Acta Biomaterialia 6 (2010) 3178–3186

Contents lists available at ScienceDirect

Acta Biomaterialia

journal homepage: www.elsevier.com/locate/actabiomat

Synthesis and characterization of poly(methyl methacrylate)-based experimental bone cements reinforced with TiO_2–SrO nanotubes

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ARTICLE INFO

Article history:
Received 1 December 2009
Received in revised form 9 February 2010
Accepted 12 February 2010
Available online 17 February 2010

Keywords:
Experimental bone cements
Strontium–titanium nanotube
Mechanical properties
Radiopacity
In vitro biocompatibility

ABSTRACT

In an attempt to overcome existing limitations of experimental bone cements we here demonstrate a simple approach to synthesizing strontium-modified titania nanotubes (*n*-SrO–TiO_2 tubes) and functionalize them using the bifunctional monomer methacrylic acid. Then, using 'grafting from' polymerization with methyl methacrylate, experimental bone cements were produced with excellent mechanical properties, radiopacity and biocompatibility. Transmission electron microscopy (TEM), scanning electron microscopy (SEM), energy-dispersive spectroscopy mapping and backscattered SEM micrographs revealed a uniform distribution of SrO throughout the titanium matrix, with retention of the nanotubular morphology. Nanocomposites were then reinforced with 1, 2, 4 and 6 wt.% of the functionalized metal oxide nanotubes. Under the mixing and dispersion regime employed in this study, 2 wt.% appeared optimal, exhibiting a more uniform dispersion and stronger adhesion of the nanotubes in the poly(methyl methacrylate) matrix, as shown by TEM and SEM. Moreover, this optimum loading provided a significant increase in the fracture toughness (K_{IC}) (20%) and flexural strength (40%) in comparison with the control matrix (unfilled) at $P < 0.05$. Examination of the fracture surfaces by SEM showed that toughening was provided by the nanotubes interlocking with the acrylic matrix and crack bridging during fracture. On modifying the *n*-TiO_2 tubes with strontium oxide the nanocomposites exhibited a similar radiopacity to a commercial bone cement (CMW® 1), while exhibiting a significant enhancement of osteoblast cell proliferation (242%) in vitro compared with the control at $P < 0.05$.

1. Introduction

Poly(methyl methacrylate) (PMMA)-based bone cements in clinical use today are beset by detrimental effects on their mechanical properties due to inorganic radiopacifying agents ($BaSO_4$ and ZrO_2). Poor wetting and weak interfacial interactions between the inorganic particulates and the non-polar polymer matrix [1–3], along with a lack of chemical bonding, means the filler particles act as stress concentration sites [4]. When stress is applied to the bone cement these sites facilitate implant failure, causing bone resorption, thus adversely affecting the clinical life of the cemented arthroplasty [5,6]. Bone cement failure is responsible for a significant portion of the estimated 36,000 hip arthroplasty revisions performed in 2003 in the USA, which are primarily caused by the poor mechanical properties of the commercial acrylic cement [7,8]. Therefore, there has been a sustained interest in alternative radiopacifiers which can also act as reinforcing agents for PMMA bone cements. Radiopacity allows post-operative assessment of the cement and cemented joint prostheses.

Abboud et al. [9] incorporated alumina (Al_2O_3) particles into a PMMA matrix in an attempt to produce reinforced radiopaque cements. In order to establish strong interfacial adhesion, the Al_2O_3 particles were treated with the coupling agent 3-(trimethoxysilyl)propyl methacrylate (γ-MPS) to create a covalent chemical bond with the PMMA polymer matrix. This coupling agent enhanced the reinforcement effect, with the modulus of elasticity improved by 3.40 GPa. However, the formulations required high processability because of poor wetting of the filler surface with liquid monomer, resulting in a very large void formation inside the cement [10]. In another attempt, Lewis et al. [11] reported the incorporation of strontium oxide (SrO) particles as an alternative radiopacifier in an acrylic cement matrix. Besides providing a radiopacity as high as that exhibited by a $BaSO_4$-containing cement, SrO showed the potential to act as a bacterial growth inhibitor and increased the biocompatibility of the cement [12]. However, SrO fillers did not provide a significant increase in fracture toughness and fatigue properties compared with a cement containing $BaSO_4$ particles. In a recent study, Hernandez et al. [13] used radiopaque strontium hydroxyapatite (SrHA) as filler particles in a

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doi:10.1016/j.actbio.2010.02.024

PMMA based cement. In order to obtain better integration between the filler particles and the acrylic matrix the SrHA particles were treated with MMA, which played an important role in reinforcing the cement by enhancing the compressive properties of the resulting composites. A significant increase in compressive modulus compared with the control was obtained at 20 wt.% loading of the treated SrHA particles. However, this high filler load had a deleterious effect on the rheological properties of the cement.

Nanotechnology provides a promising alternative to reinforce composite materials through the strong interfacial interactions between the nanostructured fillers and the polymer matrix. However, little is known on how nanostructured particles in experimental bone cements act as reinforcing and radiopacifying agents, and their resulting biocompatability. Gomoll et al. [14] achieved a significant enhancement in tensile strength of an acrylic bone cement by incorporating 100 nm radiopaque $BaSO_4$ particles. A 70% increase in tensile work of fracture was reported for a cement containing 10 wt.% nanosized $BaSO_4$ particles compared with a commercial cement containing 1–3 μm sized $BaSO_4$ particles. The better performance was attributed to increased interfacial adhesion between the nanoparticles and the acrylic matrix. However, without any chemical bonding between the PMMA matrix and the nanoparticles, the ultrafine nanoparticles can potentially separate from the PMMA matrix and reach the surrounding biological tissue, resulting in inflammation and implant loosening. In another attempt, Goto et al. [15] incorporated silanized *n*-TiO_2 particles (60 wt.%, average diameter 200 nm) into a cement matrix. The flexural modulus of this composite was no better than the control commercial cement, probably due to the presence of agglomerates of nanosized titania particles at a higher percentage loading, which acted as stress concentration sites [16,17].

In this study we have attempted to address the disadvantages of previous studies by synthesizing titania nanotubes (*n*-TiO_2 tubes) and integrating them into an experimental bone cement. In order to enhance the reinforcing effect, the nanotubes were functionalized with the monomeric coupling agent methacrylic acid (MA) before 'grafting from' polymerization as described previously using titania nanofibers [18]. As the *n*-TiO_2 tubes showed low radiopacity, they were modified with strontium oxide (*n*-SrO–TiO_2 tubes) to increase the radiopacity and biocompatibility of the resulting cements. The mechanical properties, radiopacity and biocompatibility of the resulting experimental bone cements were examined. The hypothesis of this study is that functionalized *n*-SrO–TiO_2 tubes added to a PMMA matrix will significantly enhance its mechanical properties, radiopacity and biocompatibility.

2. Materials and methods

2.1. Materials

Titanium oxide nanopowder (<100 nm, 99.9% metal basis, Sigma–Aldrich), strontium acetate powder (~3% H_2O, Sigma–Aldrich), reagent grade 37% hydrochloric acid (Sigma–Aldrich) and sodium hydroxide pellets (0.0002% Ca, 0.007% K, 0.4% Na_2CO_3, <0.001% Cl, <0.001% Cu, <0.0002% Mg, J.T. Baker) were used as received. PMMA beads (99.2 wt.%, Ivoclar Vivadent) having an average particle diameter of 57.5 μm (as measured by laser diffraction using a Malvern Mastersizer 2000) and an average molecular weight of 207 kDa (as measured by gel permeation chromatography, supplied as supporting document), with the free radical initiator BPO (0.8 wt.%), were used as received. 2-Propanol, MA (99.99%, Sigma–Aldrich) and MMA monomer (95.9 wt.%) containing the cross-linker butanediol dimethacrylate (4 wt.%) and an activator (0.1 wt.%) were used as received (Ivoclar Vivadent). The commercially available cement CMW® 1 (Depuy, Warsaw, IN) (for its composition see supporting document), with an average molecular weight of the pre-polymerized PMMA mixed into the powder part of 535 kDa (as measured by GPC, see supporting document), was used.

2.2. Synthesis of *n*-TiO_2 and *n*-SrO–TiO_2 tubes

The *n*-TiO_2 tubes were synthesized using the alkaline hydrothermal technique in accordance with the work of Kasuga et al. [19,20]. The synthesized titanate [$H_2Ti_3O_7$ or $H_2Ti_2O_4(OH)_2$] nanotubes were converted to anatase TiO_2 with a tubular morphology (*n*-TiO_2 tubes) after calcining in air at 400 °C [21–24]. To synthesise the *n*-SrO–TiO_2 tubes 0.24 g of strontium acetate powder was dissolved in 30 ml of 10 M NaOH solution in a 125 ml Teflon-nalgene flask and subjected to constant stirring for 24 h. An aliquot of 2 g of titanium oxide nanopowder was then mixed into the solution of strontium acetate in 10 M NaOH and the whole mixture was kept under constant stirring for another 24 h. The contents were transferred to a 40 ml Teflon flask in a 125 ml stainless steel autoclave (Parr 4748, Parr Instruments, IL). The reaction was carried out at 120 °C for 20 h without stirring. The alkali-treated powders obtained were rinsed with distilled water followed by 0.1 M HCl solution until pH 7 was achieved. Then the titania-based powder was subjected to vacuum drying at 80 °C overnight. Finally, the dried powder was calcined in air at 400 °C for 2 h at a heating rate of 10 $°C\ min^{-1}$.

2.3. Functionalization of nanotubes

In order to functionalize the surface of the nanotubes, 0.1 g of calcined powder was dispersed in 35 ml of 2-propanol with the aid of ultrasonic agitation, followed by reaction with 3 ml of MA at 80–85 °C for 24 h with constant stirring. The reaction was carried out at pH 5.5 (as measured by pH meter UWR SB301), adjusted by adding a few drops (5–12) of potassium hydroxide solution (0.3 N) to the reaction mixture prior to the reaction. The treated powder was then filtered and washed with distilled water and 2-propanol to remove any unreacted MA. Finally, the wet powder was dried at 80 °C under vacuum for 5 h.

2.4. Preparation of nanocomposites

The nanocomposites were prepared according to the bone cement manufacturer's recommended technique by mixing the prepolymerized PMMA beads containing the initiator with the liquid part, consisting of MMA containing a redox activator. During nanocomposite preparation the functionalized nanotubes were dispersed in the liquid portion by ultrasonic agitation for 15 min. The powder portion was then added to the liquid monomer containing the dispersed *n*-TiO_2 tubes at a ratio of 2.18 and hand mixed to a dough state, then loaded into Teflon molds and kept for 24 h at room temperature for complete curing. Nanocomposite specimens with 1, 2, 4 and 6 wt.% loading of functionalized *n*-TiO_2 tubes, 2 wt.% of non-functionalized *n*-TiO_2 tubes and 2 wt.% of functionalized *n*-SrO–TiO_2 tubes were prepared. Control specimens were produced using the unfilled PMMA matrix. Moreover, bone cement specimens of commercial CMW® 1 were prepared to compare the radiopacity of the resulting nanocomposites. However, the mechanical properties of the CMW® 1 specimen were not evaluated in this study, as its pre-polymerized PMMA beads had a different molecular weight from the PMMA beads used in preparing the nanotube–PMMA composites.

2.5. Characterization of nanotubes and nanocomposites

The morphology and microstructure of the functionalized *n*-TiO_2 and *n*-SrO–TiO_2 tubes were investigated by transmission electron