



A novel and easy-to-prepare strontium(II) modified calcium phosphate bone cement with enhanced mechanical properties



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ABSTRACT

The aim of this study was to evaluate two different approaches to obtaining strontium-modified calcium phosphate bone cements (SrCPCs) without elaborate synthesis of Sr-containing calcium phosphate species as cement precursors that could release biologically effective doses of Sr²⁺ and thus could improve the healing of osteoporotic bone defects. Using strontium carbonate as a strontium(II) source, it was introduced into a hydroxyapatite-forming cement either by the addition of SrCO₃ to an α -tricalcium phosphate-based cement precursor mixture (A-type) or by substitution of CaCO₃ by SrCO₃ during precursor composition (S-type). The cements, obtained after setting in a water-saturated atmosphere, contained up to 2.2 at.% strontium in different distribution patterns as determined by time-of-flight secondary ion mass spectrometry and energy-dispersive X-ray spectroscopy. The setting time of CPC and A-type cements was in the range of 6.5–7.5 min and increased for substitution-type cements (12.5–13.0 min). Set cements had an open porosity between 26 and 42%. Compressive strength was found to increase from 29 MPa up to 90% in substituted S-type cements (58 MPa). SrCPC samples released between 0.45 and 1.53 mg g⁻¹ Sr²⁺ within 21 days and showed increased radiopacity. Based on these findings, the SrCPC developed in this study could be beneficial for the treatment of defects of systemically impaired (e.g. osteoporotic) bone.

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1. Introduction

Strontium(II) (Sr²⁺) has been shown to effectively stimulate bone formation and to inhibit bone resorption in various studies over the last years. This has led to its clinical application in the form of strontium ranelate as a frequently used drug in osteoporosis therapy [1–4]. However, recent studies have shown that the bioavailability of orally administered strontium is only ~20% [5], so that a local release of strontium ions into the bone defect site might be preferential in order to increase the local strontium dosage. The introduction of strontium into bone cements, which can be applied for treatment of osteoporotic bone fractures, is therefore of interest and has first led to the incorporation of strontium into conventional, resin-based cements. In 2000, Li et al. reported good in vitro biocompatibility and enhanced radiopacity of a bisphenol A diglycidylether dimethacrylate (D-GMA)-based cement filled with strontium-substituted hydroxyapatite [6]. Calcium phosphate cements (CPCs) are capable of substitution of various ions, as recently reviewed by Boanini et al. [7]. Sr²⁺ can be substituted into calcium phosphates due to the chemical resemblance to Ca²⁺ without impairing the possibility to participate in a

cement reaction. In the case of hydroxyapatite, this substitution causes an expansion of the crystal lattice and thus increases its solubility [8,9]. This is also the case for other calcium phosphates, e.g. β -tricalcium phosphate (β -TCP), that can also be substituted with strontium(II) during synthesis [10], giving rise to a variety of possible strontium-containing calcium phosphate cement formulations. A first cement preparation routine was described by Guo et al., who prepared Sr²⁺-substituted calcium phosphate bone cements by substitution of calcium hydrogen phosphate (CaHPO₄) by strontium hydrogen phosphate (SrHPO₄) in a tetracalcium phosphate-based cement system. Sr²⁺ substitution resulted in an increased strength of the cement but also had a retarding influence on the setting time [11,12]. Sr-substituted α -tricalcium phosphate (α Sr-TCP), synthesized by cofiring CaCO₃, SrCO₃ and Ca₂P₂O₇, was also demonstrated to form a strontium-containing hydroxyapatite (SrHA) cement during hydrolysis. However, the set cement exhibited poor mechanical properties compared to pure α -TCP cement [13]. Furthermore, calcium hydrogen phosphate dihydrate (DCPD, brushite, CaHPO₄·2H₂O), calcium oxide (CaO) and strontium carbonate (SrCO₃) form a cement precursor setting to SrHA with enhanced mechanical properties and increased radiopacity [14]. Brushite-forming, strontium-containing cements can be prepared as well, based on α -tricalcium phosphate (α -TCP) or a mixture of

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β -TCP and monocalcium phosphate monohydrate (MCPM), both setting to brushite after mixing with citric acid [10,15].

However, all those techniques require the synthesis of Sr^{2+} -containing calcium phosphate species, involving elaborate thermal or precipitation techniques. In a different approach, a Sr^{2+} -containing solution was used as liquid phase in an α -TCP-based cement system, also leading to the formation of SrHA and resulting in an increase of diametral tensile strength [16]. Recently, Tadier et al. compared SrHA cements obtained from CaCO_3 -vaterite/DCPD either by the addition of solid SrCO_3 or by using SrCl_2 solution as a liquid component. They found sustained release of Sr^{2+} ions under physiological conditions and a higher cell proliferation for SrCO_3 -containing cements but did not report on the mechanical properties of the set cement [17].

In this study, our aim was to compare two simple approaches based on SrCO_3 to manufacture SrCPC: strontium(II) was introduced into a hydroxyapatite-forming, α -tricalcium phosphate-based cement by (a) the addition of strontium carbonate or (b) complete or partial substitution of CaCO_3 (as a component of the standard cement precursor formulation) by SrCO_3 . Both approaches could lead to enhanced mechanical properties of the set cements by the presence of SrCO_3 in the cement matrix [14] or the formation of SrHA [12,16]. Physico-chemical methods were employed to study the effects of Sr-modification on the cement properties as well as the release of potentially biologically active Sr^{2+} ions from the set cements to evaluate the applicability of SrCPCs as bone defect fillers in osteoporotic bone.

2. Materials and methods

2.1. Cement modification with strontium(II)

2.1.1. Precursor preparation

A calcium phosphate bone cement (CPC) originally described by Driessens et al. [18] was used as the starting material in this study. The precursor powder consisted of 58 wt.% α -TCP (α - $\text{Ca}_3(\text{PO}_4)_2$), 25 wt.% calcium hydrogen phosphate (DCPA or monetite, CaHPO_4), 8.5 wt.% calcium carbonate (CaCO_3) and 8.5 wt.% hydroxyapatite ($\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$) and was supplied by InnoTERE GmbH (Radebeul, Germany).

Strontium was introduced into the cement either (a) by the addition (A-type samples) of strontium carbonate (SrCO_3 , 99.994%, Alfa Aesar, Karlsruhe, Germany) or (b) by complete or partial substitution (S-type samples) of CaCO_3 by SrCO_3 in the precursor powder synthesis as shown in detail in Table 1. CPCs are known to have a high capacity to set in the presence of filling materials. Therefore, 5–10 wt.% strontium carbonate was added to the precursor and intermixed using a mortar and pestle (samples denoted as A5 and A10, respectively) to obtain a cement matrix filled with SrCO_3 crystals. This resulted in a strontium content of up to 1.39 at.%.

Substitution replaced 50–100 wt.% of CaCO_3 by SrCO_3 during cement precursor preparation (including intense milling) in powders

labelled as S50 and S100, resulting in up to 2.21 at.% strontium in the cement. Note that in A-type samples the Ca/P ratio of the precursor remained constant and (Ca + Sr)/P increased with SrCO_3 addition, whilst the latter was kept constant in S-type samples (Table 1).

2.1.2. Paste characterization and sample preparation

To form a mouldable paste, cement powders were mixed thoroughly with aqueous 4 wt.% disodium hydrogen phosphate (Na_2HPO_4 , Merck, Darmstadt, Germany) solution. The liquid-to-powder (l/p) ratio was varied to obtain comparable mouldability for A- and S-type cements. However, to avoid an influence of different l/p ratios on characteristics of the set cements, a fixed liquid-to-powder-ratio of $350 \mu\text{l g}^{-1}$ was used for the preparation of samples for subsequent characterization for better comparability. Initial and final setting time (t_i and t_f) of the cements were assessed using a Gillmore apparatus according to ASTM C266-99. Cement setting was allowed for 6, 24, 48, 72 or 168 h in water-saturated atmosphere at 37 °C before subsequent experiments. These setting conditions instead of ageing in water were chosen to prevent uncontrolled release of ions from the cement.

2.2. Characterization of set cements

2.2.1. Microstructure analysis

A scanning electron microscope (SEM; Phillips ESEM XL30) equipped with an energy-dispersive X-ray (EDX) microanalysis system (EDAX Inc., Mahwah, USA) operated in SEM mode was used for cement microstructure analysis and imaging of Sr^{2+} distribution in freshly prepared cement samples. Furthermore, strontium(II) on the sample surface as well as within the bulk material was investigated by time-of-flight secondary ion mass spectrometry (ToF-SIMS) mapping and three-dimensional (3-D) reconstruction. Subsequently, set samples were ground into fine powder with an agate mortar and pestle for XRD analysis. X-ray diffraction data were collected in the range of $15^\circ \leq 2\Theta \leq 55^\circ$ in increments of 0.05° using a Bruker D8 Discover diffractometer equipped with a Vantec 2000 detector and $\text{Cu K}\alpha$ radiation ($\lambda = 1.542 \text{ \AA}$). Rietveld refinement and semi-quantitative phase analysis were performed on XRD data collected from powdered cement samples.

2.2.2. Density and mechanical characterization

Density of cuboidal cement samples was measured by helium-pycnometry (Ultrapyc 1200e, Quantachrome, Boynton Beach, USA) at different ageing times and porosity was calculated from the quotient of apparent (ρ_{app}) and pycnometrically obtained density (ρ_{pyc}) according to Eq. (1):

$$\text{Porosity [vol - \%]} = \left(1 - \frac{\rho_{\text{app}}}{\rho_{\text{pyc}}}\right) \cdot 100\% \quad (1)$$

For mechanical characterization, the cement pastes were moulded into a silicone mould to obtain cuboid-shaped samples of $\sim 12 \times 6 \times 6 \text{ mm}$. Testing was performed with uniaxial compression loading of 1 mm min^{-1} using an Instron 5566 testing machine equipped with a 10 kN load cell (Instron, Darmstadt, Germany).

2.2.3. Sr^{2+} release

For Sr^{2+} -release experiments and ToF-SIMS analyses, disc-shaped cement samples were submerged in TRIS (Roth, Karlsruhe, Germany) buffered 0.9% NaCl (Merck, Darmstadt, Germany) solution at pH 7.4 and aged at 37 °C. Strontium ion release was investigated in semi-dynamic mode (change of immersion liquid after every measurement). At every time point (after 3, 5, 7, 14 and 21 days), collected immersion liquid was filtered using a syringe filter to remove released particles and stored until measurement.

Table 1
Composition of Sr-modified calcium phosphate bone cement powders.

Label	Composition (wt.%)					Sr (at.%)	Ca/P	(Ca + Sr)/P
	α -TCP	DCPA	HA	CaCO_3	SrCO_3			
CPC	58.00	24.00	8.50	8.50	–	–	1.514	1.514
A5	55.80	23.10	8.20	8.20	4.80	0.72	1.514	1.570
A10	53.20	22.00	7.80	7.80	9.20	1.39	1.514	1.626
S50	58.00	24.00	8.50	4.25	4.25	1.10	1.431	1.514
S100	58.00	24.00	8.50	–	8.50	2.21	1.348	1.514

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