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Shape memory polymer foams for cerebral aneurysm reparation: Effects of plasma sterilization on physical properties and cytocompatibility

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Abstract

Shape memory polyurethanes (SMPUs) represent promising candidate materials for aneurysm embolization, since they could enable clinical problems still associated with these clinical procedures to be overcome. In this work, we report on the characterization of physicochemical, thermomechanical and *in vitro* interface properties of two SMPU foams (Cold Hibernated Elastic Memory, CHEM), proposed as a material for embolization devices in minimally invasive procedures. Moreover, because device sterilization is mandatory for in vivo applications, effects on the properties of the foams after plasma sterilization were also evaluated. Both foams (CHEM 3520 and CHEM 5520) showed excellent shape recovery ability (recovery rate, R_r, up to 99%) in conventional shape recovery tests, performed at constant heating rate. Transition temperatures (T_{trans}), determined by $\tan\delta$ peaks in dynamic mechanical analysis (DMA), were 32.2 and 45.1 °C, for CHEM 3520 and 5520, respectively. The value of T_{trans} affects shape memory ability in the recovery test at 37 °C, which simulates the behavior after implantation of the device: in fact, R_r was significantly higher for lower T_{trans} foam ($R_r \approx 82\%$ and $R_r \approx 46\%$, respectively, for CHEM 3520 and CHEM 5520). After plasma sterilization performed by a Sterrad® sterilization system, an increase in open porosity was observed: this is probably due to the sterilization cycle; however, no effects on shape recovery behavior were observed. Furthermore, plasma treatment had no significant effect on L929 cells in *in vitro* cytotoxicity tests, performed on cell culture medium extracts in contact with foams for up to 7 days. Moreover, direct cytocompatibility tests showed a good colonization and growth from L929 cells on CHEM foams, suggesting the effectiveness of an in vivo healing process. All these results seem to suggest that CHEM foams could be advantageously used for manufacturing devices for mini-invasive embolization procedures of aneurysms.

Keywords: Shape memory polymers; Minimally invasive structures; Plasma sterilization; Cytocompatibility; Polyurethane foams

1. Introduction

Endovascular surgery represents the more recent and innovatory frontier in vascular surgery: when compared to traditional vascular procedures, it is significantly less invasive, resulting in shorter hospitalization and faster return to a normal life. For this main reason, together with a reduction of associated medical costs, during the last 10 years endovascular procedures have gained recognition as an alternative to open surgery for several vascular diseases treatments, including arterial aneurysms [1–3]. In 1991 the introduction of Guglielmi detachable coils (GDCs) changed the therapeutic approach to cerebral aneurysms [1,4]. GDCs are used in devices to be used in minimal invasive techniques for treating selected types of cerebral aneurysms, with the insertion of an occlusive coil into the aneurysm, to promote its embolization. The surgical procedure can be performed by

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using a catheter inserted inside the blood vessel, either under general anesthesia or light sedation, and using imaging techniques to observe in real time the patient's vascular system [2].

The US Food and Drug Administration approved the use of these devices in 1995; today, manifold variations of the original GDC coil design are available [5]. Encouraging results obtained via GDC devices account for their rapid and progressively broadened use: in many medical centers, endovascular treatments represent the primary choice for at least 60–70% of all ruptured aneurysms and their effectiveness in aneurysm rupture prevention has also been established by different multicenter studies [5–7].

Along with the positive results, many endovascular teams of surgeons have progressively experienced different types of negative events. Most endovascular interventions on aneurysms can have, in fact, important drawbacks, the more frequent being a significant incidence of residual lesions, deficient neck healing and recurrences [6,8,9]. Therefore, basic research has been focused on identification or design of new materials to allow the fabrication of more effective occlusive devices [10–12]. Among the possible candidate materials, polyurethanes (PUs) represent an interesting option, due to the possibility of tailoring chemicophysical properties in a simple and effective way. Moreover, because of their low thrombogenicity, they are widely used in cardiovascular applications [13]. Recently, shape memory polyurethanes (SMPUs) have been proposed by several authors [14] and their use is particularly interesting in the realization of minimally invasive devices [15]. SMPUs could be effectively used as occlusive embolization materials because their shape and dimensions can be minimized to achieve a less invasive insertion; an original application in this sense was proposed by L'H. Yahia et al. [16,17]. A similar approach has been also adopted by Maitland et al. for the fabrication of a device for aneurysm reparation based on SMP foams, in which shape memory recovery is activated by a laser source. Data acquired in an *in vitro* basilar aneurysm model confirmed the successfulness of this approach [18].

In this work, two shape memory polyurethane foams, Cold Hibernated Elastic Memory (CHEM), with potential for biomedical applications as an aneurysm filler, were investigated. The materials were provided by W. Sokolowski from Jet Propulsion Laboratory (JPL, Pasadena, CA, USA) and have been synthesized by Mitsubishi Heavy Industry (Nagoya, Japan) [19–21]. Materials were fully characterized in order to obtain a set of parameters for GDC device design: in particular, the ability of shape recovery at constant heating rate [14] was compared to recovery at body temperature. Moreover, because a device sterilization is mandatory for this application, effects on morphological and thermomechanical properties of the CHEM foams after plasma sterilization were also evaluated. Finally, *in vitro* cytotoxicity and cytocompatibility of the two CHEM foams were evaluated before and after sterilization, using L929 fibroblasts cells line.

2. Materials and methods

2.1. Materials

Two poly(ether urethane) foams, kindly provided by Jet Propulsion Laboratory (Pasadena, CA, USA) were studied: CHEM 3520 (#0406352037) and CHEM 5520 (#0406552012). For both materials, glass transition temperature activates the shape memory effect ($T_{trans} = T_g$). Nominal glass transition temperature values were $T_g = 35\ ^\circ C$ and $T_g = 55\ ^\circ C$, for CHEM 3520 and CHEM 5520, respectively. Cylindrical specimens (diameter = 15 mm, $h = 10$ mm) were obtained from foams with a manual die and used (if not otherwise specified) in morphological, chemicophysical, thermomechanical, shape memory characterization and for *in vitro* cytotoxicity and cytocompatibility tests.

2.1.1. Plasma sterilization

Foam specimens were sterilized using a plasma Sterrad® sterilization system (100S, Johnson & Johnson) at Istituto Nazionale per lo Studio e la Cura dei Tumori (Milan, Italy) according to producer indications. A schematic description of temperature, pressure and gas of the plasma process involved in a Sterrad® sterilization system can be found in Ref. [22]; briefly, 400 W radiofrequency power (RF, 13.56 MHz) is applied at a pressure of 500 mTorr (67 Pa) to create a plasma, after injection of vaporized chemical phase of H_2O_2. The overall plasma sterilization cycle is about 52 min.

2.2. Morphological and chemicophysical characterization

2.2.1. Scanning electron microscopy

Surface morphology was evaluated by scanning electron microscopy (SEM). Samples were gold sputter-coated (Edward S150B) and observed with a StereoScan 360 SEM (Cambridge) at 10–20 kV. Surface microanalyses were performed with an energy dispersion X-ray spectroscope (EDS, Oxford INCA 200).

2.2.2. Average foam pore diameter

The average pore diameter was determined according to the ASTM D3576, based on the number of pore walls intersecting a reference line. Thin slices ($0.2 \div 0.3$ mm, $n = 3$) were cut from the foams, and observed with a stereo microscope (Leika, Wild Heerbrugg). Using a reference line drawn (chord) on a glass slice, it was possible to evaluate the pore size by using the following equation:

$$\text{diameter} = Al_0/n \quad (1)$$

where $A = 1.623$ (by assuming pores to be uniformly distributed and spherical), $l_0 = 40$ mm (chord length) and n is the number of intersections.

2.2.3. Density

The density values of foams were calculated according to the standard practice ISO 845, by using 12 cylindrical samples (diameter = 15 mm, $h = 10$ mm) for each CHEM foam.