Polyurethanes in Biomedical Applications

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1. INTRODUCTION

Polyurethanes are the most commonly used materials in the production of blood contacting devices such as heart valves or artificial veins and arteries. They comprise a large family of materials with the only common characteristic of the presence of urethane linkages along the large molecular chains. In general urethane linkages form by the reaction of isocyanates and alcohols. During the preparation and the curing processes of polyurethanes, besides the formation of urethane linkages, many other reactions take place and lead to formation of various bonds such as allophanate, biuret, acylurea or isocyanurate and these bonds may lead to further branching or crosslinking affecting the whole physical, chemical and mechanical properties as well as the biocompatibilities of the resulting polymers[1,2].

The synthesis of polyurethanes was first achieved in the 1930's and the polymers obtained by the reaction of diisocyanates with glycols possessed interesting properties as plastics and fibers. During World War II, polyurethanes found many applications such as rigid foams, adhesives, resins, elastomers and coatings.

Development of polyurethane elastomers[3] and flexible foams[4] based on polyesters was achieved in 1950's and shortly thereafter they came into commercial production. Polyurethanes developed for industrial purposes demonstrated very good long term mechanical properties when exposed to static or dynamic loads, and therefore, they also found various application areas in medical technology.

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The first generation of polyurethanes used for implant studies were industrial grade and commercially available. But it was reported that, when implanted into the muscle of dogs or when used as monocusp valvular prosthese polyester urethanes degraded rapidly[5].

This type of degradation and calcification limited the use of these polyurethanes in medical applications. On the other hand, it was reported that polyester-polyether polyurethanes demonstrated good blood compatibility, particularly with regard to long term stability and thromboresistance in intravascular replacement[6].

The initial observations showed that it was not easy to reach a general conclusion about the biocompatibility of polyurethanes since they cover a very wide range of compositions and structures in this family of polymers. Polyurethanes differ in their interactions with blood, their tendencies to calcify and their propensity toward biodegradation. This is the reason that many research groups began to search new compositions and new methods to produce new polyurethanes and to modify available ones to improve their properties to obtain materials with the desired properties for medical applications and biocompatibilities.

1.1 Types of Polyurethanes

The urethane linkages usually represent a small component in the total chain, with the greatest number of linkages contributed by the macroglycol. Therefore, many of the properties are derived from the macroglycol portions of the chain, and depending on the choice of macroglycol, the polyurethanes have been found to perform differently in varying clinical applications[7-9]

The basic classification can be given as follows:

1. Polyester-based polyurethanes undergo rapid hydrolysis when implanted in the human body, and thus are not preferred in medical applications.
2. Polyether-based polyurethanes are the polymers of choice in medical applications because they are virtually insensitive to hydrolysis, and are thus very stable in the physiological environment.
3. Polycaprolactone-based polyurethanes, due to their quick crystallization, can be used advantageously as medical, solvent-activated, pressure-sensitive adhesives.
4. Polybutadiene-based polyurethanes have been evaluated, but limited medical applications has been found to date.
5. Castor oil-based polyurethanes can be used as potting and encapsulating compounds, but due to their poor tear resistance, find limited use in medical applications.

As it can be seen polyurethanes are a very diverse family of polymers capable of exhibiting a wide range of properties varying from smooth

elastomeric membranes to porous or smooth rigid bulk structures depending on their molecular compositions.

Segmented polyurethane elastomers are the ones used in the production of blood contacting devices like heart valves and artificial arteries or veins. Segmented polyurethanes are composed of soft and hard segments where hard segments are stiff blocks composed mainly of isocyanate groups while soft segments are flexible high molecular weight chains of polyether or polyesters. These segments form some domains distributed in the three dimensional structure of the polymer. Physical and mechanical properties are directly related to chemical structure of these domains as well as their ratio in the resulting polymer[10,11].

Even for a certain well defined type of polyurethane, it is possible to find contradictory results and disagreements in literature, and this might be associated with a specific application and related to various parameters such as blood flow rate, device type, time of implantation, etc.

1.2 Phase Separations of Polyurethanes

Soft and hard domains distributed in segmented polyurethanes cause phase separation and control the properties of the resultant polyurethanes. The type and the ratio of hard and soft segments are generally examined by spectrophotometric methods. Small-angle X-ray scattering was used by Garrett et al. to examine phase-separated microdomain morphology of the multiblock copolymers, synthesized from 4,4'-methylene di(p-phenyl isocyanate), poly(tetramethylene oxide), ethylenediamine, and/or 1,4-diaminocyclohexane. The hard segment content was in the range of 14 to 47 wt percent and it was reported that copolymers have relatively low overall degrees of phase separation contrary to the common notion that these copolymers are well phase separated materials. The introduction of the second diamine reduced phase separation; presumably as a consequence of disruption of hydrogen bonding in hard segment domains[12]. The phase separated morphology affects the blood compatibility properties of polyurethanes. It was claimed that hydrophilicity creates surfaces resembling the natural tissue and decreases thrombus formation. In the literature it was given that at a certain surface concentration of soft segments the number of adhered and deformed platelets on the surface of polyurethanes was minimized[13-15]. But it was also shown that the percentage of soft segments on the surface did not relate to the blood compatibility of polyurethanes[16].

2. BIOMEDICAL APPLICATIONS

Polyurethanes, having extensive structure/property diversity, are one of the most bio- and blood-compatible materials known today. These materials

played a major role in the development of many medical devices ranging from catheters to total artificial heart. One very important point is the medical purity of the materials. There should be no leachable toxic solvent, monomers, chain extender or other chemicals, which may cause toxic effects in the body[17]. Properties such as durability, elasticity, elastomer-like character, fatigue resistance, compliance, and acceptance or tolerance in the body during healing, became often associated with the chemical composition of polyurethanes. Furthermore, propensity for bulk and surface modification via hydrophilic/hydrophobic balance or by attachments of biologically active species such as anticoagulants or bio-recognizable groups are possible via chemical groups typical for polyurethane structure. These modifications are designed to mediate and enhance the acceptance and healing of the device or implant. Many innovative processing technologies are used to fabricate functional devices, feeling and often behaving like natural tissue. The hydrolytically unstable polyester polyurethanes were replaced by more resistant but oxidation-sensitive polyether polyols based polyurethanes and their copolymers containing silicone and other modifying polymeric intermediates.

The first biomedical grade polyether polyurethane was synthesized by two groups. Boretos and Pierce[18,19] introduced the biomedical application of segmented polyether polyurethanes containing hard segments of urea and soft segments of polyether linked by the urethane group. These materials sustained high modulus of elasticity, biocompatibility, resistance to flex-fatigue and excellent stability over long implantation periods.

Lyman and associates[20] based on their previous experience in the synthesis of polyurethanes for dialysis membranes, introduced a segmented polyether polyurethane which demonstrated very good thromboresistance.

Nylias, the developer of Avcothane^R, synthesized a copolymer of polyurethane and polydimethyl siloxane[21] which is blood compatible and used in the making of heart assist balloon pumps. Lelah et.al.[22] reported that, materials having higher surface soft segment concentration are more thromboresistant, but in contrast Hanson[23] reported that platelet consumption decreased as the percentage of surface carbon atoms forming hydrocarbon bonds increased.

Research on the artificial heart (carried out at Termedics, Inc., U.S.A.) has stimulated interest in the segmented polyurethane elastomers. The polymers exhibit high flexure endurance, high strength, and inherent non-thrombogenic characteristics, and therefore, have a maximum impact in medical prostheses, the most immediate and promising applications appear to be in the cardiovascular area, where chronic, nonthrombogenic interfacing with blood is of paramount importance[24].

The armory of cardiac surgeons would not be as impressive as it is without the outstanding contribution of polyurethanes in intra–aortic balloons, blood sacs for ventricular assist devices, catheters, pacemaker leads to name the most important. Results of PUs as blood conduits have still not found a niche because of the unresolved lack of long–term resistance to

degradation. Breast implants covered with PU foam are part of a scientific controversy. The use of PU in contraception is limited but these materials present some interesting features. Wound dressings and scaffolds for tissue engineering could permit new developments.

On the other hand polyurethanes are also prepared in the form of microspheres as carriers for drug or bioactive substances, or can be used as liners in dentistry, coatings for metallic heart assist devices, membranes or tubes for hemodialysis systems, scaffolds for tissue engineering purposes, etc[25-27]. Table 1 shows the general applications of polyurethanes in the biomedical area.

Table 1: Current biomedical application areas of polyurethanes

Blood bags, closures, fittings	Leaflet heart valves
Blood oxygenation tubing	Mechanical heart valve coatings
Breast prostheses	Orthopedic splints, bone adhesives
Cardiac assist pump bladders, tubing, coatings	Percutaneous shunts
Catheters	Reconstructive surgery materials
Dental cavity liners	Skin dressing and tapes
Endotracheal tubes	Surgical drapes
Heart pacemaker connectors, coatings,	Suture materials
Hemodialysis tubing, membranes, connectors	Synthetic bile ducts
Lead insulators, fixation devices	Vascular grafts and patches

The human body's acceptance of synthetic polymers is highly complex, and most polymers have a tendency to form surface thrombus. A good biomaterial would have wide range of applications, including as an prosthesis device material or as coating material for components of various devices such as components of dialysis units, extracorporeal circuits, blood pressure monitors, sensors or catheters. Polyurethane elastomers are known as inherently thromboresistant. Although compatibility and non-thrombogenicity are subject to many complex factors, among which are polymer surface composition, device configuration, and blood-flow characteristics, in general the polyurethanes have performed well in numerous device configurations. Therefore, several methods have been developed for evaluating the blood interactions of polyurethanes.

3. MODIFICATIONS OF POLYURETHANES

The applications of polyurethanes are almost limitless in the medical industry. However, one should ascertain that polyurethanes are indeed the best materials to manufacture devices for specific applications. The capacity

of polyurethanes to undergo modifications increase their suitability for biomedical applications.

3.1 Modifications for Blood Compatibility

When an artificial substance or an implant is exposed to blood some interactions such as protein deposition, platelet adhesion and activation, and initiation of coagulation and thrombi formation occurs. It is believed that when blood comes in contact with an artificial surface, the first reaction is the adsorption of plasma proteins on the surface. This forms a layer 100-200Å thick. It is also believed that the first adsorbed protein plays an important role in blood compatibility and adsorption of serum albumin greatly reduces, or totally prevents platelet adhesion reaction, thus passivating the surface toward the formation of mural thrombus[28]. The apparent thromboresistance of polyurethanes is thought to reside in the polyurethanes, ability to preferentially adsorb albumin. However, not all polyurethanes are equally biocompatible.

One short-term approach for the case of an implant application has been the use of a systemic anticoagulant such as heparin to prevent thrombus formation on the polymer surface, but this has serious drawbacks, in some cases it may cause hemorrhaging, and even death. To circumvent this problem, and localize the anticoagulant effect, heparin has been coated and chemically combined with the blood-contact surfaces of the polymers. This approach can be used succesfully, but after the heparin has been eluted from the coated surface, thrombotic episodes can be expected .

Some scientists prepared polyurethane and ethylene vinylacetate copolymers by adding heparin in the system during preparation, and examined the thermal stability and biological activity of the released heparin[29]. Modification by heparin grafting was studied since heparin was inexpensive and rapidly neutralized by the administration of protamine. But one drawback was that it may induce thrombocytopenia and that may lead to massive thromboembolism. Due to decrease of the amounts of clotting factors, high risk of excessive bleeding is exists in heparin applications[30]. Some scientists examined the effects of anticoagulants coated or immobilized on the surfaces of polyurethanes. The most commonly examined proteins were heparin[31], albumin[32,33] , hirudin[34] or conjugates of heparin-albumin[35]

Studies for improving blood compatibility also include the use of more biocompatible hydrophobic polymers[36], endothelial cell seeding[37], fibrinolytic enzymes[38] and self-assembly strategies[39]. Polyethylene oxide coupling is one method to increase hydrophilicty[40,41] and prevent thrombus formation. Static blood compatibility and hemocompatibility was studied in in vitro tests under a shear of blood flow by using various stearyl poly(ethylene oxide) coupled polyurethanes[42].

To modify the surfaces of polyurethanes by using negatively charged ions to resemble the endothelium layer of veins is another approach for

blood compatibility. Chen et.al.[43] prepared polyurethane structures by using sulfonated or carboxylated chain extenders. and it was reported that especially for carboxylate group the degree of platelet adhesion and platelet activation was significantly reduced.

Modification with ionic functional groups such as poly(sodium vinyl sulfonate[44], propyl sulfonate[45] were also achieved and increase in biocompatibility was observed. For MDI-based polyurethanes it was reported that, at the same ionic content, sulfonate incorporation significantly reduced platelet deposition compared to carboxylate incorporated ones[46]. In contrast, it was also reported that sulfonate containing polyethylene surface had much higher platelet adhesion than the carboxylic acid containing ones[47]. Presence of charged groups decrease the contact angle of the surfaces by increasing hydrophilicities and it was shown that contact angle dropped from 70° to 43° for Biospan ™ (Segmented poly(ether urethane urea) linear block copolymer of 4,4'-diphenylmethane diisocyanate extended with a mixture of ethylenediamine, 1,3-cyclohexanediamine and polytetra methylene oxide) when it was modified and covalently coupled with p-aminosalicylic acid and the ratio of absorption of albumin to fibrinogen increased with drug content on the surface[48].

Modifications of segmented polyurethanes with methacryloyloxyethyl phosphorylcholine by forming semi-interpenetrating polymer networks[49] or by forming alloys[50] increased the antithrombogenic property of the surfaces. Phospholipid layers[51,52] or sulfoammonium zwitterionic molecules also demonstrated lower platelet aggregation on segmented polyurethanes[53]

Use of hydrophobic materials which exhibit slow NO release is another way to create a nonthrombogenic surface since endothelial cells produce NO and it is known that this prevents platelet adhesion and activation. NO releasing polymers can be prepared by incorporating some diazeniumdiolate molecules, which donates NO onto polymeric substances[54]. Movery etal.[55] prepared solid and stable several diazeniumdiolate NO donors and incorporated them into polymers by uniform dispersion, covalent attachment or ion-pairing. These molecules spontaneously react with water and produce NO and residual di- or poly-amines. Enhanced thromboresistance compared to conventional polymers was reported and in vitro platelet adhesion decreased significantly

Polyurethanes were modified by L-cysteine by covalent immobilization and treated with S-nitroso-bovine serum albumin to supply NO in order to decrease platelet aggregation[56]. The control of release rate of NO is very important since high release may lead to toxic effects while insufficient release may not be effective to prevent platelet aggregation.

Immobilization of functionalized dextrans or biological compounds[57] or nonsteroidal antiinflammatory drugs such as salicilic acid and their derivatives[58] also increase antithrombogenic effects.

It was shown that, grafting the surfaces of vascular PU scaffolds (Estane, made of polyester type polyurethane), with biomacromolecules increased their biocompatibility. For this purpose, surfaces were aminolyzed by using

1,6-hexanediamine and the produced free amino groups were reacted with gelatin, collagen or chitosan via glutaraldehyde coupling. A drop in surface contact angle from ~83° to ~40°, and enhanced cell-material interaction and faster cell proliferation were observed on modified surfaces compared to control PU scaffolds in the carried out with human endothelial cells[59].

However upto date none of these mentioned methods have been completely successful platelet activation and coagulation and thrombi formation occurs on the interface when a polymer based medical device in come to interaction with blood in vivo. Therefore there is still and will be more intense research ion chemical and surface properties of implant materials.

3.2 Modifications for Gas Permeability

Permeability of polyurethanes is an important feature for a broad range of applications including packaging, bio-materials (e.g. for controlled release or encapsulating membranes, catheters, dialysis membranes or wound dressings, etc.), barrier materials, high performance impermeable breathable clothing and membrane separation processes. The gas permeation rate of PU membrane could be modified by controlling the ratio of hard domain to soft domain. The gas permeation property is dependent on the type, amount and molecular weight of polyols and chain extenders. The effect of chemical composition on the gas permeability might be through the degree of phase separation and the nature of chain packing.

For the PU films prepared from different isocyanate and glycol components (such as toluene diisocyanate and 1,4-butanediol hard segments; and hydroxyl terminated polybutadiene, hydroxyl terminated polybutadiene/styrene and hydroxyl terminated polybutadiene/acrylonitrile soft segments), it was reported that free volume size and fractional free-volume decreased with the increase of hard segment content. A direct relationship between the gas permeability and the free-volume has been established based on the free-volume parameters and gas diffusivity measured[60].

In vivo and in vitro stabilities of modified poly(urethaneurea) (BioSpan MS/0.4) blood sacs were reported in literature. Blood sacs were utilized primarily in left ventricular assist devices that were implanted in calves for times ranging from 5 to 160 days. In vitro cyclic testing was also conducted on similar sacs. Various analytical methods were employed to characterize the properties of the sacs after in vivo or in vitro service. The methods included ATR-FTIR spectroscopy, scanning electron microscopy and gel permeation chromatography. In general, the characteristics of implanted and in vitro cycled sacs were similar to their control sacs. It was reported that thermal and microtensile properties were unchanged after testing. The same

was true for the ATR-FTIR spectra, indicating relative chemical stability for the time frames explored here. The only significant changes occurred in molecular weight and gross surface morphology. A modest increase in weight average molecular weight was observed for most implanted blood sacs, indicating some type of chain extension or branching reaction in vivo. Although the surface morphologies of implanted blood sacs were often similar to their control, sometimes limited pitting was observed on the nonblood contacting surfaces in regions that experience maximum bending during service[61].

Polyurethaneurea-polyether (PEUU) multiblock copolymers were synthesized to elicit lower permeability to water vapor and gases. For this purpose, polyisobutylene (PIB) segments were linked to the PEUU copolymer as combs. By using macromonomers with two hydroxyl sites, amphiphilic copolymers, with a polyurethaneurea-polyether multiblock backbone and polyisobutylene combs, were synthesized by condensation reaction. PIE incorporation varied between about 2 and 30%, with comb lengths ranging from around 3000 to 29 000 g/mol. Characterization of this new multiblock multicomb copolymer was performed by GPC, FTIR, solid state C-13 NMR, and Soxhlet extraction[62].

A nanocomposite approach for biomedical poly(urethane urea)s, that results in a significant reduction in gas permeability without sacrificing mechanical properties was reported. PUU/alkylammonium modified montmorillonite nanocomposites were prepared containing relatively low volume fractions of the layered silicate. X-ray diffraction experiments showed a silicate gallery spacing increase, indicating the formation of intercalated PUU/silicate structures. With higher silicate content, modulus and strength increased with no loss of ductility. Water vapor permeability was reduced by five times at 6 vol% silicate, as a result of polymer/inorganic composite formation. It was proposed that, these concurrent property enhancements are well beyond what can be generally be achieved by chemical modification of PUU polymers[63].

A series of polyurethanes with varying hard/soft segment ratio were prepared from toluene diisocyanate and polypropyleneglycol, and oxygen permeabilities were examined. It was reported that increase in the amount of soft segment increased oxygen permeation while addition of chain extender caused a drop in permeability[64].

It was reported that, for separation of gases such as O_2/N_2 and CO_2/N_2, the small addition of PDMS into polyether-based PU matrices led to both higher gas permeabilities and selectivities of O_2/N_2 and CO_2/N_2. This might be because the incorporation of PDMS leads to the phase separation in both hard segment (MDI/BD) and soft segment (polyethers) due to the difference in solubility parameter, and the dispersed PDMS phases serve to produce a more tortuous route for diffusing molecules. While the small addition of polyethers into PDMS-based PUU matrix decreased gas permeability and

did not affect the selectivity of O_2/N_2. It, however, increased the selectivity of CO_2/N_2[65].

Chronic in vivo instability, however, observed on prolonged implantation, became a major roadblock for many applications. Presently, utilization of more oxidation resistant polycarbonate polyols as soft segments, in combination with antioxidants such as Vitamin E, offer materials which can endure in the body for several years. The applications cover cardiovascular devices, artificial organs, tissue replacement and augmentation, performance enhancing coatings and many others. In situ polymerized, cross-linked systems could extend this biodurability even further. The future will expand this field by revisiting chemically controlled biodegradation, in combination with a mini-version of RIM technology and minimally invasive surgical procedures, to form, in vivo, a scaffold, by delivery of reacting materials to the specific site in the body and polymerizing the mass in situ. This scaffold will provide anchor for tissue regeneration via cell attachment, proliferation, control of inflammation, and healing[66].

3.3 Modifications for Calcium Deposition

Calcification of polyurethane prosthetic heart valves is a major problem. Solidification leads to deterioration of the prosthesis and at the same time formation of tears and cracks in the prosthesis. Calcification, defined as the deposition of calcium compounds, occurs in a wide spectrum of medical devices.

The actual mechanism of calcification is not completely understood and is associated with practically all the soft implants such as bioprosthetic heart valves, polymeric blood pumps and heart valves, contact lens, etc. It is related to host metabolism as well as to the chemistry and structure of the implant. It is known that the implanted medical devices lead to the most dystrophic calcification, where the tissues are necrotic or otherwise altered in normocalcemic subjects. The glutaraldehyde (GA) treatment of tissues for crosslinking would be the major cause by deteriorating the tissue structure, while fresh tissues do not calcify. In addition, glycoaminoglycan components in the tissues are extracted during the GA treatment to provide the sites for the initial nucleation of calcium compounds. Blood components or lipids deposited would have a contribution, too. There have been a number of approaches to prevent the calcification, and aminooleic acid, after-treatment or heparin coupling, etc. is a representative one.

Decrease in calcification was reported when the bioprosthetic tissue (BT) was coupled with sulfonated PEO derivative via glutaraldehyde crosslinking. Such a decreased calcification might be explained by several effects as following; the amino end groups of NH_2-PEO-SO_3 were coupled to the residual GA groups to remove the possible contribution of GA residues for the calcification. PEO-SO_3 segments would have filled the space in the

collagen matrix which was reported as nucleating sites for calcification. The enhanced blood compatibility of PEO-SO_3 might decrease the adhesion of blood or cellular components. This method can be a useful anticalcification treatment for implantable tissue valves and pericardium tissue patch[67].

In several reports, the complexation of calcium ions with PEO chain segments was hypothesized for the calcification of PU as in the case of PEO-polybutylene terephthalate containing PEO main chain[68].

Calcification properties of polyurethane composites made from biaxially drawn ultrahigh molecular weight polyethylene were examined by incubating the samples in calcium phosphate metastable solution. The results demonstrated that the membranes were susceptible to extrinsic calcification that was closely related to the matrix polyurethane material used. Calcification was postponed for composites compared to solution cast polyurethane membranes[69].

Polyurethane composite membranes were prepared by solution casting and then subjected to heat-compaction. It was reported that the heat compaction induced distortion of macromolecules and physical changes on microstructures and demonstrated higher affinity to calcium ions than the non-heat compacted samples[70]

Ventricles made from segmented polyurethane membranes and used in the fabrication of a totally implantable artificial heart are known to undergo biomaterial-associated calcification. As there is no effective method currently available to prevent such biomaterials from calcifying, a practical solution is to use only materials with a relatively high resistance to calcification to extend ventricular durability and ensure a longer functional life for the manufactured device. In this study, an in vitro calcification protocol was used to determine the relative resistance to calcification of six different polyurethanes, namely, Carbothane (R) PC3570A, Chronoflex (R) AR, Corethane (R) 80A, Corethane (R) 55D, Tecoflex (R) EG80A, and Tecothane(R) TT1074A. The results demonstrated that all six polyurethanes became calcified during the 60-day incubation period in the calcification solution. The degree of calcification was found to be related with the surface chemistry of the particular polyurethane, with the Tecothane TT1074A exhibiting the highest level. The Corethane 80A and 55D polymers showed a relatively low propensity to calcify. These two membranes can, therefore, be considered as the most appropriate materials for the fabrication of ventricles for a totally implantable artificial heart. In addition, since the calcification occurred primarily at the surface of the membranes, without affecting the bulk microphase structure, the issue of modifying the surface chemistry to reduce the incidence of calcification is discussed[71].

Some scientist examined the calcification and apatite formation on porous polyurethane foams. The foams were used as matrices for the production of hydroxyapatite-based calcium phosphate ceramics, which are important as bone defect fillers[72].

4. PLASMA SURFACE MODIFICATION

Surface modification of vascular and cardiac implants as well as other medical devices by use of glow discharge plasma application is a concept studied in the last decades. The process has many consequent steps and depends on various factors including the geometrical shape of the reaction chamber, type and power of electrical discharge, type and flow rate of gas used, and properties of substrate. In glow discharge surface modifications generally radiofrequency energy is applied at low pressures.

The generated plasma contains free electrons, radicals, excited atoms and neutral particles. Constant bombardment of the substrate surface with these active particles leads to breaking some bonds of the surface molecules, and react with them by forming new bonds. Therefore, a chemical change on the surface about 30 Å occurs while the bulk structure of the substrate stays intact.

Depending on the type gas used, it becomes possible to change hydrophilicity of the surface or create a coat having completely different structure than the bulk. Most generally used gases are oxygen, nitrogen, argon, or various monomeric substances. Previous studies have shown that it is even possible to coat a very porous substrate such as activated charcoal granules by polymerisation of hexamethyldisiloxane and create a biocompatible surface[73]. Various properties of polyurethanes prepared by using different diisocyanate compounds (such as diphenylmethane-, hexamethylene-,2,6-toluene- and 2,4-toluene-diisocyanates) and different glycols (such as polypropylene-ethyleneglycol, polypropylene glycol) were examined along with their biocompatibilities.

Plasma application by using monomers such as hydrophilic hydroxyethyl methacrylate or hydrophobic hexamethyl disiloxane changed the surface properties.

When the segmented polyurethanes prepared from toluene diisocyanate and polypropylene-ethyleneglycol were subjected to oxygen and argon plasmas it was observed that the adsorbed protein levels decreased upon treatment and the adsorption was the lowest for oxygen plasma treated samples where albumin levels were higher than fibrinogen and gammaglobulin[74].

Polyurethane elastomeric films which were prepared from toluenediisocyanate and poly(propylene-ethylene)glycol did not cause any blood cell aggregation or fibrin formation (except the one which contained high amount of glycol). Aging or accelerated aging did not demonstrate any change in mechanical properties[75,76].

For polyurethanes prepared from 2,4-2,6-toluene diisocyanate, and poly propylene glycol, it was observed that tensile strength and ultimate elongation values were both increased in the presence of chain extender, propanediol, in the structure. Oxygen permeabilities of the prepared elastomers increased as the soft segment content increased [64,77,78].

For polyurethane elastomers prepared from diphenylmethane diisocyanate (MDI) or hexamethylene diisocyanate (HDI) and poly(propylene glycol)[11], and from toluenediisocyanate (TDI) and polyol[79], without using any other ingredients such as chain extender, catalyst or solvent, it was shown that the ratio of the ingredients used initially affected the mechanical properties. An increase in the amount of MDI, HDI or TDI led to production of stiffer membranes. When MDI and HDI containing polymers were brought in contact with blood no clotting was observed even after 1 hour of contact.

Surface modification by oxygen plasma application increased surface hydrophilicity of the TDI containing membranes and the contact angle values decreased from 67 to 46 degrees. Such a surface modification is reported to affect cell attachment capability of the membranes. For Vero cells, it was observed that as the applied power increased, number of attached cells increased for 10 watt but decreased for 100 watt power applied samples. This observation indicated the hydrophobic nature of adhesion of the cells on polyurethanes[80].

The attached cell numbers were about 42-45 cells per cm^2 for the pristine membranes depending on the preparation composition. The highest attachment numbers were obtained for membranes modified with 10 watts and the cell densities were in the range of 62-70 cells per cm^2. The lowest values were observed with the samples modified with 100 watts and were in the range of 27-40 cells per cm^2. These results showed that a certain level of hydrophilicity is needed for cell attachment. Figure 1 shows the adhered Vero cells on pristine and plasma modified polyurethane membranes.

All these experiments showed that, the mechanical properties, physical forms, as well as biocompatibilities and hemocompatibilities of polyurethanes all depended on their chemical compositions (types and amounts of diisocyanate and glycol components), preparation conditions (types and amounts of solvents, chain extenders, catalysts, reaction type and temperature, curing conditions, etc), and modification parameters (by chemical molecules, irradiation by UV or gamma, or by plasma glow discharge applications).

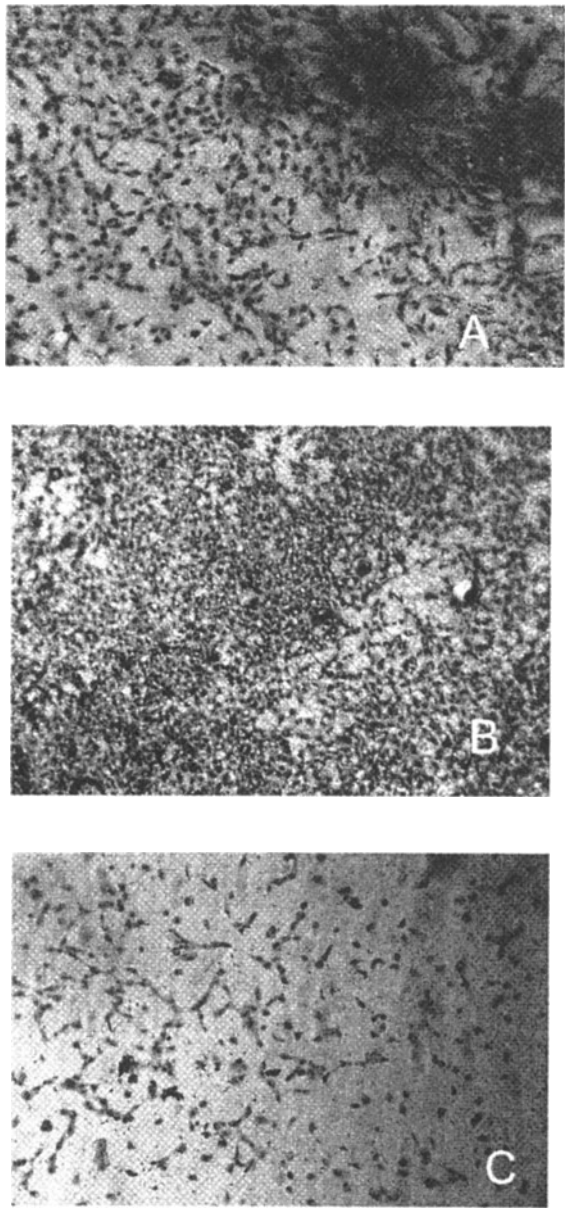

Figure 1. Attachment of Vero cells on segmented polyurethane surfaces. A) Untreated polyurethanes, B) Treated with 10 Watt oxygen plasma, C) Treated with 100 Watt oxygen plasma

5. CONCLUSION

Polyurethanes have very high importance in the production of medical devices or systems because of their excellent mechanical properties high biocompatibilities and the availabilities in different forms changing from elastomeric membranes to porous sponges. Still an intense research is going on to synthesize new formulations, to modify the existent ones with various techniques in order to increase their bio and blood compatibilities. Most of the research is concentrated on understanding the interactions between chemical structure and cell attachment, thrombus formation or calcification under stress applications. At the moment polyurethanes are the only family of polymers used in cardiovascular applications because of their inherent hemocompatibilities.

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REFERENCES

1. Hasirci, N., 1991, Polyurethanes. In *High Performance Biomaterials: Comprehensive Guide to Medical and Pharmaceutical Application* (M. Szycher, ed), Technomic Pub.Co., Lancaster, pp.71-91.
2. Hasirci, N., 1994, Polyurethanes as biomedical materials. In *Surface Properties of Biomaterials*, (R. West and G. Batts, eds), Butterworth- Heineman Ltd., Oxford, pp.81-90.
3. Bayer, O., Muller, E., Peterson, S., Piepenbrink, H.F., and Windemuth, E., 1950, Polyurethanes VI. New Highly Elastic Synthetics, Vulcollans, *Rubber Chem. Technol.*, 23: 81
4. Bikales, M.N., 1969. Polyurethanes. In *Encyclopedia of Polymer Science and Technology*, Interscience Publishers John Wiley and Son Inc., New York, 11: 507.
5. Mirkovitch, V., Akutsu, T., and Kolff, W.J., 1962, Polyurethane Aortas In Dogs-Three-Year Results. *Trans .Am.Soc.Artif.Intern.Organs*, 8: 79.
6. Sharp, W.V., Gardener, D.L., and Anderson, G.J., 1966, A Bioelectric Polyurethane Elastomer for Intravascular Replacement. *Trans.Am.Soc.Artif.Intern.Organs*, 12: 1979.
7. Szycher, M., Poirier, V.L., and Dempsey, D.J., 1983, Development of an aliphatic biomedical-grade polyurethane elastomer. *J.Elast.Plast.*, 15: 81.
8. Szycher, M., Poirier, V.L., and Dempsey, D.J., 1983, Development and Testing of Melt-Processable Aliphatic Polyurethane Elastomers. *Trans.Soc.Biomater.*, 6: 49.
9. Ulubayram, K. and Hasirci, N., 1991, Polyurethanes: Chemistry and Properties. *Proceedings of Second Mediterranean School on Science and Technology of Advanced Polymer -Based Materials*. pp.1-4.

10. Ulubayram, K. and Hasirci, N., 1995, Preparation of Polyurethane Elastomer For Biomedical Applications. In *Proceedings of the Second National Symposium on Biomedical Science and Technology* (V.Hasirci, ed.), pp.65-66.
11. Kutay, S., Tincer, T. and Hasirci N., 1990, Polyurethanes as Biomedical Materials. *British Polymer Journal*, 23: 267-272.
12. Garrett, J.T., Runt, J., and Lin, J.S., 2000, Microphase separation of segmented poly(urethane urea) block copolymers. *Macromolecules* 33(17): 6353-6359.
13. Nojima, K., Sanui, K., Ogata, N., Yui, N., Kataoka, K., and Sakurai, Y., 1987, Material characterization of segmented polyether poly(urethane-urea-amide)s and its implication in blood compatibility. Polymer, 28: 1017-1024.
14. Takahara, A., Tashita, J.I., Kajiyama, T., Takayanagi, M., and MacKnight, W.J., 1985, Microphase separated structure, surface composition and blood compatibility of segmented poly(urethaneureas) with various soft segment components. *Polymer* 26: 987-996.
15. Takahara, A., Okkema, A.Z., Wabers, H., and Cooper, S.L., 1991, Effect of hydrophilic soft segment side chains on the surface properties and blood compatibility of segmented poly(urethaneureas). *J Biomed Mater Res*, 25: 1095-1118.
16. Lelah, M.D., Grasel, T.G., Pierce, J.A., and Cooper, S.L., 1986, Ex vivo interactions and surface property relationships of polyetherurethanes. *J Biomed. Mater. Res.*, 20: 433-468.
17. Hasirci, N., 1993, Synthesis of Polyurethane Elastomers for Biomedical Use. In *Ohio Science Workbook- Polymers* (M.R.Steward, ed.) The Ohio Academy of Sci., Columbus, Ohio, USA, pp. 38-41.
18. Boretos, J.W., and Pierce, W.S., 1968, A Polyether Polymer. *J. Biomed. Mat. Res.* 2: 121.
19. Boretos, J.W., 1973, *Concise Guide to Biomedical Polymers, Their Design Fabrication and Molding,* Charles C. Thomas-Publisher, Springfield, IL, pp.10.
20. Lyman, D.J., Loo, B.H., 1967, New Synthetic Membranes for Dialysis IV- Copolyether Urethane Membrane Systems. *J.Biomed.Mat.Res.*, 1: 17-26.
21. Nylias, E., 1970, Develpoment of Blood Compatible Elastomers Theory, Practice and In-Vivo Performance. *23rd Conference on Engineering in Medicine and Biology*, 12: 147.
22. Lelah, M.D., Lambrecht, L.K., Young, B.R., and Cooper, S.L., 1983, Physicochemical characterization and in vivo blood tolerability of cast and extruded Biomer. *J. Biomed. Mater. Res.*, 17: 1-22.
23. Hanson, S.R., Harker, L.A., Ratner, B.D., and Hoffman, A.S., 1980, In vivo evaluation of artificial surfaces with a nonhuman primate model of arterial thrombosis, *J. Lab. Clin. Med.*, 95(2): 289-296.
24. Szycher, M., and Poirier, V.L., 1984, Polyurethanes in Implantable Devices. *Plastic Technology*, pp.45.
25. Bouchemal, K., Briançon, S., Perrier, E., Fessi, H., Bonnet, I., and Zydowicz, N., 2004, Synthesis and characterization of polyurethane and poly(ether urethane) nanocapsules using a new technique of interfacial polycondensation combined to spontaneous emulsification, *Int. J. Pharmaceutics*, 269(1):89-100
26. Buma, P., Ramrattan, N.N., van Tienen T.G. and Veth R.P.H., 2004, Tissue engineering of the meniscus, *Biomaterials*, 25(9), 1523-1532.
27. Shukla, P.G., Kalidhass, B., Shah, A., and Palaskar, D.V., 2002, Preparation and characterization of microcapsules of water soluble pesticide monocrotophos using polyurethane as carrier material. *J Microencapsulation*, 19(3): 293-304.
28. Szycher, M., and Poirier, V.L., 1984, Polyurethanes in Implantable Devices. *Plastic Technology*, pp.45.

29. Huang, J.C., and Jennings, E.M., 2004, The effect of temperature on controlled release of heparin from polyurethane and ethylene vinyl acetate copolymer. *Int. J. Polym. Mater.*, 53: 69-78.
30. Han, D.K., Park, K.D., Ahn, K., Jeong, S.Y., and Kim, Y.H., 1989, Preparation and surface characterization of PEO-grafted and heparin-immobilized polyurethanes. *J. Biomed. Mater. Res.*, 23: 87-104.
31. Weerwind, P.W., van der Veen, F.H., Lindhout, T., de Jong, D.S., and Calahan, F.T., 1998, Ex vivo testing of heparin-coated extracorporeal circuits: Bovine experiments. *Int. J. Artif. Organs*, 21: 291-298.
32. Marois, Y., Chakfe, N., Guidoin, R., Duhamel, R.C., Roy, R., Marois, M., King, M.W., and Douville, Y., 1996, An albumin-coated polyester arterial graft: in vivo assessment of biocompatibility and healing characteristics. *Biomaterials*, 17: 3-14.
33. DeQueiroz, A.A., Barrak, E.R., Gil, H.A., and Higa, O.Z., 1997, Surface studies of albumin immobilized onto PE and PVC films. *J.Biomater Sci Polym Ed*, 8: 667-681.
34. Seiferd, B., Romaniuk, P., and Groth, T., 1997, Covalent immobilization of hirudin improves the haemocompatibility of polylactide-polyglycokide in vitro. *Biomaterials*, 18: 1495-1502.
35. Bos, G.W., Scharenborg, N.M., Poot, A.A., Engbers, G.H., Beugeling, T., van Aken, W.G., and Feijen, J., 1999, Blood compatibility of surfaces with immobilized albumin-heparin conjugate and effect of endothelial cell seeding on platelet adhesion. *J. Biomed. Mater. Res.*, 47: 279-291.
36. Yoda, R., 1998, Elastomers for biomedical applications, *J. Biomater. Sci. Polym. Ed.*, 9: 561-626.
37. Pasic, M., Muller Glauser, W., von Segesser, L., Odermatt, B., Lachat, M., and Turina, M., 1996, Endothelial cell seeding improves patency of synthetic vascular grafts: manual versus automatized method. *Eur. J. Cardio Thorac Surg.*, 10: 372-379.
38. Ryu, G.H., Han, D.K., Park, S., Kim, M., Kim, Y.H., and Min, B., 1995, Surface characteristics and properties of lumbrokinase immobilized polyurethane. *J.Biomed Mater Res*, 29: 403-409.
39. Ratner, B.D., 1998, Molecular design strategies for biomaterials that heal. *Macromol Symposia*, 130: 327-335.
40. Morra, M., Occhiello, E., and Garbassi, F., 1993, Surface modification of blood contacting polymers by poly(ethyleneoxide). *Clin Mater* 14: 255-265.
41. Han, D.K., Jeong, S.Y., and Kim, Y.H., 1989, Evaluation of blood compatibility of PEO grafted and heparin immobilized polyurethanes, *J.Biomed Mater Res: Appl Biomater*, 23 (A2): 211-228.
42. Wang, D.A., Ji, J., Gao, C.Y., Yu, G.H., and Feng, L.X., 2001, Surface coating of stearyl poly(ethylene oxide) coupling-polymer on polyurethane guiding catheters with poly(ether urethane) film-building additive for biomedical applications. *Biomaterials*, 22: 1549-1562.
43. Chen, K.Y., Kuo, J.F., and Chen, C.Y., 2000, Synthesis characterization and platelet adhesion studies of novel ion-containing aliphatic polyurethanes. *Biomaterials*, 21: 161-171.
44. Ito, Y., Iguchi, Y., Kashiwagi, T., and Imanishi, Y., 1991, Synthesis and nonthrombogeneity of polyetherurethaneurea film grafted with poly(sodium vinyl sulfanate). *J. Biomed. Mater. Res.*, 25: 1347-.1361.
45. Okkema, A.Z., Yu, X.H., and Cooper, S.L., 1991, Physical and blood contacting characteristics of propyl sulfonate grafted Biomer. *Biomaterials*, 12: 3-12.

46. Okkema, A.Z., and Cooper, S.L., 1991, Effect of carboxylated and/or sulfanate ion incorparation on the physical and blood-contacting properties of a polyetherurethane. *Biomaterials*, 12: 668-676.
47. Lee, J.H., Khang, G., Lee, J.W., and Lee, H.B., 1998, Platelet adhesion onto chargeable functional group gradient surfaces. *J. Biomed. Mater. Res.*, 40: 180-186.
48. Abraham, G.A., Queiroz, A.A., Roman, J.S., 2002, Immobilization of a nonsteroiddal antiinflammatory drug onto commercial segmented polyurethane surface to improve haemocompatibility properties. *Biomaterials*, 23: 1625-1638.
49. Morimoto, N., Iwasaki, Y., Nakabayashi, N., and Ishihara, K., 2002, Physical properties and blood compatibility of surface-modified segmented polyurethane by semi-interpenetrating polymer networks with a phospholipid polymer. *Biomaterials*, 23(24): 4881-4887.
50. Ishihara, K., Fujita, H., Yoneyama, T., and Iwasaki, Y., 2000, Antithrombogenic polymer alloy composed of 2-methacryloyloxyethyl phosphorylcholine polymer and segmented polyurethane. *J. Biomater. Sci. Polym. Edn.*, 11(11): 1183-1195.
51. Yoneyama, T., Sugihara, K., Ishiara, K., Iwasaki, Y., and Nakabayashi, N., 2002, The vascular prosthesis without pseudointima prepared by antithrombogenic phospholipid polymer. *Biomaterials*, 23: 1455-1459.
52. Korematsu, A., Takemoto, Y., Nakaya, T., and Inoue, H., 2002, Synthesis, characterization and platelet adhesion of segmented polyurethanes grafted phospholipid analogous vinyl monomer on surface. *Biomaterials*, 23: 263-271.
53. Zhang, J., Yuan, J., Yuan, Y., Zang, X., Shen, J., and Lin, S., 2003, Platelet adhesive resistance of segmented polyurethane film surface-grafted with vinyl benzyl sulfo monomer of ammonium zwitterions. *Biomaterials*, 24: 4223-4231.
54. Smith, D.J., Chakravarthy, D., Pulfer, S., Simmons, M.L., Hrabie, J.A., Citro, M.L., Saavedra, J.E., Davies, K.M., Hutsell, T.C., Mooradian, D.L., Hanson, S.R., and Keefer, L.K., 1996, Nitric oxide releasing polymers containing [N(O)NO]$^-$ group. *J. Med. Chem.*, 39: 1148-1156.
55. Movery, K.A., Schoenfisch, M.H., Saavedra, J.E., Keefer, L.K., and Meyerhoff, M.E., 2000, Preparation and characterization of hydrophobic polymeric films that are thromboresistant via nitric oxide release. *Biomaterials*, 21: 9-21.
56. Duan, X., and Lewis, R.S., 2002, Improved haemocompatibility of cystein-modified polymers via endogenous nitric oxide. *Biomaterials*, 23: 1197-1203.
57. Logeart-Avramoglou, D., and Jozefonvicz, J., 1999, Carboxymethyl benzylamide sulfonate dextrans [CMDBS] , a family of biospecific polymers endowed with numerous biological properties: a review. *J. Biomed. Mater. Res. Appl. Biomater.*, 48(4):578-590.
58. Roman, S.J., Bujan, J., Bellon, J.M., Gallardo, A., Escudero, M.C., Jorge, E., Haro, J., Alvarez, L., Castillo, J.L., 1996, Experimental study of the antithrombogenic behavior of Dacron vascular grafts coated with hydrophilic acrylic copolymers bearing salicilic acid residues. *J. Biomed. Mater. Res.*, 32: 19-27.
59. Zhu, Y., Gao, C., He, T., and Shen J., 2004, Endothelium regeneration on luminal surface of polyurethane vascular scaffold medified with diamine and covalently grafted with gelatin, *Biomaterials*, 25:423-430.
60. Wang, Z.F., Wang, B., Yang, Y.R. and Hu C.P., 2003, Correlations between gas permeation and free-volume hole properties of polyurethane membranes, European Polymer J., 39(12):2345-2349.
61. Liu, Q., Runt, J., Felder, G., Rosenberg, G., Snyder, A.J., Weiss, W.J., Lewis, J., and Werley, T., 2000, In vivo and in vitro stability of modified poly(urethaneurea) blood sacs. *J. Biomat. Appl.*,14 (4): 349-366.

62. Weisberg, D.M., Gordon, B., Rosenberg, G., Snyder, A.J., Benesi, A., Runt, J., 2000, Synthesis and characterization of amphiphilic poly(urethaneurea)-comb-polyisobutylene copolymers. *Macromolecules*, 33 (12): 4380-4389.
63. Xu, R.J., Manias, E., Snyder, A.J., Runt, J., 2001, New biomedical poly(urethane urea) - Layered silicate nanocomposites. *Macromolecules*, 34 (2): 337-339.
64. Ulubayram, K., and Hasirci, N., 1992, Polyurethanes: Effect of Chemical Composition on Mechanical Properties and Oxygen Permeability. *Polymer*, 33(10): 2084-2088.
65. Park, H.B., Kim C.K., and Lee Y.M., Gas separation properties of polysiloxane/polyether mixed soft segment urethane urea membranes, *J. Membrane Science*, 204: 257-269.
66. Zdrahala, R.J., and Zdrahala, I.J., 1999, Biomedical applications of polyurethanes: a review of past promises, present realities, and a vibrant future. *J. Biomater. Appl.*, 14:67-90.
67- Kim, Y.H., Han, D.K., Park, D.K., and Kim, S.H., 2003, Enhanced blood compatibility of polymers grafted by sulfonated PEO via a negative cilia concept, *Biomaterials*, 24(13):2213-2223.
68. van Blitterswijk, C.A., van der Brink J., Leenders, H., Hessling, S.C., and Bakker, D., 1991, Polyactive: a bone bonding polymer effect of PEO/PBT proportion, *Trans Soc Biomater,* 14:11
69. Tang, Z.G., Teoh, S.H., McFarlane, W., Poole-Warren, L.A., and Umezu, M., 2002, In vitro calcification of UHMWPE/PU composite membrane, *Materials Sci. Eng.*, C-20:149-152.
70. Tang, Z.G., Teoh, S.H., McFarlane, W., Warren, L.P., and Umezu, M., 2003, Compression- induced changes on physical structures and calcification of the aromatic polyether polyurethane composite. *J. Biomater. Sci. Polym. Ed.*, 14(10): 1117-1133.
71. Yang, M., Zhang, Z., Hahn, C., King, M.W., and Guidoin, R., 1999, Assessing the resistance to calcification of polyurethane membranes used in the manufacture of ventricles for a totally implantable artificial heart. *J. Biomed. Mater. Res.*, 48(5): 648-659.
72. Miao, X., Hu, Y., Liu, J., and Wong, A.P., Porous calcium phosphate ceramics prepared by coating polyurethane foams with calcium phosphate cements, *Materials Letters*, 58:397-402.
73. Hasirci, N., 1987, Surface modification of charcoal by glow-discharge: the effect on blood cells. *J. Appl. Polym. Sci.*, 34: 2457-2468.
74. Kayirhan, N., Denizli, A., Hasirci, N., 2001, Adsorption of Blood Proteins on Glow-discharge Modified Polyurethane Membranes. *J. Appl. Polym. Sci.*, 81: 1322-1332.
75. Hasirci, N., and Burke, A., 1987, A novel polyurethane film for biomedical use. *J. Bioactive and Compatible Polymers*, 2: 131-141.
76. Burke, A., Hasirci, V.N.and Hasirci, N., 1988, Polyurethane Membranes, *J. Bioactive and Compatible Polymers*, 3: 232-242.
77. Ulubayram, K., and Hasirci, N., 1991, Polyurethanes: Chemistry and Properties, *Procedings of Second Mediterranean School on Science and Technology of Advanced Polymer -Based Materials* , pp: 1-4.
78. Ulubayram, K., and Hasirci, N., 1993, Properties of plasma modified polyurethane surfaces. *J. Colloids and Surfaces: Biointeractions*, 1: 261-269.
79. Ozdemir, Y., and Hasirci, N., 2002, Surface modification of polyurethane membranes. *Technology and Health Care*, 10: 316-319.
80. Ozdemir, Y., Serbetci K., and Hasirci, N., 2002, Oxygen Plasma Modification of Polyurethane Membranes. *J. Mat. Sci, Materials in Medicine, JMS: MIM*, 13: 1147-1152.