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Tricalcium phosphate powder: Preparation, characterization and compaction abilities

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Abstract: In this work, we characterize tricalcium phosphate powders $Ca_9(HPO_4)(PO_4)_5(OH)$ resulting from a reaction between calcium hydroxide and orthophosphoric acid at room temperature, without pH adjustment and in absence of ionic impurities. The prepared powder has an atomic ratio Ca/P of 1.512 ± 0.005. The real density is 2.68 ± 0.02 g/cm^3 and the specific surface area is 80 ± 02 m^2/g. During compression, the microstructure of Ca-deficient apatite powder with the presence of HPO_4 groups seems to support the cohesion between particles. The transmission ratio is 90%, the transfer ratio is 41.8 and the ratio of the die-wall friction is 0.22. These results show that apatitic tricalcium powder gives a good aptitude to the compaction which leads to a good tensile strength (0.79 MPa). The heat treatment of the prepared powder shows the precise temperature for the formation of pyrophosphate, β-TCP and α-TCPa phases. The purity and aptitude to compaction of the prepared powders are very promising for pharmaceutical and medical applications.

Keywords: Tricalcium phosphate; Neutralization method; Compaction; Thermal treatment.

Introduction

Tricalcium phosphate: $Ca_9(HPO_4)(PO_4)_5(OH)$: (TCPa)) and $Ca_3(PO_4)_2$ (α/β-TCP) with molar ratio Ca/P=1.50 are commonly used in pharmaceutical and medical field [1-3]. Tricalcium phosphates are used in pharmaceutical industry as excipient in the formulation of pharmaceutical tablets. In the medical field, tricalcium phosphate was used to satisfy patient's therapeutical needs [4]. It is used as implants with a shape adapted to the bone defect [4]. TCPa and α/β- TCP are widely used as precursor in the preparation of biomaterials [5]. These products must comply with the regulations of use. It is therefore necessary to control their physical and chemical properties. α and β-TCP, cannot be precipitated from aqueous solutions but they are obtained by thermal treatment of the TCPa. A specific difficulty in this treatment is the high variability of the powder composition after calcinations. Pure α/β- TCP is formed after calcinations of apatitic tricalcium phosphate with Ca/P= 1.50. For Ca/P values higher than 1.50, HAP is formed as a second phase. For Ca/P values lower than 1.50 another second phase appears: Calcium pyrophosphate $Ca_2P_2O_7$. The purity of calcined tricalcium phosphate depends strongly on the chemical composition and the method of preparation of apatitic tricalcium phosphate (TCPa). This compound is usually prepared by precipitation in aqueous medium at high temperature (70-85°C) and basic pH (8-11) in the presence of ionic impurities, such as NO_3^{2-}, NH_4^+, Na^+, Cl^- etc [6,7]. The presence of these impurities may affect the granular properties and the shaping of the prepared powders.

Materials and methods

Synthesis of the powder

100g of apatitic tricalcium phosphate powders are prepared by reaction of calcium hydroxide and orthophosphoric acid according to the method described by Akao et al.[8] with some modifications. The orthophosphoric acid solution (1mol/l) is added to the $Ca(OH)_2$ suspension (0.5 mol/l) using an automatic titration (100 ml/min) and vigorous stirring (500T/min). The Ca/P atomic ratio is equal to 1.52 and the used reagents have analytical grade. The precipitation is performed at room temperature (25°C) without pH adjustment. The obtained precipitate, with final pH equal to 5.6, is carried to maturation during 12 hours. The product is filtered, dried at 105°C during 24 hours, ground in a mortar and sieved to obtain particle size lower than 125 µm.

Characterization of powders

The physical and chemical analysis are carried out on the dried precipitate at 105°C and on the calcined powder at 1000°C for 15 hours according to norms [9].

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The formed phases are identified by the atomic ratio Ca/P, determined by infrared spectroscopy (Perkin-Elmer FTIR 1600), and by X-ray diffraction (Counter D500, λ_{Cu}=1.5408 Å). The ratio of calcium and phosphorus is determined by an atomic emission spectrophotometer with argon plasma and inductive coupling (ICP-AES). Laser diffraction is used to analyze particle size on the Mastersizer 2000 (from Malvern Instruments Ltd.). The true density ((ρ_{true} g/cm^3) is determined using a helium pycnometer (Accupyc 1330, Micrometrics Instruments). The Morphology of granules is observed using a Scanning Electron Microscope.

Powder compaction

Tablets of 0.4±0.01 g of powder are prepared by compaction using a reciprocating press (Frogerais OA). The powder is poured into the die and compacted at 70 MPa. Once the tablet ejected, its mass is measured with an electronic balance (CP 224S — Sartorius Germany) and its dimensions are measured with digital micrometer (Mitutoyo). The apparent and relative densities are recorded. The diametrical crushing load is also measured with the Erweka TBH 30 apparatus.

Characterization of the compaction

In the compaction process, two ratios are classically used to compare and analyze the behavior of the powders. The transmission ratio (1), defined as the ratio of the transmitted pressure (σb) to the bottom punch over the applied pressure (σu) on the upper punch. This ratio measures the capacity of powder to transmit the load from the top to the bottom of the powder bed. The transfer ratio (2) represents the ratio of the radial pressure (σr) over the applied pressure (σu) [10].

$$tr = \sigma_b / \sigma_u \quad (1)$$

$$\alpha = \sigma_r / \sigma_u \quad (2)$$

During the compaction, the die wall friction is the dominant property that controls the density distribution and the load transmission over the powder bed. Assuming the Coulomb friction and adopting the ‘method of differential slices’ [11], the die-wall friction may be obtained as follows:

$$\mu = \ln(\sigma_b/\sigma_u)/(-4xH/D) \quad (3)$$

Results and discussion

Characterization of the prepared powder

The result of Infrared Spectrometry (Fig.1) shows that the prepared powder is apatitic tricalcium phosphate: ($Ca_9(HPO_4)(PO_4)_5(OH)$) (TCPa) which was identified by the vibration bands of PO_4^{3-} groups: ν_2 PO_4 (474 cm^{-1}), ν_4 PO_4 (571-601 cm^{-1}), ν_1 PO_4 (962 cm^{-1}) and ν_3 PO_4 (1026-1107 cm^{-1}). The band at 875 cm^{-1} could be attributed to P-O(H) stretching mode of hydrogenophosphate groups. The bands at 630 and 3560 cm^{-1} are characteristic of OH groups. The long maturation times (12h) leads to the formation of stable and a well-defined structure of the prepared TCP.

The Fourier Transform Infrared Spectroscopy of the powder calcined at 1000°C for 15 hours (Fig. 2) shows several absorption bands including those with 552, 594, 606, 945.972, 1025, 1042, 1120 cm^{-1} that are attributed to the vibration of PO_4^{3-} groups in the β-TCP structure. This analysis shows also the absence of characteristic bands of pyrophosphate ($P_2O_7^{2-}$) groups (1200-1100 cm^{-1}) and OH^- ions attributed to hydroxyapatite phase (3560 cm^{-1} and 630 cm^{-1}). The calcination of the TCPa to 1000 °C leads to the formation of pure β-TCP phase.

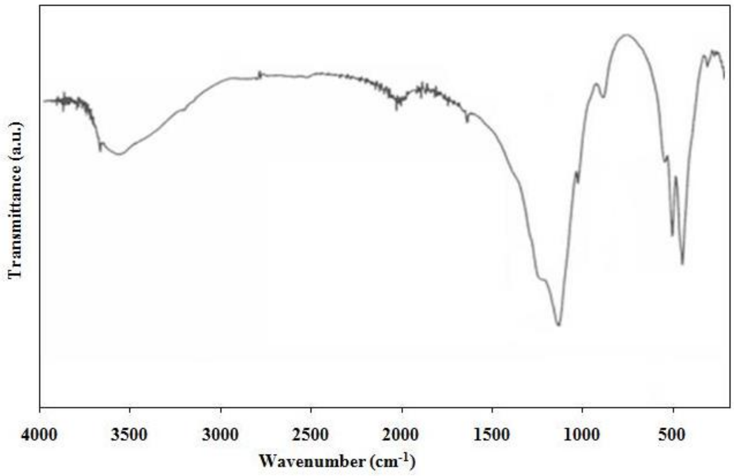


Figure 1. Infrared absorption spectrum of prepared powder dried at 105 °C

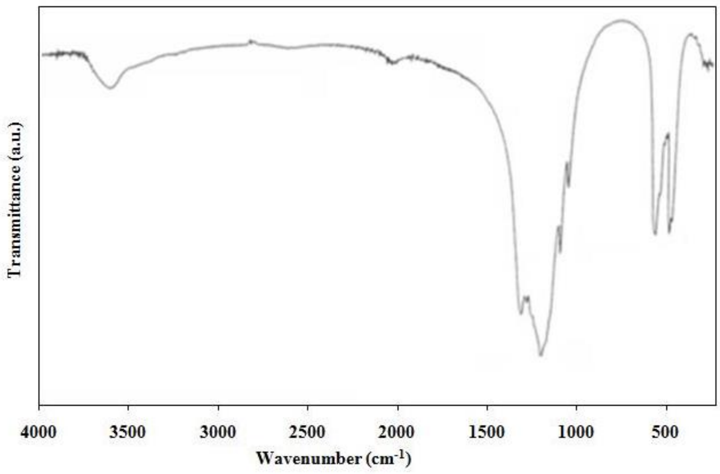


Figure 2. Infrared absorption spectrum of tricalcium phosphate calcined at 1000 °C

The formation of pure β-TCP phase is confirmed by X-ray diffraction analysis (Fig. 3). The analysis indicates the presence of well crystallized β-TCP phase. The diffraction pattern is in agreement with the JCPDS file (file N°: 9-169). The structural refinement shows that the volume and lattice parameters of prepared β-TCP are in agreement with the theoretical values of β-TCP$_{the}$ (Table 1).

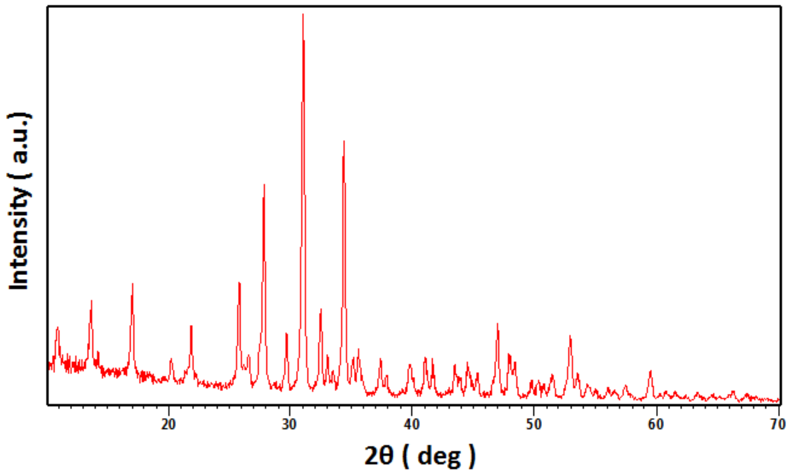


Figure 3. XRD pattern of TCPa calcined at 1000 °C for 15 hours

Table 1. Volume and lattice parameters of prepared β-TCP and β-TCP$_{the}$

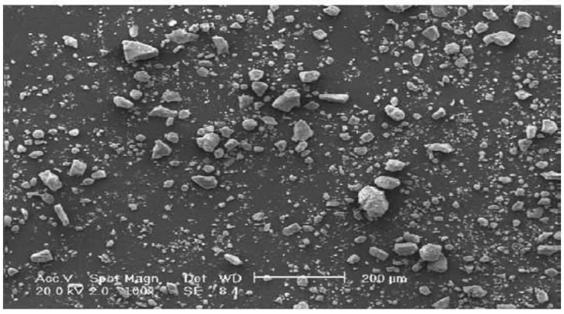
Sample	**β-TCP**	**β -TCP$_{the}$**
a (Å)=b (Å)	10.417	10.435
c (Å)	37.329	37.403
α(°)=β(°)	90.000	90.000
γ(°)	120.00	120.000
Space Group	R3C	R3C
V(Å^3)	3508.16	3527.28

The chemical analysis of Ca and P of the prepared β-TCP are rigorously consistent with the results of the FTIR and XRD, the calculated molar ratio of Ca/P is 1.512 ± 0.005. This molar ratio shows a slight excess of calcium compared to the theoretical value β-TCP$_{the}$ (Ca/P = 1.50). This can be explained by the effect of the concentration selected for the starting reactants (Ca/P= 1.52).

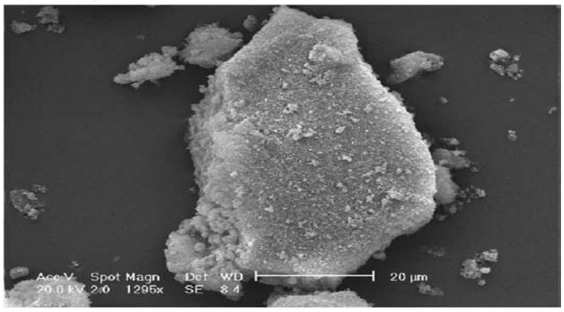
Calcium excess leads to the absence of pyrophosphate ions and the presence of traces of HAP that are not detected by FTIR and DRX of calcined powder. The presence of traces of HAP is favorable for the biological properties of the prepared materials.

Scanning Electron Microscopy images of the prepared powder (Fig. 4) show poly-dispersed population (a), irregular granule shape, composed of small spherical particle agglomerates (b), and a rough surface (c). The typical agglomerate size of these powders is 91.2±1.0 µm (Table 3). The real density is 2.68±0.02 g/cm^3 and the apparent density is 0,403 g/cm^3. The specific surface area of the prepared powder is 80±02 m^2/g.

(a) 200 µm



(b) 20 µm



(c) 1 µm

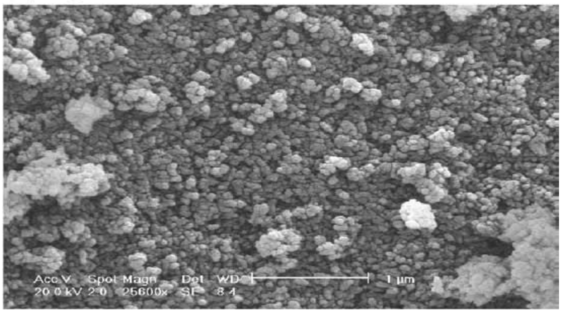


Figure 4. SEM micrographs of the synthesized powder
(a) poly-dispersed population, (b) granules of the powder, (c) typical surface morphology.

Table 3. Characteristics of synthesis granules

Ca/P molar ratio	**Mean particle size (µm)**	**True density g/cm^3**	**Bulk density g/cm^3**	**Specific surface area (S_{BET}) m^2/g**
1.512±0,005	91.2±0 .1	2.68±0.02	0.403	80±02

Thermal analysis curves (ATD / TG) are shown in Fig. 5. The mass loss and the associated thermal effects in temperatures below 300 °C are mainly the consequence of the departure of the water associated with the powder.

Between 300°C and 700°C, part of the weight loss is due to the condensation of hydrogenophosphate ions to pyrophosphate ions which precedes the decomposition of the apatite according to a mechanism similar to that proposed by Mortier and al. [12].

$$2Ca_9(HPO_4)(PO_4)_5(OH)$$

$$446.60°C \quad \downarrow \quad 2HPO_4^{2-} \longrightarrow P_2O_7^{4-} + H_2O$$

$$2Ca_9(P_2O_7)_{0,5}(PO_4)_5(OH) + H_2O$$

At 748.56°C, the mass loss and the associated endothermic peak correspond to a second reaction involving the transformation of the pyrophosphates ions $P_2O_7^{4-}$ according to the following reaction:

$$Ca_9(P_2O_7)_{0,5}(PO_4)_5(OH)$$

$$748.56°C \quad \downarrow \quad P_2O_7^{4-} + 2OH^- \longrightarrow 2PO_4^{3-} + H_2O$$

$$3Ca_3(PO_4)_2 + 0,5H_2O$$

The observed loss of mass is significant of departure of water that accompanies the reaction of transition at 748.56°C - 909.25°C. This departure is due to a reaction between pyrophosphate group and hydroxyl groups leading to the formation of β-TCP. The crystallographic parameters of this phase are shown in Table 1.

Figure 5 indicates also that at high temperatures (after 909.25°C), structural rearrangements may lead to the endothermic peak at 1167.06°C associated with the allotropic transformation of ß to α tricalcium phosphate.

Indeed, according to Destainville et al. the transformation of the β-TCP in α-TCP occurs at 1150°C [13]. Ryu et al. [14] have also shown that the β-TCP is transformed in α-TCP phase when it is treated above 1200°C. The transformation temperature of the prepared TCP is within the range found in the literature.

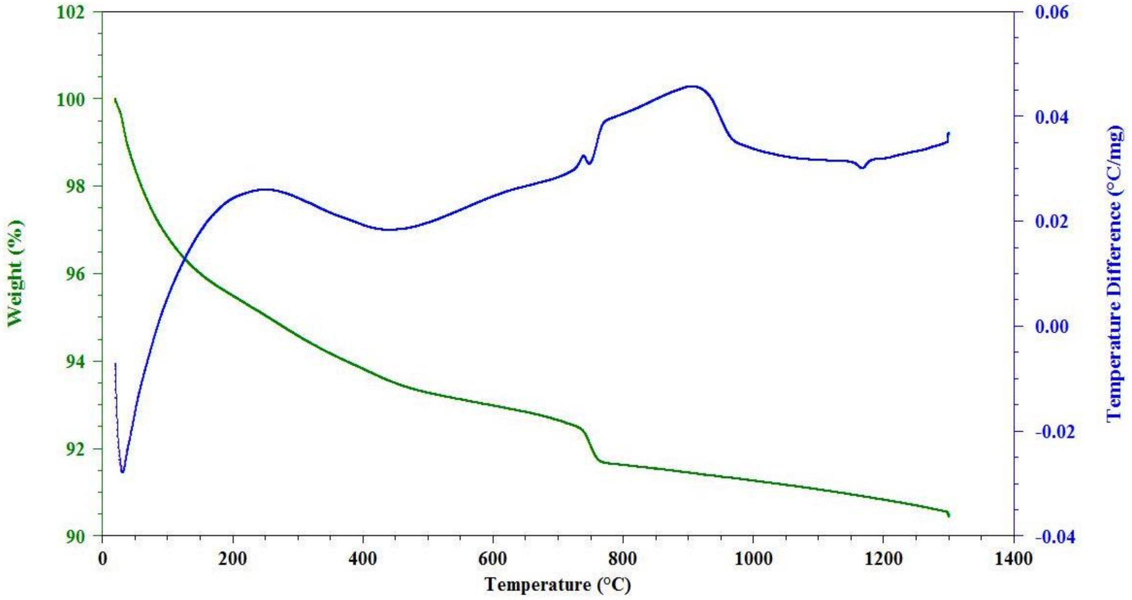


Figure 5. ATD/ATG of the prepared powder.

The values of the transmission ratio, the transfer ratio and the die-wall friction are reported in Table 4. The transmission ratio is 90%, the transfer ratio is 41.8%. The ratio characterizing the die-wall friction gave complementary information on the behavior of the powders, this ratio is 0.22. These results show that apatitic tricalcium powder gives a good aptitude to the compaction which leads to a better tensile strength (0.79±0.02 MPa).

We can conclude that the prepared compact exhibits good mechanical properties. Indeed, the morphology of the granules, the microstructure of Ca-deficient apatite and the HPO_4 groups seem to support the cohesion and connection between particles during the compaction. The prepared granules have compressibility characteristics superior than other calcium phosphates as hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$,) prepared at the same conditions (hydroxyapatite with molar Ratio Ca/P = 1.676 has tensile strength of 0.55±0.03 MPa); Therefore, the prepared powder can be favorably used as excipient in the formulation of pharmaceutical tablets or as precursor in the preparation of biomaterials.

Table 4. Mechanical properties of the compact.

Relative density	Transmission ratio	Transfer ratio	Die-Wall friction	Tensile strength (MPa)
0.4905	90	41.8	0.22	0.79±0.02

Conclusion

Tricalcium phosphate ($Ca_9(HPO_4)(PO_4)_5(OH)$: TCPa) with molar ratio Ca/P = 1.512 ± 0.005 is prepared by neutralization method at room temperature without pH adjustment. The prepared powder offers higher surface area with improved reactivity, greater drug loading capacity and interaction with biological environment. During compression, the granular properties of Ca-deficient apatite powder and the presence of HPO_4^{2-} groups seem to support the cohesion between particles. The transmission ratio, the transfer ratio and the ratio characterizing the die-wall friction lead to a better tensile strength. The heat treatment of the powder leads to the condensation of hydrogenophosphate ions to pyrophosphate at 446.60°C, the transformation of TCP-a to β-TCP at 748.56°C and the transformation of ß to α TCP at 1167.06 °C. The properties of the prepared products, such composition and microstructure, aptitude to compaction and thermal behavior make them interesting candidates for further applications in both pharmaceutical industry and medical field.

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