Water Content and Thermoplastic Polyurethane Effects on Thrombosis Clotting

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Abstract

One of the main factors that can increase the chance of heart disease is unwanted blood clotting, or thrombosis. In addition, implantable biomaterials and/or medical devices are likely to trigger a series of adverse reactions that can lead to unwanted blood clotting. Herein, we study a thromboresistant polymeric material, specifically thermoplastic polyurethanes (TPUs), on their physical properties and anticoagulation performance. Their hydrophobic nature and superior mechanical properties make them an ideal candidate for coating materials on implantable medical devices, such as vascular stents. Our results show that hydrophobic TPUs absorbed minimal to negligible water content and provided excellent thromboresistant properties against human plasma.

1. Introduction

Over the years, various implantable medical devices such as heart valves, heart stents, scaffolds, and other aortic devices have been developed to improve the health conditions of patients associated with heart diseases. However, these implantable medical devices promote serious problems with blood clotting and thrombosis formation that limit their uses for a prolonged period of time [1].

The use of polymeric coatings on the implantable medical devices is one of the possible solutions to provide desirable surface characteristics against blood clotting and thrombosis formation. In particular, thermoplastic polyurethanes (TPUs) exhibit good physicochemical properties [2] and have shown excellent abilities in thrombosis resistance [3]. In addition, TPUs are biocompatible to cells and tissues [4] and are chemically stable making them an ideal candidate for thromboresistant coatings. According to a previous study, the clotting effects on TPU surfaces showed that TPU membranes exhibited the same clotting time as human plasma with no surface, suggesting that TPU had minimal contribution to blood clotting and thrombosis formation [5].

In this study, we investigate the effect of hydrophobicity and water content of TPU surfaces (in comparison with a control glass surface) on the clotting time. We hypothesize that surfaces with hydrophobic characteristics inhibit formation of blood clots. Our results provide significant understanding to inform future development of thromboresistant coatings on implantable biomaterials and/or medical devices in the field.

2. Experimental

2.1 Materials

TPU ester film (0.1mm thick, 85A shore hardness) was obtained from Ying Chang Co., China. Citrated Pooled Normal Human Plasma (1.0 mL) was bought from George King Bio-Medical, Inc., USA. Calcium chloride (Sigma-Aldrich) was prepared in deionized water at a working concentration of 25 mM.

2.2 Physical Characterizations

The surfaces of the films were analyzed by water contact angle. The contact angle data were obtained using a single droplet of phosphate-buffered saline (5μL) in size. Using an image analysis tool (ImageJ), an angle was acquired thought various measurements (n = 3). Water absorption data was obtained through immersing the specimens (1" in diameter) into 3mL of phosphate-buffered saline for 2h. Disk samples were kept in an incubator at 37°C under constant shaking. At pre-determined time points of 1, 5, 10, 60, and 120 min, samples were removed from the liquid and gently wiped-dry to

record the mass of the disk samples. Percentage change in water content was calculated using the equation below (n = 3),

$$\%Water\ Content = \frac{W_t - W_i}{W_i}$$

where W_t is the initial dry weight and W_t is the dry weight at each time interval.

2.3 Blood Coagulation

In vitro clotting was measured using an Organon Teknika Coag-A-Mate®XM to perform activated partial thrombin time (APTT) assays. All surfaces were cleaned by typical household detergents and ethanol (75%) before each clotting experiment. Coagulation times were measured briefly as follows: 150μL of plasma was added to a test tube along with 20μL or 40μL of $CaCl_2$. The solution was mixed thoroughly and then placed onto surfaces of a glass plate (contact activation positive control) and TPU samples to wait for 0, 7, 10, 14, 17 and 22 minutes (contact time). At each time interval, 100μL of the plasma/$CaCl_2$ sample was then placed into the Coag-A-Mate®XM and was immediately activated, using this step as a warming process, with a time of 180 seconds. An additional 100μL of $CaCl_2$ was added to the plasma/$CaCl_2$ sample and clot formation was then recorded (clot time) (n = 3).

3. Results and Discussion

3.1 Physical Characterizations

Water contact angle determines the hydrophobicity of a surface. A contact angle between the water droplet and film surface that is less than 90˚ indicates the film surface is hydrophobic [6]. Figure 1A shows a representative image of 5μL water droplet when in contact with the surface of TPU film. As seen from the image, the water droplet forms a sphere-like shape due to the balanced net force between surface hydrophobicity of the film and the surface tension of the droplet, indicating the surface of the film is hydrophobic. Figure 1B shows quantitative analysis of the water contact angles between TPU films and the glass plate. Average contact angles are 156.0 ± 2.3 and 74.2 ± 0.6 degree for the glass plate and the TPU films, respectively. The significant low value of contact angle from TPU ($p < 0.05$) suggests that the TPU films are much more hydrophobic than the glass surface.

Water absorption determines the amount of water uptake in a material over a period of time. Higher water absorption rate may lead to a change in surface hydrophobicity and faster degradation rate. Figure 1C shows the percentage change on the mass of the TPU samples over 2h of incubation. Our results suggest that there is a minimal to negligible change on the mass of TPU specimens by ± 1% after incubation. As a result, TPU is stable under physiological condition without noticeable degradation.

3.2 Blood Coagulation

Blood clotting and thrombosis formation on an implantable medical device can greatly affect the therapeutic outcome of the initial treatment. If the implantable device induces even very low levels of persistent pro-thrombotic reactions, secondary procedures are typically required to properly restore the initial function of the device and to increase the survival rate for the patient. As such, clot formations on artificial surfaces are important information for the determination of device lifetime. Figure 2 shows the clot time for TPU films and glass substrates as a function of plasma contact time on the surface of both materials. At low levels of calcium (20μL; roughly 3 mM calcium in the citrated plasma), the average clot time is 125s and 170s for glass substrate and TPU films, respectively (Figure 2A). However, when increasing the level of calcium (40μL; roughly 5 mM in the citrated plasma), the average clot time is reduced to 23s for the glass substrate while the average clot time for TPU films is maintained at 170s (Figure 2B). The linear slopes in the log-log plot increase from a 6-fold difference to a 38-fold difference when doubling the amount of calcium in the clotting assay. Our results suggest that TPU exhibit excellent anti-coagulation property primarily due to the inert bulk properties and more importantly because of the hydrophobicity.

4. Summary

TPUs present themselves to be good alternative coating material in the creation of implantable medical devices that help to combat heart disease. Because of its hydrophobic nature, it repels liquids more efficiently. The repelling ability may be able to provide a barrier between the device and the internal fluids of the body. In addition, the anti-coagulation properties of TPUs inhibit blood clotting and thrombosis formation. With the presentation of these properties from TPU, it becomes clear that they are suitable for the use of coating materials on implantable medical devices.

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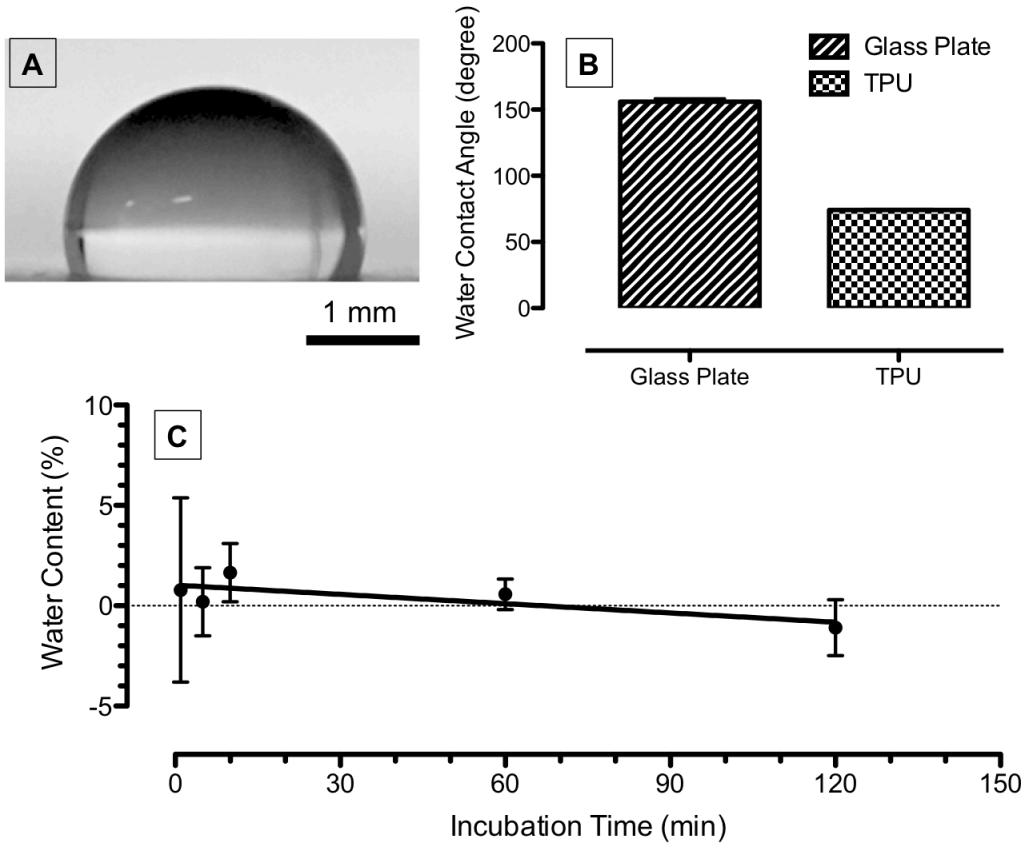

Figure 1. Physical characterizations of TPU films. (A) Image of water droplets on TPU, (B) Quantitative analysis on water contact angle of a glass plate and TPU films (n = 3), and (C) Water content profile of TPU films after incubation at 37°C for 2h (n = 3).

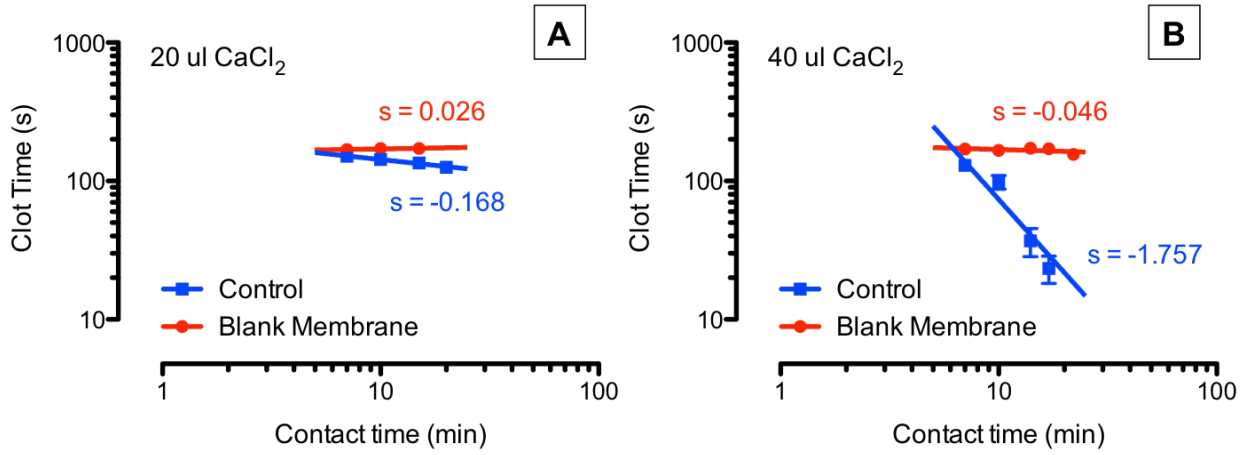

Figure 2. Clot time using human plasma for various contact times with TPU and glass plate. Effects of (A) 20μL and (B) 40μL of $CaCl_2$ added to the plasma immediately before the contact of the surfaces (n = 3).