Journal of Materials and Electronic Devices 4 (2022) 52-56

FYTRONIX
JOURNAL OF
MATERIALS AND ELECTRONIC DEVICES
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Microwave-Assisted Synthesis of Ion-Doped β-Tri-Calcium Phosphate Powders

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Bioceramic materials have become prominent among the other biomaterials due to their exceptional properties such as high biocompatibility, corrosion and wear resistance, aesthetic appearance, etc. β-Tri-calcium phosphate (β-TCP, $Ca_3(PO_4)_2$) is a well-known bioceramic material. It is widely used in coating, powder, or paste/putty form due to its bioresorbable character that enables rapid healing of the damaged hard tissues. Therefore, several methods are developed to obtain β-TCP practically. Nowadays, the microwave-assisted synthesis technique draws attention owing to advantages like producing sub-micron-sized and uniform particles in shorter operation durations than conventional methods, easy control of the process parameters, etc. In this research, β-TCP powders doped with antibacterial ions and ions that promote osteogenesis were fabricated following the microwave-assisted synthesis procedure. Briefly, the preparation of the Ca and P sources, the reaction between them in the modified household-type microwave oven, centrifuging, drying, and heat treatment steps were sequentially applied to achieve the un-doped and ion-doped β-TCP powders. X-Ray Diffraction (XRD) and Scanning Electron Microscope (SEM) were used to analyze the chemical phases and surface features of the powders, respectively. The bioactive behavior of the microwave-assisted synthesized powders was evaluated according to the simulated body fluid (SBF) immersion tests.

Keywords: *Bioceramics, Microwave-assisted synthesis, β-Tri-calcium phosphate, Ion doping, Powder characterization.*
Submission Date: 01 November 2022
Acceptance Date: 08 December 2022

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1. Introduction

CaP compounds with different chemical compositions are frequently used in several biomaterial applications [1-3]. CaP-based mineral crystals can be found as the inorganic phase in hard tissues like natural bone and tooth enamel. Apatite compounds are composed of these minerals, and the (Ca/P) molar ratio is a key parameter that determines the solubility level of the apatite compound in the in vivo and in vitro environments [2,4-7]. Wet chemical precipitation, sol-gel process, hydrothermal synthesis, solid-state reactions, emulsion technique, mechanochemical method, pyrolysis technique, combustion method, etc. can be used to produce CaP-based biomaterials [8-11]. However, these conventional techniques introduce limiting disadvantages such as long and complicated process steps, many process parameters and, control difficulty. The last item is especially valid for the wet methods, problems in synthesizing pure products due to the chemical contamination possibilities, heterogeneity in particles sizes, and risk of agglomeration formation. On the contrary, microwave-assisted synthesis technique enables the fabrication of pure and homogeneous nano and sub-micron sized particles in shorter process times than conventional production procedures. Moreover, factors like the restriction of the formation possibility of secondary phases, practical control of process parameters, and lower energy consumption have recently made the microwave-assisted synthesis technique attractive for bioceramic powder fabrication [11-13].

Microwaves reside in the frequency range between the radio waves and infrared waves in the electromagnetic spectrum, extending from 300 MHz to 300 GHz frequency values. The applied microwave radiation can be reflected, transmitted, or absorbed by the material. Absorbed microwave energy favors the temperature increase of the material in very short times. However, conventional synthesis techniques such as wet systems, longer reaction, and maturation [14-17] cause agglomeration and abnormal grain growth. Drying and calcination steps implemented following the precipitation stage promote grain coarsening [16,17]. Conversely, as a result of reaching the target temperature in minutes, the reaction between the starting materials, i.e. Ca and P sources, in this case, completes rapidly, and sub-micron-sized particles can be obtained without the need to wait for the reaction products to precipitate [2,4-6]. Since heat forms inside the material that is exposed to the microwave radiation, the material itself becomes a heat source. Thus, heat can rapidly and homogeneously spread throughout the whole material volume. This situation enables the synthesis of sub-micron and nano-sized particles in such short times without allowing the grain growth or coarsening problems [9,12,18-20]. Moreover, sub-micron sized β-TCP particles can be doped with various ions to reduce the infections that may occur within the implant operation and to enhance the bone regeneration. Thus, in this work, it was aimed to produce Ce^{+3}, Sr^{+2} and SeO_3^{-2} doped β-TCP particles by reacting the Ca and P source solutions under microwave radiation owing to the antibacterial influence of the Ce^{+3} and SeO_3^{-2} ions and the positive contributions of the Sr^{+2} ions to the bone functions [21-24].

2. Experimental

A household-type microwave oven was modified to be utilized in the microwave-assisted synthesis experiments. The experimental set-up (**Fig.1**) is actually composed of three components. These are the modified domestic microwave oven, a reflux condenser to gain the evaporated water back, and the glass reactor. The junction between the glass reactor and reflux condenser was managed with an adaptor. As can be realized that the experimental set-up is pretty practical and cost-effective. First, the Ca and P source solutions were prepared. Calcium nitrate tetrahydrate ($Ca(NO_3)_2.4H_2O$, Sigma-Aldrich, ACS Reagent, 99%) and diammonium hydrogen phosphate ($(NH_4)_2HPO_4$, Sigma-Aldrich, ACS Reagent, ≥98%) were used as the Ca and P sources, respectively. The concentrations of the Ca and P precursors were arranged considering the (Ca/P) molar ratio, which is 1.5 for stoichiometric β-TCP. Mole 1% cerium (III) nitrate hexahydrate ($Ce(NO_3)_3.6H_2O$, Aldrich, 99% trace metals basis) and mole 1% strontium nitrate ($Sr(NO_3)_2$, Alfa Aesar, ACS, 99% min.) as the Ce^{+3} and Sr^{+2} sources respectively, were added to the Ca source solution, while mole 1% sodium selenide ($Na_2(SeO_3)$, Sigma, 99%) as the SeO_3^{-2} source was added to the P source solution. Doping was enabled by the replacement of the SeO_3^{-2} ions with the $(PO_4)^{-3}$ ions and, Ce^{+3} and Sr^{+2} ions with the Ca^{+2} ions. After stirring the solutions vigorously and adding a proper amount of ammonia solution (Isolab, NH_4OH, 25%) to adjust the pH value to 8, the solution mixture was taken to the household-type microwave oven and exposed to microwave radiation at 800 W for 5 min and then allowed to cool down to room temperature outside of the oven. The resultant slurry was centrifuged at 5000 rpm for 1 min., washed with de-ionized water and the achieved precipitate was dried in an oven at 70-80 °C for ~36h. The dried precipitates were ground manually with a mortar&pestle and finally calcined at 900 °C for 1h to obtain crystalline ion-doped β-TCP powders.

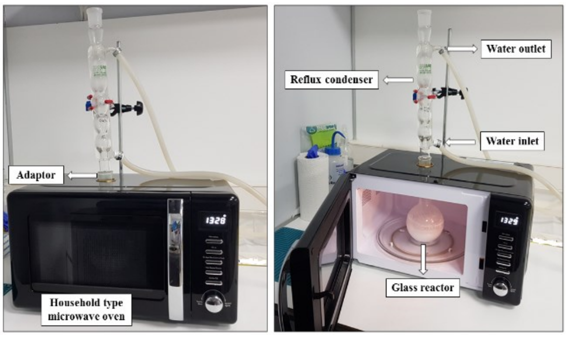

Fig. 1. Experimental set-up used for the production of β-TCP powders via the microwave-assisted synthesis technique.

Phase determination of the fabricated powders were carried out with XRD. Microstructure observation of the fabricated powders were realized with SEM after coating the surface of the samples with a thin film of Au to enable conductivity. Powder samples were immersed in the SBF solution, which is prepared according to Prof. Tadashi Kokubo's protocol [25], for 7 and 21 days at 37 °C to evaluate the bioactivity behavior. The difference between the precipitation regime and morphology of the CaP based structures formed on the sample surfaces depending on the immersion time were investigated with SEM.

3. Results and Discussion

XRD studies of the calcined samples were conducted at 2 deg./min scan speed and the results are shown in **Fig. 2**. The main phase that exists in the microwave-assisted synthesized and calcined samples is β-TCP (Whitlockite, syn., JCPDS Card No: 09-0169). However, there are also secondary phases (JCPDS Card No: $Ce(PO_4)$ (01-084-0247) and $Sr_2P_2O_7$ (00-013-0194)) detected in the ion-doped powders. Studies to optimize the process parameters and thus, to eliminate these secondary phases are still continuing. In the SEM images given in **Fig. 3**, microstructure properties of the non-doped and ion-doped powders are observed. Raw powders and calcined powders distinctly separate from each other in terms of particle shape and agglomeration tendency due to the influence of the calcination step. This situation was examined both in the non-doped powders and ion-doped powders. The dried (raw) β-TCP powders prepared by using the microwave-assisted synthesis technique have a plate-like or flake-like particle shape. Particles gain a spherical-like morphology after calcination, which was performed at 900 °C for 1h depending on the maturation/crystallization mechanism. Therefore, it is understood that ion-doping did not change the particle shape and/or sub-micron size particle size of the microwave-assisted synthesis powders, but the calcination stage was effective on them. Raw powders have a tendency to agglomerate both for un-doped and ion-doped samples. SEM images shown in **Fig. 4** belong to the precipitates formed on the surfaces of the non-doped β-TCP and ion-doped CaP based powders that were produced via microwave-assisted synthesis technique depending on the immersion time in the SBF solution at 37°C. It is noticed that precipitate formation behavior of the non-doped β-TCP and ion-doped CaP based powders on their surfaces are similar to each other. The formation of these precipitates indicates the bioactive character of the samples.

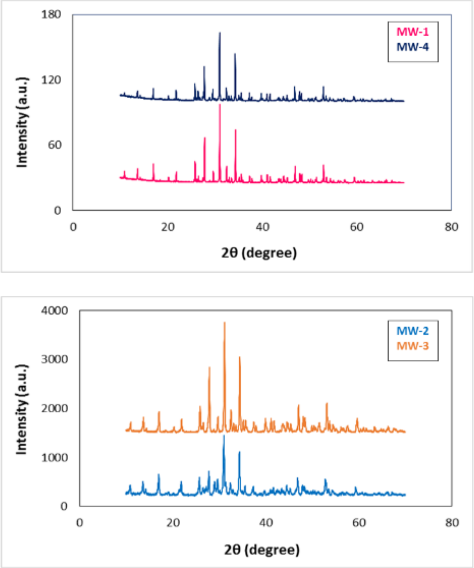

Fig. 2. XRD results of the calcined non-doped and ion-doped powders produced with the microwave-assisted synthesis technique. (MW-1 (β-TCP), MW-2 (β-TCP + Ce^{+3}), MW-3 (β-TCP + SeO_3^{-2}), and MW-4 (β-TCP + Sr^{+2})).

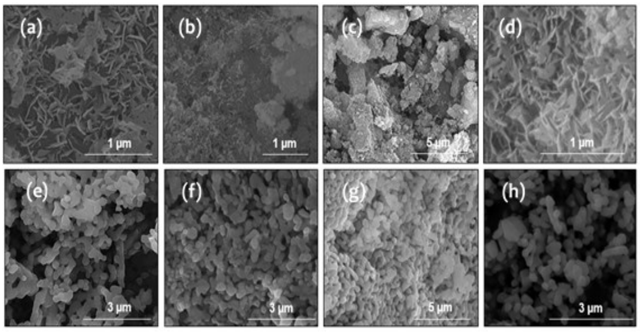

Fig. 3. SEM images of the non-doped β-TCP and ion-doped CaP based powders produced via microwave-assisted synthesis technique. (**a, e**: MW-1 (β-TCP); **b, f**: MW-2 (β-TCP + Ce^{+3}); **c, g**: MW-3 (β-TCP + SeO_3^{-2}), and **d, h**: MW-4 (β-TCP + Sr^{+2})) (**a, b, c, d**: dried (raw) powders; **e, f, g, h**: calcined powders)

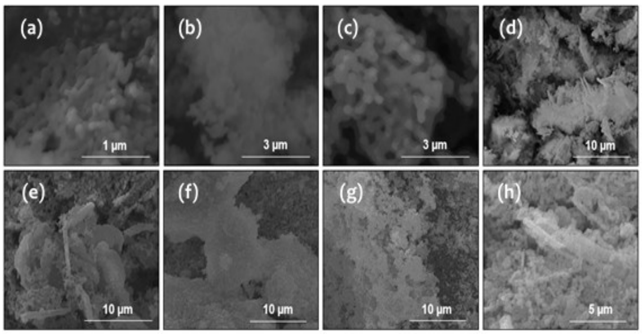

Fig. 4. SEM images of the precipitates formed on the surfaces of the non-doped β-TCP and ion-doped CaP based powders that were produced via microwave-assisted synthesis technique depending on the immersion time in the SBF solution at 37°C. (MW-1 (β-TCP) (**a**: 7, **e**: 21 days); MW-2 (β-TCP + Ce^{+3}) (**b**: 7, **f**: 21 days); MW-3 (β-TCP + SeO_3^{-2}) (**c**: 7, **g**: 21 days), and MW-4 (β-TCP + Sr^{+2}) (**d**: 7, **h**: 21 days)).

4. Conclusions

Uniform and spherical-like shaped sub-micron sized non-doped β-TCP and ion-doped CaP based powders were produced via the microwave-assisted synthesis technique. Besides the main phase, β-TCP, peaks of secondary CaP based phases were detected in the ion-doped samples. Optimization of the process parameters of microwave-assisted synthesis procedure is still continuing. Development and growth of the precipitates depending on immersion in the SBF solution for 7 days and 21 days revealed promising bioactive behavior of the fabricated powders.

Acknowledgement

This study was funded by the Scientific Research Projects Coordination Unit of Istanbul University-Cerrahpasa. Project number: FBA-2021-34751.

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