RF plasma-treated polymers for biomedical applications

*N. Gomathi, A. Sureshkumar and Sudarsan Neogi**

The choice of polymers for various biomedical applications depends on their surface properties. All polymers do not possess the surface properties required for biomedical applications. Surface properties of the materials like surface free energy, hydrophilicity and surface morphology, which influence the cell–polymer interaction, decide the choice of the polymer. Radio frequency (RF) plasma offers a unique route for surface modification of polymers without affecting their bulk properties. This process results in a smooth, pinhole-free ultrathin film. Plasma treatment of polymers can render the material surface either hydrophilic or hydrophobic through the use of the respective plasma gases. It has found various applications in automobile, electronic, biomedical and chemical industries. In this article the properties and effects of RF plasma treatment of polymers are discussed with reference to their biomedical applications, such as in body implants, bioseparation, sterilization, biosensors, ophthalmology, etc.

Keywords: Antimicrobial, bio/blood compatibility, polymeric biomaterials, RF plasma, surface modification

PLASMA technology is widely used to alter the surface properties of polymers without affecting their bulk properties. The treated polymers have found various applications in automobiles, microelectronics, biomedical and chemical industries. Specific surface properties like hydrophobicity, chemical structures, roughness, conductivity, etc. can be modified to meet the specific requirements of these applications. The major effects observed in plasma treatment of polymer surfaces are cleaning of organic contamination, micro-etching, cross-linking and surface chemistry modification[1]. Biomaterials that have contact with the human body need an optimal combination of mechanical properties and surface characteristics that results in superior performance in the biological environment. Physico-chemical properties of the surface of the material such as surface free energy, hydrophilicity and surface morphology, which influence the cell–polymer interaction, determine the choice of the polymer. Since in general all polymers do not possess the surface properties needed for biomedical applications, radio frequency (RF) plasma treatment plays a crucial role in incorporating them. Surface modification in a controlled fashion, deposition of highly cross-linked films irrespective of the surface geometries, formation of multilayer films, eco-friendly nature and the prospect of scaling-up make the RF plasma treatment extremely suitable for biomedical applications. This article provides an overview of recent advances in the biomedical applications of plasma surface-modified polymers. The primary focus is on contemporary literature concerning RF plasma treatment of polymeric biomaterials. Plasma treatment and its effects on the surface of polymers and the results reported on RF plasma treatment in various biomedical applications are summarized.

The authors are in the Department of Chemical Engineering, Indian Institute of Technology, Kharagpur 721 302, India.
*For correspondence. (e-mail: sneogi@che.iitkgp.ernet.in)

Plasma: Introduction

Plasma, a quasi-neutral gas, is referred to as the fourth state of matter. It consists of a collection of electrons and ions as well as neutrals, atomic and molecular species that exhibit a collective behaviour in the presence of an electromagnetic field. Plasma, mainly generated by electric field could also be generated by other means, including magnetic field, combustion and nuclear reactions.

In an electric discharge, when an exciting field and a medium are coupled, plasma is generated. The quality of coupling determines the character of the electrical discharge. Based on energy coupling mode, RF plasma can be classified as inductively coupled plasma (ICP) and capacitatively coupled plasma (CCP). In the ICP reactor, a magnetic field created around the coil, on passing electric current generates plasma. Inductively coupled discharges have relatively high electron density in the range of 10^{15} cm^{-3}. These reactors are free from contaminants since the electrodes are kept outside the reaction chamber. In the CCP reactor, of the two metal electrodes, one is connected to the power supply and the other one is grounded. Since this configuration is similar to the ca-

pacitor in an electric circuit, it is called a CCP reactor. ICP and CCP are also referred to as electrode-less discharges. RF plasma has the advantages of convenience of handling, ease of availability and low energy requirements[2].

The various kinds of reactions in the plasma include excitation, ionization and dissociation. The excitation process involves increase of translational energy and transition of internal energy to a higher state. Metastable atoms that collide with other atoms or molecules have a relatively long lifetime of about 10^{-3} s or more. Table 1 shows the metastable levels of several atoms and their lifetimes[3]. When energy is given in excess of that required for excitation, most loosely bound electrons are removed from an atom causing ionization. The electron impact ionization is the major source of charged species in the discharge. The energy required for ionization is greater than that of dissociation. Ionization potential is the minimum voltage required for the ionization process. The first, second and third ionization potentials correspond to removal of the respective electrons from an atom. Excitation and ionization may be due to the reactions by electron collision, ion collision, neutral particle collision and radiation. Electron impact dissociation of gases plays an important role in the chemistry of low-pressure reactive discharges. Dissociation occurs as a result of inelastic collision of a molecule with an electron, ion or photon. When neutral fragments, either hot or in an excited state that are generated by this process, hit the substrate surface they affect the process chemistry. The various active species generated in a CCP reactor are shown in Figure 1.

Table 1. Properties of metastable atoms[3]

Atom	Metastable state	Energy (eV)	Lifetime (s)
He	2^3S_1	19.82	6×10^{-5}
	2^1S_0	20.61	2×10^{-2}
Ar	4^3P_2	11.55	55.9
	4^3P_0	11.72	44.9
H	$2^2S_{1/2}$	10.20	0.12
N	$2^2D_{5/2}$	2.38	6.3×10^4
	$2^2D_{3/2}$	2.38	1.4×10^5
	$2^2P_{3/2}$	3.58	13
	$2^2P_{1/2}$	3.58	13
O	2^1D_2	1.96	1.1×10^2
	2^1S_0	4.17	8.8×10^{-1}
	3^5S_2	9.13	–

Effects of plasma on a polymer surface

Plasma generated in a vacuum environment influences the surface of the polymer to make it suitable for a specific application. It has sufficiently high energy to break the covalent bonds of polymers exposed to the plasma. The surface of a biomaterial is what the body encounters first when a new device is used or implanted. In the case of polymers, the surface should be compatible to the biological system, which can be effectively modified by the plasma. Plasma treatment can improve wettability, oxidize the surface and enhance cell growth and adhesion. The various effects of plasma on a polymer surface may be categorized as: (i) surface modification, (ii) grafting and (iii) film deposition[4].

Plasma surface modification

Surface modification by plasma treatment is achieved using gases such as air, O_2, N_2, argon and helium. The objectives of plasma surface modification in biomedical applications are adhesion promotion, enhanced surface wettability and spreading, and reduced surface friction. Factors that contribute to improved adhesion are removal of surface contaminants and weakly bound polymer layers, etching and substitution of chemical groups on the surface that permit covalent bonding.

Removal of surface contaminants: Low-pressure plasma is used for cleaning polymer surfaces of contaminants

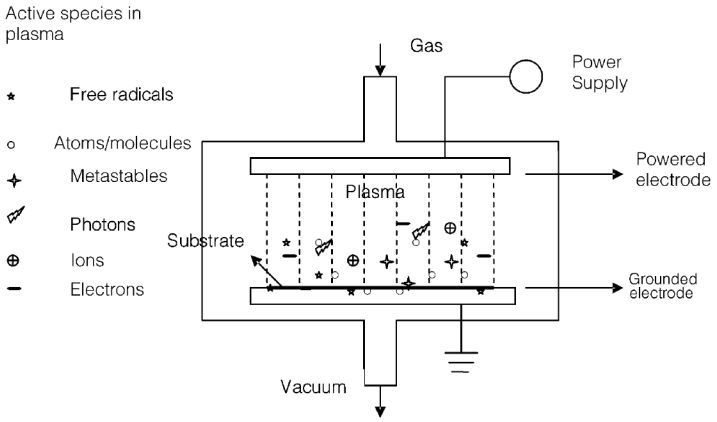

Figure 1. Schematic diagram of capacitatively coupled reactor.

such as air pollutants, fingerprints, oxide layers, weakly bonded surface layers and other surface additives. It is possible to remove contaminations by simple plasma sputtering with the help of noble gases, by oxidation of organic contaminants with oxygen plasma or by reduction of oxides or sulphides by hydrogen plasma[5]. The efficient removal of organic contaminants from a semiconductor surface can also be achieved by plasma processes[6,7]. In the case of contaminant removal, lower molecular weight polymer fractions that comprise the weak boundary layers are removed by plasma. When the virgin polymer is exposed to plasma, free radicals are created on its surface and are coupled with active species from the plasma environment, and cause surface modification. It enhances adhesion by allowing interlinking of molecules on the surface. Active species in the plasma react with the polymer surface to form by-products like CO_2, H_2O and low molecular weight hydrocarbons, which are later removed by means of vacuum. The choice of gas used for contaminant removal depends on the nature of the contaminant and the substrate.

Etching: Plasma etching is a key to removal of material from surfaces[8–10]. Parallel or serial combination of four processes, namely sputtering, chemical etching, energetic ion etching and ion inhibitor etching, is commonly used to remove material from surfaces. During etching the surface material is selectively removed by chemical reactions and/or physical sputtering. Etching in gas discharge plasma is also used for cleaning and polishing surfaces, processing plate edges, cutting plates into separate crystals, etc.[11]. Plasma cleaning is a form of etching based on a combination of chemical reactions between surface impurities and radicals formed in the discharge volume and on the surface, and sputtering through ion bombardment. Roughening the surface by plasma etching increases the area of contact. Increased surface energy of the substrate above the surface tension of the adhesive makes it wet the entire surface of the polymer substrate, in turn increasing the adhesive bond strength. Plasma surface modification enhances adhesion strength by facilitating covalent bonding between the adhesive and the substrate surface. This also allows a liquid to spread over, penetrate the surface and form a strong bond between the substrate and the adhesive.

Substitution of chemical groups: Alteration of surface characteristics is also possible by substitution of chemical groups present on the polymer chain being modified[12–15]. Different process gases can incorporate large varieties of chemical groups such as hydroxyl, carbonyl, carboxylic, amino or peroxyl groups. Oxidation, nitration, hydrolization and amination processes induced by plasma are used to improve the surface energy of the substrate. Substituting the functional groups increases the surface energy and reactivity. The gases used to generate plasma are reactive, unlike in plasma-induced grafting.

Plasma-induced grafting

Plasma-induced grafting is a two-step process of incorporation of functional groups and reactive sites to the polymer surface. Free-radical formation using inert gas plasma is followed by the introduction of an unsaturated monomer such as allyl alcohol into the reaction chamber. The monomer reacts with the free radical to yield a grafted polymer. This process differs from activation in a way that it adds the material to the polymer backbone instead of functionally modifying the surface polymer chains. It differs from plasma polymerization in which the plasma gas itself is a monomer. This process results in enhanced adhesion[16,17].

Plasma polymerization

The plasma polymerization process, which can produce thin films with unique chemical and physical properties, has found various biomedical applications[18–20]. In this process, gases in the plasma undergo polymerization through a free-radical initiation process. Methane, ethylene, propylene, fluorocarbon monomers and organosilicon compounds can be polymerized by this method. When the process gas mixture contains hydrocarbons, the hydrocarbon molecules are fractured into free-radical fragments. These free radicals initiate polymerization. As the molecular weight of the polymer increases, it is deposited on the surface of the substrate. Polymerization at an atomic level is also possible when sufficient energy is supplied to break all the bonds on the monomer. The plasma-polymerized thin films are generally pinhole-free, highly cross-linked and strongly bound to the surface. A list of gases used in plasma processing, including polymerization is provided in Table 2.

Polymeric biomaterials

The biomedical application of polymers requires knowledge in areas such as computational chemistry, molecular biology, surface physics and chemistry, nanofabrication and materials science. In March 1986 the Consensus Conference of the European Society for Biomaterials, Chester, England, precisely defined the biomaterial as a nonviable material used in a biomedical device intended to interact with biological systems. Biocompatibility of a biomaterial is defined as the ability of a material to perform with an appropriate host response in a specific application. Blood compatibility, considered as a derivative of biocompatibility, is a complex function involving many parameters such as characteristics of the blood, material and time[21].

Groups of materials, namely metals, alloys, ceramics, polymers and composites find applications as biomate-

Table 2. Plasma gases and their applications[1]

Plasma gas	Application
Oxidizing gases (O_2, air, H_2O, N_2O)	Removal of organics by oxidation and to leave oxygen species in the polymer surface
Reducing gases (H_2, mixtures of H_2)	Replacement of F or O in surfaces, removal of oxidation-sensitive materials, conversion of contaminants to low molecular weight species that do not polymerize or re-deposit on adjacent surfaces
Noble gases (Ar, He)	To generate free radicals in surfaces to cause cross-linking or to generate active sites for further reaction
Active gases (NH_3)	To generate amino groups
Fluorinated gases (CF_4, SF_6 and other perfluorinated gases)	To make the surface inert and hydrophobic
Polymerizing gases (monomer gases for direct polymerization, Ar or He pretreated)	Polymerization of layers onto substrates by direct polymerization or by grafting on Ar or He pretreated polymer surface

rials. Rigid metal alloys, ceramics, fibre reinforced composites and high molecular weight polymers are used to replace bone and dentin, while soft and pliable elastomers are used for soft-tissue reconstruction. Polymers used as biomaterials include polyolefin, polyester, polyamide, polyurethane, polyacrylate, polyether, poly-hydroxy ethyl methacrylate (pHEMA), polyvinyl alcohol (PVA), polyglycolic acid (PGA), polylactic acid (PLA), polysulfone and silicone rubber. Biodegradable polymers such as polyesters and polyamides are employed as biodegradable sutures or as bone plates to provide temporary scaffolding or support while natural-tissue regeneration takes place[22]. A list of polymers and their biomedical applications is presented in Table 3.

Surface modification of polymeric biomaterials by RF plasma

The capability of RF plasma to modify surface physical and chemical properties without affecting bulk properties is advantageous for the design, development and manufacture of biocompatible polymers. Either by surface modification or by thin-film deposition, protein–surface interaction and cell adhesion can be optimized for improving biocompatibility. The RF plasma-treated polymeric biomaterials, which adversely affect bacterial adhesion, have found wide applications in antimicrobial coatings. Antimicrobial coating on RF plasma-treated polymers can prevent microbial adherence on the surface, thus preventing biofilm formation.

Improving biocompatibility/blood compatibility

Biocompatibility is not an inherent property of a material, but results from complex interactions between an implant and the surrounding tissues. Any polymer used in biomedical application should be biocompatible, which requires it to have a low friction coefficient and hydrophilicity. Several materials used for medical devices are selected for mechanical strength or stability in the body, but suffer from problems associated with surface-induced thrombosis. When they are in contact with blood or blood products, thrombosis is initiated by the deposition of a plasma protein layer on the surface of the implanted biomaterial. Platelets, fibrin and possibly leukocytes adhere to the deposited protein. The interaction between the plasma proteins and the surface of the implant determines the adhesion, activation and spreading of platelets, activation of coagulation, cell attachment and protein deposition.

Polymeric materials can easily be modified to meet the needs of tissue engineering. Cell attachment and cell growth are influenced by wettability of the surface, surface energy and charge of the material. Immobilization of protein with antithrombogenic or thrombolytic qualities is a way of introducing the antithrombogenic characteristics on blood-contact materials. Accordingly, polymers such as nylon, polyester, polyethylene, polypropylene, polyurethane and fluorine resin, incorporated with substances having antithrombogenic property and compatibility with a living body are used in such medical devices. Various antithrombogenic materials such as heparinated high molecular weight materials, urokinase immobilized high polymer materials or plasma-treated high molecular weight materials are used in various fields of application. Many investigations have been performed to immobilize various proteins with antithrombogenic properties like recombinant hirudin (rHir), thrombomodulin and human thrombomodulin on polymers[23–25]. To prevent thrombus formation, they are pre-lined in the inner surface of the vascular graft and this process is called hybridization. It has been demonstrated that the inner surface of the segmented polyurethane tube modified by air-plasma treatment holds good as a suitable substrate for hybrid vascular grafts[26]. Lahann *et al.*[27] investigated the influence of plasma modification of poly (2-chloroparaxylylene) on the adsorption of the human blood protein, fibrinogen. Polyethyleneterephthalate (PET) films grafted with acrylic acid using oxygen plasma were immobilized with insulin, heparin to improve blood compatibility[28] and collagen to enhance the growth of smooth muscle cells[29].

Table 3. Biomedical applications of polymers[22]

Polymer	Biomedical application
Polyethylene	Tubes for various catheters, hip-joint, knee-joint prostheses
Polypropylene	Suture materials
Polytetrafluroethylene	Vascular and auditory prostheses, catheters, tubes
Polyester	Vascular grafts, resorbable systems
Polyvinyl chloride	Flexible or semiflexible medical tubes, catheters, inner tubes, components of dialysis installation and temporary blood-storage devices
Polyacetals	Hard-tissue replacement
Polymethylmethacrylate	Bone cement, intraocular lenses, contact lenses, fixation of articular prostheses, dentures
Polycarbonate	Syringes, arterial tubules, hard-tissue replacement, hemodialysers, blood pumps, oxygenators
Polyethyleneterephthalate	Vascular, laryngeal, esophageal prostheses, surgical sutures, knitted vascular prostheses
Polyamide	Intracardiac catheters, urethral sound, surgical sutures, films for packages, dialysis device components, heart mitral valves, three-way valve profusion, hydrodynamic syringes, sutures
Hydrogel (pHEMA, PVA)	Contact lens, reconstructive joint surgery
Biodegradable polymers (PGA, PLA, PVA)	Sutures, drug-delivery matrix, adhesives, temporary scaffolding, temporary barrier
Polyurethane	Adhesives, dental materials, blood pumps, artificial heart, and skin and blood contacting devices
Silicone rubber	Encapsulant for pacemakers, burn treatment, shunt, mammary prostheses, foam-dressing, valves, catheters, contact lenses, intraocular lenses, finger joints, membranes, maxillofacial implants

Polymer-coated encased stents, facilitating endothelial cell growth on the inner lining of the stent, are used to prevent platelet aggregation. Surface modification of the polymer decreases the interfacial tension between the blood components and the treated surface, which in turn reduces the driving forces for protein deposition. De *et al.*[30] showed the potential application of plasma treatment for confluent cell growth with strong adhesion to the substrate to withstand the arterial blood flow shear stress. Helium plasma treatment improved the wettability, oxidized the surface and enhanced endothelial cell growth and cell adhesion on polyurethane surfaces. Endothelial cell adhesion is also achieved by ion implantation[31] and carbon deposition[32]. The adhesion of endothelial cells on plasma-treated polystyrene varies with plasma treatment time. Stronger adhesion is observed with longer plasma treatment time[33]. PET used as fibre-reinforced composite in prosthetics shows poor adhesion. PET fibres are treated with O_2 plasma to improve their adhesion in fibre matrix composite and to increase the surface energy[34].

Antimicrobial coating

Adherence of bacteria to a polymer surface results in biofilm formation. Biofilm resistance to antibiotics makes the device-associated infection difficult to treat and necessitates the removal and replacement of the infected device. Antibacterial agent is coated on medical polymers to prevent biofilm formation. Surface treatment prevents the initial adhesion of bacteria to the polymer surface or kills the bacteria as they come in contact with the surface. To obtain the antimicrobial properties, the substrate is usually impregnated or compounded with an antimicrobial agent in a matrix. As silver ions possess good antimicrobial properties, silver has been used as an antimicrobial coating on medical devices. It also possesses anti-inflammatory properties and enhances healing rates[35]. The properties of the surface, like its hydrophobicity, composition, mechanical properties and morphology, influence bacterial adhesion. It is promoted on rough surfaces and at defect sites such as scratches or pits[36]. Both metallic and ionic silver have been incorporated into several biomaterials such as polyurethane[37], hydroxypapatite[38], and bioactive glasses[39,40]. Ultrathin (1–2 nm) antibacterial polyammonium coating given on plasma-treated polyethylene (PE) surface required much smaller quantities of the antibacterial agent than other conventional methods[41]. Zhang *et al.*[42] coated triclosan and bronopol on PE to enhance the antibacterial properties by making the polymer surface more hydrophilic, which was achieved by treating PE in O_2 plasma followed by argon and hydrogen plasma. The results revealed that Ar plasma was better than H_2 plasma in improving the antibacterial properties. High levels of antibacterial effects of triclosan-coated PE against *Staphylococcus aureus* (Gram-positive) and *Escherichia coli* (Gram-negative) were observed even after six weeks, while that of bronopol was better in the beginning but degraded with time and showed no antibacterial effect after six weeks.

Specific biomedical applications

The surface-modified polymeric biomaterials have found specific applications in various areas of the medical field

such as implants, bioseparation, plasma sterilization, biosensors and ophthalmology. Plasma treatments are given to the polymers to achieve the above-mentioned properties, namely antimicrobial properties and bio/blood compatibility.

Implants

The use of medical implants ranges from simple catheters for drawing blood to life-saving devices such as artificial heart, lung and kidney. The time for the body tissue–biomaterial interaction ranges from several minutes for one-time use like catheters to several years for total replacement of organs like total artificial hearts and total joint prostheses. The applications of plasma treatment in various implants are reviewed below.

Orthopedic implants: Any material having desirable mechanical properties and biocompatibility with the bone is used in bone replacement. Though the bulk properties govern their mechanical properties, their surface chemistry and structure largely control the biological responses to biomaterials and other biomedical devices. Orthopedic implants are mainly constructed using titanium alloys for strength and lined with polymers that act as artificial cartilage. The major obstacle to long-term use of metallic substrates is bone resorption due to stress shielding[43], leading to their degradation after 10–15 years[44].

A large variety of organic materials are employed as materials of construction for prostheses and external stabilizers of bone fragments. Polymers like ultra high molecular weight polyethylene (UHMWPE) and polytetrafluoroethylene (PTFE) are used in joint socket and polyurethane in bone joint due to their excellent wear, abrasion, corrosion and fatigue resistance. UHMWPE is used in surgical replacement of damaged cartilage in total joint/diseased joint. The biocompatibility of UHMWPE was modified by means of cross-linking, functionalization using various plasmas such as Ar, C_3F_6, C_2H_4, NH_4, CH_4 and HMDSO, and no cytotoxicity was observed. Argon and Ar/CH_4 plasma-treated samples showed little red blood cell destruction and thus are more blood compatible among others[45]. Carbon-fibre-reinforced polyether ether ketone (PEEK), investigated for hip-joint endoprostheses[46] and fracture fixation plates[47], was treated by oxygen plasma[48] and N_2/O_2 plasma to get better surface activation for subsequent joining and coating processes[49]. This provides initiation sites for the formation of calcium phosphate coatings in supersaturated solutions. Calcium phosphate deposition by Ar plasma sputtering on the O_2 plasma-treated polyethylene showed a low Ca/P ratio near the interface on PE[50], which is similar to that on polystyrene[51].

Cardiac implants: Both non-biodegradable polymers such as polyurethane, silicone rubber, ethylene vinyl acetate, and biodegradable polymers such as poly(glycolic-lactic acid), and high molecular weight polyanhydride are used in cardiac implants as implant leads, artificial hearts, stents and controlled drug release devices[22]. To prevent the cardiovascular system from the adverse effects of drugs and to optimize drug concentrations, controlled drug release implants are used either as reservoir configured controlled release systems or drug dispersions in polymeric matrices[52]. Polyurethane matrix synthesized with pore formers and loaded with ciprofloxacin releases antibiotic at a controlled rate when coated with *n*-butyl methacrylate by RF plasma deposition[53,54].

Dental implants: Polymethylmethacrylate (PMMA) is used in dental implants for different purposes such as denture bases, artificial teeth, removable orthodontics, surgical splinting and aesthetic filling in anterior teeth. Many other polymers have been explored for several dental applications such as dentures, crowns, bridges, fillings, mouth protectors, sutures and implants[22]. Biofilm formation due to the adhesion of *Candida albicans* on PMMA causes denture-induced stomatitis, which is a common intraoral disease. Surface loading of histatin 5 either by adsorption or chemical cross-linking provides a higher concentration of active molecules on the PMMA denture, leading to reduction of *C. albicans* biofilm formation. Modification of PMMA by copolymerization of methyl methacrylic acid resulted in twofold increase of the adsorption of the added amount of histatin 5 per unit surface area[55]. The amount of histatin adsorption on PMMA increases more than six times when PMMA is treated with O_2 plasma compared to that adsorbed onto untreated PMMA[56].

Bioseparation

Membranes used for biomedical applications should have high ion/solute permeability, blood compatibility, mechanical stability and dimensional stability upon swelling. Hydrophilic composite membranes consisting of acrylic acid polymer and porous polypropylene with high ion permeability and dimensional stability were developed by plasma interpenetrating polymer network techniques[57]. Lai *et al.*[58] deposited hydrophilic monomers, namely 1-vinyl-2-pyrrolidone, 2-hydroxyethyl methacrylate (HEMA) and methyl methacrylate by plasma deposition onto chemical and O_2 plasma-treated Nylon 4 membrane. It was found that the HEMA plasma-deposited membrane possessed the highest potential as haemodialysis material among the other plasma-deposited membranes considered. Plasma-deposited polymer layer of dimethylaniline and acrylic acid on the surface of PET track membranes that has application in bioseparation changed their transport properties, especially water permeability, depending on the value of filtrate pH[59]. Membranes used for bioseparation

are fouled and clogged when non-specific proteins are adsorbed on it. Yianni *et al.*[60] invented a process for reducing the thrombogenicity of blood-contacting surfaces or inhibiting/preventing the non-specific adsorption of protein surfaces by polymerizing a phospholipid. They used plasma polymerization as pretreatment for phospholipids and found better reduction in platelet adhesion compared to that in untreated polymer.

Plasma sterilization

Plasma sterilization, a new application of low-pressure plasma, is a promising technique and an alternative to other conventional sterilization methods like high temperature sterilization, ethylene oxide sterilization and sterilization by radiation, especially for treatment of heat-sensitive materials. It promotes an efficient inactivation of the microorganisms and minimizes damage to the materials. UV photons and reactive species like atoms and radicals play a major role in plasma sterilization. Pérez-Martínez *et al.*[61] developed RF normal pressure plasma-discharge technologies to cleanse and sterilize dental cavities. Ohkawa *et al.*[62] used a mixture of helium and oxygen at atmospheric pressure as a sterilization medium in continuous plasma processing of medical-care materials. It was found that destruction of the cell wall was the major mechanism of disinfection. Various treatment times were found to be effective for various microorganisms. Low temperature radio frequency glow discharge plasma was found to be the most suitable for sterilizing polyester devices in tissue engineering applications. Polymers sterilized by plasma showed little or no change in their 3D morphology, molecular weight or mechanical properties[63,64]. When cellulose strips that contained *Bacilli stearothermophili* were directly exposed to Ar plasma, complete inactivation took place after 7 min of exposure[65]. It has also been reported that plasma sterilization diminishes platelet deposition without affecting the coagulation time[66].

Biosensors/biomedical devices

Biosensors require two and three-dimensional microstructured substrates with a chemically suited surface to mimic the basic functions of natural tissue. Chemical micro-patterning of cell culture by plasma processing allows the introduction of functional groups on the polymer surface, without affecting its bulk properties. It enables covalent bonding for fixation and immobilization of biomolecules on various substrates. Chen *et al.*[67] used pulsed RF plasma for polymerization of allylamine and for successful DNA adsorption and hybridization. Micropatterning of amine groups, used in DNA array technology, was achieved with excellent thickness controllability and uniformity in a relatively short time by selective deposition of plasma polymerized ethylene diamine on glass slides[68]. RF plasma treatment yields a more compatible interface with biological fluids. Hydrophobic polypropylene membrane has been made hydrophilic on one side when treated with ammonia plasma and coupled to urease to construct a urea sensor, and an appreciable reduction in the response time has been achieved[69].

Ophthalmology

The contact lenses should have high oxygen permeability, good wettability by tears and resistance to deposition of protein, mucus, lipid, microorganisms and other foreign substances on the lens surface. CF_4 plasma-treated PMMA intraocular lens reduced the adhesion of proteins, the development of inflammatory cells and the formation of cellular debris[70]. Hettlich *et al.*[71] modified the surface of silicone with O_2 and CO_2 plasma and found CO_2 plasma to be more suitable for grafting functional groups on the surface of poly(dimethylsiloxane), since CO_2 could be used for a longer period without causing surface damage, unlike O_2 plasma. Silicone rubber grafted with pHEMA by plasma-induced graft polymerization was found to be suitable for cell attachment and growth[72]. Latkany *et al.*[73] demonstrated argon RF plasma treatment of polyvinyl alcohol copolymer hydrogel as optimal for epithelial cell migration and proliferation. They found that this treatment allowed for the migration, proliferation and synthesis of matrix and adhesion molecules *in vitro*. No inflammatory response was detected on the treated surface. George and Pitt[74] developed a model to determine the cellular growth rate on different plasma-treated polymeric materials such as polyvinyl alcohol, silicone rubber, polystyrene and polycarbonate, and found that plasma-induced graft-copolymerized pHEMA on silicone rubber provided the best growth rate.

Conclusion

The RF plasma treatment of polymeric biomaterials has been a topic of extensive investigations pertaining to a wide range of applications. Biomaterials, which have permanent contact with the body and tissues, require unique surface properties like surface free energy, hydrophilicity and specific surface morphology, for improved cell/protein adhesion on the polymer surface. Ability to modify a surface in a controlled way, deposition of cross-linked films on complex geometries, formation of multilayer films, rapidity, sterility and the prospect of scaling-up are the salient features of RF plasma processing that makes it suitable for biomedical applications. The RF plasma treatment produces three major effects on biomaterials: surface modification, grafting and film deposition. Surface modification improves adhesion, enhances surface wettability and spreading, and reduces surface friction. In

plasma-induced grafting, the functional groups and reactive sites are incorporated in the polymer surface. Methane, ethylene, propylene, fluorocarbon monomers and organosilicone compounds can be polymerized by the plasma polymerization process. Antimicrobial coatings on RF plasma-treated biopolymers can prevent microbial adherence on polymer surface, thus preventing biofilm formation. Either by surface modification or by thin-film deposition, protein–surface interactions and cell adhesion can be optimized for improving biocompatibility. Modified polymeric biomaterials are widely used in implants, bioseparation, plasma sterilization, biosensors and ophthalmology. Intensification of applications is in sight in the years ahead.

1. Liston, E. M., Plasma treatment for improved bonding: A review. *J. Adhes.*, 1989, **30**, 199–218.
2. Herman, V. B., *Plasma Science and Technology*, Cornell University Press, London, 1982, p. 37.
3. Mitsuharu, K., *Film Deposition by Plasma Techniques*, Springer Series on Atoms and Plasmas, Springer-Verlag, Berlin, 1992, pp. 1–48.
4. Kolluri, O. S., Plasma surface engineering of plastics. In *ASM Handbook, Vol. 5* (eds Cotell, C. M., Sprague, J. A. and Smidt, F. A.), Surface Engineering, Materials Park OH, ASM International, The Material Information Society, 1996, pp. 892–899.
5. Lee, C., Kim, H. W. and Kim, S., Organic contaminants removal by oxygen ECR plasma. *Appl. Surf. Sci.*, 2007, **253**, 3658–3663.
6. Kim, D. K., Park, Y. K., Biswas, S. and Lee, C., Removal efficiency of organic contaminants on Si wafer surfaces by the N_2O ECR plasma technique. *Mater. Chem. Phys.*, 2005, **91**, 490–493.
7. Krüger, P., Knes, R. and Friedrich, J., Surface cleaning by plasma-enhanced desorption of contaminants (PEDC). *Surf. Coat. Technol.*, 1999, **112**, 240–244.
8. Collaud Coen, M., Dietler, G., Kasas, S. and Gröning, P., AFM measurements of the topography and the roughness of ECR plasma treated polypropylene. *Appl. Surf. Sci.*, 1996, **103**, 27–34.
9. Harth, K. and Hibst, H., Surface modification of polypropylene in oxygen and nitrogen plasmas. *Surf. Coat. Technol.*, 1993, **59**, 350–355.
10. Samukawa, S., High-performance and damage-free neutral-beam etching processes using negative ions in pulse-time-modulated plasma. *Appl. Surf. Sci.*, 2007, **253**, 6681–6689.
11. Lieberman, M. A. and Lichtenberg, A. J., *Principles of Plasma Discharges and Materials Processing*, John Wiley, New Jersey, 2005, pp. 571–617.
12. Sanchis, M. R., Blanes, V., Blanes, M., Garcia, D. and Balart, R., Surface modification of low-density polyethylene (LDPE) film by low pressure O_2 plasma treatment. *Eur. Polym. J.*, 2006, **42**, 1558–1568.
13. Kwon, O. J., Myung, S. W., Lee, C. S. and Choi, H. S., Comparison of the surface characteristics of polypropylene films treated by Ar and mixed gas (Ar/O_2) atmospheric pressure plasma. *J. Colloid Interface Sci.*, 2006, **295**, 409–416.
14. Friedrich, J. F., Mix, R. and Kühn, G., Adhesion of metals to plasma-induced functional groups at polymer surfaces. *Surf. Coat. Technol.*, 2005, **200**, 565–568.
15. Mühlhan, C., Weidner, S. T., Friedrich, J. and Nowack, H., Improvement of bonding properties of polypropylene by low-pressure plasma treatment. *Surf. Coat. Technol.*, 1999, **116–119**, 783–787.
16. Dogué, L. J., Mermilliod, N., Boiron, G. and Staveris, S., Improvement of polypropylene film adhesion in multilayers by various chemical surface modifications. *Int. J. Adhes. Adhes.*, 1995, **15**, 205–210.
17. Choi, H. S., Kim, Y. S., Zhang, Y., Tang, S., Myung, S. W. and Shin, B. C., Plasma-induced graft co-polymerization of acrylic acid onto the polyurethane surface. *Surf. Coat. Technol.*, 2004, **182**, 55–64.
18. Sipehia, R. and Chawla, A. S., Characterization of plasma polymerized polypropylene coatings. *Biomaterials*, 1986, **7**, 155–157.
19. Yasuda, H. and Gazicki, M., Biomedical applications of plasma polymerization and plasma treatment of polymer surfaces. *Biomaterials*, 1982, **3**, 68–77.
20. Cheng, T. S., Lin, H. T. and Chuang, M. J., Surface fluorination of polyethylene terephthalate films with RF plasma. *Mater. Lett.*, 2004, **58**, 650.
21. Williams, D. F., *Progress in Biomedical Engineering*, Elsevier, Amsterdam, 1987, p. 67.
22. Bhat, S. V., *Biomaterials*, Narosa Publishing House, New Delhi, 2002, pp. 51–206.
23. Phaneuf, M. D., Berceli, S. A., Bide, M. J., Quist, W. C. and LoGerfo, F. W., Covalent linkage of recombinant hirudin to poly(ethylene terephthalate) (Dacron): Creation of a novel antithrombin surface. *Biomaterials*, 1997, **18**, 755–765.
24. Kishida, A., Ueno, Y., Fukudomef, N., Yashima, E., Maruyama, I. and Mitsuru, A., Immobilization of human thrombomodulin onto poly(ether urethane urea) for developing antithrombogenic blood-contacting materials. *Biomaterials*, 1994, **15**, 848–852.
25. Sperling, C. *et al.*, Immobilization of human thrombomodulin onto PTFE. *J. Mater. Sci. Mater. Med.*, 1997, **8**, 789–791.
26. Kawamoto, Y., Nakao, A., Ito, Y., Wada, N. and Kaibara, M., Endothelial cells on plasma-treated segmented-polyurethane. *J. Mater. Sci. Mater. Med.*, 1997, **8**, 551–557.
27. Lahann, J., Klee, D., Thelen, H., Bienert, H., Vorwerk, D. and Hocker, H., Improvement of haemocompatibility of metallic stents by polymer coating. *J. Mater. Sci. Mater. Med.*, 1999, **10**, 443–448.
28. Kim, Y. J., Kang, K., Huh, M. W. and Yoon, S., Surface characterization and *in vitro* blood compatibility of poly(ethylene terephthalate) immobilized with insulin and/or heparin using plasma glow discharge. *Biomaterials*, 2000, **21**, 121–130.
29. Gupta, B., Plummer, C., Bisson, I., Peter, F. and Hilborn, J., Plasma-induced graft polymerization of acrylic acid onto poly (ethylene terephthalate) films: Characterization and human smooth muscle growth on grafted films. *Biomaterials*, 2002, **23**, 863–871.
30. De, S., Sharma, R., Ali, N. and Mazumder, M. K., Enhancement of blood compatibility of implants by helium plasma treatment. In Industry Application Conference, IAS, IEEE, 2004, pp. 932–936.
31. Lee, S., Kaibara, M., Iwaki, M., Sasabe, H., Suzuki, Y. and Kusakabe, M., Selective adhesion and proliferation of cells on ion-implanted polymer domains. *Biomaterials*, 1993, **14**, 958–960.
32. Kaibara, M., Iwata, H., Wada, H., Kawamoto, Y., Iwaki, M. and Suzuki, Y., Promotion and control of selective adhesion and proliferation of endothelial cells on polymer surface by carbon deposition. *J. Biomed. Mater. Res.*, 1996, **31**, 429–435.
33. Van Kooten, T. G., Spijker, H. T. and Busscher, H. J., Plasma-treated polystyrene surfaces: Model surfaces for studying cell–biomaterial interactions. *Biomaterials*, 2004, **25**, 1735–1747.
34. Cioffi, M. O. H., Voorwald, H. J. C. and Mota, R. P., Surface energy increase of oxygen-plasma-treated PET. *Mater. Charact.*, 2003, **50**, 209–215.
35. Liedberg, H. and Lundeberg, T., Silver alloy coated catheters reduce catheter-associated bacteriuria. *Br. J. Urol.*, 1990, **65**, 379–381.
36. Kim, T. N., Feng, Q. I., Kim, J. O., Wu, J., Wang, H., Chen, G. C. and Cui, F. Z., Antimicrobial effect of metal ions (Ag^+, Cu^{2+}, Zn^{2+}) in hydroxyapatite. *J. Mater. Sci. Mater. Med.*, 1998, **9**, 129–134.
37. Bellantone, M., Coleman, N. J. and Hench, L. L., Bacteriostatic action of a novel four component bioactive glass. *J. Biomed. Mater. Res.*, 2000, **51**, 484–490.

38. Clupper, D. C. and Hench, L. L., Bioactive response of Ag-doped tape cast bioglass^{R} 45S5 following heat treatment. *J. Mater. Sci. Mater. Med.*, 2001, **12**, 917–921.
39. Sanger, F., Nicklen, S. and Cioulson, A. R., DNA sequencing with chain-terminating inhibitors. *Proc. Natl. Acad. Sci. USA*, 1977, **74**, 5463–5467.
40. Maxam, A. and Gillbert, W., A new method for sequencing DNA. *Proc. Natl. Acad. Sci. USA*, 1977, **74**, 560–564.
41. Thome, J., Hollander, A., Jaeger, W., Trick, I. and Oehr, C., Ultra-thin antibacterial polyammonium coatings on polymer surfaces. *Surf. Coat. Technol.*, 2003, **174–175**, 584–587.
42. Zhang, W., Chu, P. K., Ji, J., Zhang, Y., Fu, R. K. Y. and Yan, Q., Antibacterial properties of plasma-modified and triclosan or bronopol coated polyethylene. *Polymer*, 2006, **47**, 931–936.
43. Hench, L. L., Bioceramics. *J. Am. Ceram. Soc.*, 1998, **81**, 1705–1728.
44. Spector, M., Biomaterial failure. *Orthop. Clin. N. Am.*, 1992, **23**, 211–217.
45. Klapperich, C., Puritt, L. and Komovopoulos, K., Chemical and biological characteristics of low temperature plasma treated ultra high molecular weight polyethylene for biomedical applications. *J. Mater. Sci. Mater. Med.*, 2001, **12**, 549–556.
46. Kwarteng, K. B. and Stark, C., Carbon fiber reinforced PEEK (APC-2/AS4) composites for orthopaedic implants. *Sampe. Quart.*, 1990, **22**, 10–14.
47. Jockish, K. A., Brown, S. A., Bauer, T. W. and Merritt, K., Biological response to chopped-carbon-fiber-reinforced PEEK. *J. Biomed. Mater. Res.*, 1992, **26**, 133–146.
48. Ha, S. W., Hauert, R., Ernst, K. H. and Wintermantel, E., Surface analysis of chemically etched and plasma treated polyetheretherketone for biomedical applications. *Surf. Coat. Technol.*, 1997, **96**, 293–299.
49. Ha, S. W. *et al.*, Surface activation of polyetheretherketone (PEEK) and formation of calcium phosphate coatings by precipitation. *J. Mater. Sci. Mater. Med.*, 1997, **8**, 683–690.
50. Feddes, B., Wolke, J. G. C., Vredenberg, A. M. and Jansen, J. A., Initial deposition of calcium phosphate ceramic on polyethylene and polydimethylsiloxane by rf magnetron sputtering deposition: The interface chemistry. *Biomaterials*, 2004, **25**, 633–639.
51. Feddes, B., Vredenberg, A. M., Wolke, J. G. C. and Jansen, J. A., Initial deposition of calcium phosphate ceramic on polystyrene and polytetrafluroethylene by rf magnetron sputtering deposition. *J. Vac. Sci. Technol. A*, 2003, **21**, 363–368.
52. Levy, R. J., Johnston, T. P., Sintov, A. and Golomb, G., Controlled release implants for cardiovascular disease. *J. Controlled Release*, 1990, **11**, 245–254.
53. Kwok, C. S., Wan, C., Hendricks, S., Bryers, J. D., Horbett, T. A. and Ratner, B. D., Design of infection-resistant antibiotic-releasing polymers: I. Fabrication and formulation. *J. Controlled Release*, 1999, **62**, 289–299.
54. Kwok, C. S., Horbett, T. A. and Ratner, B. D., Design of infection-resistant antibiotic-releasing polymers II. Controlled release of antibiotics through a plasma-deposited thin film barrier. *J. Controlled Release*, 1999, **62**, 301–311.
55. Edgerton, M., Raj, P. A. and Levine, M. J., Surface-modified poly(methylmethacrylate) enhances adsorption and retains anticandidal activities of salivary histatin 5. *J. Biomed. Mater. Res.*, 1995, **29**, 1277–1286.
56. Yoshinari, M. *et al.*, Adsorption behavior of antimicrobial peptide histatin 5 on PMMA. *J. Biomed. Mater. Res. Part B: Appl. Biomater. B*, 2006, **77**, 47–54.
57. Karakelle, M. and Zdrahala, R. J., Membranes for biomedical applications: Utilization of plasma polymerization for dimensionally stable hydrophilic membranes. *J. Membr. Sci.*, 1989, **41**, 305–313.
58. Lai, J. Y., Shih, C. Y. and Tsai, S. M., Plasma deposition modified Nylon 4 membranes for hemodialysis. *J. Appl. Poly. Sci.*, 1991, **43**, 1431–1440.
59. Kravets, L. I., Dmitriev, S. N., Drachev, A. I., Gilman, A. B., Lazea, A. and Dinescu, G., Controlled change of transport properties of poly(ethylene terephthalate) track membranes by plasma method. *J. Phys.: Conf. Ser.*, 2007, **63**, 012031.
60. Yiannakis, P. and Yianni Martin, C., Polymeric coating, US Patent No. 5496581, 1996.
61. Pérez-Martínez, J. A. *et al.*, An RF micro plasma facility development for medical applications. *Surf. Coat. Technol.*, 2007, **201**, 5684–5687.
62. Ohkawa, H., Akitsu, T., Tsuji, M., Kimura, H., Kogoma, M. and Fukushima, K., Pulse-modulated, high frequency plasma sterilization at atmospheric pressure. *Surf. Coat. Technol.*, 2006, **200**, 5829–5835.
63. Holy, C. E., Cheng, C., Davies, J. E. and Shoichet, M. S., Optimizing the sterilization of PLGA scaffolds for use in tissue engineering. *Biomaterials*, 2001, **22**, 25–31.
64. Lerouge, S., Guignot, C., Tabrizian, M., Ferrier, D., Yagoubi, N. and Yahia, L., Plasma-based sterilization: Effect on surface and bulk properties and hydrolytic stability of reprocessed PU electrophysiology catheters. *J. Biomed. Mat. Res.*, 2000, **52**, 774–782.
65. Moreira, A. J., Mansano, R. D., Andreoli Pinto, T. J., Ruas, R., Luis da Silva, Z. L., da Silva, M. V. and Verdonck, P. B., Sterilization by oxygen plasma. *Appl. Surf. Sci.*, 2004, **235**, 151–155.
66. Stavridi, M., Katsikogianni, M. and Missirlis, Y. F., The influence of surface patterning/sterilization on the haemocompatibility of polycaprolactones. *Mater. Sci. Eng.*, 2003, **23**, 359–365.
67. Chen, Q., Forch, R. and Wolfgang, K., Characterization of pulsed plasma polymerization of allylamine as an adhesion layer for DNA adsorption/hybridization. *Chem. Mater.*, 2004, **16**, 614–620.
68. Jung, D., Yeo, S., Kim, J., Kim, B., Jin, B. and Ryu, D. Y., Formation of amine groups by plasma enhanced chemical vapor deposition and its application to DNA array technology. *Surf. Coat. Technol.*, 2006, **200**, 2886–2891.
69. Wang, Y. J., Chen, C. H., Yeh, M. L., Hsiue, G. H. and Yu, B. C., A one-side hydrophilic polypropylene membrane prepared by plasma treatment. *J. Membr. Sci.*, 1990, **53**, 275–286.
70. Eloy, R., Parrat, D., Duc, T. M., Legeay, G. and Bechetoille, A., *In vitro* evaluation of inflammatory cell response after CF_4 plasma surface modification of poly(methyl methacrylate) intraocular lenses. *J. Cataract Refract. Surg.*, 1993, **19**, 364–370.
71. Hettlich, H. J., Otterbach, F., Mittermayer, C. H., Kaufmann, R. and Klee, D., Plasma-induced surface modifications on silicone intraocular lenses: Chemical analysis and *in vitro* characterization. *Biomaterials*, 1991, **12**, 21–524.
72. Lee, S. D., Hsiue, G. H., Chen, Y. K. and Chang, P. C. T., Artificial cornea: Surface modification of silicone rubber membrane by graft polymerization of pHEMA via glow discharge. *Biomaterials*, 1996, **17**, 587–595.
73. Latkany, R., Tsuk, A., Sheu, M. S., Hloh, I. and Randall, T., Plasma surface modification of artificial corneas for optimal epithelialization. *J. Biomed. Mater. Res.*, 1997, **36**, 29–37.
74. George, A. and Pitt, W. G., Comparison of corneal epithelial cellular growth on synthetic cornea materials. *Biomaterials*, 2002, **23**, 1369–1373.

Received 2 November 2007; revised accepted 24 April 2008