discussed below (Archer 2001; Rahimi 2004).

1. ***Wholly Inorganic Polymers***: They are the major components present in soil, sand and mountains. They find applications as abrasives, fibres, coating materi-

als, cutting materials, building and construction materials, flame retardants, lubricants, catalysts, etc. Common examples are carborundum (silicon carbide), fibrous glass, Portland cement, boron nitride, silica, antimony(III) oxide, poly(sulphur nitride), etc.

2. ***Inorganic-Organic Polymers***: They contain organic moieties attached to inorganic units in the chain. The area of this class of polymers is voluminous, the most important being polysilanes, poly(carbosilane), polysiloxanes, polyphosphazenes, polycarbophosphazenes, etc. They generally possess strong electronic absorption, high conductivity, photoconductivity, photosensitivity and find applications in semiconductors, non-linear optical materials, electro-optical materials, carrier species for biologically active agents, chemotherapeutic models, etc.
3. ***Organometallic Polymers***: The organometallic polymers are made of more than 40 elements consisting of main group of metals (such as Si or Ge), transition metals or rare earth elements along with the elements (C, H, N, O, B, P, halides) which are found in organic polymers. The variations of organometallic polymers appear to be endless. These new types of materials have salient features of both organic and inorganic materials such as low density, different structural and functional properties, high electrical conductivity and high temperature stability. Metals may be pendent or may be present in the main chain.
4. ***Hybrid Organic-Inorganic Polymers***: Countless different combinations of the organic and inorganic moieties are possible, and hence, a library of hybrid organic-inorganic polymers of fascinating properties can be synthesized by the incorporation of appropriate building blocks. They are multifunctional with a wide range of interesting properties and applications. Some of these polymers display enhanced mechanical strength, resistance to abrasion, improved weathering and outstanding corrosion resistance, excellent adhesion on metal surfaces, reduced effect on health and environment, etc. These new materials are also sought for improved optical properties, electrical properties, luminescence, ionic conductivity, as well as chemical or biochemical activity. Some examples are epoxy polysiloxanes, perfluorosulfonic acid polymers, polyaryletherketones, polyarylethersulfones, sulfonated polyimides, polybenzimidazoles, etc.

9.2.9 Polymer-Anchored Metal Complexes

The polymer-anchored metal complexes are of immense interest in industry and academia due to their extensive and interesting applications. This technique of immobilization on an inert support has ground much care due to their simple separation from the reaction mixture, resulting in ease of handling, operational flexibility, greater thermal stability, higher efficiency, better product selectivity, and economy in various industrial processes. Transition metal complexes on polymer support have a wide range of applications in organic synthesis, as curing agent for epoxy resin, as ion exchanger, as catalyst, as oxidizing agents, as reducing agents, as photosensitizers, as agriculturally active reagents, as pharmacologically active reagents, etc.

9.3 Analysis of Polymers

Average molecular weight concept, number average concept (determined by cryoscopy, ebulliometry and osmometry methods), weight average concept (measured by light scattering and ultracentrifuge techniques), viscosity average concept (determined using viscometer), etc., are the various ways molecular weights of polymers can be expressed.

Various techniques can be used for the chemical analysis of polymers. Some of them are listed: nuclear magnetic resonance spectroscopy, elemental analysis, powder x-ray diffraction studies, infrared spectroscopy, mass spectrometry, gas chromatography, electron magnetic resonance spectroscopy, light microscopy, scanning electron microscopy, differential calorimetric analysis, differential thermal analysis, thermogravimetric analysis, etc. The important test methods for measuring the physical properties of polymers are as follows: tensile strength, fatigue, brittleness, ductility, hardness, tear resistance, abrasion resistance, etc.

9.4 Factors Affecting Activity of Antimicrobial Polymers

Antimicrobial activity of polymers is generally reflected as function of counterbalance between multiple factors. Various factors such as molecular weight, hydrophilicity, pH, charge density, temperature, presence of moisture, alkyl chain length, etc., contribute to the antimicrobial activity. Some of the notable factors which affect the antimicrobial activity are portrayed below.

9.4.1 Molecular Weight (MW) Versus Alkyl Chain Length of Polymer

Molecular weight (MW) plays a role in regulating the physical as well as chemical properties of polymers. For polyacrylates and polymethyl acrylates comprising biguanide as sidechain, molecular weight is the deciding factor in governing the bactericidal action. The gilt-edge range reported in the literature is in between 5×10^4 and 1.2×10^5 Da; significant decrease in activity arises beyond the range of the above molecular weight (Palermo and Kuroda 2009).

In the same way, poly(tributyl-4-vinylbenzyl phosphonium chloride) also exhibits the most favourable antimicrobial activity in the range of 1.6×10^4–9.4×10^4 Da (Epand et al. 2004). Further, the role of molecular weight is paradoxical for chitosan, and different reports findings are reported from different research groups. Gram-negative bacteria endured larger challenge than Gram-positive bacteria (Svenson and Tomalia 2005; Lichter and Rubner 2009). Meanwhile, ε-PL, with varying length of the alkyl chain, displayed compelling effects on activity. Polymers of L-lysine residues possessing the chain length of nine displayed excellent inhibition of microbial growth (Park et al. 2004).

9.4.2 Charge on the Polymers

When the positively charged polymers are used, they interact with the bacterial cells in a better way via electrostatic interaction. In chitosan system, as the degree of deacetylation increases, the charge density also increases. Further, this will increase the electrostatic interaction and consequently enhance the antimicrobial activity (Takahashi et al. 2013). A better antibacterial inhibition towards *Staphylococcus aureus* at larger degree of deacetylation by chitosan system was also described (Porter et al. 2000). Furthermore, the modification in chitosan structures like guanidinylated chitosan (Schmitt et al. 2006) and asparagine N-conjugated chitosan oligosaccharide (Schmitt et al. 2004) produced very high antimicrobial activity. But, in the case of N-carboxyethyl chitosan, there is no amino group. So, this compound fails to show any antimicrobial activity (Tossi et al. 2000).

9.4.3 Hydrophilic Interaction of Polymers

One of the most indispensable prerequisites for the compound to demonstrate antimicrobial activity is hydrophilicity. By changing the MW and hydrophobic groups in the amphiphilic polymethacrylate derivatives, the antimicrobial activities were enhanced (Venkataraman et al. 2010). In addition, derivatization of chitosan such as saccharization, acylation, alkylation, metallization and quaternization showed high water solubility and also higher antimicrobial activity than the underivatized original form (Mowery et al. 2007; Dohm et al. 2010).

9.4.4 Role of Counter Ions

In the case of quaternary ammonium/phosphonium compounds, counter ion effect played a crucial role. Due to the strong interaction affinity of counter ions with quaternary compounds, less antimicrobial activity was sensed for these, resulting in sluggish release of free ions in the reaction medium. When compared to free quaternary ammonium compounds, higher antimicrobial activity was observed for quaternary ammonium compounds having chloride and bromide as counter anions (Zhang et al. 1999).

9.4.5 Effect of pH

In the case of chitosan and other polymers having amphoteric nature, a variation in activity with the change in pH has been reported. The antimicrobial activity was controlled by pH for chitosan. Due to increased water solubility and formation of polycations at acidic pH, the activity was maximum in this condition. Yet, at basic pH, there are no reports on antimicrobial activity (Epand et al. 2008).

9.5 Antibacterial Activity

Table 9.2 lists the microorganisms used in this chapter. The terminology used in this chapter consists of: minimum inhibitory concentration (MIC), which is the lowest concentration of the compound or drug that prevents visible microorganism growth after overnight incubation; minimal bactericidal concentration (MBC), which is the lowest concentration of an antibacterial compound/drug mandatory to kill a bacterium over a fixed, somewhat extended period, under a specific set of conditions; and IC_{50} which is the half-maximal inhibitory concentration.

Table 9.2 Microorganisms described in the text

Gram-negative bacteria	*Bacteroides forsythus, Chlamydia pneumoniae, Cellulophaga lítica, Chlamydia trachomatis, Escherichia coli, Enterobacter aeruginosa, Haemophilus influenzae, Klebsiella pneumoniae, Mycoplasma gallisepticum, Neisseria gonorrhoeae, Pseudomonas fluorescens, Proteus vulgaris, Pseudomonas putida, Porphyromonas gingivalis, Pseudomonas aeruginosa, Pseudoalteromonas haloplanktis, Proteus mirabilis, Serratia liquefaciens, Stenotrophomonas maltophilia, Salmonella typhi, Spiroplasma citri, Salmonella typhimurium, Spiroplasma floricola, Salmonella enteritidis, Shigella boydii, Shigella dysenteriae, Shigella sonnei, Spiroplasma melliferum, Yersinia pseudotuberculosis, Yersinia enterocolitica*
Gram-positive bacteria	*Actinomyces viscosus, Acholeplasma laidlawii, Bacillus subtilis, Bacillus cereus, Bifidobacterium bifidum, Brochothrix thermosphacta, Bacillus macroides, Bacillus coagulans, Bacillus megaterium, Bacillus thuringiensis, Bifidobacterium breve, Clostridium difficile, Enterococcus faecium, Enterococcus faecalis, enterococcus hirae, lactobacillus salivarius, Listeria monocytogenes, lactobacillus casei, Mycobacterium tuberculosis, mycobacterium smegmatis, Micrococcus luteus, Pediococcus pentosaceus, Streptococcus pneumonia, Staphylococcus hominis, Streptococcus pyogenes, Staphylococcus epidermidis, Streptococcus mutans, Staphylococcus aureus, Staphylococcus haemolyticus, Staphylococcus citreus, Staphylococcus saprophyticus*
Fungi	*Alternaria alternata, Aspergillus terreus, Aspergillus fumigatus, Aspergillus Niger, Aspergillus flavus, Botrytis cinerea, Byssochlamys fulva, Cladosporium cladosporioides, Chaetosphaeridiaceae globosum, Eurotium tonophilum, Fusarium oxysporum, Fusarium moniliforme, Mucor circinelloides, Microsporum gypseum, Pyrobaculum islandicum, Penicillium funiculosum, Penicillium digitatum, Penicillium citrinum, Penicillium pinophilum, Rhizopus oryzae, Rhizoctonia bataticola, Rhizopus stolonifer, Stachybotrys chartarum, Sporotrichum pulverulentum, Trichophyton mentagrophytes, Trichoderma virens, Trichoderma lignorum, Trichoderma viridis, Trichophyton rubrum*
Yeasts	*Aureobasidium pullulans, Candida glabrata, Candida albicans, Cryptococcus neoformans, Candida tropicalis, Candida parapsilosis, Candiada utilis, Debaryomyces hansenii, Hanseniaspora guilliermondii, Kluyveromyces fragilis or marxianus, Pichia stipitis, Pichia jadinii, Rhodotorula rubra, Saccharomyces cerevisiae*
Algae	*Amphora coffeaeformis, Dunaliella tertiolecta, Navicula incerta*
Viruses	*Herpes simplex, Human Immunology, Influenza A, Simian 40, Varicella zoster*

9.5.1 Polyethyleneimines

A variety of polymers such as polyamines, polyamino acids, polystyrene, polyvinyl chloride, etc., can be used to anchor metal complexes. This chapter focuses only on polyethyleneimine (PEI) as the polymeric backbone, as it is beyond the scope of this chapter to cover all types of polymer backbones.

Polyethyleneimines (PEIs) are synthetic, non-biodegradable, cationic molecules. The polymer molecule contains amine function as repeating units between two aliphatic carbon chains. A branched polyethyleneimine (BPEI), on the other hand, contains all kinds of 1°, 2°, and 3° amino functional groups in its structure. But, in the case of linear polyethyleneimine (LPEI), only 1° and 2° amine groups are present in its structure. Ring-opening polymerization of aziridine route was generally adopted for the synthesis of BPEI. When the reaction condition is altered, different degrees of branching can be achieved (Fig. 9.6).

LPEI synthesis was made effective by ring-opening polymerization reaction of 2-ethyl-2-oxazoline and followed by hydrolysis. LPEI has a melting point ~75 °C and is solid at room temperature. It is soluble in hot water at low pH. They are readily soluble in organic solvents. Irrespective of the molecular weight, BPEI is liquid. PEI have enormous range of applications in diverse fields, because of their polycationic character. Some of applications of PEI are discussed here.

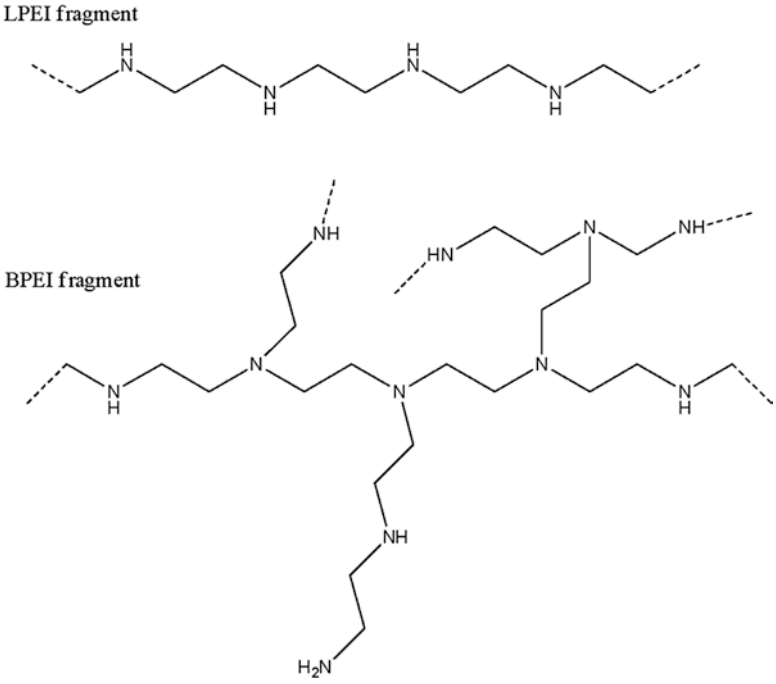


Fig. 9.6 Structure of PEI

PEI has a large number of reactive amino groups. To attain enticing desirable physicochemical properties, modification in PEI is generally carried out. First, for the unsubstituted PEI, antimicrobial activity was scrutinized by the covalent interaction of PEI on the surface of glass material. But, in this case, when compared with an untreated surface of glass, no reduction in microbial count was seen. The primary significant requirements of antimicrobial activities are hydrophobicity and positive charge density. Incorporation of alkyl groups of varying lengths improves both these effects. Many efforts were done towards the incorporation of N-alkyl-PEI to numerous macroscopic and nano-scaled particles, commercial plastics, textiles, glass, different natural and synthetic materials, organic and inorganic compounds and monolithic and porous surface materials. All these above-mentioned derivatives stemmed in near 100% refrainment of air- and water-borne microbes, together with antibiotic- and pathogenic-resistant strains without any report of emergence of resistance. The foremost criterion reported for the mechanism of antibacterial activity was cell membrane rupture. For the mammalian cells (monkey kidney), these surfaces are nontoxic. A significant bacterial activity against several air-borne bacteria was exhibited in the case of N-alkylated PEI immobilized over a wide range of woven textiles such as wool, cotton and polyester. There is a compelling correlation between MW of the PEI and its activity. When MW of the PEI is high, excellent antimicrobial activity is generally observed, whereas negligible activity is observed for PEI polymers having low molecular weight. Substituted PEIs were also employed as contrary to *Candida albicans*. Dimethylaminoethyl methacrylate anchored to PEI produces a reduction in bacterial growth of up to 92% in the prosthetics used by laryngectomized patients. Substituted PEIs are encouraging coating materials of various other medical accessories.

The minimum inhibitory concentration (MIC) was analysed for the PEI to understand the antimicrobial activities. It is the least strength of PEI needed to entirely suppress the bacterial growth under standard experimental conditions. Both LPEI and BPEI are having different water solubilities, and hence, various procedures were followed for the preparation of solutions required for the antibacterial assay. BPEIs are soluble in hot water; LPEIs have poor water solubility even at low concentrations. But, they are willingly soluble in ethanol. Hence, in order to prepare the assay stock solution with a variety of polymer concentrations, LPEI was dissolved in ethanol initially, and then, consecutively, twofold of 0.01% acetic acid was added. The BPEIs are highly soluble in water, and the bulk solutions were thus made in tris-buffered saline. Bacteria solution was taken in Mueller-Hinton broth, and then, this was treated with the bulk solutions in order to figure out the MIC. Five percent ethanol was the highest concentration of alcohol in the solution to be estimated. Further, the control experiments using different solvents did not show any notable variation in the bacterial upsurge even after incubating for 18 h, which was evaluated by turbidity of the solution as well as OD_{600}.

Various BPEIs were examined; it was inferred that B-$PEI_{1.1}$ showed the minimum MIC value of 250 mg mL^{-1} against *Escherichia coli*, whereas $BPEI_{12}$ did not show any significant activity (MIC > 1000 mg mL^{-1}). These results indicated

that increasing molecular weight does not increase the antibacterial activity. For comparison, under the same assay conditions, natural antimicrobial peptide magainin 2 (MW = 2300) showed MIC of 125 mg mL^{-1}. In addition, from the titration results, it was registered that $BPEI_{12}$ had 68 mol% of positively charged ammonium groups, whereas other BPEIs had greater content of positively charged ammonium groups. The results of reversed-phase high-performance liquid chromatography suggested that the intrinsic hydrophobicity of $BPEI_{1.1}$ was lower than that of $BPEI_{12}$. Though it was described earlier that in the case of cationic amphiphilic PEIs (Pasquier et al. 2008) and poly-(propylene imine) dendrimers (Chen et al. 2000; Chen and Cooper 2002) increasing the hydrophobicity increases their antimicrobial activity, PEI_{12} exhibited a curtailed activity against *E. coli* when compared with remaining PEIs. MIC value of LPEIs was found to be 31 mg mL^{-1} (*E. coli*), which was most likely due to the similar molecular weight (MW = 4400 and 6500). Additionally, most active $BPEI_{1.1}$ displayed MIC value eight times higher than that of the LPEIs. The observation suggested that the LPEIs inhibit the growth of *E. coli* to a greater extent. BPEIs quaternized with long alkyl groups were reported to have reduced antibacterial activity due to excess hydrophobicity. This could be due to the formation of aggregates, which results in the lowering of the number of polymer chains available for interaction with the cell membranes of the bacteria (Pasquier et al. 2008). Based on the results of dynamic light scattering studies, it was inferred that unmodified BPEI and LPEI did not show any light scattering in MH broth assay solution or in the phosphate buffer solution. This implies that, under the studied experimental conditions, they did not form any aggregates that can reduce the interaction with the bacterial cell membranes, thereby decreasing the efficiency.

The hydrophilic nature of unmodified BPEIs was found to be effective to magnify the number of active polymer chains against bacterial cells. The MICs of BPEIs were found to be 16–31 mg mL^{-1}, when the activity was screed against the Gram-positive bacteria *S. aureus*; however, under similar conditions, magainin-2 showed no potent activity (MIC > 250 mg mL^{-1}). As inferred from the results, the MIC values obtained were considerably lower than those for *E. coli*. $BPEI_{12}$ did not produce any activity against *E. coli* (MIC > 1000 mg mL^{-1}); however, *S. aureus* showed MIC value of 16 mg mL^{-1}, yielding a MIC selectivity index (i.e., the ratio of MIC *E. coli* to that of MIC *S. aureus*) of greater than 64. Other BPEIs were also found to exhibit the MIC selectivity index higher than 8. From these results, it was understood that the BPEIs were more selective active against *S. aureus* than *E. coli*. Similarly, both LPEIs showcased an MIC value of 8 mg mL^{-1} for *S. aureus*, which was fourfold lesser when compared to that of *E. coli*. Thus, the LBEIs showcased greater selectivity towards *S. aureus* when compared to that of *E. coli* (having MIC selective index of 4). It was further described that antibacterial activity can be altered by modifying the counter anions used for ammonium groups, although the mechanism and mode of interaction is still unclear (Chen et al. 2000; Kanazawa et al. 1993; Lienkamp et al. 2009). So it was believed that negatively charged ions, if present, may influence the antibacterial activity of PEIs.

9.5.2 Hyperbranched and Dendritic Polymers

Highest positive charge density on BPEI plays a vital role in its antimicrobial activity. Modification of substituents in the amine groups to change the hydrophobic interaction in the BPEI polymeric backbone was found to reinforce the antimicrobial activity. Water solubility is generally preserved in the case of quaternized BPEI, but they have competence to absorb the bacterial membrane also. As such, numerous reports are there to improvise the degree of quaternization and the substituents on the alkyl chain in the ammonium groups. By using tertiary amination reaction protocol, quaternized BPEI was synthesized (Gao et al. 2007). *E. coli* bacterium was used to the study the antibacterial properties of these quaternized BPEI by colony counting method and by using enzyme activity method. The effect of pH on the biocidal activity was also evaluated. The outcome of the study revealed magnificent results due to the presence of cationic groups that influence the activity of the polymer. For the *E. coli* protein, the isoelectric point is 4.5, signalling a minimum response in antibacterial activity with change in pH. In the case of quaternized BPEI, for pH more than this isoelectric point value, increase in the antimicrobial activity was described and reaching a constant value in weakly acidic to basic pH.

Sterilization is the key factor that results in the activity of polymer. This was confirmed by enzyme activity studies. Small quaternary ammonium salts are used to imitate this work. Cell death in polymer was as a result of eruption of cell membranes. The contents between the cells are thus released, similar to that reported in the case of small molecular quaternary ammonium compounds. BPEI was further prepared by functionalization of the 1° amine groups with tetrasubstituted ammonium groups, varying the length of the alkyl chains and introduction of allylic and benzylic groups (Pasquier et al. 2007, 2008). This strategy fine-tunes the length of the hydrophobic groups and modulates the hydrophilic to hydrophobic balance in the BPEIs and also the molecular weight of the functionalized BPEIs. Their antimicrobial activity was then evaluated against *Bacillus subtilis* and *E. coli*. The MICs of *B. subtilis* in the range of 0.03–0.04 mg mL^{-1} were reported, whereas the MICs for *E. coli* were ten times higher. It was inferred that, in this case, the activity decreases with increasing molecular weight. Moreover, increase in the ratio of hydrophobic moiety when compared to the cationic groups increases the activity (Pasquier et al. 2008).

9.5.3 Polymer-Metal Complexes

Arunachalam and co-workers reported a variety of polymer metal complexes containing copper(II), in which the percentage of Cu(II) in the polymer was varied. Complexes of the formulation [Cu(phen)(L-tyr)BPEI]ClO_4, [Cu(phen)(L-thr)(BPEI)]$ClO_4 \cdot 2H_2O$, [Cu(phen)(L-arg)BPEI]Cl, [Cu(phen)(L-phe)(BPEI)]$ClO_4 \cdot 4H_2O$, and [Cu(phen)$_2$(BPEI)]$Cl_2 \cdot 4H_2O$, (where L-Thr = L-theronine, L-arg = L-arginine, L-tyr = L-tyrosine, L-phe = L-phenylalanine, phen = 1,10-phenanthroline)

were synthesized (Kumar and Arunachalam 2007, 2009; Kumar et al. 2008; Lakshmipraba et al. 2013, 2017). Disc diffusion method was employed against various bacteria and fungi (*C. albicans, Pseudomonas aeruginosa, E. coli, B. subtilis, S. aureus*) to evaluate the antimicrobial activity, and the results were compared with control drugs such as clotrimazole and ciprofloxacin. The studies implied that the antimicrobial activity of the polymer metal complexes was higher in the case of bacteria. Further, the antimicrobial studies and cytotoxicity studies were performed using MTT assays and other in vitro studies. The results revealed that the polymer metal complexes possessing a greater degree of coordination exhibited higher activity and were specific for cell rupturing.

9.5.4 Nanoparticles

Numerous advantages of nanoparticles arise from their small size and unique properties (Prasad et al. 2016). So, many studies were carried out by incorporating metallic nanoparticles (such as titanium oxide, silver, copper) into polymeric material so as to obtain pivotal antibacterial activity. It is an added advantage of nanosized materials. Moreover, antimicrobial activities in many health care areas using polymer-nanoparticles have gained significant attention.

Dental research is one of the areas where, in the last few years, dental restoration materials has attained much attraction due to their clinical survival, which was considered as an important criteria and timely replacement (Beyth et al. 2014a, b). To answer this situation, nanoparticles from cross-linked quaternary PEI incorporated into resin were synthesized and were then optimized for charge, size, thermal stability and antibacterial action (Farah et al. 2013). The above-mentioned nanoparticles were effective against S. *aureus, Staphylococcus epidermidis, P. aeruginosa* and *E. coli*. One percent loading of nanoparticles on resin shows complete inhibition of *E. faecalis* and *S. aureus*, whereas a 2% loading of nanoparticles was required for other bacteria. Nanoparticles on resin offer the advantage of being biocompatible. But, they are not able to diffuse in agar plate (Beyth et al. 2006, 2008).

Antimicrobial action of PEI nanoparticle-containing composite resins was investigated. They removed the formation of bacterial plaque. Further, they protect the surface of composite resin from roughness, which then inhibits the formation of secondary carriers (Beyth et al. 2010). Quaternary ammonium PEI nanoparticles possessing *N*-octyldimethyl residues were reported to have good antibacterial action (Domb et al. 2013). Silica nanoparticles with functionalized quaternary ammonium moieties were also reported by addition of PEI into silica nanoparticle. This was further cross-linked with diiodopentane, followed by alkylation using octyl iodide and quaternization using methyl iodide (S-QAPEI). The size of particles ranges from 2 to 3 μm with the zeta potential of +50–60 mV. They were found to have strong antibacterial activity (Farah et al. 2014; Yudovin-Farber et al. 2010).

9.5.5 Nanopolymers

PEI showed MICs values of 195.31 mg^{-1} for bacteria and 48.83 mg^{-1} for yeast strains. MLCs corresponded to 326 MIC for *S. aureus* ATCC 29213, *S. aureus* (Sa1) and *Acinetobacter baumannii* (Ab1). For *S. epidermidis* ATCC 155, *S. epidermidis* (Se1) and *A. baumannii* ATCC 19606, the minimal lethal concentration (MLC) value was equivalent to 8 × MIC. For *C. albicans*, the MIC and MLC value was reported as 48.83 mg L^{-1}. The MIC of nanoPEI was 1250 mg L^{-1} for *S. epidermidis* (Se1), *C. albicans* ATCC 90028, *S. aureus* ATCC 29213, *C. albicans* (Ca1), S. aureus (Sa1), *S. epidermidis* ATCC 155, and 2500 mg L^{-1} for *A. baumannii* ATCC 19606 and *A. baumannii* (Ab1).

9.5.6 Biofilm Activity

When PEIs of concentrations equivalent to MLC, MIC, 2 × MIC and 0.56 MIC were used, an appreciable decrease in the biofilm metabolic activity was observed. It showed a dose-dependent activity of both clinical and ATCC strains of *A. baumannii* and of *S. aureus* ($P < 0.05$). Also, for *S. epidermidis*, produced inhibition, at all the concentrations, which were not dose-dependent ($P < 0.05$) for the concentration studied, remarkably inhibited the biofilm metabolic activity. However, in the case of yeasts, significant inhibition of the metabolic activity of the biofilm was observed at the concentration of ε48.83 mg^{-1} (MIC, 2 × MIC and 4 × MIC). The lowest concentration of 24.42 mg^{-1} (0.5 × MIC) did not tarnish the metabolic activity of the biofilm. Biofilm metabolic activity of all *S. aureus, A. baumannii* and *S. epidermidis* ($P > 0.05$) strains showed curtailed activity when nanoPEI with the concentration of 0.56 MIC and 0.5 × MIC were used. In the case of *C. albicans,* appreciable metabolic activity of biofilm of both clinical and ATCC strains was observed only at concentration 2 × MIC (2500 mg^{-1}). Thirty-four percent of biofilm inhibition and 57% of ATCC stain inhibition were observed for the clinical yeast. For concentrations equivalent to the MIC and 0.5 × MIC, no inhibition of biofilm was observed. Some Gram-negative bacteria, Gram-positive bacteria and yeast were chosen for the antimicrobial action of PEI and nanoPEI and also effect on biofilm formation on PUR-Catheters. The antimicrobial activity of both PEI and nanoPEI was understood by the analysis of the obtained results. These results were similar for all the strains studied. Surprisingly, PEI with low concentration was found to inhibit yeast growth predominantly when compared to bacterial strains. From the literature reports, it was inferred that strong antibacterial effect was exhibited by nanoPEI (Beyth et al. 2006, 2008). This is due to the strong interaction between the polycationic nature of polymer and negatively charged surfaces of bacteria (Beyth et al. 2008). This interaction may be responsible for the high activity of polymers in cell permeability and rupturing of cell membranes. Beyth et al. (2006) reported substantial antibacterial effect of PEI nanoparticles against *Streptoccocus mutans.* The same antimicrobial properties were maintained over 1 month for the composite

resin materials containing PEI nanoparticles. In addition, quaternary ammonium-PEI (QAPEI) nanoparticles were reported to comprehensively inhibit the growth of Gram-positive (*Staphylococcus aureus*) bacteria as well as Gram-negative (*E. coli*) bacteria. QAPEI particle- composite resin produced complete inhibition of growth of *Streptococcus mutans*. The above studies imply that quaternary ammonium moieties attached to polymer play an important role in the inhibition of bacterial growth in vitro. The result further revealed that they can possibility act as additives in medical equipment (Yudovin-Farber et al. 2010). The results were further supported by Beyth et al. (2008) by differential bacterial sensitivity towards nanoPEI. The most effective QAPEI derivative was QAPEI alkylated with octyl halide at 1:1 mole ratio (primary amine of PEI monomer units/alkylating agent), which inhibited $>10^6$ *S. aureus* growth at a concentration of 80 μg mL^{-1}. There was a strict correlation between the activity of the compounds and their overall octyl content. Although several structural parameters influenced the antibacterial potency of the QAPEI nanoparticles, the most important features appear to be the degree of alkylation and degree of methylation, whereas other parameters had less significant impact (Beyth et al. 2008; Yudovin-Farber et al. 2008). Incorporation of QAPEI nanoparticles in bone cements produced durable antibacterial effect without changing the biocompatibility of the cement (Beyth et al. 2014a, b). NanoPEI produced cell membrane disruption and in cell depolarization except in the case of *A. baumannii* strains. When *C. albicans* were used, cell depolarization was detected. Interestingly, in biofilm, covalently bounded quaternized polydimethylaminoethylmethacrylate (poly-DMAEMA) and PEI reduced biofilm activity up to 92%, which was observed for *C. albicans* (De Prijck et al. 2010). The high bacterial activity against both bacteria was also observed when alkylated PEI attached to flat macroscopic surfaces and to surfaces of nanoparticles was used. The overall studies implied that at sub-inhibitory concentration was prominent for all bacteria tested for the anti-biofilm effect of nanoPEI. Further, biofilm metabolic activity was observed only at 2 MIC for the inhibition of *C. albicans*. In the special case, the MLC was not analysed.

9.6 Conclusion

The antimicrobial action of polymer macromolecules was examined by employing different bacteria, fungi and yeast. PEI has high molecular weight and polydispersity. Under these conditions, the interaction of PEI with cell membranes is strenuous to rationalize. But, development of variation of end group and monodisperse molecular weight is shown as a path to improve antimicrobial activity. Incorporation of metal complexes to BPEI generally showed a potential activity towards bacteria. The antimicrobial activity of PEI nanoparticles and resins showed biocompatibility and also good antimicrobial activity. NanoPEI were studied with different bacteria, fungi and yeast strains, and they resulted in excellent MIC values. NanoPEI showed significant metabolic activity, many of which are under clinical trial. Numerous PEI and nanoPEI reported in the literature exhibited interesting activity against bacteria and fungi.

9.7 Future Outlook

The variation of counter anions on in the PEI polymer on the antibacterial activity would be of considerable interest for further investigation. PEI and nanoPEI appear to be promising candidates for the augmentation of novel and indwelling catheters. By using the above materials, construction of novel medical devices that have little susceptibility to bacteria, fungi and yeast infection can be produced on a large scale. In vitro analysis of nanoparticles also creates new scope for the production of effective devices for clinical trials. The in vivo studies of PEI and nanoPEI require animal testing and can be only speculated for the time being. The fascinating antimicrobial results on the surface of polyurethane (PUR) catheters and their derivatives signify the need for probing their possible application in the field of medicine. Further research has to be explored in the field of water-soluble polymer metal complexes in order to enhance the biocompatibility in device formation.

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