Fabrication of pH sensitive nanovalves using smart surface coated nanopores

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Abstract. A pH sensitive nanovalve was fabricated using different smart surfaces covalently attached to an anodized aluminium oxide membrane (AAO). The smart surfaces were synthesized using a mixture of aliphatic and aminated silanes. Effect on the contact angle of the aliphatic silane chain length was evaluated. The smart surface, in conjunction with a nanoporous membrane, allowed the formation of a hydrophobic plug which controlled the transport of the molecule safranine depending on the pH of the solution. It was demonstrated that mixtures of butyl and methyl-trimethoxysilane with aminopropyl-trimethoxysilane were able to perform as effective nanovalves creating a plug that remained closed at pH>7 and opened up at pH<5.

1. Introduction
Fabrication of smart nanomaterials is an area of active research due to its broad field of applications [1–4]. Especially in medicine, the search of a valve that can be opened and closed upon application of external stimuli to release a molecule of interest constitutes a fundamental need to develop an effective drug delivery system. A number of nanovalves have been proposed in the literature with different degrees of complexity [5,6].

Rios et al. demonstrated the use of smart surfaces as a simple and effective way to control the mass transport through a nanopore [7]. The system was based on the use of an alumina membrane coated with a smart hydrophobic surface. Such a hydrophobic surface was basically a mixture of two silanes, one aminated and one aliphatic, and had the property of being hydrophobic at pH>7 but hydrophilic at pH<5. If the system is modulated properly it could, in principle, be used as an efficient drug release mechanism. Although pH smart surfaces have been known for a while [8,9], the approach proposed here possesses more degrees of freedom allowing tuning of the contact angle response based through the different properties of the species used in the modification.

Once an adequate formulation is obtained, the smart surface can be covalently attached to a nanopore, forming an effective plug to the entrance of an aqueous media when in its hydrophobic state [10]. However, it is difficult to predict the right conditions to reach the “on” or “off” states which makes the experimental evaluation of different formulations necessary. In this work, we report the influence of the aliphatic silane chain length on the response of the smart surface, for a flat substrate, as well as a nanovalve in an alumina membrane. Was verified that the length of the aliphatic chain effectively varies the switching contact angle at different values of pH.
2. Experimental

Anodized aluminium oxide membranes (AAO) were fabricated using soft anodization as described elsewhere [11]. Briefly, high purity aluminium plates (99%, Goodfellow) were used as substrates. Pretreatment of aluminium included sonication in ethanol for 5 minutes, immersion in a solution of sodium hydroxide for 5 minutes and electropolishing in a solution of perchloric acid and ethanol (1:4V/V) at 10°C and 20V for 1min to obtain a mirror finished surface.

Anodization was carried out using an aqueous solution of oxalic acid (0.3M) as electrolyte in a two step method. During the first step, a potential difference of 60V was applied between the working and counter electrode for 2 hours. The first layer of oxide was dissolved with a solution of chromic acid (2%) and phosphoric acid (6%). A second step, at the same voltage, allowed the formation of an ordered alumina membrane which was separated from the aluminium using a solution of CuSO4 and HCl.

AAO and flat glass slides were used as substrates for surface modification as described previously [12,13]. Glass slides were cleaned using piranha solution (35% H2O2-65% H2SO4) for 20min at 70°C, washed with deionized water and dried in an oven for 30min at 115°C. AAO were cleaned in boiling water for 20min and dried in the oven 30min at 115°C. Silanization of the substrates was performed overnight in 2% v/v toluene solution of silane mixtures. The mixture was 2% of APTS and 98% of aliphatic silane: octadecyl-trimethoxysilane (OTS), Butyl-trimethoxysilane (BTS) and methyl-trimethoxysilane (MTS). After modification, membranes were cured at 130°C for 1h.

Membranes were characterized using SEM to determine morphology, pore size and thickness. Contact angle analysis were performed in a Dataphysics SCA20 instrument using the sessile drop method. Droplets were buffered with a 0.1M phosphate buffer for pH 7 and an acetate buffer for pH 5. All measurements were performed at 25°C.

Diffusion experiments were carried out at 25°C in a diffusion cell made of two plastic cuvettes (1cm path) which held the different membranes in the middle. Effective area of transport through the membrane was 12mm². Solution on both sides had the same pH and ionic strength, but only one reservoir contained safranine dye.

3. Results and analysis

Figure 1 shows SEM images of a typical AAO membrane. Measured pore diameter is ~100nm and the thickness of the membranes is ~50µm. The anodization process produced well ordered pores and, after dissolution of the protecting oxide layer and the remaining aluminium metal, the membranes were modified and used for transport experiments.

Flat glass substrates were used as a mean to evaluate the hydrophobic switching of the smart surface. Figure 2 shows contact angle behaviour of the different mixtures with different pH solutions. At a high pH, both APTS:BTS and APTS:OTS surfaces are hydrophobic, which is opposite of the mixture APTS:MTS. If the formation of a monolayer is assumed, the previous result is expected since the mixture APTS:MTS will leave more of the amino groups exposed on the surface favouring its hydrophilic character. In the case of the other two mixtures, the aliphatic molecules will take a more dominant role giving the surface more of a hydrophobic character.

At pH 5, the surface APTS:OTS remains hydrophobic while the mixtures APTS:BTS and APTS:MTS produce hydrophilic surfaces. It is important to notice however, that all surfaces demonstrated a reduction in their contact angle, which suggests the presence of amino groups. In the case of mixtures made with OTS, the long aliphatic methylene chains produce a more hydrophobic environment, which forbids a hydrophilic contact angle. From a practical standpoint in its use as a pH controlled valve, the mixture APT:BTS shows a better response, since it is hydrophilic at low pH and hydrophobic at a higher pH.
Figure 1. SEM analysis of alumina membranes fabricated using two step soft anodization. (a) Top view of the membrane showing the homogeneity of the membrane (b) Top view zoom. Pore size is \(\sim 100\) nm. (c) Cross-section view. Thickness of the membranes was \(\sim 50\) \(\mu\)m.

Figure 2. Contact angle measurements. (a) Change of contact angle at pH=7 (b) Change of contact angle at pH=5. (c) Contact angle profiles on different surfaces with solutions of pH 5 and 7.
All three modifications were carried out on homemade AAO membranes. Figure 3 shows results for the different transport experiments. At pH 7, the unmodified membrane shows passage of safranine while modifications with APTS:OTS and APTS:BTS block the pores in accordance to the presence of a hydrophobic plug as expected. On the other hand, it was also observed that the mixture APTS:MTS shows a blockage of the pore. There is a possibility that an increase in rugosity on the alumina surface can also produce an increase in the contact angle, thereby producing the hydrophobic plug, although further verification of this fact is necessary.

At pH 5, all membranes allowed the transport of safranine, with the exception of the one modified with APTS:OTS. It can be observed that the surfaces APTS:BTS and APTS:MTS, although they allow safranine passage, show a higher mass transport rate than an unmodified membrane during the first minutes, however this rate decreases afterwards. This behaviour cannot be explained yet since the presence of salt in the solution would eliminate most of the charge effects on the walls. On the other hand, the hydrophobic plug would hinder transfer at the beginning, during the transition to an open state, and hence a smaller rate of mass transport would be expected, not higher. This and other aspects are currently under research in our lab.

![Figure 3](image)

**Figure 3.** Transport experiment through a nanopore membrane modified with a pH sensitive surface. (a) pH=7. (b) pH=5.

4. Conclusions

We have demonstrated the influence of the length of aliphatic silanes on pH sensitive smart surface modifications. Although all mixtures show pH sensitivity, it is clear that the longer the aliphatic change, the higher the hydrophobic character of the membrane will be. Two mixtures, APTS:BTS and APTS:MTS, performed as an effective pH sensitive valve maintaining an “on” state at pH<5 and an “off” state at pH>7.

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