Hindawi Publishing Corporation
Journal of Nanomaterials
Volume 2012, Article ID 841971, 9 pages
doi:10.1155/2012/841971

Research Article

Hydroxyapatite Nanopowder Synthesis with a Programmed Resorption Rate

Dariusz Smoleń,[1] Tadeusz Chudoba,[1] Stanisław Gierlotka,[1] Aleksandra Kedzierska,[1] Witold Łojkowski,[1] Kamil Sobczak,[2] Wojciech Święszkowski,[3] and Krzysztof Jan Kurzydłowski[3]

[1] *Institute of high Pressure Physics, Polish Academy of Science, Sokolowska 29/37, 01-142 Warsaw, Poland*
[2] *Institute of Physics, Polish Academy of Science, Al. Lotnikow 32/46, 02-668 Warsaw, Poland*
[3] *Faculty of Materials Science and Engineering, Warsaw University of Technology, Woloska 141, 02-507 Warsaw, Poland*

Correspondence should be addressed to Dariusz Smoleń, smolendarek@gmail.com

Received 11 September 2012; Revised 18 October 2012; Accepted 1 November 2012

Academic Editor: Yan-Yan Song

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A microwave, solvothermal synthesis of hydroxyapatite (HAp) nanopowder with a programmed material resorption rate was developed. The aqueous reaction solution was heated by a microwave radiation field with high energy density. The measurements included powder X-ray diffraction (PXRD) and the density, specific surface area (SSA), and chemical composition as specified by the inductively coupled plasma optical emission spectrometry technique (ICP-OES). The morphology and structure were investigated using scanning electron microscopy (SEM) and transmission electron microscopy (TEM). A degradation test in accordance with norm ISO 10993-4 was conducted. The developed method enables control of the average grain size and chemical composition of the obtained HAp nanoparticles by regulating the microwave radiation time. As a consequence, it allows programming of the material degradation rate and makes possible an adjustment of the material activity in a human body to meet individual resorption rate needs. The authors synthesized a pure, fully crystalline hexagonal hydroxyapatite nanopowder with a specific surface area from 60 to almost 240 m^2/g, a Ca/P molar ratio in the range of 1.57–1.67, and an average grain size from 6 nm to over 30 nm. A 28-day degradation test indicated that the material solubility ranged from 4 to 20 mg/dm^3.

1. Introduction

The number of cases of bone defects requiring replacement has increased rapidly in recent years [1, 2]. Nevertheless, there is no solution presently available that overcomes the disadvantages and disabilities of current medical practices. Techniques are needed to repair large bone defects and to return patients to their previous quality of life. A primary difficulty is the lack of a proper material which enables the creation of bone scaffolds with the appropriate mechanical strength and a controllable resorption rate. Currently, autografts are the clinical gold standard for bone replacement therapy. Autografts provide the primary factors for effective bone regeneration, but they also impose a significant cost and risk [3–5].

One potential solution marketed as filler for small bone gaps and defects is a bioactive ceramic made of micro- and sub-microhydroxyapatite. Due to their strong similarity to the mineral phase of native bone, called apatite, bioactive ceramics display appropriate levels of osteoconductivity and biocompatibility [6, 7]. Additionally, the interaction of osteogenic cells with this material leads to good bone bonding and bone regeneration [8]. Although micro- or sub-microhydroxyapatite powder is suitable for recovering small bone gaps, in more complicated cases it has several drawbacks like the lack of possibility to control the material resorption rate [9, 10]. These disadvantages may be reduced or eliminated by replacing the micropowder by a hydroxyapatite nanopowder. The latter has grains much smaller than 100 nm, possibly giving it unexpected

properties that are necessary to achieve a proper bioactivity and biodegradability levels. These nanoparticles have a significantly greater surface-to-volume ratio than powders with larger grains; thus, they have increased surface energy [11, 12]. Consequently, the surface energy-related features such as the solubility may be controlled. According to the Ostwald-Freudlich equation [13], the material solubility increases with increased specific surface area. A decrease in the HAp particle size to a few nanometers should significantly increase the material solubility [13]. The ability to regulate the particle size thus enables the control of the material degradation rate. Additionally, as the literature shows [14], osteoblast adhesion is strongly driven by the material surface area and topography. A decrease in the particle size increases the osteoblast adhesion as it is directly related [14] to the greater surface area.

A second important feature which influences the HAp bioactivity is its stoichiometry. Bone mineral has a Ca/P molar ratio near 1.50, which is close to the tricalcium phosphate (TCP) stoichiometry, but structurally and chemically it is similar to the stoichiometric HAp with a Ca/P molar ratio equal to 1.67 [15]. The ion exchange or degradation rate is strongly dependent on the bioactive ceramic stoichiometry. With calcium deficiency increase, the number of crystalline structure defects caused by calcium ions vacancies increases which is reducing material stability and in consequence increasing its solubility [15, 16].

The literature presents various methods for hydroxyapatite nanoparticle synthesis; these include processes conducted by mills [17, 18], hydrothermal syntheses conducted in a typical vessel with conventional heating [19, 20], sol-gel methods [21, 22], and even synthesis by emulsion [23, 24]. In most cases, the synthesized powder is stoichiometric hydroxyapatite, and in many cases it includes additional phases and substances such as byproducts or unreacted substrates. Usually the powder's degradation rate is too low to adjust to bone scaffolding needs and it is not possible to program its solubility in advance, which is necessary for bone implant development to overcome the previously described barriers. Microwave heating is a potential solution, as it may result in a product that fulfills the previously described requirements. It has been used as a source of energy [25–27], but to our best knowledge, never in a closed system with an energy density equal to or above 5 W/mL. Microwave radiation is able to evenly and rapidly heat an entire volume of a vessel almost without a temperature gradient in the heated materials [28, 29]. Additionally, it enables the necessary control of the reaction parameters, so there is the possibility of obtaining a fully crystalline, nonequilibrium structure with a programmed grain-size distribution [30, 31].

The purpose of this work was to develop a microwave solvothermal synthesis method (MSS) based on high energy density microwave radiation [32] which results in pure, nonstoichiometric hydroxyapatite nanoparticles with a programmed particle size, that is, able to regulate the degradation rate of bone scaffolds. The novelty of the presented method lies in its extremely short synthesis time, ranging from 90 seconds to 10 minutes, which is made possible by the implementation of a microwave reactor with a high energy density reaching 5 W/mL. This paper presents the chemical, physical, and biological properties of the obtained material, including its chemical composition, structure, morphology, and solubility.

2. Experimental Methods

2.1. Material Preparation. The hydroxyapatite nanocrystals were obtained by the following method, described in detail in [33]. The starting materials used for the HAp synthesis were calcium hydroxide ($Ca(OH)_2$, CHEMPUR, pure) and phosphoric acid (H_3PO_4, 85% solution, CHEMPUR, pure for analysis); the reactants were used in a molar ratio Ca/P of 1.67. To form a reaction solution, phosphoric acid was added dropwise to the calcium solution at a rate of 0.01 mL every 3 seconds, and the solution was intensively stirred at room temperature. After 30 minutes of additional stirring, the reaction solution was transferred into a capped Teflon vessel and heated using microwave radiation. The microwave reactor was produced by ERTEC (Wroclaw, Poland) and was operated at 2.45 GHz and at a power density adjusted to approximately 5 W/mL. The time, temperature, pressure, and microwave power were computer-controlled. The synthesis conditions encompassed pressures ranging from 1 to 32 MPa and times ranging from 1.5 min to 10 min. After the synthesis, the obtained powder was washed by anhydrous ethanol and dried in an air flow at a temperature of 30°C for 16 h. Herein, this resulting material is referred to as "GoHAP" with the addition of the reaction time (e.g., GoHAP 1.5 min).

The hydroxyapatite nanopowder NanoXIM201 (FLUIDINOVA, ENGENHARIA DE FLUIDOS, SA TECMAIA-Parque de Ciência e Tecnologia da Maia Rua Eng° Frederico Ulrich, 2650 4470-605 Moreira da Maia, Portugal) was used as a reference material in the degradation test and in the PXRD analysis. To the authors' knowledge, this commercially available hydroxyapatite powder had the lowest available particle size on the market. Its characteristics were a density of 2.93 g/dm^3, an SSA of 120 m^2/g, an average particle diameter calculated from SSA of 17 nm, and a Ca/P molar ratio declared by the producer and confirmed by the authors of 1.66. Figure 1 presents SEM micrograph of NanoXIM201 nanopowder.

Additionally, an XRD analysis using a plate from a pig's shank bone was used as a reference for natural apatite.

2.2. Material Characterization. The density measurements were performed using a helium pycnometer (Micromeritics AccuPyc, model 1330) using an in-house procedure [34]. The specific surface area (SSA) of the powders was measured by the Brunauer-Emmett-Teller (BET) method (Micromeritics AccuPyc, model Gemini 2360). The average diameter of the particles was calculated based on the specific surface area and density, assuming that all of the particles were spherical and identical [34].

The phase composition of the reaction products was analyzed by powder X-ray diffraction (Panalytical X'Pert

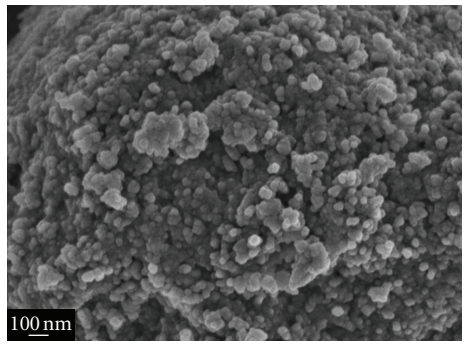

Figure 1: SEM micrograph of NanoXIM201 nanopowder produced by the Fluidinova Company.

PRO diffractometer, Cu Ka1 radiation). The patterns were collected at room temperature in the 2 theta range 10–150° and with a step of 0.03°. The pattern analysis was performed by whole pattern fitting (the Rietveld method) using the DDM software suite [35]. The particle size was determined by the Scherrer equation.

The morphology of the nanopowder samples was examined with SEM (ZEISS LEO 1530) and TEM (JEOL JEM2000EX). The TEM investigations, high-resolution TEM (HRTEM), and selected area electron diffraction (SAED) were conducted at 200 kV. The specimens for the TEM observations were prepared by dropping the methanol particle dispersion, created by an ultrasonic technique, on a carbon film supported on a 300 mesh copper grid. Additionally, TEM studies were used to determine the nanoparticle size distribution. The grain size histograms were obtained by considering a region of a sample having about 250 nanocrystals and approximating the shape of each nanocrystal by a sphere. The obtained histograms were fitted to either normal or log-normal distributions (Chi-square test and Person's coefficient).

The chemical composition of the powders was determined by inductively coupled plasma optical emission spectrometry (ICP-OES), with induction in argon plasma (Jobin-Yvon, model 138 Ultrace).

The determination of material solubility was performed according to norm ISO 10993-14: biological evaluation of medical devices—identification and quantification of degradation products from ceramics. The material was tested in the form of a 6 mm disk (each disk was around 35 mg and was created from the nanopowder using a laboratory hydraulic press under 5 MPa pressure) and was placed in 200 mL of buffer solution (TRIS-HCl buffer with pH 7.4 ± 0.1). A simulation solution test, lasting 28 days, was conducted without buffer solution exchange during the entire test. During the degradation test the samples were incubated at 37.0°C. Along with the degradation of the samples, the calcium ion concentration value was measured three times per week with an ion selective electrode (Schott ProLab 2000 GLP equipped with ion electrode type CA60). Additionally, the material solubility was determined by the gravimetric method.

3. Results and Discussion

With the shortest reaction of 1.5 min of microwave radiation, the obtained GoHAP had a density equal to 2.91 g/cm^3, which is 4% lesser than the value given in the literature for hydroxyapatite, 3.05 g/cm^3 [36]. It was observed that with nanoparticles, there was a reduction in the material density probably caused by the high contribution of surface layers, which are less densely packed than the bulk [37]. The material's specific surface area was 236 ± 5 m^2/g, and the average particle diameter calculated based on SSA was 9 nm. Longer microwave radiation slowly increased the material density and significantly decreased the specific surface area (Figure 2); details are presented in Table 1. For the 2.5-minute reaction, the specific surface area of GoHAP was reduced by over 60 m^2/g to 174 m^2/g, and the density increased to 2.94 g/cm^3 comparing to the 1.5 min reaction. The average particle size calculated based on the specific surface area increased to 12 nm. With 5 minutes of microwave radiation, the SSA decreased to under 100 m^2/g. The density increased by 0.02 g/cm^3 to 2.96 g/cm^3; the average particle size exceeded 20 nm. Within extension of the reaction time over 5 minutes, there was a decrease in the specific surface area to 81 m^2/g for the 7.5-minute reaction and 63 m^2/g for the 10-minute reaction. Consequently, the density became 3.00 g/cm^3 and the particle size became 25 nm for the 7.5-minute reaction. For the 10-minute reaction, the resulting particles had an average size of 32 nm and a density of 3.03 g/cm^3, which was almost equal to the literature values for hydroxyapatite [36].

The ICP-OES analysis indicated that for 1.5 min reaction, the Ca/P molar ratio was equal to 1.57, which is close to the molar ratios of the natural bone calcium and phosphor elements [36]. Longer microwave heating increased the Ca/P molar ratio to values close to stoichiometric HAp (Figure 3); with 2.5 minutes of reaction the Ca/P molar ratio changed to 1.65 which is a value frequently indicated in papers presenting HAp synthesis [17–24]. After 5.0 minutes of reaction, the ratio was equal to 1.66, and further radiation led to fully stoichiometric hydroxyapatite. In all cases the obtained powder included 0.20–0.22 wt% magnesium ions.

The XRD analysis was conducted on GoHAP powders obtained from 1.5-, 2.5-, 5.0-, and 10.0-minute reactions and using a plate from a pig's shank bone as a reference for natural apatite (Figure 4). The results confirmed that the GoHAP powders were a pure well-crystalline hexagonal hydroxyapatite with nanosized particles. No indication of the presence of other crystalline phases or any amorphous component was found. The lattice parameters for the GoHAP powders are presented in Table 2, and the pig bone results were $a = 9.42(5)$ Å and $c = 6.87(7)$ Å. Other crystal structure parameters could not be derived with satisfying precision due to the considerable anisotropy size and the very small absolute crystal size. However, it was apparent that the crystals obtained in the reaction with 10 minutes of microwave radiation were approximately 10 times larger than the crystals of GoHAP obtained from the 1.5 minute reaction.

The morphology investigation was conducted with SEM and TEM techniques. Figure 5 shows SEM micrographs

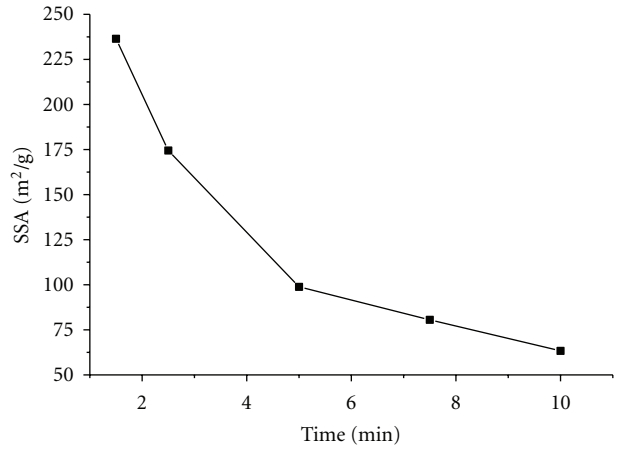

Figure 2: Effect of the microwave radiation time on the specific surface area.

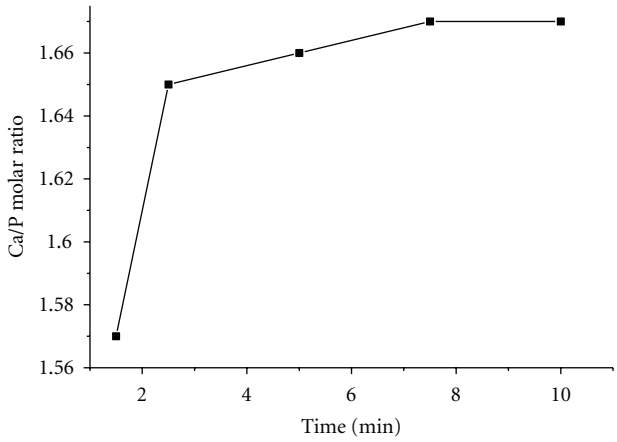

Figure 3: Effect of the microwave radiation time on the Ca/P molar ratio.

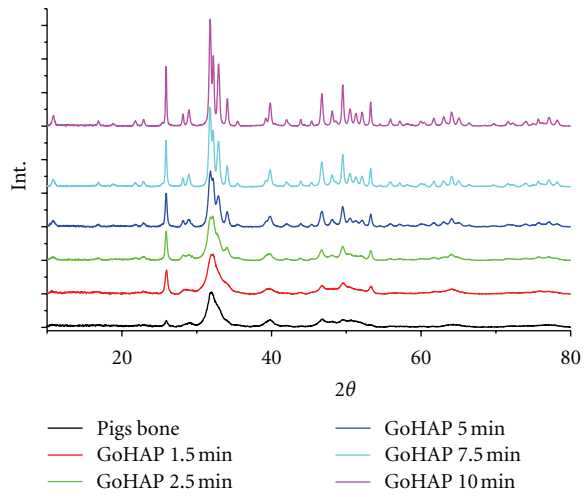

Figure 4: XRD patterns of HAp particles in pig bone and GoHAP powders synthesized with microwave radiation times of 1.5, 2.5, 5.0, and 10.0 minutes.

Table 1: Effect of the microwave radiation time on the material specific surface area, the density, the grain size calculated on the basis of SSA measurements, and the Ca/P ratio established by the ICP-OES measurements.

Radiation time (min)	SSA (m^2/g)	Density (g/cm^3)	Grain size (nm)	Ca/P
1.5	236	2.91	9	1.57
2.5	174	2.94	12	1.65
5.0	99	2.96	21	1.66
7.5	81	3.00	25	1.67
10.0	63	3.03	32	1.67

Table 2: Effect of the microwave radiation time on the lattice parameters determined by the XRD analysis.

Radiation time (min)	Lattice parameter a (±0.001 Å)	Lattice parameter c (±0.0007 Å)
1.5	9.433	6.8745
2.5	9.439	6.8775
5.0	9.429	6.8772
7.5	9.425	6.8767
10.0	9.423	6.8777

of GoHAP nanoparticles for reaction times of 1.5 min, 2.5 min, 5.0 min, and 10.0 min. Figure 5(a) presents the strong homogeneity of GoHAP obtained from the 1.5 min reaction and confirms that the average particle size of the synthesized hydroxyapatite was less than 10 nm. The powder obtained with 1 minute longer reaction (2.5 minutes) had a larger average particle size as observed on a SEM micrograph (Figure 5(b)). Instead of being homogeneous as with the powder from the shortest reaction time, this powder appeared in the form of agglomerates with diverse sizes. Further microwave heating (5.0- and 7.5-minute reactions) increased the size of both the single particles and their agglomerates. The nanopowder presented in Figure 5(c) was obtained from the 5-minute reaction. Compared to GoHAP synthesized in the shortest reaction, its morphology was highly diverse, and several times the larger particles were grouped in agglomerates with sub-micro- and microsizes. Finally, the reaction with 10 minutes of microwave radiation led to a significant increase in the single particle size and decreased the powder agglomeration degree (Figure 5(d)). The GoHAP powder after the longest reaction time was in form of large, slightly agglomerated particles with an average grain size close to 50 nm.

A TEM examination showed that for all microwave radiation times, the obtained hydroxyapatite had the space group P.P63/m of a hexagonal crystal structure with the parameters $a = 9.424(4)$ Å and $c = 6.879(4)$ Å [38]. An increase in the reaction time did not have any visible impact on the phase composition and lattice parameters. In all cases the result was pure hexagonal hydroxyapatite without phase impurities. Figure 6 shows the SAED with identified planes for hydroxyapatite synthesized during the 1.5-minute reaction; in the remaining cases SAED was identical. No

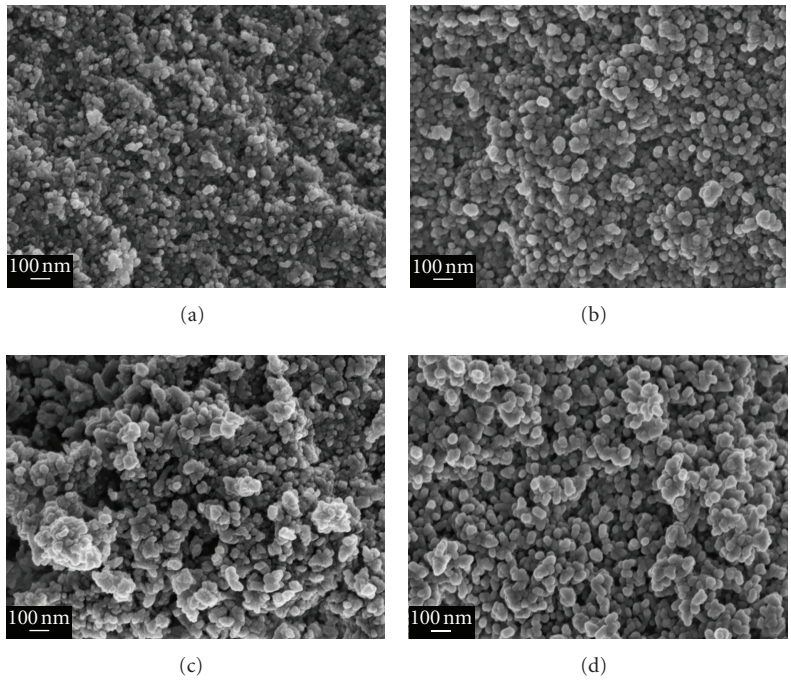

Figure 5: SEM micrographs of GoHAP synthesized in (a) 1.5-minute reaction, (b) 2.5-minute reaction, (c) 5.0-minute reaction, and (d) 10.0-minute reaction.

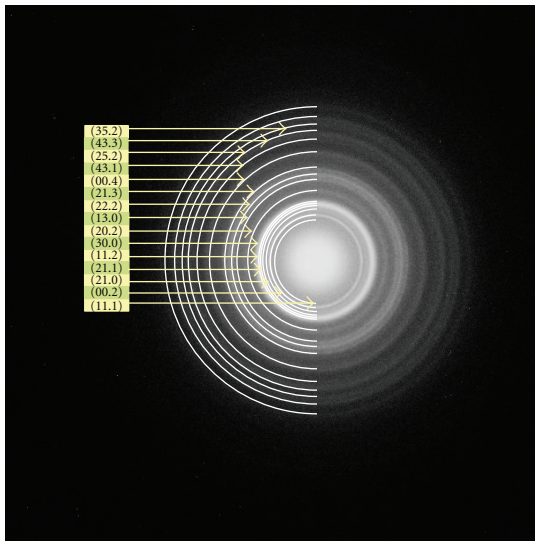

Figure 6: SAED with the identified planes.

other phases have been found in tested samples. The average grain size for GoHAP synthesized during the 1.5-minute reaction was 5.6 nm (Figure 7). After increasing the reaction time to 2.5 minutes, the average grain size barely changed; it was 5.8 nm but studies indicated that the particles were in the form of large, stable agglomerates. Further microwave heating caused an increase in the particle size and a decrease in the sample homogeneity. Figure 8 shows an image taken in the dark field of particles obtained from the 7.5-minute reaction, with a morphology ranging from spherical to almost needle-like shapes. The average grain size after the 7.5-minute reaction was 26.2 nm. Reactions longer than 7.5 minutes increased the grain size to over 30 nm.

A degradation test was conducted for GoHAP obtained during reactions with microwave radiation times of 1.5, 2.5, 5.0, and 10.0 minutes. Commercially available HAp nanopowder, NanoXIM, was used as a reference material. The initial pH of the test solution was 7.47, the conductivity was 6.82 mS/cm, and the calcium ion concentration was 0.479 μmol/dm^3. The results of the calcium ion concentration changes are shown in Figure 9. These results showed that in each day the GoHAP obtained from the shortest reaction (1.5 minutes) had the highest rate of degradation. Along with an increase in the microwave radiation time for the GoHAP synthesis there was decrease in the material solubility, until finally, in the case of GoHAP obtained from the longest (10 minutes) reaction, the achieved solubility value was close to the NanoXIM results. After 21 days of tests, the calcium ion concentration in the sample with NanoXIM remained nearly constant and achieved a value of 40.37 μm/dm^3 by the end of test, which can be recalculated based on weight solubility to 4.0 mg/dm^3. After three weeks of tests, the GoHAP obtained in 1.5 min reaction had twice as much solubility as NanoXIM, and, furthermore, in the fourth week there was an acceleration of solubility which led to a concentration of 199.6 μmol/dm^3 calcium ions by the end of the test, equal to 20.0 mg/dm^3. The GoHAP obtained with microwave radiation times longer than 1.5 minutes achieved solubility values in the range between the NanoXIM and GoHAP 1.5 min solubility, decreasing as a function of microwave radiation time. In the case of GoHAP obtained with the 2.5-minute reaction, the final

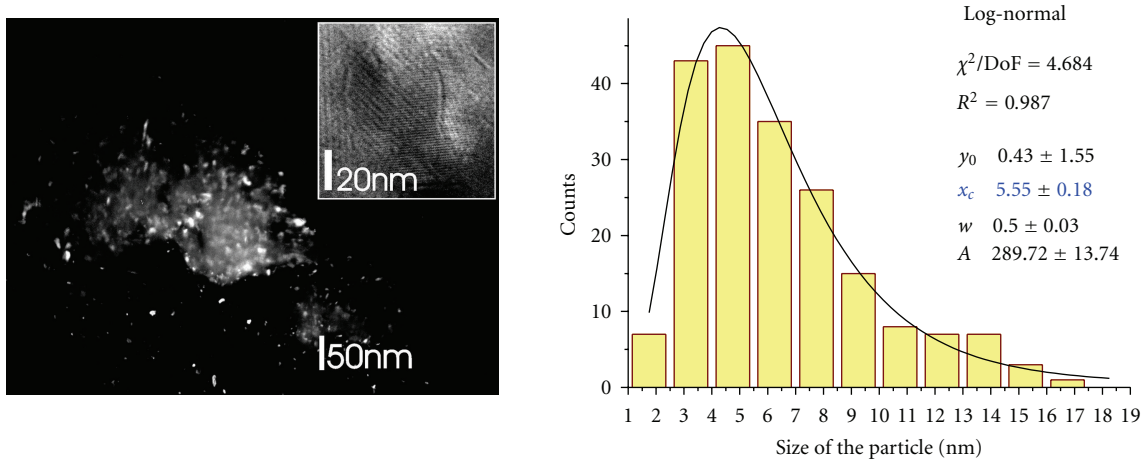

Figure 7: The dark field TEM image of GoHAP synthesized with a 1.5-minute reaction, and the histogram of the particle size distribution.

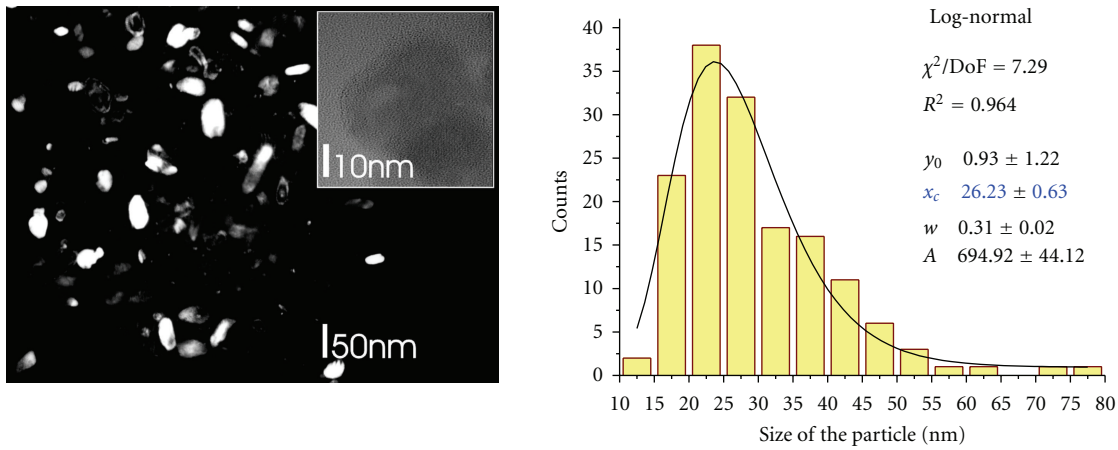

Figure 8: The dark field TEM image of GoHAP synthesized with a 7.5-minute reaction, and the histogram of the particle size distribution.

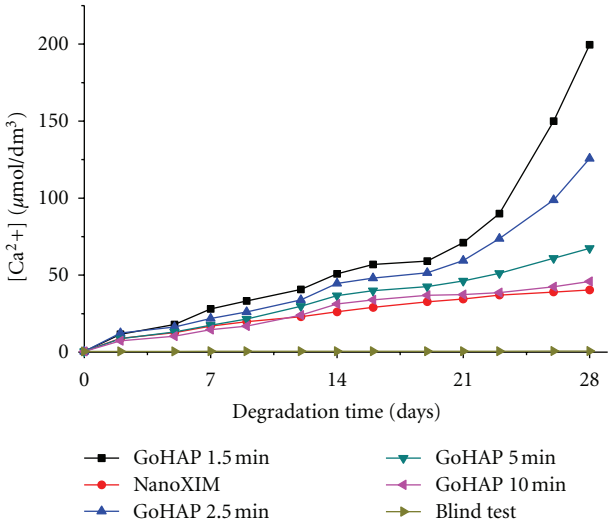

Figure 9: Calcium ion concentration changes for GoHAP synthesized with microwave radiation times of 1.5, 2.5, 5.0, and 10.0 minutes, and for the commercial nanopowder, NanoXIM used as a reference material.

calcium ion concentration was 125.7 μmol/dm^3 which is equal to 12.6 mg/dm^3 solubility. The GoHAP obtained with the 5-minute reaction achieved 67.4 μmol/dm^3 calcium ion concentration equal to 6.8 mg/dm^3 solubility, and that from the longest (10 minutes) microwave reaction had 4.6 mg/dm^3 solubility (45.8 μmol/dm^3 calcium ion concentration).

The degradation test was additionally followed by determining the weight loss after 28 days of tests. During the test, NanoXIM lost 4% of its original weight, resulting in 7.0 mg/dm^3 of solubility, and GoHAP obtained with 1.5-minute reaction time lost over 22% of its initial weight, equal to 38.5 mg/dm^3. GoHAP from the 2.5-minute reaction had a solubility of 25.6 mg/dm^3, from the 5-minute reaction had solubility of 14.1 g/dm^3, and from the 10 min reaction had solubility of 8.7 mg/dm^3, as determined from weight loss measurements. The solubility measured by the gravimetric method was in all cases approximately twice as large as the solubility measured by changes in the calcium ion concentration, probably due to nanopowder dispersion. The samples of GoHAP synthesized in 1.5 min reaction were deeply cracked on whole sample surface, but the test disk still was keeping its original shape, when the NanoXIM sample

was cracked only in few places and was very weak. In case of the rest GoHAP samples, the density and depth of cracks were decreasing with powder reaction time increase—the GoHAP obtained in 10-minute reaction presented similar cracking to the NanoXIM disk, but it was much more stable during the mechanical operations, like disk transport, and so forth.

Such a high solubility rate should ensure a short degradation time of future scaffold. In degradation time longer than 28 days of conducted ISO test, GoHAP samples should keep or even accelerate their degradation rate, but in case of the real bone implants, the scaffolds degradation rate for time perspective longer than 28 days will depend on many other factors like new tissue formation process, and so forth, so that for long-time periods it should be checked by in vivo tests.

The degradation test showed that the developed method has the potential to adjust the material solubility according to the individual case needs in range from 4 to 20 mg/dm^3, according to the ISO 10993-14 norm. The synthesis of this material with a programmable degradation rate was possible due to the implementation of a unique microwave heating technology (MSS) with very high energy density, which enables precise control of the material grain size growth. Compared to conventional heating, microwaves transmit energy directly to the entire volume almost without causing temperature gradients in the reaction vessel. The microwave radiation time may be regulated with 1 s precision, which enables precise grain size growth control.

The rapid microwave heating process leads to overheating of the reaction solution. From the overheated solution, a fine dispersion of nano-HAp precipitates starts to crystallise. Most likely, for short crystalisation times, kinetic processes dominate its growth, and nonstoichiometric crystallites grow with an nonequilibrium structure. Our experimental data show that this is the case for extremely short reaction times of 1.5 minutes. With increase of microwave radiation time the precipitates structure approaches the equilibrium one, and a fully stoichiometric structure is achieved for radiation times longer than 5 minutes (Figure 2). In consequence, precise microwave radiation time regulation allows to control hydroxyapatite stoichiometry and grain size growth. Furthermore the solution is rapidly cooled, so no secondary grain growth takes place [29, 39]. As it was described in the introduction section a material solubility depend on material specific surface area—the material solubility increases with material grain size decrease [13] and its nonstoichiometry [15, 16]. The decrease of Ca/P molar ratio was increasing calcium ion concentration in tested solution due to increase of crystalline defects in the hydroxyapatite structure. The higher calcium deficiency is, the more defected crystalline structure will be, which is decreasing material stability and in consequence increases its solubility.

Precise grain size growth control which determines material specific surface area, together with material stoichiometry control both available via microwave radiation time regulation made the programming of hydroxyapatite solubility possible. The microwave solvothermal synthesis (MSS) with the high energy density allowed obtaining GoHAP powder with unique features which is a promising material for resorbable ceramic bone implants fabrication [40].

4. Conclusions

A fully crystalline hydroxyapatite nanopowder with programmed solubility rate was successfully synthesized by a novel MSS method using high-density microwave radiation as a heating mechanism. The material degradation rate was regulated by the amount of applied microwave radiation, which determined the particle size and stoichiometry of the obtained hydroxyapatite nanopowder and consequently enabled the material solubility to be programmed. The obtained nanopowder has unique properties. It is a pure crystalline, hexagonal hydroxyapatite nanopowder with a specific surface area ranging from 60 to almost 240 m^2/g and a Ca/P molar ratio in the range of 1.57–1.67; these values are fully regulated by the applied microwave radiation time. The average particle size estimated by the TEM investigation was regulated between 6 nm to over 30 nm. As the degradation study demonstrated, the developed method was able to control the material solubility in conditions simulating the human body in the range from 4 mg/dm^3—which is close to NanoXIM, a commercial HAp nanopowder—to 20 mg/dm^3. The presented material has the potential to significantly improve the properties of ceramic bone scaffolds by allowing the implant degradation rate to be adjusted to individual situations.

Acknowledgments

This work was financed by the European Regional Development Fund within the Innovative Economy Operational Programme in the frame of the BIO-IMPLANT project "Bioimplants for the treatment of bone tissue lesions in oncological patients" (*POIG.01.01.02-00-022/09*) and by the SONOSCA ERANET-MATERA project as well as by the Institute of High Pressure Physics, PAS. The research subject was carried out with the use of equipment funded by the project CePT financed by the European Regional development Fund within the Operational Programme "Innovative Economy" for 2007–2013. The authors would like also to thank J. Mizeracki and A. Presz from the Institute of High Pressure Physics PAS, P. Dłużewski from the Institute of Physics PAS, and A. Karaś from the Institute of Electronic Materials Technology.

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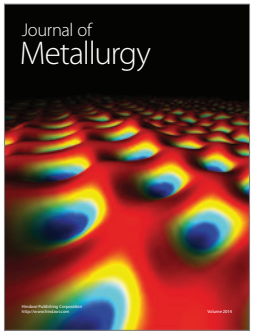

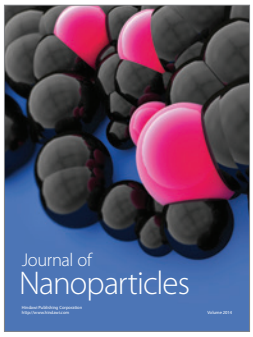

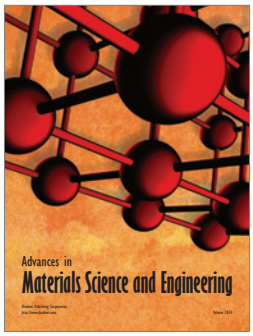

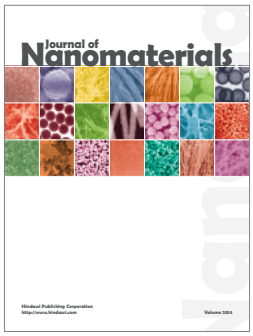

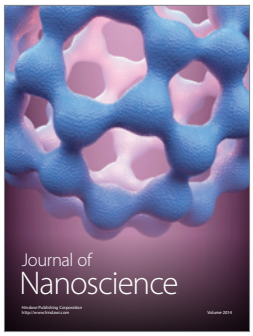

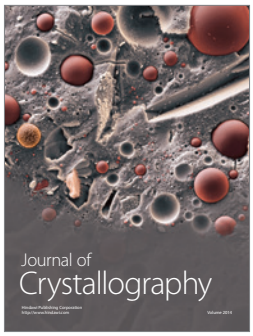

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