Colloids and Surfaces B: Biointerfaces 81 (2010) 20–26

Contents lists available at ScienceDirect

Colloids and Surfaces B: Biointerfaces

journal homepage: www.elsevier.com/locate/colsurfb

Poly(dimethyl siloxane) surface modification by low pressure plasma to improve its characteristics towards biomedical applications

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ARTICLE INFO

Article history:
Received 13 May 2010
Received in revised form 16 June 2010
Accepted 17 June 2010
Available online 25 June 2010

Keywords:
Poly(dimethyl siloxane)
Pluronic® F-68
Poly(ethylene glycol) methyl methacrylate
Plasma
Surface modification
Biomaterials

ABSTRACT

Poly(dimethyl siloxane) elastomer, (PDMS) is widely used as a biomaterial. However, PDMS is very hydrophobic and easily colonized by several bacteria and yeasts. Consequently, surface modification has been used to improve its wettability and reduce bacterial adhesion.

The aim of this work was to modify the PDMS surface in order to improve its hydrophilicity and bacterial cell repulsion to be used as a biomaterial. Plasma was used to activate the PDMS surface and sequentially promote the attachment of a synthetic surfactant, Pluronic® F-68, or a polymer, Poly(ethylene glycol) methyl methacrylate, PEGMA. Bare PDMS, PDMS argon plasma activated, PDMS coated with Pluronic® F-68 and PEGMA-grafted PDMS were characterized by contact angle measurements, X-ray photoelectron spectroscopy (XPS) and atomic force microscopy (AFM). The influence of the surface modifications on blood compatibility of the materials was evaluated by thrombosis and haemolysis assays. The cytotoxicity of these materials was tested for mouse macrophages.

After modification, AFM results suggest the presence of a distinct layer at the surface and by the contact angle measures it was observed an increase of hydrophilicity. XPS analysis indicates an increase of the oxygen content at the surface as a result of the modification.

All the studied materials revealed no toxicity and were found to be non-haemolytic or in some cases slightly haemolytic.

Therefore, plasma was found to be an effective technique for the PDMS surface modification.

1. Introduction

Silicone elastomer polymers, poly(dimethyl siloxane), have many properties that make them excellent materials for biomedical use, namely optical transparency, chemical and biologically inertness, non-toxicity, permeability to gases and excellent mechanical resistance [1–3]. Among many applications, some particular examples can be pointed, such as drug delivery systems, ophthalmic and blood-contacting biomaterials [3,4]. However, the use of these elastomers in medical devices (e.g. catheters, vascular grafts and voice prostheses) is usually compromised by their high hydrophobicity that causes adsorption of significant amounts of proteins from the surrounding biological environment, followed by microbial adhesion and biofilm formation [5]. In many cases, the adsorption of non-specific proteins leads to the failure of the devices [5–7]. Therefore, it is desirable the modification of the surface in order to improve some properties like wettability and/or cell repulsion (inhibition of microbial adhesion) [2,6]. Several techniques, involving physical or chemical treatments, or a combination of both, have been reported to modify the surface properties of PDMS [8]. Among these techniques, plasma, ultraviolet light and corona discharge have been the most commonly used [9–12]. Plasma treatment is a simple and the most widespread technique used to change surface hydrophobicity [4]. The modifications obtained by this technique depend not only on the characteristics of the particular plasma created, but also on the system used [13]. Nevertheless, these modifications are only temporary as the surface quickly recovers its native hydrophobic state. [1,3,12].

Owen and co-workers explained this hydrophobicity recovery as being the result of the reorientation of surface silanol groups into the bulk polymer, cracking of the SiO_x structure, which provides the movement of free PDMS chains from the bulk to the surface, condensation of silanol groups at the surface, loss of volatile oxygen or other species into the atmosphere, and changes in surface roughness [3,12].

Depending on the gas used in the plasma treatment, plasma can itself introduce groups at the substrate surfaces or can be used to

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doi:10.1016/j.colsurfb.2010.06.014

activate surface for subsequent linkage of water soluble polymer chains that are known to suppress biofouling [3].

Furthermore, the incorporation of Poly(ethylene oxide) (PEO) molecules on a substrate surface generally results in a reduction of the adsorption of biomolecules such as proteins and bacteria [2,12,14,15]. Also, biosurfactants have been used to modify the surface characteristics and consequently reduce and/or inhibit microbial adhesion [16]. Alternatively to biosurfactants, synthetic surfactants, such as Pluronic® that proved to be useful for biomedical purposes, can be used with the advantage of being purer and well-known compounds. Pluronic®, a segmented block polymer synthetic surfactant, has been widely studied for pharmaceutical and biomedical applications, and has been used as a coating agent [2].

On the other hand, Poly(ethylene glycol) (PEG) and its derivatives, such as Poly(ethylene glycol) acrylate and Poly(ethylene glycol) methyl methacrylate, have also been used to coat PDMS surfaces in order to improve its characteristics. Structurally, PEG is the low molecular weight equivalent (Mw < 10000) of PEO. Surface modification procedures have ranged from simple physical adsorption to structural alteration via covalent bonding of PEO molecules [9,10].

In the present study, the modification of bare PDMS surfaces was conducted by argon plasma treatment followed by coating with Pluronic® F-68 or PEGMA grafting. The evaluation of the surface morphology was studied by atomic force microscopy (AFM). Moreover, the extent of surface modification, namely the surface elemental composition, was confirmed by X-ray photoelectron spectroscopy (XPS). Also, contact angles were measured to determinate the surface free energy and the recovery of hydrophobicity of the modified surfaces. Finally, *in vitro* assays were performed to evaluate the blood interactions and cytotoxicity of the modified PDMS.

2. Materials

2.1. Reagents

Pluronic® F-68 and Poly(ethylene glycol) methyl methacrylate (Mw ≈ 10,000) were purchased from Sigma–Aldrich. Sylgard® 184, a PDMS kit containing two parts, a liquid silicon rubber base and a curing agent, was purchased from DOW-Corning.

2.2. Methods

2.2.1. Preparation of PDMS films

Sylgard® 184 PDMS pre-polymer and cross-linking agent were mixed at the ratio of 10:1 by mass and degassed under vacuum. Films with 0.5 mm thickness were cured at 65 °C during 4 h. The PDMS films were washed thoroughly with acetone.

2.2.2. PDMS surface modification

In order to create reactive sites for subsequent attachment of other compounds, PDMS surface was treated with argon plasma. A plasma system FEMTO (low pressure plasma) manufactured by Diener Electronics was used. The process includes two steps: exposure of the PDMS films to argon plasma and impregnation either with a synthetic surfactant, Pluronic® F-68 or polymer (PEGMA) solution. The operational conditions used in the plasma treatment were: 0.6 mbar of the chamber pressure, 2 min of irradiation and 100 W of power.

Afterwards plasma treatment, the films were dipped in Pluronic® F-68 and PEGMA solutions at 10% (m/v) and placed in an oven during 24 h at 60 °C. Next, the films were washed thoroughly with distilled water.

2.3. Surface characterization

2.3.1. Contact angle determination

The determination of contact angles is a simple and direct method to characterize the hydrophilic nature of surfaces [17].

In order to evaluate the surface free energy of the modified PDMS, static contact angles were measured with four standard liquids: distilled water, formamide, ethylene glycol and propylene glycol. The reported angles consist in the average of 7 independent measures. The measurements were performed at room temperature using the sessile drop method.

Surface free energy values, as well as the dispersive and polar energy components, were obtained according the Owens–Wendt–Rabel and Kaelbe method (OWRK) [18,19,20].

Contact angle measurements were carried out with OCA 20 from Dataphysics.

2.3.2. X-ray photoelectron spectroscopy

X-ray photoelectron spectroscopy (XPS) was used to evaluate the elemental composition at the surface. XPS analysis was performed on a VGS ESCALAB 200A spectrometer with an Al Kα X-ray source. The operation conditions were set to 15 kV [13,21].

Binding energies were all referred to the C1s at 285.0 eV. The core-level signals were obtained at a photoelectron take-off angle of 0° relative to sample surface. The C1s spectrum was analysed and peak-fitted using a combination of Gaussian and Lorentzian peak shapes obtained from the XPSpeak 4.1 software [4,13,21,22].

2.3.3. Atomic force microscopy

The morphology of the surfaces was studied by AFM using a Nanoscope IVa Veeco Metrology, in the tapping mode (scan size 4.0 μm, scan rate 1.0 Hz). The average roughness (*Ra*) was calculated directly from the AFM images [13].

2.3.4. Haemocompatibility

Biological response of both bare and Pluronic® F-68 and PEGMA coated PDMS were carried out. Thrombogenicity and haemolysis assays were performed with rabbit blood with ACD (acid-citrate-dextrose).

2.3.4.1. Thrombogenicity assay. Thrombosis is the clotting of blood within a blood vessel. It occurs when a blood clot obstructs the flow through the circulatory system [23].

In vitro thrombogenicity assay was carried out by gravimetric analysis, an adaptation of the method described by Imai and Nose [23,24].

Before testing, the films were kept in contact with phosphate-buffered saline solution (PBS), at 37 °C for 24 h. Briefly, 250 μL of blood with ACD anticoagulant and 25 μL of 0.1 M $CaCl_2$ were placed on the surface of each film (one film, in triplicate, for each contact time) and incubated at 37 °C. The clotting process was stopped by adding distilled water (5.0 mL) after 20 and 40 min. Clots were fixed using 36.5% (w/w) formaldehyde solution (5.0 mL), dried and finally weighted. This assay includes a positive (+) (glass Petri dish) and a negative (−) control (absence of sample and blood) [23]. The thrombose degree is calculated as follow:

$$\text{Thrombose } (\%) = \frac{\text{mass test sample} - \text{mass}(-)\text{control}}{\text{mass}(+)\text{control} - \text{mass}(-)\text{control}} \times 100 \quad (1)$$

2.3.4.2. Haemolysis assay. Haemolysis is the rupture of the red blood cells and the release of haemoglobin into the surrounding fluid [23,25].

These assays were conducted in accordance with ISO 10993-4:20002 [25] and ASTM F756-87 standards [26]. Briefly, triplicate samples of each film were placed in polypropylene tubes with 7 mL

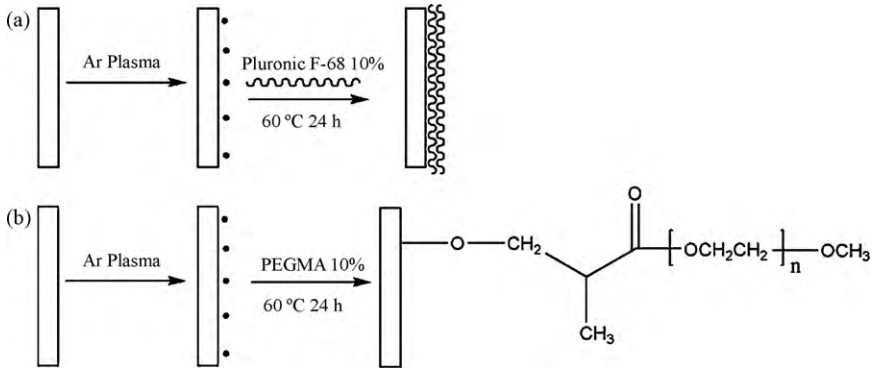

Fig. 1. Scheme of (a) Pluronic® F-68 coating on PDMS surface and (b) PEGMA grafting on PDMS surface.

of PBS during 48 h at 37 °C. Materials were then incubated with diluted ACD blood (1 mL of diluted blood for each 7 cm^2 of material), during 4 h, at 37 °C, under static conditions. Positive (+) and negative (−) controls were produced by adding rabbit blood to distilled water and PBS solution, respectively. After centrifugation at 750 × *g*, the haemoglobin released by haemolysis was measured by the cyanmethemoglobin method described elsewhere, determining the supernatants adsorption at 540 nm [23,24,26]. The haemolytic index (H.I.) was calculated as follows.

$$\text{H.I. } (\%) = \frac{\text{OD of test sample} - \text{OD}(-)\text{control}}{\text{OD}(+)\text{control} - \text{OD}(-)\text{control}} \times 100 \quad (2)$$

2.3.5. Viability and cytotoxycity assays

Peritoneal macrophages were harvested from Balb C mice[1] and cultured according to the protocol established by the Biophysics/Biomathematics Institute, Faculty of Medicine of the University of Coimbra [27] that was optimized from the Weir's method [28]. Complete RPMI 1640 medium was used as culture medium in sterile conditions in a laminar flow chamber.

Macrophages' viability and cytotoxicity were tested with Trypan Blue and the MTT (3-(4,5-dimethylthriazol-2,5-diphenyltetrazolium bromide)) assays, respectively, at 3 and 5 days of incubation, triplicate samples for each incubation time (37 °C, 5% CO_2, with complete RPMI 1640) [27,29,30].

The MTT colorimetric assay measures the mitochondrial and respiratory chain activity. When these mechanisms are intact, the enzyme succinate dehydrogenase is active and reduces the yellow tetrazolium (MTT) to purple formazan crystals, which can be photometrically quantified at 570 nm. The quantity of formazan crystals is directly proportional to the number of viable cells [31].

The macrophage were maintained in the culture medium and, after the incubation during the two selected times, the old medium was removed and 270 μL of sterile RPMI and 30 μL of MTT solution were added to each well and incubated for 3 h in the same conditions. Afterwards, the whole solution was removed and 300 μL of isopropanol acid were added and incubated for 30 min at room temperature to ensure that all the formed crystals were dissolved. Absorbance was determined at 570 nm using a MicroELISA [31].

3. Results and discussion

3.1. PDMS surface modification

In plasma treatments, hydrogen atoms are first removed from the polymer chain to generate radicals within the polymer chains located at the surface. Some of these radicals in the polymer chain combine themselves with the radicals formed in the plasma resulting in functional groups [32]. In the present work, the PDMS surface was activated by argon plasma that cannot, by itself, introduce groups at the surface. Nevertheless, the activated surface can react with the oxygen or moisture in the air, forming SiO_2, Si–OH or Si–CH_2OH groups on the PDMS surface [3,13].

After plasma treatment, samples were impregnated with Pluronic® F-68 to adsorb it to the surface according to the scheme presented in Fig. 1(a). Also, activated PDMS surface was grafted with PEGMA solution at 10% (w/v) as represented in Fig. 1(b).

3.2. Surface characterization

3.2.1. Contact angles

Contact angle measurements were carried out for the bare and plasma treated PDMS surface with Pluronic® F-68 or PEGMA coatings. Water contact angles were measured along 14 days in order to assess the aging of the samples and some possible recovery of its hydrophobicity. Fig. 2 illustrates the contact angles variation with time for the different modifications studied. Immediately after the plasma treatment, the contact angles were found to decrease due to the presence of polar groups at the surface, such as SiO_2, Si–OH and Si–CH_2OH [8]. Also, it is important to notice that Pluronic® F-68 and PEGMA molecules have polar groups (ethylene oxide) that

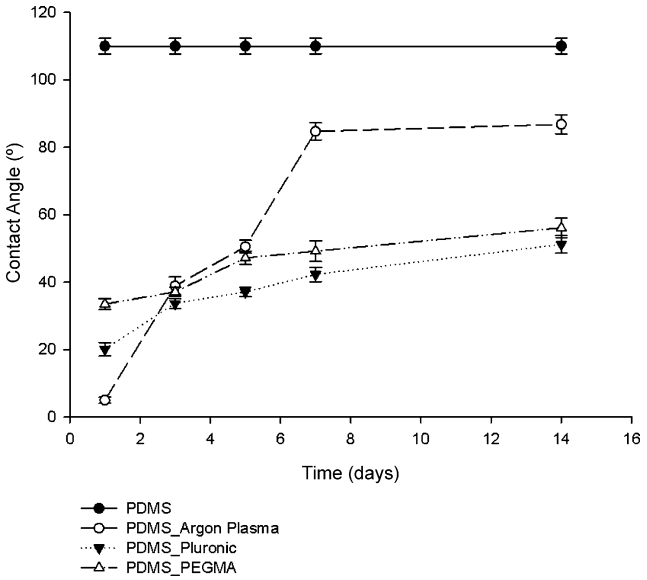

Fig. 2. Variation of the contact angles (water/surface) with time of the bare and modified PDMS (PDMS argon plasma activated, PDMS coated with Pluronic® F-68 and PEGMA-grafted PDMS).

[1] According to national and international regulations on animal wellfare.

Table 1
Surface free energy, dispersive and polar components of the surface free energy and % of polar component of the bare and modified PDMS (PDMS argon plasma activated, PDMS coated with Pluronic® F-68 and PEGMA-grafted PDMS).

	Surface energy (mJ/m^2)	Dispersive component (mJ/m^2)	Polar component (mJ/m^2)	% Polar component
PDMS	12.71 ± 2.35	11.38 ± 2.16	1.33 ± 0.91	10.5
PDMS_Plasma_Ar	94.31 ± 1.91	1.74 ± 0.22	92.57 ± 1.90	98.2
PDMS_Pluronic	111.40 ± 3.81	0.13 ± 0.12	111.28 ± 3.81	99.9
PDMS_PEGMA	85.49 ± 3.72	0.39 ± 0.22	85.09 ± 3.65	99.4

Table 2
Chemical composition data by XPS of the bare and modified PDMS (PDMS coated with Pluronic® F-68 and PEGMA-grafted PDMS).

	At%			
	PDMS	PDMS_ Plasma Ar	PDMS_Pluronic	PDMS_PEGMA
C1s	41.27	29.85	31.82	37.97
O1s	28.25	41.77	41.01	39.53
Si2p	30.47	28.38	27.18	22.49

increase dipole–dipole interactions and consequently decrease the overall contact angle. Therefore, the observed decrease represents an indirect measure of the extent of modification. Nevertheless, as discussed above and clearly shown in Fig. 2, the hydrophilicity of plasma treated PDMS without further modification is short-lived, as it quickly regains its original hydrophobic character [3,12].

Moreover, it was found that for both modifications (PDMS with Pluronic® F-68 and PDMS grafted with PEGMA) the contact angle stabilizes after 7 days. The results showed that the Pluronic® F-68 coated surface recovered about 25° when exposed to air during 14 days, while PEGMA grafting modified surface contact angle increased 15°. In the case of PDMS modified by argon plasma, the hydrophobicity recovery is faster than for the other modifications, probably due to the migration of lower molecular weight species from the bulk to the surface (about 85° in 14 days).

Water contact angle measurements of PDMS with Pluronic® F-68 and PDMS grafted with PEGMA suggest that these modifications provide more stable surfaces.

Table 1 compiles the data determined regarding the surface free energy, as well as the percentage of the energy polar component. Results showed that after argon plasma treatment, the surface energy increases drastically, as well as the % of polar component. This increase can be explained due to the presence of polar groups both from Pluronic® F-68 and PEGMA, as already mentioned to be responsible for the observed water contact angles decrease. These results suggest that the surface of PDMS was efficiently modified.

3.2.2. X-ray photoelectron spectroscopy

The elemental composition of the surface was assessed by XPS. The results in Table 2 clearly showed that after the plasma treatment, the carbon content decreases and the oxygen increases, since the interaction of the active species with air results in higher amounts of oxygen at the surface. The XPS spectra of C1s for all the studied surfaces are presented in Fig. 3. The peak located at 284.7 eV is associated with C–Si and C–H bonds. Moreover, a higher binding energy is related with oxygen binding: 286.5 eV to –C–O–C; 288 eV to –C═OC–, and 289 eV to –COO–. The relative composition ratio based on the peak areas is given in Table 3. The results obtained suggest the presence of C–OH and –C–O–C linkages due to the plasma treatment. Argon plasma generates radicals at the PDMS surface and afterwards the contact of these radicals with the air moisture originates Si–OH and Si–CH_2OH groups. Williams and co-workers [6] treated medical-grade of poly(dimethyl siloxane) elastomer using low pressure argon plasma and reported the presence of C–Si–O–Si, C–H and to –C–O–C bonds after one month of storage [6].

Furthermore, Fig. 3(c) suggests, as expected, the presence of an ether peak (C–O–C) and a hydroxyl peak (C–OH) which indicates that the Pluronic® F-68 molecules are adsorbed at the PDMS surface [24]. Also, for PDMS grafted with PEGMA (Fig. 3(d)), it was found the presence of the ether and ester (C═OOC) peaks [2]. Zou and co-workers [2] studied argon plasma-induced graft polymerization of PEGMA, on the Si (1 0 0) surface, by XPS, and also showed the presence of the hydrocarbon, ether and ester peaks.

3.2.3. Atomic force microscopy

Fig. 4 shows the AFM images obtained from the bare and modified PDMS surfaces. Based on Fig. 4 it was possible to determine the surface roughness for each modification. The average roughness (*Ra*) was determined in a 650 nm × 650 nm surface region. From the results it was found that, as expected, the surface of bare PDMS is homogeneous and smooth (as illustrated in Fig. 4(a)), with a very small average roughness value (0.49 ± 0.03 nm). As mentioned before, Zou and co-workers studied PEGMA grafting on Si (1 0 0) surfaces and obtained similar values for Si (1 0 0) roughness (0.3 nm) [2]. Furthermore, the surfaces that have been modified with both Pluronic® F-68 and PEGMA showed a great increase in the *Ra* values, 4.79 ± 0.11 nm and 2.25 ± 0.15 nm, respectively, which proves that the modification occurred [33]. Fig. 4(c) and (d) clearly shows the formation of peaks and valleys due the presence of the chains of the surfactant adsorbed and the PEGMA grafting.

3.2.4. Haemocompatibility

As described previously, the biological response of both bare and modified PDMS, namely thrombogenicity and haemolysis, was studied.

3.2.4.1. Thrombogenicity assay. Serum proteins adsorption onto materials is a key phenomenon for the thrombogenic process, as this thrombus formation represents a measure of the blood compatibility of a given material. Protein adsorption is the first step to initiate a coagulation cascade that ends in thrombus formation [34–37]. The thrombogenicity results are shown in Fig. 5(a). For contact times with blood of 20 and 40 min, Pluronic® F-68 coating presents a lower thrombogenicity as compared to the bare PDMS. For example, it was found that for a clotting time of 20 min, this modified material has a thrombogenic effect that is 20% lower than the bare surface.

Hydrophilic surfaces have been reported to reduce the protein adsorption [20,25]. Therefore, the results obtained in the present study suggest that the hydrophilic surface of PDMS with Pluronic® F-68 suppresses the clotting process. Furthermore, the bioinert property of PEO segments present in the Pluronic® F-68 molecule, which have been described to be high flexibility in aqueous media, contribute to the reduction of the thrombus weight on these modified surfaces [11].

Regarding the PDMS grafted with PEGMA, similar thrombogenicity values were obtained as compared to the bare PDMS. It was expected a reduction in the formation of thrombus according to the water contact angle results [14], however it is possible that the PEGMA end groups promoted the formation of thrombus.

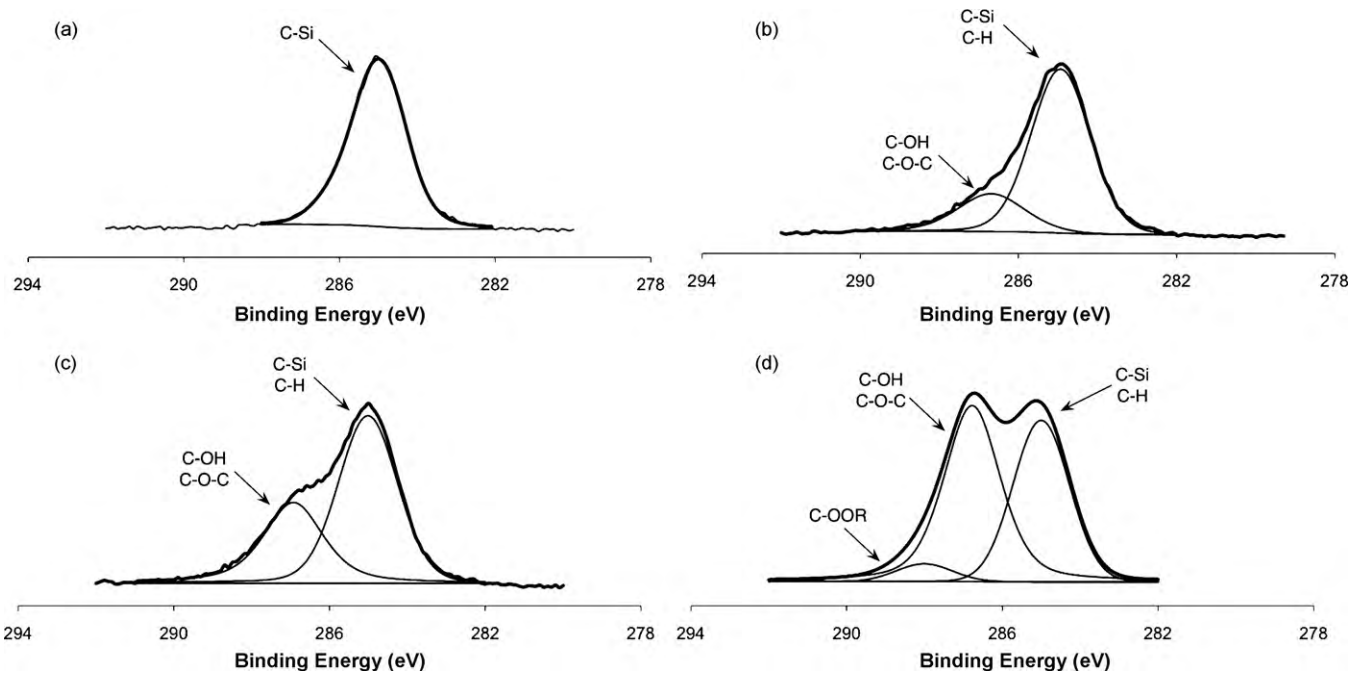

Fig. 3. XPS spectra of C1s for (a) bare PDMS, (b) argon plasma treated PDMS, (c) PDMS coated with Pluronic® F-68 and (d) PDMS with grafted PEGMA.

Table 3
Binding energy (B.E.) and relative composition ratio based on the area of C1s spectrum of the bare and modified PDMS (PDMS coated with Pluronic® F-68 and PEGMA-grafted PDMS).

B.E. (eV)		PDMS	PDMS_Plasma Ar	PDMS_Pluronic	PDMS_PEGMA
284.2–285.1	C–Si C–H	100%	78.2%	64.4%	53.7%
286.1–286.8 286.2–288	C–OH C–O–C	–	21.8%	35.6%	41.7%
288.2–288.9	–COOC–	–	–	–	4.6%

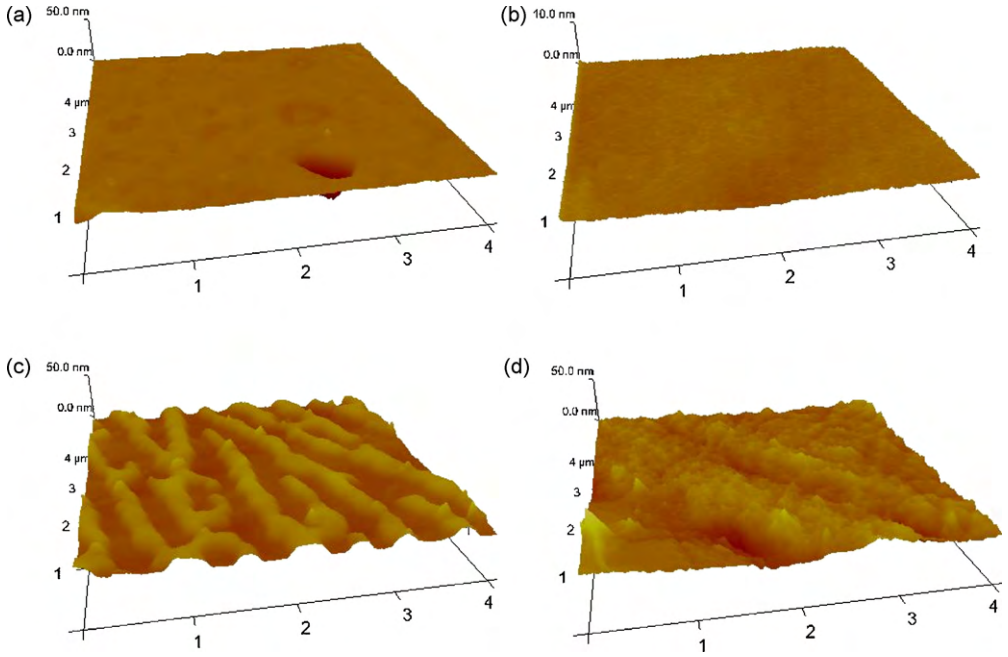

Fig. 4. AFM micrographs of the (a) bare PDMS, (b) argon plasma treated PDMS, (c) Pluronic® F-68 coated PDMS and (d) PEGMA-grafted PDMS.

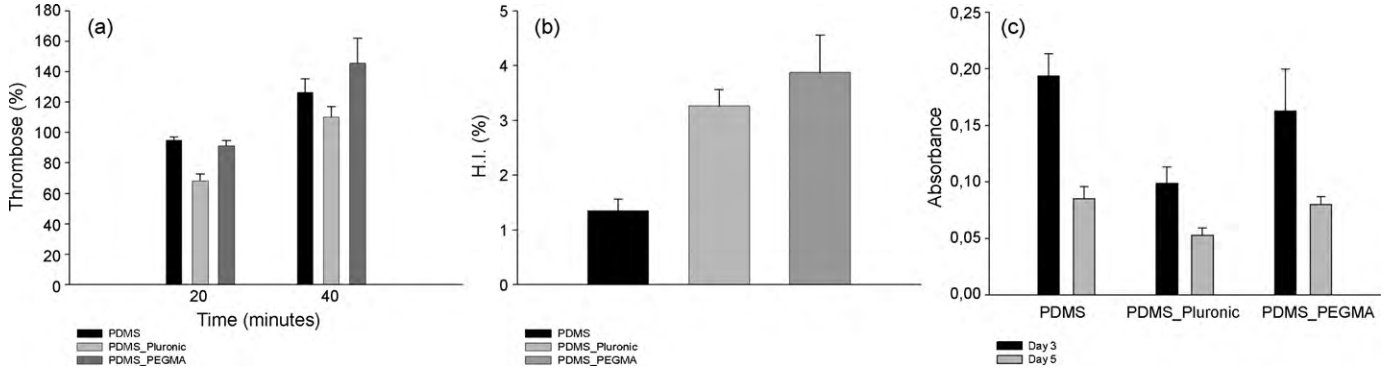

Fig. 5. (a) Thrombose values for bare PDMS, Pluronic® F-68 coated PDMS and PEGMA-grafted PDMS, for 20 and 40 min of contact with blood. (b) Haemolytic index for bare PDMS, Pluronic® F-68 coated PDMS and PEGMA-grafted PDMS. (c) Microscopic images (200×) for macrophage culture for PDMS, PDMS coated with Pluronic® F-68 and PEGMA-grafted PDMS, for 3 and 5 days of incubation.

Furthermore, for 40 min of contact, all the samples studied overcame glass thrombogenecity. This fact leads to the conclusion that these materials are not suitable to be in contact with blood, unless clotting is required.

3.2.4.2. Haemolysis assay. The haemolysis results are shown in Fig. 5(b). According to the ASTM F 756-00 standard [23], these materials can be classified as follow:

H.I. (%) < 2 – non-haemolytic
2 < H.I. (%) < 5 – slightly haemolytic
H.I. (%) > 5 – haemolytic

Any material for which the envisaged final application is on the biomedical field, should not promote haemolysis [25]. Nevertheless, it is not possible to define a universal level of acceptable or unacceptable of haemolysis index. However, by definition, a blood-compatible material should be non-haemolytic [22]. Based on this classification and on the results gathered on Fig. 5(b), the bare PDMS presented no haemolytic effect (H.I.% < 2), while PDMS with both Pluronic® F-68 and PEGMA were found to be slightly haemolytic (2 < H.I.% < 5).

Thus, although after the modifications an increase in the haemolytic index was found, the materials are still suitable to be used as biomaterials.

3.2.5. Cytotoxicity assay

Macrophages are used to assess directly the cytotoxic response to a given agent since they have the ability to maintain the immunological functions in the presence of many different chemical agents [38].

Fig. 5(c) presents the absorbance values, at 570 nm, that are proportional to the number of viable cells. Absorbance values obtained for PDMS or PDMS coated with Pluronic® F-68 and PEGMA-grafted PDMS showed that all samples are non-toxic. It is also notable that the absorbance decreased along time (from 3 to 5 days) for all samples, but still they are non-toxic. This decrease is probably due to the low proliferation rate of the macrophages in culture conditions (they do no divide *in vitro*) [39]. PDMS coated with Pluronic® F-68 presented a lower absorbance as compared with bare PDMS and PEGMA-grafted PDMS probably due to the fact that the surfactant adsorbed at surface may suffer some degradation, thus interfering with the cells viability.

4. Conclusions

Argon low pressure plasma was found to be an effective technique for the modification of PDMS surfaces. Results clearly showed that plasma treatment by itself, as well as coupled with both Pluronic® F-68 and PEGMA changed the chemical nature of the surfaces turning them more hydrophilic. Furthermore, these modified surfaces were found to be non-toxic and only slightly haemolytic. Therefore, the modified surfaces obtained in this study are potentially useful for several biomedical applications.

Acknowledgements

The present study was developed under the scope of the BIOSURFA – PTDC/SAU-BEB/73498/2006 project funded by the Portuguese Science and Technology Foundation (Fundação para a Ciência e Tecnologia – FCT).

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