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LOW-TEMPERATURE SYNTHESIS OF TRICALCIC PHOSPHATE AND RELATED MATERIALS

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Abstract: Calcium phosphate-based ceramics, in particular, biodegradable β- and α-tricalcic phosphate (TCP), have received much attention as synthetic bone substitutes. Although there is a consensus that β- and α-TCP are both high temperature polymorphs, in which the β phase transforms to the α phase at above ~1125 °C, recent extensive studies reported novel synthetic methods for TCP and related materials such as magnesium- or magnesium-free whitlockite at temperatures below 800 °C. While several synthesis methods for TCP and related materials have been reported, few have focused on the low-temperature synthesis of TCP and related materials, but rather on conventional methods. Therefore, the focus of this short review is upon the low-temperature synthesis of TCP and related materials. In addition, future strategies to synthesize three-dimensional shapes of TCP and related materials at low temperature are discussed.

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1. Introduction

Calcium phosphate (CP)-based bioceramics are widely recognized as synthetic bone substitutes due to their excellent biological performance in the human body. Several compositions of CP bioceramics comprising calcium ion (Ca$^{2+}$), phosphate ions (PO$_4^{3-}$, HPO$_4^{2-}$, H$_2$PO$_4$), hydroxyl ion (OH$^-$), and/or water (H$_2$O) have been developed. Among them, non-biodegradable hydroxyapatite (Ca$_{10}$(PO$_4$)$_6$(OH)$_2$; HA) and biodegradable tricalcium phosphate (Ca$_3$(PO$_4$)$_2$; TCP) have been clinically applied over the past few decades.

There are three polymorphs of TCP: β-, α-, and α’-TCP. β-TCP is the stable phase at room temperature and transforms at ~1125 °C to α-TCP, which can be maintained by quenching to room temperature. α-TCP transforms to α’-TCP between 1458 and 1508 °C, but cannot be maintained by quenching to room temperature. Regardless of the identical chemical compositions of β-TCP and α-TCP, their structures, densities and solubilities, which determine their applications as bioceramics, are considerably different. Both are clinically applied in dentistry, cranio-maxillo-facial surgery, and orthopedics. β-TCP is used in shapes of dense or porous granules and blocks, while the more soluble α-TCP is used as a fine powder for self-setting calcium-phosphate cements (CPC).

Whitlockite was initially reported to have the chemical composition of Ca$_6$(PO$_4$)$_3$ and a similar XRD pattern to β-TCP. Consequently, the terms whitlockite and β-TCP were used interchangeably. However, the structural differences between them were later clarified by Gopal et al., and they are regarded as distinct species today. Unlike β- or α-TCP, Mg-whitlockite (Mg-WH) can directly precipitate only in solutions containing Mg$^{2+}$ ions at low temperature.

With extensive studies in the field of bioceramics, novel synthesis methods for TCP and related materials such as Mg-WH and Mg-free whitlockite (WH) at low temperature have recently been reported. Here, low temperature is defined as a temperature that is below the conventional CaO–P$_2$O$_5$ phase diagram (Fig. 1), i.e., below 800 °C for β-TCP and below 1125 °C for α-TCP. Although a few articles have been published on synthesis methods for TCP and related materials, few have focused on low-temperature synthesis, but rather on conventional methods. Therefore, the focus of this short review is upon the low-temperature synthesis of TCP and related materials. Section 2 summarizes conventional synthesis methods for TCP and Mg-WH, while low-temperature synthesis of TCP is summarized in Section 3. Finally, strategies for low-temperature synthesis of three-dimensional shapes of α-TCP, Mg-WH, and WH are discussed in Section 4.
2. Conventional synthesis methods of TCP and Mg-WH

Solid-state reaction

β-Tricalcium phosphate (β-TCP) can be synthesized by solid-state reactions, wet-chemical reactions, and mechano-chemical reactions. According to the CaO–P₂O₅ phase diagram (Fig. 1), β-TCP can be synthesized by a solid-state reaction blending CaO and P₂O₅ in a molar ratio of 3:1 (Ca/P = 1.5). The combinations of the chemical reagents of dicalcium phosphate anhydrous (CaHPO₄·2H₂O, DCPA, monetite) and calcium carbonate (CaCO₃) have been reported frequently, and are shown in Eqs. (1)–(3). The synthesis is performed according to the common practice of solid-state reactions, i.e., solid chemical reagents are milled together to reduce the particle size and increase the contact area. After milling, the reagent mixture is directly heated above the transformation temperature (800–1125 °C) or pre-pressed to improve contact between particles. The reaction temperatures and reaction times vary between 1000 and 1100 °C and between 5 and 36 h, respectively. In some studies, the high-temperature polymorph α-TCP was reconverted to β-TCP by long-duration heat-treatment at 800–950 °C, 860–900 °C, and 1100 °C.

\[
\begin{align*}
\text{CaCO}_3 + 2\text{CaHPO}_4 &\rightarrow \text{Ca}_3(\text{PO}_4)_2 + \text{CO}_2 + \text{H}_2\text{O} \\
3\text{CaCO}_3 + 2(\text{NH}_4)_2\text{HPO}_4 &\rightarrow \text{Ca}_3(\text{PO}_4)_2 + 3\text{CO}_2 + 3\text{H}_2\text{O} + 4\text{NH}_3 \\
\text{CaCO}_3 + \text{Ca}_3\text{P}_2\text{O}_7 &\rightarrow \text{Ca}_5(\text{PO}_4)_2 + \text{CO}_2
\end{align*}
\]

α-TCP can be prepared by heating the above reagent mixtures or β-TCP itself at above 1125 °C. Reaction temperatures between 1200 and 1500 °C and reaction times between 2 and 48 h have frequently been reported.1–3,9,19,21–28 Most authors advocate the necessity of a “quench” after calcination, which is meant to avoid the α to β-TCP reverse transformation.19,21,23–25,27,28 Indeed, it was shown that even at low cooling rates (≥ 2 °C/min), the reverse transformation from α to β-TCP did not occur.1,9,22,29 However, the presence of impurities such as Mg in the starting chemical reagents led to the preferred formation of β-TCP by α to β-TCP reverse transformation,22 since the Mg²⁺ ions stabilized the low-temperature polymorph of β-TCP and increased the β to α-TCP phase transformation temperature.3,12,29

Wet-chemical process

A wet-chemical process is the most common method for synthesizing β-TCP. According to the

![FIGURE 1](image-url) High temperature phase diagram for CaO–P₂O₅ binary system. C₄P: Ca₃P₂O₇; C₅P: Ca₅(PO₄)₂; C₆P: Ca₆O(PO₄)₂. (Adapted from Ref. [1] with permission from The Royal Society of Chemistry).
classical solubility phase diagram for Ca(OH)$_2$ \( \rightarrow \) H$_2$PO$_4$ \( \rightarrow \) H$_2$O, the thermodynamically stable CP phase is HA above pH 4.2 and DCPD (Ca-HPO$_4$ \( \rightarrow \) 2H$_2$O; brushite) below pH 4.2. Therefore, β-TCP cannot precipitate directly from aqueous solutions. As such, the synthesis of β-TCP accompanies thermal transformation of a calcium-deficient hydroxyapatite (CDHA) precursor with a Ca/P molar ratio of 1.5 above the transformation temperature for CDHA to β-TCP between 700 and 800 °C.$^{32,33}$

Most syntheses employ combinations of two chemical reagents: calcium nitrate tetrahydrate (Ca(NO$_3$)$_2$ \( \rightarrow \) 4H$_2$O) and diammonium hydrogen phosphate ((NH$_4$)$_2$HPO$_4$)$^{32,34-40}$ or calcium hydroxide (Ca(OH)$_2$) and phosphoric acid (H$_3$PO$_4$)$^{33,34}$ as in reactions shown in Eqs. (4) and (5):

$$\text{Ca(NO}_3\text{)}_2 \cdot 4\text{H}_2\text{O} + (\text{NH}_4)_2\text{HPO}_4 \rightarrow \text{Ca}([\text{HPO}_4]_2\text{(PO}_4\text{)}_3\text{(OH)}$$ \hspace{1cm} (4)

$$\text{Ca(OH)}_2 + \text{H}_2\text{PO}_4 \rightarrow \text{Ca}([\text{HPO}_4]_2\text{(PO}_4\text{)}_3\text{(OH)}$$ \hspace{1cm} (5)

Thermal decomposition of CDHA into β-TCP occurs between 700 and 800 °C$^{32,33}$ as represented in Eq. (6).

$$\text{Ca}([\text{HPO}_4]_2\text{(PO}_4\text{)}_3\text{(OH)} \rightarrow 3\text{Ca}([\text{PO}_4]_3\text{(OH)} + \text{H}_2\text{O} \hspace{1cm} \text{Eq. (6)}$$

Precise control of the pH, reaction temperature, and ripening time is required to synthesize reproducible pure β-TCP with Ca/P = 1.5.$^{35,36}$ A Ca/P value higher than 1.5 resulted in HA formation as a second phase.$^{34,35,37}$ The 1% higher Ca/P molar ratio induced the formation of ~10 wt.% of HA. A Ca/P value lower than 1.5 allowed another second phase of Ca$_3$P$_2$O$_7$.$^{34,35,37}$ The reproducible synthetic conditions for pure β-TCP with Ca/P = 1.5 proposed by Destainville et al.$^{38}$ were pH 7 and 30 °C with a ripening time of 48 h.

Few studies have been reported on wet chemical synthesis of α-TCP. However, according to the CaO-P$_2$O$_5$ phase diagram (Fig. 1), α-TCP can also form by heating CDHA with Ca/P = 1.5 above 1125 °C as in the case of the solid-state reaction. However, the Ca/P discrepancy for CDHA also affects α-TCP formation. Torres et al.$^{39}$ demonstrated that the presence of a small amount of CPP led to the formation of a eutectic point at 1286 ± 0.8 °C. The liquid phase considerably lowered the activation energy for the α → β-TCP transformation, accelerating the α to β reverse transformation upon cooling. Recently, an interesting finding concerning the synthesis of α-TCP was reported by Brazete et al.$^{40}$ They demonstrated that pure α-TCP was obtained even when wet-chemically synthesized β-TCP with Ca/P = 1.51 (a slight excess of Ca), which contained a second phase of HA (1.11 ± 0.09 wt.%), was heated at 1250 or 1500 °C, followed by cooling at 20 °C·min$^{-1}$.

The synthesis of Mg-WH was also reported via wet-chemical and hydrothermal processes. A seminal study by Gopal et al.$^{2}$ showed that Mg-WH with a chemical composition of Ca$_3$Mg$_2$(HPO$_4$)$_2$(PO$_4$)$_3$ (20 mol% Mg ions for Ca ions, Mg/Ca = 0.1) was synthesized hydrothermally at 300 °C and 150 MPa for 2 weeks using 14 mM of NH$_4$H$_2$PO$_4$ 18 mM of Ca(NO$_3$)$_2$, and 2 mM of Mg(NO$_3$)$_2$. Hamad and Heughebaert$^{42,43}$ and Chickerur et al.$^{43}$ reported the synthesis of Mg-WH in CaCl$_2$-MgCl$_2$-Na$_2$HPO$_4$ and Ca(CHO$_2$O)$_2$-Mg(CH$_2$COO)$_2$-Na$_2$HPO$_4$ systems, respectively.

Systematic studies of Mg-WH were performed by Hashimoto et al.$^{44,45}$ In the Ca(NO$_3$)$_2$-KOH-H$_2$PO$_4$-H$_2$O system, Mg-WH with a composition of Ca$_3$Mg$_2$(HPO$_4$)$_2$(PO$_4$)$_3$ \( \cdot \) nH$_2$O (0 ≤ x ≤ 1, n ≈ 6) was formed in the presence of 7–15 mol% Mg$^{2+}$ ion against Ca$^{2+}$ ion at 95 °C and 10–20 mol% Mg$^{2+}$ ion at 40 °C.$^{44}$ Later, they reported that Mg-WH could also be synthesized with 20 mol% Mg$^{2+}$ ions at 25 °C$^{45}$ and 10–15 mol% Mg$^{2+}$ ions at 37 °C.$^{45}$ Using the same system, Mg-WH was also hydrothermally synthesized with 20 mol% Mg$^{2+}$ ions between 200 and 350 °C and within 1–120 h.$^{47,48}$ Incorporation of hydrated water and K$^+$ ions in Mg-WH was observed, and depended greatly on the Ca-deficiency in Mg-WH. They decreased with decreasing concentration of starting chemical reagents.

Moreover, Mn$^{2+}$, Fe$^{2+}$, Co$^{2+}$, and/or Ni$^{2+}$-substituted Mg-WH at Mg ion sites were also prepared by Hashimoto et al.$^{47,48}$ Jang et al.$^{51}$ reported the formation of Mg-WH in the presence of 23–28 mol% Mg ions at 70 °C for 24 h in the Ca(OH)$_2$–Mg(OH)$_2$–HPO$_4$ system. Tas$^{51}$ showed that DCPD crystals transformed to single-phase Mg-WH in less than a day at 70 or 115 °C in a 1.5 mM Mg$^{2+}$ solution and in less than 3 weeks at 37 °C in the same solution.

**Mechano-chemical synthesis**

Mechano-chemical synthesis of β-TCP has also been reported, and is expressed by chemical reaction formulas (Eqs. (7)–(9)).$^{33,45}$ Toriyama and Kawamura$^{33}$ demonstrated that a mixed slurry of CaCO$_3$ and CaHPO$_4$ \( \rightarrow \) 2H$_2$O milled in water for 24 h, followed by calcination at 720 °C for 12 h, allowed the formation of low aggregate β-TCP fine particles, in which the primary particle size was ~0.1 μm.

$$\text{CaCO}_3 + 2\text{CaHPO}_4 \rightarrow \text{Ca}_3([\text{PO}_4]_2 \rightarrow \text{CO}_2 + 3\text{H}_2\text{O}$$ \hspace{1cm} (7)

$$3\text{CaO} + \text{P}_2\text{O}_5 \rightarrow \text{Ca}_3([\text{PO}_4]_2$$ \hspace{1cm} (8)

$$\text{CaO} + 2\text{CaHPO}_4 \rightarrow \text{Ca}_3([\text{PO}_4]_2 \rightarrow \text{3H}_2\text{O}$$ \hspace{1cm} (9)

Mechano-chemical synthesis of α-TCP has not
been reported to date.

3. Low-temperature synthesis methods for TCP

Low-temperature synthesis of \( \alpha \)-TCP

Irrespective of the high-temperature polymorph of TCP, several studies demonstrated that \( \alpha \)-TCP was synthetized by heating amorphous calcium phosphate (ACP) at a much lower temperature than the \( \beta \) to \( \alpha \) transformation temperature of \(-1125\,^\circ\text{C}\) (Fig. 1). The contradiction that the metastable \( \beta \)-TCP appears prior to \( \beta \)-TCP can be explained by the Ostwald step rule. In the crystallization process from an amorphous phase, the least stable phase is formed first and subsequently transforms to the thermodynamically more stable phase. The literature reporting the low-temperature synthesis of \( \alpha \)-TCP is summarized in Table 1.\(^{38-69}\) The first report by Eanes\(^{38}\) showed that the ACP (\( \text{CaP} = 1.67 \)) precipitated by the wet-chemical process first crystallized to \( \beta \)-TCP and subsequently \( \alpha \)-TCP became the preferred crystal phase between 600 and 800 \( ^\circ\text{C} \). \( \beta \)-TCP re-emerged at temperatures above 1100 \( ^\circ\text{C} \). The initial concentration of the calcium and phosphate solution expressed by \([\mathrm{Ca}^{2+}][\mathrm{PO}_4^{3-}]\) for the preparation of ACP affected the ACP to \( \alpha \)-TCP transformation temperature, i.e., an increase in concentration lowered the transformation temperature. Later, Kanazawa et al.\(^{59}\) reported detailed studies on the synthesis of \( \alpha \)-TCP, including the kinetics of \( \alpha \)-TCP formation from ACP. They showed that ACP crystallized to \( \alpha \)-TCP above a \( 10^{-6} \) to \( 10^{-7} \) mM \([\mathrm{Ca}^{2+}][\mathrm{PO}_4^{3-}]\) concentration, while ACP crystallized to \( \beta \)-TCP, followed by \( \alpha \)-TCP, below \( 10^{-2} \) mM as proposed by Eanes.\(^{38}\) Based on a study by Umegaki et al.,\(^{62}\) the crystal phase after calcination of ACP at various temperatures is plotted as a function of the concentration of \([\mathrm{Ca}^{2+}][\mathrm{PO}_4^{3-}]\) \((\text{mM})\) for ACP preparation, together with other reported data (Fig. 2). Most of the reported data were within the formation region of \( \alpha \)-TCP, although some discrepancies were observed. According to Umegaki et al.,\(^{62}\) the Ca/P molar ratio for ACP also led to variations in the transformation temperature and resulting crystal phase. The Ca/P ratios reported in Table 1 are broad values between 0.95 and 2.50, which might lead to variations in the resulting crystal phase.

Moreover, Li et al.\(^{65}\) showed the importance of the synthesis parameters for ACP, such as aging time and solution pH. ACP precipitated at highly basic pH (pH 10 and 12) and with a short aging time of 0.5 h, crystallizing to single-phase \( \alpha \)-TCP. They implied that the difference in the short-range structure of ACP resulted in the formation of \( \alpha \)-TCP at low temperature. As such, the preparation parameters for ACP appear to be very sensitive to the transformation temperature and resulting crystal phase.

In contrast, Döbelin et al.\(^{61}\) demonstrated that ACP nanoparticles synthesized by a flame-spray method crystallized between 525 and 600 \( ^\circ\text{C} \), yielding \( \alpha \)-TCP with minor amounts of \( \beta \)-TCP and HA. In addition, the crystalline \( \alpha \)-TCP nanoparticles showed minimum particle fusion and intergrowth. However, this flame-spray method could not produce single-phase \( \alpha \)-TCP, since it contained byproducts of \( \alpha \)-CPP,\(^{69}\) \( \beta \)-TCP (39–62\%) and HA (trace),\(^{60}\) and

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**Table 1** Low-temperature synthesis of \( \alpha \)-TCP.

| Precipitation | [Ca/P] (mM) | Nominal Ca/P molar ratio | Calcination temperature (\(^\circ\text{C}\)) | Crystal phase | Author |
|---------------|-------------|--------------------------|------------------------------------------|--------------|--------|
| Precipitation | 18          | 1.67                     | 800                                      | \( 800\,^\circ\text{C} : \alpha \)-TCP + \( \beta \)-TCP (trace) | Eanes (1970)\(^{38}\) |
|               | 4.5 x 10\(^{-2}\) | 1.67                     | 700, 800                                 | \( 700\,^\circ\text{C} : \alpha \)-TCP + \( \beta \)-TCP (trace) |          |
|               | 4.5 x 10\(^{-5}\) | 1.67                     | 566, 600, 700, 800                        | \( 566\,^\circ\text{C} : \alpha \)-TCP + \( \beta \)-TCP |          |
|               | 2.5 x 10\(^{-5}\) | 1.50                     | 600, 700, 800                            | \( \alpha \)-TCP | Kanazawa et al. (1982)\(^{59}\) |
|               | 2.5 x 10\(^{-5}\) | 1.50                     | \(-4.7\times10^{-5}\)                   | \( \alpha \)-TCP | Umegaki et al. (1984)\(^{62}\) |
|               | 4.0 x 10\(^{-6}\) | 1.50                     | 700–800                                 | \( \alpha \)-TCP | Umegaki et al. (1987)\(^{65}\) |
|               | 1.2 x 10\(^{-6}\) | 0.95                     | 600–800                                 | \( 600\,^\circ\text{C} : \alpha \)-TCP (94\%) + \( \beta \)-TCP (6\%) | Someani et al. (2003)\(^{64}\) |
|               | 6.7 x 10\(^{-7}\) | 1.50                     | 800                                      | \( \alpha \)-TCP | Li et al. (2007)\(^{65}\) |
|               | 7.2 x 10\(^{-7}\) | 1.25                     | 700–800                                 | \( 775\,^\circ\text{C} : \alpha \)-TCP (99.5\%) + HA (0.5\%) | Vechskena et al. (2015)\(^{66}\) |
|               | 2.7 x 10\(^{-7}\) | 1.50                     | 600, 650                                | \( \alpha \)-TCP | Wang et al. (2017)\(^{67}\) |
| Flame-spray   | 1.0 x 10\(^{-7}\) | 2.50                     | 800, 1000                               | \( \alpha \)-TCP + \( \beta \)-TCP + HA (trace) | Uskoković et al. (2018)\(^{68}\) |
| synthesis     | \(-1.35-1.54\) | 584–674                  |                                          | \( \alpha \)-TCP + \( \alpha \)-CPP | Maciejewski et al. (2008)\(^{69}\) |
|               | \(-600–700\)  |                          |                                          | \( 600\,^\circ\text{C} : \alpha \)-TCP + \( \beta \)-TCP (0–6\%) + HA | Böhmer et al. (2008)\(^{70}\) |
|               | \(-550–900\)  |                          |                                          | \( 700\,^\circ\text{C} : \alpha \)-TCP + \( \beta \)-TCP (39–62\%) + HA |          |

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β-TCP (~15%) and HA (~16%). 61

Low-temperature synthesis of β-TCP

According to the classical solubility phase diagram for Ca(OH)2-H3PO4-H2O, 30,31 β-TCP cannot precipitate directly from aqueous solutions. Only Mg-WH can precipitate directly from aqueous solution in the presence of Mg 2+ ions. Nevertheless, several studies demonstrated that β-TCP, strictly Mg-free whitlockite (WH), 74 has been synthesized by hydrothermal methods in aqueous solution, 3,4,7-25 solvothermal methods in organic solvents, 75-77 wet-chemical methods in organic solvents, 76-78 or a microwave-assisted method. 82 Table 2 lists the low-temperature synthesis methods for β-TCP.

Toyama et al. 85 reported for the first time that ACP (Ca/P = 1.25) prepared from calcium dihydrogen phosphate monohydrate (Ca(H2PO4)2·MCPM) was hydrothermally reacted in 1 M formic acid solution at 220 °C for 3 h, which resulted in the formation of β-TCP (Ca/P = 1.48 ± 0.01) with the composition Ca2.98(HPO4)2.03(P2O7)1.96. Hydrothermal reaction of DCPA and calcite in water between 120 and 180 °C from 1.5 to 24 h provoked the formation of β-TCP, mostly as an intermediate product at the beginning of the reaction and some portion in the end-product. 72 The formation of β-TCP as an intermediate phase was also observed during hydrothermal transformation of sintered α-TCP blocks into CDHA blocks. 71 Hydrothermal synthesis of β-TCP using calcium propionate (Ca(C2H5COO)2) and triethyl phosphate ((CH3O)3PO) was also proposed by Kjellin et al. 74 In this reaction, only when the molar ratio of Ca/H2O was at 3.33 (15 mmol of water) was single-phase β-TCP formed in the reaction at 220 °C for 24 h.

Room temperature synthesis of β-TCP was achieved in methanol by Liou et al. 76 and Bow et al. 77 where increasing aging time induced the phase evolution in the following order: CaHPO4, intermediate ACP, and β-TCP. There were two types of Ca-PO4 chains in the β-TCP structure: straight and wavy chains due to structural imperfections.

A microwave-assisted synthetic method was carried out by Lau et al. 86 using calcium acetate monohydrate (Ca(C2H3O2)2·H2O) and phosphoric acid (H3PO4) in methanol solvent. The needle-like β-TCP nanoparticles were synthesized at 200 °C for 5 min. They also showed that only the combination of calcium acetate monohydrate and methanol gave rise to formation of β-TCP, probably due to the solubility of the precursor and the polarity index of the solvent.

Tao et al. 78,79 reported a novel method for synthesizing sub-micrometer hexagonal β-TCP platelets in ethylene glycol solvent. They demonstrated ACP-mediated transformation to β-TCP, in which the formation mechanism was explained by a “solid-solid phase transformation” of ACP. 79 The interfacial energy between the β-TCP crystals and the ACP was lower than that between the β-TCP crystals and the EG solvent. Hence, the free energy barrier between the β-TCP crystals and the ACP was far lower than that between the β-TCP crystals and the solution. The transformation of ACP to β-TCP, rather than ACP to

![FIGURE 2](image-url) Crystal phase after calcination of ACP at various temperatures plotted as a function of concentration of [Ca2+/[PO43−] for ACP preparation, together with other reported data. Data by Umegaki et al. 62 were plotted together with other reported data, where the filled and unfilled markers are single-phase α-TCP and a mixed phase of α-TCP, β-TCP, and/or HA, respectively.
HA, was therefore thermodynamically preferred. A later study by Galea et al.\textsuperscript{81} revealed that pure β-TCP platelets with a high aspect ratio ($=5–6$) were obtained under the following conditions: precursor concentration of 16 mM, reaction temperature of 150 °C, and reaction time longer than 2 min.

A recent study reported by Stähli et al.\textsuperscript{70} elucidated for the first time that the structure of β-TCP synthesized in EG fitted more precisely to the whitlockite structure model than to β-TCP, in which the Ca(4) sites were partly substituted by H along with the inversion of P(1)O$_4$ tetrahedra. Their result was corroborated by the presence of HPO$_4^{2–}$ absorption bands in the Fourier-transform IR spectrum. Due to the presence of the HPO$_4^{2–}$ groups, hydrogen-substituted β-TCP was thermally decomposed to hydrogen-free β-TCP (Ca/P = 1.5) and β-CPP (Ca/P = 1.0). Therefore, it seems that the β-TCP formed directly in the solvent should be called “Mg-free whitlockite (WH)”,\textsuperscript{70} rather than β-TCP, since it included HPO$_4^{2–}$ groups. The presence of HPO$_4^{2–}$ groups in β-TCP was also observed by Toyama et al.\textsuperscript{71}, Liou et al.\textsuperscript{76}, and Zhu et al.\textsuperscript{75}.

Stähli et al.\textsuperscript{70} explained the formation mechanism for β-TCP in EG solvent as follows: (1) the higher stability of β-TCP at elevated temperature, since the solubility of β-TCP decreases more strongly with increasing temperature (between 25 and 90 °C) as compared to HA, brushite, and monetite, as reported by Vereecke and Lemaitre\textsuperscript{30} and (2) the absence of either H$_2$O molecules or OH$^–$ ions in EG solvent, which prevents the precipitation of the brushite or HA phase.

The transformation of ACP to β-TCP was experimentally evident in the studies by Toyama et al.\textsuperscript{71}, Liou et al.\textsuperscript{76}, and Tao et al.\textsuperscript{75}, and also implied in the same manner by Lai et al.\textsuperscript{82} and Kjellin et al.\textsuperscript{74}. Based on the study by Zhu et al.\textsuperscript{75}, Konishi and Watanabe\textsuperscript{83} investigated the mechanism of β-TCP formation in ethylene glycol and $N,N$-dimethylformamide, in which ACP-mediated transformation to β-TCP was also observed. Consequently, it was found that β-TCP was the thermodynamically preferred precipitate under certain conditions, which were determined by parameters such as the type of chemical precursors, the precursor solubility, the solvent, the pH, the reaction temperature, the reaction pressure, and/or the reaction time.

### 4. Strategies for low temperature synthesis of three-dimensional materials

In this section, synthesis strategies for TCP, Mg-WH, and WH for applications as bioelectronics will be discussed. In general, α-TCP has been applied as a fine powder for self-setting CPCs, in which α-TCP undergoes hydrolysis to form the hardened cement comprising (CD)HA, Vechiskena et al.\textsuperscript{86} and Wang et al.\textsuperscript{87} fabricated CPC by the hydrolysis of low-temperature synthesized α-TCP particles. According to Vechiskena et al.\textsuperscript{86}, lyophilized α-TCP (containing 7–15% β-TCP) completed the hydrolysis reaction with deionized water within 6 h. This is a faster hydrolysis than for conventional α-TCP powder (synthesized at 1200 °C, ball-milled, and then heated from 500 °C and 800 °C), which completed 90% of the reaction after 10 h. Wang et al.\textsuperscript{87} showed that the low temperature synthesized α-TCP particles were

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**TABLE 2** Low-temperature synthesis of β-TCP.

| Synthesis method | Chemical reagent | Solvent | Nominal Ca/P molar ratio | Reaction temperature and time | Crystal phase | Author |
|------------------|------------------|---------|--------------------------|-------------------------------|---------------|--------|
| Hydrothermal method | Ca$_3$(PO$_4$)$_2$·$n$H$_2$O (ACP) from Ca(H$_2$PO$_4$)$_2$ | Formic acid | 1.25 | 220 °C, 3 h | β-TCP | Toyama et al. (2002)\textsuperscript{71} |
| | CaHPO$_4$, CaCO$_3$ (calcite) | Water | 1.68 | 120 – 180 °C, 1.5 – 24 h | HA, β-TCP | Zhang and Vecchio (2007)\textsuperscript{72} |
| | α-Ca$_3$(PO$_4$)$_2$ | Water vapor | 1.50 | 125, 150, 175, 200 °C, 2 – 72 h | CDHA, DCP, β-TCP | Galea et al. (2015)\textsuperscript{73} |
| Solvothermal method | CaCl$_2$, (CH$_3$CO)$_2$PO | Ethylene glycol, $N,N$-dimethylformamide | 0.24 | 200 °C, 12 h | β-TCP | Zhu et al. (2015)\textsuperscript{75} |
| Wet-chemical method | Ca(CH$_3$COO)$_2$·$x$H$_2$O, H$_2$PO$_4$, polyacrylic acid | Methanol | 1.50 | 12 h | β-TCP | Liou et al. (2004)\textsuperscript{76} |
| | Ca(μCH$_3$COO)$_2$·$x$H$_2$O, H$_2$PO$_4$ | Methanol | 1.50 | Room temperature, 8 h | β-TCP | Bow et al. (2004)\textsuperscript{77} |
| | CaCl$_2$, 2H$_2$O, Na$_2$HPO$_4$ | Ethylene glycol | 1.67 | 150 °C, 90 min | β-TCP | Tao et al. (2008)\textsuperscript{78} |
| | CaCl$_2$, Na$_2$HPO$_4$, CaC$_2$, 2H$_2$O | Ethylene glycol | 1.67 | heating to 150 °C | β-TCP | Tao et al. (2009)\textsuperscript{79} |
| | CaCl$_2$, H$_2$O, (NH$_4$)$_2$HPO$_4$, 2H$_2$O | Ethylene glycol | 1.50 | 150 °C, 1.5 h | β-TCP | Galea et al. (2013)\textsuperscript{80} |
| | CaCl$_2$, 2H$_2$O, Na$_2$HPO$_4$, 2H$_2$O | Ethylene glycol | 1.50 | 150 °C, 2 min – 24 h | β-TCP | Galea et al. (2014)\textsuperscript{81} |
| | CaCl$_2$, 2H$_2$O, Na$_2$HPO$_4$, 2H$_2$O | Ethylene glycol | 1.50 | 150 °C, 24 h | β-TCP | Stähli et al. (2016)\textsuperscript{76} |
| Microwave-assisted Ca(μCH$_3$COO)$_2$·$x$H$_2$O, H$_2$PO$_4$ | Methanol | 1.35 | 200 °C, 5 min | β-TCP | Lai et al. (2015)\textsuperscript{82} |
smaller and more reactive than those produced by conventional methods, which resulted in denser packing of CDHA particles through hydrolysis, in addition to higher flexural strength (12 MPa). However, for CPC prepared with the low-temperature synthesized a-TCP, research data are not sufficient to analyze its potential. Therefore, understanding of ACP and establishment of its optimal synthesis method are necessary to apply it to the low-temperature synthesis of a-TCP for CPC.

A drawback of CP-based bioceramics is their brittleness, preventing their application as load-bearing bone substitutes. Motivated by na-cre-inspired material comprising organic-inorganic building blocks reported by Tang et al., 84 Galea et al.,70,80,81 proposed that hexagonal β-TCP platelets with high aspect ratios are a potential candidate for application as ceramic-polymer composites. The CP particles would provide strength and stiffness to the composites, whereas the organic polymer would impart toughness. Moreover, Stähli et al.70 reported that β-TCP platelets with an aspect ratio of 1 may enhance the flowability of CPC, due to their non-agglomerating properties. However, no reports regarding biomedical applications of β-TCP platelets have been published to date.

Mg-WH also has not been applied to artificial synthetic bone substitutes, although it showed in vivo bone regeneration in calvarial defects in a rat model with intermediate resorbability when compared to that of HA and β-TCP.88 Mg-WH appears to be inherently an osteoconductive material, as it is evident that it occurs naturally in the human body.86–91 However, thermally unstable Mg-WH decomposes to β-TCP and β-CPP,86 which would make the Mg-WH particles impossible to sinter at high temperature. As such, three-dimensional shapes of Mg-WH ceramics such as dense, porous, or granular ones could not be produced at low temperature. This is one of the reasons why Mg-WH is not applicable as a bone substitute.

Calcium sulfate hemihydrate (CaSO₄·0.5H₂O) behaves like a self-setting CPC and hardens to form a three-dimensional gypsum (CaSO₄·2H₂O) structure. According to Batista et al.,32 the porous scaffold-like gypsum hydrothermally transforms to a biphasic product of 63 wt.% HA and 37 wt.% β-TCP at 120 °C for 6 h. However, Suzuki et al.93 and Nomura et al.94 showed discrepant results, in which gypsum transformed to HA and DCPA (trace) at 100 °C after 48 h and HA at 200 °C after 6 h, respectively, although there were some differences in experimental conditions such as the solvent and pH. Further study will be required to clarify why the gypsum transformed to β-TCP in the study by Batista et al.;32 however, transformation of gypsum to β-TCP at low temperature may be one strategy for fabricating three-dimensional materials. Moreover, as shown by Tas,32 transformation of DCPD crystals to single-phase Mg-WH in a Mg²⁺ solution may also be a useful idea in that three-dimensional brushite cement consisting of DCPA phase could be used for transformation to Mg-WH.

Marine biominerals such as those found in starfish, coral sand, sea urchins, and foraminifera, are naturally occurring three-dimensional materials, mostly consisting of calcite or aragonite. Several studies showed that marine biominerals hydrothermally transformed to Mg-WH.95–100 In terms of recycling of marine resources, these three-dimensional marine biominerals such as dead coral are a potential alternative for artificial bone substitutes by transforming them to Mg-WH.

A series of studies on melt-quenched borate glasses by Day et al.101–107 demonstrated that they could transform to HA in aqueous solutions such as phosphate buffered saline (PBS), simulated body fluid (SBF), and phosphate solution (K₂HPO₄). It is considered that due to the lower chemical durability of glass-forming networks of borate glass as compared to silicate glass, borate glass degrades faster and converts to HA. Recently, sol-gel-derived borate glass was fabricated at low temperature (~40 °C) by Lepry and Nazhat.98 The borate glass powders also converted to porous carbonate apatite within 6 h in SBF. Unlike melt-quenched glass, an advantage of the sol-gel method is that it enables the synthesis of three-dimensional materials at low temperature. On the basis of their study, sol-gel-derived borate glass would also be useful as a three-dimensional starting material for transformation to Mg-WH or WH at low temperature, although there is difficulty in finding reaction conditions that promote formation of Mg-WH or WH.

5. Conclusions

The present article summarizes low-temperature synthesis methods for TCP. Although still under development, novel low-temperature synthesis processes allow a breakthrough beyond conventional high-temperature synthetic techniques. However, neither the synthesis processes for α-TCP or WH is sufficient and further study is necessary. For example, it is necessary to find optimal synthesis conditions for ACP in order to produce α-TCP and for WH in order to determine the formation mechanism for it. Clinical applications of α-TCP, Mg-WH, and WH have also not been achieved. Thus, based on previously published data, novel ideas to synthesize three-dimensional shapes of Mg-WH or WH using gypsum, brushite cement, marine biominerals, or sol-gel borate glass as starting materials have been proposed. Low-temperature synthesis would be a potential strategy for the design of α-TCP, Mg-WH, and WH-based bone repairing bioceramics.
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