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Bioabsorbable radiopaque water-responsive shape memory embolization plug for temporary vascular occlusion

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ABSTRACT

We describe the preparation, characterization and evaluation of a biodegradable radiopaque water-triggered shape memory embolization plug for temporary vascular occlusion. The shape memory occluding device consists of a composite of a radio-opaque filler and a poly (DL-lactide-*co*-glycolide) (PLGA) blend, which was coated with a crosslinked poly (ethylene glycol) diacrylate (PEGDA) hydrogel. The mechanical properties, the degradation timeframe, the effect of programming conditions on the shape memory behaviour and the extent of radio-opacity for imaging were evaluated. Based on the tests, the mechanism responsible for the water-induced shape memory effect in such an embolization plug was elucidated. Suitable materials were optimized to fabricate an embolic plug prototype and its *in vitro* performance was evaluated as an occlusion rate (using a custom-built set up) and its biocompatibility. Finally, a feasibility study was conducted *in vivo* in a rabbit model to investigate the ease of device deployment, device migration and extent of vessel occlusion. The *in vivo* results demonstrated that the prototypes were visible under fluoroscopy and complete vascular occlusion occurred within 2 min of deployment of the prototypes *in vivo*. In conclusion, the developed embolization plug enables controlled and temporary vascular embolization, and is ready for safety studies.

1. Introduction

Embolization is a well-established and important aspect of endovascular treatment of multiple medical conditions [1]. The goal of embolization is to stop blood flow in arteries or veins via the delivery of an occlusive physical agent into the targeted blood vessel. The occlusion of blood flow is therapeutic in myriad clinical situations, for instance in the control of pelvic haemorrhage after trauma or in the induction of tumor shrinkage for the treatment of neoplasms. The occlusion of the blood vessel can be permanent or temporary, depending on the physical property of the embolic agent, and is chosen depending on clinical need. Temporary occlusion is often applied to situations where recanalization of the embolized vessels is desired for example in embolization of the hepatic artery in the transcatheter arterial chemoembolization (TACE) for the treatment of hepatocellular carcinomas where recanalization of the hepatic artery is desired for repeat procedures while permanent occlusion may be desired in certain cases of aneurysms or arterio venous malformations.

While there are many options for permanent occlusion, gelatin sponge is the only biodegradable agent in common use for temporary occlusion. Gelatin sponge is a biologic agent derived from subcutaneous porcine adipose tissue and is available as a sheet [2]. This material was originally developed for use during open surgery, to stem bleeding. When used as an agent for embolization, gelatin sponge sheet is cut into small strips, pledgets, or mashed into slurry with saline, depending on the size of the vessel to be embolized. Gelatin sponge degrades enzymatically over time. While this allows temporary occlusion, it is an unpredictable process, with vessel recanalization occurring over 3 weeks to 3 months [3–5].

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Furthermore, some vessels may not recanalize, leading to inadvertent permanent occlusion. Other drawbacks of gelatin sponge include unpredictable occlusion levels, poorly controlled target embolization, and the need to mixing this material with iodinated contrast agent, for visualization under fluoroscopy.

We aim to develop an embolic agent that has a predictable biodegradation profile, is visible under fluoroscopy, allows accurate deployment and reliable occlusion, thus negating the disadvantages of gelatin sponge. The present study describes the development of a fully-biodegradable radiopaque embolic plug based on a water-induced shape memory system for temporary embolization. Shape memory polymer (SMP) is a stimulus-responsive material that has the capability to recover its original shape, by shape memory effect (SME), after being deformed into a temporary shape through the application of an external stimuli, such as heat, light, or solvent [6–8].

In our embolic plug concept, the device is composed of a radiopaque poly (DL-lactide-*co*-glycolide) core, coated with crosslinked poly (ethylene glycol) diacrylate hydrogel, to enhance the occlusion seal. The polymer core coated with hydrogel can be thermally programmed into a temporary shape, which is then introduced into the selected artery through a micro-catheter. Vascular embolization is subsequently achieved by the device expanding, when it comes into contact with body fluid and attains body temperature, by thermal and water-induced SME. This results in complete mechanical occlusion, from the hydrogel swelling. These materials were selected for their demonstrated bio-acceptable properties and as individual components of FDA approved devices [9,10]. A unique feature of the present device is the concept of shape memory effect (SME), which is utilized for ease of deployment. The embolic plug can be programmed/deformed into a low profile strip to enable transcatheter delivery typically used in embolization procedures. The performance of this device relies on the mechanical and swelling properties of the plug, its radio-opacity, the degradation timeframe, the effect of programming conditions on the shape memory behaviour. These parameters have been quantified and a feasibility study in rabbit model has offered a preliminary validation.

2. Materials and methods

2.1. Materials

Poly(DL-lactide-*co*-glycolide) with molar ratio of 50/50 (M_w = 90,000 g/mol) was purchased from Corbion Purac, The Netherlands. Poly(ethylene glycol) diacrylate (PEGDA) (M_n = 10,000), Irgacure 2959 (2-hydroxy-1-[4-(hydroxyethoxy) phenyl]-2-methyl-1-propanone), barium sulfate ($BaSO_4$), tantalum (Ta), bismuth (III) oxychloride (BO) were purchased from Sigma-Aldrich, Singapore. Polyethylene glycol (PEG) (M_w = 2000 g/mol) was obtained from Merck, Singapore. Iohexol (Omnipaque™ 300, GE Healthcare) was a gift from the Department of Diagnostic Radiology, Singapore General Hospital. All chemicals were used as received. The deionized water used was purified with a Milli-Q system (Millipore, USA).

2.2. Preparation of PLGA composite filaments

Table 1 lists the PLGA composite with various compositions. Different radiopaque fillers were added to the PLGA to evaluate the visibility under the X-ray fluoroscopy and PEG was added as plasticizer, to modulate the composites' transition temperature. Predetermined weights of PLGA, radiopaque filler (barium sulfate, tantalum and bismuth oxychloride), and PEG were mixed and then blended in a DSM Xplore twin-screw micro-extruder (DSM, The Netherlands). Processing temperature was 130 °C and the screw speed was set to 100 rpm. Filaments were extruded through a 0.5 mm circular die. The final diameter obtained was in the range of 0.7–0.8 mm, due to die swelling. These filaments were used for subsequent studies and prototype fabrication.

Table 1
Compositions of PLGA composite.

Sample ID	PLGA (wt%)	PEG (wt%)	$BaSO_4$ (wt%)	Ta (wt%)	BO (wt%)
PLGA	100	–	–		–
PLGA002	98	2	–	–	–
PLGA004	96	4	–	–	–
PLGA-BS502	48	2	50	–	–
PLGA-TT502	48	2	–	50	–
PLGA-BO502	48	2	–	–	50

2.3. Characterization of PLGA composite filaments

The actual content of incorporated radiopaque filler was measured by Thermogravimetric analysis (TA instrument, TGA 2950). Samples were heated at a rate of 10 °C/min to 800 °C, under nitrogen atmosphere, and the residual mass due to the presence of radiopaque fillers was calculated from TGA thermograms. To examine the effect of the radiopaque filler on the radiopacity of the specimens, unfilled and filled specimens were examined by clinical fluoroscopic imaging. The polymer composite's thermal properties were probed using a TA Instruments Differential Scanning Calorimeter (Q10). 5–10 mg samples were cooled to −20 °C and then heated to 70 °C, at a heating rate of 10 °C min^{-1} under nitrogen gas. These data determined the glass transition temperature (T_g), with reported values averaged values over at least 3 samples. Tensile testing was performed with MTS Criterion C42 machine (MTS Systems, USA) at room temperature (about 22–25 °C). Extruded PLGA filaments, with a gauge length of 10 mm, were stretched with a crosshead speed of 25 mm/min, whilst recording engineering stress and strains. Young's modulus was derived from the initial linear region of the stress-strain curves and the tensile strength was defined as the stress at which fracture occurs. To quantify SME, extruded PLGA filaments were wrapped around a 4 mm diameter mandrel and kept in oven at 85 °C, for 20 min, thus setting a permanent coil shape. The PLGA coil was then uncoiled at 70 °C, followed by quenching to room temperature under constant strain to fix the temporary shape. The recovery was measured after immersing the deformed samples in water at 37 °C, with a recovery ratio (R_r) defined as:

$$R_r(\%) = \frac{l_d - l_r}{l_d - l_i} \times 100 \quad (1)$$

where l_i is initial length of the sample; l_d is the length of the deformed sample and l_r is the length of the sample after recovery, respectively. Values for three samples were averaged for each polymer formulation.

Table 2
Filler content and glass transition temperatures for PLGA filaments.

Sample ID	Input loading (wt%)	Actual loading (wt%)	T_g (°C)
PLGA	–	–	41.9 ± 0.64
PLGA002	–	–	39.1 ± 0.45
PLGA004	–	–	35.6 ± 1.42
PLGA-BS502	50	45.4 ± 0.1	33.5 ± 0.41
PLGA-TT502	50	50.0 ± 0.2	34.6 ± 1.02
PLGA-BO502	50	44.8 ± 0.3	35.3 ± 0.99