Stable hydrophilic poly(dimethylsiloxane) via glycan surface functionalization

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Abstract

Polydimethylsiloxane (PDMS) is an extremely important and versatile polymeric material for biomedical and microfluidic devices due to a range of desirable properties. Control of the hydrophilicity of PDMS surfaces is of significant interest due to the potential for developing surfaces with tunable protein adsorption or cell adhesion properties. We report the formation of stable hydrophilic PDMS surfaces by covalent modification with glycans via aryldiazonium chemistry. The PDMS surface was modified by a two step-process including an activation of the PDMS surface, followed by reaction with aryldiazonium glycosides in aqueous solution. The functionalized PDMS was characterized by atomic force microscopy, infrared and X-ray photoelectron spectroscopy, water contact angle measurements and fluorescence microscopy. Our results demonstrate that glycans immobilized via this methodology have the dual function of imparting hydrophilicity and stabilizing the modified surface against hydrophobic recovery. Importantly, the presentation of thus immobilized glycosides makes them available to specific lectin-glycan binding interactions at the polymer-solution interface while, in the absence of specific binding interactions, leads to a reduction in albumin adsorption. This approach provides a novel and efficient route to stable hydrophilic PDMS surfaces with a broad range of applications.

1. Introduction

Polydimethylsiloxane (PDMS) is a biomaterial extensively used in medicine for making catheters, stents [1, 2], ocular lenses and pacemaker encapsulants [3]. More recently it has found application in the fabrication of microfluidic chips [4-7]. Despite the many advantages of PDMS, its high hydrophobicity and low surface energy often represent a challenge for controlling sealing, adhesion and flow in microfluidics, as well as for supporting cell adhesion and proliferation in bioanalytical and bioMEMS applications.

To make PDMS more hydrophilic, its surface can be modified through various processes, most notably via dry oxidation using plasma [8, 9], corona discharge [10] and UV/ozone [11] treatments. These methods can effectively increase hydrophilicity however they are often difficult to integrate into microfabrication processes due to potential damage to other components and materials. Oxidation must be carried out under carefully controlled conditions in order to avoid severe oxidative damage and loss of mechanical properties [4]; furthermore, the above processes are not applicable to the modification of internal surfaces in pre-assembled channels and devices. Importantly, oxidized PDMS surfaces exhibit hydrophobic recovery, a process by which shorter and relatively mobile PDMS chains diffuse through the polymer and rearrange at the surface so as to lower surface free energy [12]. Recovery can take place over relatively short time scales, for instance, it has been reported that the water contact angle can increase more than 50° within 2 h after PDMS oxidation [12-20]. The rate of recovery can be decreased by keeping PDMS surfaces in contact with water or polar solvents [21]. Some authors have also proposed a two-step extraction/oxidation process to reduce the concentration of mobile PDMS oligomers: in the first step the unreacted oligomers are removed from the bulk by extraction using different organic solvents, while in the second step the PDMS is oxidized by air plasma [22].

An alternative strategy for preparing hydrophilic PDMS surfaces involves the use of covalent surface functionalization following oxidative treatment. Previous literature examples show that

oxidation, followed by covalent derivatization with bulky hydrophilic groups is a viable route for creating hydrophilic PDMS surfaces with enhanced stability. Donzel *et al*., reported on the use of oxidative treatments followed by derivatization with poly(ethylene glycols) (PEGs) as a strategy [23] to reduce hydrophobic recovery. Other chemical functionalities explored for the same purpose are aminopropyltriethoxysilane (APTES) [4], UV grafted polymers [14] and chemically vapour deposited polymers [17], among others. However, most of the methods explored thus far are not applicable to the modification of internal surfaces.

The use of solution-based flow methods can overcome this problem and expand the applications of PDMS surface modifications to complex integrated devices. Herein, we describe a novel strategy for the modification of PDMS surfaces based on a two-step solution protocol; a first step of PDMS activation and a second step of functionalization with carbohydrates via aryldiazonium chemistry. Recent work from our group has demonstrated that aryldiazonium chemistry can be employed for the direct modification of polymers such as polyethersulfone (PES), which has phenyl groups in its backbone [24]. In the current work we report on the use of a mild surface activation step to generate sites that are reactive towards aryldiazonium groups, thus expanding the applications of this chemistry to polymers with relatively inert surfaces. Our results show that glycans immobilized via this methodology have the dual role of imparting hydrophilicity and stabilizing the modified surface against hydrophobic recovery.

2. Experimental Section

Chemicals and Materials. Polydimethylsiloxane (PDMS) sheets Class VI were purchased from Goodfellow; sodium hypochlorite (bleach), sodium hydroxide, potassium hydroxide, phosphate buffered saline buffer (0.010 M PBS, pH 7.4), sodium nitrite and fluoroboric acid were purchased from Sigma Aldrich. Lectin Concanavalin A (ConA) and Bovine Serum Albumin (BSA) conjugates with Alexa Fluor 647 were purchased from Biosciences. Lectin ConA and peanut agglutinin from Arachis Hypogaea (PNA)) conjugates with fluorescein isothiocyanate (FITC) were purchased from Sigma Aldrich. 4-Aminophenyl glycosides bearing mannose

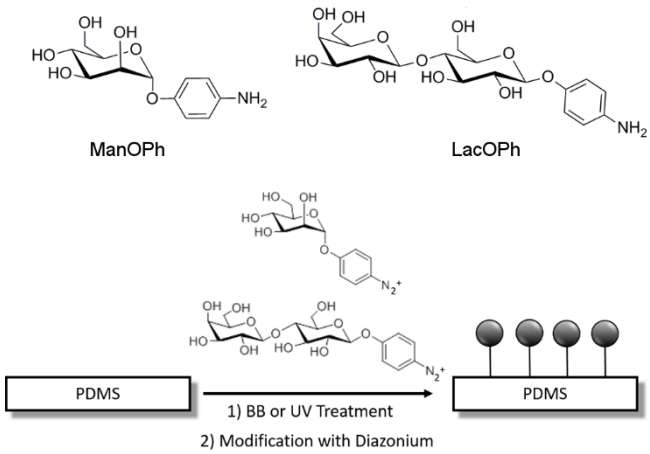
(ManOPh) and lactose (LacOPh), whose molecular structure is shown in Scheme 1, were synthesized as previously described [24, 25].

PDMS Modification. Activation of PDMS surfaces was carried out using two different methods: i) treatment with a 0.5% bleach in basic aqueous solution (KOH 1% and NaOH 1%), referred to as BB from here onwards, for 60 min in total, while changing the BB solution every 20 min with a fresh aliquot; ii) exposure to UV light in air over different time intervals (10-30 min) using a mercury grid lamp (UVP). The lamp had a peak 254 nm irradiance of approximately 6 mW cm^{-2} at the sample distance [26], and an emission at 185 nm rated at 3% of the 254 nm line by the manufacturer. After activation, functionalization of the PDMS surface pre-activated via (i) or (ii), was carried out via incubation in freshly prepared 1.0 mM solutions of aryldiazonium cations of ManOPh and LacOPh generated in situ from the aminophenyl precursor compound, following the method described by Jayasundara *et al*. [25].

Surface Characterization. Attenuated Total Reflection Fourier Transform Infrared spectroscopy (ATR-FTIR) spectroscopy measurements were collected using a Perkin-Elmer GX spectrometer, at 4 cm^{-1} resolution. X-ray photoelectron spectroscopy was performed on a VG Scientific ESCAlab Mk II system ($<2 \times 10^{-8}$ mbar), using an Al Kα source (1486.6 eV); pass energy was set at 200 eV for survey spectra and 20 eV for high resolution spectra. Spectra were collected with an emission current of 100 mA at 50% of normal operating conditions (200 mA) to minimize sample damage. Peaks were referenced to the C 1s core energy to correct for charging prior to analysis using CasaXPS software. Atomic force microscopy (AFM, Asylum Research) was carried out in tapping mode and analysis of surface topography was carried out using image analysis software (Gwyddion) from 512×512 lines images. Static contact angles were measured on a commercial system (FTA) in air, using 20 μL droplets.

Biomolecule-PDMS binding studies. PDMS samples were incubated for 1 h (Alexa Fluor conjugates) or 2 h (FITC conjugates) in a 0.5 mg/mL lectin solution in PBS buffer at pH 7.4 including 0.1 mM $CaCl_2$ and $MgCl_2$. For protein adsorption studies, PDMS samples were

incubated for 1 h in a 0.2 mg/mL BSA solution in PBS buffer at pH 7.4. After incubation, surfaces were washed with PBS solution to remove unbound protein prior to imaging. Fluorescence images were acquired using an Olympus BX51 inverted microscope with a cellSense digital image processing software. Images were acquired with a cube filter set having a 635 nm EdgeBasic long-pass edge filter, a single-edge dichroic beamsplitter filter at 649 nm and a barrier filter at 620-640 nm. Analysis of emission intensities was carried out in triplicate using Image J software.



Scheme 1. 4-aminophenyl mannoside (ManOPh) and lactoside (LacOPh) used for functionalization (top); activation and functionalization protocols used for the modification of PDMS (bottom).

3. Results and discussion

The functionalisation method consisted of a two-step process illustrated in Scheme 1. The first step consists in an activation pre-treatment of PDMS surfaces via exposure to a solution of bleach and base (BB), or via exposure to UV in air. BB solutions are known to be good oxidants [27-33] and their elevated hydroxide concentration can also chemically degrade PDMS via well known base-catalyzed depolymerization reactions [34-37]. To our knowledge, however, BB solutions have not been previously investigated as a means of activating PDMS for functionalization. UV exposure in air, on the other hand, is frequently used for the oxidative modification of PDMS [10, 38-43] and was used as a term of comparison for our studies.

Following activation, surfaces were immersed in a solution of the aryldiazonium cation of the phenylglycosides, using previously reported conditions [25].

Effect of activation pre-treatments.

The effect of UV and BB pre-treatment on the surface morphology was determined by AFM imaging in tapping mode. Analysis of neat PDMS samples yielded a root-mean-square roughness (rms) of 3.7 ± 0.6 nm. After BB-pretreatment and UV exposure for 30 min, the rms values were found to be 3.7 ± 0.7 nm and 3.7 ± 0.4 nm, respectively, thus indicating that the pre-treatments do not have a statistically significant effect on PDMS roughness.

XPS analysis was carried out to investigate chemical changes caused by BB and UV treatment on PDMS surfaces. High resolution spectra in the Si 2p, C 1s and O 1s regions of neat and treated PDMS samples are shown in Figure 1. Spectra were used to calculate peak area ratios which, corrected by relative sensitivity factors (RSF C = 1, O = 2.93, Si = 0.82), yielded the elemental atomic ratios summarised in Table 1. The neat PDMS yielded O/C and Si/O values of 0.6 and 1.0, close to those expected from the stoichiometry of the polymer, and in good agreement with previous literature results [6, 38, 39, 43-45]. UV treatments led to a slight increase in the surface O/C ratio to 0.7 after 30 min exposure to UV light; this is consistent with an increase in surface density of silanol groups which has been reported to result from UV/ozone oxidative treatments in air [43]. Treatment with BB solution was found to result in a slight reduction in oxygen content and a surface enrichment of Si atoms (Si/O = 1.2); a modest reduction in the Si 2p peak width is also observable, and suggests greater homogeneity of Si sites at the activated PDMS surface. This result suggests that treatment with BB solutions does not yield increased concentrations of surface bound O-containing groups as in the case of the UV treatment. Hydroxide ions are known to catalyze the depolymerization of PDMS which results in chain cleavage, cyclicized products and formation of insoluble and soluble silanolates [34-37]. In particular, the loss of soluble disilanolates should lead to a reduction in surface oxygen content and is likely to explain the observed change in Si/O ratio; the modest reduction

in the Si 2p peak width is also supportive of depolymerization via cyclization. Insoluble silanolates with high molecular weight are known to remain at the surface of base-treated PDMS;[46, 47] however, it is challenging to discriminate the presence of deprotonated silanolates from that of silanols via XPS, as deprotonation does not alter the C:Si:O ratio of the polymer surface.

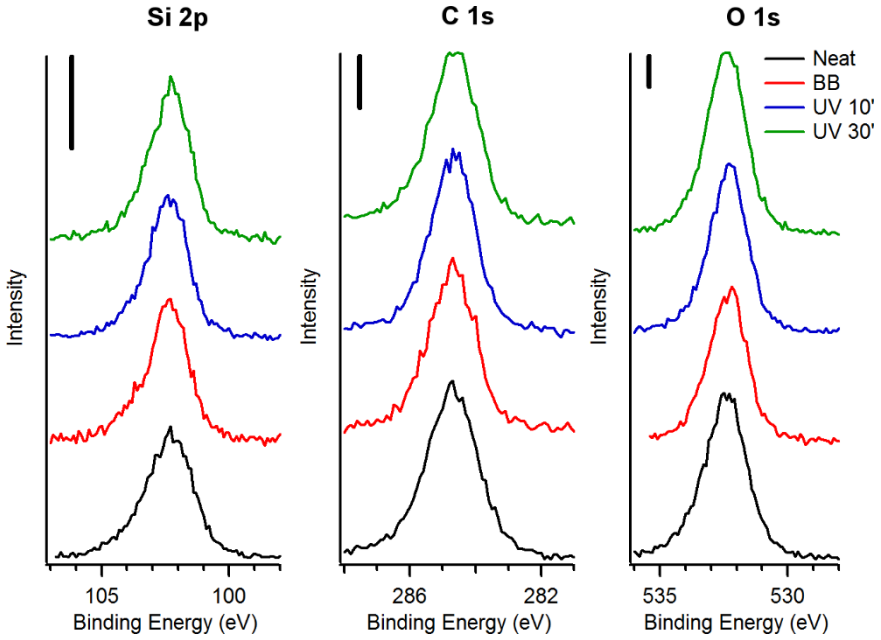


Figure 1. XPS spectra in the Si 2p, C 1s and O 1s regions of neat PDMS, BB-treated PDMS, and PDMS exposed for 10 and 30 min to UV light. Spectra were shifted to correct for charging using the C 1s peak position of 284.6 eV as reference; peaks are normalized by the height of the C 1s to facilitate comparison. The scalebar is equivalent to 500 counts in all three regions.

Material	C%	O%	Si%	WCA
PDMS neat	45	27	28	112.0 ± 0.5
PDMS BB	45	24	31	100.7 ± 0.6
PDMS UV 10’	45	26	29	92.3 ± 0.7
PDMS UV 30’	43	28	29	84.0 ± 0.3

Table 1. Atomic % composition obtained from XPS, and water contact angle of neat PDMS, PDMS pre-treated with BB solution and PDMS pre-treated with UV light after 10 min and 30 min exposure.

To investigate the effect that the pre-treatment steps have on surface hydrophilicity, we carried out studies using both infrared spectroscopy (ATR-FTIR) and water contact angle measurements. Figure 2a shows IR spectra of neat and treated PDMS in the 1800-1300 cm^{-1} region collected under identical conditions; all spectra have been normalized by the nearest peak at 1412 cm^{-1}, assigned to the asymmetric bending of $–CH_3$ groups [48]. Spectra display a broad peak between 1650-1600 cm^{-1} which can be assigned to the bending mode of water, β(HOH) adsorbed at the polymer surface [24, 49]. Exposure to UV over either 10 or 30 min leads to an increase in the integrated area of the β(HOH) peak and a shift to higher wavenumbers. This behaviour is typical of an increase in adsorbed water at polymer surfaces, as previously reported in the literature [49]. Treatment with BB shows only a small increase in the intensity of the β(HOH) peak.

Figure 2b shows the IR spectra of neat and treated PDMS in the 4000-2900 cm^{-1} region. The figure shows a broad peak centered at ~3350 cm^{-1} that arises from O—H stretching modes of silanol groups and adsorbed molecular water; the peak is convoluted with the C—H stretching vibrations of the methyl groups in PDMS at 2963 and 2906 cm^{-1}, in good agreement with the literature [43]. The C—H stretching absorbances are not shown in their entirety to more clearly compare the O—H stretching contributions. The overall intensity of the O—H stretching peak follows a similar trend to that observed for the bending modes: neat PDMS and BB-treated PDMS show the lowest peak intensities, while UV treatment, after either 10 or 30 min, leads to a visible increase in the intensity of the peak indicating a higher surface density of silanol and/or molecular water, in agreement with previous reports [43]. It is interesting to note that BB treated PDMS possesses the lowest intensity in this range among surfaces examined; this suggests that BB treatment does not lead to an increase in silanol groups, in agreement with XPS results. A reduction in O—H stretching intensity remains consistent however with formation of silanolates via exposure to BB solutions.

Water contact angle measurements using the sessile drop method were also used to determine the effect of surface treatments on wetting properties and results are summarized in Table 1. The

water contact angle of neat PDMS was found to be 112° in good agreement with literature values [6, 10]. After treatment with BB solution the water CA decreased to 100.7°; a greater decrease was obtained via UV treatment which yielded water CAs of 92.3º and 84.8º after 10 and 30 min exposure, respectively. These results confirm the trends observed via infrared spectroscopy and support the correlation between the surface concentration of oxidised groups and surface wetting behaviour. In summary, XPS, FTIR and WCA results indicate that UV treatments lead to surface oxidation and an increase in surface hydrophilicity, while the BB activation process does not lead to significant oxidation and correspondingly the change in WCA is much smaller; however, BB activation is likely to result in surface depolymerization of PDMS as suggested by XPS data.

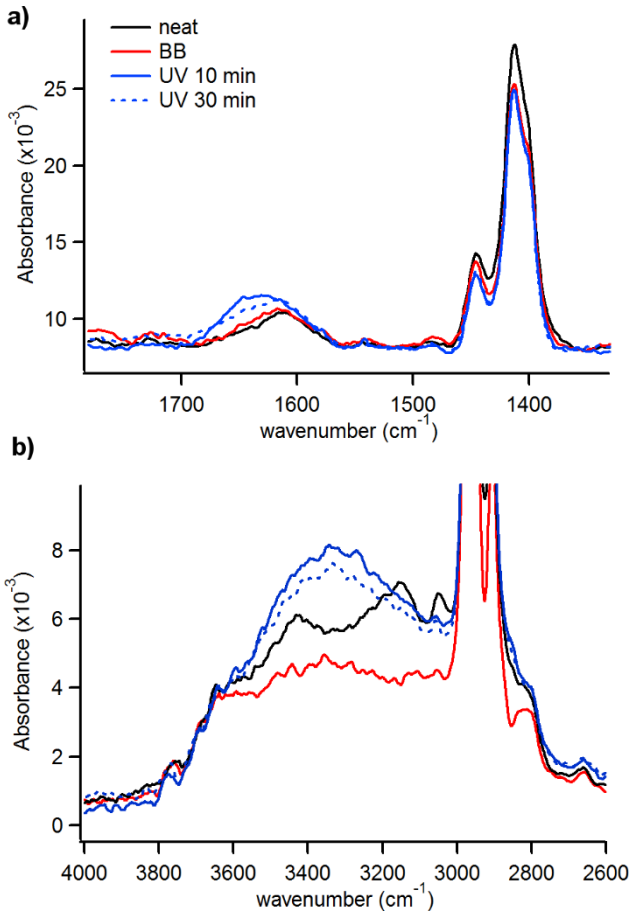


Figure 2. ATR-FT-IR of native PDMS, pretreated PDMS with BB solution, pretreated PDMS with UV light within 10 min and 30 min exposure in the HOH bending **(a)** and OH stretching regions **(b)**.

Aryldiazonium glycoside reactions on activated PDMS surfaces

PDMS surfaces treated via BB and UV exposure were functionalised via immersion in freshly prepared solutions of glycosides of aryldiazonium salts. After modification, surfaces were rinsed and dried; binding studies were then carried out to establish that glycans are immobilized via the protocols described in Scheme 1. Functionalization was first confirmed via ConA binding experiments on mannose-functionalized PDMS surfaces; specific binding interactions between ConA and mannose are well established and can be used to confirm the presence of surface-bound mannosides [50, 51]. Samples were incubated for 1 h in a solution of fluorescently labeled ConA and rinsed afterwards with PBS prior to imaging. Figure 3a shows fluorescence microscopy images after ConA incubation of PDMS surfaces corresponding to: neat PDMS, pre-treated PDMS and mannose-functionalized PDMS; Figure 3b summarises average emission intensity values obtained for samples as shown in Figure 3a. Neat PDMS surfaces were found to yield low emissions, thus indicating that the amount of ConA unspecifically bound at the PDMS surface is very low. This is consistent with the low surface free energy of PDMS surfaces, which is reported at 23 mJ m^{-2} and that is proposed to make this polymer one of the best materials in terms of protein rejection, placing it close to the minimum in the Baier curve [52, 53]. After undergoing BB or UV oxidative treatments, an increase in emission is observed indicating greater unspecific adsorption of ConA at oxidized vs. neat PDMS surfaces. After modification with ManOPh groups (PDMS-Man), a further increase in emission is observed after both oxidative pre-treatments, thus suggesting that aryldiazonium reaction increases ConA binding, as expected after immobilization of mannosides [24, 25]. Control experiments indicate that no significant ConA binding occurs on neat PDMS surfaces after exposure to aryldiazonium mannosides in the absence of pre-treatment. This indicates that the BB or UV pre-treatment steps are necessary in order to carry out aryldiazonium modification of PDMS. Although the mechanism of the reaction with PDMS surfaces is not studied in detail in this manuscript, aryldiazonium cations are highly reactive species that are known to cross-couple to nucleophilic groups, including hydroxyl groups. It is

interesting to note that in the case of BB treatments, XPS results do not provide evidence of an increase in surface hydroxyl (silanol) groups. Therefore, we propose that the role of BB treatments is to enhance the reactivity of surface nucleophilic groups; this likely occurs through both hydrolysis and deprotonation of silanol groups to form the more nucleophilic silanolate group. A proposed mechanistic route is discussed in the Supporting Information.

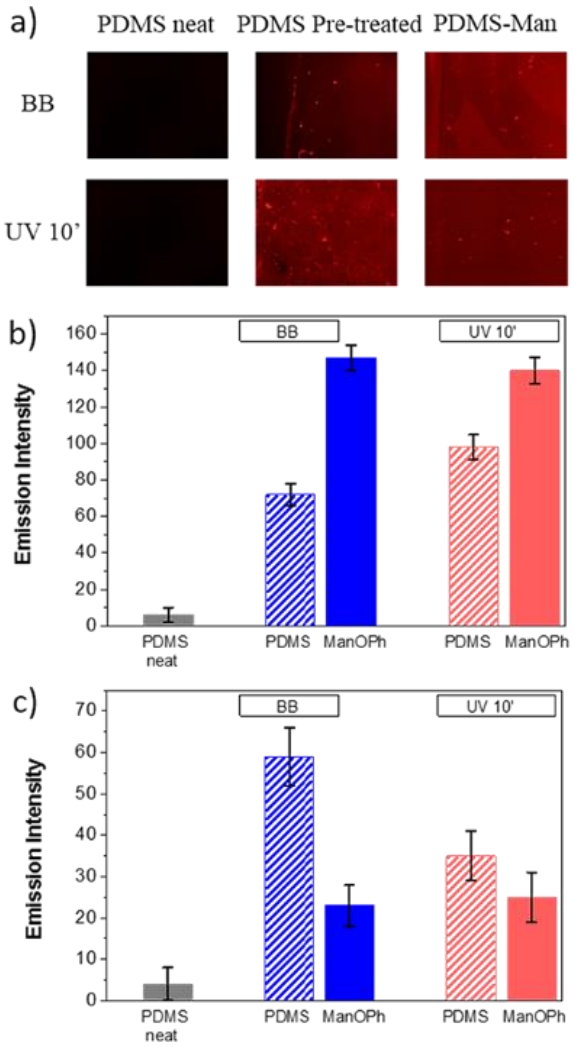


Figure 3: (a) Fluorescence images of neat PDMS, PDMS surfaces pretreated with BB and UV 10 min and PDMS coated with ManOPh after binding with ConA. (b) Summary of average emission intensities measured for surface adsorbed ConA on neat PDMS, BB-treated PDMS, PDMS treated with BB and subsequently coated with ManOPh, PDMS treated 10 min under UV light, UV-treated PDMS subsequently coated with ManOPh. (c) Summary of average emission intensities of surface adsorbed BSA on neat PDMS, BB-treated PDMS, PDMS treated with BB and subsequently coated with ManOPh, PDMS treated 10 min under UV light, UV-treated PDMS subsequently coated with ManOPh. Error bars represent standard deviations calculated over three samples.

In order to confirm that the increase in emission is due to specific mannoside-lectin interactions, we carried out the same experiments with fluorescently labeled BSA, a protein that does not display specific binding with mannoside groups. Figure 3c shows a summary of average emission intensity values obtained using BSA after identical sample treatments. After oxidation via either BB or UV the amount of adsorbed protein increases, as was the case with ConA. However, after functionalization with mannose groups a remarkable decrease in emission is observed, thus indicating that less BSA adsorbs at PDMS-Man surfaces. This indicates, first, that the increase in fluorescence observed for PDMS-Man after incubation in ConA solutions is the result of specific Man-ConA interactions. Second, that immobilization of small saccharides leads to a dcrease in unspecific protein binding compared to oxidized PDMS surfaces, in agreement with observations on the effect of glycoside coatings on polyethersulfones and carbon reported by our group [24, 25, 54], and on PDMS as reported by Zare and co-workers [55].

To further confirm that specific lectin binding interactions are observed after immobilization of glycans via aryldiazonium chemistry, experiments were also carried out using FITC conjugates of ConA and PNA, which display affinity for mannosides and galactosides, respectively [50, 51]. ManOPh and GalOPh reacted surfaces were incubated in solutions of both ConA and PNA and the emission intensity was measured to compare protein binding at the two surfaces. Figure 4a shows the fluorescence images in top view while Figure 4b shows a comparison of the emission intensities measured under identical conditions. Results indicate that FITC emission reflects the expected binding pattern of the lectins: greater emisison is observed on Man-PDMS surfaces when exposed to ConA, while greater emission is observed on Gal-PDMS surfaces when exposed to PNA.

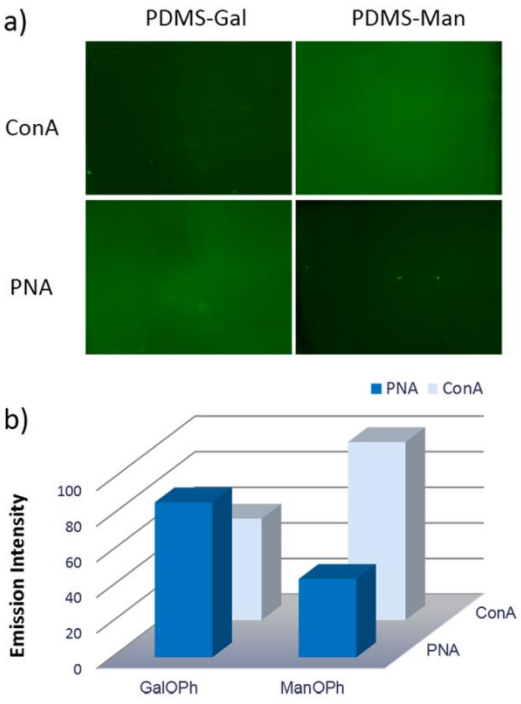
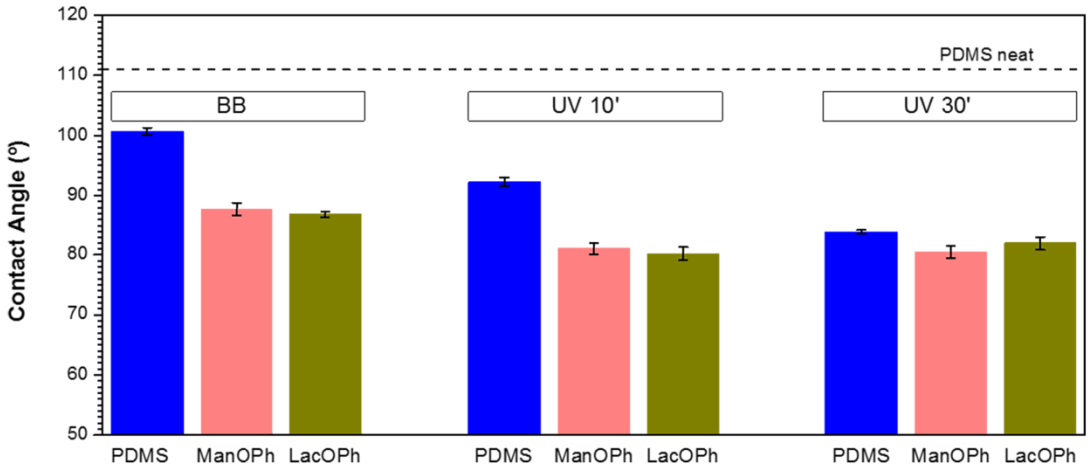


Figure 4: (a) Fluorescence images of PDMS coated with GalOPh and ManOPh after incubation in solutions of FITC conjugates of ConA and PNA. (b) Summary of average emission intensities obtained from the images in (a).

Water contact angles of neat PDMS, PDMS functionalized with mannose and PDMS functionalized with lactose for both BB and UV pre-treatments are shown in Figure 5; the contact angle for neat PDMS is represented by a dashed line. Both pre-treatments increase the hydrophilicity of the PDMS as previously discussed: BB pre-treatment produces the smallest decrease in WCA while 30 min exposure to UV produces the largest one. Functionalization leads to a further decrease in WCA for BB-treated and 10 min UV treated samples. However, for 30 min of UV exposure, functionalization with glycans was not found to lead to greater hydrophilicity. This is likely due to the high density of oxidized sites present at the PDMS surface after prolongued exposure to UV. Once the density of oxidized sites at the PDMS surface becomes greater than that required for functionaliztaion with bulky glycosides, then no further enhancement of hydrophilicity can be expected to result from the functionalization step. Interestingly, WCA values obtained after BB followed by functionalization are comparable to

292 those obtained via aggressive oxidation with UV. This indicates that the two-step solution based
293 process results in surfaces with comparable wettability to those obtained via conventional dry
294 oxidation methods.



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296 **Figure 5:** Contact angle of: PDMS, PDMS coated with mannose and PDMS coated with lactose
297 for the different pretreatments: BB, UV10' and UV30'. Dash line: neat PDMS. Error bars
298 represent standard deviations calculated over three samples.

299

300 The stability of the modified surfaces obtained via BB pre-treatment was assessed via WCA
301 measurements as a function of time. Figure 6 shows WCA values over 14 days for PDMS
302 surfaces stored under both ambient conditions and under water. No contact angle recovery was
303 observed for either mannoside- or lactoside-functionalized layers after 5 days, and no recovery
304 is observed after 2 weeks when functionalized samples are stored in water. It is worth noting
305 that even the recovery under dry conditions is relatively small, with an increase in WCA of
306 3.6% and 5.4% for mannose and for lactose, respectively, with respect to the initial WCA value.

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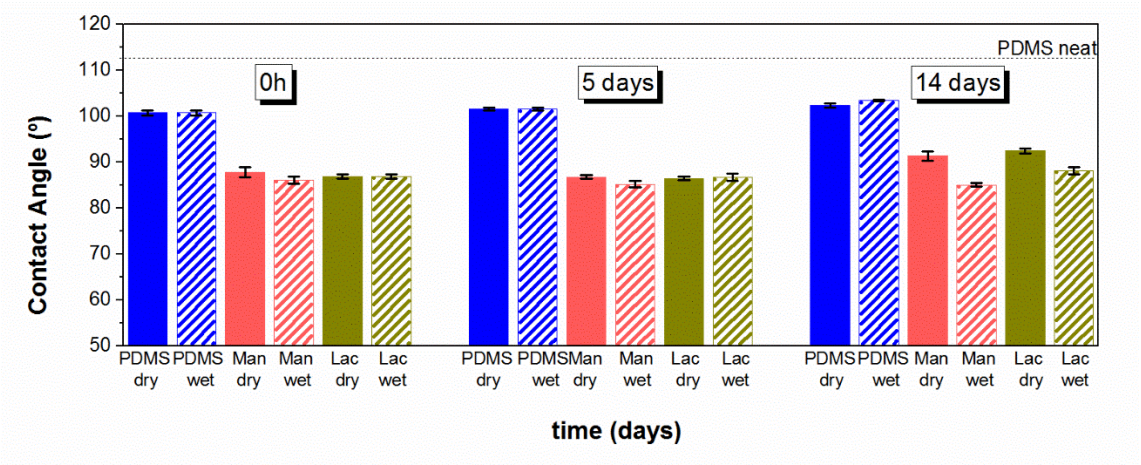

Figure 6: Contact angle of neat PDMS, PDMS oxidazed with BB, PDMS pre-treated with BB and then coated with mannose or lactose for 0 h, 5 days and 14 days. Spare bars stand for storage in air (dry) and solid bars stand for storage in distillated water (wet). Dash line: neat PDMS. Error bars represent standard deviations calculated over three samples.

Conclusions

Surface modification of PDMS via a two-step method consisting of activation followed by reaction with aryldiazonium cations was demonstrated through a combination of surface spectroscopy, protein binding and contact angle experiments. Results demonstrate that a pre-treatment via base/bleach (BB), solutions is sufficient to create reactive sites for aryldiazonium attachment. Aryldiazonium cations bearing glycosides were shown to yield PDMS surfaces with saccharide moieties whose presentation makes them available to specific lectin-glycan binding interactions at the polymer-solution interface, while in the absence of specific binding interactions, surface-bound saccharides led to a reduction in albumin adsorption. Furthermore, glycoside immobilization was found to significantly increase surface hydrophilicity, yielding surfaces with wetting properties similar to those obtained via dry oxidation methods. Studies of surface recovery via water contact angle importantly show that the wetting properties of these functional surfaces are remarkably stable over at least two weeks, especially when stored under wet conditions.

In summary, functionalization with glycans via aryldiazonium reactions offers a mild and eficient method of obtaining highly hydrophilic and/or biologically functional PDMS surfaces that display good long term stability via a solution based protocol applicable to internal or inaccessible surfaces of channels and devices. Immobilized glycans can be leveraged to either modulate protein binding or tailor surface wettability, therefore this method offers a novel route for modulating PDMS interactions with cells and organisms, an important implication given the multifaceted applications of PDMS in biomedical devices, tissue scaffolds and microfluidic chips.

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