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VANADATEAPATITE MATRIX CONTAINING STRONTIUM AND GALLIUM FOR BONE DISEASE APPLIANCES

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ABSTRACT

It has been shown that the proposed solid state synthesis technique has advantages over the most commonly used coprecipitation methodology, by avoiding the undesirable polymerization of the VO_4^{3-} ion in an aqueous medium. The formation of strontium vanadateapatite occurs at 600 ° C as a monophasic sample. According to X-ray diffraction, the substitution of strontium for calcium in the structure of apatite vanadate containing gallium was achieved. The intercalated gallium atoms produce no structural distortion or alteration of the hydroxyapatite matrix. The qualitative X-ray mappings acquired from the same area of the sample provides images of homogeneous elemental distribution in the composite, thus confirming absence of compositional variations.The characteristics of the new material containing simultaneously three bioactive components are compatible with the natural human hydroxyapatite. The results obtained open the possibilities of introducing this composite into orthopedic practice.

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INTRODUCTION

The regrowth of diseased or fractured bones is the problem faced by the current science of biomaterials and tissue engineering. The orthopedic applications of hydroxyapatite (HA) include its usage for stand-alone implants, such as in bone graft substitutes for the filling of bone defects or part of an implant to provide a specific property or feature as a coating on metallic implants. The literature devoted to these materials is enormous. However, to obtain better mechanical properties, biocompatibility and absorption, alternative synthetic pathways have been proposed to replace calcium and /or phosphorus by their chemical analogues in this classic crystalline matrix (Mukalo, 2015). For example, strontium was substituted into HA molecules increasing bone formation by specific cells and offering a structural in fractures integrity due to bone demineralization (Masala, 2014). Recently, the hydrated form of strontium hydroxyapatite $Sr_{10}(PO_4)_6(OH)_2 \cdot 10H_2O$ has been successfully synthesized at room temperature and proposed for orthopedic applications. The presence of this loosely bonded water, and low crystalline structural organization made the compound suitable for the preparation of bone-strengthening biodegradable implants (Melnikov, 2015). Another promising candidate for substitution is a trace element vanadium, which can be easily incorporated into HA lattice (Petit, 2017). Recently, vanadium compounds have been reported in the literature as osteogenic agents due to their actions on specific bone related cells and on collagen formation. At the same time. *in vivo* reports showed little, if any, toxicity in longterm administration of this important element, at least in the vanadium (V) valence state (Michibata, 2012). Gallium ions also are clinically effective against bone resorption and for the treatment of osteoporosis and cancer-related hypercalcemias. They increase calcium and phosphorus content of the bone and have direct nontoxic effects on osteoclasts (Bernstein, 1998, Melnikov, 2008). Gallium ions were successfully introduced into a crystalline lattice of common hydroxyapatite using gallium nitrate and

sodium gallate solutions as dopant reagents (Melnikov, 2009a). Later, the same composition was shown to be biocompatible with mouse fibroblast cells, and appropriate for application in orthopedic implants (Kurtjak, 2016). In particular, it has been used with good results for the correction of bone defects in animals (Cassino, 2018). Finally, not long ago, the substitution of vanadium for phosphorus was carried out in a gallium-doped hydroxyapatite matrix (Melnikov, 2019b). The gallium-containing $Ca_5(VO_4)_3(OH)$ composite thus obtained was characterized as a non-toxic biologically compatible material (Petr Melnikov, 2019). The goal of this research is to employ a strontium analog of the above compound to produce Sr-V-Ga composite that simultaneously contains a set of the three promising bioactive elements.

MATERIALS AND METHODS

Thestarting materials used were strontium hydroxideoctahydrate $Sr(OH)_2 \cdot 8H_2O$, and ammonium metavanadate NH_4VO_3 of analytical grade purity purchased from Sigma-Aldrich and Merck, respectively Gallium hydroxide Ga (OH) was specially prepared by slow precipitation from a 10% solution of gallium nitrate hexahydrate (Aldrich) with a 2% solution of ammonium hydroxide (Merck). It was dried at 90 ° C for 36 hours, ground and redried to constant weight. Gallium as a dopant must come from $Ga(OH)_3$, the decomposition of which produces exclusively gallium ions and water. On the other hand, in the solid state nitrate ions from $Ga(NO_3)_3 \cdot 6H_2O$ would immediately polymeraze ammonium vanadate into inert solid vanadic acid H_3VO_4 ($V_2O_5 \cdot H_2O$), and the interaction would stop. This occurrence is easily discovered by a bright yellow coloration.

Synthesis of strontium vanadium hydroxyapatite was carried out by means of a chemical reaction in solid state between the above reagents. This method seems to have advantages over the most commonly used coprecipitation technique (Melnikov, 2015), making it possible to avoid the undesirable polymerization of the vanadate ion in an aqueous milieu. The exact amounts of starting materials for pure vanadate were 0.34 g of NH_4VO_3 and 1.3 g of $Sr(OH)_2 \cdot 8H_2O$, mixed in order to obtain the ratio Sr:V = 3.85, which is characteristic of this hydroxyapatite. After thorough grinding, 0.16 g of gallium hydroxide corresponding to 0.1 g of gallium elemental was added and the mixture was re-ground. With regard to the reaction mechanism we can assume that the process can be described by the equation:

$$5Sr(OH)_2 \cdot 8H_2O + 3NH_4VO_3 = Sr_5(VO_4)_3(OH) + 3NH_3 + 46H_2O$$

Characterization was carried out by the thermal gravimetric analysis of the material (TG) used to control mass losses at different temperatures, employing a TGA Q50 V20 13 Build 39 instrument. Test specimens of the starting material (5 mg) were heated in a flux of argon (50 mL min^{-1}, 99.998% purity, oxygen content < 5 ppm) in a 30 – 600 °C temperature range, at a heating rate of 10 °C min^{-1}. In parallel, this operation was performed in the air, and the patterns obtained were identical. The morphologies of the samples were characterized with field emission scanning electron microscopy using a Hitachi TM3000 Desk-top instrument. The X-ray diffraction (XRD) patterns were recorded on a Rigaku Ultima IV diffractometer in the 2θ degree range from 20° to 80° with a step size of 0.02° with 5 s per step using CuKα radiation (40KV and 40mA). The Fourier transform infrared (FTIR) spectra were recorded using a Bruker Vertex 70 spectrometer in a range 400 to 4000 cm^{-1}. FTIR measurements were conducted using pellets prepared froma few milligrams of the sample mixed with fine KBr powder.

RESULTS AND DISCUSSION

Unlike hydrated strontium hydroxyapatite, which can be prepared by a low temperature autocatalytic process (Melnikov, 2015), strontium gallium vanadate apatite is formed at a temperature above 450 °C corresponding to a mass loss of 57.2%, which matches a calculated value of 58%.

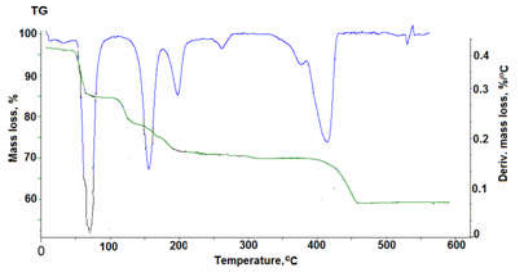

Figure 1. TG curve reflecting $Sr_5(VO_4)_3(OH)$ synthesis

The TG curve of the reaction mixture (Fig. 1) shows that the initial mass losses at 25-124 and 162-213 ° C are due to the partial dehydration of $Sr(OH)_2.8H_2O$ octahydrate. This is confirmed by the IR spectra of samples heated at 100 and 150 °C (Fig. 2), identical to the vibrational pattern of NH_4VO_3 at high temperatures (Heyns, 2000). The effects in the region of 203-414 °C most probably reflect the removal of the remaining water from strontium hydroxide octahydrate, which, at this stage, eventually becomes $Sr(OH)_2$. The reaction is complete at 511 ° C with no further mass loss observed.

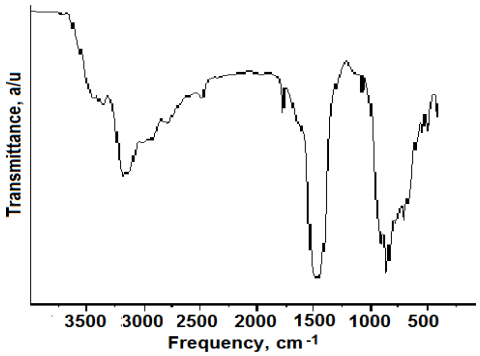

Figure 2. IR spectrum of the sample obtained at 150 °C.

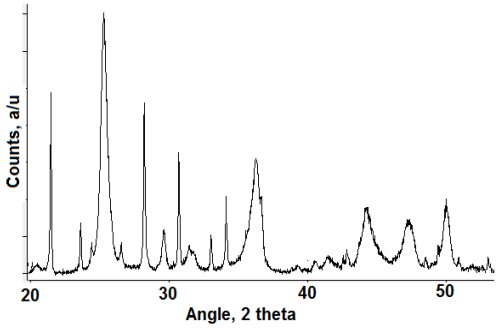

Figure 3. X-ray difractogram of the sample obtained at 150 °C.

On the other hand, the X-ray phase analysis of the samples obtained at 150 ° (Fig. 3) C has been also compatible with the mixture of starting reagents, in addition to $(NH_4)_3VO_8$ (PDF file 14-668), which is the product of NH_4NO_3 thermal polymerization. As for the morphology of the final composite, the SEM micrograph (Fig 4) shows at moderate magnification (x 4.000) a pattern of a typical ceramics with loose small crystallites resulting directly from the rhomboid-like plates present as broken multilayer aggregates. The microcrystals and amorphous particles usually show a better affinity to the newly formed layers on the bone surface. Some of the aforementioned plates are well preserved as those located in the center of the image and separated by layers of semi-crystalline material. The two sides of the upper one, in the shape of a relatively regular rhombus, were measured obtaining the ratio 3.79 / 2.87 = 1.32. On the other hand, the ratio of hexagonal network parameters ***a*** and ***c*** is 10.047 / 7.411 = 1.35 (PDF file 28-1772), which constitutes the strong morphological confirmation of the intactness of the hydroxyapatite matrix.

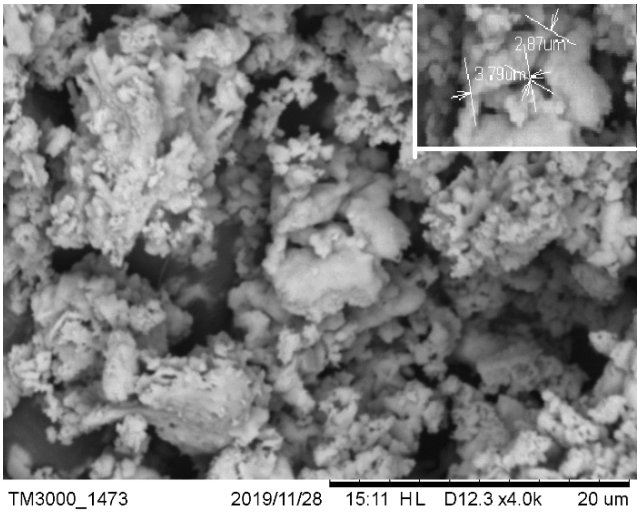

Figure 4. Representative SEM image of vanadate apatite with strontium and gallium. The measurements are shown in the upper right quadrant

As can be seen from Fig. 5, the energy dispersive spectrum of the material is dominated by Lαline of strontium and Kα line of vanadium. Gallium is represented by Lα and Kα smaller peaks presente therein.

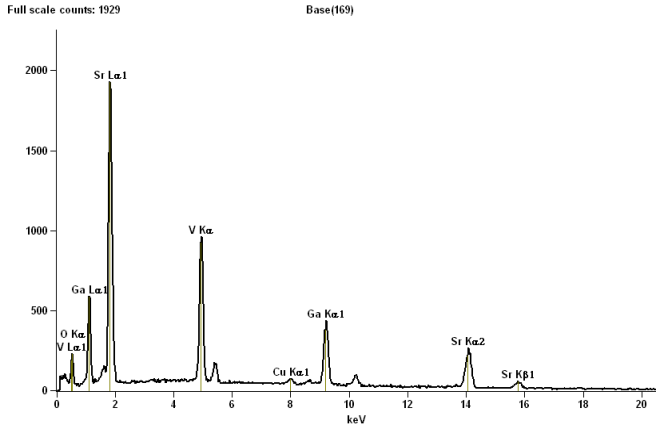

Figure 5. Energy dispersive X-ray spectrum of the material

The qualitative X-ray mappings for gallium and strontium from the same area of the sample provide an additional confirmation as for the doping homogeneity (Fig 6).

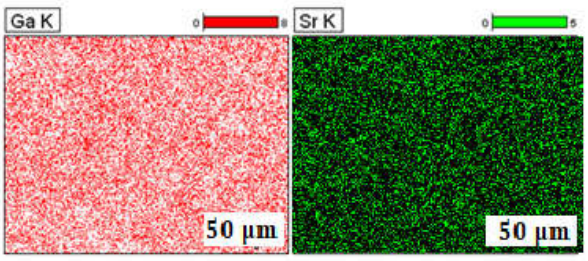

Figure 6. Gallium and strontium content mapped by energy dispersive X-ray analysis

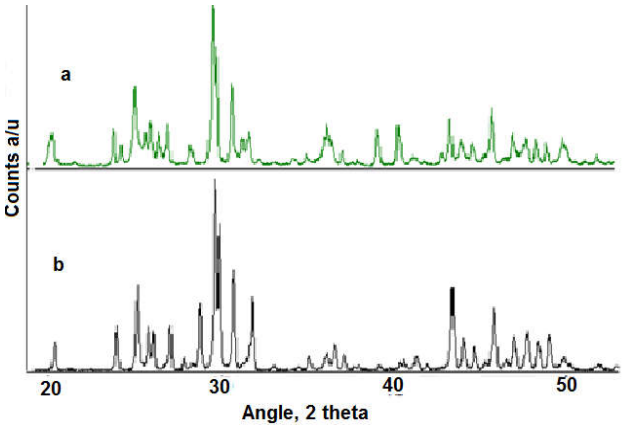

Figure 7. X- ray difractograms matrix (a) (Bucio, 2009) and of strontium-vanadium hydroxyapatite doped with gallium (b)

Table 1. Indexation of strontium-vanadium hydroxyapatite gallium difractogram

I/I_0	2θ	d, Å	h k l
3	24.0201	3.7019	2 0 1
4	24.3295	3.6555	0 0 2
5	26.4797	3.3633	1 0 2
6	27.4630	3.2451	2 1 0
7	30.1051	2.9661	2 1 1
8	30.3568	2.9420	1 1 2
9	31.2279	2.8619	3 0 0
10	32.1351	2.7832	2 0 2
11	33.6012	2.6650	3 0 1
12	36.2140	2.4785	2 2 0
13	36.8527	2.4370	0 0 3
14	37.0129	2.4268	2 1 2
15	37.7474	2.3813	3 1 0
16	38.3151	2.3444	1 0 3
17	38.3642	2.3444	1 0 3
18	39.7793	2.2642	3 1 1
19	39.9770	2.2535	3 0 2
20	41.2562	2.1870	1 1 3
21	42.0620	2.1464	4 0 0

The X-ray diffractograms of strontium-vanadium hydroxyapatite matrix (a) and gallium-doped strontium-vanadium hydroxyapatite (b) are shown in Fig. 7. The corresponding indexation is given in Table 1. Lattice parameters calculated a= 9.914 Å and b = 7.311 Å are very close to those of the pure matrix, a = 10.047 and b =7.411 (ICSD file 259900). As can be seen, the pattern of the gallium-containing sample is practically identical to that of the matrix, which the dopant has been previously introduced into. With regard to the crystalline lattice of the compound, the coincidence of the interplanar distances eliminates doubts as to any type of structural deformation that could have occurred. As the gallium trapped in the hydroxyapatite does not produce structural distortions or alterations, its presence logically would not compromise the compatibility of this compound with either the natural human hydroxyapatite or the related phosphates available in situ. On the contrary, this rare element

will be easily accessible to bone cell enzymes (Melnikov, 2008). As mentioned elsewhere (Melnikov, 2009), virtual crystallographic distortions should not be confused with the imperfections of the microcrystals themselves, since the half-amorphous character makes artificial hydroxyapatite compatible with the natural bioactive environment. Moreover, since both gallium and strontium ionic radii (76 and 132 ppm), as their charges (+3 and +2), are sterically incompatible without adequate compensation, the formation of substitution solid solutions can be excluded, and we deal therefore with the classic solid solution of intercalation. As for the binary system $Ca_5(VO_4)_3(OH)$ - $Sr_5(VO_4)_3(OH)$ in general, it represents substitutional solid solutions, in which phosphorus and vanadium can be continuously replaced. Their polycrystalline samples were synthesized and studied showing homogeneous distribution of vanadium within the solid and the surface, with no anionic vacancies present (Bauer, 2000). This opens the possibility of preparing a series of tailored composites with fixed P/V ratio and gallium intercalated in the structure. They can be used alone in their purest form or be part of combinations with common calcium hydroxyapatite according to the appropriate clinical circumstances.

Conclusion

It has been shown that the proposed solid state synthesis technique has advantages over the most commonly used coprecipitation methodology, by avoiding the undesirable polymerization of the VO_4^{3-} ion in an aqueous medium. The formation of strontium vanadate apatite occurs at 600 ° C as a monophasic sample. According to X-ray diffraction, the substitution of strontium for calcium in the structure of apatite vanadate containing gallium was achieved. The intercalated gallium atoms produce no structural distortion or alteration of the hydroxyapatite matrix.The qualitative X-ray mappings acquired from the same area of the sample provide images of homogeneous elemental distribution in the composite, thus confirming absence of compositional variations.The characteristics of the new material containing simultaneously three bioactive components are compatible with the natural human hydroxyapatite and its cellular environment. The results obtained open the possibilities of introducing this composite into orthopedic practice.

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