

## Investigation of HA Cement Preparation and Properties By Using Central Composite Design

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**Abstract.** The goal of the present work was to investigate the effects of several cement preparation parameters on setting and hardening reaction mechanisms and hydroxyapatite (HA) cement properties. A central composite experimental design (CCD) was conducted by choosing particle size, solid to liquid ratio, pH, seed concentration and buffer concentration as design parameters along with compressive strength and setting time being the responses. Tetracalcium phosphate (TTCP) powders were prepared by heat treatment of calcium and phosphate source mixtures in the 1200-1400°C temperature range followed by quenching to room temperature in a dessicator. The second phase used in the formulations (brushite) was prepared by aqueous chemical methods. A series of HA pastes/cements were prepared by changing the above mentioned design parameters. Cements were characterized by a standardized setting time test, mechanical testing machine, SEM and XRD. HA cements with the desired properties can be formulated by using CCD in which the responses were expressed by a second order polynomial equation of the parameters. Compressive strengths for the majority of HA cements were determined to be in the 100-160 MPa range which is significantly higher than those reported in the literature.

### Introduction

Calcium phosphate cements (CPCs) have been increasingly used for bone repair and regeneration of defects since their discovery in 1983[1]. Moldable CPC paste self setting in vivo offer significant advantages in several clinical applications. CPCs may also have great potential in drug delivery. CPCs are obtained by mixing one or several calcium phosphate phases with an aqueous solution forming a paste which sets and then hardens in minutes. The nature of these setting and hardening reaction mechanisms are still under investigation. The dissolution rates of the components and the nucleation/growth rate of the cement phase have a determining role in establishing the cement properties. The commonly known most important parameters used for controlling the rate of these reactions are solid to liquid ratio, characteristics of the powder phases, pH and composition of the liquid phase, HA seed amount, particle sizes/ratios of the solid phases, use of inhibitors, etc. [2,3].

The ability to control these reaction rates is essential in providing sufficient time to the surgeon, necessary viscosity and hardened strength for the success of the application. The main goal of a significantly large number of CPC formulations developed since their discovery is the control of the development of cement paste/structure/properties as a function of time. Various current and proposed CPC applications all have specific setting and hardened cement properties.

The goal of the present work was to investigate the dependence of the cement setting time and hardened cement compressive strength on five important cement formulating parameters by using a five-factor central composite experimental design approach. The use of these generated equations relating the two important properties to these processing/powder parameters may thus allow the design of a particular cement directed towards a specific application.

## Experimental

**Cement Preparation and Characterization.** Tetracalcium phosphate (TTCP) powders were prepared by heat treatment of calcium and phosphate precursor mixtures in the 1200-1400°C range in a Carbolite 1600 HS high temperature furnace. The alumina crucibles containing the TTCP phases were quenched from 1200°C to room temperature in a dessicator. The second cement forming calcium phosphate phase,  $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$  Brushite, was prepared by chemical precipitation from calcium and phosphate precursors dissolved in aqueous solutions [4]. The cement pastes corresponding to the parameters outlined in the following section were placed in plastic tubes about 4.5 mm in diameter. Home-made Vicat Needle Apparatus with weight and sizes described in “ASTM C 187-04 Standart test method for normal consistency of hydraulic cement” was used for the determination of setting times of the cements. Compressive strengths of cylindrical HA cement samples with L/D ratios of 2 were determined with a M500-100KN Testometric Mechanical Test device. Morphological and phase analysis were conducted by using FEI Quanta FEG250 and Philips X/Pert Pro XRD.

**Central Composite Design.** Experimental design was performed to investigate the influence of several process parameters on HA based cement setting time and compressive strength. In that respect a five-factor, three level central composite design (CCD) was applied to develop an empirical relationship between the response and factors [5]. Response surface model and optimal factors of the system was elucidated, as well. Five independent variables having 3 levels which were -1, 0 and +1 and two responses for each set of experiment were chosen (Table 1). A total of 78 different combinations were selected in random order according to a CCD configuration. Design-Expert 8.04 trial version was used to carry out the CCD design, statistical analysis and numerical optimization.

Table 1. Central composite design for five variables.

Variables	Coded	Levels
Particle Size	A	- 0 +
pH	B	- 0 +
Solid / Liquid	C	- 0 +
Seed Concentration	D	- 0 +
Buffer Concentration	E	- 0 +
Responses		
Setting Time	R <sub>1</sub>	
Compressive Strength	R <sub>2</sub>	

## Results and Discussion

The SEM pictures of the synthesized TTCP powder and one of the HA cements prepared in this work are shown in Figure 1. TTCP displays characteristic high temperature synthesized particle morphology around 5µm in size. Typical plate like HA crystallites formed during setting reactions of HA cement precursors can be seen in the right picture in Figure 1. The presence of the major peaks of HA and TTCP are shown in XRD patterns given in Figure 2 for the prepared HA cement samples and the synthesized TTCP powder.

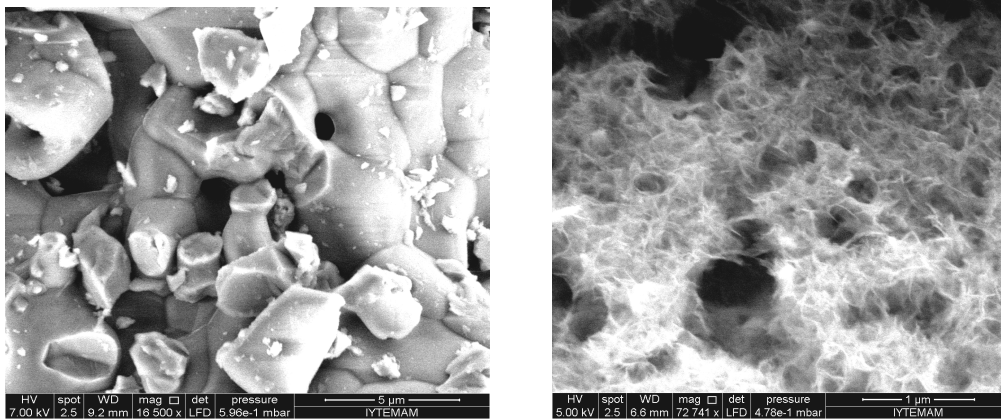


Figure 1. Scanning electron micrographs (SEM) of synthesized TTCP powder (left) and HA cement (right).

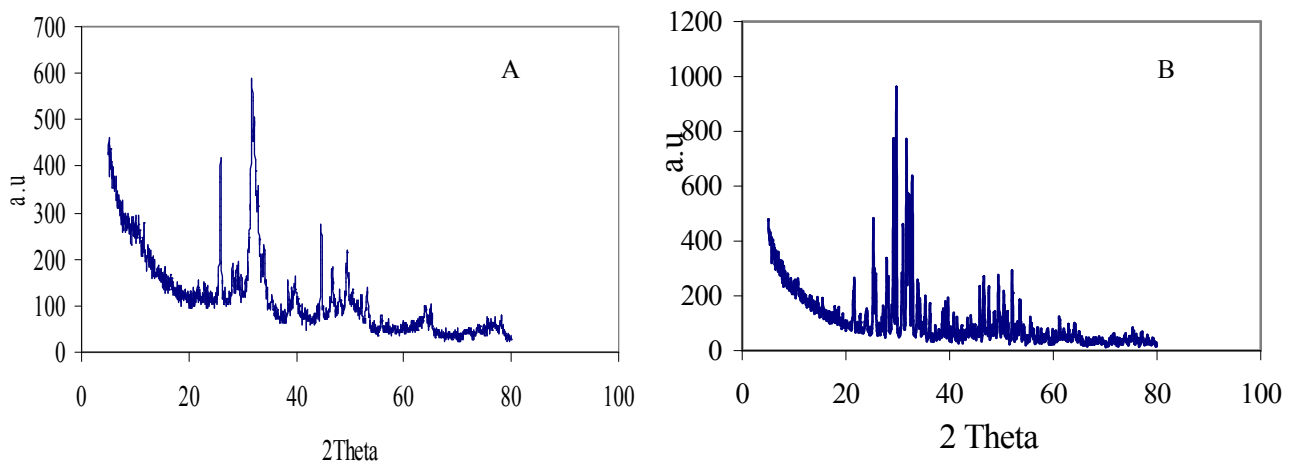


Figure 2. XRD patterns of (A) HA Cement (B) TTCP powder.

A second-order polynomial equation given below [Eqn (1)] was used to express the setting time of HA based cements as a function of the parameters which are presented along with their linear, quadratic and interaction terms within the 0.95 ( $\alpha=0.05$ ) confidence interval.

$$R_t = 12.64 + 7.79*A - 1.74*B + 2.97*C - 14.11*D - 24.71*E + 4.06*A*B + 2.12*A*C - 8.91*A*D - 6.91*A*E - 2.78*B*C - 1.94*B*D + 1.37*B*E - 7.31*C*D - 6.31*C*E + 13.34*D*E + 3.28*A^2 + 3.78*B^2 + 0.28*C^2 + 9.78*D^2 + 6.78*E^2 \quad (1)$$

The factors D (seed concentration) and E (buffer concentration) have the greatest effect on setting time of HA based cements and their interaction also plays an important role in the system. The effects of particle size (A), pH (B), and solid/liquid ratio (C) and their interactions with each other are not very significant on setting time. Particle size-seed concentration (AD) and particle size-buffer concentration (AE) interactions decrease whereas seed concentration-buffer concentration (DE) interaction increases the setting time of the cement.

The effect of seed-buffer concentration (DE) interaction on setting time of HA based cements are shown in response surface and contour plots which are given in Figure 3.

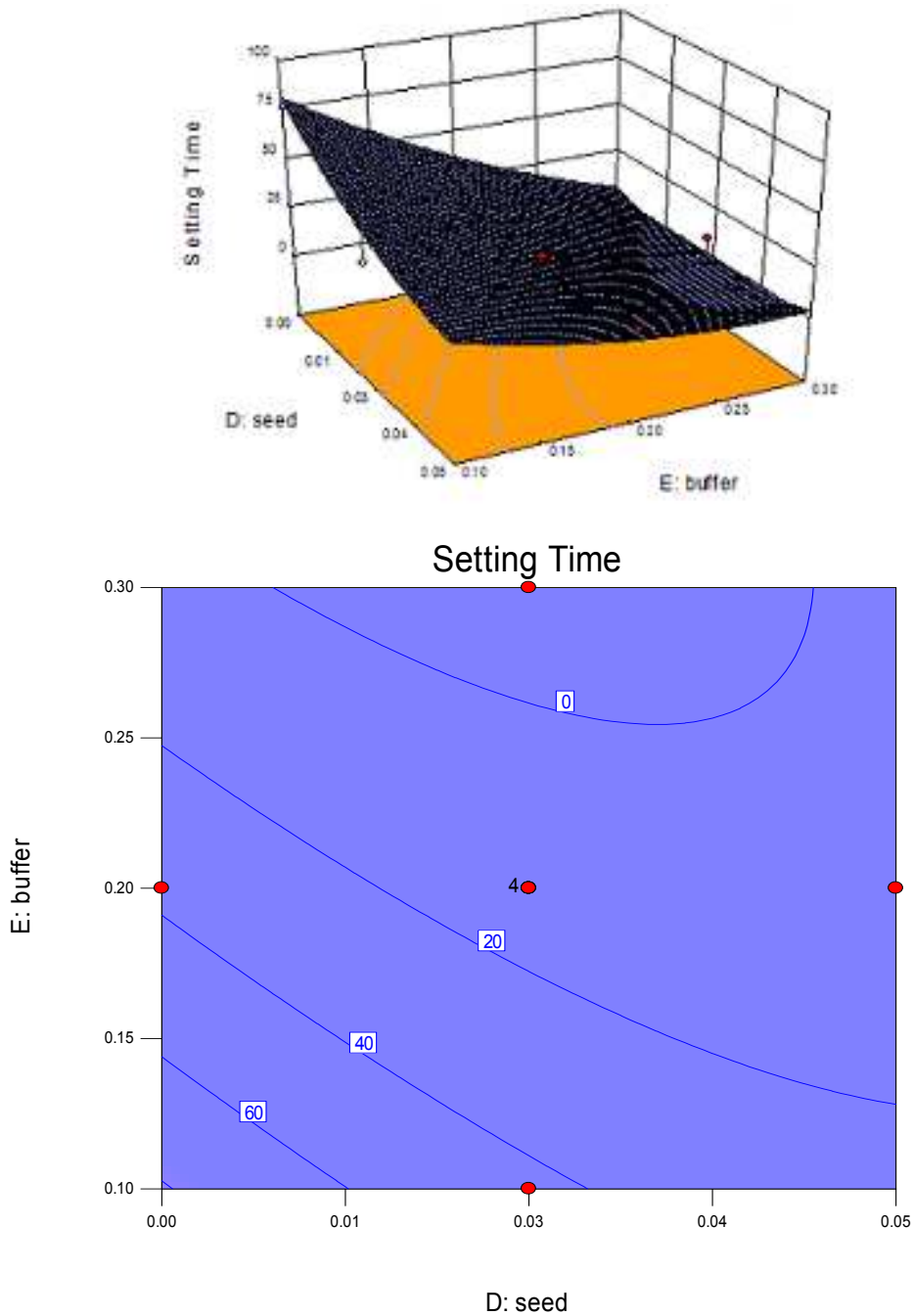


Figure 3. Seed concentration-buffer concentration (DE) interaction on setting time of HA based cement (Top: Response surface ;Bottom: Contour plot)

The three-dimensional response surface plot has a curvature which shows the effect of seed concentration (D), buffer concentration (E) and their interaction. The setting time attains its highest value when seed concentration has the highest and buffer concentration has the lowest level. However to obtain minimum setting time, seed concentration and buffer concentration should have the highest values.

Similarly, compressive strength is represented in Eqn(2) below, a second-order polynomial equation as a function of parameters presented along with their linear, quadratic and interaction terms within the 0.95 ( $\alpha=0.05$ ) confidence interval.

$$R_2 = +140.22 - 5.77*A + 3.59*B + 9.32*C + 12.50*D + 7.02*E - 4.73*A*B - 8.70*A*C + 7.48*A*D + 6.17*A*E + 2.33*B*C - 0.11*B*D + 2.14*B*E + 10.11*C*D + 16.98*C*E - 13.89*D*E - 11.09*A^2 - 1.09*B^2 - 19.09*C^2 - 4.09*D^2 + 6.91*E^2 \tag{2}$$

Although all the main factors are affecting the compressive strength response of HA based cements, the seed concentration (D) has the highest effect. The solid/liquid ratio-seed concentration (CD) and solid/liquid ratio-buffer concentration (CE) interactions increase whereas seed concentration-buffer concentration (DE) interaction decreases the compressive strength.

The effect of solid/liquid ratio (C) and buffer concentration (E) on compressive strength of HA based cements are shown in response surface and contour plots which are given in Figure 4.

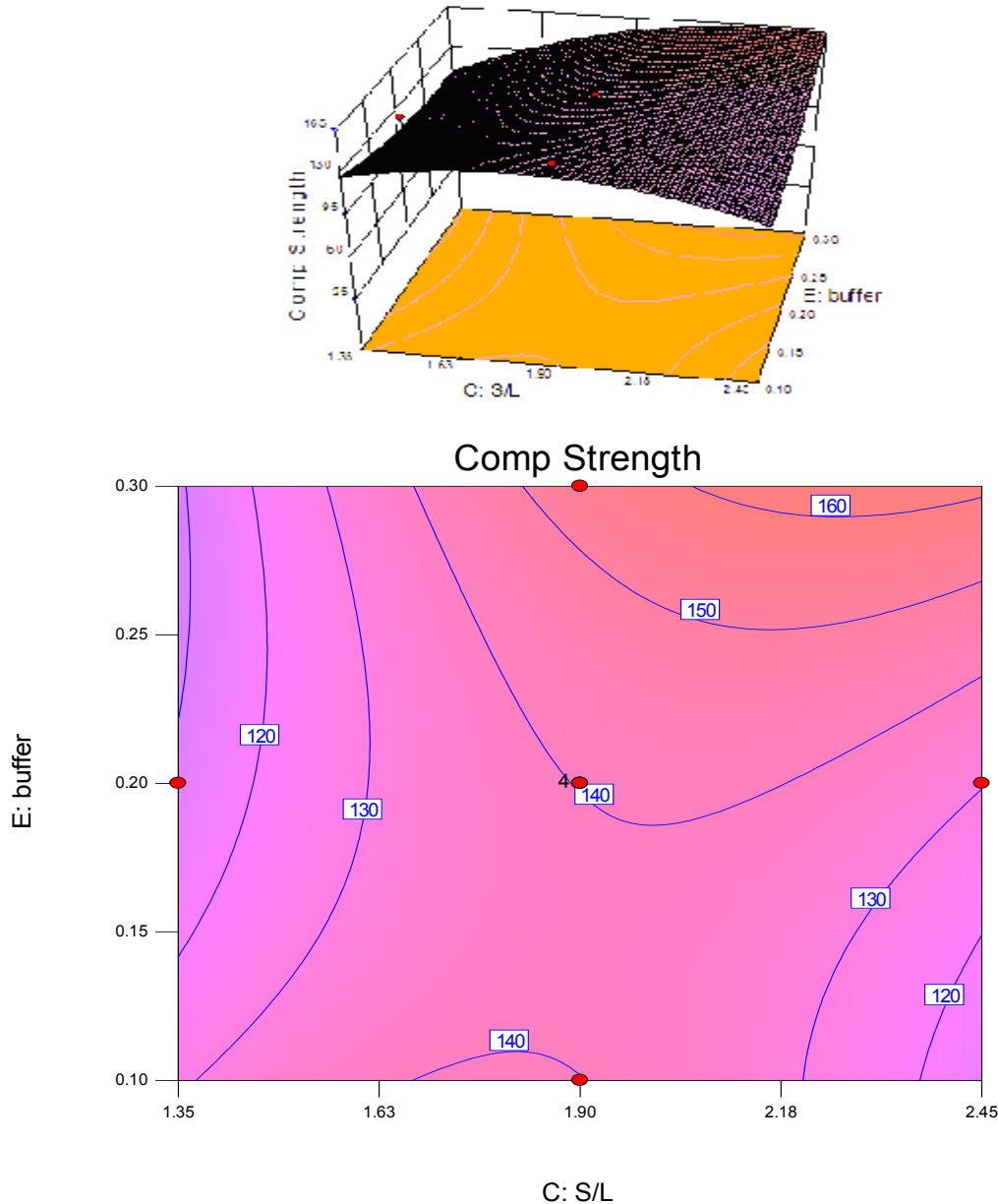


Figure 4. Solid/liquid ratio-buffer concentration (CE) interaction on compressive strength of HA based cement (Top:Response surface; Bottom:Contour plot).

The response surface (Figure 4:top) shows a curvature and has a maximum point which shows the effect produced by changing solid/liquid ratio (C) and buffer concentration (E) and their interaction. The compressive strength initially increases with increasing solid/liquid ratio (C) and decreases after reaching to a maximum point. Similar effect was obtained with buffer concentration (E) where compressive strength increased initially however after an optimum value it decreased.

The three-dimensional response surface plot shows a curvature which indicates the effect of C, E and their interaction. The highest compressive strength value was attained at C's and E's highest (+) level however high compressive strengths were also obtained for different combinations of factors/interactions and their levels.

**Summary**

Setting time and compressive strength HA based cement properties can be expressed by the second order polynomial CCD model. Analysis of variance (ANOVA) having high  $R^2$  value of  $\approx 0.99$  reveal that the model predicts the experimental data well. Setting time of HA cements is varied 4min to 7min and for the majority of the cement samples was determined to be in the 100-160 MPa range which is almost 2 to 3 times compared to the literature values (50-60 MPa).

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