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Effects of strontium in modified biomaterials

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ABSTRACT

Strontium (Sr) plays a special role in bone remodelling, being associated with both the stimulation of bone formation and a reduction in bone resorption. Thus, the modification of biomaterials by partial or full substitution by Sr is expected to increase both bioactivity and biocompatibility. However, such effects have to be studied individually. Although no phase transition was found in Sr-substituted hydroxyapatite (Sr–HA), Sr-containing calcium silicate (Sr–CS) or Sr-containing borosilicate (Sr–BS), their biological performance was substantially affected by changes in the physico-chemical properties and Sr content of the materials. Three distinct outcomes were found for the presence of Sr: (1) increased HA solubility; (2) no significant effect on the degradation rate of CS; (3) apparent inhibition of the otherwise rapid degradation of BS. In each case the released Sr affected osteoblast proliferation and alkaline phosphatase activity, with clear evidence that an optimum Sr dose exists. Such chemical and biological variations must be disentangled for the behaviour to be properly understood and materials design to be advanced.

1. Introduction

Strontium (Sr), a trace element in the human body, has been reported to play a special role in bone remodelling, being associated with both the stimulation of bone formation and a reduction in bone resorption [1,2]. The mechanism is thought to lie in Sr^{2+} having the ability not only to increase osteoblast-related gene expression and the alkaline phosphatase (ALP) activity of mesenchymal stem cells (MSCs), but also to inhibit the differentiation of osteoclasts [3]. As a result, Sr is thought to be effective in enhancing the bioactivity and biocompatibility of biomaterials and, in particular, to have potential in the treatment of osteoporosis [4,5].

A poly(methyl methacrylate) bone cement containing Sr-containing calcium phosphate has been reported to have enhanced bioactivity and biocompatibility, said to be due to the release of Sr^{2+}, which not only promoted osteoblast proliferation, but also facilitated precipitation of apatite, and thus increased the mechanical strength of the bone–implant interface [6,7]. An injectable, Sr-containing calcium phosphate bone cement (CPC) could meet the requirements of vertebroplasty because its radio-opacity was three times that of cortical bone [8]. Furthermore, well-ordered SrTiO3 nanotubes, formed on the surface of titanium implants by hydrothermal treatment, were reported to significantly enhance their osseointegration and to increase the torque for removal [9,10]. This was attributed to enhanced osteoblast differentiation and new bone apposition in both cortical and cancellous bone [10].

Recently, attention has been given to the modification of bioceramics with Sr, which has tended to enhance their biological performance, including 45S5 bioglass® [11], hydroxyapatite (HA) [12] and α- and β-tricalcium phosphate [13,14]. Not only is the required Sr provided at the interface with the biological medium, but also the dose of Sr delivered is said to be controlled under physiological conditions [11]. Even so, the reported biocompatibility was still limited, although all the claimed better effects were achieved, assumed to be due to the release of Sr ions [13,14]. A complication lies in the fact that the osteoblast response depends not only on the physico-chemical properties of the materials, but also the Sr content. Sr has been shown to increase the solubility of HA [15], but is also said to inhibit the rapid dissolution of calcium silicate (CS) [16]. In the case of the latter Sr was postulated to occupy a greater volume in the CS crystal lattice due to its larger ionic radius (Sr^{2+} 113 pm, Ca^{2+} 99 pm), and thus inhibit the movement and release of other ions [16]. As a result, the effects of Sr need to be studied individually. In particular, for biodegradable bioceramics their degradation may significantly change the micro-environment, e.g. local ion concentrations, which may in

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turn affect osteoblast response. Likewise, borosilicate (BS) [17–19] and calcium silicate (CS) [20–22] materials have been claimed to show potential in bone regeneration, since released substances apparently not only enhance osteoblast proliferation, but also facilitate apatite nucleation. However, both suffer from cytotoxicity due to their rapid degradation [16,23]. Thus, although Sr may have some benefits, all aspects need careful investigation.

Given the above, Sr-containing BS and CS were both prepared to study the influence of Sr, using Sr-substituted HA as a comparison. Structure, composition, degradation behaviour and biological responses were investigated.

2. Materials and methods

2.1. Fabrication

2.1.1. Strontium-substituted apatites (Sr–HA)

Sr*x*–HA, with x = Sr/(Ca + Sr) = 0, 10, 40, 100 mol.%, were synthesized using a hydrothermal method at 150 °C for 14 h by adding $(NH_4)_2HPO_4$ solution (analytical grade, Merck, Darmstadt, Germany) drop-wise into a solution containing $Sr(NO_3)_2$ and $Ca(NO_3)_2$ in the appropriate molar ratio (both analytical grade, BDH, Poole, UK) to produce the target (Ca + Sr)/P ratio of 1.67 (stoichiometric for HA), while being stirred with a PTFE-coated magnetic bar at 500 rpm. Ammonium hydroxide solution was used to adjust the pH to 10.0 ± 0.5 during titration. The precipitate was washed three times each with deionized water and absolute ethanol and, finally, dried at 90 °C overnight in air. For the surface bioactivity test the prepared powder was compressed into a stainless steel mould with a diameter of 5 mm, 2 mm deep, at room temperature under 30 MPa. Sintering was inappropriate due to the possibility of phase transitions.

2.1.2. Strontium-containing calcium silicate (Sr–CS)

Strontium-substituted $CaSiO_3$ (Sr–CS) powders were prepared by the precipitation method previously described [24], with Ca partially replaced by the required Sr content (0, 5, 10 or 20 mol.%). Briefly, the required solution of $Ca(NO_3)_2$ and $Sr(NO_3)_2$ was added drop-wise to a Na_2SiO_3 solution (analytical grade) at room temperature (25 ± 1 °C) with vigorous stirring, to a final (Sr + Ca)/Si ratio of 1.0. After addition, the solution was stirred for 24 h and the precipitate filtered and washed with deionized water and absolute ethanol several times, dried at 60 °C for 24 h, then heated to 800 °C for 2 h. Finally, the prepared powder was compressed into a stainless steel mould with a diameter of 5 mm, 2 mm deep, and sintered at 1200 °C for 2 h in air.

2.1.3. Strontium-containing borosilicate (Sr–BS)

Borosilicate glass (BS), with the composition $6Na_2O$–$8K_2O$–$8MgO$–$22CaO$–$36B_2O_3$–$18SiO_2$–$2P_2O_5$ was prepared in the conventional manner, melting appropriate reagent grade materials (BDH) in a platinum crucible at 1200 °C for 2 h with stirring [25], then quenched between cold stainless steel plates. The Sr-substituted materials were made by replacing Mg and Ca. Thus, Sr6–BS (6MgO replaced by 6SrO) and Sr12–BS (8MgO and 4CaO replaced by 12SrO) were prepared. The quenched material was sliced into 5 × 5 × 2 mm pieces using a diamond saw (Exact 300, Exact, Norderstedt, Germany) for further study.

2.2. Characterization

The constitution and composition of the prepared materials (Sr–HA, Sr–CS and Sr–BS) were characterized by, respectively, X-ray diffraction (XRD) (Model D/max 2550 V, Rigaku, Tokyo, Japan) using Cu K_α radiation (λ = 1.5406 Å) in step-scan mode (2θ = 0.02° per step) and Fourier transform infrared (FTIR) spectroscopy (Lambda 2S, Perkin–Elmer, Waltham, MA). The atomic concentrations of key elements (Ca and Sr for Sr–HA and Sr–CS, Ca, Mg and Sr for Sr–BS) were quantified by X-ray fluorescence (XRF) (PW 2404, Philips, Eindhoven, The Netherlands). Checks were made for the presence of heavy metals, e.g. Cr, Ni, Fe and Cu.

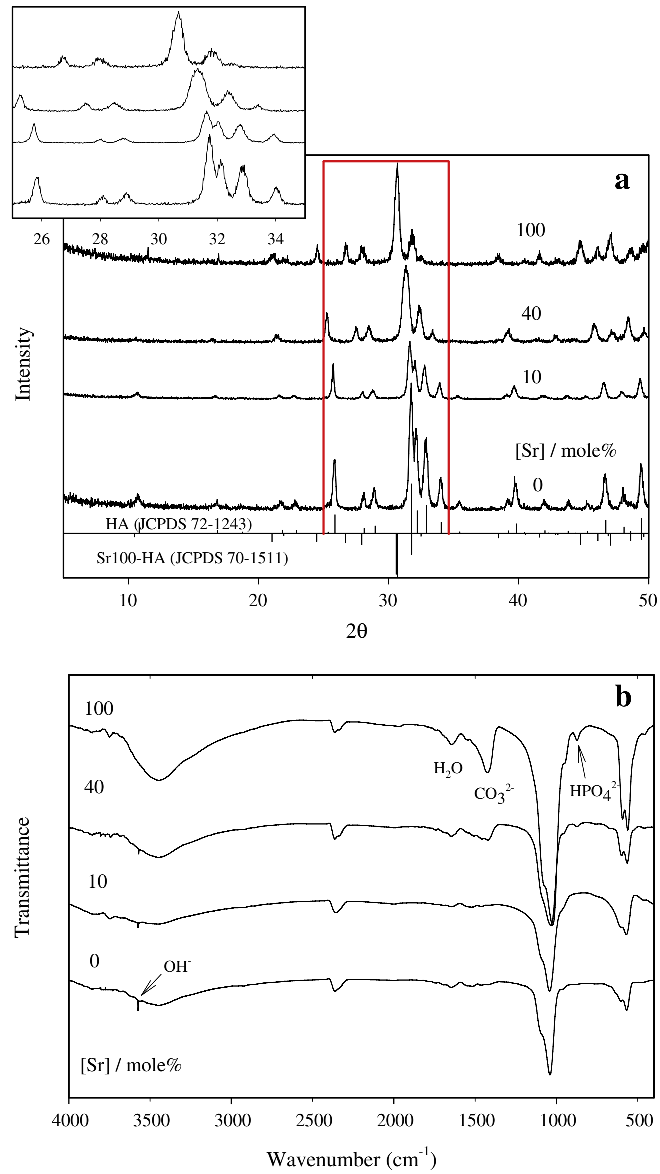

Fig. 1. Characterization of Sr–HA: (a) XRD patterns; (b) FTIR spectra.

Table 1
Calculated degree of substitution of Ca (and Mg) by Sr, as determined by XRF (mean ± SD, n = 5).

Material	Sr/(Ca + Sr)	Sr/(Mg + Sr)	Sr/(Ca + Mg + Sr)
HA	0		
Sr10–HA	8.73 ± 0.31		
Sr40–HA	37.95 ± 1.21		
Sr100–HA	100		
CS	0		
Sr5–CS	3.3 ± 0.5		
Sr10–CS	6.7 ± 0.8		
Sr20–CS	15.8 ± 2.7		
BS		0	0
Sr6–BS		6.3 ± 1.5	NA
Sr12–BS		NA	11.9 ± 1.9

No heavy metals were detected.
NA, not available/applicable.