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Review

Biomedical applications of plasma polymerization and plasma treatment of polymer surfaces

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Thin polymer films obtained by plasma polymerization usually show good biocompatibility when compared to classical biomaterials such as Silastic. The thicknesses of these films (from several hundreds of Å to several μm) make them suitable for the purpose of changing the surface properties of the substrate without altering its bulk properties. Both the above features together indicate the possible biomedical use of plasma polymerization as well as plasma treatment of polymer surfaces processes. The purpose of this review is to present the most significant efforts to develop such applications with the specification of particular fields where these efforts are directed.

Keywords: Polymerization, plasma, surface properties, biocompatibility

When an organic vapour is introduced into an electric glow discharge of a gas, such as He, Ar, etc., or an electric glow discharge is created using an organic vapour alone, polymeric material deposits on surfaces exposed to the glow. Such a group of materials are generally recognized as 'glow discharge polymers' or 'plasma polymers'. In the latter case, 'plasma' refers to an ionized state of gas. Since the word 'plasma' is used in the biological sciences, some workers prefer to use 'glow discharge polymerization' in order to avoid confusion. Although glow discharge is only a kind of plasma, as far as the formation of polymeric materials is concerned, 'glow discharge polymerization' and 'plasma polymerization' can be used synonymously, at least for all practical purposes.

Plasma polymerization has unique practical advantages which include (i) conformative ultra thin film deposition, (ii) good adhesion to the substrate material, and (iii) chemically stable and physically durable nature of the polymers. Consequently, plasma polymerization has drawn considerable attention in the past decades, from viewpoints of possible applications and of academic interest. A review on glow discharge polymerization appeared recently and the details of polymerization may be seen in reference 1.

Because of these advantageous features of plasma polymers, one of the very obvious areas of application of plasma polymerization is biomedical application, where the modification of surfaces without altering the bulk properties of materials deserves special merit. The surface modification of materials, particularly of polymeric materials, can also be achieved by non-polymer forming plasma; e.g., plasma of oxygen, nitrogen and argon, etc., and such a process is termed as plasma treatment of surfaces. Except that no polymer deposits on the substrate surface, the process is essentially the same. In many cases, equipment for plasma polymerization can also be used for plasma treatment of surfaces; however, plasma polymerization generally requires more elaborate set up than that for plasma treatment.

Despite considerable amounts of effort to use plasma polymerization and plasma treatment in biomedical materials, relatively few publications appeared in recent years. This may be due, at least in part, to the complexity of the subject and the difficulty of presenting quantitative data. For instance, one of the reviewers (H. Yasuda) has been reluctant to publish data in this particular area of application due to the difficulty of obtaining clear-cut interpretation of test results, although over eight year's study was carried out on blood compatibility of plasma polymers.

The complexity of the subject stems both from the complexity of the biological phenomena and from plasma polymerization or plasma treatment. For instance, vague terminology such as blood compatibility or biocompatibility are often used in literature; there is no clear-cut definition of blood compatibility or biocompatibility and data presented are often of a very narrow view on a special phenomenon related to blood or biocompatibility.

Plasma polymerization and plasma treatment deal with overall effects of very complex reactions and the processes are highly system dependent. It must be noted that there is no process which can be defined by plasma polymerization of a monomer nor any material that can be fully described as plasma polymer of a monomer, e.g., ethylene. In other words, using an organic vapour, e.g., ethylene, a wide variety of materials can be formed under

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the influence of plasma. This is a strong contrast to the conventional polymerization methods. Polymerization of ethylene by conventional methods produce materials which can be, by and large, characterized as polyethylene. This aspect is particularly important for evaluation of the true value of plasma polymerization and plasma treatment in biomedical applications.

Although most practitioners of the processes are aware of the system-dependent aspect of the processes, there is the obvious tendency to draw conclusions in general terms of plasma polymers or plasma treatment. Another notable trend found in literature reviewed is that studies are more or less on an exploratory basis and of a preliminary nature, lacking in-depth studies and conclusive evidence. Therefore, the entire subject should be dealt with awareness of these factors. Pessimistic indications do not necessarily mean that the processes arenot suitable for such applications. Conversely, the promising findings do not necessarily guarantee successful use of the processes in biomedical applications.

Although, as it was mentioned above, the clear-cut definitions of biocompatibility as well as blood compatibility do not exist, the respective keywords have been used in this review, and in order to simplify its organization, subject areas related to these keywords have been grouped in the following sections.

BLOOD COMPATIBILITY

One of the early attempts to improve the biocompatibility of polymer surfaces by means of plasma treatment has been done by Hollahan *et al.*[2]. The authors used either hydrogen-nitrogen or ammonia plasmas to introduce amino groups onto the surfaces of some conventional polymers. The polymers chosen for this study were considered in these times as the possible candidates for the artificial heart materials and they were as follows: poly(vinyl chloride), polytetrafluoroethylene, polycarbonate, polypropylene, polyurethane and poly(methyl methacrylate). The idea of the work was to quaternize the plasma introduced amino groups to create sites which would then be able to form stable complexes with the negatively charged sulphate ester groups of heparin which was known as a good blood anticlotting agent. The following reaction has been used in order to quaternize the sites:

$$-NH_2 + 3CH_3I \xrightarrow{CH_3OH} -[N(CH_3)_3]^+I^- + 2HI$$

The polymers have been then complexed with heparin, tagged with radioactive ^{35}S, which enabled to calculate the attached amino sites concentration. Since the reflective i.r. analysis failed to show any $-NH_2$ groups at the polymer surfaces the heparin attachment was the only proof of their existence.

In general, the concentration of amino groups increased with increasing discharge power and reaction time. Usually the ammonia plasma seemed to work similarly to nitrogen-hydrogen plasma with some variations along the polymers used. The highest amino groups concentrations were obtained in the case of $CaCO_3$ filled poly(vinyl chloride) subjected to ammonia discharge. In every case reported, the plasma treatment led to heparin attachment which retarded the coagulation of blood but did not prevent it.

A number of quantitative results of blood coagulation tests have been reported in the work of Yasuda *et al*[3]. The authors employed the statistical analysis of blood coagulation time test known as Linholm blood coagulation test and applied to some plasma-polymerized ultra thin (500 Å) films. They polymerized the following monomers: tetrafluorethylene, hexamethyldisiloxane, ethylene/N_2 mixture and allene/N_2/H_2O mixture. In most cases they used Mylar films as the substrates but some additional experiments using such substrates as porous and nonporous polysulphones and Silastic films have also been done in order to follow the substrate influence on the results of blood coagulation tests. The control tests have been performed with noncovered Mylar films as well as with argon plasma treated glass slides. The results of this study shown in *Table 1* indicate the significant increase of blood coagulation times on the Mylar surfaces covered by plasma polymerized thin films. The best results were obtained in the case of ethylene-nitrogen mixture polymerization; Mylar samples covered by this monomer combination showed coagulation times about 40% longer than the uncovered samples. As far as the substrate material influence is concerned the authors chose only hexamethyldisiloxane as the monomer for this study. The results indicated no particular difference existing between the substrates with an exception of porous polysulphone which showed about 15% shorter coagulation times than the remaining ones. This difference seems to be a result of the porosity of the substrate which may still influence the outer surface of the coating which is actually extremely thin.

One of the most important conclusions drawn out of this work, besides the general trend of blood compatibility improvement for plasma covered substrates, is that the reproducibility of the surface prepared by glow discharge polymerization is very good. The standard deviations of every test result were usually within the range of 10%. Since the reference surfaces (uncovered Mylar films and argon plasma cleaned glass slides) showed at least the same range of deviations the results of this statistically performed study should be considered to indicate the good reproducibility of plasma polymerization.

Further studies of blood compatibility of selected plasma polymers (tetramethyldisiloxane, tetrafluorethylene) have been carried out using various *in vivo* and *ex vivo* testing procedures. Although data are not published in journals, they are available in a series of Annual Reports[4]. Some of these results are also cited in a number of review publications dealing with polymer surfaces interaction with blood[5-8].

The findings of studies may be summarized as follows.

Since each testing procedure, *in vitro, in vivo* and *ex vivo,* requires a special form of samples and the adaptability of polymer sample preparation (including other conventional polymer preparation) to such a required form of sample tends to influence results obtained by each testing procedure. In any case, no single polymer, (regardless of conventional polymers or plasma polymers) scored the highest ratings in every testing procedure. However, if the ranking of surfaces for each kind of testing is taken, and the rankings of a particular polymer surface are averaged over different testings, plasma polymer of tetramethyldisiloxane and plasma polymer of tetrafluorethylene with high oxygen content are ranked at the top group of surfaces which have been tested. Therefore, it appears that some plasma polymers are very promising as the biomaterial surface with contacts in blood.

Table 1 Statistical evaluation of Lindholm blood coagulation time values (min) for glow discharge polymers and controls[3]

Lindholm clotting time							
Date tested		Allene, N_2, H_2O	Tetrafluoro-ethylene	Hexamethyl-disiloxane	Ethylene N_2	Mylar control	Argon-treated glass control
3-28-74	Test 1	124	104	128	136	92	52
		124	108	136	142	92	50
	Test 2	132	148	136	144	114	52
		144	134	146	154	108	54
		(131)*	(124)	(137)	(144)	(102)	(52)
4-4-74	Test 1	96	114	130	124	102	44
		94	108	124	128	98	44
	Test 2	100	118	126	130	96	46
		100	112	130	138	102	42
		(100)	(113)	(128)	(130)	(100)	(44)
4-11-74	Test 1	116	114	136	136	112	52
		124	108	140	146	116	52
	Test 2	136	122	130	144	100	56
		130	120	136	150	104	58
		(127)	(116)	(136)	(144)	(108)	(55)
5-13-74		136	148	130	144	94	44
		126	136	142	148	96	44
		(131)	(142)	(136)	(146)	(95)	(44)
5-24-74		106	124	132	142	84	64
		102	118	136	136	84	66
		(93)	(114)	(119)	(132)	(79)	(59)
AVG		119	121	134	140	99.6	51
SD		15.7	13.8	5.94	8.18	9.64	7.2
SD/AVG		13.2%	11.4%	4.43%	5.84%	9.68%	14%

*Weekly averages are included in parentheses
AVG = Average of all values
SD = Standard deviation of all values

Another interesting observation made with plasma polymers is that there seems to be a correlation between oxygen content in plasma polymers and blood compatibility, i.e., high oxygen content seems to improve the blood compatibility. A striking difference was observed between plasma polymers of tetrafluorethylene with high and low oxygen contents. When tetrafluorethylene is polymerized under the conditions of low *W/FM*, where *W* is discharge wattage, *F* is flow rate and *M* is molecular weight of monomer, the polymer formed has a little oxygen and surface properties are similar to those of polytetrafluorethylene (Teflon), and the blood compatibility is very poor. However, when the same monomer (tetrafluoroethylene) is polymerized under the condition of high *W/FM*, the surface has fewer fluorine atoms and has high oxygen content. The blood compatibility of such a polymer was found to be among the best polymer surfaces tested in the studies. Those findings confirm that one cannot discuss the blood compatibility of plasma polymer of tetrafluoroethylene in a similar manner in which one may be able to deal with conventional polytetrafluorethylene (Teflon). Namely, the surface properties of plasma polymers depends entirely on conditions of plasma polymerization. This implies that, as far as results obtained with plasma polymers are concerned, the conclusion based on general terms, such as 'blood compatibility of plasma polymer of tetrafluoroethylene . . .', should be avoided.

Another blood compatibility test and its application to plasma polymerized thin films has been reported by Chawla[9]. This test is based on the microscopic examination of the numbers of blood elements (platelets and leucocytes) adhered to tested surfaces after a standard period of samples incubation in contact with blood. The author was investigating the plasma polymerization of two cyclic siloxanes, D_3 (hexamethylcyclotrisiloxane) and D_4 (octamethylcyclotetrasiloxane) on some different substrates such as microporous polypropylene membranes (MPM), polypropylene filters and glass slides. For the blood compatibility tests however, he used only D_4 covered MPMs. Uncovered surfaces of medical grade Silastic as well as the glass slides have been also used in this study as the control.

The results presented in this work and shown in *Table 2* are neither elaborated statistically well enough nor do they show the satisfactory reproducibility. In spite of these facts, however, the results seem to indicate the general tendency that plasma polymerization coated surfaces show much better blood compatibility. Moreover they are worth citing because of the test itself.

TISSUE COMPATIBILITY

The tissue compatibility of plasma polymerized coatings *in vivo* has been reported by Hahn *et al*[10,11]. The concept of both of these studies was to investigate the tissue response for the plasma coatings surgically implanted in rats' or rabbits' muscles. The biocompatibility of the implants was evaluated by two different techniques i.e. the graded inflammatory cell response technique and the connective tissue capsule technique, both as a function of time. The principle of both tests was to implant the investigated materials into the chosen muscles of a certain number of animals then divided into the groups for necroscopies in the arbitrarily chosen intervals of time (up to a number of weeks). The removed and prepared implants together with the

Table 2 Adhesion of platelets (Plat.) and leucocytes (WBC) to MPM surfaces covered by plasma polymerized octamethylcyclotetrasiloxane in comparison to the references of uncovered glass and silastic surfaces[9]

Sample code no.	Initial blood platelet count 10/mm	Cell no. 1				Cell no. 2			
		Glass		MPM		Silastic		MPM	
		Plat.	WBC	Plat.	WBC	Plat.	WBC	Plat.	WBC
CGD-41	228	93.6	0.1	19.7	0	167.4	0	0.7	0
CGD-41	256	60.0	0.3	45.0	0	52.1	0	65.1	0
CGD-42	186	18.3	0	16.3	0	94.3	0.3	39.4	0
CGD-44	224	9.1	0.1	10.5	0	45.7	0.3	17.7	0
CGD-45	264	0.1	0	0	0	0.5	1.4	0	0
CGD-45	224	31.0	0.2	11.8	0.1	39.0	1.4	0	0
CGD-46	228	0.2	0.2	0	0	0.9	0	0.1	0.1
CGD-47	224	1.3	0	0.2	0	10.0	0.3	0.5	0
CGD-47	241	0.5	0.1	0.4	0	0.3	0.1	0.1	0
CGD-52	193	3.0	0	3.0	0	0.3	0.1	0	0
CGD-52	285	79.6	0.1	4.8	0	132	0	0.5	0
CGD-54	183	0.8	0	0	0	9.2	1.2	0	0.1
CGD-54	275	66.2	0.5	47.7	1.0	25.6	2.5	40.6	0.8
CGD-55	245	84.4	2.7	23.8	0.3	110.5	0.5	72.1	0.2

surrounding tissue were then subjected to the microscopic examinations concerning inflammatory cell reaction and connective tissue thickness. The first test consists in counting of the inflammatory cells surrounding the implant and it is based on the four grade scale depending on the number of cells while the connective tissue reaction test is based on the thickness measurements (in μm) of the capsule surrounding the implant at four locations 90° apart.

The first of the papers cited[10] contains the preliminary data concerning the wide range of monomers such as vinyl chloride, ethylene, allene, tetrafluoroethylene, styrene, acrylonitrile, vinyl chloride and chlorotrifluoroethylene. Based on these preliminary data as well as on the data of toxic interaction tests for the respective coatings performed *in vitro* the authors had chosen three monomers for the further studies. These monomers were as follows: ethylene, styrene and chlorotrifluoroethylene and the biocompatibility of the coatings produced out of these monomers was the subject of a statistically performed study reported in the next paper[11].

All of the tests presented in reference 11 concerned the coatings deposited on substrates in Silastic Medical Grade Tubing cut into 6-7 mm lengths and were accompanied with the reference of the uncoated Silastic samples. It meant that every rat had both coated and uncoated samples implanted to its skeletal muscle.

The first result of this study was that there was no evidence of any systemic toxicity to the rats as evaluated by gross and microscopic examinations of major animals' organs. Grossly, the implant showed only a glistering connective tissue capsule surrounding it. The capsule characteristics were grossly indistinguishable between coated and uncoated implants.

The results of the graded inflammatory cell response tests are summarized in *Figure 1*, where the frequency or number of times of particular grade appearance is shown over the course of the implantation time. It can be seen that the significant response is still observed after 4 weeks for both, coated and uncoated implants. Although coatings did improve over the control, difference became indistinguishably small after 4 weeks.

Figure 2 illustrates the results of the connective tissue capsule thickness tests. It can be seen that both plasma formed polymers and Silastic showed significant changes in capsule thickness as a function of implantation time. However, occurrence of the peak response was dependent on the type of polymer implanted. In general, the fibrous connective tissue reactions elicited by each of the plasma formed polymers was significantly greater than the respective control polymer during the early phase of the experiment, but in 24 weeks, both the Silastic and plasma formed polymers had capsule thickness measurements which were not significantly different. The same picture illustrates also the confidence limits of the results based on statistical analysis called Analysis of Variance (ANOVA) and calculated by the authors. Concerning these limits one should point out that the reprodicibility of the results presented is also satisfactory.

Three major conclusions may be drawn from these studies. First, the lack of general systemic toxicity associated with the implantation of plasma polymerized materials has been demonstrated in the cases of rats and rabbits. Second, the tissue response for the plasma coated implants, at least in skeletal muscle of rats was almost indistinguishable from that of Silastic, a material known to be relatively inert in biological tissue. Third, the statistical evaluation of the results showed their satisfactory reproducibility of plasma polymerized surfaces.

The possibility of the ultrathin film production by means of plasma polymerization as well as the good biocompatibility shown by these films have been utilized by Yasuda *et al* to apply coatings to corneal contact lenses[12]. They covered the poly(methyl methacrylate) contact lenses by about 200 Å thick films of plasma polymer of acetylene/water/nitrogen mixture. The coated and uncoated lenses were then placed onto rabbit eyes for the sake of biocompatibility comparison. With the uncoated lenses the accumulation of mucous matter in a week time was sufficient to affect the optical clarity of the lenses, whereas the coated lenses showed no change after three months of continuous wearing. The comparative degree of adhesion of corneal epithelium cells onto glass, modified glass, PMMA and coated PMMA surfaces have also been studied *in vitro* using tissue cultures and phase contrast microscopy. The coated PMMA surfaces exhibited a degree of tissue adhesion lower than that of the reference PMMA and higher than that of glass, and no sign of toxicity was observed by the tissue cultures.

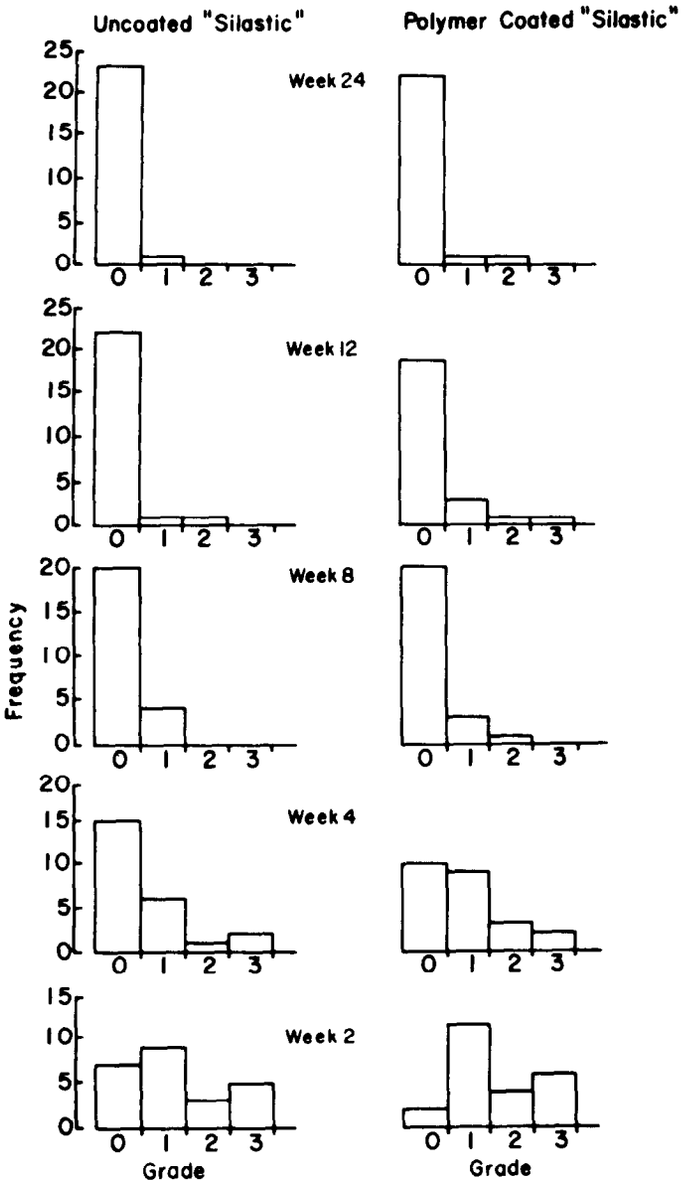

Figure 1 Distribution of grades assigned by microscopical observation of inflammatory cells present in 10 high power fields (400×) surrounding each implant. The grades are as follows: grade 0, ≤ 1 cell; grade 1, 2-3 cells; grade 2, 4-10 cells; grade 3, > 10 cells in 10 high power fields. 'Polymer coated Silastic' represent Silastic samples covered by plasma polymerized coatings from the monomers of styrene, ethylene and chlorotrifluoroethylene which were indistinguishable in this test[11].
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PREVENTION OF THE LEACHING OF SUBSTANCES FROM PLASTICS

The low permeability of plasma polymerized coatings is the parameter which has been investigated for the applications requiring the effusion or leaching barrier on the surface of the biomaterial. One of these applications is a prevention of the low molecular weight additives release from the polymers used as prosthetic implants. There are evidences that the release of materials like plasticizers, antioxidants, initiators, residual monomers or degradative products can cause harmful effects to the body of the host.

Chang *et al*[13] investigated the barrier effect of both inert gas plasma surface treatment and plasma polymerization coating on the total amount of impurities leaching from several polymeric materials into the surrounding fluid. They had chosen five materials, polypropylene, poly (ethylene terephthalate), poly(vinyl chloride, poly(dimethylsiloxane) and poly(methyl acrylate) and treated them either by argon plasma or by ethylene-argon plasma. For the leaching tests they used a simulated body fluid known as pseudoextracellular fluid (PECF). Each sample had been sealed in ampoules containing PECF and the ampoules were autoclaved at 115°C at a pressure of 31 psia for 62 h. After cooling, the ampoule was broken, the solution was filtered and the dissolved organic liquids were extracted with CCl_4. The amount of extracted material was then determined by means of i.r. spectroscopy.

The results of both kinds of treatments are shown in *Figures 3 and 4*. The parameter ϕ in these figures is defined as the amount of impurities leached from the treated polymer divided by that leached from the untreated polymer and is therefore a good measure of treatment effectiveness. It can be seen that generally argon plasma treatment was much less effective than the plasma polymerization of ethylene. It is also evident that the treatment had different effects on different polymers. The results of this study confirmed the work of Asai *et al*[14] where the authors succeeded in reducing the leaching of dioctyl phthalate (plasticizer) from PVC by blood from 60 to 1-2 μg/day m^2 by applying plasma polymerized coatings.

A similar attempt was made to prevent the leaching from PVC tubing by applying plasma polymer of tetramethyldisiloxane, which showed as promising a blood compatibility as mentioned earlier[4]. The leaching was examined by using a peristaltic pump (a coated surface was flexed in the presence of aqueous surfactant solution). In this case, however, the argon plasma treatment of the inner surface of PVC tubing provided better reduction that that obtained by the plasma polymer coated samples. The leach rate was reduced to as low as 30% of that for untreated tubing. For a non-flow test involving no bending or flexing of the tubing (e.g., as would be expected for a blood bag) the leach rate was reduced to as little as 5% of that for untreated tubing. Plasma polymer of tetramethyldisiloxane was much less effective in inhibiting leaching although a reduction to 30% of untreated leach rate was found in a non-flow test.

CONTROL OF DRUG RELEASE RATE

Since a thin layer of plasma polymer can change the solubility and the diffusivity of substance through the substrate polymer, plasma polymer coating can be utilized as the means of modifying the drug release rate from a drug impregnated polymer device.

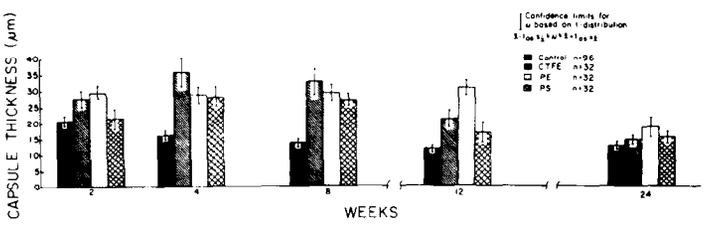

Figure 2 Connective tissue capsule thicknesses for different coatings as a function of time. Results for control (Silastic) are pooled for the three groups[11].
(Reproduced from J. Biomed. Mat. Res. 1979, 13, 299-315 with permission of the Publisher)

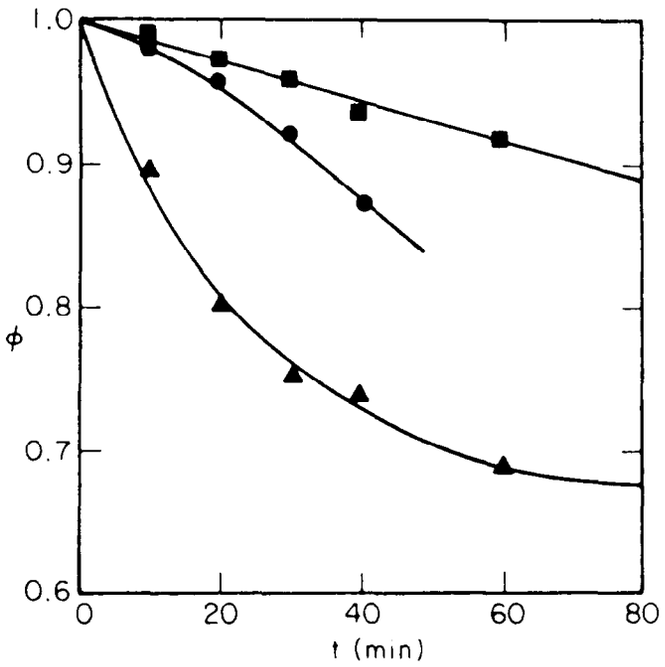

Figure 3 Fractions (φ) of impurities released from polymers treated by argon plasma surface treatment, plotted against the treatment duration (t). ■: polypropylene; ●: poly(ethylene terephthalate; ▲: poly(methyl acrylate)[13]*.*
(Reproduced from J. Appl. Polym. Sci. 1973, 17, 2915-2917 with the permission of the Publisher)

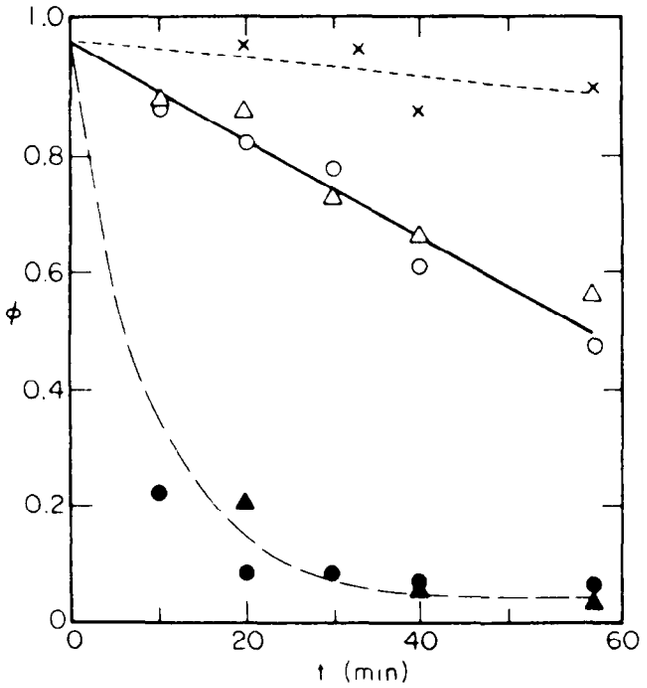

Figure 4 Fractions (φ) of impurities released from polymers coated by plasma polymerized ethylene, plotted against the polymerization duration (t) X: poly(vinyl chloride); ●: poly(ethylene terephthalate); ▲: poly(methyl acrylate) plasticized with dioctyl phthalate. All coated by ethylene plasma at 2.0 torr pressure and 100 watts power. ○: poly(ethylene terephthalate); △: poly(methyl acrylate) plasticized with dioctyl phthalate, coated at 1.8 torr and 80 watts[13]*.*
(Reproduced from J. Appl. Polym. Sci. 1973, 17, 2915-2917 with the permission of the Publisher)

Barriers produced by means of plasma techniques have been studied in terms of the controlled release of at least two different drugs i.e. pilocarpine hydrochloride[15] and progesterone[16].

As far as the pilocarpine hydrochloride is concerned it is used in the traditional therapy for glaucoma and is usually administered several times daily in order to maintain its more or less stable concentration in the eye. There exists the more advanced technique where the pilocarpine solution is sequestered in a hydrogel, from which it is released at a slow rate when inserted into the eye. This technique is more efficient since it really maintained the stable drug concentration. The problem is, however, the rate of pilocarpine release from hydrogel without any surface barrier is too high. Understanding this problem Colter *et al*[15] investigated the application of plasma techniques to forming such barriers.

The substrates used in this study were the hydrogel type materials photopolymerized from the different acrylates and methacrylates and the authors studied four different plasma treatments of these substrates. The gases used were as follows: argon, ethane, ethylene and tetrafluoroethylene. The authors tried to use a number of different schemes of samples preparation and once again the inert gas (argon) plasma treatment turned out to be inefficient. The best results seemed to be obtained for the following scheme. After photopolymerization, preparation and cutting into the desired geometry the poly (2-hydroxyethyl methacrylate) disc samples were soaked for a week in a 4% by weight aqueous solution of pilocarpine hydrochloride and then immediately inserted into the vacuum system for the application of plasma polymerized ethylene coating. This was the only scheme where the authors applied coatings onto the discs in the swollen state and this provided the best results. These results are shown in *Figure 5*. In all other schemes the coatings were applied on dried hydrogel and then allowed to swell in water. Due to swelling of the substrate, cracking of the coating occurred and caused their inefficiency.

The same team of authors investigated the same techniques for the controlled release of progesterone through silicone membranes[16]. The principle used in this study is almost identical as of the former one. There is only a difference in a drug and in an organ into which the drug releasing capsule is to be implanted. The drug is progesterone this time and the organ is the uterus. The problem remains the same, too fast drug release. Both of the Colter's studies are very similar; they used the same techniques, the same monomers and even the same plasma parameters. The major differences between the studies are as follows: substrates are Silastic membranes in comparison to hydrogel, the drug under investigation is progesterone, and the technique of the released drug indication is based on the

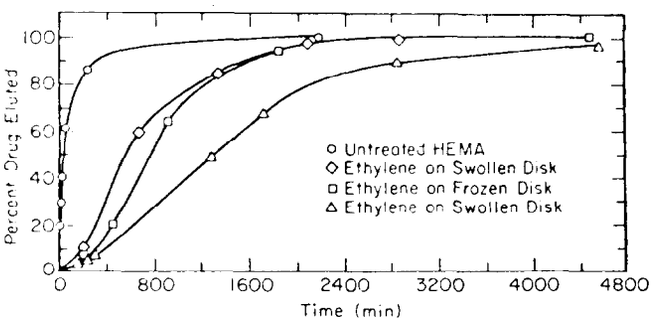

Figure 5 Pilocarpine hydrochloride release curves from poly(2-hydroxyethyl methacrylate) discs coated in a swollen state by plasma polymerized ethylene[15]*.*
(Reproduced from Biomat., Met. Dev., Art. Org. 1977, 5(1) 1-12 by courtesy of Marcel Dekker, Inc.)

radioactive labelled material in comparison to the u.v. spectroscopy.

The results of this study are summarized in *Table 3*. Once again it was proven that argon plasma treatment was the least effective and once again ethylene polymerized coating turned out to be the most effective. The authors met some problems concerning the cracking of the coatings in this study also. Unfortunately the cracking tendency followed usually the diffusion reduction efficiency but this problem does not seem to be extremely difficult to solve. According to the authors' suggestion the future efforts should be directed at finding an optimum balance between flux reduction and durability of plasma produced coating.

PROTECTIVE COATINGS OF MEDICAL DEVICES

As it was pointed out before, the plasma polymerized coatings may show extremely good adhesion to the substrate. This particular feature of these coatings has been utilized by Hahn *et al*[17,18]. In these studies they applied plasma polymerized propylene to the polarographic electrodes used as a sensor to measure tissue oxygen concentration in order to protect them against the poisoning and aging influences. Due to these phenomena the electrodes are not stable enough for quantitative results within continuous long range of time without frequent recalibrations (usually every 6-12 h). The idea of this work was to apply very thin film which would not present a barrier for oxygen but would protect the catalytic surface of platinum against poisoning and aging. The schematic picture of the electrode is shown at the *Figure 6*. The surface to be protected is the very little front platinum oxygen sensing surface. According to this, the whole electrode assembly except the tip was carefully marked with aluminium foil when being deposited by plasma polymerized propylene.

The polarograms of uncoated and coated electrodes in 0.9% saline solution and different oxygen concentrations are shown in *Figure 7*. It is seen that for all the coated electrodes, the current responses are lower and the plateau regions are extended over the larger voltage range. The linear response of coated electrodes to different oxygen

Table 3 Diffusion of progesterone through silastic membranes either covered by plasma polymerized coatings of different monomers or surface treated by argon plasma. Diffusion through untreated membrane is given as a reference[16]

	Un-treated	Plasma polymerization			Plasma treatment
		C_2H_4	C_2H_6	C_2F_4	Argon
Pressure (Torr)	–	0.50	0.20	0.075	1.20
Flow rate (cm^3/min STP)	–	80	20	3	10
Power (Watts)	–	50	50	50	100
Treatment (Time – min.)	–	15.0	30.0	15.0	20.0
Deposition rate (mg/h – cm^2)	–	0.083	0.044	0.104	–
Estimated thickness (microns)	–	0.200	0.200	0.250	–
Progesterone flux (μg/day – cm^2)	101.5	2.99	6.86	20.5	34.8

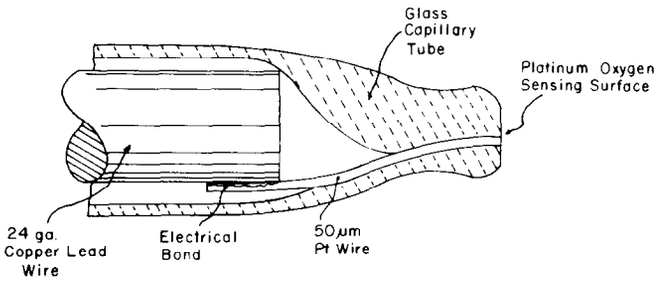

Figure 6 A sketch of the oxygen sensing electrode. The ultrathin polymer film is applied to the exposed platinum end[17]. *(Reproduced by permission of Plenum Press, New York)*

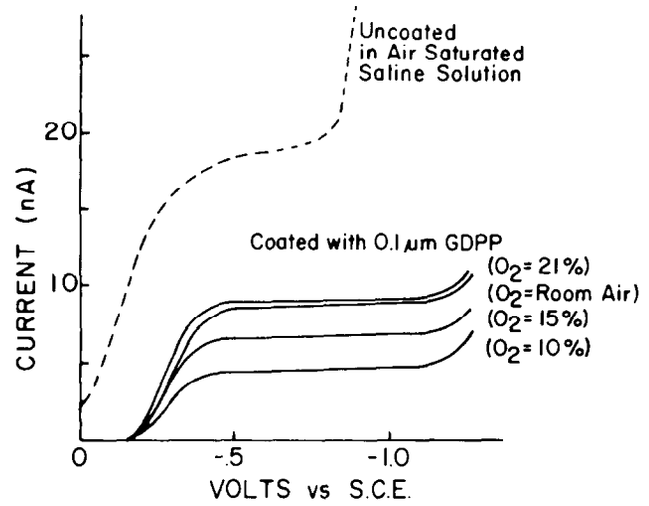

Figure 7 Polarograms of platinum oxygen sensing microelectrodes, in 0.9% saline solution and different oxygen concentrations. Response of an uncoated sensor is shown as a dashed line[17]. *(Reproduced by permission of Plenum Press, New York)*

concentrations is also worthy to notice. The long period (measured over 72 days) calibration responses have been also tested. It turned out that 0.1 μm thick plasma polymerized propylene coated electrode showed only about 10% of current response drift during this period while the uncoated electrode behaviour was much worse (over 100% drift).

IMPROVEMENT OF ADHESION OF INSULATOR TO METAL SURFACES

An ultra thin film of plasma polymer applied onto a metal surface can be utilized as an adhesion promoting polymer coating for a thicker layer of conventional polymer coating. The poor adhesion of an insulating material to a metal surface is one of the most serious problems associated with the implantable devices with either stimulating or recording electrodes. The electrodes usually must be partially insulated, leaving small areas of metal uncoated. Thus the boundary of metal to the insulator, or the interface of metal to insulator, is exposed to the body fluid, which contains aqueous solutions of numerous electrolytes. Under such conditions, the adhesion characteristics of insulator to the electrode material is very often a critical parameter which influences the efficiency and the longevity of the performance of electrodes. The poor adhesion, particularly under the influence of water, electrolytes, and applied electric field, causes water and ions to penetrate along the surface of electrode which eventually results in the lowering of the electrode impedance.

A series of papers have appeared on the work to improve adhesion of parylene to platinum electrodes, as a model of stimulating electrodes used in neural prosthesis[19–21].

Parylenes (polymers of paraxylene and derivatives of paraxylene) are excellent insulating materials. Their electrical properties, thermal properties, mechanical properties and the feature that thin conforming coating can be prepared by vacuum deposition made Parylene one of the best insulating materials for biomedical devices. However, the problem that hampers full utilization of excellent properties of Parylene up to the expectation, is their characteristically poor adhesion to most substrate surfaces. The poor adhesion of Parylene is an inherent problem in the adhesion of low surface energy polymers to high surface energy surfaces of metals. In order to overcome this problem, a plasma polymer was used as an intermediate layer between Parylene and platinum surfaces. A thin layer of plasma polymer of methane or tetrafluoroethylene was applied onto the surface of platinum and then approximately 3 μm thick Parylene was applied. The effects of the new primer coatings were examined by (i) test of adhesion failure in boiling 0.9% NaCl solution, (ii) pull test performed after coating of samples were boiled in 0.9% NaCl solution, (iii) cyclic voltametry using a model electrode, (iv) examination of adhesion failure under repeated strain introduced by vibrating samples in 0.9% NaCl solution. All tests indicated remarkable increase in adhesion of Parylene by the plasma polymer primer coating. Perhaps the most intriguing results so far as biomedical application is concerned, may be found in the test results of cyclic voltametry, which is shown in *Figure 8*.

CONCLUDING REMARKS

As it was pointed out in introduction of this review, the use of plasma polymers and/or plasma treated polymer surfaces in biomedical applications is still more or less in the preliminary stage. The results reviewed merely indicate the potential of the process in biomedical application. The following common trends could be drawn as a measure of the potential.

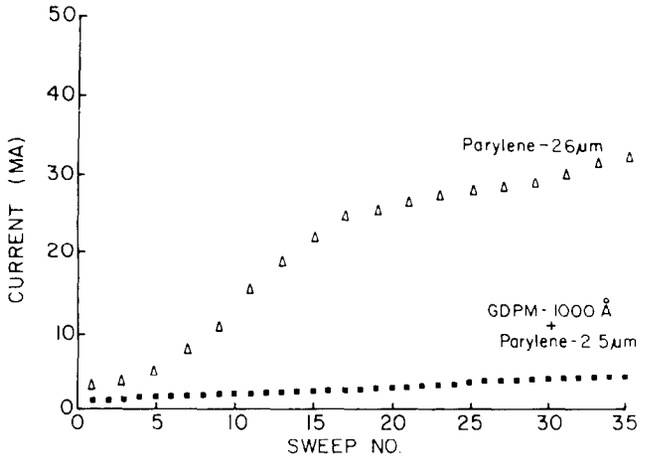

Figure 8 Cyclic voltametry in 1 N K_2SO_4 solution on the composite ■ (glow discharge polymerized methane + Parylene-N) and non-composite △ (Parylene-N alone) electrodes. Maximum current at 3.0 VDC vs. SCE for 35 consecutive sweeps on the respective electrodes. Temperature 25°C[20].
(Reproduced from Biomaterials, 1981, 2, 161-165)

1. Many plasma polymers could be made so that they are chemically inert and show no acute toxicity in biological systems.
2. Plasma polymers can be used to effectively modify the surface properties of materials, thus it is possible to control the interaction between a biomaterial and a biological system.
3. Plasma polymers can provide a means of controlling transport of substances in and out of biomaterials.
4. Plasma polymers can be used as protective coating of biomedical devices.
5. Plasma polymers may be used to improve adhesion of different materials used in composite biomedical devices.

Table 4 is provided as a summary of effects reviewed. This table refers to original publications only and that is why review papers (references 1, 5, 6, 7 and 8) as well as Annual Reports (reference 4) are not included.

According to what we have seen in literature, it appears that the true potential of plasma polymers in biomedical applications has not yet been thoroughly evaluated. It appears also that the great potential of plasma polymers has not been well recognized by scientists and engineers who are engaged in dealing with various phases of biomaterials. This review was written with the hope that it would draw attention of many readers and stimulate interest to utilize this relatively unknown material and technology.

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Table 4 Biomedical properties and possible applications of plasma polymerized coatings and surface modification

Ref	Substrates	Plasma	Tr.	System	P /torr/	F SCCM	f
(2)	polypropylene poly(vinyl chloride) polytetrafluoroethylene polycarbonate polyurethane poly(methyl methacrylate)	NH_3 or $N_2 + H_2$	Mod.	tube, flow, capac. coupl.	0.3–1.5		13.56 MHz
(3)	Mylar Silastic porous polysulphone nonporous polysulphone	C_2F_4, Me_6Si_2O, $C_2H_4 + N_2$, allene + N_2 + H_2O	Pol.	tube flow, induct. coupl.	0.03–0.06	5	13.5 MHz
(9)	polypropylene membranes polypropylene filtres glass slides	D_3, D_4	Pol.	tube, flow capac. coupl.		33	RF puls.
(10)	glass polystyrene Silastic	C_2H_3Cl, C_2H_4, allene, C_2F_4, C_2F_3Cl, $C_2H_3C_6H_5$, acrylonintrile C_2H_3F	Pol.	tube flow induct. coupl.			3.95 MHz
(11)	Silastic	C_2F_3Cl, $C_2H_3C_6H_5$, C_2H_4	Pol.	tube flow, induct. coupl.			3.95 MHz
(12)	poly(methyl methacrylate)	C_2H_2 + $N_2 + H_2O$	Pol.	tube, flow, induct. coupl.	0.065	5	13.5 MHz
(13)	polypropylene poly(ethylene terephthalate) poly(vinyl chloride) poly(dimethyl siloxane) poly(methyl acrylate)	Ar, C_2H_4	Mod. Pol.	bell, jar, flow, capac. coupl.	1.5 2.0		13.56 MHz
(14)	dioctyl phthalate plastified poly(vinyl chloride)	pyridine, C_2F_4, Et_3SiH	Pol.				
(15)	poly(2-hydroxyethyl methacrylate) hydrogels poly(2-hydroxyethyl methacrylate-co-methyl acrylate) membranes	Ar, C_2H_4, C_2H_6, C_2F_4	Mod. Pol. Pol. Pol.	bell, jar, flow, capac. coupl.	1.2 0.5 0.2 0.075	10 80 20 3	13.56 MHz
(16)	poly(dimethyl siloxane)	Ar, C_2H_4, C_2H_6, C_2F_4	Mod. Pol. Pol. Pol.	bell, jar, flow, capac. coupl.	1.2 0.5 0.2 0.075	10 80 20 3	13.56 MHz
(17) (18)	platinum	C_3H_6	Pol.	tube, flow, induct. coupl.	0.2	7.6	27.12 MHz
(19) (20) (21)	platinum	CH_4	Pol.	bell, jar, flow, capac. coupl.	0.05	1	10 KHz

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W (Watt)	Tests	Way	Suggested use
75–400 usually 100–200	heparin attachment	in vitro	blood compatibility improvement
30	blood coagulation times	in vitro	
30	adhesion of blood cells	in vitro	blood oxygenators
	toxic interaction with cells, inflammatory cell response, connective tissue capsule thickness	in vitro in vivo in vivo	
6	inflammatory cell response, connective tissue capsule thickness	in vivo	
30	coatings wettability, adhesive affinity of corneal cells, possible toxicity, accumulation of mucous matter	in vitro in vitro in vivo	contact lenses
80 100	low molecular weight substances leaching from prosthetic materials	in vitro	low molecular substances release barrier from prosthesis
	dioctyl phthalate leaching in blood	in vitro	plasticizer release barrier from prosthesis
100 50	rate of pilocarpine hydrochloride diffusion through plasma polymerized coating	in vitro	open eye glaucoma therapy
100 50	diffusion of progesterone through Silastic membranes coated by plasma	in vitro	birth control
100	polarographic characteristics of coated electrodes	in vitro	tissue oxygen concentration measuring devices
80	adhesion of Parylene to platinum with plasma polymerized interfacial film, cyclic voltametry of the composite electrodes, biocompatibility of the composite electrodes	in vitro in vitro in vivo	Parylene adhesion improvement to platinum electrodes used as implantable

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