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Porous calcium phosphate ceramics prepared by coating polyurethane foams with calcium phosphate cements

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Abstract

Porous calcium phosphates have important biomedical applications such as bone defect fillers, tissue engineering scaffolds, and drug delivery systems. While a number of methods to produce the porous calcium phosphate ceramics have been reported, this study aimed to develop a new fabrication method. The new method involved the use of polyurethane foams to produce highly porous calcium phosphate cements (CPCs). By firing the porous CPCs at 1200 °C, the polyurethane foams were burnt off and the CPCs prepared at room temperature were converted into sintered porous hydroxyapatite-based calcium phosphate ceramics. The sintered porous calcium phosphate ceramics could then be coated with a layer of the CPC at room temperature, resulting in high porosity, high pore interconnectivity, and controlled pores size.

Keywords: Porosity; Ceramics; Calcium phosphate cement; Hydroxyapatite; Tetracalcium phosphate.

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1. Introduction

Calcium phosphate ceramics include a variety of ceramics such as hydroxyapatite (HA), tricalcium phosphate (TCP), calcium phosphate cement (CPC), etc. These ceramics have excellent biocompatibility and bone bonding or bone regeneration properties. They have been widely used in no or low load-bearing applications [1,2]. In orthopedic surgery, they are used for filling bone defects as a result of the removal of diseased or damaged bones. In dentistry, calcium phosphate ceramics are used for the augmentation of deficient mandibular or maxillary ridges. Dense or porous calcium phosphate ceramic coatings are often applied on strong and load-bearing core materials for biological fixation or osteointegration of load-bearing implants such as hip stems and dental roots. Porous calcium phosphate ceramics are also expected to play important roles in treating bone problems with the emerging tissue engineering approach, as it involves loading proper cells into porous ceramics (scaffolds) and implanting the cell-loaded scaffolds into a host body for achieving bone tissue regeneration. In fact, a variety of porous ceramics have been investigated for the delivery of drugs, marrow and cultured marrow cells, namely, HA [3], TCP [4], biphasic HA/TCP [5], and calcium phosphate cements (CPCs) [6].

A number of papers have reported the methods for the preparation of useful porous scaffolds. The earliest study could be the fabrication of porous HA ceramics by duplicating the macroporous structure of natural ocean corals [7,8]. Dean-Mo Liu, used polyvinyl butyral (PVB) particles as a

pore former to prepare porosity- controlled HA ceramics through both a solid process and a liquid process [9,10].

Sepulveda et al. [11] produced open-cell hydroxyapatite foams through the technique of gelcasting. Porous hydroxyapatite ceramics were also produced by impregnating porous polyurethane foams with a slurry containing HA powder, water and additives [12,13]. Milosevski et al. [14] produced porous tricalcium phosphate with a porosity of 55-70% using a polyurethane foam.

While CPCs have low mechanical strengths like other calcium phosphates do, they are reported to be biodegradable or actively remodeled in vivo [15]. Furthermore, due to the low-temperature involved during the setting of the cement, proteins or drugs can be incorporated into the matrix of the cement. In addition to dense CPCs, there has been significant research on the macroporous CPCs. Yoshikawa et al. [16] made porous CPC scaffolds with the addition of sucrose into the CPC paste of the powder and the liquid components. The sucrose in the cement was then removed by boiling the cement in water to produce porosity. Markovic et al. [17] reported the formation of CPC with 11 % macroporosity by the addition of mannitol to the cement during mixing with water for 20 hours. Takagi and Chow [18] used a number of water-soluble pore formers to prepare CPCs with up to 50 % microporosity. More recently, Barralet et al. [19] prepared macroporous CPCs using a mixture of frozen sodium phosphate solution particles and CPC powder. After compacting the mixture, the frozen sodium phosphate particles were allowed to thaw to set the cement and create the porosity. In addition, Del Real et al. [20] developed a new way to create macropores in calcium phosphate cements. The method involved adding NaHCO_3 to the starting cement powder and using an acid liquid to obtain CO_2 bubbles for the generation of macropores.

The purpose of this study was to demonstrate the feasibility of preparing porous calcium phosphate ceramics by coating polyurethane foams with a calcium phosphate cement, followed by firing the calcium phosphate cement at a high temperature. The fired porous calcium phosphate ceramics were then coated with the calcium phosphate cement again at room temperature. The advantage of this method was the achievement of high porosity, high pore interconnectivity, and controllable pore size. The method resulted in porous bioceramics without the problem of residual pore formers, in contrast to those methods involving the incomplete leaching of the pore formers such as sugars and salts. By coating the porous calcium phosphate ceramics with the calcium phosphate cement, the porous calcium phosphate ceramics maintained the capability of incorporation of drugs or proteins.

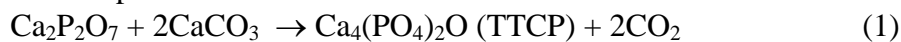
2. Experimental

The preparation of porous calcium phosphate ceramics involved the following steps: preparation of tetracalcium phosphate (TTCP; $\text{Ca}_4(\text{PO}_4)_2\text{O}$), preparation of calcium phosphate cement (CPC), preparation of porous CPC using a polyurethane foam, and preparation of porous calcium phosphate (hydroxyapatite-based) ceramics from the porous CPC. The starting materials were pyro-calcium phosphate ($\text{Ca}_2\text{P}_2\text{O}_7$), calcium carbonate (CaCO_3), dicalcium phosphate anhydrous (DCPA; CaHPO_4), sodium phosphate (Na_2HPO_4), and polyurethane foams. To prepare the TTCP powder, the $\text{Ca}_2\text{P}_2\text{O}_7$ powder was mixed with the CaCO_3 powder in an ethanol solution followed by drying and crushing into a mixed powder. The weight ratio of $\text{Ca}_2\text{P}_2\text{O}_7$ to CaCO_3 was 1: 1.27. The mixed powder was then calcined in a platinum crucible at 1350°C for 5 hours in air atmosphere, followed by quenching in air at 25°C . The calcined powder was crushed into the fine TTCP powder and stored in a dry cabinet. To prepare a dense CPC, the dry TTCP powder was mixed with the dry DCPA powder in a jar placed in a vibration mill (SPEX 8000). The molar ratio of TTCP to DCPA was 1:1 or the weight ratio was 72.9:27.1. An aqueous solution of Na_2HPO_4 with the concentration of 1 mol/liter was used as the liquid component for the CPC. The ratio of the mixed CPC powder to

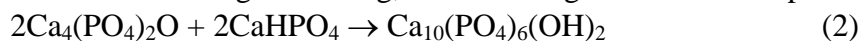
the liquid phase was 1 g:0.35 - 0.70 ml. The CPC paste or slurry was then cast in containers. Short time of vacuum degassing or mechanical vibration was used to increase the particle packing density. To produce the porous CPC, the amount of the liquid component was adjusted so that when the liquid component was mixed with the CPC powder, a flowable slurry was obtained. The slurry was then used to coat the polyurethane foams through the actions of dipping the foams in the slurry, squeezing the excess slurry out, applying the slurry again, and blowing the coated foams with air at room temperature. The CPC coated foams were then allowed to set and dry to result in a porous CPC with a certain rigidity and mechanical strength. To remove the polyurethane foams, the CPC coated foams were fired in air in an electric furnace at 1200 °C for 2 hours using the heating rate of 1 °C/min. Some of the sintered porous CPC samples were further coated with the CPC using the CPC slurry at the room temperature. The end products did not contain any toxic species or residues. Coating the fired porous CPCs led to an increase in the pore wall thickness, a reduction in the pore size, and the retention of the advantages of the CPCs. As to the characterization, the TTCP powder, the set CPC, and the fired CPC were confirmed and analyzed using stereo-optical microscopy (Leica MZ6), X-ray diffraction (XRD; Lab XRD-6000 Shimadzu), and scanning electron microscopy (SEM; JEOL-JSM 5410).

2. Results and discussion

In this study, calcium pyrophosphate ($\text{Ca}_2\text{P}_2\text{O}_7$) powder was mixed with calcium carbonate (CaCO_3) powder, lightly compacted, placed in a platinum crucible, and calcined at 1350 °C for 5 hours in air. This was followed by fast cooling (quenching) the calcined powder from the high temperature to the room temperature in air. The quenched powder after crushing was examined using XRD and the XRD pattern is shown in the bottom XRD curve of Fig. 1. All the peaks of the bottom XRD curve in Fig. 1 matched the standard XRD pattern of the TTCP (tetracalcium phosphate) phase (JCPDS No. 25-1137; JCPDS: Joint Committee on Powder Diffraction Standards). Thus this XRD result confirmed the following reaction that was assumed for the preparation of the TTCP powder:



The TTCP powder was the important starting material for preparing calcium phosphate cements. After TTCP powder was mixed with another powder named dicalcium phosphate anhydrous (DCPA; CaHPO_4), the solid component for the calcium phosphate cements was formed. The solid component was further mixed with the Na_2HPO_4 solution, which was the liquid component required for the calcium phosphate cements. After the solid component and the liquid component were mixed for some time (less than 30 min.), the mixed paste-like mass became rigid and hard. In other words the cement became set. During the setting, the following reaction was expected:



It should be noted that the above reaction was completed in aqueous environment. Water (H_2O) played an important role in the setting reaction. It was possible that both the reactants firstly dissolved in the water, then the reaction product, hydroxyapatite was formed through precipitation in the water solution. The Na_2HPO_4 species added in the water solution was to accelerate the formation of hydroxyapatite crystals, i.e., the setting of the calcium phosphate cement. Without the Na_2HPO_4 species, the cement took longer time to set - more than 60 min. While the specific detailed processes of the hydroxyapatite formation were not explored in this study, the overall reaction (2) was confirmed by our XRD analysis, as is shown in the middle curve of Fig. 2. Although the peak positions of the middle XRD curve were similar to those of the bottom XRD curve, the highest peaks of the two curves appeared at different positions. The XRD peaks shown in the middle curve were identified to belong to the major hydroxyapatite phase (JCPDS No. 09-432) and minor residual TTCP phase (JCPDS No. 25-1137) as a result of the incompleteness of reaction (2). Calcium phosphate cements are normally prepared under the ambient conditions and they are

also used at low temperatures, specifically around the body temperature. However, this study investigated the behaviour of calcium phosphate cement after being fired at high temperatures. This heat treatment was necessary for the purpose of preparing highly porous hydroxyapatite through the burning off of the polyurethane foams that were used to coat the CPC cement. It was found that after firing the set CPC at 1200 °C for 2 hours in air, the hydroxyapatite phase remained in the sintered CPC, as shown in the top XRD curve of Fig. 1. Thus, the hydroxyapatite phase formed at room temperature in the cement was basically stable up to 1200 °C, or there was no phase decomposition of hydroxyapatite, although the crystallinity and grain size were different.

The set CPC prepared at room temperature was strong and rigid enough for sample handling such as cutting and grinding. There was also little shrinkage from the as cast state (soft) to the set CPC (hard). No crack was formed in the set CPC, unlike some slip cast ceramic green bodies, which tend to form cracks after drying. To understand the behaviour of the set CPC, the fracture surfaces of the set CPC were examined using scanning electron microscopy. Fig. 2 shows that on the fracture surface, micropores with pore sizes in the micron scale were present in the set CPC. Most interestingly, whisker-like crystals were formed. Fig. 3 is another SEM micrograph from another area of the fracture surface of the set CPC. Other features are the same as in Fig. 2. The presence of the solid cores suggested the incompleteness of the reaction (2), which was also indicated by the XRD result shown in Fig. 1. The porosity present in the set CPC was responsible for the low shrinkage observed, as the micropores were initially filled with the liquid component. When the surfaces of the solid particles and the gap between the particles were saturated with the liquid component, the CPC paste became flowable. During and after the setting reaction, the liquid component would evaporate. However, the whole body did not shrink noticeably due to the geometrical constraints among the CPC particle compacts. While the porosity tended to reduce the shrinkage of the set CPC, it also decreased the mechanical strength of the set CPC. However, by manually breaking the set CPC, it was noticed that some level of mechanical strength was built up in the set CPC, which was due to the formation of the whisker crystals. The growing whiskers tended to penetrate into each other and became entangled, thus resulting in the mechanical interlocking and the mechanical strength. Based on the current knowledge about CPC, it can be seen that the whiskers were hydroxyapatite in structure, with the details of the setting mechanism of the CPC having been reported by Ishikawa et al. [21]. Briefly, the formation of the hydroxyapatite crystals in the CPC setting reaction was a result of the precipitation of calcium and phosphate ions coming from TTCP and DCPA phases which dissolved in the CPC liquid component.

The main contribution of this study was the preparation of porous calcium phosphate ceramics using the properties of the set CPC and based on the porous structure of the polyurethane foams. Fig. 4 shows a stereo-optical micrograph of the polyurethane foam. There were large pores among the polyurethane networks consisting of a large number of struts (or frames). The polyurethane foams were used to create porosities in the porous calcium phosphate ceramics after firing. Fig. 5 shows a stereo-optical micrograph of the porous hydroxyapatite, which was not prepared conventionally by dipping the polyurethane foams into a hydroxyapatite slurry followed by firing, but by dipping the foams into a slurry of the mixture of TTCP powder, DCPA powder, and Na₂HPO₄ aqueous solution. The reason for the success of the porous hydroxyapatite bodies was the absence of drying cracks in the set CPC coated on the polyurethane foams. The set CPC struts also had a sufficient mechanical strength to support the porous structure of the set CPC. Thus, even with the removal of the polyurethane foams below about 450 °C, the porous set CPC was still intact and could be self-supported. The further firing at 1200 °C for 2 hours was to remove the residual organic species completely and to modify the porous hydroxyapatite structure. Thus, a new method of preparing porous hydroxyapatite ceramics was established in this study.

While Fig. 5 shows the macropores (about 1 mm in pore size) and the high pore interconnectivity of the highly porous hydroxyapatite ceramic body, Fig. 6 shows the micropores within the struts of the

porous ceramic body. Most of the micropores appeared interconnected with pore sizes around 5 μm . Thus porous hydroxyapatite-based ceramics with both macroporosity and microporosity were obtained in the study. The high porosity and the high pore interconnectivity would be desirable for uses such as the scaffolds for bone tissue engineering, which involves placing bone forming cells into the porous ceramic bodies (scaffolds) and implanting the cell-loaded scaffolds into a bone defect, followed by bone healing. It should be noted that the porosity and the macropore size could be reduced when the sintered porous hydroxyapatite-based ceramics were coated with a layer of another CPC through CPC slurry dipping process. For this additional step to thicken the struts, no more firing would be necessary due to the setting reaction of the CPC and due to the absence of the polyurethane foam. By controlling the porosity and pore size, the highly porous ceramics would have a compressive strength comparable to the compressive strengths of cancellous bones (2-12 MPa). Another strengthening method would be the infiltration of some bioactive polymer such as PolyactiveTM [22] or some biodegradable polymer such as PLGA (poly(lactic-co-glycolic acid)) into the micropores within the struts.

3. Conclusions

Porous hydroxyapatite-based calcium phosphate ceramics with macropore sizes of about 1 mm and micropore sizes of about 5 μm were prepared by firing the calcium phosphate cement coated on the struts of the polyurethane foams at 1200 °C for 2 hours. The calcium phosphate cement was prepared at room temperature by mixing the mixture of tetracalcium phosphate ($\text{Ca}_4(\text{PO}_4)_2\text{O}$) and dicalcium phosphate anhydrous (CaHPO_4) with the solution of sodium phosphate (Na_2HPO_4) in the ratio of powder to liquid = 1 gram to 0.35 - 0.70 ml. The tetracalcium phosphate was prepared by firing the mixture of pyro-calcium phosphate ($\text{Ca}_2\text{P}_2\text{O}_7$) and calcium carbonate (CaCO_3) in the weight ratio of 1: 1.27 at 1350 °C for 5 hours, followed by quenching in air. The prepared porous hydroxyapatite-based ceramics were featured with high porosities (~ 70 %) and highly interconnected macro- and micro-pores.

Acknowledgements

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Figure captions

- Fig. 1. XRD patterns of the TTCP powder (bottom curve), the set CPC (middle curve), and the sintered CPC (top curve).
- Fig. 2. SEM micrograph of a fracture surface of the set CPC showing the micropores (black areas) and the hydroxyapatite whiskers.
- Fig. 3. SEM micrograph of a fracture surface of the set CPC showing the unreacted dense cores (arrowed), in addition to the micropores (black areas) and the hydroxyapatite whiskers.
- Fig. 4. Stereo-optical micrograph showing the pores and the struts (arrowed) of the polyurethane foam.
- Fig. 5. Stereo-optical micrograph showing the pores and the struts (arrowed) of the porous hydroxyapatite ceramic prepared by firing the set CPC coated on the polyurethane foam.
- Fig. 6. SEM micrographs of a fracture surface of a strut of the porous hydroxyapatite ceramic shown in Fig. 5. (a) magnification 3,500 X; (b) magnification 7,500 X.

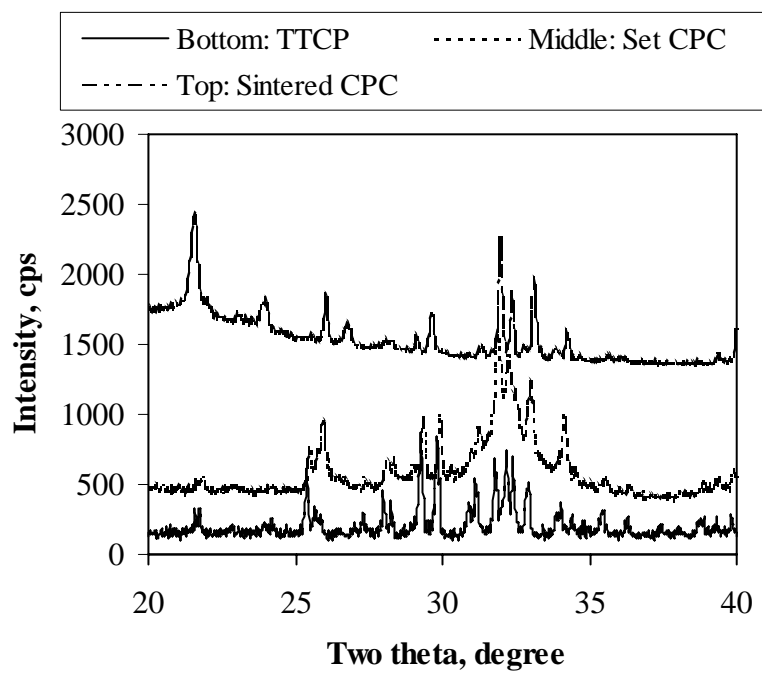


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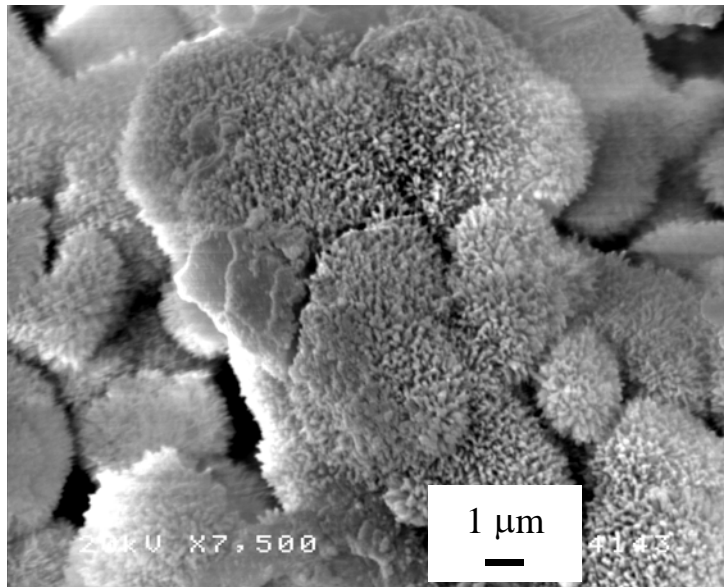


Fig. 2. SEM micrograph of a fracture surface of the set CPC showing the micropores (black areas) and the hydroxyapatite whiskers.

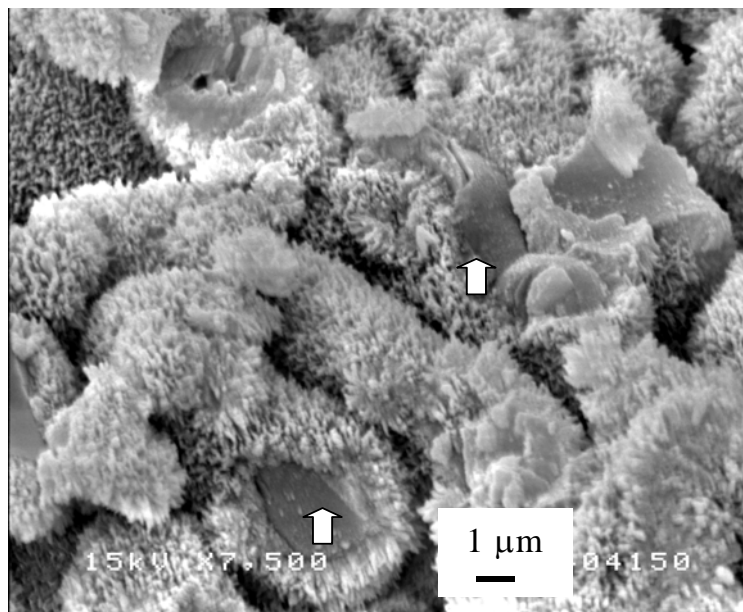


Fig. 3. SEM micrograph of a fracture surface of the set CPC showing the unreacted dense cores (arrowed), in addition to the micropores (black areas) and the hydroxyapatite whiskers.

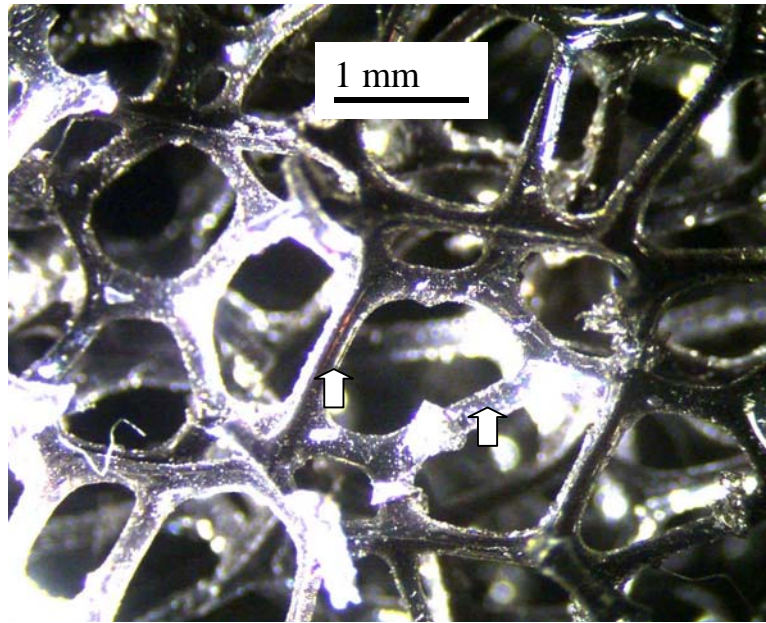


Fig. 4. Stereo-optical micrograph showing the pores and the struts (arrowed) of the polyurethane foam.

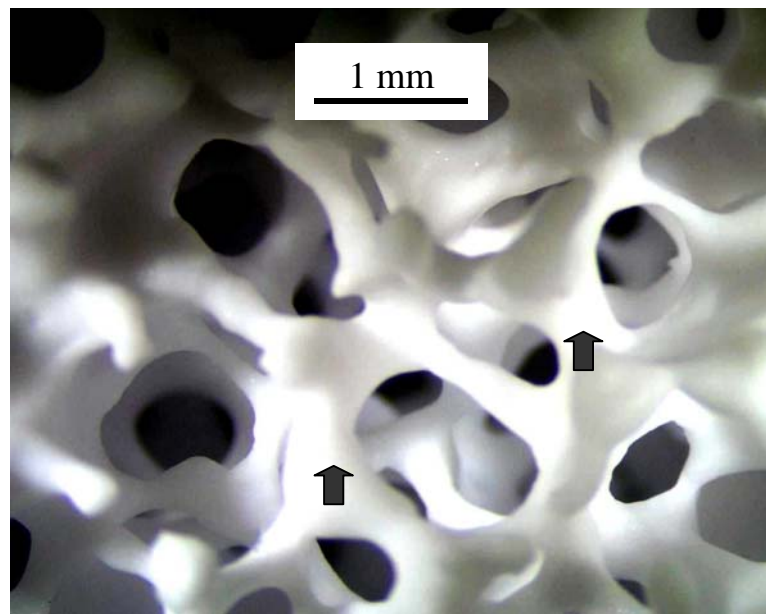


Fig. 5. Stereo-optical micrograph showing the pores and the struts (arrowed) of the porous hydroxyapatite ceramic prepared by firing the set CPC coated on the polyurethane foam.

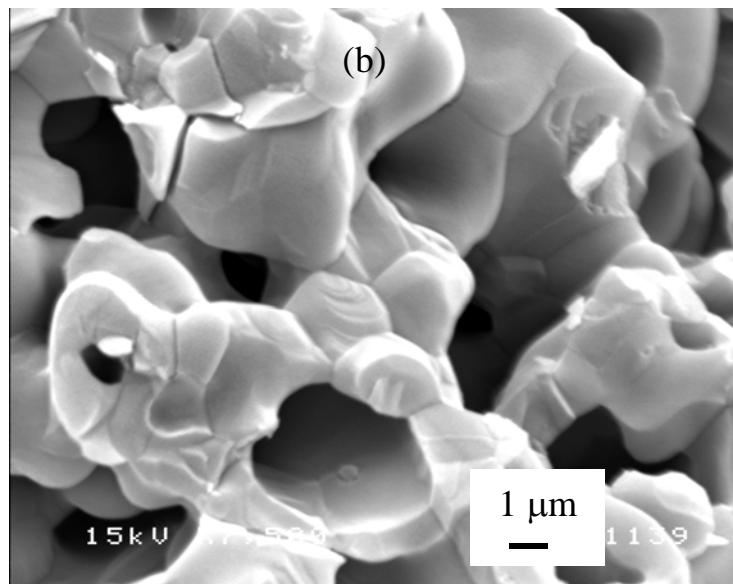
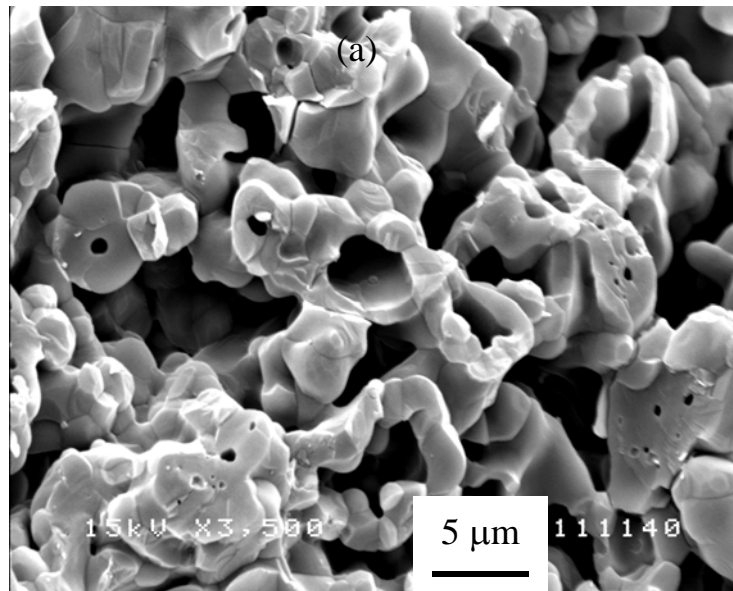


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