

## Plasma-surface modification of biomaterials

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### Abstract

Plasma-surface modification (PSM) is an effective and economical surface treatment technique for many materials and of growing interests in biomedical engineering. This article reviews the various common plasma techniques and experimental methods as applied to biomedical materials research, such as plasma sputtering and etching, plasma implantation, plasma deposition, plasma polymerization, laser plasma deposition, plasma spraying, and so on. The unique advantage of plasma modification is that the surface properties and biocompatibility can be enhanced selectively while the bulk attributes of the materials remain unchanged. Existing materials can, thus, be used and needs for new classes of materials may be obviated thereby shortening the time to develop novel and better biomedical devices. Recent work has spurred a number of very interesting applications in the biomedical field. This review article concentrates upon the current status of these techniques, new applications, and achievements pertaining to biomedical materials research. Examples described include hard tissue replacements, blood contacting prostheses, ophthalmic devices, and other products. © 2002 Elsevier Science B.V. All rights reserved.

*Keywords:* Plasma processing and deposition; Biomaterials

### 1. Introduction

Bio-integration is the ideal outcome expected of an artificial implant. This implies that the phenomena that occur at the interface between the implant and host tissues do not induce any deleterious effects such as chronic inflammatory response or formation of unusual tissues. Hence, it is of paramount importance to design biomaterials used in implants with the best surface properties. Meanwhile, these biomaterials must possess bulk properties that meet other requirements, especially mechanical properties in order to function properly in a bio-environment. As it is quite difficult to design biomaterials fulfilling both needs, a common approach is to fabricate biomaterials with adequate bulk properties followed by a special treatment to enhance the surface properties. In this way, it allows one to make ideal biomaterials with surface attributes that are decoupled from the bulk properties. Furthermore, the surface properties can be selectively modified to enhance the performance of the biomaterials. For instance, by altering the surface functionality using thin film deposition, the optimal surface, chemical, and physical properties can be attained [1]. Hence, surface modification of biomaterials is becoming an increasingly popular method to improve device multi-functionality, tribological and mechanical properties, as well as biocompatibility of artificial devices while obviating the needs for large expenses and long time to develop brand new materials. It has

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become one of the key methods in biomaterials engineering. Usually more than one approach can satisfy the biomaterials requirements, and the ultimate selection must take into account the process reliability, reproducibility, and products yield [2].

A plasma which can be regarded as the fourth state of matter is composed of highly excited atomic, molecular, ionic, and radical species. It is typically obtained when gases are excited into energetic states by radio frequency (rf), microwave, or electrons from a hot filament discharge. A plasma is a highly unusual and reactive chemical environment in which many plasma-surface reactions occur. The high-density of ionized and excited species in the plasma can change the surface properties of normally inert materials such as ceramics. Plasma-based techniques combining the advantages of conventional plasma and ion beam technologies are effective methods for medical implants with complex shapes [3]. In particular, modification of the surface energetics of the materials can improve the adhesion strength, surface and coating properties, and biocompatibility, just to name a few [4]. Succinctly speaking, plasma-based techniques offer the following advantages with regard to biomaterials engineering.

1. The benefits of plasma processing arise from the good understanding of plasma physics and chemistry learned in other fields such as microelectronics, for example, plasma homogeneity and effects of non-uniform plasma on the substrate surface [5].
2. Plasma engineering is usually reliable, reproducible, non-line-of-sight, relatively inexpensive, and applicable to different sample geometries as well as different materials such as metals, polymers, ceramics, and composite [6–8]. Plasma processes can be monitored quite accurately using in situ plasma diagnostic devices.
3. Plasma treatment can result in changes of a variety of surface characteristics, for example, chemical, tribological, electrical, optical, biological, and mechanical. Proper applications yield dense and pinhole free coatings with excellent interfacial bonds due to the graded nature of the interface [9].
4. Plasma processing can provide sterile surfaces and can be scaled up to industrial production relatively easily. On the contrary, the flexibility of non-plasma techniques for different substrate materials is smaller [10].
5. Plasma techniques are compatible with masking techniques to enable surface patterning [11,12], a process that is commonly used in the microelectronics industry.

As a result, plasma-surface modification (PSM) as an economical and effective materials processing technique is gaining popularity in the biomedical field. It is possible to change in continuum the chemical composition and properties such as wettability, metal adhesion, dyeability, refractive index, hardness, chemical inertness, lubricity, and biocompatibility of materials surfaces. In the biomedical context, “good biocompatibility” refers to that a prosthesis or biomaterial device is non-toxic, does not induce deleterious reactions from the bio-medium, performs properly all the functions they have been designed for, and has a reasonable lifetime. The application of plasma-based techniques is quite diverse, and examples of applications include cleaning/sterilization, coating or depositing, and implantation modification of surface chemistry of a substrate. Orthopedic prostheses are made harder and more wear resistant by ion implantation into the articulating surfaces. Orthodontic appliances, surgical instruments, and venous catheters, are treated to improve friction, fretting resistance and biocompatibility. Orthopedic hip and dental implants need bone adhesion control on the Ti alloy surface by  $\text{Ca}^+$  ion implantation, and artificial blood vessels require endothelial cell adhesion control on polymeric surface by ion implantation for non-thrombogenicity [13]. Table 1 lists some of the more common research areas and applications of plasma treatment in biomaterials [14] and Table 2 shows the advantages of plasma deposited films in biomaterial

Table 1  
Common research areas and applications of plasma treatment in biomaterials engineering

Blood-compatible surfaces	Vascular grafts, catheters, stents, heart-valves, membranes (e.g. for hemodialysis), filters (e.g. for blood cell separation), biomolecules immobilized on surfaces
Non-fouling surfaces	Intraoculars (IOLs), contact lenses, wound healing, catheters, biosensors
Tissue engineering and cell culture	Cell growth, antibody production, essays, vascular grafts
Sterilization of surgical tools and devices	Cutting tools of surgeon, tweezers
Biosensors	Biomolecules immobilized on surfaces
Barriers coatings	Drug-release, gas-exchange membranes, device protection, corrosion protection, reduction of leaches (e.g. additives, catalysts, plasticizers, etc.)

Table 2  
Advantages of plasma-deposited films in biomaterials applications

Easy preparation
Unique film chemistry
Coated on unique substrates with good adhesion
Conformal and pin-hole free films
Excellent permeation barriers with low level of leachables
Sterile upon preparation

applications [1]. More information can be found in the article of Ratner et al. [15]. With regard to ion implantation, Table 3 lists some of the main historical events [16].

All in all, PSM of biomaterials has become a very active field, and a review of currently available methods, modification techniques, and applications is of great interests to the biomedical and plasma communities. The past decade has witnessed a revolution in our understanding of PSM in biomaterial applications. More than 1000 publications have appeared since 1996. In writing this review article, we have chosen to concentrate upon developments that have taken place during the last several years with reference to earlier publications. The principles and physical basis of PSM are described in Section 2. The requirements and influence of PSM on biomaterials are discussed in Sections 3 and 4. A number of examples are described, including the surface modification of biomedical implant materials and devices such as total joint replacements (TJRs) and artificial bone, dental implants, artificial heart-valves, vascular stents, artificial blood vessels, intraocular lenses (IOLs), artificial corneas, and artificial catheters. The aim of the treatment is to reduce fretting, increase biocompatibility, achieve bioactive or bioinert performance, enhance corrosion resistance,

Table 3  
Brief historical overview of surface modification of biomaterials by ion implantation

1906	He <sup>2+</sup> scattering investigated by Rutherford
1930s	Low energy ion sources developed
1940s and 1950s	Ion source plus acceleration system developed by nuclear physicists for light ions; also, isotope separator (low voltage implanter) for heavier ions
1960s	Major efforts to study effects of implanting dopants into semiconductors
1970s	Microelectronic devices based on ion implanted silicon fabricated and sold in volume; major research efforts to study modification of surface properties of metals
1980s	Establishment of ion implantation as a standard technique in the microelectronics industry; ion implanted biomedical components reaching market
1990s	Extensive research and applied to a myriad of biomedical products in orthopedic and medical devices: knee, teeth, bone, pedicel screw, surgical tools, etc.

improve adhesion, strengthen wear resistance, and/or reduce fatigue-related failure. They are described in details in Sections 5–8.

## 2. Plasma sources and plasma-surface modification techniques

Plasma treatment can change the surface and materials characteristics such as biocompatibility and mechanical/chemical properties. Different PSM methods and plasma sources are used for different materials and to cater to specific requirements. The common plasma sources and PSM methods are described here.

### 2.1. Plasma sources

To produce a plasma, electron separation from atoms or molecules in the gas state, or ionization, is required. When an atom or a molecule gains enough energy from an outside excitation source or via interaction (collisions) with one another, ionization occurs. There are many kinds of plasma sources, and the common ones are the gaseous, metallic, and laser-based plasma sources. The characteristics of these plasma sources, such as the electron temperature, ion temperature, electron density, and uniformity are discussed in Section 2.1.1.

#### 2.1.1. Gaseous plasma sources

In general, a gaseous plasma is ignited by applying a potential through the gas, and the breakdown potential depends on the pressure and discharge gap width. Fig. 1 depicts the relationship between the breakdown potential of air and pressure. The breakdown potential has a minimum value when the pressure is 0.7 Torr, and deviation from this value leads to an increase of the critical breakdown electric field [17]. The relationship between the current and voltage in a low-pressure gas discharge is exhibited in Fig. 2 showing four regions: (1) “dark” or “Townsend discharge” prior to spark ignition, (2) “normal glow”, (3) “abnormal glow”, and (4) “arc discharge” where the plasma becomes highly conductive. Regions (2) and (3) tend to shrink with increasing pressure. For many gases, spark ignition proceeds directly to arcing at 760 Torr [18].

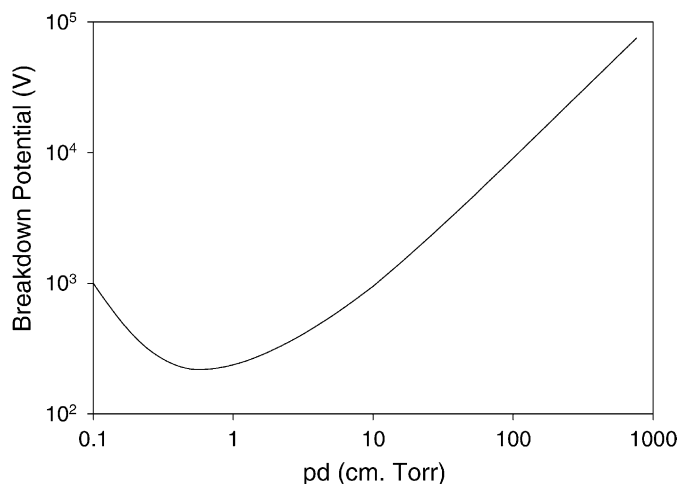


Fig. 1. Relationship between the breakdown electric field of air and pressure.

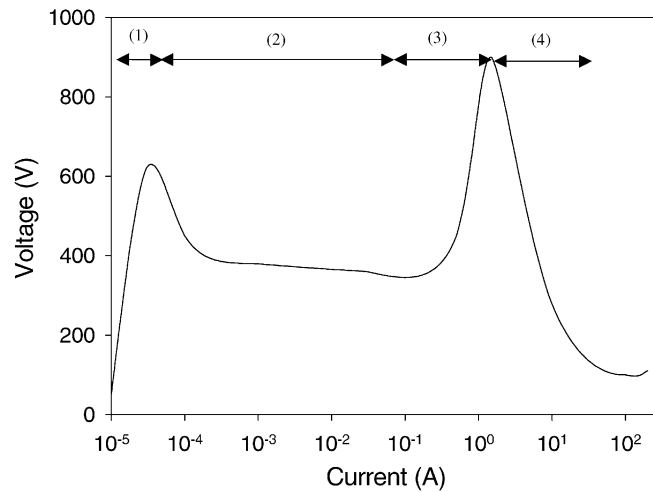


Fig. 2. Current–voltage characteristics of a low-pressure gas discharge at 1 Torr.

The current–voltage characteristic in atmospheric pressure is shown in Fig. 3. The discharge can be divided into two regions: (1) corona discharge where the discharge current is very small, and (2) arc discharge where the gas becomes highly conductive and a rapid drop in voltage with increasing current occurs. The arc discharge mode is widely used in welding, cutting, and plasma spraying [17].

Many low-pressure plasma sources, such as direct current (dc), rf glow discharge (rfGD), and electron cyclotron resonance (ECR) plasma sources are operated at low-pressure since the breakdown electric field is smaller and the current is more controllable. These plasma sources can generate large area uniform plasma with a well controlled electron density. Some other plasmas such as corona discharge and arc plasma at atmospheric pressure are also used in biomedical engineering.

*2.1.1.1. Radio frequency (rf) glow discharge plasma source.* The rfGD is one of the most widely used sources in PSM because it is able to produce a large volume of stable plasma. The rf discharges have

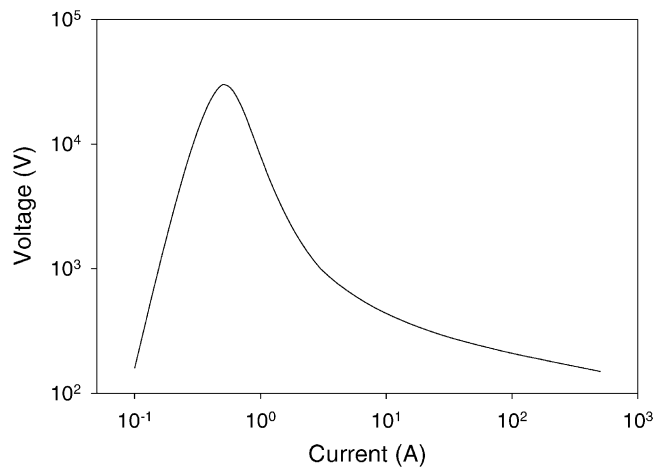


Fig. 3. Current–voltage coupled rfGD plasma source.

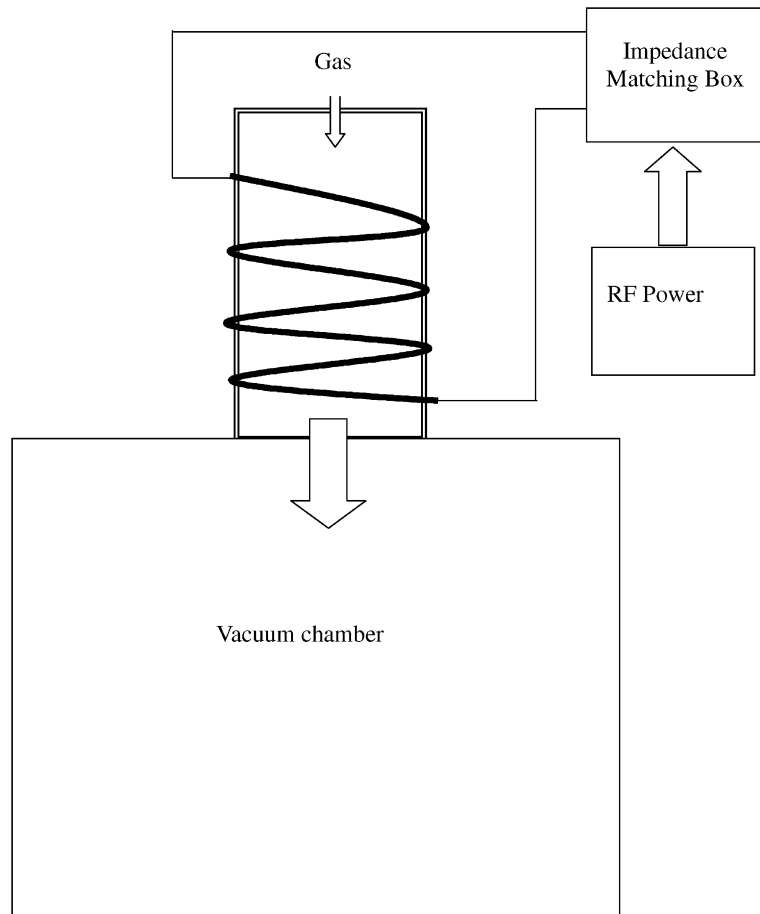


Fig. 4. Schematic of an inductively coupled rfGD plasma source.

been classified into two types according to the method of coupling the rf power with the load: capacitive coupling and inductive coupling. Both modes can use internal or external electrodes. Since the external mode uses a discharge tube that is made of glass (quartz or borosilicate glass), it is possible to reduce the effects of the electrode materials such as impurities introduced to the plasma process, and so it is a widely used coupling mode in rf plasma sources. Fig. 4 depicts a typical low-pressure inductively coupled plasma (ICP) source.

In general, 13.56 MHz is used in rfGD. The pressure during discharge is between  $10^{-3}$  and 100 Torr [19,20]. The electron density in rfGD in low-pressure ( $10^{-3}$  to 1 Torr) varies from  $10^9$  to  $10^{11}$   $\text{cm}^{-3}$ , whereas the electron density in medium pressure (1–100 Torr) can reach  $10^{12}$   $\text{cm}^{-3}$  [21]. The electron temperature is several eV and the ion temperature is very low. The uniformity of the rf plasma is quite good. Urano et al. have reported an argon plasma uniformity of several percent over a 1 m diameter in front of a substrate at 1 mTorr with the electron density reaching  $1 \times 10^{11}$   $\text{cm}^{-3}$  at an rf input power of 2.8 kW [22].

*2.1.1.2. Electron cyclotron resonance (ECR) plasma source.* A high-density ECR plasma can be generated at low-pressure. Fig. 5 depicts the schematic of an ECR plasma source. Microwave power is introduced into the plasma chamber through a quartz window. Magnetic coils are arranged around the

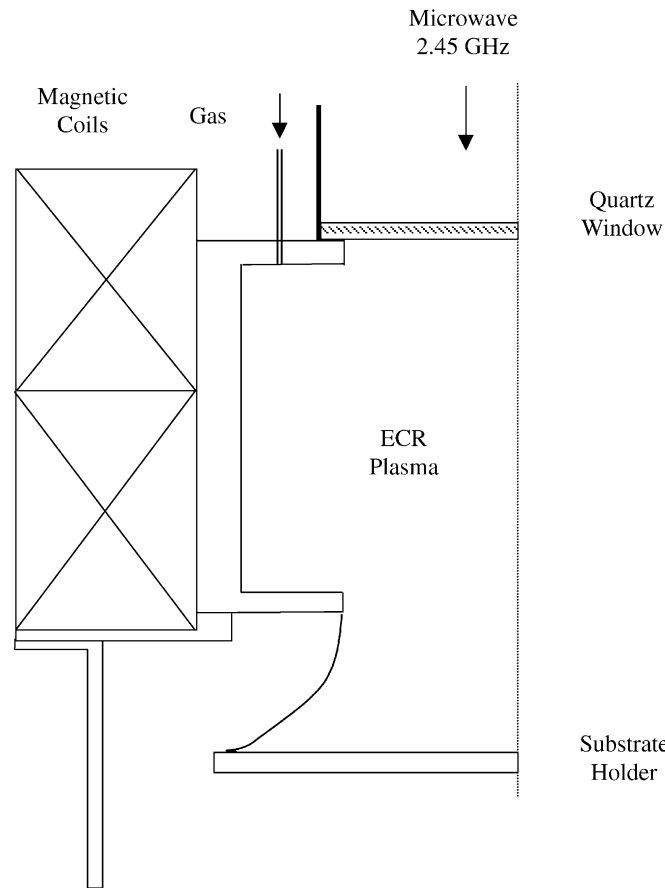


Fig. 5. Schematic of an ECR plasma source.

periphery of the chamber to achieve the ECR conditions. When a magnetic field is applied to the plasma, the electrons begin to rotate in a helical orbit about the magnetic field lines. The frequency,  $\omega$ , of the cyclotron motion in the absence of the electric field is given by

$$\omega = \frac{eB}{m} \quad (1)$$

where  $e$  and  $m$  are the charge and mass of electron, respectively and  $B$  is the magnetic field. A high-density plasma can be obtained by adjusting the magnetic field to match the cyclotron frequency of the electrons at the microwave frequency. The highest density of the plasma is obtained by enhancing the ionizing effect by trapping the electrons in the plasma.

In general, an ECR plasma source is operated at a pressure between  $10^{-5}$  and  $10^{-3}$  Torr. The electron density can reach  $10^{11} \text{ cm}^{-3}$  easily, and the maximum electron density (more than  $10^{12} \text{ cm}^{-3}$ ) can be acquired at low-pressure as well. The mean ion charge state is high because of the high collision frequency between the electrons and ions. However, the plasma distribution is not very uniform and the electron temperature is larger than that of the ion [23–25].

**2.1.1.3. Corona discharge plasma source.** Corona discharge appears as a luminous glow localized in space around a pointed tip in a highly non-uniform electric field. A corona discharge may be

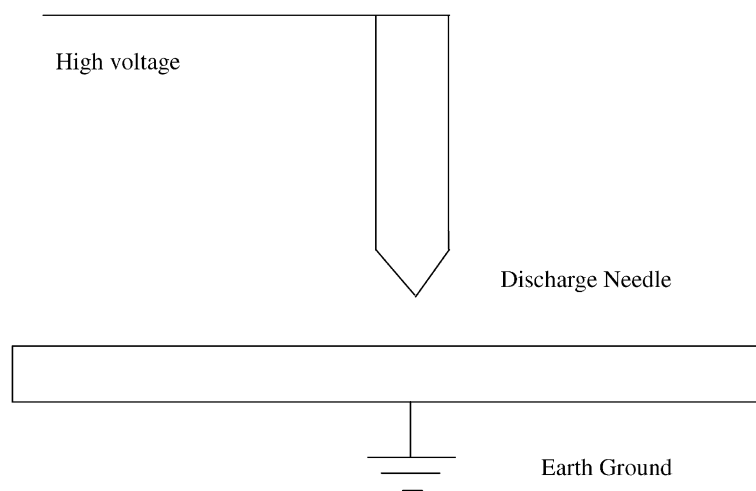


Fig. 6. Schematic of a corona discharge plasma source.

considered a Townsend discharge or a negative glow discharge depending upon the field and potential distribution. Fig. 6 depicts the schematic of a point-to-plane corona discharge system. The electric field near the anode (high voltage) is very strong because it has a very small characteristic size compared to the inter-electrode distance, and this situation typically arises when the characteristic size of the electrode is small. If the characteristic size of the anode is comparable to that of the cathode, a voltage between the wires produces a spark instead of a corona discharge. The voltage applied to the anode exceeds several kVs and the magnitude of the discharge current varies from  $10^{-10}$  to  $10^{-4}$  A. The dependence of the voltage on the current in a corona discharge in air at 760 Torr is shown in Fig. 3 [26].

In the plasma near the tip, the density of the charged species rapidly decreases with distance from about  $10^{13}$  to  $10^9$   $\text{cm}^{-3}$ . The electron temperature within the plasma averages about 5 eV, and the ion temperature is very low. In the drift region outside the discharge, the electron density is much lower and near  $10^6$   $\text{cm}^{-3}$ . The restricted area of the single point-to-plane corona discharge has limited applications in materials processing. In an attempt to overcome this problem, two-dimensional arrays of electrodes have been developed [17].

*2.1.1.4. Atmospheric arc plasma source.* The most widely used atmospheric arc plasma source in biomaterials research is a plasma spray torch. A common configuration comprises a nozzle-shaped anode serving also as a constrictor. Fig. 7 shows the schematic of a plasma spray torch consisting of a stick-type cathode with a conical tip, an outer grounded and water-cooled shield as an anode, and gas inlet components.

The relationship between the voltage and discharge current is depicted in Fig. 3. In order to sustain a plasma torch, the discharge current and power density are very high. The plasma develops between the cathode and anode where an electrically conducting gas at  $T > 8000$  K and  $10^5$  Pa for most plasma gases is common (except pure He). The electron density in the plasma torch ranges from  $10^{16}$  to  $10^{19}$   $\text{cm}^{-3}$ , and the electron temperature varies from 7.0 to 9.0 eV, but the ion temperature is an order of magnitude lower at 0.3–0.9 eV [27]. Because of the high plasma flow velocity (nearly  $1 \times 10^3$  m/s) and high-temperature in the plasma [28], almost all solid particles will be melted and a high velocity will be acquired. Atmospheric plasma torches are, thus, widely used in plasma spraying.



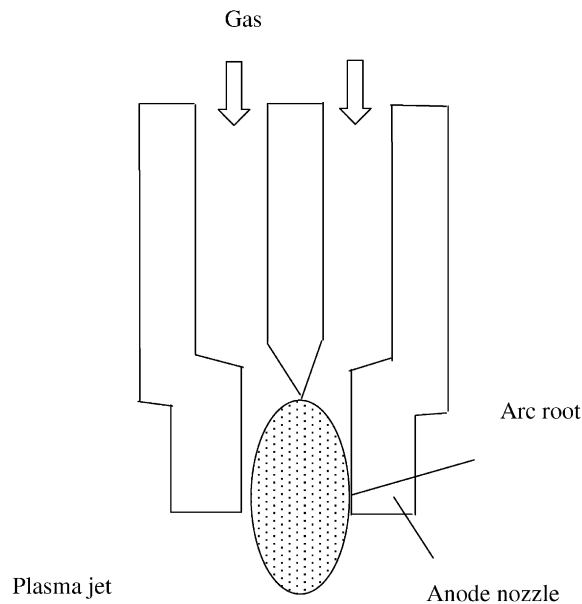


Fig. 7. Schematic of a plasma spray torch.

### 2.1.2. Vacuum arc plasma source

In general, a vacuum arc plasma source is composed of two parts: plasma production unit and macro-particle filter as shown in Fig. 8. When a high voltage pulse (several kVs) is applied to the trigger electrode, an arc discharge between the cathode and anode is ignited. The arc discharge current is concentrated at the cathode surface forming non-stationary locations of extremely high current density (of order  $10^{12}$  A/m) cathodic spots. The high current density is associated with the extremely high local power density (on the order of  $10^{13}$  W/m), which in turn provides the conditions for the localized phase transformation from the solid cathode material to fully ionized plasma. The plasma produced at the cathode spots expands rapidly into the vacuum ambient. The typical final ion velocities are in the range of  $(0.5\text{--}2.0) \times 10^4$  m/s corresponding to approximately 20 eV for light elements and 200 eV for heavy elements.

Cathodic spots are the source of not only fully ionized plasma but also droplets and debris particles that are commonly referred to as macro-particles. Curved macro-particle filters are commonly utilized to mitigate particle contamination from the cathodic arc plasma stream. Neutral macro-particles are not be affected by the magnetic field and impact the outer surface of the curved duct [29,30].

One important advantage of the cathodic arc process is the formation of a copious quantity of ions of the cathode materials and almost every electrical conductive material can be made into a cathode. The electron density in the cathode spot plasma can reach  $10^{20}$   $\text{cm}^{-3}$ , and the expanding plasma produces a highly ionized jet with ion charge states typically between 1 and 3. However, because of the high plasma flux velocity, diffusion effects have little influence on the transportation process, and the plasma flux is not very uniform in both the axial and radial directions [31,32].

### 2.1.3. Laser plasma source

Fig. 9 depicts the schematic of a laser plasma source. The plasma is generated by the interaction of high-density laser pulses with a solid target involving laser–solid interaction and plasma formation. Thus, it can be divided schematically into two different regimes [33].

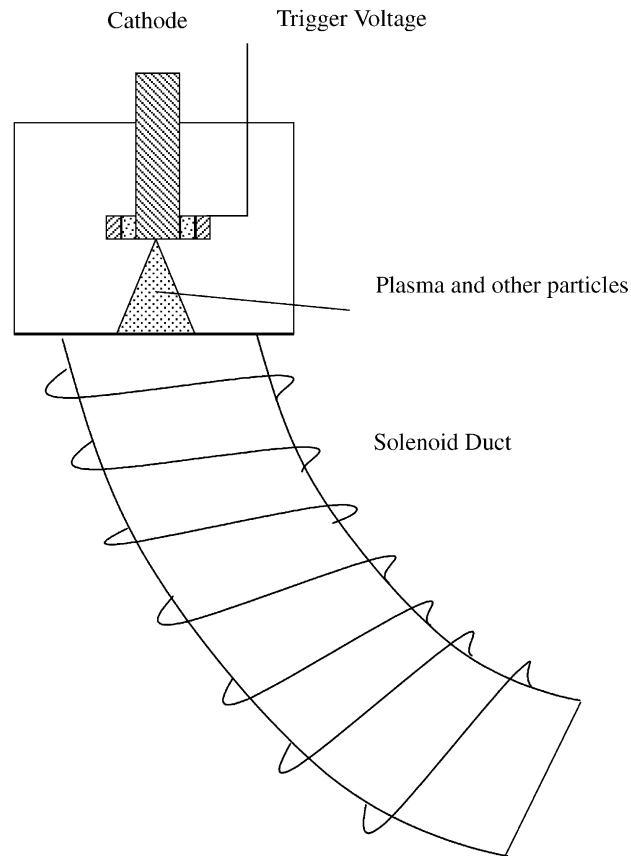


Fig. 8. Schematic of vacuum arc plasma source.

1. At low laser fluence, the vapor produced by the leading edge of the laser pulse behaves like a thin medium and the laser beam passes nearly unattenuated through the vapor. In this case, evaporation occurs from the liquid metal, and heat conduction into the solid target is the main source of energy loss. The threshold laser fluence of an ultra-short laser pulse (in ps) is on the order of  $0.1\text{--}0.2\text{ J/cm}^{-2}$ , and it increases to  $1\text{--}2\text{ J/cm}^{-2}$  for nanosecond laser pulse irradiation.
2. At high laser fluence, the vapor temperature is high enough to cause appreciable atomic excitation and ionization. In this case, the vapor begins to absorb the incident laser radiation leading to vapor breakdown and plasma formation. There are two kinds of plasma formation mechanisms for LA: inverse Bremsstrahlung (IB) and direct photo ionization (PI). IB is effective in infrared and PI occurs mainly in visible and UV LA.

The laser intensity during LA is usually on the order of  $10^8$  to  $10^{10}\text{ W/cm}^2$ . Metallic and composite targets that can absorb laser radiation can be used. Coupled with gas feeding, gaseous plasma can be generated simultaneously and it compensates for gas loss during evaporation. The electron density decreases exponentially with the distance between the target and substrate and its maximum value is about  $10^{18}$  to  $10^{20}\text{ cm}^{-3}$ . The electron temperature is in the range of  $1\text{--}5\text{ eV}$ , and the ion temperature has nearly the same order of magnitude as the electron temperature. However, since the plasma formation area in front of the target is very small and the plasma flux velocity is very large, the formation of a large area uniform laser plasma tends to be difficult in practice [34].

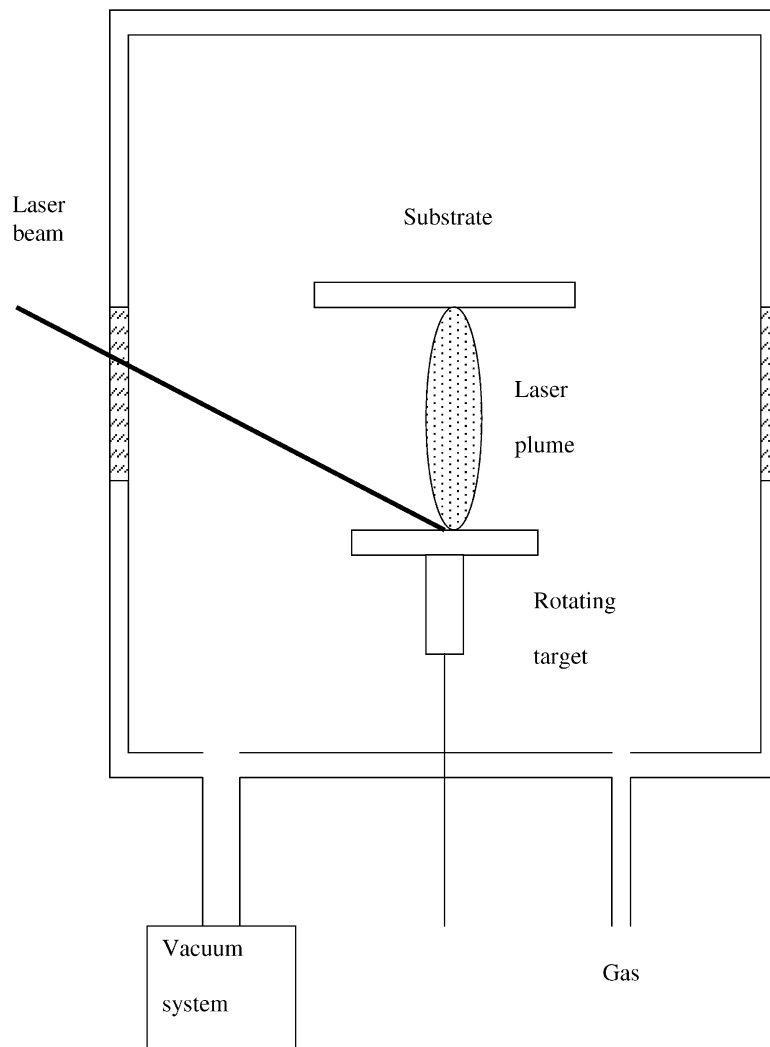


Fig. 9. Schematic of laser plasma source.

## 2.2. Plasma-surface modification techniques

In Section 2.2.1, the principle and applications of plasma sputtering, etching, cleaning, implantation, and deposition are reviewed.

### 2.2.1. Plasma sputtering and etching

In plasma sputtering and cleaning processes, materials are removed from the surface by chemical reactions to form volatile products and physical sputtering. Inert gases such as neon and argon are used for surface cleaning of materials. Argon is by far the most common inert gas used because of its relatively low cost and high sputtering yield.

Plasma sputtering is a simple plasma-surface treatment method. During the sputtering process, a negative voltage (about 1 to several kVs) is applied to the substrate and an argon plasma is generated by rfGD or ECR. The ions are accelerated towards the substrate by the applied electric field. Since the energy is not very high, the argon ions cannot go very deeply into the substrate and a big portion

of their energy is transferred to the surface atoms via elastic and inelastic collisions with the materials. Some surface atoms will acquire enough energy and escape from the substrate into the vacuum chamber. After the first layer of atoms has been sputtered off, the underlying layers will be exposed and gradually etched. With sufficient sputtering time, surface contamination will be cleaned off. This process can be used as a pretreatment for subsequent implantation and deposition.

The interaction between a plasma and polymer leads to two competitive reactions, namely modification and degradation [35]. When the modification effect dominates, the properties of the polymer will change due to ion beam interaction, plasma-graft co-polymerization, and plasma polymerization. When degradation is prominent, etching will take place on the polymer surface. Plasma etching in biomaterials research mainly focuses on argon plasma exposure of polymer materials. An etching reaction is a degradation reaction occurring at the surface of the polymers, and when polymers are exposed to plasma for a long enough time, the exposed layers of the polymers are etched off. The rate of weight loss is strongly dependent on the nature of the polymer as well as the energy of the plasma. Polymers containing oxygen functionalities such as ether, carboxylic acid, and ester groups show high plasma susceptibility, and polyolefins with no substituents exhibit low plasma susceptibility. Such weight loss is restricted to the topmost layers of the polymer, and in the inner layer, this weight loss process scarcely occurs. Therefore, polymers subjected to the plasma etching process possess similar chemical and physical properties to the original polymers. The elemental composition, chemical structure, degree of polymerization, and crystallinity of the treated polymers are hardly altered and are similar to those of the original polymers. The weight loss in the etching process is mainly due to bond scission of polymers and reactions of the radicals generated in the polymer chains upon plasma exposure. In addition to the chemical etching process, physical sputtering occurs frequently as well when polymers are exposed to plasma [36,37].

### 2.2.2. Plasma implantation

Implantation can introduce elements into the surface of the materials without thermodynamic constraints. Plasma implantation into metals/alloys and polymers are described here.

*2.2.2.1. Plasma immersion ion implantation of metals and alloys.* In plasma immersion ion implantation (PIII), sometimes also referred to as plasma implantation, plasma ion implantation, or plasma-based ion implantation, the specimens are surrounded by a high-density plasma and pulse-biased to a high negative potential relative to the chamber wall. Ions generated in the overlying plasma are accelerated across the sheath formed around the samples and implanted into the surface of the targets, as illustrated in Fig. 10. On account of the absence of ion transport optics and mass selection, PIII can provide a high ion flux. It is also a non-line-of-sight process as opposed to conventional beam-line ion implantation. PIII has many potential applications in biomaterials engineering. For example, sample possessing a sophisticated shape can be treated with good conformality and uniformity without beam scanning and special target manipulation. In addition, multiple processes such as simultaneous and consecutive implantation, deposition, and etching are possible by varying the instrumental parameters without breaking vacuum. Last but not the least, since implantation is usually conducted in low-temperature and the target can be cooled, thermal deformation of the specimens is typically minimal.

In PIII, gaseous plasma can be generated by dc, capacitively/inductively coupled rfGD, and ECR plasma sources. Metallic plasma can be generated separately or simultaneously by vacuum arc plasma sources and many elements can be introduced into the plasma at the same time.

PIII has been proven to be an effective approach to enhance the surface properties of materials such as corrosion resistance, wear resistance, and hardness. PIII can also serve as a pretreatment step

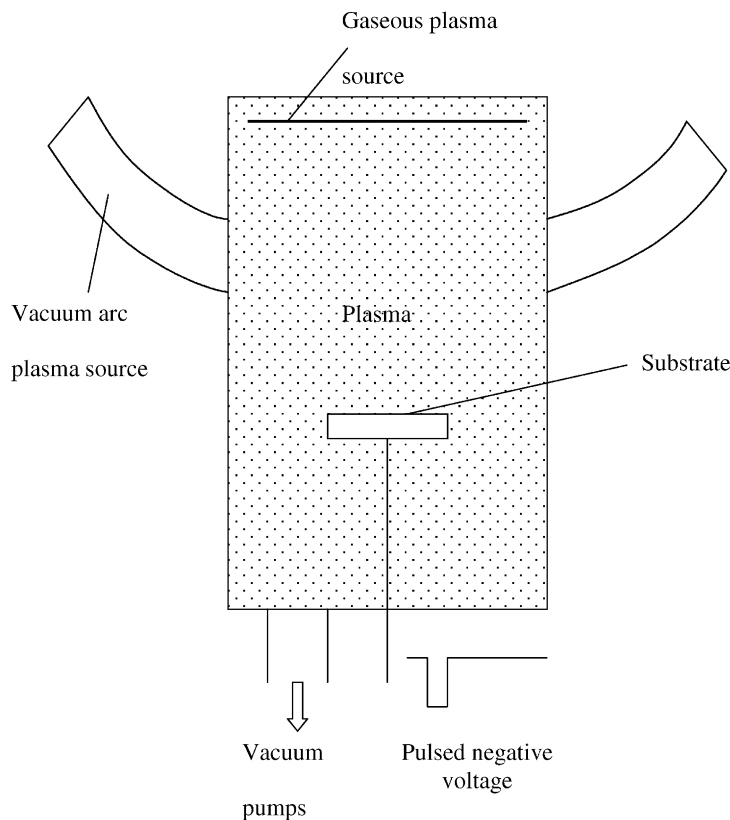


Fig. 10. Schematic of PIII.

for subsequent film deposition. By implanting the proper gaseous and/or metallic elements into the materials, characteristics such as film adhesion can be enhanced and thermal stress between the deposited and bulk materials can be allayed [38–41]. However, although PIII excels in the treatment of components with a complex geometry compared to beam-line ion implantation, the dose uniformity may not be very good unless the process is optimized. During PIII, the dose uniformity can be improved by adjusting the plasma density, pulse width, and applied voltage. For a small sample with a complex shape, a high plasma density, short pulse width, and high frequency are usually preferred in order to keep the shape of the plasma sheath conformal with the target. Theoretical modeling such as particle-in-cell (PIC) and fluid models often plays an important role in the optimization of the process window [42,43].

**2.2.2.2. Plasma implantation of polymers.** When a polymer is exposed to a plasma and if the plasma density and treatment time are proper, many functionalities will be created near the surface and cross-linked polymer chains can be formed. In a typical plasma implantation process, hydrogen is first abstracted from the polymer chains to create radicals at the midpoint of the polymer chains, and the polymer radicals then recombine with simple radicals created by the plasma gas to form oxygen or nitrogen functionalities. Radical species, rather than ion species, that are created in the plasma zone play an important role in the implantation process.

Generally, polymers are hydrophobic, and conversion of these polymers from being hydrophobic to hydrophilic usually improves the adhesion strength, biocompatibility, and other pertinent properties. Formation of oxygen functionalities by ion implantation is one of the most useful and

effective processes of surface modification. In general, oxygen plasma is used, but plasmas of other compounds consisting of carbon dioxide, carbon monoxide, nitrogen dioxide, and nitric oxide can make the polymer surface hydrophilic as well. Besides oxygen functionalities, chlorine functionalities that can contribute to an increase in the hydrophilicity are formed using  $\text{CF}_2\text{C}$  and  $\text{CCl}_4$  plasmas. On the other hand, if one wants to improve the hydrophobic properties of the polymer, higher-degree fluorinated compounds such as  $\text{SF}_6$ ,  $\text{CF}_4$ , and  $\text{C}_2\text{F}_6$  are used as plasma gases [37].

### 2.2.3. Plasma deposition

Plasma deposition is an important area in biomaterials engineering as a layer with properties distinctly different from those of the bulk materials can be synthesized. Dual plasma deposition, plasma-grafting co-polymerization, plasma polymerization, LA, and plasma spraying are common techniques in this respect.

*2.2.3.1. Dual plasma deposition.* Dual plasma deposition is a novel technology derived from PIII. In this process, gas and metal plasmas are simultaneously generated typically using an rfGD source and a vacuum arc plasma source, respectively. Dual plasma deposition has many advantages as a thin film technique. The obvious one is that a film composed of several elements (gaseous and metallic) with various compositions can be fabricated in the same instrument without breaking vacuum. In addition, since a metal vacuum arc plasma source is normally operated in a pulse mode, the ion density is high thereby inducing a high nucleation density on the surface. At the same time, the adatoms have a long time to diffuse and relax between the metal plasma pulses. Last but not the least, since the substrate is immersed in the plasma, large area uniform deposition can be achieved relatively easily. In order to control the ion energy during dual plasma deposition, a dc voltage can be applied when the deposited film and substrate are electrically conducting or semiconducting, otherwise an ac or pulsed voltage should be applied to minimize charge accumulation. The optimal pulse width and frequency can be derived according to the needs as well as ion and electron currents during the dual plasma deposition process [44,45].

Dual plasma deposition has been used to synthesize TiN and  $\text{TiO}_2$  composite thin films. Initially, the vacuum arc plasma source with Ti cathode and nitrogen rfGD plasma work simultaneously to synthesize the TiN film. After an appropriate film thickness has been achieved, the nitrogen flow is turned off and oxygen is introduced into the vacuum chamber to fabricate the  $\text{TiO}_2$  film. The composition of the film can be controlled by adjusting the flow rates of oxygen and nitrogen. Experimental results reveal that these films have good mechanical and biomedical properties. The XRD pattern in Fig. 11 is acquired from TiN and  $\text{TiO}_2$  produced by dual plasma deposition [46].

*2.2.3.2. Plasma polymerization.* In plasma polymerization, the transformation of low-molecular-weight molecules (monomers) into high-molecular-weight molecules (polymers) occurs with the assistance of energetic plasma species such as electrons, ions, and radicals. Plasma polymerization is chemically different from conventional polymerization involving radicals and ions. In many cases, polymers formed by plasma polymerization have different chemical compositions as well as chemical and physical properties from those formed by conventional polymerization, even if the same monomers are used in plasma polymerization and conventional radical or ionic polymerization. This uniqueness results from the reaction mechanism of the polymer-forming process. Polymer formation in plasma polymerization encompasses plasma activation of monomers to radicals, recombination of the formed radicals, and reactivation of the recombined molecules. Plasma polymers do not comprise repeating monomer units, but instead

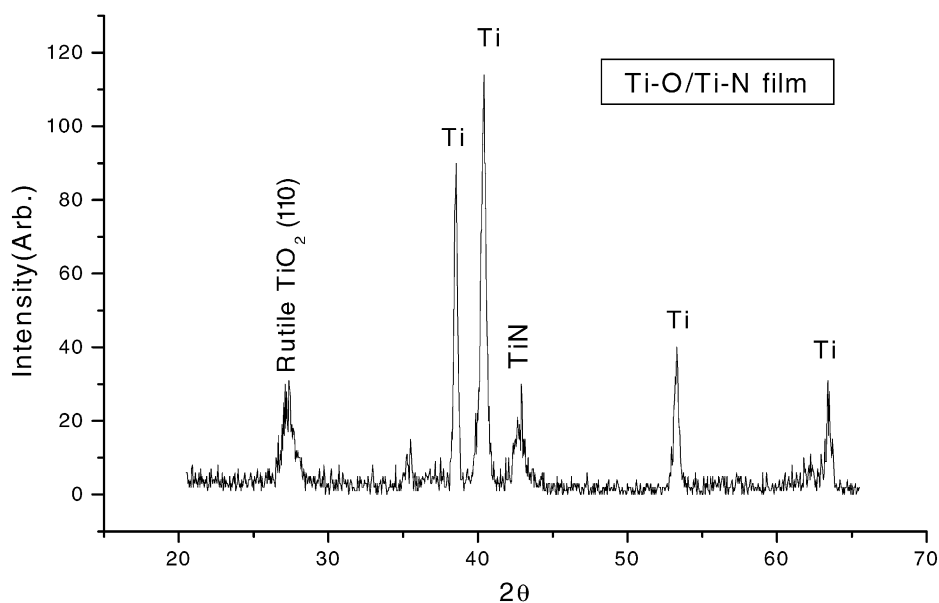


Fig. 11. X-ray diffraction patterns of TiN/TiO<sub>2</sub> film deposited on Ti-6Al-4V alloy by dual plasma deposition.

complicated units containing cross-linked, fragmented, and rearranged units from the monomers. In most cases, plasma polymers have a higher elastic modulus and do not exhibit a distinct glass transition temperature.

Hydrocarbons such as methane, ethane, ethylene, acetylene, and benzene are widely used in the synthesis of plasma polymerized hydrogenated carbon films. The enhanced microhardness, optical refractive index, and impermeability result in good abrasion resistance. Plasmas of fluorine-containing inorganic gases, such as fluorine, hydrogen fluoride, nitrogen trifluoride, bromine trifluoride, sulfur tetrafluoride, and sulfur hexafluoride monomers are used to produce hydrophobic polymers. Plasma polymers fabricated using organo-silicon monomers have excellent thermal and chemical resistance and outstanding electrical, optical, and biomedical properties. The common organo-silicon precursors include silane, disilane (SiSi), disiloxane (SiOSi), disilazane (SiNHSi), and disilthiane (SiSSi) [37,47,48].

**2.2.3.3. Plasma-grafting co-polymerization.** When polymeric materials are exposed to plasma, radicals are created in the polymer chains. These radicals can and do initiate polymerization reactions when put in contact with monomers in the liquid or gas phase. As a result, grafted co-polymers are formed on the surface. In plasma-grafting co-polymerization, polymers are first exposed to the plasma to create radicals on the surface where inelastic collisions between the electrons in the plasma and polymer surface produce radicals in the polymer chains. Afterwards, the polymers are exposed to a vapor of the monomer or an aqueous or organic solution of the monomer. Since the plasma produces radicals only close to the surface of the polymers, plasma-grafting co-polymerization is restricted to the near surface.

Plasma-grafting co-polymerization is often employed to alter the surface hydrophilicity of polymers. It is usually conducted by first exposing a polymer to a plasma such as argon, helium, or nitrogen for a short time (a few seconds). The process introduces many radicals to the surface of the polymer and experimental results reveal that these radicals can survive for several days. Afterwards, the polymer is brought into contact with the vapor of a monomer at an elevated temperature for a

period of time. Oxygen in the monomer vapor or dissolved in the monomer solution inhibit the reactions and should be avoided [49–51].

*2.2.3.4. Laser ablation (LA).* During laser ablation (LA), the plasma plume generated near the surface of the target by the laser beam is transported to the substrate to produce the film. The film quality critically depends on the density and kinetic energy of the plasma plume. A plume that is too energetic will give rise to film damage. Films prepared at a laser fluence of 1.5 J/(cm<sup>2</sup> shot) show a cosine spatial distribution in the film thickness and composition. The particles ejected from the target consist of narrow (forward directed and sharper than  $\cos \theta$ ) and broad  $\cos \theta$  components. The broad component corresponds to thermal evaporation. The film composition originating from the narrow component is close to stoichiometric whereas that from the broad component deviates from it. The distinct feature of LA is that there is no large compositional deviation from the target caused by the narrow component being directed to the substrate normal. This component increases with the laser fluence.

In LA, it is important to control the plume in order to obtain high quality films. The optimal laser fluence depends on the substrate–target spacing and ambient gas pressure. The substrate–target spacing is typically around 2–5 cm. In most cases, the crucial point is how the plume interacts with the substrate. Target preparation is also important and the target morphology affects the surface morphology of the films. A fresh target surface is preferred because after prolonged irradiation, the composition of the ablated surface often deviates from the original stoichiometric composition, especially in ablation with a low fluence. A high-density target is also required for high film quality and reducing the amount of droplets. For example, the use of a melt-quenched amorphous target is useful for eliminating particle formation.

Compared to conventional film deposition techniques, LA has some unique characteristics. Firstly, it allows the deposition of materials with a high melting point as long as the materials absorb the laser light. In addition, it does not produce as much film contamination compared to an evaporation process using a heater or filament. The process is also capable of producing films in an oxidizing environment at a relatively high-pressure because of the absence of a heater or filament in the deposition chamber. During deposition, provided that the proper parameters are used, the target composition is stoichiometrically transferred to the film. However, a large number of droplets of submicrometer size are often observed on the surface of the deposited film [52].

#### *2.2.4. Plasma spraying*

In atmospheric pressure plasma spraying, the powders of the sprayed materials is introduced into the plasma area of the plasma torch. Because of the high-temperature and flux velocity of the plasma, the melted or partially melted powders are accelerated towards the substrate at a high speed forming a coating with a lamellae structure. Owing to the high-temperature of the plasma core, plasma spraying offers the ability to deposit almost any metals and various combinations of materials. The high-temperature enables the use of coating materials with a high melting point such as ceramics, cermets, and refractory materials. Materials can be processed as long as there is a temperature difference of at least 300 K between the melting temperature and decomposition or evaporation temperature [53].

Plasma spraying has undergone a rapid expansion in the past 30 years due to a couple of important advantages. Firstly, it can conveniently treat specimens with a complex geometry. Secondly, the wide spectrum of materials that can be handled by this technique has spurred applications in the area of corrosion resistant, high-temperature, and ablation resistant coatings as well as biocompatible films. One of the disadvantages of plasma spaying is the poor adhesion between the substrate and coating, but several measures can be used to improve it. For instance, the thermal gradient at the substrate/coating interface caused by the rapid quenching of the molten



particle splats that leads to deposition of an amorphous coating can be reduced. In addition, one can prevent a steep gradient in the coefficients of thermal expansion between the substrate and coating to avoid the formation of strong tensile forces that give rise to crack generation, chipping, and/or delamination [54]. Plasma spraying is widely used in bioactive ceramics such as hydroxyapatite ( $C_{10}P_3H$ , HA) as interfacing osseoconductive layers in metallic surgical implants [55].

### 3. Biomaterials and surface modification

#### 3.1. Biomaterials

Biomaterials have been studied for many years, but its exact definition is still controversial. One current definition is that a biomaterial is any material, natural or man-made, that comprises a whole or part of a living structure or a biomedical device that performs, augments, or replaces a natural function [56]. Ratner et al. define that a biomaterial is a nonviable material used in a medical device and intended to interact with a biological system [57]. Another definition is “either naturally occurring materials in living organisms or materials designed to repair humans” [58]. There are naturally many other definitions and descriptions proposed by people in the field.

Many types of biomaterials are being used, including metals, alloys, polymers, ceramics, composites, and glasses. A single biomaterial or its synthetic product is used in substituted heart-valves, artificial hip joints, dental implants, and IOLs. The design of each type of biomaterials or device has its own challenge based on the intended function and biological site. Biomaterials research is, thus, interdisciplinary in nature, and in order to succeed, there must be close collaboration among people in materials science, physics, biochemistry, medicine, and other fields. In spite of encouraging developments, routine long-term in vivo applications still have a mountain to climb, and there is an urgent need to design and develop new suitable biomaterials. Much effort is going into the design, synthesis, and fabrication of the biomaterials and devices to ensure that they have the appropriate mechanical properties, durability, and functionality [59–61]. For instance, a hip joint ought to be able to withstand high stress, an artificial heart-valve should have good anti-thrombotic properties, a hemodialyzer should have the requisite permeability characteristics, and a pump bladder in an artificial heart should flex for millions of cycles without failure [61]. The bulk structures of the materials partly govern these properties. The biological responses to biomaterials and devices, on the other hand, are largely controlled by their surface chemistry and structure. That is to say, the surface characteristics play a vital role in the functioning of a biomaterial. The rationale for the surface modification of biomaterials is straightforward. The key physical properties of a biomaterial can be retained while only the outermost surface is modified to tailor to the bio-interactions. Hence, if surface modification is properly carried out, the mechanical properties and functionality of the device will be unaffected, but the tissue interface-related biocompatibility can be improved [59]. For instance, in the design of medical devices, it is necessary to consider potential corrosion and degradation due to the exposure to a variety of body liquids. There are two methods of prevention by either selecting a resistant material or protecting the material, and the latter is often chosen [62]. Out of the various techniques, PSM has been proven to be very effective.

#### 3.2. Physicochemical plasma treatment

The ideal biomaterials should have good mechanical properties while the surface should have good biocompatibility. Up to now, very few materials can fulfill both needs and either biological or

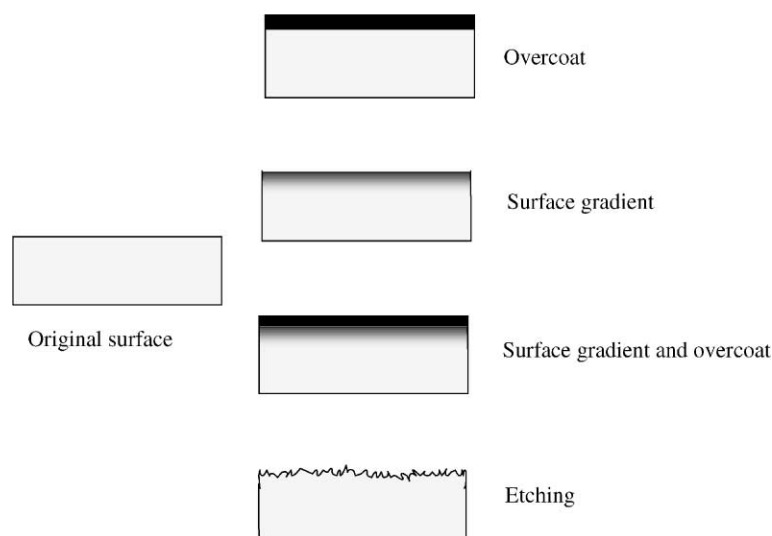


Fig. 12. Schematic representations of different plasma methods to modify surfaces of biomaterials.

physicochemical methods are often employed to modify the materials surface. The former will not be covered in this article, but PSM technology, an example of physicochemical surface treatment, is illustrated schematically in Fig. 12. Surface modification falls into two categories: (1) chemically or physically altering the atoms, compounds, or molecules on the surface (etching, and chemical alteration), or (2) coating the surface with a material having a different composition (coating, grafting, and thin film deposition). There are different views on how surface treatment should be performed. For example, Favia and d'Agostino suggest that PSM technologies should be grouped into three categories [14]: (1) plasma enhanced chemical vapor deposition (PECVD), (2) plasma treatment and (3) plasma etching. Szabo et al. [63], on the other hand, proposes that surface modification methods should be split into three general techniques: adding materials, removing materials, and changing materials.

As aforementioned, a plasma is a complex mixture composed of energetic free radicals, ions, electrons, atoms, and molecules sustained by an external energy source. By using different plasma modification methods and changing the operating conditions, such as type of discharge, reactor geometry, flow rates, pressure, and gas species, a variety of surface chemistries, otherwise unobtainable, can be achieved.

### 3.3. Necessity for surface modification

The interactions between the biological environment (such as hard and soft tissue, blood, body liquid, or saliva) and biomaterials take place on the materials surface, and the biological response from living tissues to these extrinsic biomaterials depends on the surface properties such as chemical composition, cleanliness, texture, surface energy, corrosion resistance and the tendency to denaturalize neighboring proteins. In particular, the biocompatibility of a material is determined by the interactions between the implant and biological system on the micrometer and nanometer scale [10], and the physicochemical surface properties of the materials, for example, chemical composition, wettability, surface energy, semiconductor properties and surface charge, play an important role [64–70]. The biological response of tissues to biomaterials is, to a large extent, cell-specific and also depends on the subsequent procedures after the initial surface preparation

processes. For instance, attachment of additional bioactive molecules due to the unavoidable contact with biological liquids may influence cell adhesion.

Surface modification of biomaterials has recently become an interesting topic in medicine [6,10,71,72] and is now used to improve the function and lifetime of the biomaterials used in medical components. Biomedical surface engineering is generally considered when (1) good is not good enough, (2) devices would not function without it, or (3) product differentiation is desired. The drive for surface modification by the biomedical community is briefly discussed here.

1. The surface of a biomaterial is in direct contact with living tissues in the body and the initial response of the living tissue to the biomaterial depends on its surface properties. A good biomaterial must not exhibit a strong foreign body reaction/inflammation response. However, it is rare that a biomaterial with good bulk properties also possesses the surface characteristics suitable for clinical applications, and very few surfaces are truly biocompatible. Lower tissue and blood compatibility can cause not only cellular damage and blood coagulation, but also implant failure. In these cases, a hard, wear resistant, and corrosion resistant modified layer, which is also biocompatible, would mitigate the above problems.
2. The properties of a material rarely match perfectly every requirement for a given application, and biomaterials are no exception. For instance, although an orthopedic material may have ideal mechanical properties, it may cause deleterious biological response, or a biosensor with good electrical characteristics may corrode readily in the presence of body fluids. Therefore, it often becomes necessary to strike a balance so that a material has acceptable properties in each pertinent area. For example, in a product such as a hemodialysis catheter which demands both good flexibility and low surface friction, the best candidate may be a more slippery, less flexible material rather than a mechanical strong material with unacceptably high friction. Thus, the ability to modify the surface properties while preserving the bulk attributes is important.
3. Although bulk properties dictate the mechanical properties of biomaterials, tissue–biomaterials interactions are surface phenomena and are governed by surface properties. These interactions have been hypothesized to occur within a narrow zone of less than 1 nm [70,73]. The initial interaction between the host and implant involves the conditioning of implants by serum and other tissue fluids, thereby resulting in compositional changes at the biomaterial surface. Thus, the tissue/cellular behavior at the biomaterials–tissue interface must be improved.
4. Longevity is a must for medical implants [74]. In bone replacements, especially long bone and joint replacements, metal implants are widely used. Although the metallic orthopedic implants have excellent bulk properties such as strength and elasticity, it has relatively poor surface properties, for instance, wear resistance and limited biocompatibility. It is, therefore, necessary to make a compromise between the bulk and surface properties. Fig. 13 is taken from a company advertisement illustrating the visual differences between the surface treated and untreated artificial heart-valves.
5. Surface modification of biomaterials has intensified during the last decade as a result of an aging population. The needs for alternative medical solutions have not only demanded better biomedical devices but also more diverse functionality and bioactivity.

Many major medical device companies have recognized the importance of surface engineered biomaterials and the lucrative market, but surface engineering is still far from reaching the full potential. The biomedical market shown in Fig. 14 [6] exceeds US\$ 50 billion [75]. Compared to the painstaking and time consuming processes of inventing new materials, surface engineering of biomaterials can yield a more profitable return in a much shorter time.

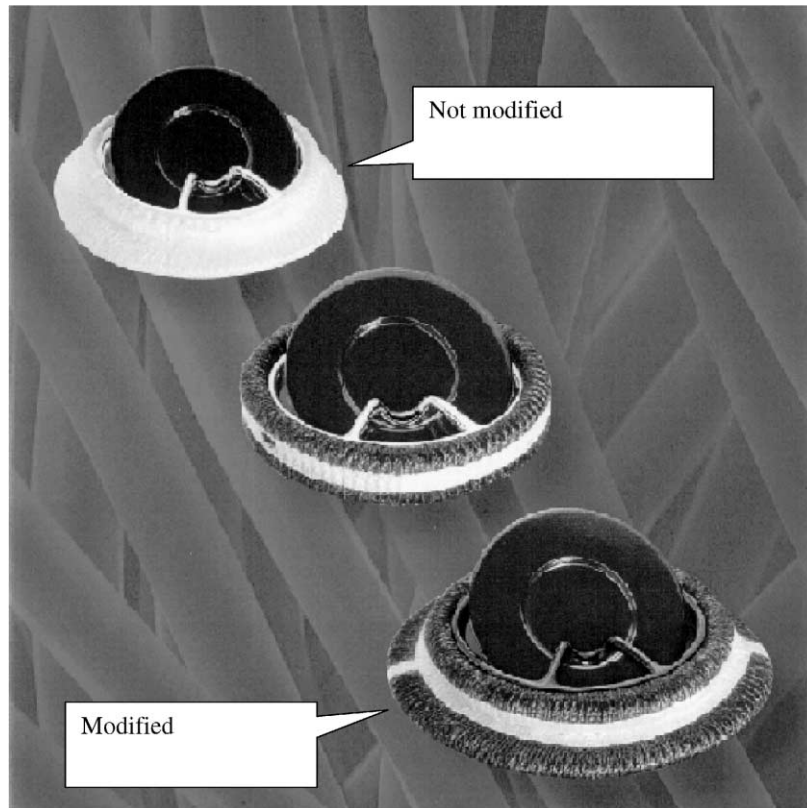


Fig. 13. Application of surface modification to artificial heart-valves showing visual differences between the treated and untreated components.

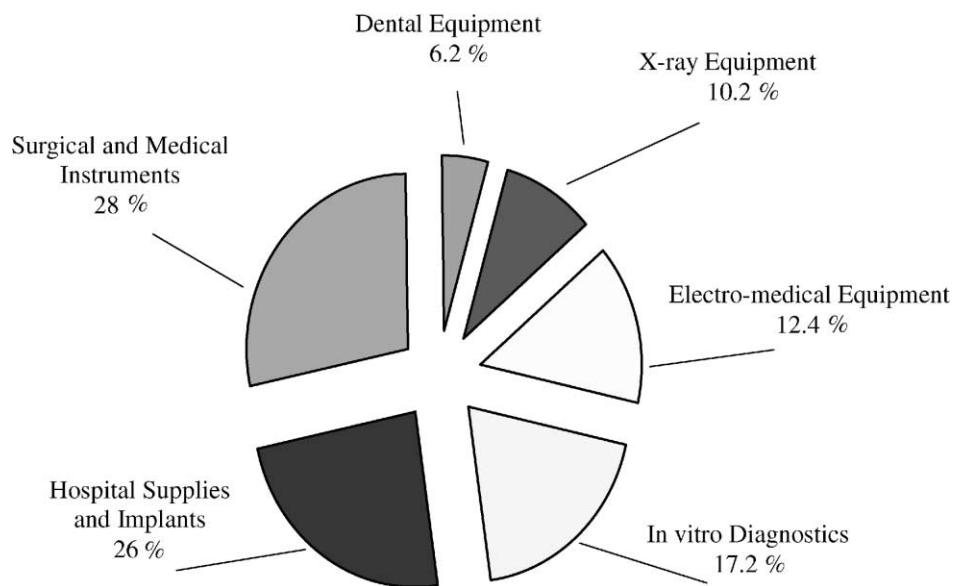


Fig. 14. Breakdown of the medical device industry markets (source: Health Industry Manufacturers Association) [6].

Table 4  
Examples of plasma-surface-modified biomaterials

Modification objections	Plasma application examples
To modify blood compatibility	Plasma fluoropolymer deposition Plasma siloxane polymer deposition PIII–D The rfGD plasma treatment
To influence cell adhesion and growth	Ammonia plasma-treated surface Plasma-deposited acetone or methanol film Plasma fluoropolymer deposition (reduce endothelial adhesion to IOLs)
To control protein adsorption	PIII–D of TiO <sub>2</sub> film Plasma treatment to create covalent bonds in fibronectin
To improve wear resistance, lubricity, and corrosion resistance	Plasma treatment PIII PIII–D of DLC film
To alter transport properties or modify electrical characteristics	Plasma depositions (methane, fluoropolymer, siloxane) Plasma depositions (insulation layer) Solvent coating (insulator or conductor) Parylene (insulation layer)

Many scientists are developing new biomedical materials by trial-and-error and the PSM approach employing plasma polymerization and plasma-grafting can expedite the process. For example, recent developments in biocompatible surface coating technologies for adherent cells concentrate on fixing the extracellular matrix proteins like fibronectin and laminin or amino acid sequences of these proteins on the surface [10]. Usually, these bioactive molecules are covalently bonded and, in many cases, plasma treatment can create these covalent bonds [76–80]. In addition, it can produce highly inert surfaces consisting of fluorinated hydrocarbons, covalent bonds of bioactive molecules that inhibit cell attachment, and covalent bonds of very hydrophilic groups to improve the biocompatibility [81–85]. Some representative examples of plasma-surface-modified biomaterials are listed in Table 4 and the plasma modification methods as well as the types of materials to which they are applied are illustrated in Table 5. It should be mentioned that plasma spraying is frequently used in medical applications, and an example is plasma sprayed HA coatings on metallic joint prostheses [86].

Table 5  
PSM methods and materials [59,62,74]

PSM methods	Polymer	Metal	Ceramic	Glass
PIII	✓	✓	✓	✓
PIII–D	✓	✓	✓	✓
Plasma sputtering		✓	✓	
Plasma etching and cleaning (e.g. argon, nitrogen, oxygen, water vapor, etc.)	✓	✓	✓	✓
Plasma sterilization	✓	✓	✓	✓
Plasma polymerization	✓			
Plasma covalently attached coatings	✓			
Plasma-grafting co-polymerization	✓			

#### 4. Effects of plasma-surface modification

A thin modified surface layer is desirable in most applications because a layer that is too thick can change the mechanical and functional properties of the materials and risks delamination. Ideally, alteration of just the outermost molecular layer (0.33–1 nm) should be sufficient, but in practice, a thicker film is necessary to ensure uniform and pinhole free coverage as well as to protect against surface reversal and mechanical erosion. Some coatings intrinsically have a specific thickness [59]. In general, the surface modification process should yield films with the minimal thickness while accomplishing the required uniformity, durability, and functionality.

##### 4.1. Surface morphology

The surface topology of the cell scaffold materials affects the cell behavior and functions [10,87]. Plasma etching, in which materials are ablated via reactions with active species generated in the plasma to form volatile products, can create the desirable micro-features and macro-features on the biomaterials to meet the requirement of biocompatibility *in vivo*. For instance, plasma-induced or plasma-assisted chemical micro-patterning of cell culturing is based on the trend to miniaturize the detailed structures of tissue culture scaffolds. By using an electroformed screen mesh mask, various patterns can be transferred from the mask to the surface by taking away the atoms from the unmasked regions. At present, plasma techniques are used preferentially to produce different topologies on surfaces to investigate their cell biological effects [88,89]. Exceptions are microscopic guidance channels for patterned neurite outgrowth [90] and microscopic patterns used to localize cells by electric-field forces [91,92]. These techniques are beyond the scope of this paper since it focuses on techniques with a high potential to induce micro-patterned cell arrangements in *in vivo* like structures. However, it should be noted that possible correlations between the different contrasting techniques have recently been considered [93,94]. Fig. 15 demonstrates the possible procedures of plasma-induced chemical micro-patterning [10]. All steps naturally have to be compatible with the bio-system and processability.

Fig. 16 depicts two examples of silicone rubber modification using electroformed screen mesh masks of square and round meshes. The  $\text{Ar}^+$  energy is 1 keV [74]. Figs. 17 and 18 show that the plasma-induced chemical micro-patterning technique is suitable for generating different patterns and different cell types.

These surface microfabricated biomaterials have the ability to regulate cell functions such as proliferation, differentiation, and apoptosis [95]. Ito's results further indicate that micropatterned-immobilized heparin, in a specific pattern by photolithography, activates the fibroblast growth factor for cell growth activity [96]. Den Braber et al. have used plasma etching to produce gratings 1.0  $\mu\text{m}$  (TiD01), 2.0  $\mu\text{m}$  (TiD02), 5.0  $\mu\text{m}$  (TiD05), and 10.0  $\mu\text{m}$  (TiD10) wide on commercial pure titanium wafers [97]. When rat dermal fibroblasts (RDFs) are cultured on these wafers, individual RDFs, their stress fibers, orientation, and focal adhesion points (FAPs) exhibit different results. Only the RDFs on the TiD05 and TiD10 surfaces protrude to the grooves and possess FAP on the walls of the grooves. Attachment to the groove floor is observed only on the TiD10 gratings. Similar size effects on RDF cellular behavior have been observed on the microtextured silicone rubber substrate [98]. The proliferation rate of the RDFs, however, is much higher on titanium than on silicone rubber. Lee et al. have used an ion implantation technique for selective cell adhesion [99]. They use an ion beam/plasma instead of ultraviolet light to conduct the lithography. Dewez et al. have reported the adhesion of some mammalian cells, such as human epithelial cells, PC12 pheochromocytoma, MSC80 schwannoma, Hep G2 hepatoblastoma, and rat hepatocytes, on patterned (produced by

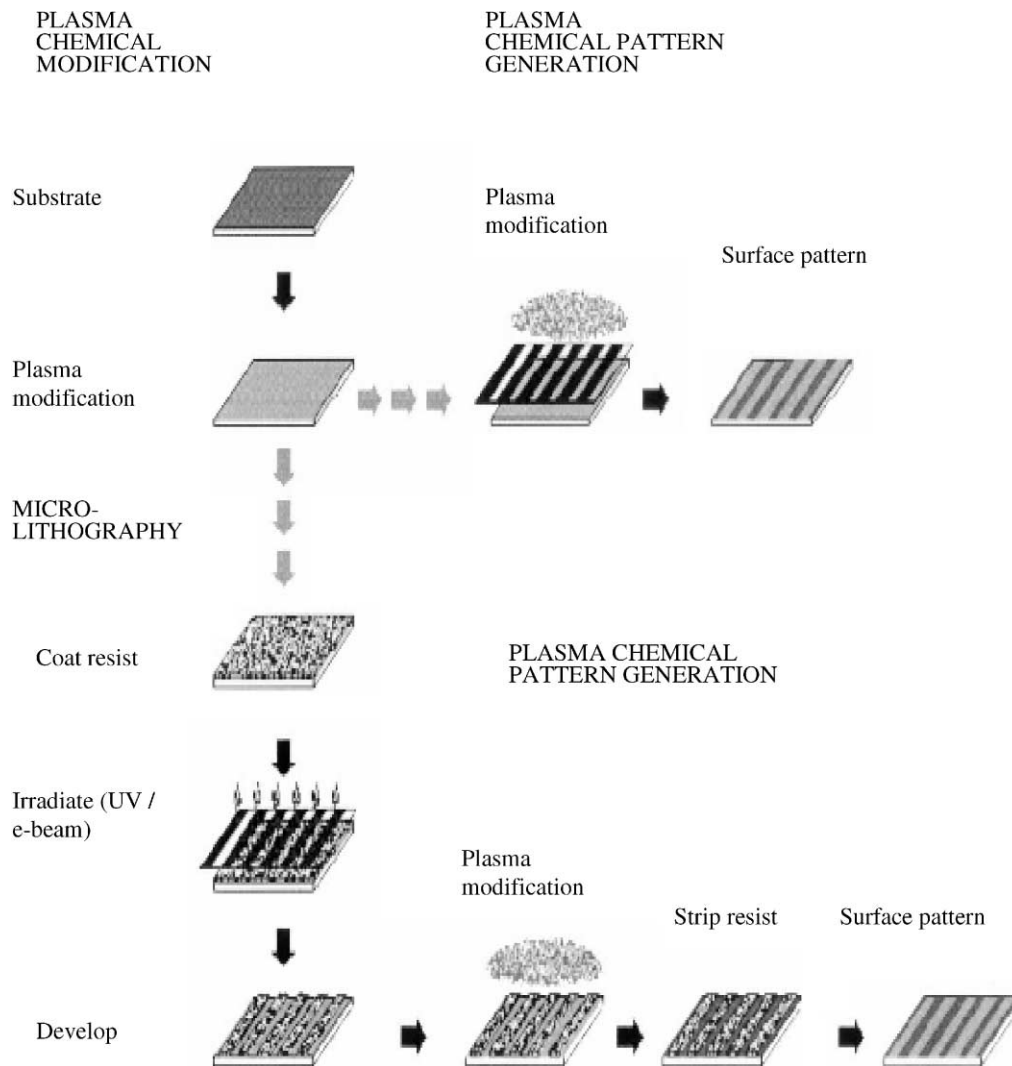


Fig. 15. Possible processing procedures of plasma-induced chemical micro-patterning [10].

photolithography and oxygen plasma treatment) polystyrene surfaces having tracks (width in the range of a few tens of  $\mu\text{m}$ ) with reduced hydrophobicity [100]. Kapur et al. also indicate that some selectively patterned three-dimensional polymer substrates may be useful in a variety of biomaterial applications [101]. Ha et al. have modified the surface of polyetheretherketone (PEEK) by chemical etching or oxygen plasma treatment, and examined the resulting characteristics and properties of the surface [102]. Their results show that chemical etching or oxygen plasma treatment causes the surface topography to become irregular with higher roughness due to the spherulitic structure of PEEK and that the wetting angle and surface energy (mainly surface polarity) are increased due to surface oxygen. It is concluded that surface activation by oxygen plasma preceding the coating processes in supersaturated physiological solution to manufacture PEEK for biomedical applications is preferred over chemical etching. In other words, the biocompatibility of the PEEK surface modified by oxygen plasma is improved by increasing the surface activity. Hence, it has been suggested that inflammatory cell responses may be spatially controlled in a manner that may be

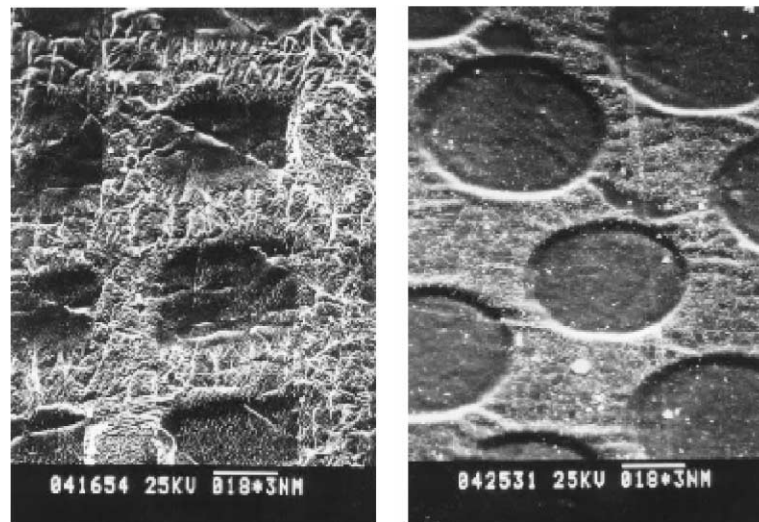


Fig. 16. SEM micrograph of silicone rubber modified using electroformed screen mesh mask of square (left) and round meshes (right).

ultimately exploited to improve the biocompatibility of medical devices [103]. The plasma-based surface patterning techniques enable visualization of the effects on cell functions and spatially controls the cellular micro-organization. All in all, it is believed that the surface morphology plays an important role in the biocompatibility of biomaterials in vivo, although the relation between the

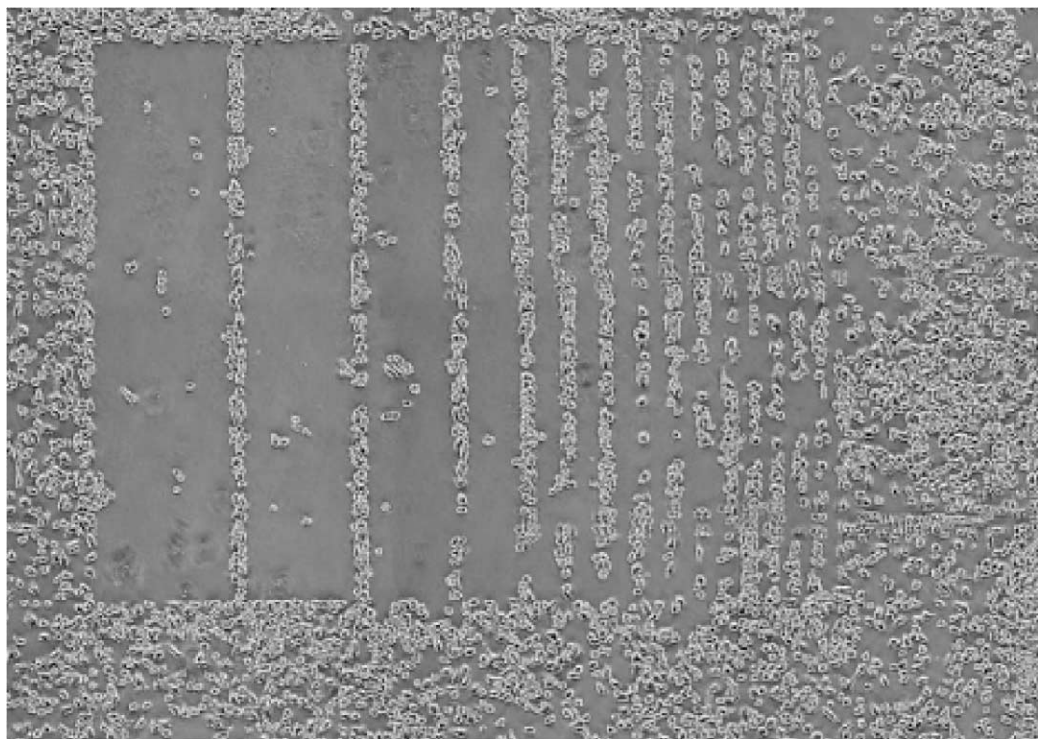


Fig. 17. Micro-patterned growth of epithelial cells (KB nasopharyngeal carcinoma cell line) on a logarithmic stripe pattern. The width of the bars is  $50\ \mu\text{m}$  and their length varies between  $30$  and  $50\ \mu\text{m}$  [10].



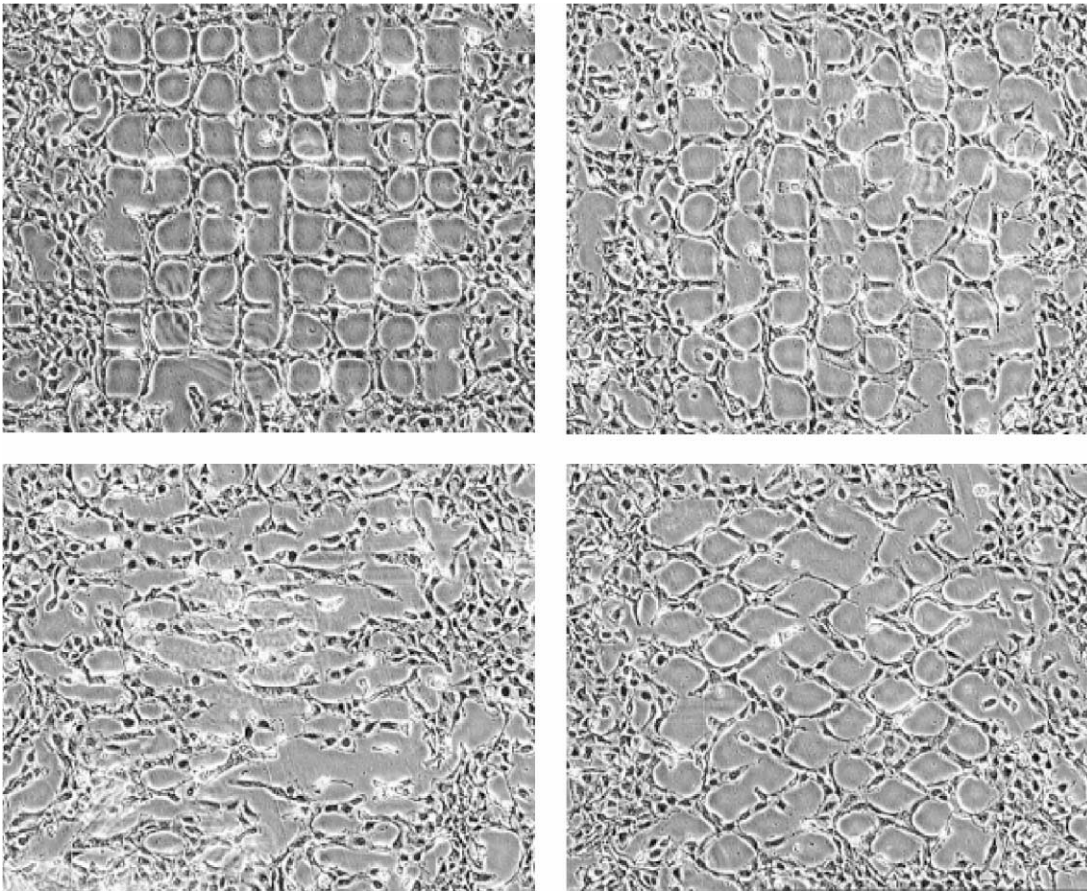


Fig. 18. Micro-patterned growth of fibroblasts (3T3 mouse fibroblast cell line) on different grid patterns. The characteristic dimension of the single pattern elements (free space) is 100  $\mu\text{m}$  and the width of the stripes is 30  $\mu\text{m}$  in each case [10].

morphology of biomaterials and their biomedical behavior in vivo is still unclear up to now, and much research work is being conducted.

#### 4.2. Surface properties

The general requirements of biomaterials are non-toxicity, stability, tissue compatibility, and reproducibility [104], and Fig. 19 is a good illustration. It suffices to say that no one single material can meet all the requirements, and surface modification is frequently utilized to improve the properties. Fig. 20 illustrates some of the biomaterial surface properties that can be altered by PSM.

Friction and wear will always be generated when two surfaces are sliding against each other, and fatigue fracture and wear have been identified as two of the major problems associated with medical implant failure [108]. Fatigue fracture and wear are frequently reported in orthopedic applications such as hip joint prostheses and can be fatal in mechanical heart-valves. Fig. 21 illustrates the fatigue fracture occurring in a hip prosthesis and mechanical heart-valve [108]. The acetabular cup made of ultra-high molecular weight polyethylene (UHMWPE) is so worn that it has fractured in a brittle manner, and fatigue fracture manifests in the low end of the cast cobalt chrome femoral stem. The polyacetal occluder of the tilting disk heart-valve shows a deep wear groove as a result of the repetitive impact-cum-sliding motion it makes with the upper metallic strut.

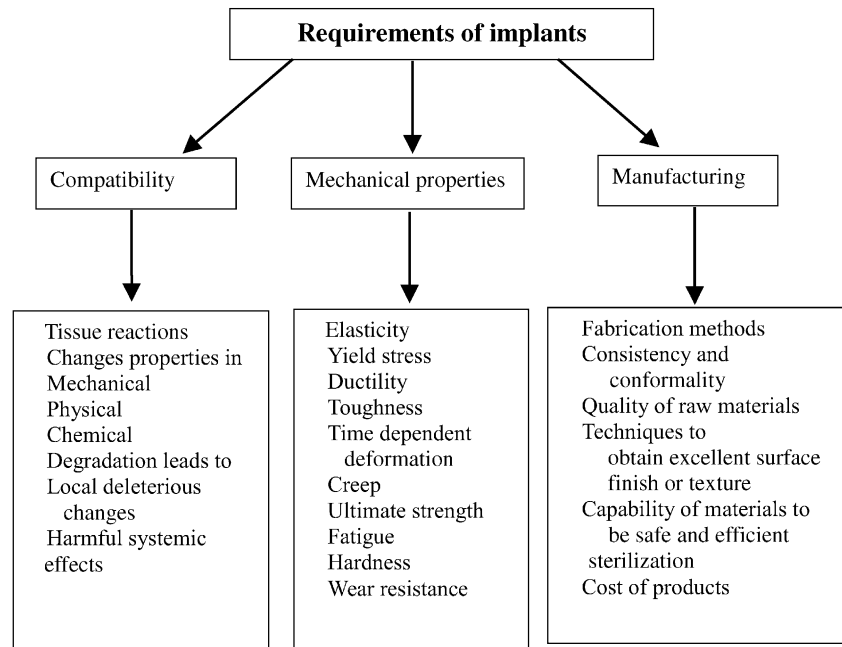


Fig. 19. Actual requirements of orthopedic applications (modified from [105,106]).

Teoh summarizes the problems related to fatigue fracture and wear of biomaterials [108]. Improvement in the wear performance has been made employing various approaches ranging from ion implantation to cushion bearing and elastohydrodynamic lubrication. The poor tribological properties of titanium alloys compared to cobalt chromium alloys used in UHMWPE acetabular cups has prompted the use of a plasma vapor deposition coating of TiN and TiC, thermal treatments (nitriding, surface hardening), and ion implantation ( $N^+$ ) [108].

#### 4.2.1. Ion implantation

In ion implantation, ions are accelerated to typically between 20 and 200 kV and directed towards a biomaterial surface. The ions penetrate the surface and create significant changes. However, because the ions do not penetrate too deeply (usually less than a micrometer), the modification zone is confined to the near-surface region, and only the surface properties are modified. The effects of ion implantation are different for metals, ceramics, and polymers [109,110]. In metal and ceramic biomaterials, the physical changes arise from atomic and nuclear collisions often leading to formation of highly disordered and sometimes amorphous structures. Chemical changes arise from the formation of hard-phase precipitates (from the use of active ion species) or surface alloys (from introduction of alloying elements). The physical and chemical changes typically combine to create surfaces that are harder and more resistant to wear and chemical attack without substantially altering the bulk properties.

Surface plasma treatment of polymers has been shown to be a viable method to enhance the adhesion properties without affecting the bulk characteristics and to modify fluoropolymer surfaces. There are four major effects [111]: (1) cleaning of organic contamination, (2) micro-etching, (3) cross-linking, and (4) surface activation. Clark and Hutton [112] have shown that a hydrogen plasma can rapidly defluorinate fluoropolymers to a depth of 2 nm. Oxygen from residual water in the reactor is incorporated after a short exposure time. Vargo et al. have used rfGDs of  $H_2/H_2O$  and

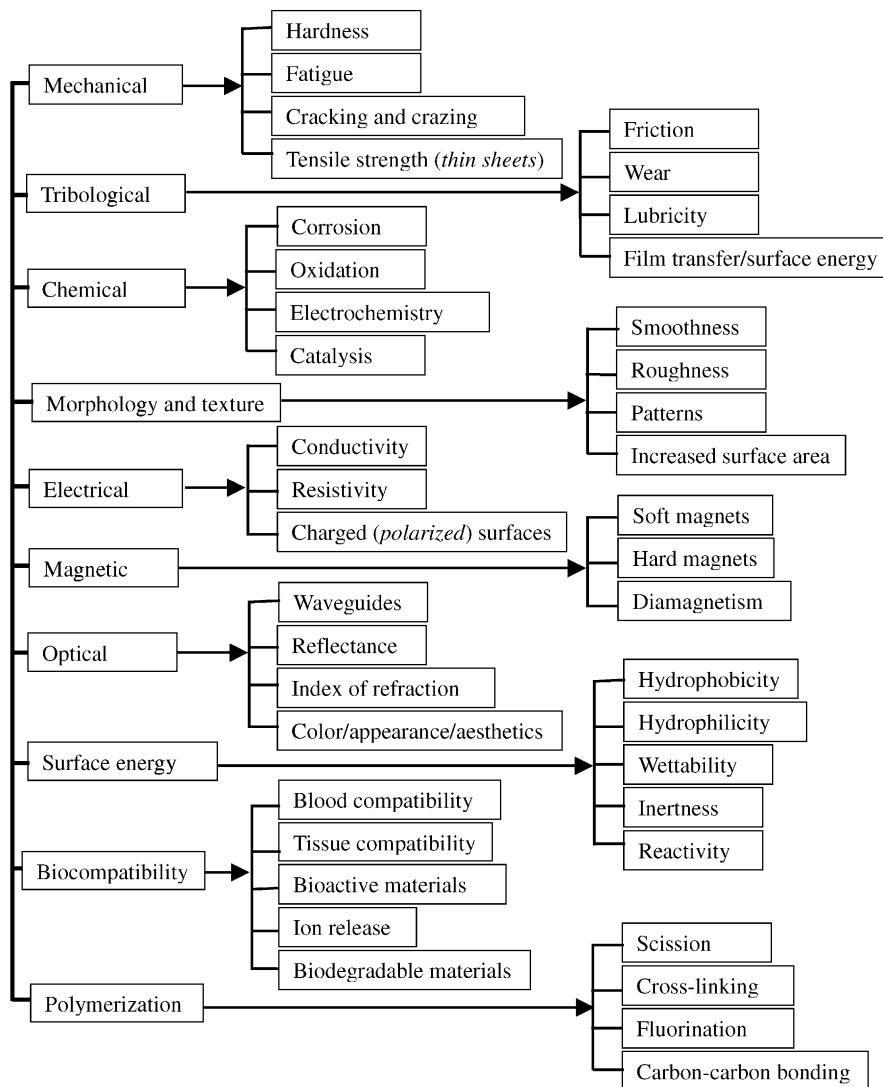


Fig. 20. Biomaterial surface properties altered by PSM [1,107].

$H_2/CH_3OH$  to modify expanded-poly(tetrafluoroethylene) (e-PTFE) achieving a hydroxylated surface with minimal morphological damage to the membrane surface [113]. Many other effects have been observed and in many ways, they are similar to those produced by common ionizing radiation. However, the larger ion size and much shallower depth of penetration result in significantly more pronounced effects confined to a very thin layer beneath the surface. Despite many complicated effects, the implantation process may generally be envisaged as two major competing processes: chain scission and cross-linking. Ions penetrating a polymer surface interact with the substrate atoms via electronic (ionization) and nuclear (recoil) interactions. Ionization is the dominant phenomenon and generally leads to cross-linking in adjacent polymer chains, whereas recoils generally lead to chain scission [114]. The former usually improves the properties while the latter may cause polymer degradation. By selecting the appropriate implantation parameters, one can create a three-dimensional cross-linked surface layer with hardness exceeding that of steel in addition to improved wear resistance [115]. Implantation sometimes also results in selective enhancement or reduction of

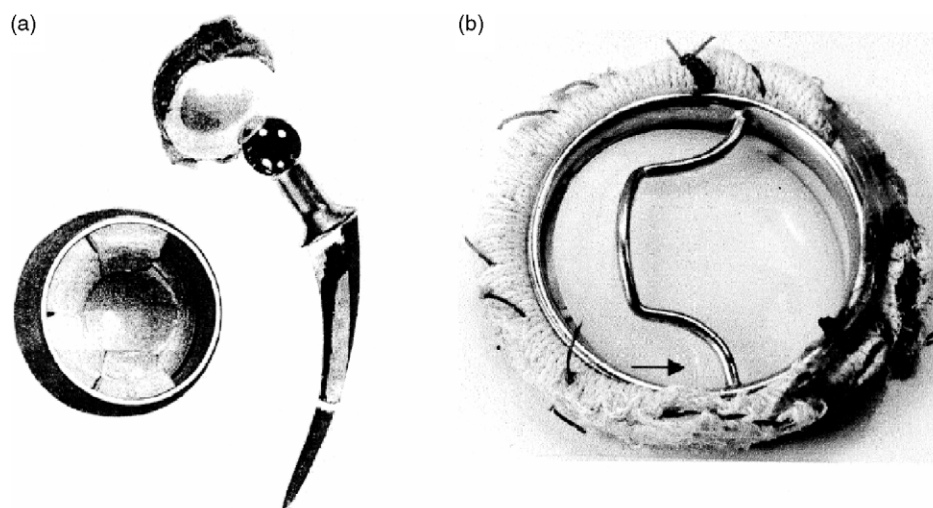


Fig. 21. (a) Examples of fatigue failure of medical devices: hip joint prosthesis, (b) explanted Bjork–Shiley polyacetal disc mechanical heart-valve (arrow indicates fatigue-wear mark).

functional chemical groups that can, by modifying the chemical interactions on the polymer surface, change the surface wettability and critical surface tension.

#### 4.2.2. Plasma deposition

Common plasma deposition techniques include PIII–deposition (PIII–D), PECVD, and rfGD plasma deposition. These techniques are finding more applications in biomaterials engineering, and one example, diamond-like carbon (DLC) and carbon nitride (CN), is discussed in details here.

DLC and CN are often used in biomedical implants. These materials possess excellent mechanical properties, and consisting of only carbon, hydrogen and nitrogen renders them biologically compatible. Some representative usages of hard DLC and CN coatings are: (a) hard carbon films for surgical instruments, (b) implanted fittings such as infusion devices and connecting parts, and (c) semi-permanent components such as heart-valves, replacement joints, and ophthalmics. DLC films can be deposited by a variety of plasma methods, including hot filament [116], microwave [117], rf or dc PECVD [118–120], laser plasma deposition [121], and graphite/metal source PIII–D [67,122]. Amorphous CN coatings have also been prepared in an attempt to synthesize  $-C_3N_4$  using several plasma-based approaches including plasma decomposition of methane and nitrogen [123] and rf sputtering of a graphite target in an argon/nitrogen plasma [124]. Figs. 22–29 show some tissue compatibility and blood compatibility results, respectively. Fig. 22 reveals no statistically significant difference between fibroblasts grown on the control polystyrene plate and those grown on DLC. Figs. 23 and 24 indicate no statistically significant difference between osteoblasts grown on the control polystyrene plate and DLC. The osteoblasts are attached, spread and proliferated on the CN films displaying morphologies varying from a spindle-shape to polygonal. These studies support the bone tissue compatibility of the DLC coating, and are also encouraging for the potential biomedical applications of amorphous CN coatings. It is also clear from Fig. 25 that there is no marked difference in the ML-1 and HEK 293 cells viability between the control and experimental cells. Both the HEK 293 cells grown on the control and DLC-coated dishes have viabilities of 60% in the first day and the viability rises to more than 90% for both the control and experimental dishes [129]. There is no indication that the DLC coating is dissolved or toxic to the ML-1 cells because there is no differentiation among the ML-1 cells. Similarly, no delayed

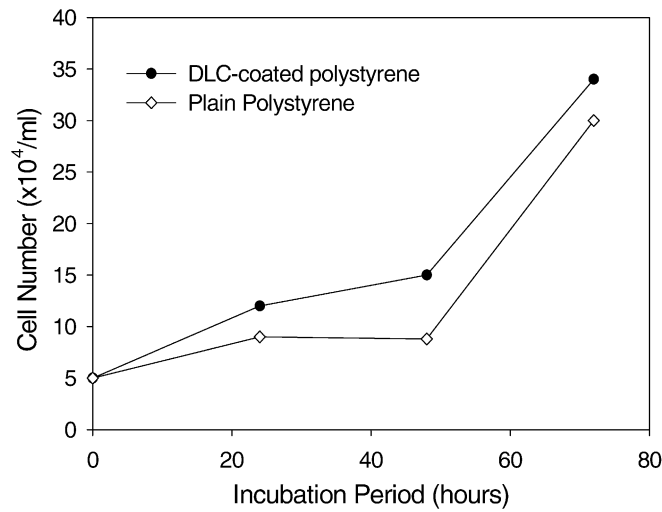


Fig. 22. Growth curves for human synovial fibroblasts on plain and DLC-coated polystyrene tissue culture plates [128].

attachment is observed when the HEK 293 cells are freshly seeded onto the DLC-coated dishes compared to cells cultured in plastic. These results demonstrate that the DLC coatings express no toxicity to the cultured human ML-1 and HEK 293 cells. Fig. 26 discloses that the DLC coatings exhibit a lower neutral granulocyte adhesion compared to the control sample. This result confirms the tissue compatibility of DLC coatings *in vitro*. The blood compatibility of DLC and CN coatings has also been performed. Dion et al. have determined the plasma protein adhesion on silicone elastomer and DLC coated Ti-6Al-4V, and found that more albumin adheres to the DLC coating than the medical grade elastomer and there is more fibrinogen than on the silicone elastomer, as shown in Table 6 [125]. Other promising results are that the albumin/fibrinogen ratio on DLC is higher than that on the silicone elastomer, implying that DLC has good blood compatibility. Fig. 27 shows single protein albumin and fibrinogen adhesion experimental results acquired from the DLC, CN and PMMA surfaces [126], and it is quite evident that the DLC coating exhibits higher albumin

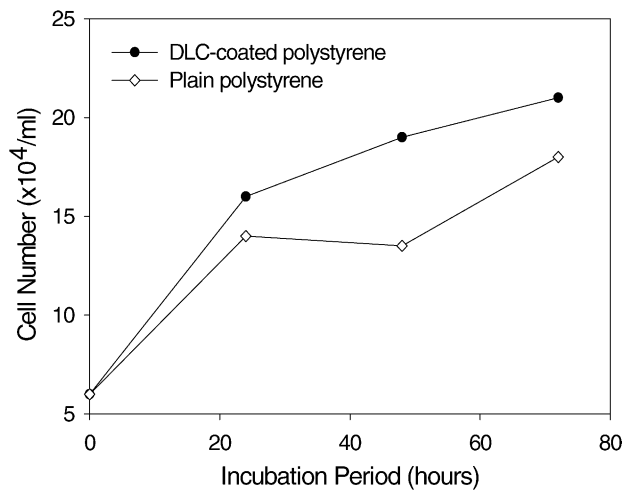


Fig. 23. Growth curves for human osteoblast-like cells on plain and DLC-coated polystyrene tissue culture plates [128].

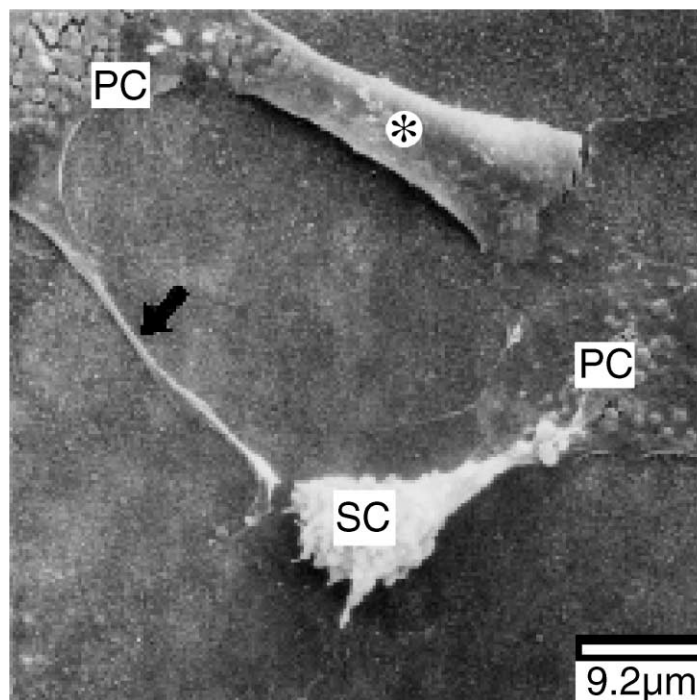


Fig. 24. SEM micrograph of osteoblast on amorphous CN film deposited on silicon after 1 week in culture. Spindle-shaped cells (SC) and well-spread polygonal cells (PC) maintain physical contact with each other through filopodia (arrow) or lamellopodia (asterisk) [126].

and fibrinogen adhesion compared to the CN and PMMA control samples. Quantitatively, the albumin/fibrinogen ratio is 1.008 for DLC, 0.49 for CN, and 0.39 for PMMA, suggesting that DLC has the best blood compatibility while CN is a slight improvement over PMMA. Additional results displayed in Fig. 28 lead to a similar conclusion [126] as the DLC films show a lower platelet adhesion count than the PMMA control sample. Our own results [67] described in Fig. 29 indicate that there are less platelets on the surface of DLC film than stainless steel used in vessel stents further corroborating the superiority of DLC as blood contact materials. Tran et al. have also synthesized DLC films on the surface of artificial heart-valve using plasma and glow charge methods and their observation is that the blood compatibility can vary based on the deposition methods and conditions [127].

#### 4.3. Plasma sterilization

Biomedical devices and surgical instruments for tissue-engineering or clinical applications must be either manufactured aseptically or sterilized after use. For economical and practical reasons, the latter strategy is employed for polyester pins and plates intended for *in vivo* use [130]. New approaches in low-temperature sterilization and high level disinfection have emerged in the last decade [131–133]. Plasma-based methods, ionizing radiation, and other advanced technologies have recently been applied to low-temperature sterilization and decontamination. Successful attempts were made to sterilize surfaces in low-pressure rfGD plasma operating below 1 Torr as early as the 1960s [134]. Usually, low-pressure glow discharge plasma is employed in combination with a working gas familiar to the healthcare and medical community, such as hydrogen peroxide or paracetic acid vapor. The glow discharge plasma is effective against a broad range of bacteria and

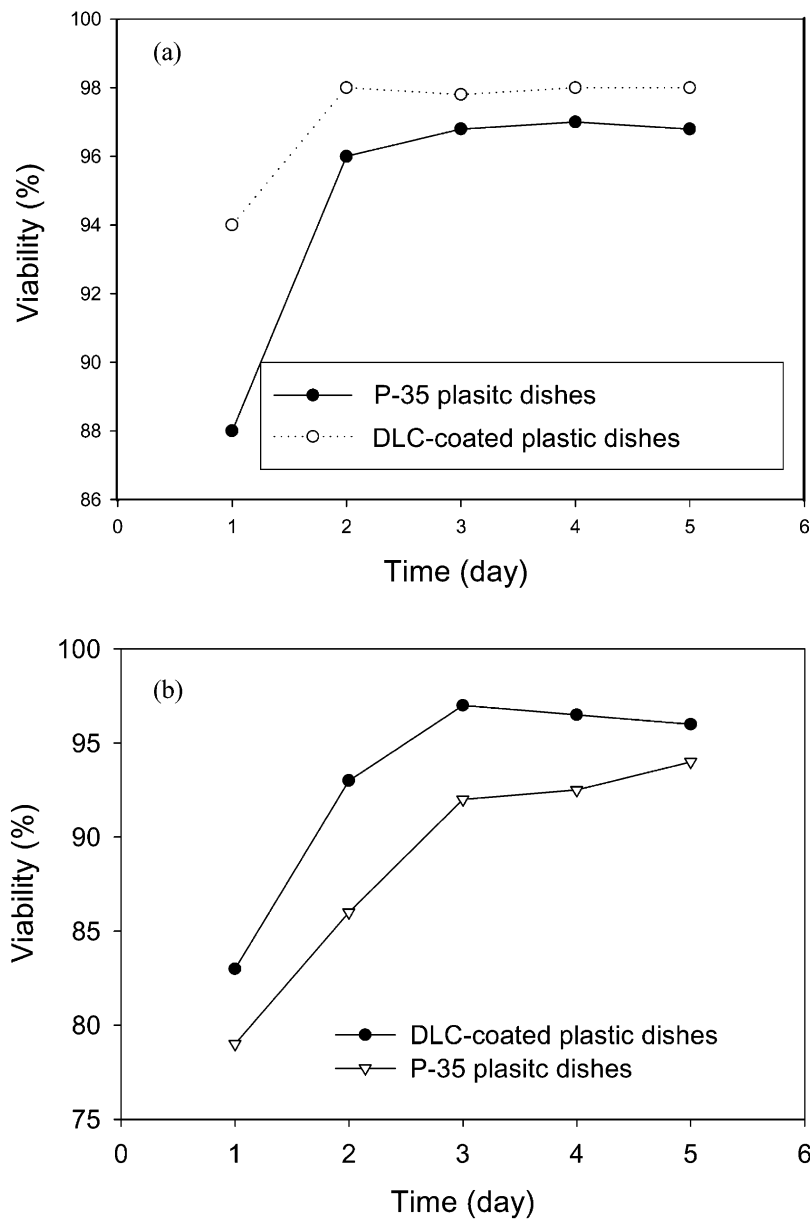


Fig. 25. Cell viability on control and DLC-coated P-35 plastic dishes [129]: (a) ML-1 cells (b) HEK 293 cells.

bacterial spores killing these microorganisms by generating oxygen, hydroxyl free radicals, and other active species, although these killing mechanisms are still being investigated [135]. In fact, plasma sterilization systems using two working gases have been approved by the US Food and Drug Administration (FDA) and commercially available since the early 1990s [131–133,136].

Plasma-based sterilization has a number of advantages. It has been shown that rf and microwave plasmas can destroy microorganisms and kill bacteria and viruses [137–139]. Plasma sterilization is a nontoxic, fast procedure without the severe drawbacks suffered by other traditional techniques when dealing with thermolabile and thermostable microsurgical instruments, routine surgical instruments like steel scissors, trephination devices, microstripper, Vitro-Cat, as well as irrigation/

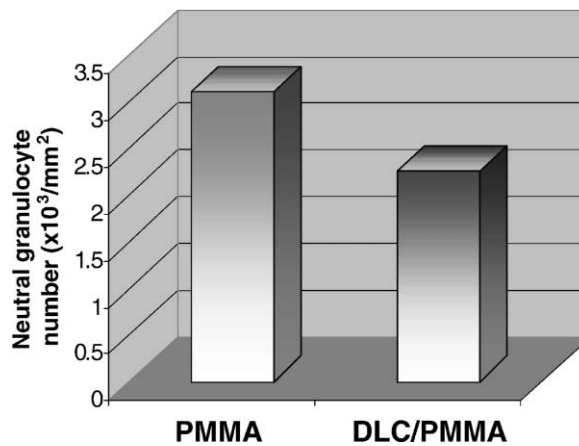


Fig. 26. Number of neutral granulocytes adhering to the control and the DLC-coated PMMA IOLs [126].

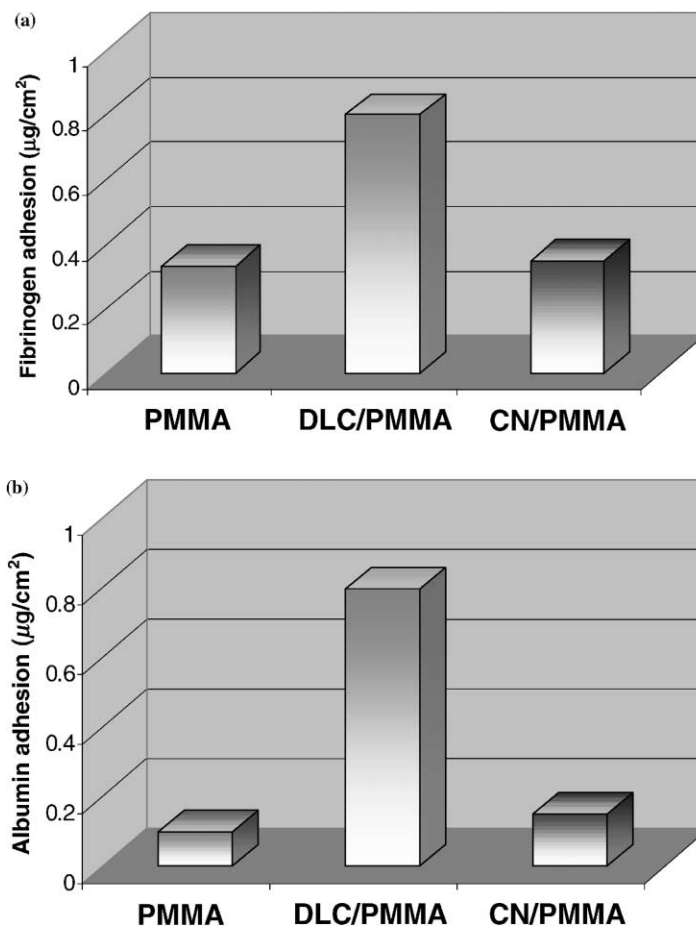


Fig. 27. Adhesion of plasma proteins from a single protein solution to different surfaces (adhesion time: 3 h; protein concentration: 0.5 mg/ml) [126]: (a) fibrinogen, (b) albumin.



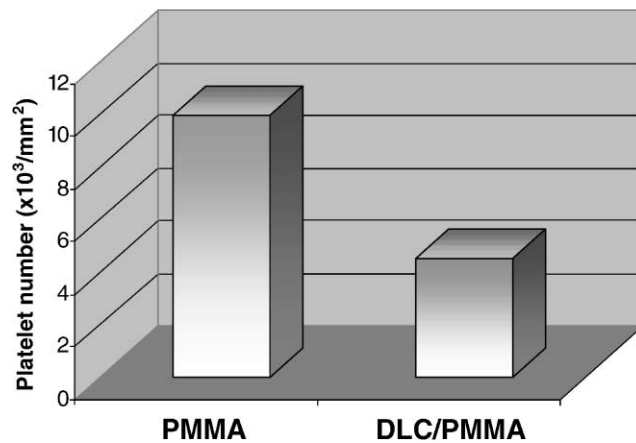


Fig. 28. Number of platelets adhering to the control and DLC-coated PMMA IOLs [126].

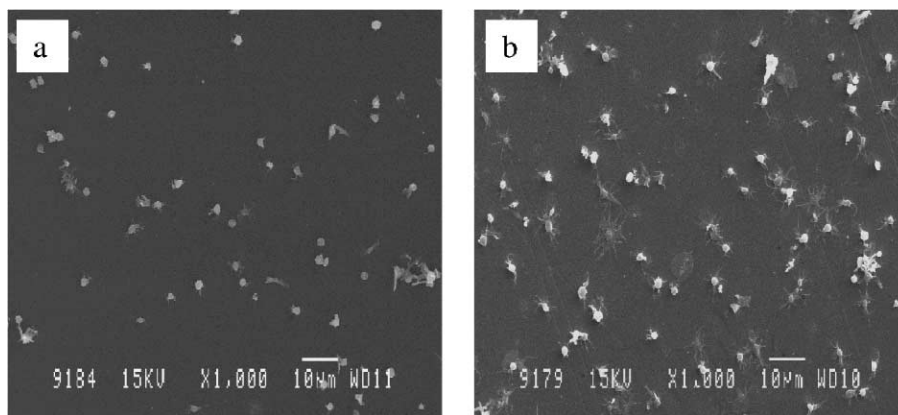


Fig. 29. Platelets adhered to the surfaces of DLC film and stainless steel (incubation 20 min in Plasma-rich-platelet): (a) DLC film, (b) stainless steel.

aspiration instruments. Plasma sterilization has been proven to be a microbiologically safe procedure with legally adequate reduction factors of  $>6 \log$  [140]. Compared to the other sterilization methods such as ethylene oxide (ETO) and formaldehyde, plasma sterilization not only kills the bacteria and viruses, but also removes the dead bacteria and viruses (pyrogens) from the surface of the objects because the sterilization process is a process similar to plasma etching [137]. Last but not the least, plasma sterilization is inexpensive, fast, and relatively safe [141].

Among new plasma low-temperature sterilization methods, the STERRAD<sup>®</sup> 100 gas-plasma technique employing hydrogen peroxide was presented a few years ago and has been successfully

Table 6  
Protein adhesion results [125]

	Silicone elastomer		DLC/Ti-6Al-4V	
	Value (g/cm <sup>2</sup> )	Value (%)	Value (g/cm <sup>2</sup> )	Value (%)
Albumin	0.0535 ± 0.008	100	0.127 ± 0.011	237
Fibrinogen	0.0704 ± 0.0057	100	0.102 ± 0.012	145

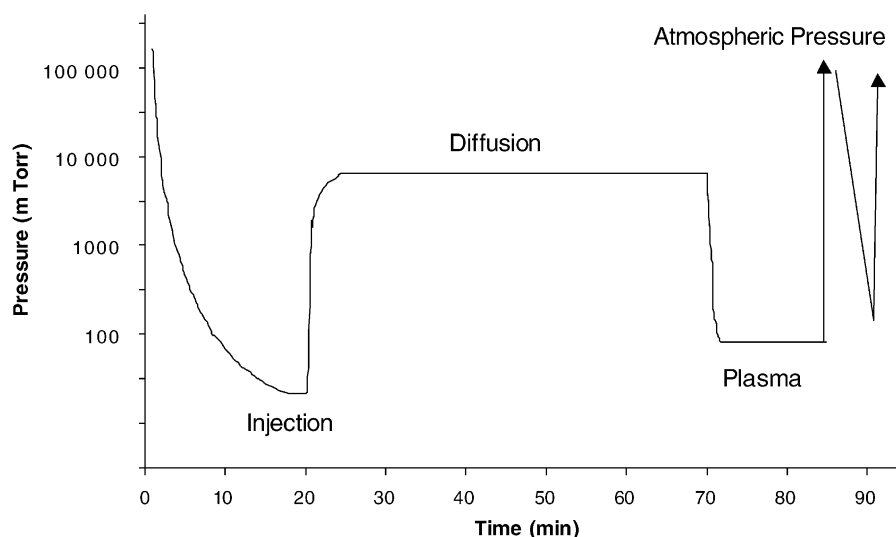


Fig. 30. Sterilization cycle curve [142].

marketed in several European countries, Japan, and the United States [142]. Fig. 30 depicts the sterilization cycle curve for the STERRAD<sup>®</sup> 100 apparatus supplied by Johnson and Johnson Medical SA (France) and manufactured by ASP Inc. [142]. It comprises a hydrogen peroxide diffusion phase in a chamber followed by a plasma phase lasting 15 min (300 W) induced by an electromagnetic wave generator (13.56 MHz, 10 eV). The chamber temperature is  $45 \pm 2$  °C. The sterilization cycles are relatively short and the sterilization process results in a  $10^5$  reduction of bacteria, bacterial endospores, yeast and bacterial viruses after a 90 s exposure to an atmospheric glow discharge plasma. The sterilization efficiency is similar to that of ETO and  $\gamma$ -irradiation [143,144]. However, equipment for the latter treatments is very costly, sterilizes samples in a volume of a few tens of liters near room temperature, and requires 1–2 h for each. Limitations of plasma processes with regard to medical uses include the restricted volume of the plasma reactor, reactivity of the chemicals or active species with materials in medical instrumentation and supplies, and an overall cycle duration which may include one or more vacuum and chemical cycles [131–133,136], but nonetheless, plasma sterilization has attracted a lot of attention.

Bathina et al. conclude that hydrogen peroxide gas-plasma sterilization provides a cost-effective means of sterilizing nonlumen electrophysiology catheters without the problem of potentially harmful chemical residuals [145]. Gadri et al. and Adler et al. arrive at a similar conclusion that plasma sterilization is simple, cost-effective and suitable for online treatment of webs and such three-dimensional workpieces as medical instruments [135,141]. Lerouge et al. study the sporicidal activity of microwave (MW) plasma sterilization and suggest that the high sporicidal efficacy is due to the higher concentration of reactive particles in the plasma [146]. The modified surface and bulk properties as well as hydrolytic stability of sterilized catheters are evaluated to assess the safety issue pertaining to plasma-based sterilization in terms of materials damage. They discover that: (i) plasma-based sterilizers induce limited oxidation at the near-surface layer, (ii) molecular weights are not changed after plasma-based sterilization, (iii) the hydrolytic stability of catheters is only slightly changed by plasma-based sterilization with a small increase in released oligomers, and (iv) different plasma-based sterilization techniques result in different impacts on the catheters, such as the degradation of an additive or a clear difference in coloration [147]. Lerouge et al. investigate the possible mechanism of plasma sterilization by low-temperature gas-plasma and believes that

chemical modification (oxidation), rather than etching, is the sterilization mechanism of STERRAD™ [148]. Holy et al. employ a novel poly (lactide-co-glycolide) scaffold (Osteofoam™) to determine the optimal sterilization procedure, and then compare three sterilization techniques—rfGD plasma sterilization, ETO, and  $\gamma$ -irradiation in terms of their immediate and long-term effects on the dimensions, morphology, molecular weight, and degradation profile of the scaffolds [144]. Scaffolds treated by rfGD plasma show no morphology change and only a small difference in the molecular weight. Furthermore, the degradation profile of the rfGD plasma-treated samples closely resembles that of the controls. It can, thus, be concluded that the rfGD plasma treatment is the best technique for sterilizing polyester devices in tissue-engineering applications because it does not alter the three-dimensional morphology of the scaffolds. Calderon et al. investigated the stability of plasma-polymerized allyamine films with an autoclaving sterilization cycle [149]. Polymerized films are deposited under pulsed plasma conditions using two duty cycles to give rise to surfaces having different initial amino group concentrations. Their results suggest that the simple one-step plasma treatment process is a viable alternative to the more cumbersome surface modification procedures currently employed to introduce amino groups into these tissue cultures. On the other hand, there have also been some not so positive results. McKellop et al. observe that sterilizing an UHMWPE acetabular cup without radiation (for example, with ETO or gas-plasma) avoids immediate and long-term oxidative degradation of the implant but does not improve the inherent wear resistance of the polyethylene [150]. Smith et al. propose that the toxic corneal endothelial cell destruction syndrome is associated with the introduction of plasma gas sterilization protocols [151].

## 5. Plasma-surface modification of hard tissue replacements

Hard tissue replacements such as artificial joints are common in patients. Natural synovial joints, e.g. hip, knee, and shoulder joints, are complex and delicate structures that must function under adverse and stressed conditions. As shown in Fig. 31, the proper performance of a human joint is dictated by the optimized combination of articular cartilage, a load-bearing connective tissue covering the bones in the joint, and synovial fluid that is a nutrient fluid secreted within the joint area [152,153]. Unfortunately, human joints are prone to degenerative and inflammatory diseases that

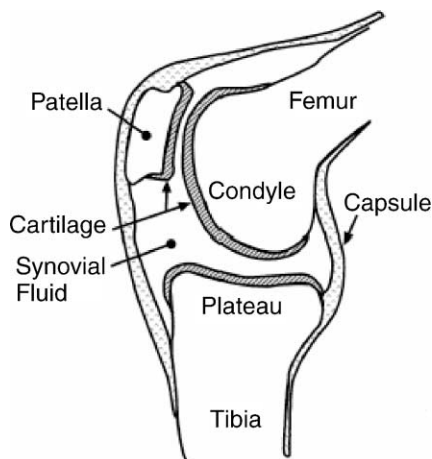


Fig. 31. Schematic representation of human knee joint.

result in pain and joint stiffness. Ninety percent of the population over the age of 40 suffers from some degree of degenerative joint disease [106]. Replacement of defective joint surfaces by metal, plastic, or ceramic artificial materials is accomplished through arthroplastic surgery when the natural joint can no longer adequately function or the patients require surgery to relieve pain and increase mobility. TJR arthroplasty is recognized as a major achievement in orthopedic surgery. It is now a fairly well established orthopedic technique involving the replacement of a growing number of hip and knee joints, and 275 000 hip and knee joints were replaced in the US in 1995 [154]. Each year, about 1 million total joint arthroplasty procedures are performed in the world [6] to cure individuals suffering from severe arthritis or joint injury.

Most artificial joints consist of a metallic component with a polymer. The metallic component is usually made of either titanium/titanium alloy or cobalt–chromium (Co–Cr) alloys and the polymer component is mainly UHMWPE. The main reason for aseptic loosening is the prosthetic wear debris [155,156]. The problem has been recognized for a long time, but only in the last several years has it received significant attention from manufacturers, surgeons and researchers. In order to enhance the tribological properties as well as wear resistance of the metallic components in the artificial joints, various procedures have been suggested including ion implantation, plasma coating, and plasma-grafting [157–159]. Ion implantation has been the most common treatment method [106,158,160]. The improvement in the sliding wear resistance of the implanted materials can turn out to be either little or substantial, but that in wear resistance is more consistent [157].

### 5.1. Ion implantation

Ion implantation into metallic materials such as titanium can harden the surface and reduce the friction coefficient, ultimately improving the wear resistance. The improvement in the hardness can be a factor of 3 or better and is attributed primarily to the formation of hard-phases of nitride, carbide and oxide precipitates. Lower friction coefficients stem from physical changes such as changes in the crystalline lattice in the near-surface region of the materials.

Fig. 32 depicts the wear test results from a pin-on-disk experiment conducted on a titanium specimen in distilled water [161]. Distilled water is used to simulate the environment around the joints for it has a viscosity close to that of synovial fluids. The data show that by using  $N^+$  implantation, the wear rate is reduced to 20% of the unimplanted value. Other researchers observe

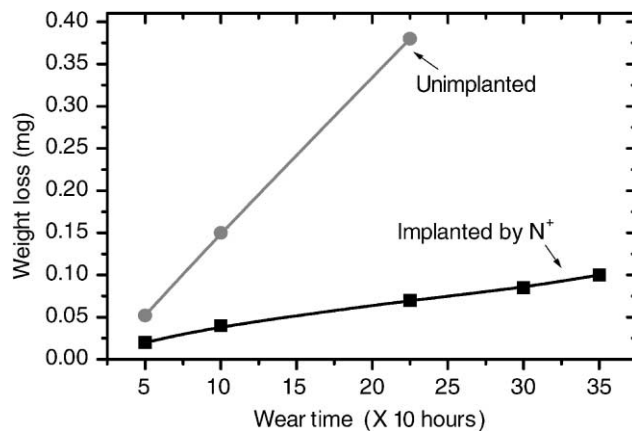


Fig. 32. Weight losses as a function of wear time for Ti-6Al-4V alloy in distilled water; wear time of 1 h corresponds to a sliding distance of 450 m.

order-of-magnitude improvements in the wear resistance of ion implanted titanium alloys [162,163] using traditional pin-on-disk wear tests. Similar improvements have been observed in other materials, for instance, 316L stainless steel, in hip and knee joint simulation studies [164]. After several million cycles, the ion implanted components exhibit much less scratching than their untreated counterparts. It has been demonstrated [165] that an order-of-magnitude improvement in the wear resistance can be achieved in 316L stainless steel. As a result, ion implantation is frequently used to improve the joint properties and prosthesis longevity [6] and has gained market acceptance. In fact, over 100 000 components are treated annually.

### 5.1.1. Titanium orthopedic products

Titanium and its alloys are among some of the most biocompatible materials while exhibiting good corrosion resistance, excellent fatigue strength, excellent formability, good machinability, and low-density. They are, therefore, used in many orthopedic and dental applications. However, titanium also has relatively poor wear resistance. Ion implantation can harden the surface and reduce the friction coefficient, but the metal surface still needs modification in order to enhance the bioactive or bioinert performance [166].

The other important objective of PSM of titanium is to improve the bone-conductivity through the formation of a calcium phosphate film, and calcium ion implantation into titanium is a promising method to enhance the bone-conductivity of titanium. Hanawa's studies yield good results [167]. Fig. 33 shows the calcium and phosphorus concentrations in calcium phosphate in unimplanted and calcium ion implanted titanium immersed in Hanks' solution for 30 days. Fig. 34 depicts the scanning electron micrographs of unimplanted titanium and calcium ion implanted titanium immersed in Hanks' solution for 30 days. It is clear that calcium ion implantation accelerates calcium phosphate precipitation in titanium [168]. Osteogenic cells on titanium are activated to form osteoid tissue when calcium ions are implanted [167,169]. A larger amount of new bone is formed on calcium ion implanted titanium compared to unimplanted titanium 2 days after implantation into rat tibia [170]. Fig. 35 displays the schematic of the modified surface layers with and without calcium ion implantation. The surface consists of calcium titanate when the ion implant dose is between  $10^{16}$  and  $10^{17}$  ions/cm<sup>2</sup>, and both calcium oxide and calcium titanate are formed when the ion implant

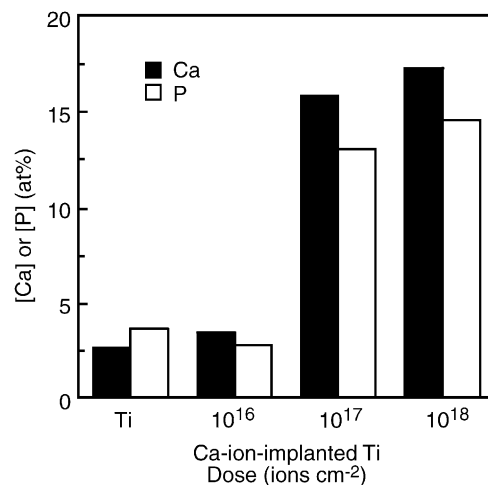


Fig. 33. Concentration of calcium and phosphorus in calcium phosphate in unimplanted and calcium ion implanted titanium specimens immersed in Hanks' solution for 30 days.

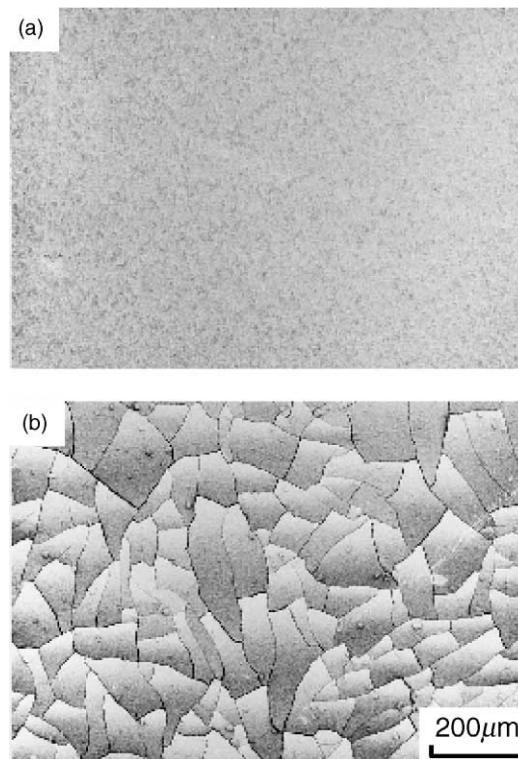


Fig. 34. SEM micrographs of samples after immersed in Hanks' solution for 30 days: (a) unimplanted titanium, (b) calcium ion implanted titanium.

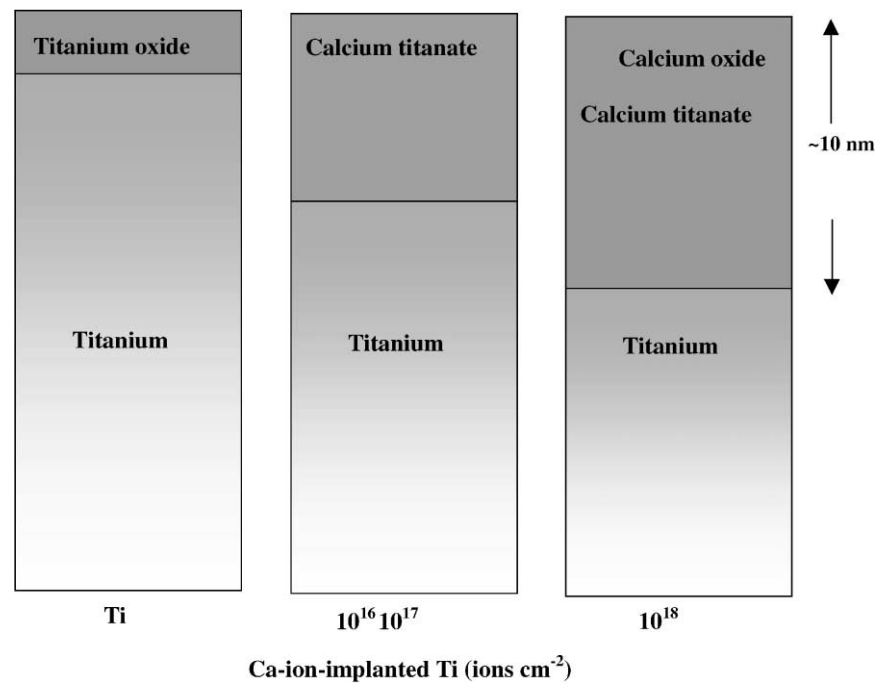


Fig. 35. Schematic illustration of the modified surface layers with and without calcium ion implantation.

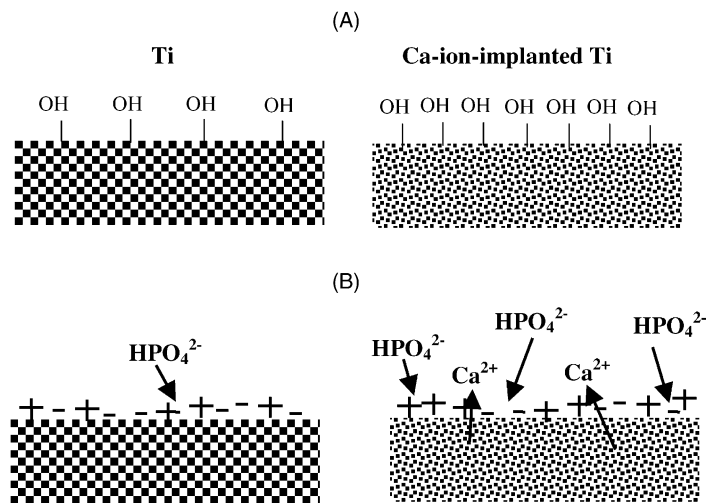


Fig. 36. Hydroxyl radicals on unimplanted and calcium implanted titanium: (A) in air, (B) in body fluid.

dose is  $10^{18}$  ions/cm<sup>2</sup> [171]. Both samples show calcium hydroxide on the surface. The modified surface layers are quite thin, about 6, 8, and 13 nm in specimens implanted with  $10^{16}$ ,  $10^{17}$ , and  $10^{18}$  ions/cm<sup>2</sup>, respectively. The calcium ion implanted titanium surface is more positively charged than the titanium surface due to dissociation of hydroxyl radicals [172] as schematically illustrated in Fig. 36, and the number of charged sites is higher. A greater number of phosphate ions from the body fluid adsorb onto the calcium-ion-implanted titanium surface because of electrostatic attraction. That is, when more phosphate ions adsorb on the surface, more calcium ions are subsequently attached resulting in the formation of a larger amount of calcium phosphate. Calcium ions are gradually released from the surface of the calcium ion implanted titanium [173,174] leading to supersaturation of calcium ions in the body fluid in the vicinity and acceleration of calcium phosphate precipitation.

### 5.1.2. Cobalt–chromium orthopedic products

Total joint arthroplasty is performed hundreds of thousands of times each year in the US [175] to restore joint functions to individuals with severe arthritis or joint injury. Most artificial hip and knee joints consist of a metallic component usually made of Co–Cr alloys besides titanium and its alloys for better durability and wear resistance. The polymeric component, UHMWPE, is pliable and provides joint conformity. However, UHMWPE is very soft compared with the metals and tends to wear out over time. The released particles activate a biological reaction that can lead to bone resorption and ultimately causing joint loosening and failure [176]. Of the metals, titanium (alloyed with small amounts of aluminum and vanadium) is generally considered more biocompatible and has mechanical properties close to those of bone [166,177], but it is softer than Co–Cr alloys and more prone to surface wear. Attempts to make the UHMWPE component more wear resistant are generally unsuccessful because the processes invariably degrade the bulk properties. A successful solution to mitigate the UHMWPE wear problem is to modify the mating Co–Cr bearing surface. By altering the dynamics of the fluid–film lubrication in the metal–polymer interface, it is possible to reduce the friction coefficient and wear. An effective surface modification method is to conduct ion implantation into the Co–Cr component [178], and the process is now employed to treat a large number of products in the US [6,74,179,180]. Sioshansi's studies show that ion implantation

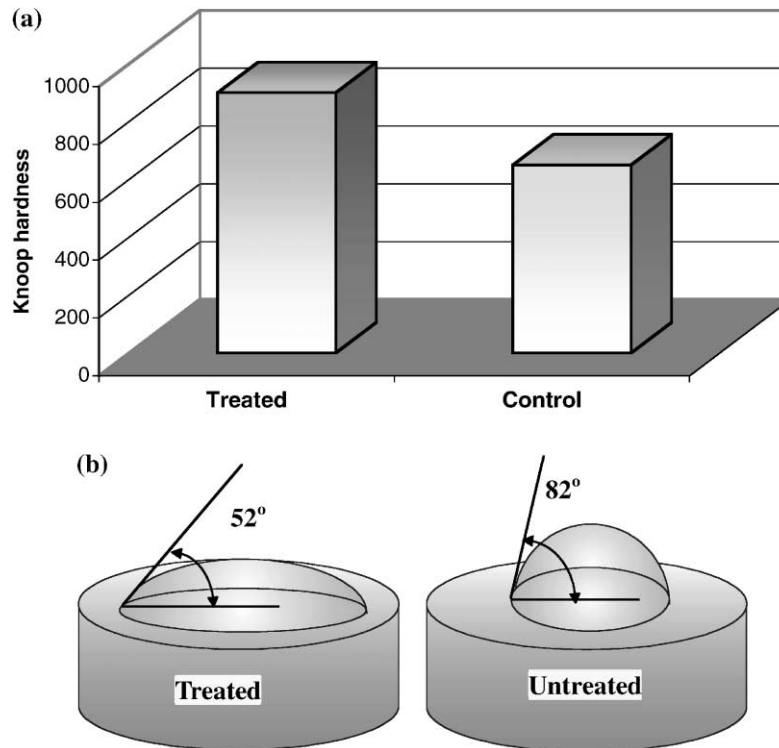


Fig. 37. Ion implantation into Co–Cr orthopedics enhances: (a) micro-hardness, (b) wettability, demonstrating lower wear on the UHMWPE surfaces [6].

decreases the friction coefficient and reduces the wear status. Fig. 37 shows that ion implantation increases the surface energy and hardness [6]. The higher surface energy as a result of the physical change in the Co–Cr allows better retention of the lubricating fluid film, resulting in less wear on the UHMWPE component. Several studies have been performed to evaluate the wear resistance of UHMWPE in contact with the treated and untreated Co–Cr. The wear of UHMWPE disks sliding against treated and untreated Co–Cr pins is compared with that using zirconia pins. The wear and friction of UHMWPE against the treated Co–Cr pins are much lower than those of the untreated pins and also slightly lower than that of zirconia, as shown in Fig. 38 [180]. In joint simulation studies conducted to 2 million cycles, the treated and untreated Co–Cr femur heads are tested against UHMWPE [181] and wear is evaluated using weight loss measurements. The results reveal approximately 25% reduction in wear and the wear of UHMWPE against the treated Co–Cr is close to that of zirconia.

### 5.1.3. Polymeric orthopedic components

Ion implantation into UHMWPE has also been actively investigated. Preliminary studies show that ion implanted UHMWPE exhibits a significantly reduced wear rate compared to the untreated materials. However, because wear is quite high (more than 1 mm in 10 years [182]), the small projected range of the ion implant is a limiting factor. Implanting the backside of tibial plateaux or acetabular cups reduces small scale fretting wear. Researchers have noted that wear debris results from micromotion between the UHMWPE and metallic liner [183]. This debris may be responsible for the same type of osteolytic response induced by debris from the articulating surface. Ohl et al. [5]



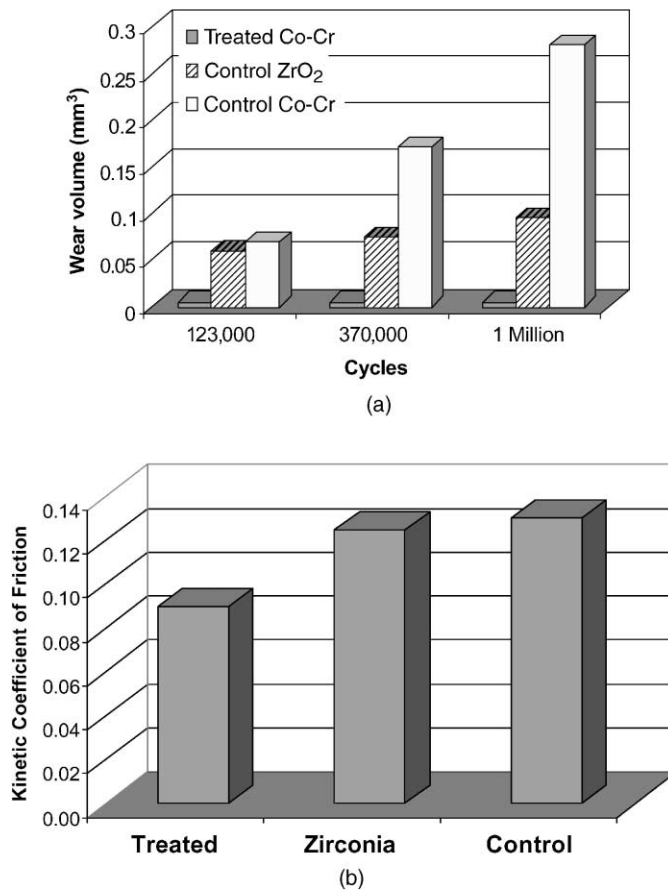


Fig. 38. Results of wear simulation studies on UHMWPE in contact with the treated and untreated Co–Cr pins showing dramatic reduction in: (a) UHMWPE wear, (b) friction [179].

show that surface oxidation in an oxygen plasma increases the wettability of polysiloxane (Dow Corning, 1-2577) spin-coated glass uniformly on the entire sample.

#### 5.1.4. Bioceramics

Al<sub>2</sub>O<sub>3</sub> ceramic is a good biomaterial because of its high hardness, chemical stability in living tissues, and good tribological properties. However, bondage with organic bone tissue requires further improvement. Zhao et al. [70] suggest low current density (<0.01 A/cm<sup>2</sup>), 80–160 kV NH<sub>2</sub><sup>+</sup> ion implantation to improve the surface properties of Al<sub>2</sub>O<sub>3</sub>. The ion implant dose is between 10<sup>15</sup> and 10<sup>17</sup> ions/cm<sup>2</sup>. The Fourier transform infrared spectroscopy (FTIR) results show evidence that the implanted NH<sub>2</sub><sup>+</sup> ions can be grafted in the form of the amidogen radicals onto the Al<sub>2</sub>O<sub>3</sub> ceramic surface and the amount of grafted –NH<sub>2</sub> radicals is proportional to the NH<sub>2</sub><sup>+</sup> dose. The most effective implantation energy is determined to be 100 keV at which the amount of –NH<sub>2</sub> radicals grafted onto the ceramic surface is maximum. Cylindrical samples prepared for animal tests are rotated about the long axis during NH<sub>2</sub><sup>+</sup> ion implantation (100 kV and NH<sub>2</sub><sup>+</sup> dose of 3 × 10<sup>17</sup> ion/cm<sup>2</sup>). Control samples of plain ceramic and ion-implanted ceramic are implanted into the jawbones of dogs for 2 weeks, 1, 3, and 6 months. In vivo investigation results demonstrate that NH<sub>2</sub><sup>+</sup> ion implantation accelerates the recovery from inflammation by enhancing the formation of osteoid

tissue and circulation vessels and making the  $\text{Al}_2\text{O}_3$  ceramic body more biocompatible with the organic tissue environment.

### 5.2. Plasma coating

Calcium phosphate apatite possesses good properties as a biomaterial in bone repair, augmentation, substitution, and surface coating [184–186]. Coating the surfaces of dental and orthopedic materials with biocompatible calcium phosphate apatite can elicit favorable biological and chemical responses and this can enable researchers to mimic the reactions occurring in the natural calcified tissues without compromising the bulk properties of the materials such as durability and inertness [187]. Hydroxyapatite (HA), which has many crystallographic features similar to those of the natural apatite present in bone, is a potential bone substitute, but its use is limited to low-load applications because of its poor mechanical strength. Much research on modifying the surface properties of calcium phosphate apatite including HA has been conducted, particularly using plasma techniques. For instance, plasma spraying of apatite on metallic materials is used to form apatite to enhance active bone formation and bone-conductivity, and an example is plasma sprayed HA coatings on metallic joint prostheses [62]. Unfortunately, the apatite/titanium interface or apatite itself can be fractured even under a relatively low stress because of the low joint strength and brittleness of the sprayed layer itself.

Although HA has a similar chemical composition to that of natural bone, it lacks sufficient strength and durability for use in load-bearing applications [188–190]. Very often it requires blending with a low modulus polymer to achieve adequate strength. However, the properties of the HA composite is highly dependent on the particle size and morphology of the HA filler. The use of nano particulate materials to attain more superior mechanical properties has been proposed. Kumar et al. [189] synthesize ultra-fine HA powders using a plasma technique. The synthesis is initiated using rf plasma spraying onto a wet suspension of HA. It is then axially injected into the rf plasma at various plate powers (plasma energies), chamber pressure, probe distances, and plasma gas flow rates. The size of the processed powders varies from medium to ultra-fine on the cyclones designed to collect the powders. In general, the particle size decreases with increasing plate power. Decomposition into other phases such as tricalcium phosphate (TCP), tetracalcium phosphate (TTCP) and calcium oxide (CaO) also increases with higher plate power. The study suggests that the processing parameters associated with the production of the ultra-fine powders interact in a complex manner but can be envisioned as an overall thermal treatment of the particulates. Zheng et al. have also prepared HA/Ti composite coatings by atmospheric plasma spraying to improve the bond strength [190].

Yttrium stabilized zirconia (YSZ) reinforced HA coatings. It has been shown to enhance the mechanical properties of the HA coatings significantly and reduce the formation of calcium oxide (CaO) [188,191,192]. In clinical applications, the interface mechanical failure is a potential weakness in prosthesis [193]. Fu et al. spray HA/YSZ composite coatings by plasma techniques to improve the interfacial strength between the HA coating and titanium alloy substrate. Their experimental results show that the spheroidized powders melt more effectively than the ball milled powders during plasma spraying and give rise to better mechanical properties. An HA/YSZ solid solution forms during deposition and plays an important role in the enhancement of the mechanical properties of the HA/YSZ composite coatings.

In addition to apatite, the inorganic part of natural bone also contains  $\beta$ -TCP and several ions such as  $\text{Na}^+$ ,  $\text{Mg}^{2+}$ ,  $\text{K}^+$  and  $\text{F}^-$ , and glasses in the  $\text{P}_2\text{O}_5$ -CaO- $\text{Na}_2\text{O}$  system have been considered to have good potential as biomaterials because of these inorganic constituents [194]. Research on

multilayered coatings composed of mixtures of HA and P<sub>2</sub>O<sub>5</sub>-based bioactive glasses reveals their potential clinical benefits in orthopedic and dental surgery, and that pre-immersion of these materials has been reported to further enhance their efficacy *in vivo*, although the precise biological effects of this treatment are not yet understood. Ferraz et al. [194–196] has prepared double-layer coatings by plasma spraying and evaluated the effects of pre-immersion on the growth and function of human osteosarcoma cells *in vitro*. The results show that the number of viable cells on the pre-immersed HA and glass-reinforced HA coatings is the same or higher following incubation compared to the non-immersed materials. In addition, there are recent reports on the deposition of DLC on hard tissue replacements using PIII, and the mechanical properties of the artificial joint prostheses are improved.

### 5.3. Plasma-grafting techniques

Experiments have been conducted on grafting poly(ethylene glycol) (PEG) onto the hydrophobic polysulfone (PSF) membrane surface by low-temperature plasma techniques to produce highly hydrophilic surfaces [197]. It is found that the hydrophilic characteristic is increased and suggested that plasma-induced polymer modification can adjust membrane performance by controlling the surface hydrophilicity and hemocompatibility.

To recapitulate, exciting results have been obtained with regard to surface modification of hard tissue replacements. It should, however, be borne in mind that although a harder layer composed of various oxides produced by surface treatment improves lubrication, no long-term data are yet available, and the limitation of such surface treatments to only a thin layer (<10 μm in best cases) may lead to catastrophic wear as the treated surface wears away or become discontinuous. Therefore, much research work must still be performed in order to bring the technology to fruition.

## 6. Plasma-surface modification of blood contacting materials

Atherosclerotic cardiovascular disease is the number one cause of morbidity and mortality in the western world. For cardiovascular patients suffering from heart-valve disease, arteriosclerosis, and so on, artificial prostheses replacements are indispensable, but unfortunately, the current products are not satisfactory with respect to biofunctionality. The problem is primarily related to the fact that the surface of the artificial organ is not recognized by blood. For instance, low-temperature isotropic pyrolytic carbon (LTIC) is usually used to fabricate artificial heart-valves because of the combination of decent blood compatibility and high resistance to degradation, wear, and fatigue. However, the main problem of LTIC mechanical heart-valves is thrombogenicity. Although the newest generation of mechanical heart-valve prosthetics constructed either partially or wholly of LTIC have significantly reduced thromboembolic complications compared to earlier-generation mechanical valves (e.g. Starr–Edwards), thromboembolism remains an important clinical complication issue [198]. As another example, vascular prostheses substituting for large arteries have been used but the failure rate of small-caliber artificial grafts, especially those with an internal diameter of less than 5 mm, is high in clinical conditions due to the localized constriction (stenosis) which ultimately stops the flow of blood through the affected vessel [199]. Treatment is essentially surgical and consists of bypassing the affected vessel segment to restore flow. Anticoagulation therapy is necessary to minimize the risk of thromboembolic complications in patients with artificial prostheses. However, it is necessary to find new biomaterials with better blood compatibility or modify current blood contacting materials as there appear to be no perfect materials. Actually these devices are generally treated to minimize thrombi and emboli generation and to increase the lifetime [14]. A number of different surface

treatment processes have been proposed, but the study is typically conducted employing a simple trial-and-error approach. The general experimental trend is: PECVD of thin films with the proper composition and the immobilization (covalent, ionic, adsorption) of anti-thrombotic molecules onto the polymers previously plasma grafted with specific chemical groups.

### 6.1. Organic blood contacting materials

In spite of the unsatisfactory behavior such as undesired coagulation, thrombi, emboli generation, variable response to natural tissues, leach of low molecular weight compounds, and others, synthetic polymers are used in implants and devices such as artificial blood vessels and artificial heart-valves [14]. Dacron (polyethylene-terephthalate (PET)) and Goretex (e-PTFE) are the materials of which modern vascular prostheses are made. Blood bags for hemodialysis are made of polyvinylchloride (PVC) with plasticizer membranes fabricated with polypropylene (PP), and heart-valves are made of Dacron or Goretex with metal leaflets coated with pyrolytic carbon.

#### 6.1.1. Poly(tetrafluoroethylene)

PTFE as a biomaterial has the following desirable bulk and surface properties [1]: (i) good thermal stability, (ii) high chemical inertness, (iii) low surface energy, and (iv) low coefficient of friction. Thus, e-PTFE has the required mechanical properties and excellent chemical stability as a synthetic material. However, thrombogenic reactions can occur between the surface of e-PTFE and blood resulting in poor performance as a small diameter, synthetic arterial substitute [200]. Immobilization of anti-thrombogenic moieties onto the surface provides one means to alter the physical and biological properties of the surface and surface modification is, therefore, required to covalently attach these organic moieties to the surface. Surface modification methods that has been used to enhance endothelial cell seeding on blood contacting prostheses include immobilization of fibronectin, laminin, collagen and peptides. The process involves the removal of the F groups from the surface and introduction of the desired functionality such as hydroxy and amino groups [1]. Various wet chemical techniques have been used, but it is difficult to control the depth of the modified zone due to the fast reaction rate [1]. Other techniques have been attempted and PSM, which has been shown to modify the surface of vascular prostheses without dramatically changing the grafting dynamics [201], is one of the choices. In fact, recent research has shown that it is an effective means to modify fluoropolymer surfaces including naturally PTFE and e-PTFE.

Clark and Hutton [202] show that hydrogen plasma can rapidly defluorinate fluoropolymers to a depth of 2 nm. Oxygen from residual water in the reactor is also incorporated after a short exposure time. Vargo et al. use rfGDs of  $H_2/H_2O$  and  $H_2/CH_3OH$  to modify e-PTFE and a hydroxylated surface with minimal morphological damage to the membrane surface is obtained [113]. Nitrogen plasma treatment of PTFE and ePTFE vascular graft surfaces also reveal enhanced endothelial cell adhesion [203,204]. However, an ideal surface coating process should allow for a normal healing process and naturalization. Baquey et al. describe how the surface of poly(vinylidene difluoride) (PVDF) can be activated with swift heavy ions and investigate the use of rfGD on e-PTFE [205]. With regard to grafting of peptide, a multi-step approach can be carried out as shown schematically in Fig. 39. It has been shown that the plasma treatment effectively alters the surface of the e-PTFE. The oxygen content rises whereas the ratio of fluorine to total carbon atomic concentrations (F/C) drops. At the same time, plasma treatment of e-PTFE results in the activation and subsequent surface functionalization, and the relevant cell attachment results are exhibited in Fig. 40.

Chandy et al. prepared a series of surface coatings by modifying the argon plasma-treated PTFE (Teflon) and polyethylene-terephthalate (Dacron) grafts with collagen IV and laminin and subsequently

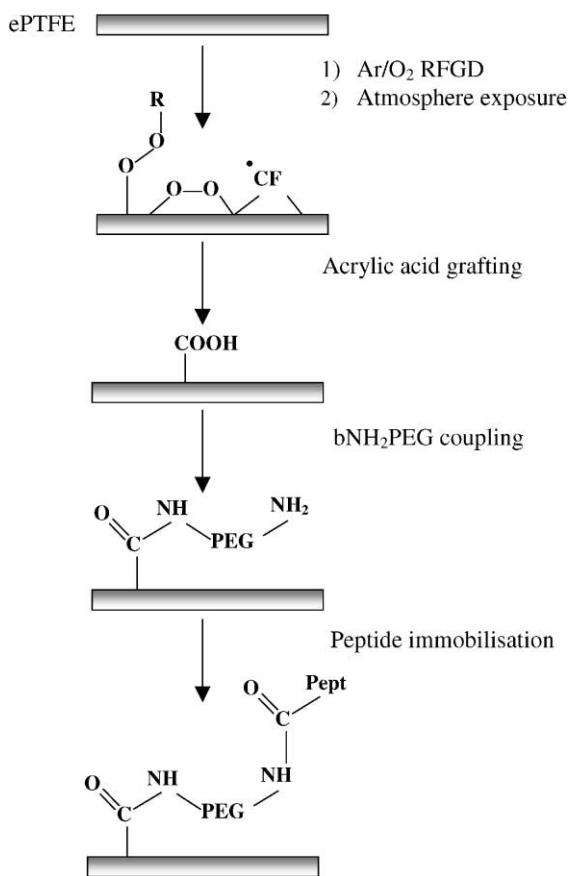


Fig. 39. Schematic of peptide immobilization [205].

immobilizing bioactive molecules like PGE<sub>1</sub>, heparin or phosphatidyl choline via the carbodiimide functionalities [206]. Fig. 41 depicts the PTFE modification sequence. In vitro studies show that fibrinogen adsorption and platelet adhesion on the modified grafts are significantly pared because surface grafting of the matrix components and immobilization of bioactive molecules change the

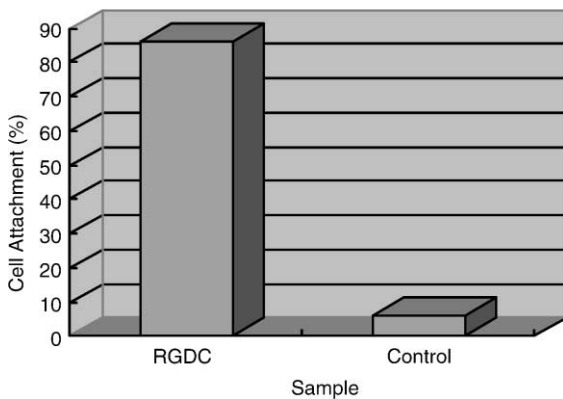


Fig. 40. Cell attachment onto the modified surface of peptide and control sample as reflected by percent of absorbance with respect to the control [205].

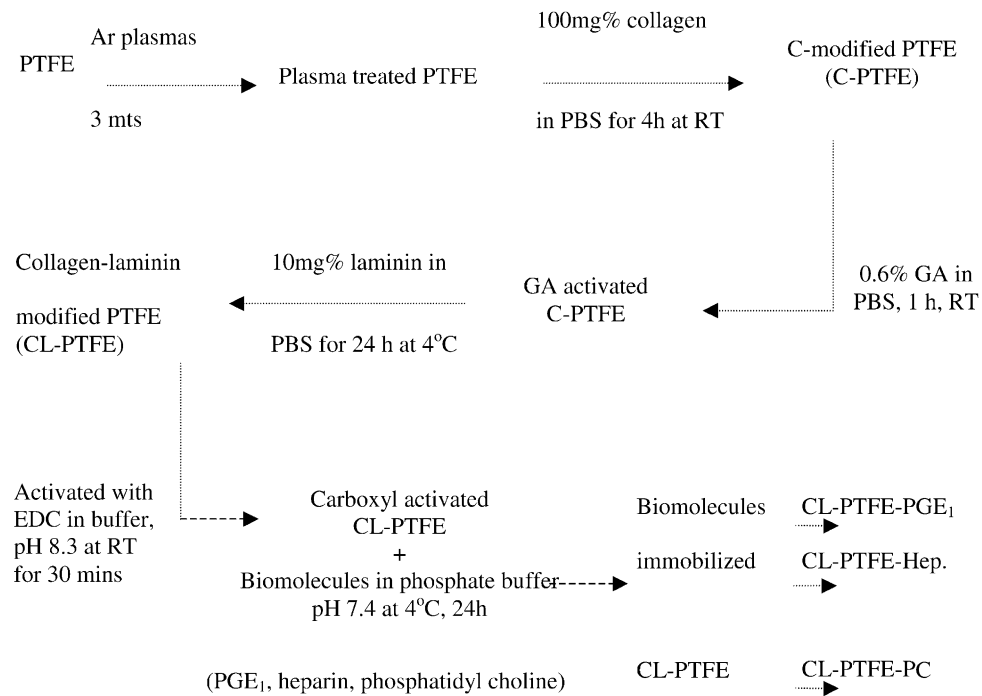


Fig. 41. Sequence of PTFE modification [206].

surface condition of the vascular grafts and consequently improve the biocompatibility. In other words, there is a higher inhibitory effect on fibrinogen deposition due to the surface modification with anti-platelet agents and plasma exposure [206]. The study suggests the possibility to control surface-induced thrombosis via the immobilization of biomolecules on collagen–laminin modified biomaterials.

### 6.1.2. Other polymers

Satisfactory results have been achieved by ion implantation into other polymer biomaterials like silicone rubber and polyurethane. Ion implantation improves the wettability, anti-coagulability, and anticalcific behavior of polyurethane, as well as the critical surface tension of silicone rubber which is thought to be a primary cause for biofouling.

Polyurethane has been used in the medical field for many years. It has several attractive properties such as high tolerance to the implant environment, good durability against continuous stress and flexing, and availability. On the other hand, its blood compatibility and anticalcific behavior are far inferior to those of body organs. Fig. 42 shows the improvement in the wettability, anticoagulability, and anticalcific behavior of polyurethane after  $\text{Si}^+$  and  $\text{N}^+$  ion implantation [207,208]. All the treated samples show a decrease in the contact angle and increase in the coagulation time and recalcification time compared to the control.

Favia and d'Agostino [14] review the research activities and materials in this field, including fluorinated coatings known as “Teflon-like” films ( $\text{CF}_x$  with  $0 < x < 2$ ), coatings deposited from organo-silicon monomers claimed to be “silicone-like”, and polyethylene oxide or “PEO-like”. It is believed that a rigorous approach to understand the plasma chemical mechanisms by means of proper diagnostics would improve the success of the plasma modification processes on biomaterial surfaces. As an example, it has been shown that it is possible to select the best working conditions for the selective grafting of  $-\text{NH}_2$  onto polyethylene in an  $\text{NH}_3/\text{H}_2$  glow discharge by using

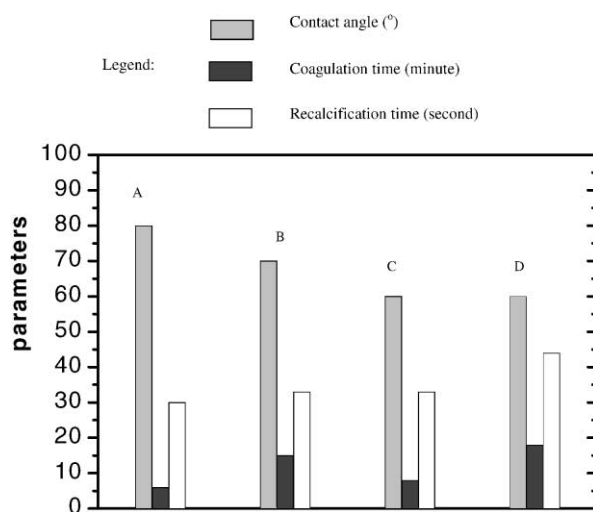


Fig. 42. Wettability, anticoagulability, and anticalcific behavior of polyurethane with and without  $N^+$  or  $Si^+$  ion implantation: (A) unimplanted polyurethane, (B)  $Si^+$  implanted polyurethane, (C)  $Si^+$  plasma implanted polymerized polyurethane, (D)  $N^+$  implanted polyurethane.

actinometric optical emission spectroscopy (AOES) to identify the species responsible for the grafting process [14]. Thus, only a “non-blind approach”, that is, using in situ gas phase and surface diagnostics combined with a good knowledge of reactor hardware and design criteria, can lead to process control and understanding. Unfortunately, many scientists working in the field of biomaterials and polymer modification often overlook this underlying concept.

Autologous saphenous veins are currently used to reconstruct occluded or diseased small diameter blood vessels in humans. However, 30–40% of patients requiring small vessel reconstruction (<5 mm in diameter) have either no or inadequate saphenous veins [209]. Because small caliber artificial vascular grafts currently available occlude within a short period of time, new approaches have been adopted to improve their biocompatibility, such as transplanting a monolayer of endothelial cells onto the luminal surface of a graft prior to implantation [210–212] and tissue engineering [213,214]. Biodegradable polymers such as poly(L-lactic acid) (PLLA), poly(glycolic acid) (PGA) and PGA coated with PLLA are employed in cell transplantation and in vivo regeneration of vascular tissue. Growth and organization of fibrovascular tissues inside polymer scaffolds lead to the occlusion of the regenerated blood vessel. Chu et al. have employed a novel ammonia plasma technique to surface modify PLLA substrates and to provide regulatory mechanisms to control the development of an inner capsule and endothelialization of the materials [215]. In this work, an rf plasma generator is capacitively coupled to a plasma reactor. The results show that the modified PLLA and fibronectin (Fn)-coated modified PLLA exhibit significant improvement in human vascular endothelial cell (HUVEC) and rabbit microvascular endothelial cell (RbMVEC) growth when compared to PLLA and Fn-coated PLLA, and that the ammonia plasma treatment provides the unique capability of modifying prosthetic biomaterials of various constructs with the eventual transplantation of mammalian cells to be used in tissue engineering or as biological implants. Sharma et al. [216] and Chandy et al. [217] have developed a method to immobilize phospholipids on polyether urethane urea (PEUU) using nitrogen plasma treatment. Free radicals are generated on PEUU to which phospholipids are attached. In a similar mechanism, free radicals generated on the graft surfaces using Ar plasma are used to couple collagen IV. It is then crosslinked and the unlinked free aldehydic groups are used to immobilizing the laminin.

Although much research work related to plasma modification has taken place, more detailed studies are needed in order to understand the mechanisms of plasma generated grafting and to investigate the physical adsorption and ionic interaction in the grafting process.

### 6.2. Inorganic blood contacting materials

Inorganic blood contacting materials such as artificial heart-valves and stents have made a big stride in the medical field due to their superior mechanical properties. However, inorganic biomaterials at present have deficiencies such as low blood compatibility. Therefore, surface modification of inorganic blood contacting materials is a hot research area.

As a blood contacting material, carbon-based films such as DLC and carbon nitride (CN) synthesized by plasma techniques have been described in Section 4 of this paper, and Huang et al. observe that both films have similar hemocompatibility [218]. In addition, titanium-based films are widely studied. Titanium oxide coatings are normally used in orthopedic and dental prostheses, but nevertheless, their chemical, biological, and mechanical properties require further improvement and better synthesis techniques are needed [219]. When a rutile titanium oxide layer is formed on the surface of a matrix, the blood compatibility can be improved significantly [220,221]. Titanium oxide films used in artificial heart-valves have been synthesized by PIII–D [222–224]. The film is polycrystalline with coexisting  $Ti^{2+}$ ,  $Ti^{3+}$ , and  $Ti^{4+}$ . The intensity of the (1 0 1) and (1 1 0) diffraction peaks goes up while that of the (0 0 2) diffraction peak diminishes with increasing oxygen partial pressure, as shown in Fig. 43 [223]. Hence, Leng et al. [223] conclude that growth on the (1 1 0) plane parallel to the surface becomes more dominant at higher oxygen partial pressure. The microhardness values obtained from  $TiO_2$  shown in Fig. 44 increase with oxygen partial pressure between 0 and  $1.7 \times 10^{-2}$  Pa. In vitro blood compatibility investigation indicates that the  $TiO_2$  film has longer clotting time, lower hemolytic rate, less amounts of adherent platelets, less aggregation,

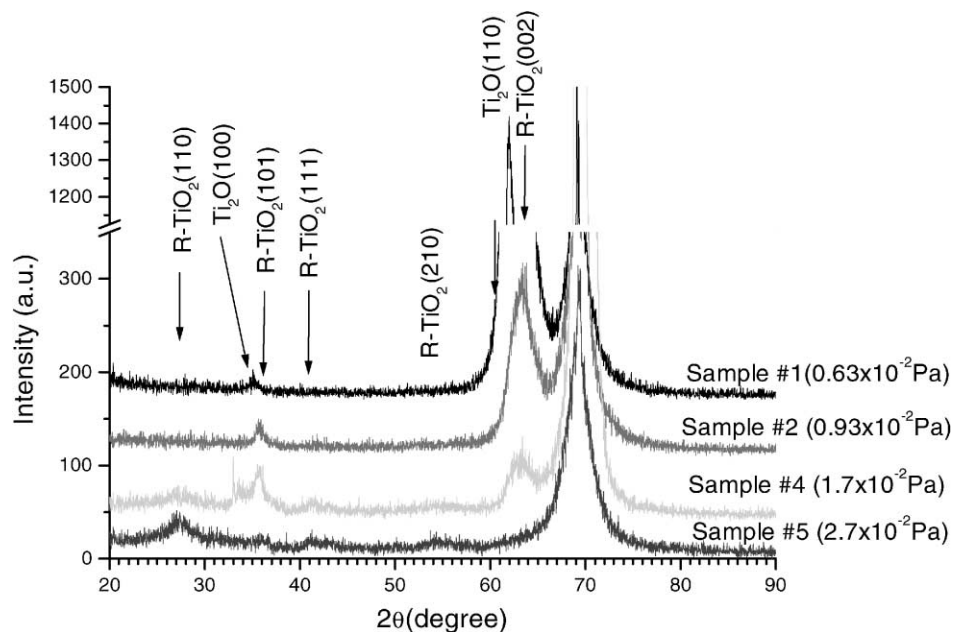


Fig. 43. X-ray diffraction patterns of the as-deposited titanium oxide films.



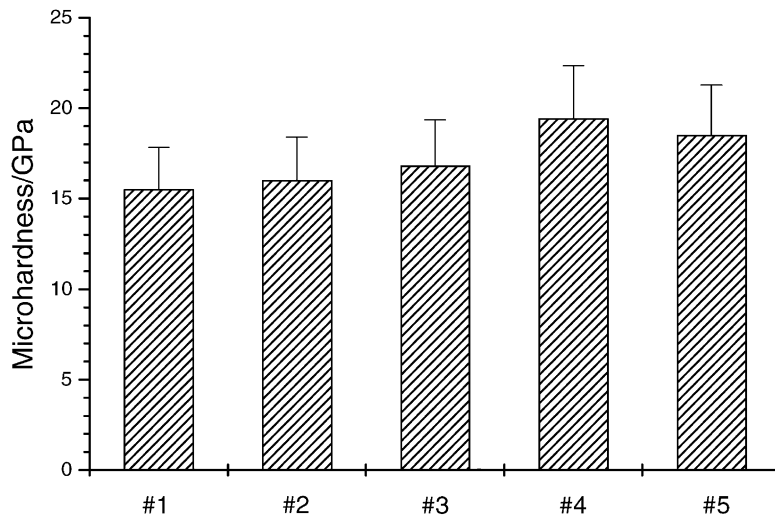


Fig. 44. Microhardness of the TiO<sub>2</sub> films in Fig. 43.

and less pseudopodium of the adherent platelet [223]. In vivo tests also demonstrate that the TiO<sub>2</sub> film has much better hemocompatibility than low-temperature isotropic carbon (LTIC) [224]. Fig. 45 displays the platelet adhesion results acquired from TiO<sub>2</sub> and LTIC.

In order to improve the mechanical properties, Leng et al. fabricate Ti–O/Ti–N duplex coatings on biomedical titanium alloys by metal PIII and reactive plasma nitriding/oxidation [225]. The presence of Ti–O improves the blood compatibility and the main effect of Ti–N is to improve the mechanical properties. Blood compatibility investigation reveals that the Ti–O/Ti–N duplex coatings are better than LTIC. In addition, tantalum nitride films with excellent mechanical and biomedical properties have been synthesized using a similar method [226]. Chen et al. prepare tantalum doped Ti–O/Ti–N and obtain good mechanical property and blood compatibility results [227]. Studies have shown that TiO<sub>2</sub> has good blood compatibility due to the n-type semiconductivity with a wider band gap of 3.2 eV, low surface energy, and low critical surface force. The good surface physical properties preclude fibrinogen from denaturation and consequently prevent the blood coagulation process [220,221,228,229]. Maitz et al. have used tantalum ion implantation–deposition to increase the X-ray contrast and hemocompatibility of vascular stents [230]. Further altering or improving the

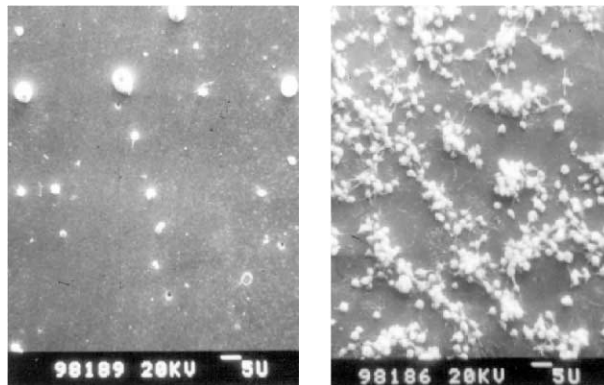


Fig. 45. SEM (1000 $\times$ ) images showing less platelet adhesion on TiO<sub>2</sub> (left) than LTIC (right).

surface physical properties of titanium based films by PSM appears to be the future direction of developing better blood contacting materials.

## 7. Plasma-surface modification of ophthalmic materials

The human eye is a complex organ and major target for a myriad of implants, biomaterial accessories, and devices. A wide range of biomaterials are used to fabricate ocular devices to correct functional deficiencies caused by disease, aging, and ocular trauma to improve, correct, or recover a patient's vision. There are approximately 35 million contact lens wearers in the US and over 1.65 million in the UK [231]. Lloyd et al. describe the importance of improving the ocular compatibility for longevity of indwelling ocular devices and indicate that surface modification is one of the methods to improve the biocompatibility of IOLs [231].

The structure of the eye and the essential physiological features are depicted in Fig. 46. Fig. 47 shows a typical intraocular artificial lens. These foldable lenses are manufactured from silicone elastomers, collagen co-polymers, poly(hydroxyethyl methacrylate) (HEMA) hydrogels and 'acrylic' polymers [231]. Fig. 48 shows the artificial lens for surgical correction of severe myopia and in the posterior chamber behind the iris, in front of the crystalline lens, and centered with the pupil [232]. The flexible haptics are supported in the sulcus. Systematic plasma-grafting techniques as well as the plasma glow-discharge grafting co-polymerization of artificial IOL (i.e. PHEMA onto a silicone base) and corneas have been developed to enhance the properties of these artificial lenses.

### 7.1. Artificial intraocular lens

Kim et al. investigate the effects of surface modification of poly(methyl methacrylate) (PMMA) by PEG grafting concerning cell adhesion. A commercially available IOL is modified and then inserted into the anterior chamber of a white rabbit [233]. Their results show that the mean number of adhered cells is  $72.5 \pm 22 \times 10^4/\text{ml}$  for the untreated PMMA. As shown in Fig. 49, after PEG

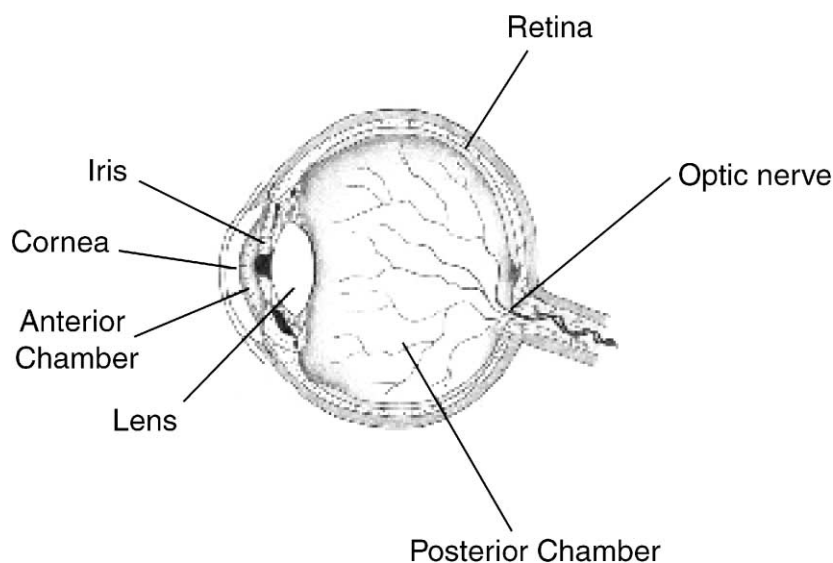


Fig. 46. Structure of the eye [231].

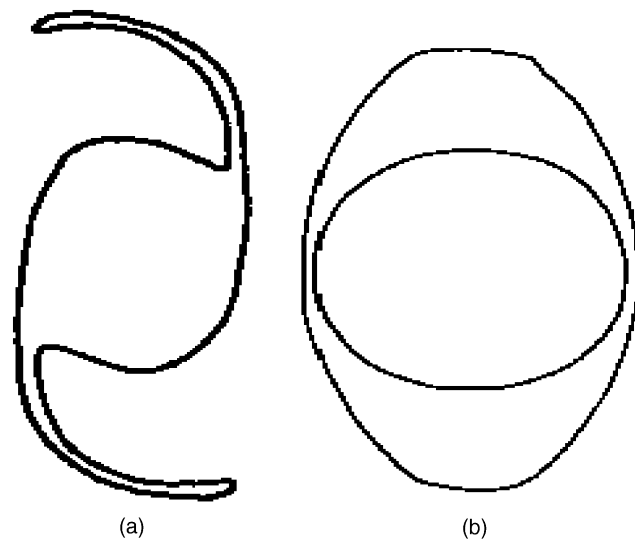


Fig. 47. Typical IOLs: (a) traditional design, (b) plate design [231].

grafting for 1 h and ozone oxidation for 2 h, the adherent cell counts decrease drastically to  $(6.5 \pm 1.7) \times 10^4$  and  $(7.6 \pm 1.6) \times 10^4 \text{ ml}^{-1}$ , respectively. Hence, surface modification of PMMA using PEG grafting reduces cell adhesion and decreases the incidents of retroprosthetic membrane formation after keratoprosthesis surgery.

Fig. 50 illustrates an example of improving the biocompatibility by modifying the retroprosthetic membranes posterior to the PMMA surface. It indicates that the anterior surface of the PEG-grafted PMMA also enhances the vision by stabilizing the tear film in the keratoprosthesis patient [233].

## 7.2. Cornea

Lee and coworkers study the surface modification of silicone rubber membrane for artificial cornea applications by grafting polymerization utilizing argon plasma glow discharge [234–237].

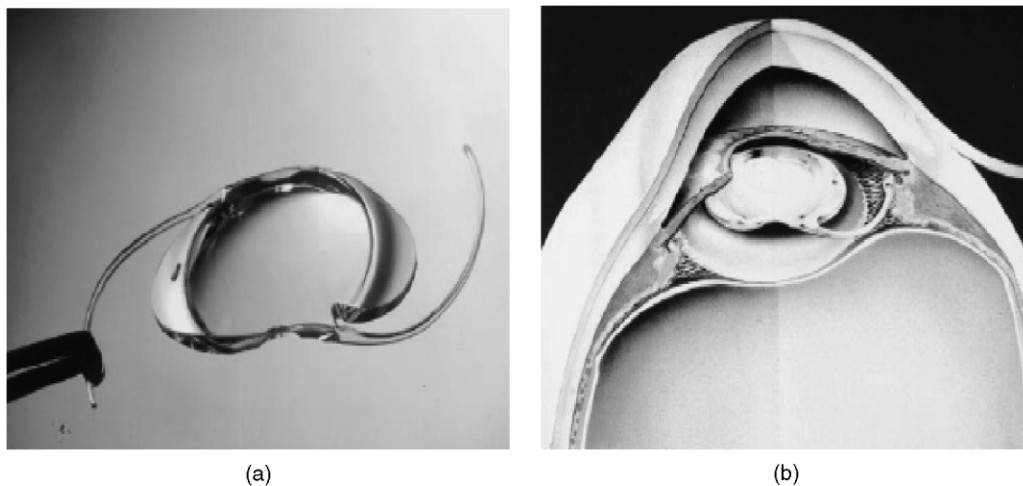


Fig. 48. Artificial lens for surgical applications to correct severe myopia: (a) the shape of lens, (b) installation of the lens [232].

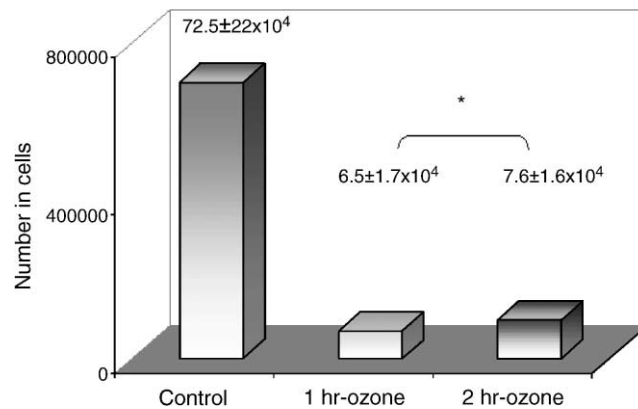


Fig. 49. Quantification of adhered cells on PEGA-grafted PMMA in a hemocytometer:  $P = 0.002$  (Kruskal–Wallis test),  $*P = 0.34$  (Mann–Whitney  $U$ -test) [233].

A method has been developed to produce various surfaces of silicone rubber membrane (SR) by grafting various amounts of poly(2-hydroxy ethyl methacrylate) (PHEMA) onto SR by plasma-induced grafting polymerization (PIP) [235]. Fig. 51 exhibits the surface concentration of generated peroxides and O 1s/C 1s values for silicone rubber membranes as a function of Ar plasma treatment time. The maximum value of the peroxide group is achieved for 60 s, and it is consistent with the O 1s/C 1s values. This condition may be the most active for plasma-induced grafting polymerization. The value of the peroxide group decreases with increasing Ar plasma treatment time, probably because of etching occurring on the treated surfaces of SRs. The influence on corneal epithelial cells (CECs) attached onto SR is deemed negligible. The *in vitro* investigation results in Fig. 52a show that after 8 h of seeding, CEC cannot attach itself to the surfaces of the control and Ar-plasma-treated SR and PHEMA

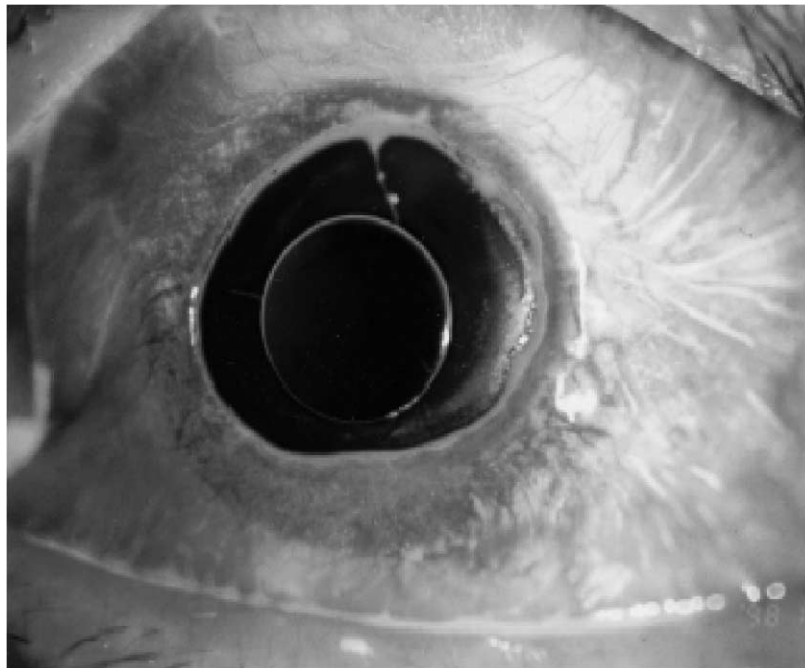


Fig. 50. Tear film stabilized on PEGA-grafted PMMA in a keratoprosthesis patient [233].

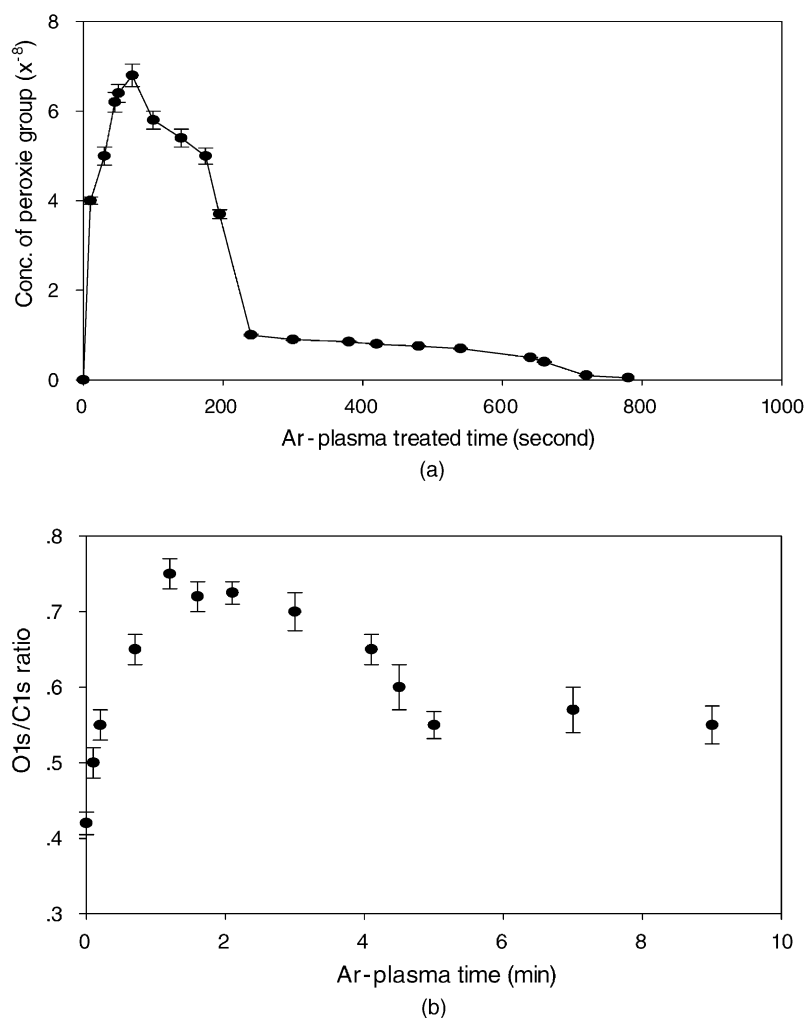


Fig. 51. Influence of Ar plasma treatment time on surface features of SR membrane: (a) concentration of peroxide group, by the 1,1-diphenyl-2-picrylhydrazyl (DPPH) method, (b) variation of XPS O 1s/C 1s values [235].

hydrogel, whereas a large of adherent CEC is found on SRs grafted with  $55 \mu\text{g cm}^{-2}$  PHEMA. The number of cells grown on modified SR determined by proliferation assay for 72 h is shown in Fig. 52b. The results suggest that CEC cannot grow on the control, Ar-plasma-treated SR, PHEMA hydrogel and SR grafted with  $570 \mu\text{g cm}^{-2}$  PHEMA. On the other hand, CEC grown on SRs grafted with  $55 \mu\text{g cm}^{-2}$  and  $75 \mu\text{g cm}^{-2}$  PHEMA shows a normal proliferation of CEC and is also confluent at 72 h. It, thus, implies that the treated surface provides an adequate environment for cell attachment and growth. Consequently, these membranes are implanted into the rabbit cornea to perform the in vivo biocompatibility study. The CEC is capable of covering the implant completely in 3 weeks, but down-growth of CEC occurs. Lee et al., thus, believe that heterbifunctional membranes should be developed in the future to prevent it from happening when the membrane is implanted into a rabbit cornea [235].

Polyacrylic acid (PAA) can be introduced into the plasma-induced grafting polymerization process when treating silicone rubber membranes [236]. Collagen (type III) is linked to the carboxylic group of PAA grafted onto the SR surface via a carbodiimine agent to obtain a secondary structure of SR. In the experiment, the SR linked to the collagen is removed by immersing into a

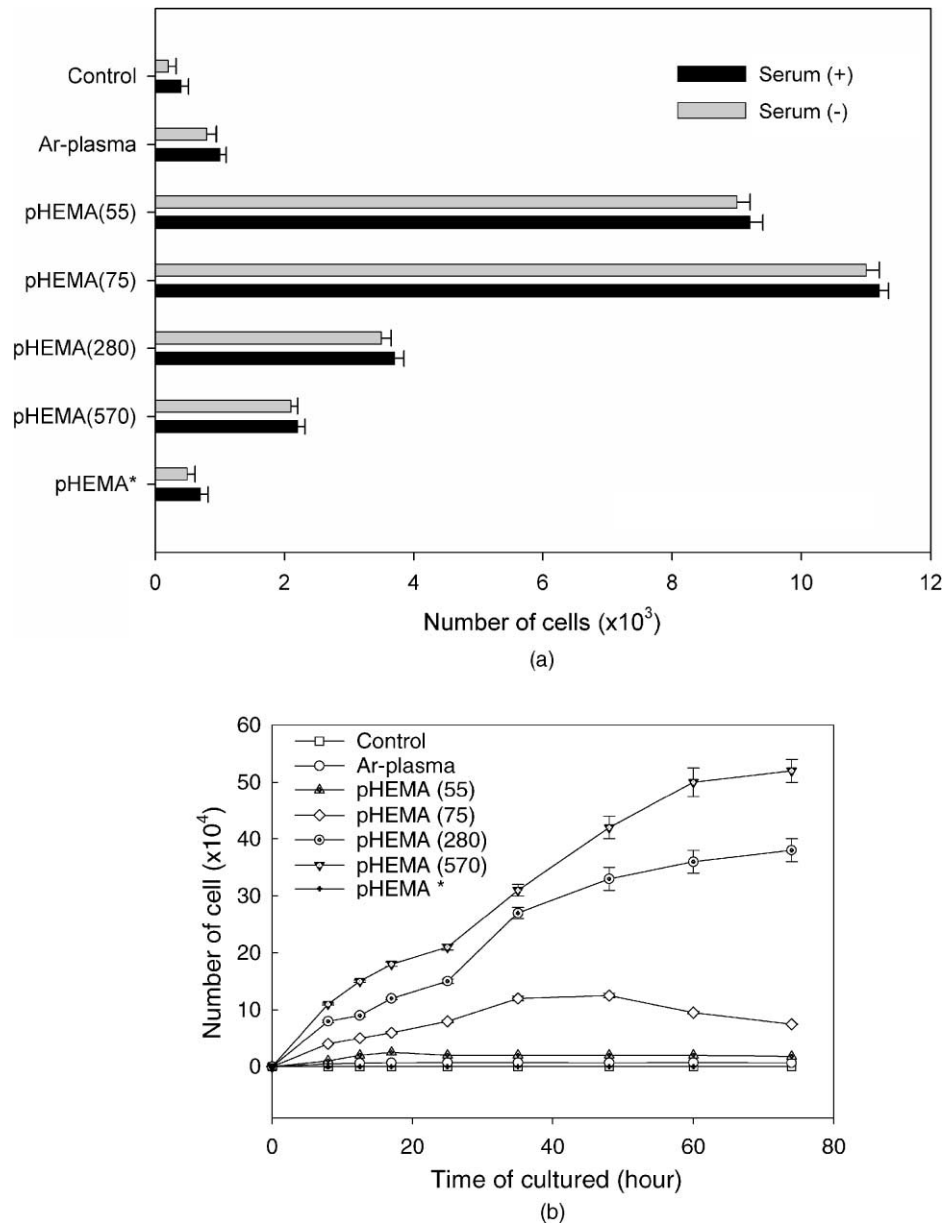


Fig. 52. In vitro investigation results: (a) number of CEC after 8 h seeding, (b) number of cells grown on modified SR determined by proliferation assay for 72 h [235].

buffer solution three times. The schematic diagram of each reaction stage is displayed in Fig. 53. The cell attachment and growth study reveals that the collagen linked to SR enhances the attachment and growth capability of the cells. Therefore, Lee et al. believe that the SR membrane fabricated by plasma-induced grafting polymerization of acrylic acid and subsequent grafting of collagen has promising potential because the collagen linked to the SR membrane provides an adequate environment for cell migration, attachment, and growth [236].

Hsiue et al. fabricate silicone rubber membrane for artificial cornea by grafting hydrophilic monomers such as 2-hydroxyethyl methacrylate (HEMA) and acrylic acid employing plasma

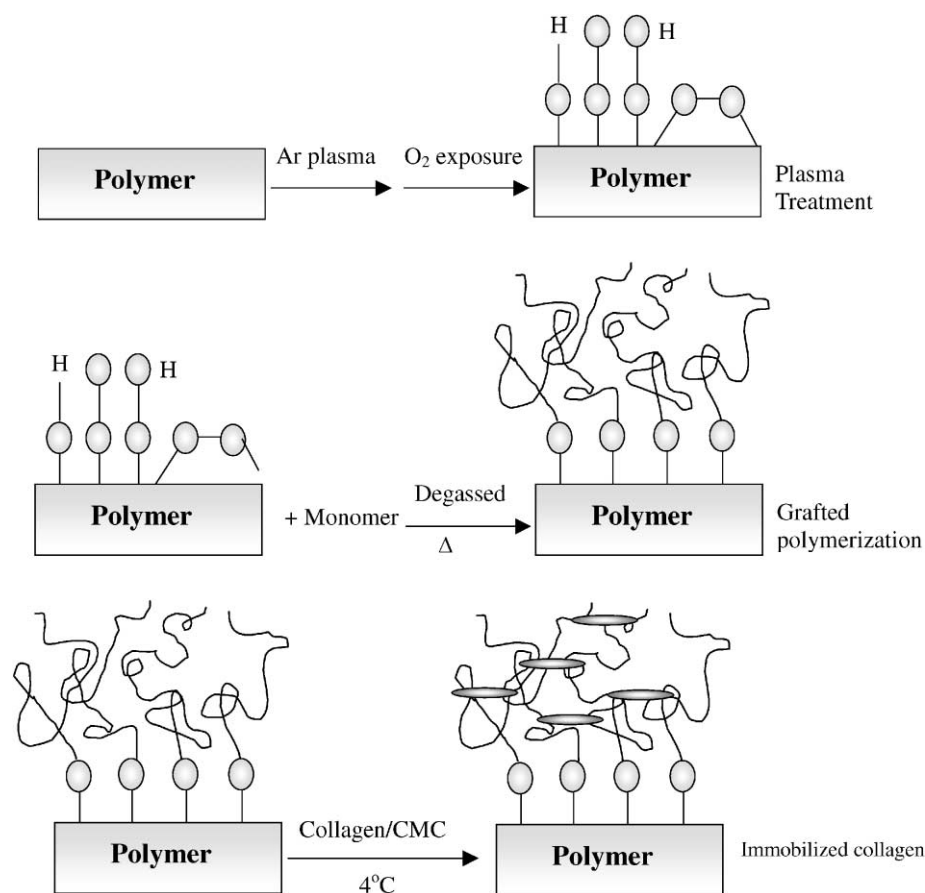


Fig. 53. Schematic diagram of immobilization of collagen on the SR membrane [236].

induced grafting polymerization [234]. The results demonstrate high biocompatibility for the modified SR membrane with the corneal epithelial cell. Chang et al. study heterobifunctional silicone rubber membranes (hetero-SR) prepared by grafting different functional polymers on each side of a silicone rubber membrane (SR) using plasma induced grafting polymerization [237]. A novel bifunctional membrane is developed with the upper-side favoring cell attachment and growth and the lower-side suppressing cell adhesion. Hence, a heterobifunctional membrane has high potential in artificial corneas.

Latkany et al. modify artificial corneas for optimal epithelialization by PSM using argon rf plasma [238]. It is found that cells become confluent on the argon-plasma-treated surfaces and turn multilayered after incubation for 2 weeks. At the same time, adhered proteins are present only when the surface is treated with argon rf plasma. The acetone- and ammonia-treated surfaces do not yield the desired results. The organ culture experiments further demonstrate the efficacy of the argon plasma technique. In addition, intact keratoprosthesis devices with modified hydrogel surfaces have been implanted into rabbit corneas, and it is found that the limbal epithelial cells can migrate to a synthetic cornea containing a modified hydrogel-treated surface and form a confluent surface of epithelium. The treated artificial corneas possess better biocompatibility.

These studies and results demonstrate that the plasma induced grafting polymerization technique can modify artificial corneas and intraocular implanted lenses. Tietze et al. [239] believe

that the use of multiple polymers with modified biological surface is promising in producing better IOLs and other prostheses such as artificial blood vessels. Attempts are being made to improve the surface wettability using plasma treatment. However, these modified surfaces tend to be unstable and, therefore, offer few long-term advantages. Many companies currently strive to improve the wettability of the lens surface by grafting hydrophilic polymers such as polyethylene glycols to the lens surface using plasma techniques.

## 8. Plasma-surface modification of other biomedical devices

Silicone rubber, besides being applied to make cornea, is the material of choice for a long-term indwelling catheter due to its biocompatibility and superior flexibility. However, the silicone surface is prone to biofouling and build-up of thrombosis that can cause catheter occlusion and necessitate catheter replacement surgery. Studies have demonstrated the efficiency of ion implantation in reducing biofouling of silicone rubber [6]. In this section, some examples related to ion implantation of silicone rubber and polyurethane catheters to reduce friction and biofouling are discussed.

The key to reducing biofouling is to increase the water wettability and critical surface tension of silicone rubber. The ion implanted surface has a critical surface tension of  $26 \text{ dyn cm}^{-1}$ , as opposed to  $14 \text{ dyn cm}^{-1}$  for the control surface as illustrated in Fig. 54. Baier, following the work of Zisman [240], predicts that surfaces with critical surface tension between  $20$  and  $30 \text{ dyn cm}^{-1}$  will resist biodeposits when exposed to body fluids [241]. According to this theory, the fibrinogen deposition rate is equal to the removal rate, and so one does not anticipate cumulative thrombus formation on ion implanted catheter tips. The work by Suzuki et al. verifies the reduction in thrombus formation on ion implanted silicone rubber catheters used at various locations in the bloodstreams of laboratory animals [242,243]. Test results in these animals using radionuclide markers reveal minimal thrombus formation in periods of 2 days to 4 weeks [6]. The study by Uldall [244] using ion implanted hemodialysis catheters in over 150 patients shows a remarkable reduction in thrombus formation. The treated catheters are placed in the internal jugular vein for up to 300 days. In the first 80 catheter insertions, only one case of jugular vein thrombosis can be attributed to the catheter. The technology is equally effective in the treatment of other polymers such as polyurethane to mitigate biofouling.

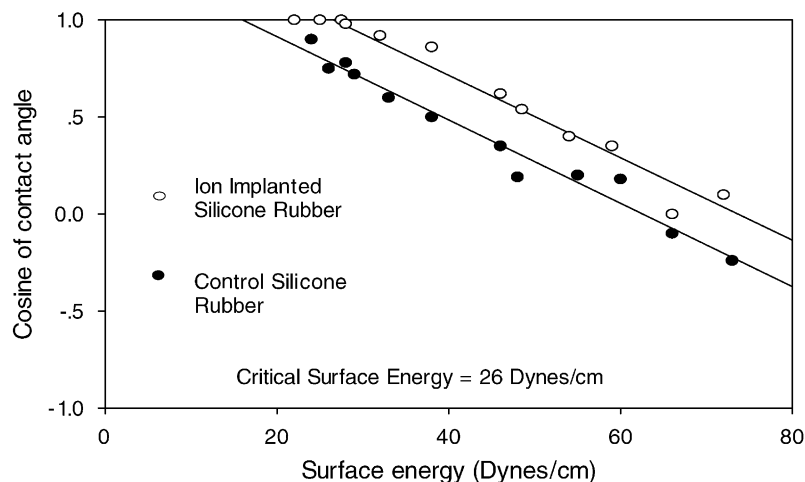


Fig. 54. Critical surface tension of ion-implanted and control silicone rubber.



It is also used on filters, membranes, and blood-collecting devices to increase the surface wettability and to minimize bubble formation. It is, thus, used on molds to enhance mold release.

Ion implantation modifies the surface tension on polymers to minimize biofouling [6]. Inoue et al. [245] select the segmented polyetherurethane (PU) as a polymer substrate in their surface modification study with the objective to improve the biocompatibility relevant to the expected clinical applications. The PU modification is carried out by surface grafting polymerization of the water-soluble monomers acrylamide (AAM) and dimethyl acrylamide (DMAA). The results by implanting the catheter tube into the inferior vena cava of rabbits from the exposed femoral vein show that the physiological liquid/materials surface compatibility is enhanced.

Nickel–titanium (Ni–Ti) and  $\beta$ -titanium ( $\beta$ -Ti) arch wires are frequently used in orthodontic treatment because of many desirable properties [6]. They are also used to manufacture vessel stents [246]. However, high frictional forces reduce their utility [247] because the high friction causes teeth to slide more slowly along the wire and forces the orthodontist to apply greater force thereby increasing the patient's discomfort. Ion implanting of Ni–Ti and  $\beta$ -Ti is shown to reduce the friction against stainless steel, the predominant material used for braces in orthodontics. In the case of  $\beta$ -Ti, the enhancement effect is nearly 75% [6].

The typical applications of biosensors include environmental monitoring and control and chemical measurements in the agriculture, food and drug industries. Biosensors can meet the needs for continuous, real-time in vivo monitoring and, thus, replace conventional analytical techniques [248,249]. The electrode supporting the substrate in biosensors can be a noble metal (gold or platinum), carbon rod or paste, or an organic conducting salt/polymer. The production techniques for the conductive supporting substrates are typically deposition, polymerization, plasma-induced polymerization, photolithography, printing, and nano-technology. The former four techniques are used to form mono- or multi-layers of a conducting film onto a supporting substrate in order to obtain direct electrical communication between the chemical/biochemical reaction site and surface. Plasma polymerization may offer a new alternative in biosensor interface design. The advantage is that an extremely thin ( $<1 \mu\text{m}$ ) film with good adherence can be produced. Furthermore, the film is pinhole free and both mechanically and chemically stable, and it allows a large amount of biological materials to be loaded onto the surface [250]. The manufacturing of integrated transducer arrays is now possible by means of plasma technology. The techniques have actually been used to increase the dynamic range and sensitivity of urea sensors [251]. However, further developments are needed to improve the long-term performance of biosensors in complex biological environments. This will inevitably involve the use of new biocompatible materials as well as novel PSM techniques. For examples, Inoue and his research institute plan to develop a biomimetic bone consisting of collagen fibers coated by appetites using ion/plasma engineering [13]. Modification of the surface of silicone probes by plasma discharge and subsequent hydrogel coating yields a less hydrophobic surface in some applications such as tracheal prostheses [252].

## 9. Summary and future directions

Plasma processes as surface treatment techniques are becoming more common in biomaterials engineering. In addition to increasing the wear resistance of orthopedic joints, plasma treatment can modify the surfaces of orthodontic devices, surgical tools and other sensitive medical components, where improvements in wear, friction, fretting and biocompatibility are required. With regard to polymeric biomaterials, the process selectively modifies the surface energy, enhances the bonding strength of substrates, minimizes biofouling, as well as hardness and scratch resistance. The most

important advantage of PSM is the ability to change the surface properties to become more biocompatible or better mimic the local tissue environment without altering the bulk attributes, thereby offering a high degree of quality control, yield, reliability and reproducibility that would be difficult by other conventional techniques. For instance, a given medical device may already have the appropriate physical properties, and PSM provides an easy means to alter only the biocompatibility of the device without the need to redesign the process, retool the entire manufacturing line, and retrain medical personnel. In spite of the high potentials, PSM is still in its infancy stage compared to other more mature biomedical techniques. The services provided by surface treatment vendors are varied but continuously expanding. New plasma treatment techniques as well as new generations of biomaterials are emerging to enable the design and production of better medical devices.

Lloyd [253] raised the question: ‘biomaterials—where are we going?’ Opportunities exist to develop new biotechnology through tissue engineering or to focus more specifically on mechanical solutions that may provide a quicker return on investment. In addition to the need for basic tissue-engineering research and good understanding of aging from the cellular standpoint, rapid

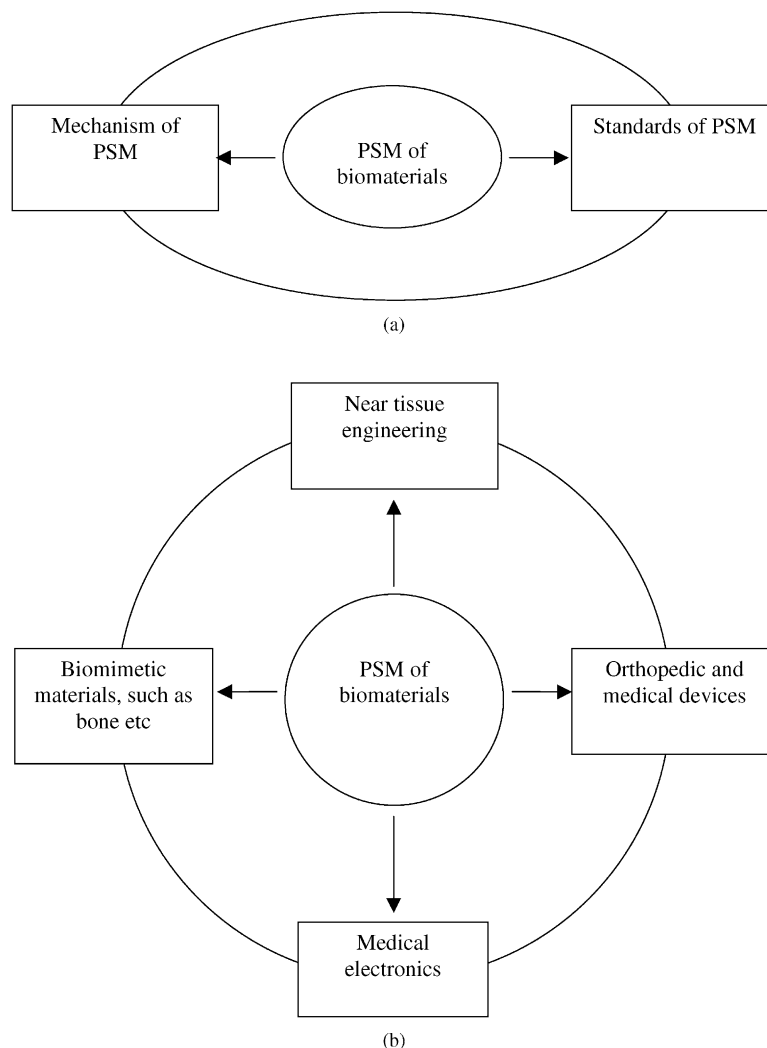


Fig. 55. Future trend and challenge of PSM: (a) basic research, (b) applications oriented development.

commercialization of functional devices is necessary. In this respect, PSM of biomaterials provides an effective means to modify the surface of existing materials to enhance the physicochemical properties and optimize the biological (biofunctionality) interaction, but wider acceptance in the medical field has several obstacles. For instance, it is still difficult to uniformly treat medical implants with complex shapes such as pedicle screws, stents, and small diameter artificial catheters or vessels, but improvement is foreseen. Biosensors will make more significant contributions in clinical real-time monitoring and in vivo diagnostics if the long-term performance of biosensors in complex biological environments is improved. The future trend and challenge of PSM is shown in Fig. 55.

The end products of biomaterials research are devices and materials that are mass-produced for use in humans. A surface modification process that is too complex will be difficult and expensive to commercialize. It is more appropriate to minimize the number of steps or design each step to be relatively insensitive to small changes in the experimental conditions. More importantly, in order to focus on the future important clinical development and avoid overdevelopment, effective collaboration among materials scientist, plasma physicists, clinicians, chemists, biologists, and bioengineers is imperative. The authors would like to thank Ricky K.Y. Fu for preparing some of the figures and thank Y.X. Leng and P. Yang for helpful discussions. The work was financially supported by Hong Kong RGC CERG #9040498 or CityU1032/00E, City University of Hong Kong SRG #7001177, NSFC #39770212, State Key Basic Research #G1999064706, and High Technology Project #00-863-102-09-01.

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