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Research Paper

Enhanced mechanical properties of a novel, injectable, fiber-reinforced brushite cement

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ABSTRACT

Injectable, brushite-forming calcium phosphate cements (CPCs) have great potential as bone replacement materials due to enhanced degradability and long-term inclusion in bone remodeling. However, the use of such brushite-forming CPCs in load-bearing areas is limited by their low mechanical strength. One approach to overcome this limitation is the use of reinforcing fibers. Thus, an injectable, biodegradable, brushite-forming CPC based on beta-tricalcium phosphate/phosphoric acid with fiber reinforcement was developed for minimally invasive surgery. The fibers (diameter 25 μm; length 0.25, 1 or 2 mm) were extruded from poly(l-lactide-*co*-glycolide) acid (PLGA) and added to the CPC (2.5, 5 or 7.5% (w/w)). Independent of the fiber content, injectability of the CPC was retained up to a fiber length of 1 mm. The addition of all PLGA fiber types increased diametral tensile strength, biaxial flexural strength, and flexural strength by up to 25% ($p \leq 0.05$ for the diametral tensile strength for the CPC with 5% (w/w) 1 mm fibers and the biaxial flexural strength of the CPC with 5% (w/w) 0.25 mm fibers). In contrast, the work of fracture strongly and significantly increased ($p < 0.01$) by up to 12.5-fold. At constant fiber content, the mechanical properties of the fiber-reinforced CPC were mostly augmented with increasing fiber length. Also, the addition of PLGA fibers to the brushite-forming CPC (up to 7.5% (w/w)) only transiently delayed cell growth and did not decrease cell viability. Fiber reinforcement of CPCs thus augments their mechanical strength while preserving the injectability and biocompatibility required for their application in modern surgery.

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1. Introduction

Minimally invasive augmentation techniques with injectable cements, i.e. kyphoplasty and vertebroplasty, have become increasingly popular for the treatment of vertebral body fractures. Especially in load-bearing areas, injectable poly (methyl methacrylate) (PMMA) cements are most frequently used, which, however, lack bioactivity and biodegradability. In addition, their supra-physiological strength and Young's modulus may lead to critical loads and subsequent fractures in adjacent vertebral bodies (Hulme et al., 2006; Nouda et al., 2009; Trout et al., 2006; Uppin et al., 2003).

Calcium phosphate cements (CPCs), as first described by LeGeros et al. and Brown/Chow in the 1980s (Brown and Chow, 1983; LeGeros et al., 1982), may represent a promising alternative in this context since they are biodegradable and have a Young's modulus comparable to that of cancellous bone (Burguera et al., 2006). However, commercially available, injectable CPCs show low mechanical strength and low fracture toughness, leading to premature damage of the cement at the implant site (Blattert et al., 2009; Wilke et al., 2006).

The mechanical properties of CPCs are governed by their composition and microstructure. In general, apatite-forming CPCs have higher mechanical strength than brushite-forming CPCs (Dorozhkin, 2011). In addition, the mechanical properties of both types of CPCs increase with decreasing porosity (Engstrand et al., 2014; Tamimi et al., 2012) which in turn requires a high powder-to-liquid ratio in the preparation process. In order to obtain injectable CPCs, however, low powder-to-liquid ratios (<2.4) are necessary (Khairoun et al., 1998). Thus, for an injectable CPC a low powder-to-liquid ratio has to be maintained which on the other hand limits the mechanical strength of the resulting CPC.

Another possibility to increase the mechanical strength and fracture toughness is the modification of the CPC with reinforcing fibers. Detailed reviews about fiber-reinforced CPCs (Canal and Ginebra, 2011; Krüger and Groll, 2012) describe the use of non-resorbable fibers consisting of aramide (Xu et al., 2000, 2001b), polyamide (dos Santos et al., 2000), polypropylene (Buchanan et al., 2007), glass (Xu et al., 2000) or carbon (Xu et al., 2001a, 2000), as well as the use of resorbable, biodegradable fibers, such as polycaprolactone, polylactide, polyglycolide or different copolymers thereof (Nair and Laurencin, 2007). If a completely resorbable CPC is to be developed, biodegradable fibers in conjunction with degradable calcium phosphate phases are desirable (see below).

Biodegradable fibers consisting of poly(l-lactide-co-glycolide) acid (PLGA) are commercially available as clinical suture material. PLGA suture material with yarn diameters of 200–350 μm has been used as biodegradable fiber reinforcement for CPCs in several studies (Burguera et al., 2005; Dagang et al., 2007; Gorst et al., 2006; Weir and Xu, 2010; Xu et al., 2007a, 2007b, 2000, 2006; Zhang and Xu, 2005; Zhao et al., 2010a, 2010b). In general, the addition of PLGA fibers results in increased strength and work of fracture (WOF) with the fiber volume fraction (Gorst et al., 2006; Xu et al., 2000, 2006) and the fiber length (Xu et al., 2000) as critical parameters. However, due to a complex interdepencency between diameter and/or length of the fibers, load transmission, and injectability, the large diameter of commercial PLGA suture material limits their application in injectable CPCs. Unfortunately, there are currently only isolated reports using PLGA fibers with smaller diameters, e.g., the application of 16 μm diameter fibers to augment the mechanical strength of a CPC in a skull defect model (Losquadro et al., 2009).

In addition to their mechanical strength, degradability and injectability of the CPCs are of central relevance for their use in minimally invasive vertebral surgery. However, all of the above-mentioned studies were focused on either non-injectable, fiber-reinforced, brushite-forming CPCs (Gorst et al., 2006) or on apatite-forming CPCs with only very restricted degradability in vivo (Apelt et al., 2004). The latter type of CPC may be of limited suitability as bone replacement material due to its quasi exclusion from long-term bone remodeling in vivo.

Therefore, the aim of this study was to develop and investigate an injectable, brushite-forming CPC with biodegradable polymer fiber reinforcement, suitable for minimally invasive surgery. Therefore, PLGA fibers with different length were incorporated at different fiber content into a brushite-forming CPC and the resulting composite CPC was then tested for injectability, mechanical properties, and microstructure, as well as reciprocal interdependencies among these parameters. Initial assessment of the biocompatibility of the developed composites was also performed.

2. Materials and methods

2.1. *Fabrication of PLGA fibers*

PLGA fibers were prepared from the granulate material PURASORB PLG 1017 (Purac, Gorinchem, Netherlands). The extrusion of the fibers was performed using a mini extrusion system (RANDCASTLE EXTRUSION SYSTEMS INC, Cedar Grove, USA), equipped with a ceramic spinning nozzle at a temperature of 217 °C and an offtake velocity of 400 m/min (resulting diameter: 25 μm).

Fibers were then cut to different lengths using a cutting mill PULVERISETTE 19 (FRITSCH GmbH, Idar-Oberstein, Germany) with two different sieve inserts (0.25 mm and 1 mm, hereafter called 0.25 mm fibers and 1 mm fibers). A third fiber length was obtained by manually cutting the fibers to a length of approximately 2 mm (hereafter called 2 mm fibers).

The mechanical properties of the extruded fibers were measured according to DIN EN ISO 2062 (2009) applying a Zwick Z005 universal testing machine (Zwick GmbH & Co. KG, Ulm, Germany). The morphology of the fibers was characterized using a Zeiss Auriga 60 scanning electron microscope (Zeiss AG, Oberkochen, Germany). The fiber lengths after cutting were determined using the quantitative image analysis software Leica QWin V3 (Leica Microsystems GmbH, Wetzlar, Germany).

2.2. *Preparation of fiber-reinforced CPCs*

The CPC powder consisted of 98.5% (w/w) β-tricalcium phosphate (β-TCP) and 1.5% (w/w) tetrasodium pyrophosphate, the liquid of an aqueous solution containing 3.0 M phosphoric