FULL PAPER

Fabrication and characterization of beta-type tricalcium phosphate sintered body with phosphorus/sulphur-complex cations

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The crystal structure of β -tricalcium phosphate (β -TCP), which is used as a bone replacement material, is known to have five crystallographically distinct positions for the Ca atom and three distinct positions for the P atom. In this paper, we have successfully synthesized a new β -type tricalcium phosphate (Na- β -TCP/S) with phosphorus/sulfur-complex cations by solid state reaction method. This was achieved by using $\text{Ca}_{20}\text{Na}_2(\text{PO}_4)_{14}$ (Na- β -TCP) as a starting material, adjusting the Ca(4) site occupied by Na atoms to become vacancies, and simultaneously adjusting the same moles of S atoms to the P(1) site. The obtained sintered bodies became dense with increasing the sintering temperature. The grain growth of the sintered bodies was inhibited with increasing sulfur content. Although the solubility of Na- β -TCP was about half of that of β -TCP, the solubility of Na- β -TCP/S powder samples slightly increased with increasing sulfur content. These results indicate that Na- β -TCP/S can be prepared by controlling not only the amounts of vacancies in the structure but also the sinterability and solubility of Na- β -TCP/S due to the substitution of phosphorus and sulfur, and that Na- β -TCP/S has potential as a new β -TCP material for bioceramics.

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Key-words : β -Tricalcium phosphate, Phosphorus/sulfur-complex cations, Sintered body, Solubility

[Received July 9, 2021; Accepted October 25, 2021]

1. Introduction

Beta-tricalcium phosphate [β - $\text{Ca}_3(\text{PO}_4)_2$: β -TCP] has been used clinically as a bone filler because of its excellent biocompatibility and bone replacement properties.^{1),2)} When such calcium phosphate materials are used as biomaterials, it is considered ideal that the rate of bone resorption *in vivo* is approximately equal to the rate of bone formation. However, β -TCP has a high rate of resorption *in vivo* and its mechanical strength is lower than that of autogenous bone, which raises the risk of fracture.

β -TCP belongs to the rhombohedral system in the space group $R3c$, and its lattice parameters are $a = b = 1.0435$ nm, $c = 3.7403$ nm, $\alpha = \beta = 90^\circ$, $\gamma = 120^\circ$ in the hexagonal setting.³⁾ β -TCP has two crystallographically independent columns, A and B, consisting of Ca polyhedral and PO_4 tetrahedra, in the unit lattice, and these two columns are parallel to the c -axis; the A column is on the c -axis (3-fold rotation axis), and the P(1)-Ca(4)-Ca(5)-P(1)-Ca(4)-Ca(5) repetition. The Ca(4) site has an atomic occupancy of about 0.5, and A column has a unique crystal

structure with vacancies. On the other hand, B column consists of a repetition of P(3)-Ca(1)-Ca(3)-Ca(2)-P(2), but the arrangement of the three Ca sites is not in a straight line but in a broken line. It is known that the substitution of various cations in β -TCP occurs mainly in relation to the Ca(4) and Ca(5) sites of the A column. Our research group has reported that the substitutional solid solution of various ions⁴⁾ in the calcium sites in the crystal structure of β -TCP improved its mechanical strength⁵⁾ and thermal structural stability,⁶⁾ and also controlled its solubility.⁷⁾ There are also many reports by other researchers.⁸⁾⁻¹²⁾ However, there are not many studies on the substitution of various ions into the anionic position in β -TCP.

We focused on sulfur, which is also an essential element for the survival of living organisms. It is an important component of the essential amino acid methionine, and is also present in another amino acid, cysteine. Sulfur is not toxic *in vivo*. Sulfur in bone is found as sulfate in proteoglycans, which maintain a constant number of osteoblasts and osteoclasts. Sulfur is mainly a hexavalent cation *in vivo* and forms SO_4 oxoate by coordination with oxygen, which may be substituted into PO_4 in the crystal structure of β -TCP.

In this study, in order to clarify the mechanism of sulfur substitution, $\text{Ca}_{20}\text{Na}_2(\text{PO}_4)_{14}$ (Na- β -TCP) was prepared as a starting material by substituting Na ions for Ca(4) containing vacancies in the crystal structure of β -TCP.⁶⁾ The

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preparation of β -TCP with phosphorus/sulfur-complex cations (Na- β -TCP/S) was attempted by substituting sulfur ions for phosphorus ions and decreasing the amount of Na ions for charge compensation. The crystal structure of the obtained product was investigated, and its sintered bodies were fabricated and their properties were evaluated.

2. Experimental procedure

2.1 Powder preparation of β -TCP with phosphorus/sulfur-complex cations

To prepare β -TCP with phosphorus/sulfur-complex cations (Na- β -TCP/S) by solid state reaction method, ammonium dihydrogen phosphate $[(\text{NH}_4)_2\text{H}_2\text{PO}_4]$; purity 99.9 %, FUJIFILM Wako Pure Chemicals, JAPAN] was used as phosphorus source, calcium oxide (CaO; purity 99.9 %, FUJIFILM Wako Pure Chemicals, JAPAN) as calcium source, sodium nitrate (NaNO_3 ; purity 99.9 %, FUJIFILM Wako Pure Chemicals, JAPAN) as sodium source and ammonium sulfate $[(\text{NH}_4)_2\text{SO}_4]$; purity 99.95 %, FUJIFILM Wako Pure Chemicals, JAPAN] as sulfur source were used as starting materials, respectively.

The $(\text{Ca} + \text{Na} + \square)/(\text{P} + \text{S})$ molar ratio was kept constant at 1.571, and the amount of sulfur added to the phosphorus position was increased by $\text{S mol \%} = \text{S}/(\text{P} + \text{S})$. The samples were prepared by changing the amount of sulfur and sodium added by solid state reaction method (Table 1). The prepared samples were wet-mixed for 48 h, and the resulting mixed powders were calcined in air at 1000 °C for 12 h. The powders were identified by X-ray diffraction (XRD; MiniFlex 600, Rigaku, JAPAN), and Fourier transform infrared (FT-IR) absorption (FT-IR-4200, JASCO, JAPAN) by KBr method, and the lattice parameter was measured by the silicon internal standard method.

2.2 Fabrication and evaluation of β -TCP sintered body with phosphorus/sulfur-complex cations

The calcined powder described in the above section was added 2 vol % PVA solution (5 wt.%) and mesh classified to less than 75 μm . Furthermore, the powder added kerosin (5 wt.%) was placed in a mold and was compacted to a size of $45\text{ mm} \times 20\text{ mm} \times 5\text{ mm}$ by uniaxial pressing (CDM-20M, RIKEN KIKI, JAPAN) at the conditions of 57 MPa for 1 min. After molding, cold isostatic pressing (CIP) (Labo CIPLCP80-200A, NPA Co., Ltd., JAPAN) at 200 MPa for 10 min was performed. The compacts were

defatted at 380 and 500 °C for 5 h, and then sintered at 1100–1200 °C for 24 h. The sintered bodies were examined by the Archimedes method for the measurement of porosity and bulk density, and the microstructure was observed using a scanning electron microscope (VE-7800, KEYENCE, JAPAN).

2.3 Evaluation of solubility of β -TCP with phosphorus/sulfur-complex cations

A 0.08 mol L^{-1} acetic acid solution was prepared using acetic acid (purity 99.9 %, FUJIFILM Wako Pure Chemicals, JAPAN) and a 0.08 mol L^{-1} sodium acetate solution was prepared using sodium acetate (purity 98.5 %, FUJIFILM Wako Pure Chemicals, JAPAN). Each solution was mixed to pH 5.50 ± 0.02 using a pH meter (F-32, HORIBA, JAPAN) to prepare a 0.08 mol L^{-1} acetic acid-sodium acetate buffer solution. After pouring 60 ml of the 0.08 mol L^{-1} acetic acid-sodium acetate buffer solution into a polyethylene bottle, a Ca ion electrode was inserted, and 0.10 g of the sample was placed in the bottle while stirring at $430 \pm 15\text{ rpm}$ to measure the amount of Ca ions dissolved from Na- β -TCP/S.

3. Results and discussion

3.1 Substitutional solid solution mechanism of β -TCP with phosphorus/sulfur-complex cations

The XRD of β -TCP with sulfur/phosphorus complex cation (Na- β -TCP/S) obtained in this paper is shown in Fig. 1. It can be seen from the figure that the XRD of the sample with Na ions substituted at the Ca(4) position corresponds to the diffraction peak of the β -TCP structure (ICDD No. 055-0898), while the diffraction peaks of the byproducts HAp and α -TCP are not observed. The diffraction peaks obtained were shifted to a slightly higher angle side, suggesting the formation of $\text{Ca}_{20}\text{Na}_2(\text{PO}_4)_{14}$, which was the stoichiometric composition of the preparation. The diffraction peaks of all the samples obtained from the different formulations were exclusively due to the β -TCP structure. The specific diffraction peaks shifted to a lower angle with increasing sulfur content. This was suggested to be due to the formation of vacancies at the Ca(4) site, which is occupied by sodium in the crystal structure and the substitutional solid solution of sulfur at the phosphorus site.

The FT-IR spectra of Na- β -TCP/S are shown in Fig. 2. It can be seen from the figure that the FT-IR spectrum of Na- β -TCP containing phosphorus shows four reference

Table 1. Formulation and chemical composition of Na- β -TCP/S

S/(P + S) mol %	Na/(Ca + Na + $\square$) mol %	$\square$ /(Ca + Na + $\square$) mol %	Chemical formula
0	9.1	0	$\text{Ca}_{20}\text{Na}_2(\text{PO}_4)_{14}$
2.0	7.8	1.3	$\text{Ca}_{20}\text{Na}_{1.72}\square_{0.28}(\text{PO}_4)_{13.71}(\text{SO}_4)_{0.28}$
4.0	6.6	2.5	$\text{Ca}_{20}\text{Na}_{1.44}\square_{0.56}(\text{PO}_4)_{13.44}(\text{SO}_4)_{0.56}$
6.0	5.3	3.8	$\text{Ca}_{20}\text{Na}_{1.16}\square_{0.84}(\text{PO}_4)_{13.16}(\text{SO}_4)_{0.84}$
8.0	4.0	5.1	$\text{Ca}_{20}\text{Na}_{0.88}\square_{1.12}(\text{PO}_4)_{12.88}(\text{SO}_4)_{1.12}$
10.0	2.7	6.4	$\text{Ca}_{20}\text{Na}_{0.60}\square_{1.40}(\text{PO}_4)_{12.60}(\text{SO}_4)_{1.40}$
12.0	1.5	7.6	$\text{Ca}_{20}\text{Na}_{0.33}\square_{1.67}(\text{PO}_4)_{12.33}(\text{SO}_4)_{1.67}$
14.3	0	9.1	$\text{Ca}_{20}\square_2(\text{PO}_4)_{12}(\text{PO}_4)_{12}(\text{SO}_4)_2$

$\square$: Vacancy, $(\text{Ca} + \text{Na} + \square)/(\text{P} + \text{S})$ mol ratio = 1.571.

Fig. 1. XRD patterns of Na- β -TCP/S. Sulfur content; (a) 0 mol %, (b) 2.0 mol %, (c) 4.0 mol %, (d) 6.0 mol %, (e) 8.0 mol %, (f) 10.0 mol %, (g) 12.0 mol %, (h) 14.3 mol %.

Fig. 2. FT-IR spectra of Na- β -TCP/S. Sulfur content; (a) 0 mol %, (b) 2.0 mol %, (c) 4.0 mol %, (d) 6.0 mol %, (e) 8.0 mol %, (f) 10.0 mol %, (g) 12.0 mol %, (h) 14.3 mol %.

vibrations of PO_4 group at around $1122\text{ cm}^{-1}(\nu_3)$, $1020\text{ cm}^{-1}(\nu_3)$, $945\text{ cm}^{-1}(\nu_1)$, $603\text{ cm}^{-1}(\nu_4)$, $550\text{ cm}^{-1}(\nu_4)$ and $432\text{ cm}^{-1}(\nu_2)$. With the addition of sulfur, besides the absorptions attributed to the PO_4 group, the absorptions attributed to the SO_4 group were observed around 1200 cm^{-1} and the shoulder of the higher wavenumber of the absorption at 603 cm^{-1} and those peaks intensity increased with the increase in the amount of sulfur addition. These results mean that β -TCP containing both PO_4 and SO_4 was produced in the prepared sample.

Fig. 3. Changes in lattice parameters of Na- β -TCP/S with sulfur content.

The lattice parameter of Na- β -TCP/S with respect to the amount of sulfur added is shown in Fig. 3. It can be seen from the figure that the a -axis was constant regardless of the amount of sulfur added, while the c -axis increased linearly with the amount of sulfur added up to 14.3 mol %. The reason for the constant a -axis is that the SO_4 tetrahedron (average bond distance: 0.149 nm) substituted for the PO_4 tetrahedron (average bond distance: 0.154 nm) also has a comparable interbond distance. On the other hand, the reason for the linear increase in the c -axis is that the positively charged Na ion at the Ca(4) site changes to vacancy, weakening the bond with the PO_4 tetrahedron just above the Ca(4) site, which causes expansion along the c -axis. From the above results, it can be concluded that the chemical composition of the obtained sample can be expressed as $\text{Ca}_{20}\text{Na}_{2-x}\square_x(\text{PO}_4)_{14-x}(\text{SO}_4)_x$ ($0 < x < 2$, $\square$: vacancy), because the sulfur ion is substituted in the P(1) site up to 14.3 mol % in the β -TCP structure, and the Na ions in the Ca(4) sites are changed to vacancies for the charge compensation.

3.2 Evaluation of β -TCP sintered body with sulfur/phosphorus-complex cations

The change in the volumetric shrinkage of Na- β -TCP/S compacts before and after sintering is shown in Fig. 4. It can be seen that the change of volumetric shrinkage before and after sintering was not so large at the sintering temperature of 1100°C . The volumetric shrinkage increased with the increase of sulfur addition under the condition of sintering temperature of 1150°C , suggesting the progress of sintering. The volumetric shrinkage was larger than that at 1150°C suggesting that the sintered bodies became dense at a sintering temperature of 1200°C . These results indicate that the sintering reaction of Na- β -TCP/S occurs significantly above 1150°C .

Fig. 4. Change in volume shrinkage of Na- β -TCP/S compacts before and after sintering. Sintering temperature; (a) 1100 °C, (b) 1150 °C, (c) 1200 °C.

Fig. 5. Changes in open porosity (dotted line) and bulk density (solid line) of Na- β -TCP/S sintered body. Sintering temperature; (a) 1100 °C, (b) 1150 °C, (c) 1200 °C.

Fig. 6. SEM image of Na- β -TCP/S sintered body at 1150 °C. Sulfur content; (a) 0 mol %, (b) 6.0 mol %, (c) 10.0 mol %, (d) 14.3 mol %.

The changes in open porosity and bulk density of Na- β -TCP/S sintered body are shown in Fig. 5. It can be seen that the sintered bodies did not occur much densification and grain growth at the sintering temperature of 1100 °C, even though the amount of sulfur was changed, because the sintering was in the early stage. The densification of sintering progressed with increasing sulfur content at a sintering temperature of 1150 °C. This was probably due to the evacuation of internal pores and the shrinkage of the compact. However, the grain growth of the sintered body was inhibited with increasing sulfur content. The densification and inhibition of grain growth became more remarkable when the sintering temperature was increased

to 1200 °C. In particular, the sintered bodies with the highest bulk density were obtained when the sulfur content was between 4 and 10 mol %. It was found that Na- β -TCP/S could be sintered at 1200 °C without alpha-formation, while pure β -TCP would be partially alpha-formed when sintered at 1150 °C for a long time. This suggests that the structural stability of Na- β -TCP/S is improved at high temperature compared with that of pure β -TCP.

SEM microstructural images of Na- β -TCP/S sintered bodies at sintering temperatures of 1150 and 1200 °C are shown in Figs. 6 and 7, respectively. The specimens were prepared by mirror polishing, thermal etching at 1050 °C for 3 h, and gold deposition. The sintered bodies became

Fig. 7. SEM image of Na- β -TCP/S sintered body at 1200 °C. Sulfur content; (a) 0 mol %, (b) 6.0 mol %, (c) 10.0 mol %, (d) 14.3 mol %.

denser with increasing sulfur content at the sintering temperature of 1150 °C and the grain growth was inhibited. In particular, the sintered bodies with the high bulk density were obtained when the sulfur content was 6 and 10 mol %. The grain growth and densification of the sintered bodies at the sintering temperature of 1200 °C are more progressed than those at 1150 °C.

3.3 Evaluation of solubility of β -TCP with phosphorus/sulfur-complex cations

The solubility of calcium phosphate powder *in vitro* was evaluated.¹³⁾ The Ca ion concentration of pure β -TCP was 4.05 mM after 30 min, and that of Na- β -TCP was 1.55 mM after 30 min. Compared with β -TCP, the solubility of Na- β -TCP was reduced to about 40 %. Substitution of Na ions into Ca(4) sites of β -TCP structure decreased the solubility, because substitution of Na ions into Ca(4) sites (occupancy 0.5) improved the thermal stability of β -TCP structure. We have already reported on this in a previous paper.^{6),7)}

Figure 8 shows the change of Ca ion concentration from Na- β -TCP/S with sulfur contents. The solubility of Na- β -TCP/S gradually increased with the increase of sulfur addition, and the Ca ion concentration of $\text{Ca}_{20}\square_2(\text{PO}_4)_{12}(\text{SO}_4)_2$ (β -TCP/S) with 14.3 mol % sulfur was 2.0 mM after 30 min. However, this value was sufficiently low compared to pure β -TCP. The solubility of a substance is expressed by the equation $\Delta G = RT \ln K_{sp}$, and it is known that as ΔG decreases, the K_{sp} value also decreases. In other words, when the amount of sulfur in the phosphorus site of Na- β -TCP was increased and the amount of sodium in the Ca(4) site was decreased, vacancies were induced in the Ca(4)

Fig. 8. Change in Ca ion concentration from Na- β -TCP/S with sulfur contents. Sulfur content; (a) 0 mol %, (b) 4.0 mol %, (c) 8.0 mol %, (d) 12.0 mol %, (e) 14.3 mol %.

site. We speculated that the formation of these vacancies slightly reduced the thermal stability and slightly increased the solubility of β -TCP/S compared to Na- β -TCP.

4. Conclusion

Na- β -TCP/S was successfully prepared by substituting sodium for calcium and sulfur for phosphorus based on the β -TCP structure by solid state reaction method, and at the same time, reducing the sodium to introduce vacancies for

charge compensation. The grain growth of Na- β -TCP/S sintered compacts was inhibited with increasing sulfur content, and dense sintered bodies were successfully obtained at sulfur contents of 4–10 mol %. The solubility of Na- β -TCP/S was sufficiently low compared with that of pure β -TCP, indicating the possibility of using Na- β -TCP/S as β -TCP ceramics for biomaterials with a new composition. We found that Na- β -TCP/S can control the sintering and solubility compared with Na- β -TCP and pure β -TCP not only by replacing sulfur with phosphorus but also by controlling the amounts of vacancies in the structure.

Acknowledgement This work was partially supported by the JSPS KAKENHI grant number 25350554 and grant number JP20K09990.

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