Development of a Drug Delivery System by Plasma at Atmospheric Pressure

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Introduction
Most of the strategies aiming at developing hemocompatible arterial prostheses target the recruitment of endothelial cells (EC) to reproduce native artery intima (1). In practice, the implantation of arterial prostheses leads to neointimal hyperplasia, which is characterized by the obstruction of the vessel due to the migration and proliferation of smooth muscle cells (SMC) on the internal prosthetic wall. In vitro co-culture experiments combining EC and SMC already demonstrated the potential of some drugs to inhibit SMC proliferation while promoting EC proliferation (2). Plasma based technologies have been used in the past to coat the surface of biomedical devices to improve their biocompatibility (3). By selecting the
appropriate precursor molecular structure and plasma experimental conditions, one can build up a plasma polymer layer with tailored properties. The question is how to correlate those plasma conditions to obtain a drug delivery system (DDS) that could prevent SMC proliferation without delaying endothelialization. The hypothesis of this research project is that it is possible to synthesize a biodegradable polymer by plasma at atmospheric pressure on one hand, and that this polymer could be used as a DDS to prevent SMC proliferation on arterial prosthesis on the other hand.

Materials and Methods

A dielectric barrier discharge was utilized to build up a biodegradable plasma polymer that will be used as a drug delivery system. Ethyl lactate was used as precursor. The influence of plasma power, deposition time, and carrying gas (Ar, N2) were studied and correlated with the in vitro degradation rate of the coating. The layers were characterized by Fourier Transformed Infrared spectroscopy with an Attenuated Total Reflectance accessory (ATR-FTIR) and X-ray Photoelectron Spectroscopy (XPS),
while surface profilometry was used to follow the plasma polymer degradation kinetics in PBS. Finally, live/dead viability experiments were carried out in triplicate to assess the in vitro biocompatibility of this plasma based drug delivery system.

Results

XPS analyses (not shown) demonstrated that the layers synthesized using nitrogen as carrying gas (N2 layers) contained 50 to 58% carbon, 25 to 45% nitrogen, with the remaining molecular composition consisting of oxygen. The IR spectrum (Figure 1; black curve) displayed features around 2200 cm⁻¹, assigned to nitrile groups. Amide functionalities were also observed through the simultaneous presence of the C=O stretching mode near 1650 cm⁻¹ along with the features near 1550 cm⁻¹ (N-H wagging mode) and around 3000-3500 cm⁻¹ (N-H stretching mode). In addition, surface profilometry clearly evidenced the possibility of controlling the layer thickness by increasing the plasma deposition time. These results also demonstrated that more material was deposited on the region at the entrance of the carrying gas. The layers deposited
under argon (Ar layers) were made of 70 to 80% of carbon and 20 to 30% of oxygen, as determined by XPS spectroscopy. The IR spectrum (Figure 1; red curve) showed a carbonyl peak near 1720 cm\(^{-1}\), which is characteristic of ester groups. Unlike N\(_2\) layers, Ar coatings clearly contained hydrocarbon functionalities, as observed by the presence of features in the 2700-3000 cm\(^{-1}\) (CH\(_2\) and CH\(_3\) stretching modes) and 1300-1500 cm\(^{-1}\) (CH\(_2\) and CH\(_3\) deformation modes). Moreover, a feature near 3350 cm\(^{-1}\) is assigned to -OH moieties. Based on profilometry, the thickness of these coatings was more homogeneous depending on the plasma region, contrary to N\(_2\) layers. The behavior of both N\(_2\) (Figure 2) and Ar (Figure 3) layers in terms of degradation in aqueous environment was ascertained through profilometry experiments. Despite different initial thickness profiles, the coatings degraded faster at the entrance of the plasma region for both Ar and N\(_2\) layers. In addition, Ar coatings seemed to degrade slower and more homogeneously than N\(_2\) layers. Moreover, the layer degradation rate decreased with an increase of the plasma power input. Cytotoxicity tests (not shown) showed that the layers are apparently non toxic to
EC. However, the number of living cells after the test was slightly higher for Ar than for N2 layers.

**Discussion and Conclusion**

The idea of injecting ethyl lactate as a precursor in a dielectric barrier discharge at atmospheric pressure was to enable its plasma polymerization, and therefore to obtain a biodegradable polymer assembly similar to poly(lactic acid). On one hand, the FTIR data showed that the N2 coatings were likely deprived of a hydrocarbon skeleton, while containing a large amount of hydrophilic functionalities. This explains the fast solubilization/degradation of these plasma polymerized coatings upon exposure to an aqueous environment. On the other hand, both XPS and FTIR indicated that the Ar layers contained CH2 and CH3 groups, in agreement with the formation of a more conventional polymer structure. This hydrocarbon structure, coupled with the presence of hydrolysable moieties, led to a degradation behavior similar to lactide-based polymers. In addition, both N2 and Ar layers were non cytotoxic, therefore showing the potential of plasma deposited
films for drug delivery applications.

Figure 1: Infrared spectra of polymer plasma layers synthesized with N2, 10 kHz, 2.1 W/cm², 5 min (black curve) and Ar, 15 kHz, 0.2 W/cm², 15 min (red curve).
Figure 2: Degradation study of polymer plasma layer deposited under N2 at 2.1 W/cm² for 5 min. Thickness followed by profilometry after different aging times in PBS and at different positions (0=entrance of carrying gas; 3=exit). 2.a Absolute thickness; 2.b Relative thickness compared to t=0.
Figure 3: Degradation study of polymer plasma layer deposited under Ar at 0.2 W/cm² for 15 min. Thickness followed by profilometry after different aging times in PBS and at different positions (0=entrance of carrying gas; 3=exit). 2.a Absolute thickness; 2.b Relative thickness compared to t=0.

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