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SYNTHESIS OF VANADATE APATITE WITH GALLIUM FOR ORTHOPEDIC APPLICATIONS

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ABSTRACT

The vanadate apatite containing gallium has been synthesized. As intended, gallium is not chemically fixed in the HA–V crystal matrix because of the differences in the ionic radii and charges of Ca and Ga. The latter is distributed homogeneously in the sample without any compositional variations. It was concluded that in vivo, before the vanadate host dissolves completely, the ionic form of Ga3+ would be accessible to perform its strengthening action on the bone. The results open up the possibilities of introduction into clinical practice a material that contains promising less common elements gallium and vanadium.

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INTRODUCTION

Hydroxyapatite (HA–Ca-P) is a highly valuable material for biomedical applications because of its known biocompatibility, osteoconductive properties, and strong chemical similarity to the natural inorganic phase of human bone. Given its inherent tendency to form strong bonds to natural bone tissue placed in apposition to it, hydroxyapatite has become a widely used bone graft material in orthopedics (Mucalo, 2015). Hydro xyapatite containing vanadium or vanadate apatite (HA-Ca-V) has long been recognized as a structural and electronic analogue of phosphate with similar protonation reactions. This analogy is most evident in the tetrahedral trianionic forms VO_4 and PO_4 (Crans *et al*., 2004). Therefore, from a chemical point of view, partial substitution of vanadium for phosphorus in the apatite lattice of bone tissue is totally sustainable. These derivatives, in particular $Me^{2+}{}_{10}(VO_4)_3(PO_4)_3(OH)_2$ (Boechat *et al*, 2000) are excellent candidates for bioceramics since vanadium has been described in the literature as osteogenic agents because of its pronounced influence on bone-related cells and on the formation of collagen (Michibata, 2012). Determination of solubility products of phosphate and vanadate apatitesat 37 °C in 0.165 M solution of sodium chloride showed that vanadium-containing compound is more soluble probably because the covalent radius of VO_4^{3-} (0.122 nm) is greater than that of PO_4^{3-} (0.110nm) (Gupta et al., 1987). As a result, the increase in bioavailability allows bringing key reactivity to a reaction center of bone proteins (Crans *et al*., 2004). On the other hand, the usage of a less common element gallium increases calcium and phosphorus content of the bone and brings about direct nontoxic effects on osteoclasts. Gallium ions are clinically effective against bone resorption for the treatment of osteoporosis and cancer-related hypercalcemias (Bernstein, 1998; Melnikov *et al*., 2008; Melnikov *et al*., 2009). A novel material, HA-Ca-P-Ga, recommended for grafts and implants stimulating bone growth has been obtained by introducing gallium ions into crystalline lattice of common hydroxyapatite. The doping was carried out using gallium nitrate and sodium gallate solutions. The composition was shown to be biocompatible with mouse fibroblast cells (Kurtjak *et al*., 2016) and appropriate for application in orthopedic implants. Recently, it was successfully employed for the correction of bone defects in animals (Cassino *et al*., 2018). The purpose of this research is to produce a vanadate analog, HA-Ca-V-Ga of the above material to form a single unit that simultaneously contains the three promising bioactive components, and recommend it for orthopedic applications.

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MATERIAL AND METHODS

The starting materials were calcium hydroxide, $Ca(OH)_2$, ammonium metavanadate NH_4VO_3 and gallium nitrate hexahydrate $Ga(NO_3)_3 \cdot 6H_2O$, all of analytical grade purity purchased from Merck and Sigma-Aldrich, respectively. The exact amounts of starting materials were 3.7 g of $Ca(OH)_2$, 3.5 g of NH_4VO_3 and 0.2 g of $Ga(NO_3)_3 \cdot 6H_2O$ (containing 0.04 g of gallium elemental). Distilled water containing gallium salt was added to form a paste of consistency corresponding to the toothpaste. The mixture was reduced to powder, then dried for 24 h at 90 °C, reground and treated again for 30 min. Finally, the sample was heated in a platinum crucible at 600 °C for 24 h. These precautions are necessary to ensure the removal of NH_3 trapped in the vanadate crystal network. The process can be described by the equation: $5Ca(OH)_2 + 3NH_4VO_3 = Ca_5(VO_4)_3(OH) + 3NH_3 + 9H_2O$. The X-ray diffraction (XRD) pattern of the samples was recorded using a Rigaku Miniflex diffractometer with Cu Kα radiation (λ =1.5418 Å) at a 2θ range from 20 to 90° with a 0.02° step size, and measuring time of 5 s per step. Scanning electron microscopy (SEM) and energy dispersive X-ray spectroscopy (EDS) were performed in a JEOL-JSM 5800 equipment. The compound was identified by comparison of experimental X-ray pattern with available database files on the Inorganic Crystal Structures Database (ICSD).

RESULTS AND DISCUSSION

At high magnifications (x 8,000), scanning electron microscopy allows observing freely associated aggregates consisting of elongated rod-shaped crystals (Fig. 1). It is a clear reference to the hexagonal character of the lattice. As expected, the energy dispersive X-ray spectrum of the material (Fig. 2) is dominated by Kα lines of calcium and vanadium. The insertion of gallium is confirmed by the two smaller lines present therein. The qualitative X-ray mappings acquired from the same area of the sample for calcium, vanadium and gallium (Fig. 3) provide an additional assurance regarding the homogeneity of the material and the absence of compositional variations. At the same time, it is necessary to take into account that the color patterns cannot be reproduced satisfactorily in printed form. The set of interplanar distances of the sample is presented in Table 1. The indexing of the X-ray pattern was successfully done on a hexagonal cell with the parameters: a = 9.62 and c = 6.98 Å, according to the data available for HA-Ca-V (ICSD file 92044.)

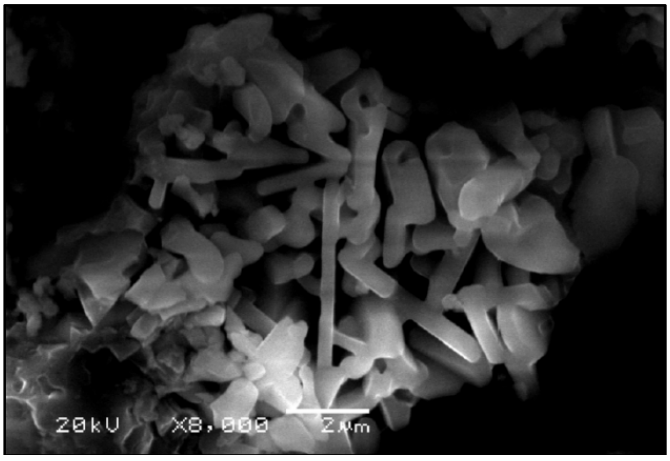

Figure 1. SEM image of rod-shaped crystals

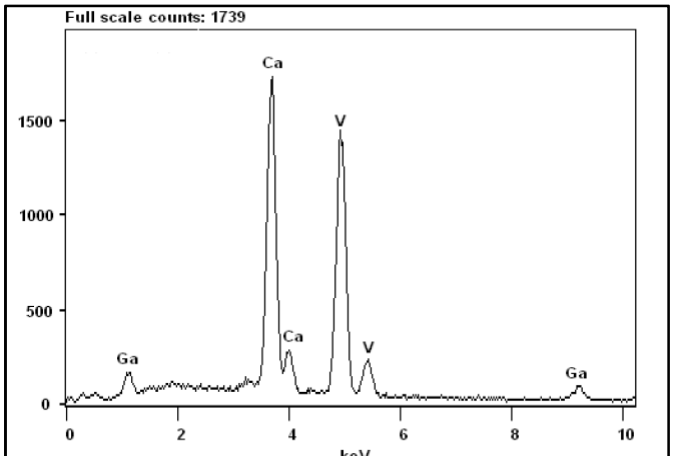

Figure 2. Energy dispersive X-ray spectrum of the material

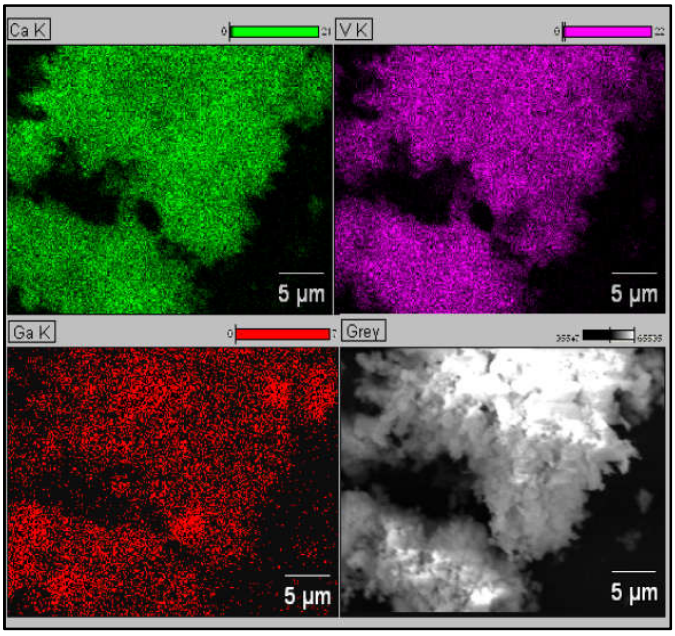

Figure 3. Elemental content and distribution of calcium vanadium and gallium mapped by energy dispersive X-ray analysis

Table 1. Indexing of vanadate hydroxyapatite X-ray pattern

Intensity	d_{calc}	h k l	d_{obs}
20	8.50	1 0 0	8.49
11	5.39	1 0 1	5.40
5	4.90	1 1 0	4.50
100	4.01	1 1 1	4.00
5	3.63	2 0 1	3.66
40	3.49	0 0 2	3.47
13	3.21	2 1 0	3.25
50	2.92	2 1 1	2.92
47	2.85	1 1 2	2.84
70	2.83	3 0 0	2.80
25	2.69	2 0 2	2.62
27	2.01	2 2 2	2.04
30	1.88	2 1 3	1.91
12	1.87	2 3 1	1.84

No reflections belonging to new phases, gallium phosphate or gallium oxide are present although Ga_2O_3 might have been expected as the product of gallium nitrate decomposition over 600°C (Melnikov *et al*., 2012). The same is characteristic for other trivalent elements, in particular for lanthanum (Mayer *et al*., 1999) Moreover, while the X-ray results have shown the formation of only the apatite phase, the lattice constant values showed no dependence on La content and thus do not give any

indication that La^{3+} might be part of the HA phase. The formation of substitution solid solutions does not seem likely because the difference in the ionic radii of the solvent metal (calcium) and the solute element (gallium) is much larger than 15%, and their charges are also unequal (Ca^{2+}*vs* Ga^{3+}). That means that the gallium cannot be chemically fixed in the crystal lattice, therefore, before the vanadate host dissolves completely, the ionic form will be available to perform its action on the bone.

Conclusion

The synthesis of vanadate apatite containing gallium has been successfully achieved. As intended, gallium is not chemically fixed in the HA–V crystal matrix because of the differences in the ionic radii and charges of Ca and Ga. The latter is distributed homogeneously in the sample without any compositional variations. It was concluded that *in vivo*, before the vanadate host dissolves completely, the ionic form of Ga^{3+} would be accessible to perform its strengthening action on the bone. The results open up the possibilities of introduction into clinical practice a material that contains promising less common elements gallium and vanadium.

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