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Processing and properties of injectable porous apatitic cements

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Injectable Calcium Phosphate Cements (CPC) are the emerging class of bone substitute materials as they can be moulded and shaped to fill intricate bone cavities and narrow dental sites. Various amounts of hydroxyapatite (HA) were mixed with tri-calcium phosphate (TCP) using sodium hydrogen phosphate as the liquid medium. The formulations have a setting time of 15–30 min. These cements with setting time around 20 min, which is also clinically preferred, were found to have better wash out resistance. The X-ray diffraction method (XRD) and Fourier transform infrared spectroscopy (FT-IR) analysis confirmed HA as the setting phase. Gelatin has been incorporated to the selected formulations to induce porosity in the above selected cements. Scanning electron microscopy (SEM) reveals a macroporous structure as also confirmed by BET measurements. Injectability of the cement is being evaluated using chitosan.

Key-words: Calcium phosphate cements, Setting time, Injectability, Cohesion and porosity

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1. Introduction

The increased life expectancy in the developed countries has led to a serious rise in the number of musculoskeletal disorders, such as osteoporosis and osteoarthritis.[1)] Minimally invasive surgical techniques have been shown to have significant clinical potential for stabilizing such disorders.[2)] Calcium phosphate cements (CPCs) have been developed since 1983 and are suitable for the repair and reconstruction of the bone. In general, all CPCs are formed by a combination of one or more calcium orthophosphates, which upon mixing with a liquid phase, usually water or an aqueous solution, form a paste which is able to set and harden after being implanted in the body.[3)] Additionally, CPC harden through a slow exothermic reaction without any shrinkage and hence more preferred than conventional PMMA cement.[4)] The most attractive property of CPCs is its ability to transform into an apatite structure through a dissolution and precipitation mechanism. However, the lack of macroporosity prevents faster bone ingrowth and subsequent integration of this cement. This work investigates novel formulations of CPCs which will result in a porous, injectable and cohesive paste.

2. Materials and methods

Commercially available high purity beta-tricalcium phosphate (beeta sympl-TCP) and hydroxyapatite (HA) were used for the preparation of the cement powder (Sigma Aldrich Chemicals USA). Pharmaceutical grade, sodium hydrogen phosphate was procured locally (SD fine chemicals, India). The cement powder (β-TCP and HA) of varying ratios were thoroughly mixed with 2.5 mass% sodium hydrogen phosphate in a watch glass. The liquid medium sodium hydrogen phosphate was prepared with double distilled demineralised water. The cement powder was prepared by mixing thoroughly β-TCP and HA powder. The wetting ratio, i.e. the amount of the medium to be added to the cement, was decided on the basis of workability of the putty formed. The different cement systems were prepared by varying the volume of the liquid medium and were coded as indicated in **Table 1**. An appropriate aqueous solution of gelatin content was prepared at 30°C. Fine cement powder was added to it and the slurry was stirred with a magnetic stirrer. The gelatin bound cement was heated for an hour at 550°C to burn off the gelatin. The porous cements thus obtained were further characterized as indicated. Injectability of cement paste was studied using chitosan solutions. The evaluation was done by measuring the load required to extrude the unset cement through an 18 gauge needle. The synthesized porous cement samples were characterized by X-ray powder diffraction (XRD) method (Shimadzu XDD1 X-Ray diffractometer, reflection mode, Japan) using Cu$K\alpha$ (radiation. The functional groups present in the cement were ascertained by Fourier transform infrared spectroscopy (FT-IR) method (Bruker, IFS66V FT-IR spectrometer, Germany). The morphology of the porous cement was observed under a scanning electron microscopy (JOEL JSM 5410 & JSM 5300, Japan). The surface area and porosity of the cement was determined by the triple-point BET method (Sorptomatic 1990, USA) with nitrogen as the adsorbate gas and helium as an inert non-adsorbable carrier. The setting time of the cement was assessed using a fabricated Vicat type apparatus. It consists of a steel needle that moves vertically under a constant load of 100gf. An attached dial gauge measures the distance traveled by the tip. The freshly mixed cement was filled in a tray and the needle was allowed to penetrate. The distance traveled by the tip is

Table 1. Setting Times, Phases and Volume of Liquid of the Cement Formulations

Code	System (0.5 g)	Vol of liquid medium (mg)	Setting time(min)	Setting Phase
TH980.5L	98% TCP and 2% HA	0.5	30	HA
TH981.0L	98% TCP and 2% HA	1.0	20	HA
TH981.5L	98% TCP and 2% HA	1.5	18	HA
TH900.5L	90% TCP and 10% HA	0.5	15	HA
TH901.0L	90% TCP and 10% HA	1.0	18	HA
TH901.5L	90% TCP and 10% HA	1.5	20	HA
TH800.5L	80% TCP and 20% HA	0.5	32	multiphase
TH801.0L	80% TCP and 20% HA	1.0	35	multiphase

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measured in the gauge at regular intervals of a minute till the cement hardens. The wash out resistance test was studied by monitoring the morphological changes on exposing the cement to water.[5)]

3. Results and discussion

The setting time of the cements studied by varying the wetting ratios is indicated in Table 1. The cement formulations have a setting time of 15–30 min. However, cements with setting time around 15–20 min, which is also clinically preferred,[6)] were found to have better wash out resistance. The cohesive properties of the cements were compared by exposing them to water. The cohesion was studied by the decrease in extent of dispersion of the pellet. The cement samples show good cohesion and retain their shape when immersed in water except for slight bulging at the periphery. The cement is seen to set in water with a prolonged setting time. The wash out resistance test is very important to determine whether the unset cement has a tendency to get washed away from the surgical site.

The phase compositions of the prepared cement were ascertained from XRD analysis. The XRD pattern of the finally powdered oven dried cement samples of TH980.5L, TH981.5L and TH901.0L are shown in **Fig. 1**. The patterns of the cement pattern are well resolved and correspond to hexagonal HA crystal (JCPDS 9–432). The presence of other calcium phases is not detected. The phase composition indicates the clinical advantage of the cement as HA phase has proven osteoconductive properties and bone ingrowth. The FT-IR spectra (**Fig. 2**) of the above mentioned cement samples show all typical absorption characteristics of HA. The absorption bands at 1050–1070 cm^{-1} and 490–580 cm^{-1} correspond to phosphate group. The absorption bands for carbonate appeared at 1420–1430 cm^{-1}. Hydroxyl bands corresponding to 3400–3500 cm^{-1} and 1640–1660 cm^{-1} were obtained as similar to HA.

The injectability of the samples was increased significantly by the addition of chitosan solutions. The injectability was assessed by plotting the load needed to move the plunger to extrude the cement through an 18 gauge needle. The experiment was started after two minutes of mixing the cement. The initial load was found to increase which eventually comes to a constant value. The values obtained for the cement samples ranged between 0.15 to 0.25 kN. An optimum concentration of 2.5% chitosan solution gave appreciable injectability. The maximum thumb force measured to be around 0.5 kN[7)] was far greater than those obtained for the cement formulations. Thus the cements prepared had efficient injectability.

The SEM micrographs (**Fig. 3**) reveal a porous structure

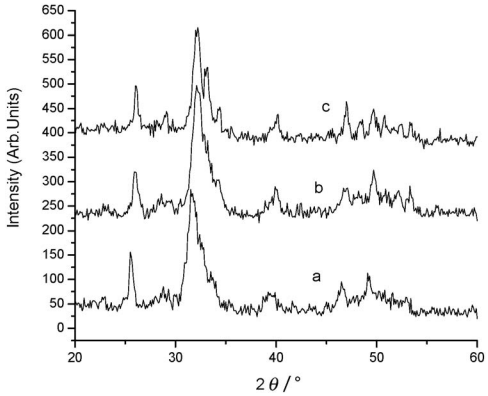

Fig. 1. XRD of TH980.5L (a) TH981.5L (b) and TH901.0L (c) samples.

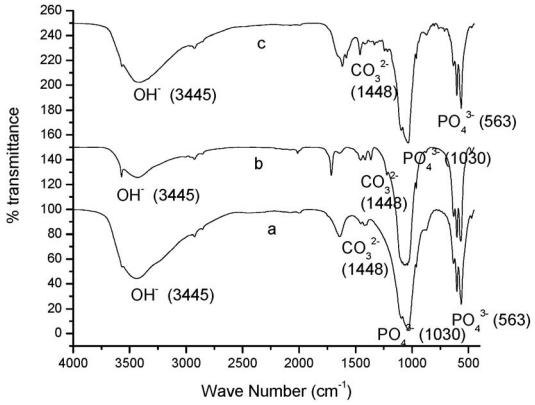

Fig. 2. FT-IR spectra of TH980.5L (a) TH981.5L (b) and TH901.0L (c) samples.

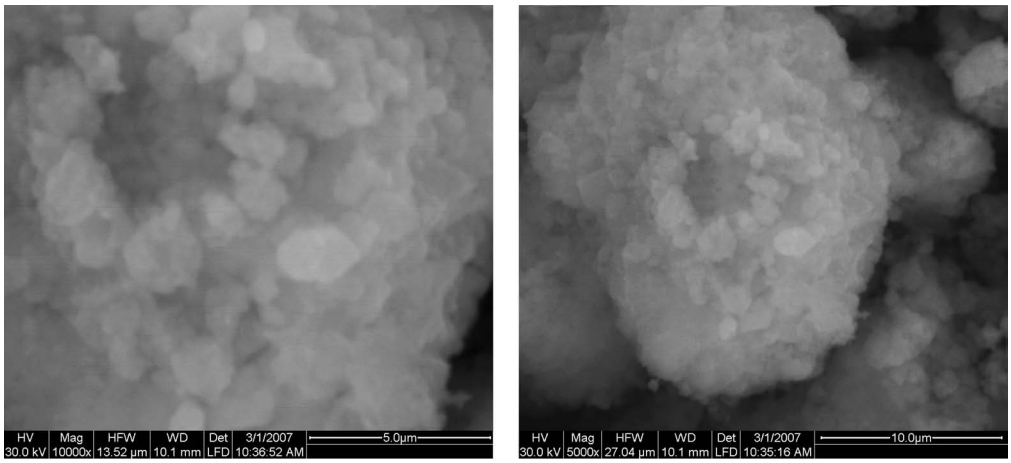

Fig. 3. SEM micrographs of TH901.0L (a), TH980.5L (b) porous cements.

produced by the gelatin in the cement pastes. Various concentrations of gelatin were studied to determine its effect on porosity. An optimum concentration of about 5% gelatin was sufficient to produce macropores in the range 15–20 nm. XRD analysis of the porous cements does not reveal any other peaks thus confirming the phase purity of the porous cements. The BET measurements reveal an obvious distribution in 2–40 nm range, which might belong to the gelatinous pores. With the increase in the concentration of gelatin the pore volume of the pores in the 2–40 nm range increased. Thus with the gelatinous pores in the above mentioned range it might be suitable for the entry of physiological ions to promote bone repair reactions.

4. Conclusion

Novel formulations of CPCs that will result in a porous, injectable and cohesive paste were prepared. Studies on the setting characteristics show the properties were within the range of interest. Macroporosity was introduced with the aid of gelatin solutions. SEM analysis reveals the apatite to be of porous morphology. Injectability has been achieved using optimum concentration of chitosan solutions.

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