

PLASMA SURFACE MODIFICATION IN BIOMEDICAL APPLICATIONS

Ih-Houng Loh, Sc.D.
 AST Products, Inc.
 9 Linnell Circle, Billerica, MA 01821, USA
 TEL 978.663.7652 • FAX 978.663.7746
 www.astp.com

ABSTRACT

New medical products, materials and surgical procedures keep improving current health-care practices. Many of these innovations involve polymeric devices that must meet certain clinical and cost requirements. Chief among these pressures is the need for biocompatibility between the physiological environment and the biomaterial surface. Plasma surface modification can improve biocompatibility and biofunctionality. This article reviews the capabilities and applications of the technology.

Engineered Biocompatibility

The use of synthetic materials in biomedical applications has increased dramatically during the past few decades. Although most synthetic biomaterials have the physical properties that meet

Physical	Chemical	Radiation
Physical adsorption Langmuir-Blodgett film	Oxidation by strong acids Ozone treatment Chemisorption Flame treatment	Plasma (glow discharge) Corona discharge Photo-activation (UV) Laser Ion beam Electron beam γ irradiation

Table I. Surface Modification Methods

or even exceed those of natural tissue, they often result in a number of adverse physiological reactions such as thrombosis formation, inflammation and infection. Modifying the surface of a material can improve its biocompatibility without changing its bulk properties. Several methodologies have been considered and developed for alter the interactions of biomaterials with their biological environments (see Table I), plasma surface modification is one of these methodologies.

The Process

In the plasma surface modification process, a glow discharge plasma is created by evacuating a vessel, usually quartz because of its inertness, and then refilling it with a low-pressure gas, see Figure 1. The gas is then energized using techniques such as radio-frequency energy, microwaves, alternating current of direct current. The energetic species in a gas plasma include ions, electrons, radicals, metastables, and photons in the short-wave ultraviolet (UV) range. Surfaces in contact with gas plasmas are bombarded by these energetic species and their energy is transferred from the plasma to the solid, see Figure 2. These energy transfers are dissipated within the solid by a variety of chemical and physical processes as

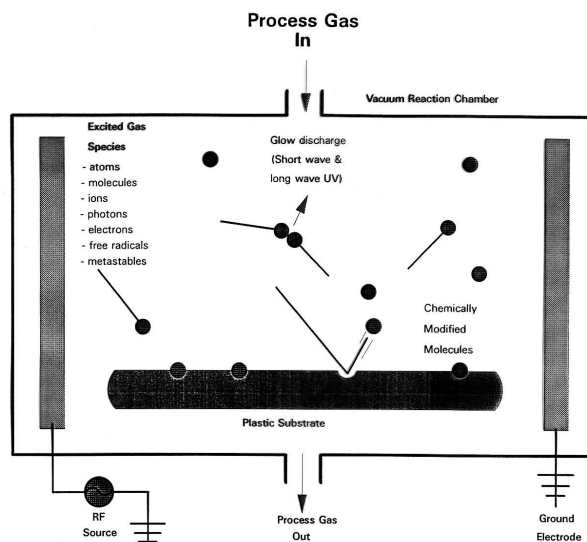


Figure 2: Schematic of plasma surface modification within the plasma reactor.

schematically illustrated in Figure 3, to result in the surface modification.

- Adhesion Promotion
- Enhanced Surface Wettability and Spreading
- Biocompatibility Improvement
- Surface Functionalization
- Reduced Surface Friction and Tackiness
- Molecular Immobilization
- Non-Fouling Coating
- Barrier Surface Coating

Table II. Applications of Plasma Processes for Biomaterials Surface Modification

The unique surface modification that can be achieved using the plasma process results from the effects of the photons and active species in the plasma these react with surfaces in depths from several hundred angstroms to 10 μm without changing the bulk properties of the biomaterial.

A wide variety of parameters can directly affect the chemical and physical characteristics of a plasma and subsequently affect the surface chemistry obtained by plasma modification. Processing parameters, such as gas types, treatment power, treatment time and operating pressure, can be varied by the user; and system parameters, such as electrode location, reactor design, gas inlets and vacuum, are set by the design of the plasma equipment. This wide range of parameters offers greater control over the plasma process than that offered by most high-energy radiation processes.

Other advantage of this technology include low environmental impact; no line-of-sight problem compared with electron-beam, laser or UV radiation; and a pinhole-free coating. In addition, although gas plasma treatments are typically carried out in a batch process, continuous on-line treatment of fibres, tubing membranes, fabrics and films, is also common. In many cases, a custom-designed reactor is necessary to maintain a high level of throughput and maximize the economic feasibility of the process.

Capabilities

Plasma processes have been developed to attain specific surface properties of biomaterials, see Table II.

Promotion adhesion. Improving adhesion between two surfaces is a common application. Good adhesion requires strong interfacial forces via chemical compatibility and/or chemical bonding. Plasma surface treatment can assist the creation of chemically active functional groups, such as amine, carbonyl, hydroxyl, and carboxyl groups, to improve interfacial adhesion. Common applications include

pretreatment for catheters, syringe components, dialysis pump parts, and plastic films for blood and drug bags.

Controlling surface energies. The process can also be used to tailor surface energies. Hydrophilic and hydrophobic surfaces can be created on polymers through interaction with a gas plasma. Using oxygen to create hydroxyl functionality will

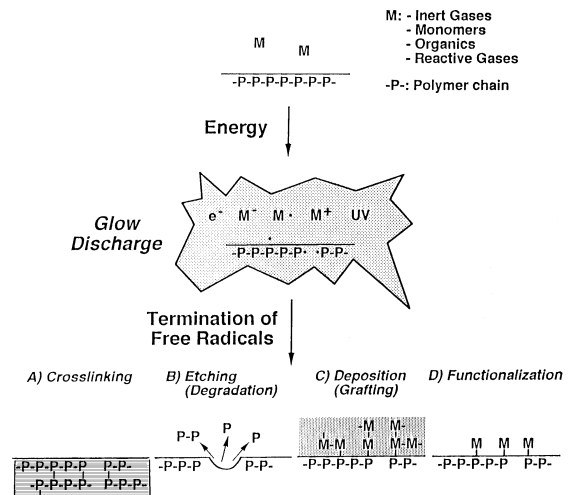


Figure 3: Schematic of the reaction mechanisms of plasma surface modifications.

increase the wettability of the surface. This has been used to enhance the performance of a catheter by the creation of a wettable surface on the polymer tubing. In a similar way, surfaces can be specifically engineered to modify protein binding and improve blood compatibility.

Improving biocompatibility. Biomaterials that come in contact with blood or protein require special surface treatments to enhance biocompatibility. Amine functional groups, which are attached by ammonia plasma treatment, act as hooks for anticoagulants, such as heparin, and thereby decreasing thrombogenicity¹. Synthetic polymeric implant materials can be surface activated using radio frequency plasma techniques to enable covalent immobilization of cell-binding peptides derived from the extra cellular matrix proteins: fibronectin and laminin. The resulting grafted peptides can promote complete coverage of a surface with a monolayer of intact, healthy endothelial cells to form a natural blood compatibility surface. The endothelialized bioimplants will have improved biocompatibility and reduce antigenicity and thrombogenicity. Tetrafluoroethylene plasma coatings on small-diameter Dacron vascular grafts have demonstrated a dramatic improvement in patency and decreased embolization².

Enhancing performance. Surface crosslinking is often used to enhance the performance of polymers. The activity of the plasma creates a higher crosslinking density within the material to a depth of a few thousand angstroms. The resulting increase in hardness and chemical resistance can be used to enhance performance in many applications. For example, silicone rubber components treated in an inert gas plasma can be modified to form a hard "skin" on the surface. This results in a substantial decrease in surface tack and coefficient of friction. Recently a plasma immobilization process has been developed to directly crosslink precoated molecules onto polymer surfaces.³ The molecules immobilized by this process can be organic compounds, surfactants, polymers, or proteins, and do not require unsaturated double bonds in the molecules.

Plasma polymers also have been used in conjunction with parylene coating to provide tough barriers that strongly adhere to the substrate⁴. Many other types of coatings can be enhanced in a similar manner.

Biomedical Applications

Plasma surface modification is appropriate for a variety of biomedical applications^{5,6}. Some of the more important examples are summarized in Table III and selectively described below.

Bioseparation. Polymer membranes with selective permeation are widely used in many bioseparation applications, such as haemodialysis,⁷ protein purification, artificial organs and biosensors. Membrane materials should exhibit high selectivity of

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permeation to achieve high product purity while retaining high permeation rates to maximize productivity. High selectivity can be enhanced by incorporating chemical functionality (grafting) or physical restriction (controlled pore size) into the membranes.

Sterilization. Plasma technology has also been considered for disinfection and sterilization of medical devices.⁸ The most convenient aspect of plasma technology is the potential for simultaneous surface modification and sterilization in biomedical device fabrication. Plasma sterilization may be suitable for

medical implants and devices that are sensitive to temperature, radiation and chemicals.

Ocular prostheses. Products such as contact lenses and intraocular lenses⁹ have been successfully modified by plasma treatment to impart

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protein- and cell-repelling characteristics, decrease bacterial adhesion, improve wettability and enhance patient comfort. To enhance corneal epithelial cell attachment and growth, an ammonia plasma treatment has been applied to artificial corneas fabricated from poly (hydroxyethyl methacrylate).¹⁰ Immobilization of fibrinogen and fibronectin on plasma treated surfaces has also been carried out to provide an adequate matrix for the migration of corneal epithelial cells during wound healing. Argon plasma was used to modify a synthetic cornea containing polyvinyl alcohol (PVA) hydrogel for enhanced epithelialization.¹¹ Results from both the organ culture study and in vivo implantation in a rabbit model indicate that a confluent epithelial layer was obtained on the plasma modified PVA surface.

Orthopedic applications. Plasma processes have been employed to modify the surface of metal implants for adhesion promotion to bone cements, or enhancing cell attachment and growth. Plasma crosslinking of a bioabsorbable polymer surface has been shown to regulate the material's degradation rate.¹² Plasma technology can also improve the mechanical properties of totally absorbable composite bone plates strengthening the interfacial bonding between reinforced absorbable fibers and absorbable matrix, and retarding the water penetration into the reinforced fibers and matrix to slow down the rate of degradation.¹³

Tissue culturing. The surfaces of culture substrates, such as petri dishes, roller bottles, microcarriers and membranes can be modified by plasma treatment to improve cell growth, protein binding or non-binding, and cell-specific attachment by controlling surface chemical structures, surface energies, and/or surface charge states.

Taking commercial advantage. Of the different surface modification techniques, (see Table IV), plasma treatment offers flexibility, effectiveness, safety and environmental friendliness. The plasma is effective at near-ambient temperature without

damage for most heat-sensitive biomaterials. Plasma treatment modifies only the near surface of treated substrates and does not change the bulk material properties. Plasmas can modify almost any kind of substrate geometry. The most important feature is its ability to surface functionalize, which chemical processing cannot offer.

There are, however, some disadvantages, including the need for a vacuum environment, relatively high cost and poorly defined chemistry. In addition, it is extremely difficult to generate plasma in small pores or within long, small-diameter tubing.

Table III. Biomaterial applications of plasma surface modifications

Applications	Devices	Materials	Purposes
Biosensor	sensor membranes diagnostic biosensors	PC, Cellulose, Cuprophane, PP, PS	immobilization of biomolecules non-fouling surfaces
Bioseparation	separation membranes hemodialysis membranes	PP, cellulose derivatives, PSF	anti-fouling surfaces wettability enhancement enhanced biocompatibility
Cardiovascular	vascular grafts catheters	PET, PTFE PE, SiR, PVC, PU	improved biocompatibility (endothelialization) wettability enhancement improved biocompatibility lubricious coatings reduced friction anti-microbial coatings
Dental	dental implants	Ti alloys	enhanced cell growth
Fundamental Research		Polymers, Metals, Glass, Ceramics, Composites	Biological interactions with plasma gas discharge- modified surfaces
Ophthalmological	contact lenses intraocular lenses artificial corneas	PMMA, SiR PMMA, SiR PVA, PHEMA	wettability enhancement improved biocompatibility anti-microbial coatings wettability enhancement enhanced cell growth
Orthopedic	metal implants joints ligaments bone plates	Ti-Ni, Co-Cr alloys UHMWPE PET PGA, PLA	surface cleaning (etching) enhanced cell adhesion/growth improved biocompatibility enhanced bone cement adhesion enhanced tissue in-growth prolonged mechanical strength loss
Pharmaceutical	drug controlled release devices	SiR, hydrogel, PGA, PLA	reduced molecule diffusion controlled degradation for drug release
Tissue culturing	tissue culture dishes	PS, PET	enhanced cell adhesion/growth wettability enhancement non-fouling coatings
Others	general devices		sterilization surface cleaning (etching) adhesion promotion

Abbreviation of polymers: PET: poly(ethylene terephthalate); PTFE: polytetrafluoroethylene; PE: polyethylene; SiR: silicone rubber; PVC: poly(vinyl chloride); PU: polyurethane; PMMA: poly(methyl methacrylate); UHMWPE: ultra high molecular weight PE; PGA: poly(glycolic acid); PLA: poly(lactic acid); PS: polystyrene; PC: polycarbonate; PP: polypropylene; PSF: polysulfone.

There are also a number of obstacles opposing the commercial use of plasma depositions and reactions in the biomedical field. One major barrier is the lack of clearly defined United States Food and Drug Administration guidelines on how surface modifications will be regulated. In addition, although plasma processes and applications have been proposed and studied extensively in academic settings, process reproducibility has often been overlooked. There is a

pressing need for the biomaterials industry to work with research institutions on process optimization and scale-up economics. On the whole, however, the advantages of plasma surface treatment outweigh any disadvantage because it allows many types of modifications that cannot be generated by other methods.

	Plasma	UV-activation	Ion- Beam	Corona	Hydrogel
Wettability	yes	yes	limited	yes	yes
Dry Lubricity	limited	limited	yes	no	no
Wet Lubricity	yes	yes	limited	limited	yes
Hemocompatibility	yes	yes	limited	no	yes
Reduce Bacterial Adherence	yes	yes	yes	no	yes
Drug Delivery	limited	limited	no	no	yes
Reduce Protein Adsorption	yes	yes	no	no	limited
Immobilize Biomolecules	yes	yes	no	limited	no
Improve Cell Adhesion	yes	yes	limited	yes	no
Improve Tissue Integration	yes	yes	yes	limited	no
Anti-fog	yes	yes	no	no	limited
Improve Adhesion	yes	yes	no	yes	no
Improve Metal Hardness	no	no	yes	no	no
Reduce Metal Corrosion	yes	no	yes	no	no
Manufacturing Benefits					
Ambient Pressure	no	yes	no	yes	yes
Ambient Temperature	yes	yes	yes	yes	yes
Scale-Up Capability	limited	limited	no	yes	yes
Low Cost Equipment	no	yes	no	yes	yes
Environmental Safe	yes	yes	yes	no	yes
Dry Process	yes	no	yes	yes	no
Coating Stability	yes	yes	yes	no	yes
Process Cost Overall	medium	medium	high	low	low

Table IV: The Comparison of Various Popular Surface Modification Processes

REFERENCES

1. S. Yuan, G. Szakalas-Gratzl, G., N.P. Ziats, D.W. Joacobsen, K. Kottke-Marchant and R.E. Marchant, "Immobilization of High-affinity Heparin Oligosaccharides to Radiofrequency Plasma-Modified Polyethylene", *J. Biomed. Mat. Res.*, **27**, 811 (1993).
2. D. Kiaei, A.S. Hoffman, B.D. Ratner, T.A. Horbett, and L.O. Reynolds, "Interaction of Blood with Gas Discharge-Treated Vascular Grafts," *J. Appl. Polym. Sci.: Appl. Polym. Symp.*, **42**, 269 (1988).
3. M.-S. Sheu, A.S. Hoffman and J. Feijen, "A Glow-Discharge Treatment to Immobilize Poly(ethylene Oxide)/Poly(propylene Oxide) Surfactants for Wettable and Non-fouling Biomaterials," *J. Adhesion Sci. & Tech.*, **6**, 995 (1992).
4. I.H. Loh and D.M. Hudson, "Polymerization Process", U.S. Patent, no. **5,447,799** (1995).
5. M.S. Sheu, D.M. Hudson and I.H. Loh, "Biomaterials Surface Modification Using Plasma Gas Discharge Processes," in **Encyclopedic Handbook of Biomaterials and Bioengineering, Part A. Materials**, edited by D.L. Wise, D.J. Trantolo, D.E. Altobelli, M.J. Yaszemski, J.D. Gresser and E.R. Schwartz, Marcer Dekker, New York, , Vol. 1, p.865-894 (1995).
6. B.D. Ratner, A. Chilkoti and G.P. Lopez, "Plasma Deposition and Treatment for Biomedical Applications," in *Plasma Deposition, Treatment and Etching of Polymers*, edited by R. d'Agostino, Academic Press, San Diego, CA, p. 463-516 (1990).
7. F. Poncin-Epaillard, G. Legeay and J.-C. Brosse, "Plasma Modification of Cellulose Derivatives as Biomaterials," *J. Appl. Polym. Sci.* **44**, 1513 (1992).
8. P.T. Jacobs and S.M. Lin, "Hydrogen Peroxide Plasma Sterilization System", U.S. Patent , 4,643,876 & 4,756,882 (1987).
9. J.S. Brinen, S. Greenhouse and L. Pinatti, "ESCA and SIMS Studies of Plasma Treatments of Intraocular Lenses," *Surface and Interf. Anal.*, **18**, 233 (1991).
10. R. Sipehia, "X-ray Photoelectron Spectroscopy Studies, Surface Tension Measurements, Immobilization of Human Serum Albumin, Human Fibrinogen and Human Fibronectin onto Ammonia Plasma Treated Surfaces of Biomaterials useful for Cardiovascular Implants and Artificial Cornea Implants," *Biomat. Art. Cells & Biotech.*, **21**, 647 (1993).
11. R. Latkany et al., "Plasma Surface Modification of Artificial Corneas for Optimal Epithelialization," *J. Biomed. Mater. Res.* **36**, 29-37 (1997).
12. I.H. Loh, H.-L. Lin and C.C. Chu, "Plasma Surface Modification of Synthetic Absorbable Sutures," *J. Appl. Biomaterials*, **3**, 131 (1992).
13. M. Ibnabddjalil, I.H. Loh, C.C. Chu, N. Blumenthal, H. Alexander and D. Turner, "Effect of Surface Plasma Treatment on the Chemical, Physical, Morphological, and Mechanical Properties of Totally Absorbable Bone Internal Fixation Devices," *J. Biomater. Med. Res.*, **28**, 289 (1994).