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Solubility of strontium-substituted apatite by solid titration

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Abstract

Solid titration was used to explore the solubility isotherms of partially (Srx-HAp, $x = 1$, 5, 10, 40, 60 mol.%) and fully substituted strontium hydroxyapatite (Sr-HAp). Solubility increased with increasing strontium content. No phase other than strontium-substituted HAp, corresponding to the original titrant, was detected in the solid present at equilibrium; in particular, dicalcium hydrogen phosphate was not detected at low pH. The increase in solubility with strontium content is interpreted as a destabilization of the crystal structure by the larger strontium ion. Carbonated HAp was formed in simulated body fluid containing carbonate on seeding with Sr10-HAp, but the precipitate was strontium-substituted on seeding with Sr-HAp. Strontium-substituted HAp might be usable as a template for the growth of new bone, since nucleation appears to be facilitated.
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1. Introduction

Hydroxyapatite (HAp), $Ca_5(PO_4)_3OH$, is the principal parent mineral of bone and tooth tissue. However, it is never found in a pure form in nature since substitution of, for example, sodium, magnesium, carbonate and fluoride, occurs readily; such substitutions can occur at all three site types: calcium, phosphate and hydroxide. In particular, strontium may substitute at Ca sites, forming a continuous solid-solution (Srx-HAp) up to full substitution (Sr-HAp) due to chemical similarity. Strontium is believed to play an important role in the treatment of osteoporosis and enhancement of bone remineralization as it is associated with a reduction of bone resorption, an increase in the formation of new bone, and a decrease in the risk of bone fracture [1]. Consequently, a number of strontium-containing materials have been extensively used as a bone filler, such as partially strontium-substituted HAp [2–5], α-tricalcium phosphate [6] and $CaSiO_3$ [7], as well as strontium-containing cement [8,9]. In addition, strontium-containing toothpaste was developed to enhance the remineralization of dental enamel [10], and recently drugs such as strontium ranelate (SrR) [11] have been suggested for use as a daily supplement to increase bone mineral density.

However, the mechanism and behaviour of strontium in such systems are controversial. Grynpas [12] thought that the incorporation of strontium induced hypomineralization by weakening the apatite lattice and so increasing bone mineral solubility, while it was recently reported that no stimulation of new bone formation was found in ovariectomized rats after SrR intake for 3 months [13]. On the other hand, Christoffersen et al. [14] and Dedhiya et al. [15] found that strontium significantly inhibited the dissolution of HAp, and a "surface complex", $Ca_3Sr_2(PO_4)_3OH$ (40% Sr-substituted HAp, Sr40-HAp), has been postulated to account for such dissolution retardation [16]. However, as indicated by Christoffersen et al. [14] themselves, the solubility of strontium-substituted apatite increases with increasing strontium content. The question, therefore, arises of how a more soluble phase could cover a more stable phase spontaneously at equilibrium? A thorough check of the effect of strontium on the solubility of these phases is necessary.

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One immediate concern is that the incongruent dissolution of HAp [17–19] has been known since at least the 1930s: the apparent solubility increases with increasing amounts of solid present. The conclusion of Levinskas and Neuman [20] that no solubility product (SP) for HAp can be calculated can be attributed to this. In fact, although a number of dissolution models have been discussed before [19], consideration of the method itself is usually neglected. For calcium phosphates, difficulties arise from the formation of intermediate phases such as dicalcium hydrogen phosphate (DCPD), octacalcium phosphate (OCP) and amorphous calcium phosphate (ACP), which have been reported to nucleate more easily, leading to shifts in solution equilibria. Crucially, however, seldom has the attempt been made to analyze the composition and phase constitution of the solid at equilibrium as it has been assumed that no phase transformation occurs (HAp is reported as the most stable phase at pH >4.2 [21]), despite the solution Ca/P ratio varying greatly. Problems are commonly ascribed to the formation of complexes [19,22,23]. Any such determined solubility does not correspond to the original solid, and lacks both precision and accuracy. Furthermore, the calculation of a solubility product (SP) requires knowledge of all relevant equilibria, but the presence of a dozen or so equilibria has been neglected or ignored, such as for $CaH_2PO_4^+$, $CaPO_4^-$ [24]. Such simplification is an unwarranted and crude approximation; such calculated SPs are therefore, meaningless.

Recognizing these difficulties, the solid titration approach for determining mass solubility was developed [25,26]. In this, a series of only very small increments of the relevant solid are added to the test solution as the end-point is approached, with the end-point of remnant solid (or new precipitate) being detected by a low-angle laser-scattering system; the system depends on the complete dissolution of each increment before the next is added. Thus, although the dissolution of the solid itself may still be incongruent whilst there is solid present, at the end-point the excess solid is vanishingly small, thus avoiding both the appreciable supersaturation and uncertain solution composition which arise from a large excess of solid. Using this technique, HAp has been confirmed to be substantially less soluble than previously reported [26]. In particular, DCPD has been found not to be the most stable phase at low pH as hitherto believed; rather, a calcium-deficient HAp phase is the most stable. Meanwhile, the reliability and reproducibility of solid titration has been confirmed for a relatively simple system, CaF_2 [27], with the experimental solubility isotherm consistent both with the theoretical results over a wide pH range and with other reports [28,29]. Therefore, solid titration may be the only viable approach to explore true solution equilibria for complicated systems such as the calcium phosphates. The extension to other systems is natural, and in particular the effect of strontium is of special interest here, where the debate might arise from failure to understand the true solution equilibria.

However, the literature contains little in the way of solubility data for Srx-HAp [30]. Thus, in the present context determination of the true solubility of strontium-containing apatites is both necessary and urgent. The aim of the present work was, therefore, to determine the solid titration curves for Srx-HAp, with the composition of the precipitate at equilibrium needing to be determined in order to ascertain whether such curves represent solubility isotherms for the titrant solid composition. In addition, seeding of these solids in simulated body fluid (SBF) solution might be helpful to understand the effect of strontium in vivo.

2. Materials and methods

2.1. Titrant preparation

Srx-HAp ($x = Sr/(Ca + Sr) = 1, 5, 10, 40\ 60$ mol.%) and Sr-HAp were synthesized using an hydrothermal method at 150 °C for 14 h by adding $(NH_4)_2HPO_4$ solution (analytical grade, Merck, Darmstadt, Germany) into a solution of $Sr(NO_3)_2$ and $Ca(NO_3)_2$ in the corresponding molar ratio (both analytical grade, BDH, Poole, UK), with the product (Ca + Sr)/P ratio 1.67 (stoichiometric for apatites) as previously described [31]. Ammonium hydroxide solution (Aristar, BDH) was used to adjust to initial pH 10. The precipitate was washed several times each with deionized water and absolute ethanol, and finally dried at 90 °C overnight.

2.2. Solid titration

The solubility of each solid Srx-HAp in 600 ml of 100 mM KCl solution at 37.0 ± 0.1 °C was investigated. The solution was flushed with nitrogen, and all conditions were as previously reported for HAp [26]. The end-point of the titration was determined by a semiconductor-diode laser-scattering system (1 mW CW, 194-010, RS Components, UK). The intensity of the initial signal was approximately proportional to the amount of added solid. Each addition of the solid, even if less than 0.5 mg, caused an obvious step-increase in the laser-detector output signal. With time, this signal decreased due to the dissolution of the solid. The time taken depended on the particle dissolution rate. When a stable signal was obtained for an hour or more at or very close to the original baseline value, it was taken as indicating that the solid added had completely dissolved; the next solid addition could then be made. Therefore, the end-point of the titration could be unambiguously detected by the output signal remaining higher than the original baseline, indicating that no more solid could dissolve or that a new solid had precipitated, or both. The estimate of the end-point of the titration was refined by interpolation as previously described [26], after a further small increment. The pH value could then be adjusted to a lower value by adding HCl (1 M solution, analytical grade, BDH; dropwise) until all solid had dissolved, permitting a further determination.

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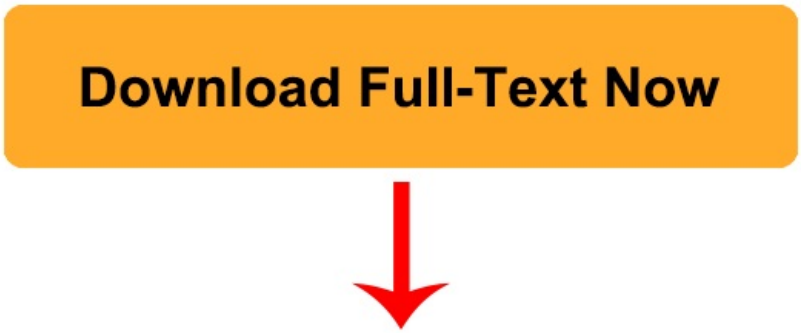

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