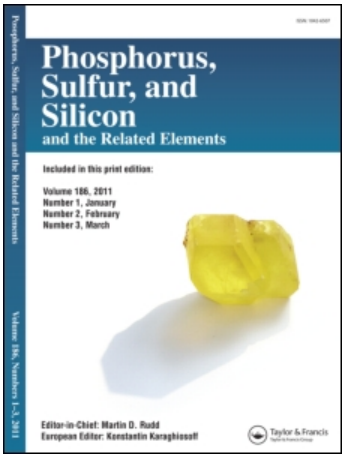

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Central Composite Design and Optimization by Response Analysis of β-Tricalcium Phosphate Elaboration

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Elaboration of β-tricalcium Phosphate (β-TCP) was studied using a two-block central composite design including 4 factors. Analysis of the response allowed the definition of one set of experimental conditions in which β-TCP was obtained after powder calcination at 900°C.

Keywords β-Tricalcium phosphate; blocked central composite design; elaboration; optimization

β-tricalcium phosphate (β-TCP), having the formula β-$Ca_3(PO_4)_2$, cannot be synthesized directly in aqueous solution.[1–5] The compound that may precipitate is the apatitic Tricalcium phosphate (TCP), $Ca_9(HPO_4)(PO_4)_5(OH)$, which transforms into β-TCP by heating above 750°C.[6,7]

$$Ca_9(HPO_4)(PO_4)_5(OH) \xrightarrow{T \geq 750^\circ C} 3\,\beta = Ca_3(PO_4)_2 + \overrightarrow{H_2O} \qquad (1)$$

Several routes of synthesis were proposed to prepare TCP.[1–7] It was obtained by the hydrolysis of brushite $CaHPO_4, 2H_2O$ (DCPD)[1] and by the double decomposition method from calcium chlorure, $CaCl_2$, and disodic phosphate, $Na_2HPO_2^4$, and from calcium nitrate, $Ca(NO_3)_2$, and ammonium phosphate, $(NH_4)_2HPO_4$.[3–7]

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In this work, calcium carbonate and orthophosphoric acid were selected as calcium and phosphorus precursors for the precipitation of the calcium phosphate. The difficulty with most of the conventional precipitation methods used is in exactly obtaining a solid with a given Ca/P ratio.[8–10]

In order to avoid this difficulty, we performed a systematic study of TCP precipitation by considering the effect of 4 experimental parameters: pH, the concentration of the acidified calcium carbonate solution ($[Ca^{2+}]$), the temperature (T), and the precipitation duration of TCP (D), with fixing the atomic ratio Ca/P of the reagents at 1.50 and stirring to 600 turns/min.

A schematic diagram of the experimental apparatus is shown in Figure 1. The first stage of the synthesis consists in preparing the solutions:

The phosphorus solution is prepared by the neutralization of the orthophosphoric acid with ammonia.

The calcium solution is prepared by the acid attack of calcium carbonate according to the following reaction:

$$CaCO_3 + 2HNO_3 \longrightarrow Ca(NO_3)_2 + \overset{\nearrow}{CO_2} + H_2O \qquad (2)$$

The second stage of the synthesis consists in heating the reactor containing the calcium solution to the synthesis temperature. The

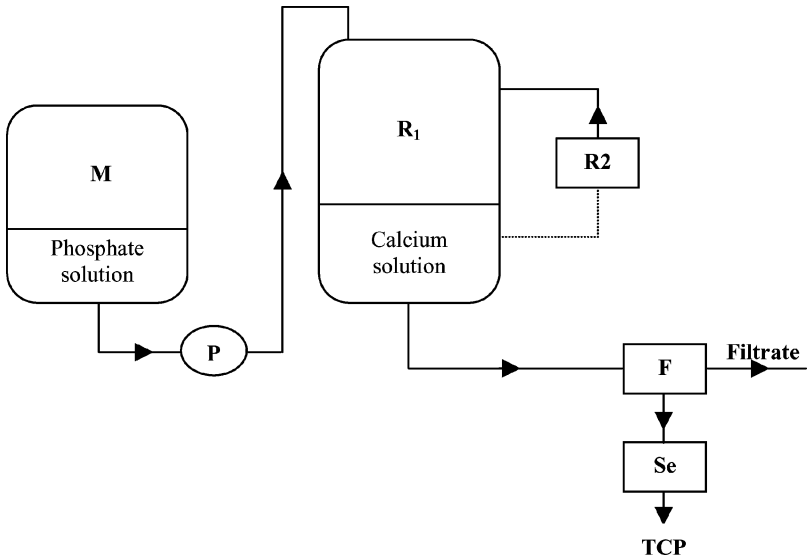

FIGURE 1 Process of the synthesis of tricalcium phosphate apatitic. R_1: Reactor; R_2: pH-stat; P: Pump, M: Mixer, F: Filtration system; Se: Dryer.

TABLE I Study Field and Coded Factors

		Levels X_i				
Factor	Unit	−2	−1	0	1	2
$x_1 = pH$	/	5	5.5	6	6.5	7
$x_2 = [Ca^{2+}]$	mol/l	0.8	1	1.2	1.4	1.6
$x_3 = T$	°C	50	55	60	65	70
$x_4 = D$	h	2	3	4	5	6

The coded values $X_j = \pm 1$ are obtained by the equation $X_j = (x_j - (\bar{x}_j)/\Delta x$.

phosphorus solution, heated to the same temperature, is introduced into the reactor under a controlled flow. The reacting medium is then kept stirring for the chosen length of time. The synthesis pH and temperature were automatically controlled. Depending on the parameter effects, the following reaction can take place:

$$9\ Ca(NO_3)_2 + 6(NH_4)_2HPO_4 + 6NH_4OH \longrightarrow Ca_9(HPO_4)(PO_4)_5(OH) + 18NH_4NO_3 + 5H_2O \quad (3)$$

At fixed times, samples were withdrawn by filtration, dried at 80°C, and heated to 900°C. They were then examined by chemical analysis (determination of Ca/P atomic ratio) by X-ray diffraction and FTIR.

This study was carried out using an orthogonally blocked central composite design,[11] which was also rotatable. In this design, the factors are the experimental parameters previously considered: pH, the concentration of the calcium carbonate solution, the temperature, and the duration of precipitation (D). The values used in this design and the levels X_i of the 4 factors are indicated in Table I.

The 30 experiments were done in the two following blocks: the first block with a complete factorial design 2^4 with 4 center points, and the second block according to an axial design with the distance to center α equal to 2 and with 2 center points. The values of the factors used in this design and the response (atomic ratio Ca/P) are reported in Table II.

In experimental design, the equation of estimated responses ($\hat{y}$) can be written as follows:

$$\hat{y} = b_0 + \sum_{j=1}^{4} b_j X_j + \sum_{j=1}^{4} \sum_{j'=1}^{4} \sum_{j' \neq j} b_{jj'} X_j X_{j'} + \sum_{j=1}^{4} b_{jj} X_j^2 \quad (4)$$

Using JMP,[12] we found the values reported in Table II.

The 15 coefficients are easily calculated by the least squares method (Table III). So, the estimated response can be written as follows:

TABLE II Experimental Design and Results

Order		Coded units of variable				($Ca/P)_{whs.exp}$	$(Ca/P)_{whs.cal}$	Residues
Logical	Actual	X_1	X_2	X_3	X_4	y_{exp}	$\hat{y}$	$e_i 10^3$
01	30	−1	−1	−1	−1	1.450	1.451	−01
02	22	−1	−1	−1	1	1.430	1.432	−02
03	21	−1	−1	1	−1	1.460	1.456	04
04	26	−1	−1	1	1	1.470	1.472	−02
05	01	−1	1	−1	−1	1.460	1.464	−04
06	05	−1	1	−1	1	1.440	1.437	03
07	29	−1	1	1	−1	1.445	1.444	01
08	04	−1	1	1	1	1.449	1.452	−03
09	27	1	−1	−1	−1	1.466	1.464	02
10	25	1	−1	−1	1	1.467	1.467	00
11	20	1	−1	1	−1	1.486	1.489	−03
12	13	1	−1	1	1	1.530	1.527	03
13	10	1	1	−1	−1	1.512	1.509	03
14	08	1	1	−1	1	1.500	1.504	−04
15	18	1	1	1	−1	1.510	1.509	01
16	23	1	1	1	1	1.539	1.538	01
17	24	0	0	0	0	1.487	1.488	−01
18	31	0	0	0	0	1.489	1.488	01
19	12	0	0	0	0	1.486	1.488	−02
20	03	0	0	0	0	1.490	1.488	02
21	06	−2	0	0	0	1.450	1.448	02
22	28	2	0	0	0	1.547	1.548	−01
23	15	0	−2	0	0	1.464	1.464	00
24	19	0	2	0	0	1.490	1.489	01
25	07	0	0	−2	0	1.464	1.462	02
26	11	0	0	2	0	1.501	1.502	−01
27	16	0	0	0	−2	1.440	1.441	−01
28	17	0	0	0	2	1.454	1.452	02
29	09	0	0	0	0	1.487	1.488	−01
30	14	0	0	0	0	1.488	1.488	00

$$\widehat{(Ca/P)}_{whs} \times 10^3 + 1488 - 25X_1 + \cdots + 3X_4 + 8X_1X_2 + \cdots + 9X_3X_4 + 3X_1^2 + \cdots - 10X_4^2 \quad (5)$$

From this equation, it is possible to compute estimated values ($\hat{y}$) and the corresponding residuals $e_i = y_i - \hat{y}_i$ (Table II). An estimate of the variance of the experimental error (s_r^2) was obtained by dividing the residual sum of squares Σe_i^2 (Table II) by ν (number of degrees of freedom = number of experiments minus number in the model, i.e., $30 - 15 = 15$) (Table IV):

$$s_r^2 = (0.00013108)/15 = 9.10^{-6} \quad (6)$$

TABLE III Estimated Coefficients of the Model and Their Significances

	Coefficient (b_u)	Degree of freedom	Sum of squares	F_{exp} value	Significance
b_0	1.4878333	1	–	–	–
b_1	0.0250000	1	0.01500000	1716.4650	S
b_2	0.0061667	1	0.00091267	0104.4374	S
b_3	0.0099167	1	0.00236017	0270.0763	S
b_4	0.0026667	1	0.00017067	0019.5296	S
b_{12}	0.0080000	1	0.00102400	0117.1774	S
b_{13}	0.0047500	1	0.00036100	0041.3096	S
b_{14}	0.0055000	1	0.00048400	0055.3846	S
b_{23}	−0.0063750	1	0.00065025	0074.4088	S
b_{24}	−0.0021250	1	0.00007225	0008.2676	NS
b_{34}	0.0086250	1	0.00119025	0136.2015	S
b_{11}	0.0026042	1	0.00018601	0021.2855	S
b_{22}	−0.0027710	1	0.00021058	0024.0973	S
b_{33}	−0.0013960	1	0.00005344	0006.1152	NS
b_{44}	−0.0102710	1	0.00289344	0331.0994	S

S: Significant at a level 1% ($F_{0.01}(1.15) = 8.68$).[11]
NS: No significant.

The experimental value of the F distribution is obtained by dividing the mean square of the coefficient $b_u(MS_u)$ by the variance of the experimental error (s_r^2):

$$F_{exp} = MS_u/s_r^2 \tag{7}$$

The mean square estimate of the coefficients (MS_u) is obtained by dividing the sum of squares estimates of the coefficients (SS_u) by their degree of freedom ($\nu_u = 1$):

$$MS_u = SS_u/\nu_u \tag{8}$$

TABLE IV Regression Variance Analysis for the Model

Source of variation	Sum of squares	Degree of freedom	Mean square	F_{exp}[a]	S[b]
Regression	0.02567788	14	0.001834	209.8819	[c]
Residue	0.00013108	15	0.000009	–	–
Sum	0.02580897	29	–	–	–

[a] F_{exp}: Snedecor factor.
[b] Significance test.
[c] Significant at a level 0.1% $F_{0.001}(14.15) \approx 5.68$.[11]

The sum of squares estimates of the coefficients (SS_u) is obtained by multiplying the square of the coefficient (b_u) by the sum of squares of X_u values.

The significance of the effects can be estimated by comparing the F distribution of the experimental values to a critical value ($F_{0.01}(1.15) = 8{,}68$).[11] According to the results shown in Table III. It appears that only the interactions T-T and $[Ca^{2+}]$-D are no significants.

The estimated response is then conveniently written as follows:

$$\begin{aligned}(Ca/P)_{whs} \times 10^3 &= 1488 + 25(\pm 0.6)X_1 + 6(\pm 0.6)X_2 + 10(\pm 0.6)X_3 + 3(\pm 0.6)X_4 \\ &+ 8(\pm 0.7)X_1X_2 + 5(\pm 0.7)X_1X_3 - 6(\pm 0.7)X_2X_3 + 6(\pm 0.7)X_1X_4 \\ &+ 9(\pm 0.7)X_3X_4 + 3(\pm 0.5)X_1^2 - 3(\pm 0.5)X_2^2 - 10(\pm 0.5)X_4^2 \end{aligned} \quad (9)$$

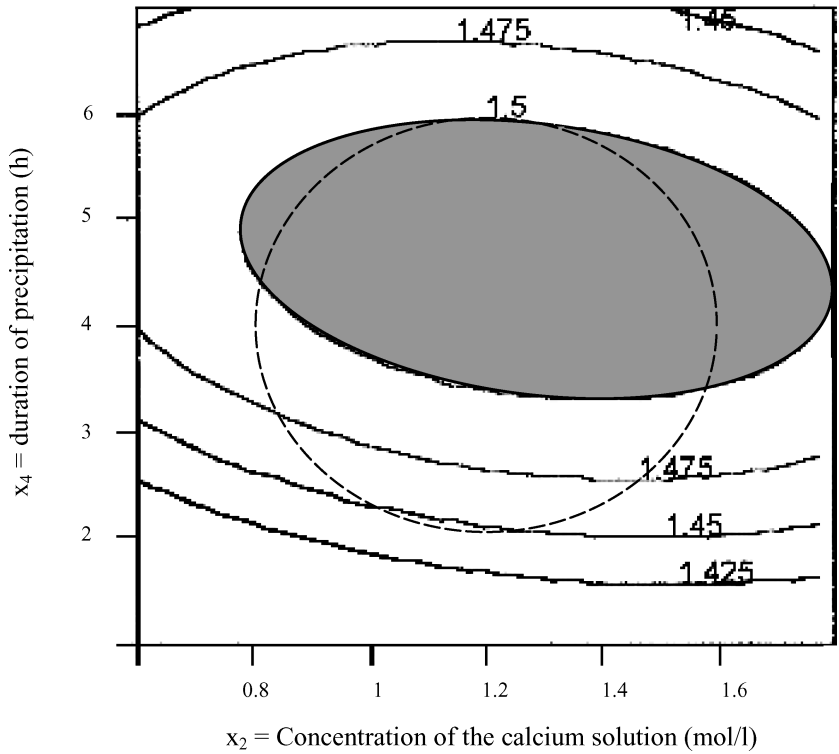

FIGURE 2 Level contours for Ca/P with $x_1 = pH = 6.25$; $x_3 = T = 65°C$. Broken line shows the experimental range.

The numbers in parentheses are the standard errors of the coefficients which we obtained.

The investigation of equation (9) showed that if $X_1 = 0.5, X_2 = 0, X_3 = 1$ and $X_4 = -0.5$, $(Ca/P)_{whs} = 1.504 \approx 1.500$. This value corresponds to Ca/P of β-TCP.[1–7] The experimental checking in this point, i.e., under the conditions, such as pH = 6.25, $[Ca^{2+}] = 1.2$ mol/l, T = 65°C and D = 3 h 30 mn with $(Ca/P)_{reagents} = 1.50$, and Ag = 600 turns/mn, confirms this result.

A geometrical representation of this response, which is dependent on the duration of precipitation and the calcium concentration of $CaCO_3$ solution for constant values of the pH and the temperature, is indicated in Figure 2. In the experimental range, when the duration of precipitation and the calcium concentration of $CaCO_3$ solution increase together or when the duration of precipitation increases and the calcium concentration of $CaCO_3$ solution remains unchanged, the Ca/P ratio of the precipitate increases up to 1.50 (grey area).

NOMENCLATURE

$(Ca/P)_{whs}$	Ca/P ratio of washed heated solid
b_u	coefficient of the polynomial model
e_i	residual of the i^{th} experiment $e_i = y_i - \hat{y}_i$
s_r^2	residual variance, $s_r^2 = \Sigma\, e_i^2/n$
MS_u	mean square of the coefficient b_u
SS_u	sum of squares of coefficients
x_j	natural variable x for element j, and $\bar{x}_j$ its mean, i.e., either pH, $[Ca^{2+}]$, T and D
X_j	coded variable x for element j
y_i	measured response for the i^{th} experiment
$\hat{y}_i$	calculated response for the i^{th} experiment
α	distance from the center of the design
Δx	difference between x and $\bar{x}$
ν	number of degrees of freedom = number of experiments − number of coefficients in the model

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