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The effect of phosphate source on the sintering of carbonate substituted hydroxyapatite

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Abstract

Carbonate hydroxyapatite (CHAp) was synthesized by a wet precipitation method. In the synthesis, calcium oxide, H_3PO_4 and $(NH_4)_2HPO_4$ were applied as reactants. NH_4HCO_3 in the amount of 0.05–0.20 mol per 0.3 mol of H_3PO_4 or $(NH_4)_2HPO_4$ was used as the source of CO_3^{2-} groups. Sintering was carried out using powders and uniaxially pressed samples of carbonate and non-carbonate hydroxyapatites. The influence of synthesis conditions as well as sintering atmosphere on sinterability and phase composition of the final ceramic materials was evaluated. It was found that using properly synthesized CHAp powders and CO_2 atmosphere during heat-treatment it was possible to obtain dense CHAp ceramics with 1% of $CaCO_3$ as the secondary phase at the temperature 300–350 °C lower than that required for non-carbonate hydroxyapatite. Chemical stability and bioactive potential of CHAp–$CaCO_3$ ceramics were confirmed by *in vitro* tests.

Keywords: A. Sintering; Bioactive ceramics; Bone substitution materials; Carbonate hydroxyapatite; Synthesis

1. Introduction

The ideal bone graft substitute should be biocompatible, bioresorbable, osteoconductive, osteoinductive, structurally similar to bone, easy to use and cost-effective. For several decades, many efforts have been put to improve the effectiveness of bone substitutes, but the clinical results of these procedures have not been satisfactory. The gold standard for the reconstruction of bone defects is still the autograft, despite serious shortcomings. Concerning of widely used allografts problems associated with disease transmissions, allergic and rejection reactions, inflammations and other negative effects inspire many research to develop new hard tissue synthetic implantation materials. Fabrication of the superior artificial bone replacement is the main concept to promote bone healing today, especially in the case of critical sized bone defects. The main attempt is to obtain bioactive bone substitutes with their ability to resorb at a rate similar to bone growth.

Biological apatites present in natural bone, dentin and enamel are the OH^- apatites modified by the presence of many other ions. Substitutions of calcium with various cations (e.g. Mg^{2+}, Sr^{2+}, Na^+, K^+) are accompanied by changes in apatite lattice parameters. These changes are generally related to the size of the ionic radius of the cation compared to that of Ca^{2+}. In biological apatites, many cations have been assumed to be only adsorbed on the apatite surface. Some anionic substituents have been also observed (e.g. Cl^-, F^-, CO_3^{2-} for OH^- or CO_3^{2-} for PO_4^{3-}). Substitutions affect physical and chemical properties of natural apatites.

Among a variety of biomaterials, calcium phosphate-based (CaPs): hydroxyapatite (HAp), β tricalcium phosphate (βTCP) and BCP (biphasic calcium phosphate) appear to be excellent bioactive implantation materials with different rates and degrees of resorption. They are used in the form of porous blocks, granules, metal coatings, polymer fillers, cements and – rarely – as dense implants.

Currently, a very popular approach to improve biological properties of synthetic HAp is to adjust more closely its chemical composition and morphology to that of cancellous

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bone. The incorporation of carbonate ions into the HAp structure is the most common example of this. The content of carbonate (CO_3^{2-}) in natural bone, dentin and enamel is 7.4, 5.6 and 3.5 wt.%, respectively. Sintered carbonate hydroxyapatites are regarded as promising bone substitutes. Depending on the conditions of their preparation, such as pH, temperature and/or on the presence of other elements, they can reveal differences in solubility and resorption rate in a living body [1–8]. Another approach involves silicon substitution which results in the preparation of Si–HAp materials [9]. Synergistic effects of Mg^{2+} and CO_3^{2-} on crystallinity and dissolution properties of synthetic apatites was confirmed [10].

Numerous studies have been devoted to synthesis and characterization of carbonate hydroxyapatite ceramics (CHAp). Various techniques have been used to prepare CHAp initial powders with wet chemical methods [11,12] and solid-state reactions [13] being the most popular ones. The kinetics of CHAp formation at 38 °C in serum has been investigated by isothermal calorimetry [14]. The mechanochemical–hydrothermal method for the preparation of nanocrystalline CHAp and NaCHAp powders with controlled carbonate substitution has been also applied [15]. The increasing interest concerns CHAp precipitation in the cement system, i.e. α-$Ca_3(PO_4)_2$–$Ca(H_2PO_4)_2$–$CaCO_3$ [16].

In previous studies the effect of sintering parameters on the density, phase composition and microstructure of CHAp has been evaluated [11,17].

In this work we demonstrate that sinterability of initial CHAp powders in CO_2 atmosphere and in air as well as the properties of CHAp ceramics depend on reagents used in the wet chemical synthesis. The usefulness of *in vitro* studies for predicting chemical stability and bioactive potential of obtained biphasic CHAp–$CaCO_3$ ceramics has been also the subject of our research.

2. Materials and methods

Carbonate hydroxyapatite powders were produced by a wet method [12]. In such synthesis, H_3PO_4 and $(NH_4)_2HPO_4$ served as the source of phosphorus. CaO (analytically pure – Ubichem Co.) was applied as the calcium reagent in all procedures. Ammonium hydrogen carbonate (NH_4HCO_3) was used in the amounts of: 0.05, 0.1 and 0.2 mol per 0.3 mol of H_3PO_4 or $(NH_4)_2HPO_4$ as a reactant introducing CO_3^{2-} groups. Hydroxyapatite powder without any additives was synthesized as a reference. pH of the reaction mixtures was stabilized at $\geq$11 using ammonium hydroxide solution and the temperature controlled at ~20 °C. When CaO and $(NH_4)_2HPO_4$ were used as reagents, NH_4HCO_3 was mixed with $(NH_4)_2HPO_4$ and added dropwise during the whole synthesis, whereas in the case of CaO and H_3PO_4 ammonium hydrogen carbonate was added in the final part of the preparation procedure. In the last case mixing of orthophosphoric acid with NH_4HCO_3 was impossible because resulted in decomposition of NH_4HCO_3. The following Ca/P molar ratios were applied: 1.67, 1.69, 1.75. The suspensions were aged for 48 h at room temperature and decanted. The resultant precipitates after washing with deionized water and filtration were dried at 90 °C. The carbonate hydroxyapatite powder of Ca/P molar ratio equal to 1.75 was calcined at 900 °C in air and in CO_2 atmosphere. Specific surface area of the powder before and after calcination was determined by BET method (Sorpty 1750). The powder particle size was determined by TEM (Philips CM20).

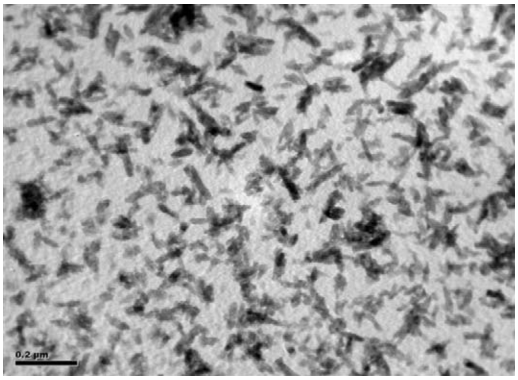

Fig. 1. TEM micrograph of CHAp powder.

The initial CHAp powders were ground to the size below 0.06 mm, sieved and uniaxially pressed under the pressure of

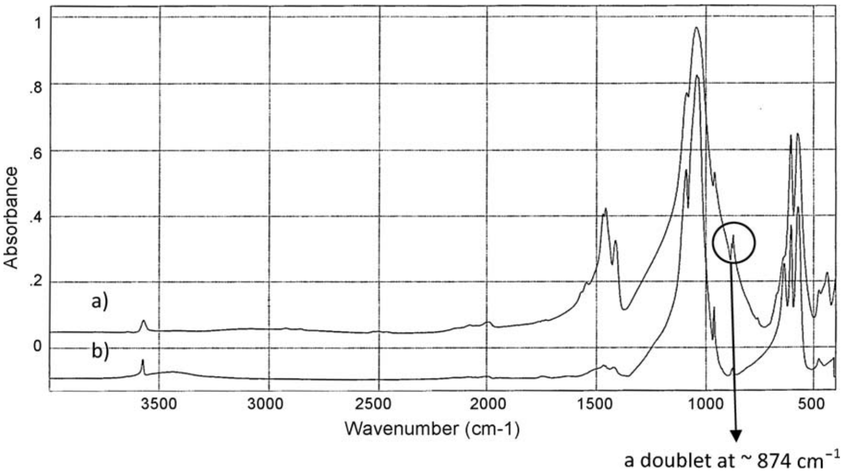

Fig. 2. FTIR spectra of CHAp after sintering at 900 °C: (a) in CO_2 atmosphere and (b) in air.

100 MPa to discs of 11 mm in diameter and 5 mm in height. Additionally, rectangular samples 80 mm × 8 mm × 3 mm in dimensions were produced. The samples were sintered in air and in CO_2 atmosphere for 1 h at 900 °C. The sinterability of the CHAp was evaluated on the basis of the mass loss, shrinkage and relative density of the heat-treated samples (the apparent density of the materials was measured by Archimedes method). Phase composition of the ceramics was examined by X-ray diffraction (X'Pert Pro, Panalytical diffractometer). Phase quantification was made by the Rietveld method. Fourier transform infrared spectroscopy (FTIR) studies were carried out on a Digilab FTS 60 spectrometer. Flexural strength was determined for the best sintered material in the three point bending test using a Zwick 1435 tester. Chemical stability of CHAp ceramics was evaluated *in vitro* by measuring pH (CP-401 pHmeter – Elmetron Co. Poland) and ionic conductivity (CC-401 conductometer – Elmetron Co., Poland) vs. time of immersion of the samples in SBF and distilled water, respectively (SBF: Na^+-142.0, K^+-5.0, Ca^{2+}-2.5, Mg^{2+}-1.5, Cl^--147.8, HCO_3^--4.2, HPO_4^{2-}-1.0, SO_4^{2-}-0.5 mM/dm^3; pH 7.4). The mass changes of immersed samples were calculated. Surfaces of the samples before and after immersion in SBF were examined by SEM (Nova NanoSem 200, FEJ Co.).

3. Results and discussion

Nanosized carbonate hydroxyapatite powders were synthesized at room temperature by a wet chemical method (Fig. 1). After heat-treatment in the CO_2 atmosphere at 900 °C, the presence of CO_3^{2} groups in all investigated hydroxyapatite structures was confirmed (FTIR bands between 1415 and 1450 cm^{-1} and at approximately 874 cm^{-1} originating from carbonate groups) (Fig. 2). In the synthetic CHAp powders CO_3^{2-} for PO_4^{3-} substitution was stated. A doublet at 874 cm^{-1} may suggest an AB-type CHAp (some fraction of OH^- groups was also replaced). BET surface area of the initial CHAp powder for Ca/P molar ratio equal to 1.75 starting from CaO and $(NH_4)_2HPO_4$ was equal to 81.3 ± 1.2 m^2 g^{-1}. After calcinations at 900 °C in air, the surface area of this powder has decreased to 20.2 ± 1.0 m^2 g^{-1}, whereas heat-treatment in the CO_2 atmosphere resulted in much lower surface area with the value of 2.7 ± 0.8 m^2 g^{-1} (Table 1). This confirms that the process of carbonate hydroxyapatite sintering is effective only in CO_2 atmosphere (more efficient in wet than dry carbon dioxide [16]). Presence of CO_2 in a furnace during heat-treatment prevents the CO_3^{2-} groups from evolution from the CHAp structure. Modification of HAp structure by the carbonate groups results in different structural parameters. The

Table 1
The effect of sintering atmosphere on the specific surface area of CHAp powder (Ca/P = 1.75; CO_3^{2-} = 12 wt.%).

CHAp powder	Specific surface area (m^2/g)
Non-calcined	81.3 ± 1.2
Calcined at 900 °C in air	20.2 ± 1.0
Calcined at 900 °C in CO_2 atm.	2.7 ± 0.8

Table 2
The effect of synthesis parameters and sintering atmosphere on the sinterability of CHAp and HAp bioceramics.

Series of synthesis	Symbol of synthesis	Reagents				Weight loss (%)		Shrinkage (%)			
		Ca^{2+}	PO_4^{3-}	CO_3^{2-}	Ca/P mol/ratio	Air[a] atm.	CO_2[b] atm.	h		d	
								Air atm.	CO_2 atm.	Air atm.	CO_2 atm.
I	I-O	CaO	H_3PO_4	–	1.69	8.1	7.8	6.1	4.1	6.6	4.6
	I-1			0.1 M	1.69	9.2	8.5	6.4	3.9	5.6	3.9
	I-2			NH_4HCO_3	1.75	10.2	9.6	14.7	11.8	14.3	11.9
II	II-O	CaO	$(NH_4)_2HPO_4$	–	1.69	8.6	8.4	6.1	4.1	4.2	3.4
	II-1			0.1 M	1.67	12.8	10.8	23.6	22.4	26.8	27.8
	II-2			NH_4HCO_3	1.69	12.8	11.3	17.3	25.1	18.7	26.5
	II-3				1.75	15.0	13.7	18.5	27.2	20.8	27.7

h: shrinkage calculated by measuring the samples height; *d*: shrinkage calculated by measuring the samples diameter.

[a] The samples sintered in air atmosphere.

[b] The samples sintered in CO_2 atmosphere.

Table 3
Sinterability of CHAp bioceramics vs. amount of NH_4HCO_3 additive.

Symbol of material	Ca/P molar ratio	NH_4HCO_3 additives (M)/0.3 mol $(NH_4)_2HPO_4$	Weight loss (%)		Shrinkage (%)				Relative density (%)	
			In air	In CO_2 atm.	h		d		In air	In CO_2 atm.
					In air	In CO_2 atm.	In air	In CO_2 atm.		
II-0	1.69	–	8.6	8.4	6.1	4.1	4.2	3.4	43.9	41.9
II-A/0.05	1.69	0.05	10.8	9.6	6.5	6.1	8.9	7.3	48.1	46.8
II-A/0.10	1.69	0.10	12.8	11.3	17.3	25.1	18.7	26.5	69.4	97.2
II-A/0.20	1.69	0.20	12.6	11.4	25.5	18.9	21.6	16.9	72.4	60.6[a]

[a] Bloating of the samples resulting from the worse sinterability of the CHAp powder with too high content of CO_3^{2-} groups in the structure.

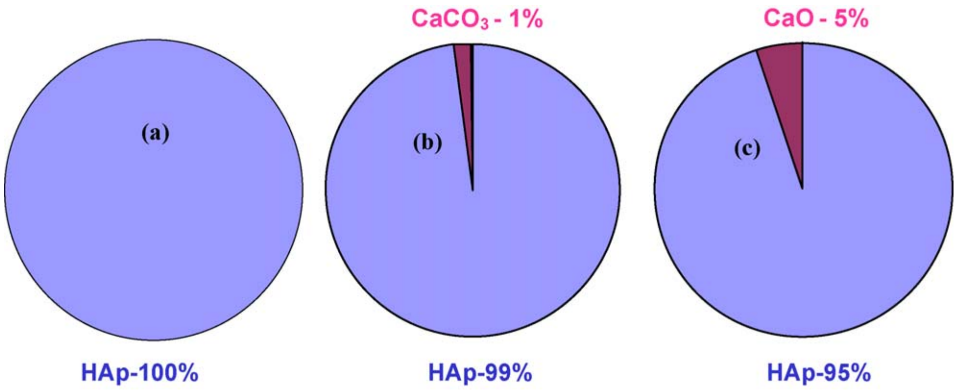

Fig. 3. Phase composition of CHAp II-3 bioceramics after sintering: (a) at 700 °C in CO_2 atm., (b) at 900 °C in CO_2 atm., and (c) at 900 °C in air.

calculated lattice parameters of unit cells for CHAp and HAp (both were sintered with Ca/P = 1.69 in CO_2 atmosphere at 900 °C) were as follows:

CHAp: $a = 9.4150$ Å; $c = 6.8887$ Å.
HAp: $a = 9.4116$ Å; $c = 6.8826$ Å.

The fitting error in the determination of above parameters was 0.0002 Å.

Differences in reactivity between carbonate and non-carbonate powders were revealed during the sintering of the shaped samples. After heat-treatment at 900 °C, the sinterability of CHAp-based materials is better than that of those produced from non-carbonate HAp powder. These differences are observed after sintering in both, CO_2 atmosphere and air (Table 2). Significant influence of the source of phosphorus (Table 2) and the amount of NH_4HCO_3 additive (Table 3) on shrinkage and relative density of CHAp ceramics was revealed. We found that more reactive powders are obtained when $(NH_4)_2HPO_4$ instead of H_3PO_4 is used in the wet synthesis. The optimum NH_4HCO_3 amount in the precipitation process is 0.1 mol per 0.3 mol of $(NH_4)_2HPO_4$. This carbonate content according to the previous studies gives after heat-treatment the level comparable to that typical of natural apatites (4–8 wt.%) [8]. Sintering at 900 °C with 1 h soaking time in CO_2 atmosphere the green bodies obtained from the powder II-2 recognized as the best initial powder, leads to dense CHAp material (II-A/0.10). The relative density of this material is >97% of theoretical. Our results confirmed that CHAp ceramics can be fired in CO_2 atmosphere at the temperature 300–350 °C lower than that required for hydroxypatites without CO_3^{2-} groups in their structure.

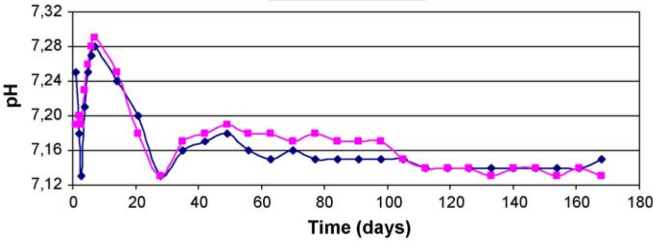

Fig. 4. pH vs. time of immersion in SBF of CHAp and HAp ceramics.

The microstructure of CHAp sinters obtained from the initial powders synthesized with applying $(NH_4)_2HPO_4$ as a source of phosphate ions with Ca/P = 1.69 and sintered at CO_2 atmosphere is homogenous with the average size of hydroxyapatite grains equal to ca. 1 μm. Flexural strength for the best sintered material (II-A/O.10) was 67.7 ± 11.4 MPa.

The obtained ceramics are biphasic: HAp–$CaCO_3$ with max. 1 wt.% of $CaCO_3$ (after sintering in CO_2 atmosphere) or max.

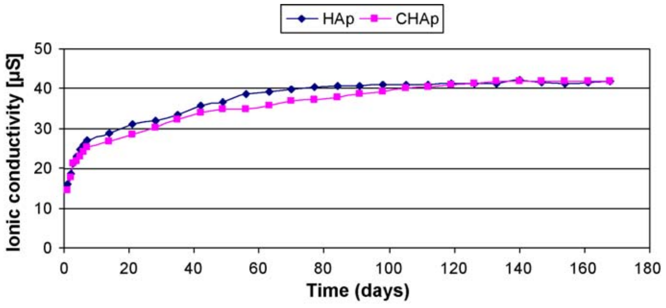

Fig. 5. Ionic conductivity vs. time of immersion in distilled water of CHAp and HAp ceramics.

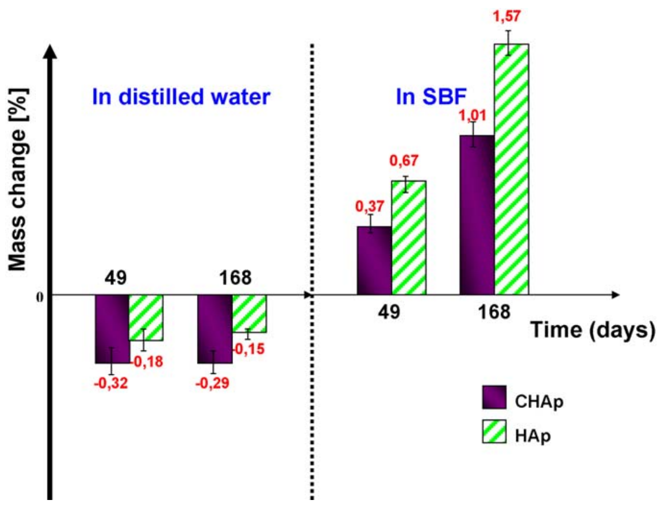

Fig. 6. The mass changes of CHAp and HAp (Ca/P = 1.69) after 49 and 168 days of immersion in SBF and distilled water.

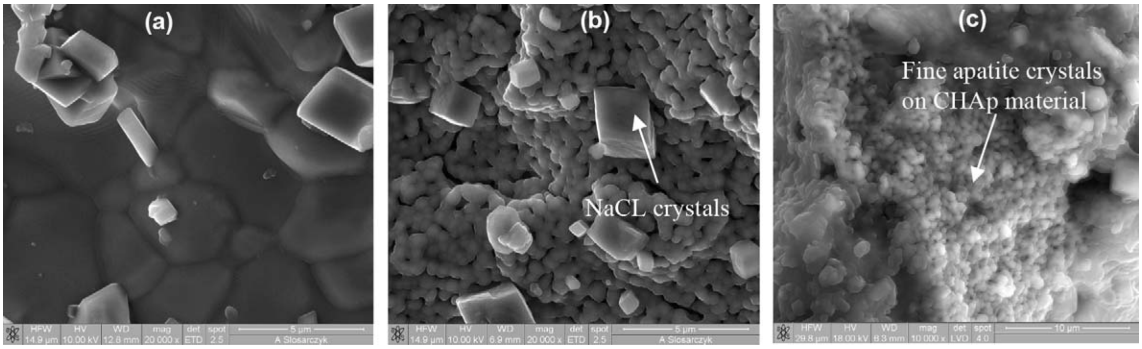

Fig. 7. SEM micrographs of HAp (a) and CHAp (b and c) after 49 days (a and b) and 168 days (c) immersion in SBF.

5 wt.% of CaO (after sintering in air) (Fig. 3). The content of $CaCO_3$ depends on the sintering atmosphere and the Ca/P molar ratio in the initial powders. Presence of calcite ($CaCO_3$) as a secondary phase in carbonate hydroxyapatite materials is regarded as not harmful. Even monophase calcite-based implants are promising in tissue regenerative medicine of bone [18]. It has been reported [19] that calcium carbonate in the body is able to compensate acidity and to buffer within the physiological pH range. In order to produce dense CHAp without harmful CaO, sintering conditions have to be carefully established and controlled.

Chemical stability of the materials was evaluated based on changes in pH of simulated body fluid (SBF) (Fig. 4) as well as on changes in ionic conductivity of distilled water in which the samples were immersed (Fig. 5). Results of the studies are presented as average values of five independent measurements carried out for optimum CHAp ceramics (II-A/0.10 with apparent density 3.029 g cm^{-3}) and non-modified HAp ceramics as a reference material (sintered in air at 1250 °C with apparent density 3.009 g cm^{-3}). The measurements were performed every day during the first 7 days and then – every week during 168 days of immersion. Changes in the mass of the samples after 168 days of incubation in SBF and H_2O were also determined (Fig. 6). Both, CHAp and HAp ceramics did not cause significant pH changes of SBF which shows that they are chemically stable. pH values for CHAp and HAp materials were similar and varied during the experiment from 7.13 to 7.29. These values are close to the physiological pH values. Ionic conductivity of aqueous extracts of the investigated materials was low and after 60 days it stabilized at the value of ca. 40 μS. The reached level was stable until the end of the experiment.

The mass of all samples soaked in SBF increased by 0.37–0.67% after 49 days and 1.01–1.57% after 168 days, whereas that of the samples incubated in water lowered by 0.32–0.18 and 0.29–0.15%, respectively. These changes, caused by dissolution and precipitation processes, respectively, were more pronounced for carbonate hydroxyapatite in water, and hydroxyapatite in SBF; this data suggest that CHAp is more soluble, but HAp enhances precipitation from SBF.

Fine apatite crystals on the surface of CHAp material were clearly visible in SEM investigations. Precipitation of NaCl crystals from SBF solution was also observed (Fig. 7). High biocompatibility of carbonate hydroxyapatite was earlier confirmed [5,8]. Barralet et al. [20] found that dissolution rate of dense monophase CHAp ceramics implanted subcutaneously in rats was intermediate between βTCP and HAp. In our former animal studies [21], we found that the healing process after implantation of carbonate hydroxyapatite into bone defects was faster as compared to that of pure HAp. The continuous and uniform thickness of the new trabeculous bone found around the samples of CHAp is the proof of higher osteointegration properties of this material.

4. Summary

The presence of CO_3^{2-} in the structure of apatites influences their thermal stability, sinterability as well as microstructure of CHAp implantation materials. Carbonate hydroxyapatite powders show very good sinterability at relatively low temperatures, ca. 300–350 °C lower than that required for the sintering of non-carbonate hydroxyapatite materials. Sinterability of CHAp powders depends significantly on the synthesis conditions. It is more advantageous to use $(NH_4)_2HPO_4$ instead of H_3PO_4 as the source of phosphate ions. The optimum NH_4HCO_3 additive in the precipitation process is 0.1 mol per 0.3 mol of $(NH_4)_2HPO_4$. Heat-treatment at 900 °C with 1 h soaking time in CO_2 atmosphere leads to dense materials (relative density >97% of theoretical). In sintered CHAp ceramics, biocompatible $CaCO_3$ as the secondary phase is present. Chemical stability and bioactive potential of biphasic CHAp–$CaCO_3$ was confirmed *in vitro*, which is in a good agreement with the results of our former animal studies.

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