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Plasma Techniques in Polymeric Treatment for Membrane Applications: a Review

EWA ŁUKOWSKA*

Nałęcz Institute of Biocybernetics and Biomedical Engineering,
Polish Academy of Sciences, Warsaw, Poland

Polymers are the most often applicable materials in biomedicine. Technical developments require materials with specific surface properties. Low temperature plasma treatment is a method that competes with a classic physical or chemical treatment due to its time saving, economy. It also ensures modification of very thin surfaces of materials without any changes in bulk properties.

The article describes plasma techniques that modify materials which are used as substrates for proteins immobilisation, cellular or tissue cultures and materials which are exploited to produce artificial organs. Author focused on the popular polymers: polyarylosulfones, polyurethanes and polyacrylonitrile and its modification to various application: artificial organs, cellular and tissue cultures, bioreactors, biosensors and medicine dosage. The paper also provides the description of some technical solutions concerning plasma reactors with both vacuous and atmospheric pressure.

K e y w o r d s: low temperature plasma surface modification, plasma generator, membrane's modifications, plasma treatment

1. Introduction

The most commonly applied materials for bioengineering applications are polymers due to their excellent mechanical properties, chemical resistance and flexibility. Manufactures by injection holding and cost-effectiveness are of significant importance. However, their surface properties often do not meet the demands regarding scratch resistance, wettability, biocompatibility, gas transmission, adhesion or friction. Hence, additional surface modification is required to achieve the desired properties, while maintaining the characteristics of volume.

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* Correspondence to: Ewa Łukowska, Nałęcz Institute of Biocybernetics and Biomedical Engineering, Polish Academy of Science, ul. Trojdena 4, 02–109 Warsaw, Poland, email: ewaluk@ibib.waw.pl
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Plasma treatment is a method that competes with a classic physical or chemical treatment that modifies materials which are used as substrates for proteins immobilisation, cellular or tissue cultures and materials that are exploited to produce artificial organs. Polymers which are being modified by plasma technique are also used in medical appliance as separation methods and for medicine dosage.

Plasma technique ensures modification of very thin materials' surfaces without changing of bulk physical and chemical properties. In addition, this technique involves less chemical reagents intakes, it is less costly and easy to control and what is more, modifications are repetitious. For cellular and tissue cultures' purposes it also guarantees an excellent sterility of modified substrates.

2. Basic Information

2.1. Definitions

Plasma, the fourth state of matter, is a mixture of ionized (partially or completely) gas which consists of ions, photons, molecules, electrons, radicals and neutral particles. From macroscopic point of view, plasma is electrically neutral. However, it contains free charge carriers and is electrically conductive.

2.2. Plasma Generation

Temperature inside of low-temperature plasma is lower than 10^4 K. It is generated while electric discharges in gas, under the influence of oscillating electromagnetic field, in low-pressure chamber which is called discharging chamber. Average temperature in chamber slightly exceeds ambient temperature, and electrons' concentration stays between 10^{16}–10^{18} electrons/cm^3. Electromagnetic field is being created between electrodes in chamber (Fig. 1).

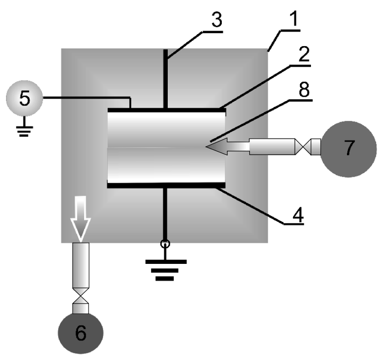

Fig. 1. Scheme of plasma generator with electrodes inside of discharging chamber: 1) enclosure of discharging chamber; 2) discharging electrode (cathode); 3) insulating bracket of discharging electrode; 4) grounded electrode (anode); 5) high voltage generator; 6) vacuum pump; 7) source of gas; 8) area of plasma creation. (Reprinted with permission [1] from the publisher 2000 Science Press (WNT), Warsaw, Poland)

Non electrodes system using large frequencies of feeding voltage is also applied. In those systems coil winding which is placed on outer walls of discharging chamber performs electrodes' function (Fig. 2).

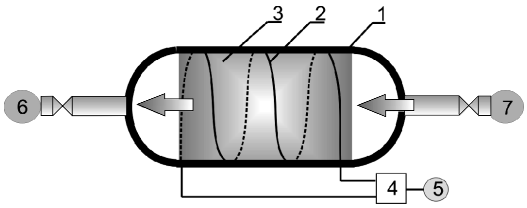

Fig. 2. Scheme of non electrodes discharging system: 1) wall of discharging chamber; 2) coil winding; 3) area of plasma creation; 4) matching system; 5) generator; 6) vacuum pump; 7) source of gas. (Reprinted with permission [1] from the publisher 2000 Science Press (WNT), Warsaw, Poland)

2.3. Discharge Models

Electric discharges in gases show differences depending on work parameters. The basic parameters of generator are:

- type of gas,
- gas pressure,
- temperature of gas,
- intensity of electric field,
- uniformity or nonuniformity of electric field,
- type of electric field (constant discharges or impulsing discharges),
- frequency of electric field,
- power of the electric field source,
- intensity of discharge current,
- presence or absence of magnetic field,
- electrodes' material,
- shape of electrodes,
- temperature of electrodes,
- walls' material of reactor,
- walls' temperature of reactor

Intrinsic discharges can be divided into: dark, corona, glow, spark and arc. Whether it will find itself in one or another type of those discharges depends on: pressure of gas, intensity of discharge current (potential difference) and resistance outer discharge circuit.

3. The Usage of Plasma Treatment

Plasma treatment can be used in many different fields, especially due to the ability to modify different materials (ceramics, polymers, glass, textiles), and mentioned before, diversity of electrical discharges. From a bioengineering point of view, the surface treatment of polymers which is made by using glow or corona discharges in radio or microwave frequency is of paramount importance.

The advantages of plasma treatment:

1. Ability to impose thin surface's layers (2–20 nm) that show high resistance to delamination;
2. Ability to use different types of substrates: polymers, metals, ceramics, glass;
3. No need to special surface preparation;
4. Changes can be made on very thin surface's layers without destroying the interior structures of substrates;
5. The process is fast (seconds);
6. The layers which are modified by plasma are not toxic for the fragile cellular and tissue cultures and what's more, they are sterile;
7. The costs of modifications are low;
8. A strong, specific interaction can be seen between most of the layers made by plasma and biological systems [2].

Those advantages cause high interest in the plasma modification, both of plastic and other materials for the bioengineering purpose. The way each material is being made depends on its purpose and use. Thus, for instance, materials intended to create artificial organs have to be characterized by both biocompatibility and minimal cell and protein adhesion. In turn, polymers dedicated to cellular culture have to be characterized by strong cells adhesion and hydrophilic properties and ability to introduce active centres (Table 1). Most of the modifications can be done by plasma functionalisation. Only biomolecule's immobilisation cannot be done with this method due to very high temperatures in generators that causes protein denaturation.

4. Types of Plasma Generators

Plasma generators are being widely described in literature [33, 68–75]. Typically, low temperature discharges are conducted in radio or microwave frequency and in pressure in range from 10^{-1} to 10^{2} Pa. Polymers can be modified without fear of destroying their structure, because those processes proceed in low temperatures. The main disadvantage of low pressure discharges is high cost of vacuous systems. Therefore, the reactors in which discharges in atmospheric pressure are being conducted, are very attractive alternative. There are two types of the plasma reactors operating at atmospheric pressure.

The first one is based on corona discharge. It is characterized by an asymmetric electrode arrangement – point-to-plane or wire-to-plane. The corona discharge can be used for many chemical reactions, with the usage of reactive gases or gaseous

Table 1. Modifications of polymers for biomedical application

Artificial organs	Cellular and tissue cultures	Bioreactors	Biosensors	Medical devices based on separation	Medicine dosage
Biocompatibility [3–7]	Biocompatibility [3, 4, 6, 8–11]	Decrease of fouling effect [12–14]	Increase of hydrophilic properties [15–18]	Biocompatibility [17, 19–22]	Biocompatibility [17, 19–21]
Decrease of cell's and protein's adhesion [23]	Bringing in of active centres [6, 24–31]	Introducing of active centres [32, 33]	Adding of active centres [15, 24, 34, 35]	Adding of active centres [36–38]	Providing with adequate structure [39]
Providing with adequate structure [40–42]	Providing with adequate structure [40, 43–47]	Hydrophilic properties [18, 39]	Grafting [34, 48–50]	Decrease of fouling effect [12–14]	Introduction of activity center for biomolecules and specific ligands immobilisation [51–55]
Biodegradability [5, 43, 45, 56–59]	Increase of cell's adhesion [14, 44, 60–65]	Giving of adequate physical structure [40, 43–47]	Immobilization of enzymes and antibodies [35, 66, 67]	Immobilization of specific proteins (e.g. heparinisation) [20]	
				Providing suitable quantity of voids [43]	

substances because high-field electrode can be dipped in gas media. The planar electrode is situated far away from the place where ion and free radicals are being created, and only slight amount of them reach the restricting place where surface treatment is being conducted.

In the second type of reactor two planar electrodes with coaxial or parallel geometry, which are situated very close to each other, have to be applied. In such type of a reactor, discharges which are formed in the one electrode can easily reach another one, causing spark breakdown in the full extent of the interelectrode's scope. One or both electrodes are covered with dielectric material in order to save from penetrating. The streams of discharges, in contact with the dielectric, tend to spread across and form the surface of discharge. The whole process of forming, spreading and extinguishing discharges lasts a few nanoseconds and leads to creation of low temperature plasma, also in high pressure (from 100 mbar to a few atmospheres) [68].

There are in principle two kinds of plastic surfaces modification which are conducted in the plasma generators: plasma treatment and plasma polymerisation. The plasma treatment is a process whereby the polymer is not being formed, and can run in chemically reactive or non-reactive plasma atmosphere. It is a mild technique of generating of hydrophilic surfaces, increasing or decreasing of permeability and introducing of active centres which are able to immobilisation of enzymes, specific proteins, antibodies [76].

The plasma polymerisation involves polymers' formation by reason of incomplete discharges and leads to the setting of permanent, ultra-thin layers of the polymer on the substrate of membrane, and it does not bring the destruction and deformation of the membrane in the deeper layers [77–79]. Nowadays it is one of the better techniques of obtaining a composite membrane for separation [76, 80] as well as materials for biomedical usage [19, 81, 82].

For the biomedical purposes most of the modifications concerning the changes of the structure of the plastic's outer layer are performed with usage of low temperature plasma (Table 1). Plasma technique can be applied to adding polar groups (e.g. $–NH_2$; –OH; –COOH; $CONH_2$) to the hydrophobic surface of polymers in order to ensure hydrophility, enabling immobilization of the specific biomolecules and increasing of cells' adhesion. It finds the application in producing of materials for medicine [14, 21] and producing of semi-permeable membranes for variable applications [18, 30, 83], therein proteins' separation and fractionation. The increase of adhesion, and, as a result, the increase of ability of cells' accretion by the increase of hydrophilic properties, protects from the fouling effect and enhance the transport membrane's abilities [84]. Plasma surface's modification in the presence of gaseous compounds (e.g. acrylic acid) leads to adding –COOH groups [37]. A substrate with such changes of structure can be applied to cellular culture, immobilization of biomolecules and bioreactors [25].

Plasma technique can change free surface's energy of polymers by changing polarity, ability to soak (hydrophobic properties) and adhesion features [14, 79]. The activation of surfaces takes place during the plasma process, mainly by removing hydrogen and creating/producing radicals, which causes only modification of the thin outer/exterior layer with the thickness of nanometers. Furthermore, plasma can do such modifications, which cannot be achieved by classic methods [85]. Modification of polymers with void structure e.g. polysulfones or polyethersulfones change their hydrophilic/hydrophobic properties [18, 21, 86]. Plasma treatment in the nitrogen atmosphere is widely used for polymers' membranes modification. There are systems which are applied to introduce amine, imine, amide, nitrile and other groups [38, 87]. Implantation of amino groups with surrounding changes of polarity and reactivity can be broadly applied to creating of biocompatible materials and substrates which are used to immobilize antibodies [25].

The porous membranes' ability of adsorption, biomolecules' adhesion and its permeability and hydrophilic properties can be changed by covering them with ultra-thin monomer or polymer active layers. This way, microfilterable, ultrafilterable polysulfonic membranes can be saved from fouling phenomenon (polluted by adsorbed biomolecules) [88]. Heterogenic grafting or graft copolymerization induced by plasma is a very attractive alternative for typical chemical techniques as it is the combination in situ of both layers' formation and addition. Treating of hydrophobic membranes with oxygen or nitrogen plasma produces hydrophilic changes and pores increase [89]. By adding of acrylic acid to the plasma chamber, the ultrafiltration is improved [82]. Ammonia plasma has been used to polysulfonic membranes' functionalisation which has improved selectivity and filtration of molecules with smaller molar mass [88]. Hemocompatibility's improvement has being achieved by covering of polysulfonic membranes with thin hydrofluorine layers [19].

Hydrophobic character of polysulfone is the reason of protein adhesion (fouling) which most probably results from proteins' denaturation on the polysulfonic membrane's surface [90]. The methods of modification of surfaces of polysulfonic membranes in order to increase hydrophilic properties in the heterogenic or homogenic reactions have been described in the literature [66, 91–93]. The selection of reaction conditions (dissolvents, catalyst, temp) allowing to avoid destroying of microporous structure and polymer degradation is complicated [13, 93–95]. The plasma treatment does not require such restrictive conditions, and the selection of process' parameters is much easier. An asymmetrical, polysulfonic membrane has been successfully used as a solid support for composite membranes [36]. The increase of hydrophility of polysulfonic membranes has been obtained in the plasma treatment with water vapour [16]. Another method for the increase of hydrophilic properties and simultaneously the decrease of fouling effect is membranes grafting by monomers in plasma [88]. The hydrophilic surface has been obtained with grafting by poly(2-hydroxy-ethyl)methacrylate (PHEMA), acrylic acid (AA) or methacrylic acid (MAA). This way the surfaces of polysulfonic and polyacrylonitrile membranes have been modified. Polyethersulfone membranes has been modified by a very similar approach. The membranes have been grafted in the plasma reactor with corona discharge by PHEMA and AA. Oxygen has been used as a carrier gas [12].

Other authors modified polysulfone in amine plasma to immobilize enzymes (glucoisomerase) later on [38]. Amino groups have been substituted with the usage of plasma generator with ammonia or amines used as a reactive gas [96, 97]. Such modified membranes have been used to form substrates for cellular culture [98] and to change proteins adsorption [17, 99].

Polysulfonic membranes have been modified by n-butylamine in plasma of microwave frequency [100]. Authors have examined two competitive processes proceeding in plasma environment where compounds of n-$BuNH_2$ which are capable of polymerization are present: digestion and covering. Whether obtained pores are increased or decreased is dependent on the speed of process (Increasing or decreasing of obtained pores depended on the speed of process). Argon presence stabilizes plasma yet makes process more aggressive. Plasma with n-butylamine decreases pores, whereas its mixture with argon increases.

Polyacrylnitrilic membranes have been improved by chemical modification of nitrile group [101, 102]. Acrylic monomers grafting and plasma treatment in helium atmosphere and in helium with water vapour increases hydrophility with a few permeability changes. During the process of inducing in plasma nitrile groups cyclise and form aromatic structures [88, 103].

Polyacrylonitrile membranes have good thermic resistance (to 130°C), and excellent chemical resistance [76]. Classical methods of phase inversion cannot be used to produce nanofiltration membranes (NF) and reverse osmosis (RO) because too big pores are formed, therefore, to such a purpose plasma treatment in noble gas (which does not form polymers) or hydrogen is used. NF and RO membranes have been made by plasma technique by monomers grafting [104]. Other authors made RO membrane by plasma polymerisation with allylamine [105]. Polyacrylnitrilic membranes for RO and water desalting have been modified by argon, helium and oxygen plasma, and plasma grafting with acrylic acid used as a monomer [76].

Polyurethane is a widely applied polymer in bioengineering, because it has very good mechanical resistance, high degree of elasticity, biocompatibility and also excellent stability during long times of implantation. Plasma treatment in nitrogen atmosphere is an ideal technique for the increase of polyurethane membranes' wettability. There are two kinds of processes which are proceeding; activation of surface by polar group addition, and radicals able to further reaction formation. Nitric plasma is less aggressive than oxidizing plasma and mainly causes polyurethane surfaces' pickling, which has a great impact on adhesion features [106].

Using oxygen plasma makes winning medically pure polymer to cells immobilization or tissue culture possible. Polyurethane has been obtained without impurities, in polymerization without additive: catalysts, dissolvents, fillers, and it has been modified in oxygen plasma [107].

Argon plasma activation is less destructive than equivalent nitric or oxygen plasma activation. Plasma treatment results in partial polymer's chains' degradation on surfaces, which changes membranes features. Hydrophobic properties of outer layers of polyurethane membranes have been increased by adding fluoric compounds to the inert gas in reactor. Also, the porosity of the membrane has decreased. Functionalisation has been proceeded without polymer's degradation on the surface. The membranes have been easy to clean and resistant to mechanical damage [108, 109].

Other authors have grafted polyurethanes and silicones with acrylic acid. Layers which have been obtained on the surface of the treated material were similar to the films which have been made in a traditional way from poly(acrylic acid). With this method features of membranes' permeability have been modified [110, 111].

Low temperature plasma has been used for cleaning of carbon and polymer surfaces, glass and metal, from impurities such as oxidized layers, weakly bounded top layers, degraded chains, stabilizers and additives which changes surfaces' features. It is possible in plasma with the presence of noble gases, oxygen (organic substances' oxidation) and hydrogen (oxide and sulfide reduction) [112, 113].

With the aim of increasing the number of carboxylic and sulfonic groups on the surface, polyurethane has been grafted with thioles. It has resulted in increase of biocompatibility and mechanical features' improvements in comparison with non-grafted polyurethane. Carboxylic groups in light segments of chains have increased mechanical resistance and ability to adsorb proteins. Such polymers have been used to tissue culture [114].

Whether the surface can be modified with heavy particles in higher temperature or with light particles in lower temperature is dependent on architecture of generator and on distance between sample and active electrode [115, 116]. In the distant plasma, radicals interact with polymer's surface and take part in the functional group formation. While the surface is not bombarded with ions and electrons. This way ethylene-co-tetrafluorethylene (ETFE) has been modified with oxygen, hydrogen and argon plasma. Selective modifications of CH_2-CH_2 and CF_2-CF_2 groups have been performed. Hydrogen plasma has reacted with -CF_2, whereas oxygen plasma with both of groups [117].

Two new types of generators to homogenic low temperature plasma production deserve attention. Glow discharge plasma is produced in the generator which is made of cathode with the shape of a needle and a cylindrical anode with the inside covered with non-conductor. In the second type of generator, a cathode is made of a cylindrical and flat part, and an anode is a disc which is parallel to the flat part of the cathode (Fig. 3). Instead of non-conductor or dielectric, an aluminum with the electromechanically oxidized surface has been applied to the electrode [69].

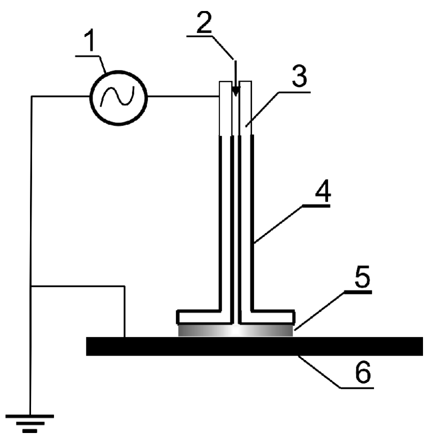

Fig. 3. Schematic diagram of atmospheric pressure cold plasma generator: 1) RF 13.56 MHz; 2) He-gas; 3) cathode; 4) oxidated layer; 5) area of plasma creation; 6) anode

5. Conclusion

Plasma treatment is a very attractive method of industrial modification as a simple, easy to apply, reliable, which does not produce pollutions and not expensive technique.

Plasma modification proceeds only in thin outer layer up to few hundreds nanometers thick and properties in bulk do not change. Moreover, the plasma treatment is a sensitive and delicate modification technique which does not cause problems with toxic discards as it is in chemical treatment. Plasma consists of electrons, ions, and radicals which can interact with material surface and modify its chemical and physical features. Plasma can cause such effects as: cleaning, digesting, grafting, addition, substitution, crosslinking and producing of new chemical structures (functional groups) both in situ and as an effect of exposition to atmospheric conditions. Such effects depend on presence and type of active particles in plasma.

In literature there are two kinds of generators of plasma described: generator with nearby plasma and with far plasma. For plasma treatment different gases are applied: argon, helium, hydrogen, nitrogen, ammonia, nitric oxides, oxygen, carbon dioxide, sulfur dioxide, water. In the atmosphere of inert gases, treatment which is less aggressive leads to surfaces' etching and to pores' increasing. Oxygen increases hydrophility by adding functional groups which consist of oxygen: carbonyl, carboxyl or hydroxyl to the surfaces. Nitrogen produces amine, imine, amide groups. While fluorine plasma is used to increase hydrophobic character. Furthermore, monomers as additives are applied, such as the most popular acrylic and methacrylic acids, and other compounds (e.g. tetrafluormethane) which allow to surface treatment grafting.

Regarding reviews can lead to the conclusion that plasma treatment is suitable for polymer materials' surfaces' preparation for biomedical purposes such as cellular and tissue cultures or biomolecules immobilization. From all variable techniques, the most proper ones are those techniques which require using generators with atmospheric pressure, because it does not require pressure chambers. In order to obtain functional groups on the surface, there are such active gases as: nitrogen, ammonia, oxygen and also water vapour and simple, volatile amines. It will guarantee that on the surface of polymer amine, imine, amide, hydroxylic, carbonylic and carboxylic groups obtain. All of these groups allows adding of biomolecules to the surface of the material.

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