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Surface properties of segmented poly(ester urethane)s and evaluation of *in vitro* blood compatibility and *in vivo* biocompatibility

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The correlation between the surface tension parameters and the chemical composition of poly(ester urethane) and poly(ether urethane) thin films with different soft and hard segments, both before and after plasma treatment, was investigated. For all investigated films, the polar terms contribute significantly to the total surface tensions, as due to the large electron-donor, γ_{sv}^{-}, interactions. Plasma treatment alters the surface energy of samples by changing their surface polarity and hydrophilicity. The polyurethane samples with higher hydrophilicity were tested for the blood protein adsorption, preliminary blood compatibility analyses and the tissue compatibility. The studied polyurethane had satisfactory balance between water uptake and blood protein adsorption, thrombogenic and hemolytic proprieties. Subcutaneous implantation of polyurethanes samples showed a good tolerance for the tested material. None of the animals died and none of chronic cellular inflammatory reactions observed so the studied material may be considered to be biomaterials.

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1. Introduction

Polyurethanes represent an important class of polymers permitting to obtain of the desired properties by a proper selection of different segments in their composition. The combination of polyols, diisocyanates and low molecular chain extenders gives a considerable position as useful biomaterials for implants or biomedical devices [1-4].

Polyurethanes have been widely used for various commercial and experimental blood-contacting and tissue-contacting applications, such as vascular prostheses, blood pumps, endotracheal tubes, mammary prostheses, heart valves, pacemaker lead wire insulations, intra-aortic balloons, catheters, artificial hearts, sensors and transducers, because of their generally favorable physical and mechanical properties, together with their fairly good biocompatibility and antithrombogenic characteristics [5-10].

An important goal in material science, biochemistry, cell biology and bioanalytics is to establish a relationship between the properties of a polyurethane surface and its interaction with biological structures. In this diligence, a balanced hydrophilic–hydrophobic surface properties are essential to achieve an improved biocompatibility of polyurethanes. Plasma treatments (discharge application in the presence of gases or monomers [11-13]) or other types of stimuli, such as those induced by heat or electrical potential [14], may alter the surface energy of most polymers, thus changing their surface polarity, hydrophilicity and adhesiveness.

Our previous publications [15-22] presented the synthesis and some properties of a series of new segmented and crosslinked polyurethanes. The influence of polymer structure on thermal stability, its behavior in different organic solvents, and the structure and morphology of these compounds were analyzed.

The present paper studies the effects of the chemical structure of segmented polyurethanes on their surface properties such as the blood protein adsorption, the haemocompatibility and the tissue biocompatibility. Investigations are based on the geometric mean approach of Owens, Wendt, Rabel and Kälble [23-25], on the Lifshitz-van der Waals acid/base approach of Van Oss, Good and Chaudhury [26-28], as well as on the theoretical methods involving quantitative structure-property relationships [29].

The balance between surface hydrophilicity and hydrophobicity was determined by contact angle, surface tension and free energy of hydration investigations. For improving hydrophilicity, the samples were submitted to a low pressure plasma treatment.

The polyurethane samples with higher hydrophilicity were tested for the blood protein adsorption, preliminary blood compatibility analyses and the tissue compatibility.

2. Materials and methods

The samples were prepared by the reaction of aromatic diisocyanates such as 4,4'-methylene diphenylene diisocyanate (MDI) or 2,4-tolylene diisocyanate (TDI) with poly(ethylene glycol)adipate (PEGA), and diethylene glycol (DEG) as chain extender, by using a two step polyaddition process in N,N-dimethyl formamide (DMF) [30].

The general chemical structure is:
$-(O-C_1-O-CO-NH-D_{1,2}-NH-CO-O-P_1-O-CO-NH-D_{1,2}-NH-CO-)_q-$

where:
D_1 = $-C_6H_4-CH_2-C_6H_4-$
derived from MDI
D_2 = $-C_6H_3(CH_3)-$
derived from TDI
C_1= $-(CH_2)_2-O-(CH_2)_2-$
derived from DEG
P_1 = $-[(CH_2)_2-O-CO-(CH_2)_4-CO-O]_n-(CH_2)_2-$ derived from PEGA
"q" and "n"subscripts are the polymerization degrees

Preparation of casting films

Each polyurethane was dissolved in DMF, to reach a concentration of 1 g dL^{-1}. The solutions were cast on a glass plate and initially solidified by slow drying in DMF saturated atmosphere, for 7 days and finally by drying at 50 °C under vacuum (48 h). The polyurethane films thus prepared were subjected to surface analysis. Also, the same types of samples were plasma-treated. The low pressure plasma treatment was performed on an installation with the following characteristics: intensity - 3 000 V cm^{-1}, frequency - 1.3 MHz, pressure - 58 Pa, duration - 10 min. Uniform drops of the test liquids with a volume of 2 μL were deposited on the film surface and the contact angles were measured after 30 s, with a video-based optical contact angle measuring device equipped with a Hamilton syringe in a temperature-controlled environmental chamber. All measurements were performed in air, at a temperature of 25 °C. Repeated measurements of a given contact angle were all within $\pm 3^\circ$. As probe liquids, double-distilled water, ethylene glycol and glycerol were used, as purchased at maximum obtainable purity.

Plasma protein adsorption

For adsorption experiment were used bovine serum albumin (from Sigma Co) solution (1mg/ml and 3 mg/ml) in phosphate buffered saline (PBS) with pH 7,4. A fresh solution of BSA was always prepared for every adsorption experiment. Prior to adsorption experiment, the samples were equilibrated with PBS for 24h. In order to perform adsorption experiments, polyurethane films with known surface area were introduced into tubes with containing 5 ml BSA solution at 37^0C for 15 min. The adsorption was carried out by gently shaking the tubes. Any air bubbles were removed by allowing the samples to cross the buffer surface several times. After 15 min of incubation, the films of polyurethane were removed and the amount of adsorbed protein was determined by assaying the remaining concentration of BSA by a UV-spectrophotometry. The adsorbed amount of BSA was calculated by following equation:

$$\text{Adsorbed BSA } (mg/cm^2) = (Co - Ce)\ V/S, \quad (1)$$

where Co and Ce are the initial and equilibrium concentrations of BSA solution (mg/ml), V is the volume of protein solution (ml) and S is the surface of the polyutethane sample.

In vitro haemocompatibility tests

The thrombogenic potential of the surface film was judged by the blood clot formation test, as described in the literature [31,32]. The polyurethane film (2x2 cm^2) was incubated in water saline (0.9 % w/v NaCl, pH = 7.4) for 24 h at 37 °C. To this swollen sample 0.2 mL human blood from a healthy donor was added on 3.8 % sodium citrate (9:1 v/v), followed by the addition of 0.2 mL $CaCl_2$ solution (0.1 mol L^{-1}) to start the thrombus formation. After 8 min, 2 mL deionized water was added to stop the reaction. After another 5 min, the water was removed from the sample and the formed thrombus was taken out with a spatula. The separated thrombus was soaked in 1 mL 37 % formaldehyde solution for 5 min, at room temperature, and then soaked in water for another 5 min. The fixed thrombus was blotted with pieces of filter paper, entirely collected and weighed. The thrombus weight percentage on the polyurethane film was calculated on the basis of the equilibrated thrombus on the glass, which under the same conditions, is assumed to be 100 %.

Haemolysis experiments were performed on the film surface, as described in the literature [33]. In a typical experiment, a dry polyurethane film (2x2 cm^2) was equilibrated in physiologic serum for 24 h at 37 °C, human blood from a healthy donor on sodium citrate (0.25 mL) being added on the polyurethane film. After 20 min, 2 mL physiologic serum was added on the film to stop haemolysis, and the sample was incubated for 60 min at 37 °C. Positive ($A_{(+)control}$) controls of absorbance ($A_{test\ sample}$) were obtained by adding 0.25 mL human blood from a healthy donor on sodium citrate to 2.0 mL bidistilled water; negative ($A_{(-)control}$) controls of absorbance were obtained by adding 0.25 mL physiologic serum, again to 2.0 mL bidistilled water. The incubated sample was centrifuged at 1000 g for 20 min. The supernatant was taken out and on a spectrophotometer the absorbance was recorded at 545 nm. The percent of haemolysis was calculated with the following relationship:

$$\%\ Hemolysis = \frac{A_{test\ sample} - A_{(-)control}}{A_{(+)control} - A_{(-)control}} \quad (2)$$

In vivo biocompatibility test

In vivo biocompatibility was performed on male rats 200g weight. Testing protocol was performed with respect of European Convention, Romanian Association for Laboratory Animals Sciences and University of Medicine and Pharmacy of Iassy regulations regarding the protection of vertebrate animals used for experimental and other scientific purposes. *In vivo* biocompatibility was assessed by inserting small polyurethane film disks (10 mm diameter size), under dorsal skin; the disks were removed after 16 days together with the adherent tissue. All surgical procedures were done under thiopental anesthesia. After prelevation the disks and the tissue were prepared for light microscopy observation. The fragments were fixed in 10% formaldehyde water solution, embedded in paraffin wax, sliced in 15 μm pieces and stained with hematoxylin – eosin - methyl blue and acid periodic – Schiff (PAS). The samples were analyzed with a Nikon E600 light microscope (Nikon, Japan).

3. Results

Surface characterization

The methods used for the determination of surface tension [34] are based on contact angle measurements between the liquid meniscus and the polyurethane surface. A contact angle below 90° indicates that the substrate is readily wetted by the test liquid, while an angle over 90° shows that the substrate will resist wetting.

Table 1 lists the contact angles between double-distilled water, ethylene glycol or glycerol and polyurethane samples, before and after plasma treatment. A decrease of the contact angle after plasma treatment indicates a higher oxygenation of the surface, leading to an increase in hydrophilicity.

Table 1. Compositional parameters of soft and hard segments, number average molecular weights, polydispersity indices and contact angle of different liquids - polyurethane samples, before$^{a)}$ and after$^{b)}$ plasma-treatment.

Samples	Weight ratio (%) $P_1:(D_{1\ or\ 2}:C_1)$	Mn	$\frac{M_w}{M_n}$	Water	Ethylene glycol
PEGA/MDI-DEG	75.43:(16.36:8.21)	20 800	1.77	$62^{a)}$	$45^{a)}$
				$25^{b)}$	$31^{b)}$
PEGA/TDI-DEG	80.11(13.24:6.65)	20 100	1.67	$53^{a)}$	$41^{a)}$
				$17^{b)}$	$22^{b)}$

For the calculation of the surface tension parameters the geometric mean method (Eqs. (3) and (4)), the acid/base method (LW/AB) (Eq. (5), (6) and (7)) and the theoretical method based on the structure-property relationships considering the group contribution techniques (Eq. (8)) were used.

$$\frac{1+\cos\theta}{2}\cdot\frac{\gamma_{\mathrm{lv}}}{\sqrt{\gamma_{\mathrm{lv}}^{\mathrm{d}}}}=\sqrt{\gamma_{\mathrm{sv}}^{\mathrm{p}}}\cdot\sqrt{\frac{\gamma_{\mathrm{lv}}^{\mathrm{p}}}{\gamma_{\mathrm{lv}}^{\mathrm{d}}}}+\sqrt{\gamma_{\mathrm{sv}}^{\mathrm{d}}} \qquad (3)$$

$$\gamma_{\mathrm{sv}}=\gamma_{\mathrm{sv}}^{\mathrm{d}}+\gamma_{\mathrm{sv}}^{\mathrm{p}} \qquad (4)$$

where θ is the contact angle determined for water, ethylene glycol and glycerol, subscripts "*lv*" and "*sv*" denote the interfacial tensions between liquid-vapor and surface-vapor, respectively, and superscripts "*p*" and "*d*" denote the polar and disperse components, respectively, of total surface tension, γ_{sv}.

$$1+\cos\theta=\frac{2}{\gamma_{\mathrm{lv}}}\cdot\left(\sqrt{\gamma_{\mathrm{sv}}^{\mathrm{LW}}\cdot\gamma_{\mathrm{lv}}^{\mathrm{LW}}}+\sqrt{\gamma_{\mathrm{sv}}^{+}\cdot\gamma_{\mathrm{lv}}^{-}}+\sqrt{\gamma_{\mathrm{sv}}^{-}\cdot\gamma_{\mathrm{lv}}^{+}}\right) \qquad (5)$$

$$\gamma_{\mathrm{sv}}^{\mathrm{LW/AB}}=\gamma_{\mathrm{sv}}^{\mathrm{LW}}+\gamma_{\mathrm{sv}}^{\mathrm{AB}} \qquad (6)$$

$$\gamma_{\mathrm{sv}}^{\mathrm{AB}}=2\cdot\sqrt{\gamma_{\mathrm{sv}}^{+}\cdot\gamma_{\mathrm{sv}}^{-}} \qquad (7)$$

where superscripts "*LW*" and "*AB*" represent the disperse and polar components, respectively, of total surface tension, $\gamma_{\mathrm{sv}}^{\mathrm{LW/AB}}$.

$$\gamma(298\mathrm{K})\approx 0.75\cdot\left[\mathrm{E_{coh}}/\mathrm{V}(298\mathrm{K})\right]^{2/3} \qquad (8)$$

where γ - total surface tension, $\mathrm{E_{coh}}$ - cohesive energy, V - molar volume.

The obtained results from Table 2 and 3 shown that the sample with MDI in hard segment has a higher hydrofilicity, which increases through plasma treatment. From this reason, sample with MDI in hard segment was selected for biomedical analysis *in vitro* by water uptake tests [35], adsorption experiment, clot formation tests, hemolysis assay [33] and *in vivo* biocompatibility experiments [38].

Table 2. Surface tension parameters for untreated$^{a)}$ and plasma treated$^{b)}$ polyurethanes films according to Eqs. (3), (4) and (8).

Sample	Eqs. (3), (4)			Eq. (8)
	γ_{sv}^{d}	$\gamma_{\mathrm{sv}}^{\mathrm{p}}$	γ_{sv}	γ
PEGA/MDI-DEG	$0.62^{a)}$	$67.65^{a)}$	$68.03^{a)}$	47.30
	$0.73^{b)}$	$89.02^{b)}$	$89.76^{b)}$	-
PEGA/TDI-DEG	$5.44^{a)}$	$43.83^{a)}$	$49.28^{a)}$	47.66
	$0.61^{b)}$	$89.06^{b)}$	$89.67^{b)}$	-

Table 3. Surface tension parameters for untreated$^{a)}$ and plasma treated$^{b)}$ polyurethanes films according to Eqs. (5) and (6).

Sample	Eq. (5), (6)			
	γ_{sv}^{LW}	γ_{sv}^{-}	γ_{sv}^{+}	$\gamma_{\mathrm{sv}}^{\mathrm{LW/AB}}$
PEGA/MDI-DEG	$4.24^{a)}$	$59.01^{a)}$	$7.87^{a)}$	$47.35^{a)}$
	$2.93^{b)}$	$79.66^{b)}$	$13.42^{b)}$	$68.31^{b)}$
PEGA/TDI-DEG	$9.89^{a)}$	$38.72^{a)}$	$5.83^{a)}$	$39.94^{a)}$
	$1.39^{b)}$	$81.20^{b)}$	$15.99^{b)}$	$73.46^{b)}$

Following the plasma treatment, the disperse component of surface tension, $\gamma_{\mathrm{sv}}^{\mathrm{d}}$, decreases, while the polar component surface tension, $\gamma_{\mathrm{sv}}^{\mathrm{p}}$, increases, leading to higher values of the total surface tension of the treated samples comparatively with those of the untreated ones. This observation arises also from Table 1, where the relatively hydrophobic surface (higher contact angle) is converted into a more hydrophilic surface (lower contact angle), by plasma treatment of the studied polyurethanes.

Furthermore, according to Table 3, the polar term γ_{sv}^{P} or γ_{sv}^{AB} gives a large contribution to γ_{sv} or $\gamma_{\mathrm{sv}}^{\mathrm{LW/AB}}$, due to the large electron-donor, γ_{sv}^{-}, interactions. This effect is intensified by the plasma treatment. Before and after plasma treatment, all samples exhibit predominant electron-donor properties.

Surface properties

The biocompatibility of materials depends on their ability to swell in aqueous media. A high water level on the surface of the biomaterial provides a low interfacial tension with blood, thus reducing fibrinogen adsorption, cell adhesion and clot formation [30, 32]. Thus, the water uptake is a precursory test for hemocompatibility analysis. The water uptake correlated with the value of adsorbed BSA, the amount of blood clot and the degree of hemolysis is presented in Table 4.

Table 4. Water uptake, amount of blood clot, hemolysis degree and adsorbed BSA on polyurethane samples.

	Water uptake (%)	Clot weight (mg)	Hemolysis (%)	Adsorbed BSA (mg/cm^2)	
				1mg/ml BSA solution	3mg/ml BSA solution
PEGA/ MDI-DEG	22.14 ± 8.6	13.10 ± 0.63 (30%)	6.67 ± 0.21	0,063±0,02	0,30±6,4
glass	-	45.15 ± 0.61 (100%)	12.94 ± 0.20		

Comparing our data with those from literature [33,35,37,38], it can be concluded that the studied polyurethane have satisfactory balance between water uptake and blood protein adsorption, thrombogenic and hemolytic proprieties which shows that the material is hemocompatible and may be considered to be biomaterials.

In vivo biocompatibility test

Subcutaneous implantation is an important *in vivo* step to test various polymers for their biocompatibility and degradation properties. Rats are suggested to be of choice for soft tissue degradation studies because of their low cost and the rich background data for the animal [39].

In our studies, subcutaneous implantation of polyurethanes samples showed a good tolerance for the tested material. None of the animals died and the histomorphologic analyses demonstrated light fibrous collagen structures around the implants as well as the absence of cellular inflammatory reactions (Fig.1, 2, 3). In implant area it can be seen debris of polyurethane with pronounced porous structure (Fig.3).

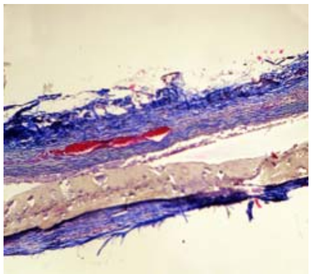

Fig. 1. Rat skin. Polyurethane sample, collagenised and well vascularised derm, hypoderm's remainder. HEA stain, ×40. (PU) polyurethane; (FT) fibrous tussue.

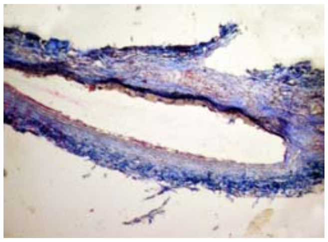

Fig. 2. Rat skin. Gap in the area of implant insertion with polyurethan wreckage, surrounded by conjunctive fibrilar tissue. HEA stain, ×100. (PU) polyurethane; (FT) fibrous tussue.

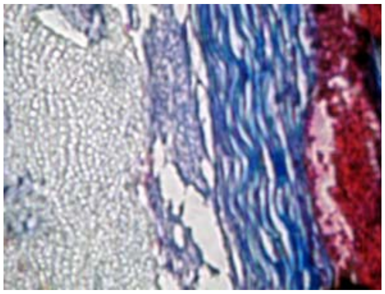

Fig. 3. Rat skin. Polyurethane implant with porous structure; fascicular conjunctive tissue. HEA stain, ×100. (PU) polyurethane.

Although on some areas of histologyc samples it was seen vascular hyperemia, moderate lymphocytes, macrophages and fibroblasts infiltration, these had a regressive post surgical reparatory character (fig.4,5).

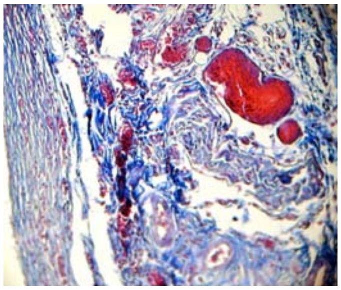

Fig. 4. Rat skin. Hyaline venous crom. Periferic fibrocellular reaction, capillary neoangiogenesis. HEA stain, ×400.

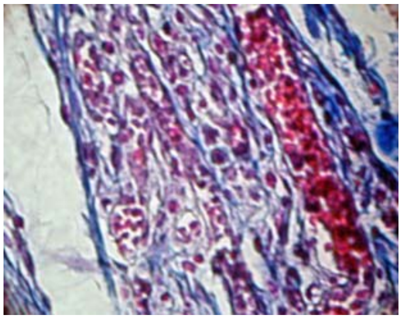

Fig. 5. Rat skin. Polymorfic cellular hyperplasy with lymphocytes, histocytes and fibrocytes. Vennular hyperemy. HEA stain, ×400.

4. Discussions

The segmented poly(ester urethane)s and poly(ether urethane)s prepared in a two-step polyaddition process were investigated to obtain information on their surface tension parameters and hydrophilicity, both before and after plasma treatment. Calculations of the surface tension parameters are based on the geometric mean method, on the acid/base method, and on theoretical methods involving structure-property relationships.

Surface hydrophilicity, evaluated by the free energy of hydration between compounds and water, confirms the influence of different hard segments and, on the other hand, the influence of the plasma treatment. This treatment creates a desirable increase in the polar surface free energy of the samples for potential applications.

Future studies on the design and characterization of hydrophilic/hydrophobic character of these segmented polyurethanes surfaces would benefit from considering the surface topology in potential biological and coating applications. In the present work, an initial evaluation for biomedical applications was made. The balance between hydrophilicity and hydrophobicity, blood protein adsorption proprieties, as well as the thrombogenic and the hemolytic properties of PEGA/MDI-DEG sample represents the first favorable results for biomedical applications. Furthermore, the results from *in vivo* experiments brought out more argues regarding the biocompatibility of PEGA/MDI-DEG polymer. The implantation of PEGA/MDI-DEG polymer didn't produce any kind of chronic inflammatory reactions so we can consider this material to be biocompatible.

After these preliminary tests performed *in vitro* and *in vivo*, we believe that the quality of our new polyurethanes can be enhanced by adjusting surface proprieties of these materials in order to be used in biomedical applications.

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