

# Improved injectability and in vitro degradation of a calcium phosphate cement containing poly(lactide-co-glycolide) microspheres

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## Abstract

An injectable calcium phosphate cement (CPC) containing 30 wt.% poly(lactide-co-glycolide) (PLGA) microspheres was developed in the present study. Sodium citrate solution was used as the cement liquid phase. The effects of sodium citrate concentration on the injectability, rheological properties, mechanical strength and self-setting properties of CPC containing PLGA microspheres were systematically investigated. The in vitro degradation behavior of the composite during immersion in phosphate buffer solution was also studied. With an increase in sodium citrate concentration, the viscosity and yield stress of the paste were reduced, thereby improving the injectability. At a sodium citrate concentration of 15%, the injectability of the paste reached 95%. The compressive strength of the specimen was also enhanced by the addition of sodium citrate. The specimens had a compressive strength of  $32.24 \pm 2.72$  MPa at 15% sodium citrate concentration, compared to  $22.15 \pm 3.60$  MPa for the specimen without sodium citrate. The in vitro degradation results demonstrate that incorporated PLGA microspheres can provide the required high strength to CPC in the early stage, which would gradually degrade to create macropores for bone ingrowth. In conclusion, an in situ macropore-generable CPC exhibited excellent injectability and high early strength, and should be a promising material for bone repair and bone reconstruction.

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**Keywords:** Calcium phosphate cement; PLGA microsphere; Injectability; Strength; In vitro degradation

## 1. Introduction

With the development of minimally invasive surgical methods, such as percutaneous surgery, directly injectable biomaterials are needed [1,2]. Because of its similarity to the mineral phase of bone and the nature of setting in situ, calcium phosphate cement (CPC) has been regarded as a promising material for use in minimal invasive surgery for bone defect repair [3]. Since the discovery of CPC by Brown and Chow in 1986 [4], it has been the subject of much research [5–7]. The current challenge is to place the

material at the site of surgery by the least invasive method possible. It has been shown that using minimally invasive bone cement injection to treat vertebral fracture has significant clinical potential [8,9].

CPC has been developed as an injectable bone substitute material because of its good biocompatibility, excellent bioactivity, self-setting characteristic, low setting temperature, adequate stiffness and easy shaping in complicated geometries [10,11]. However, the drawbacks of CPC, including its inferior mechanical strength, poor injectability and lack of macroporosity for bone ingrowth, have restricted its clinical applications [12,13]. There is a general conflict between macroporosity and mechanical strength in CPC [14–16]. For example, the compressive strength of CPC without macropores was shown to be approximately 37 MPa, which decreased to 2.9 MPa with 29% macropores and further decreased to 0.4 MPa with 40% macropores

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[17]. Therefore, attempts have been made to increase the strength of CPC with macropores. In some studies, a variety of fibers and water-soluble porogens were incorporated into the CPC to obtain strength as well as macropores for bone ingrowth [18,19]. In another study, chitosan was introduced into macroporous CPC to improve the compressive modulus and yield stress [20]. However, these methods greatly limited the injectability of CPC.

The objective of the present study was to develop an injectable CPC containing poly(lactide-co-glycolide) (PLGA) microspheres. The biodegradable PLGA microspheres were used to impart in situ macroporosity to the cement. PLGA degrades by random hydrolysis into lactic and glycolic acids, and is considered to be non-toxic and biocompatible both in vitro and in vivo [21,22]. After implantation in vivo, CPC containing PLGA microspheres can maintain a relative high strength during the initial stage, before the PLGA microspheres degrade to create macropores for bone ingrowth. Some recent studies have reported the biocompatibility and in vivo properties of CPC containing PLGA microspheres [23–25]. However, the rheological properties, injectability and setting properties of the composites have not been studied systematically. It is clear that these are important factors for the direct injection of cement in clinical applications. In this study, sodium citrate solution was used as the liquid phase to improve the injectability of the composite, and the influence of the concentration of the solution on the mechanical strength, self-setting and rheological properties was investigated. The in vitro degradation behavior of the composites was also studied.

## 2. Materials and methods

### 2.1. Materials and preparation

The CPC powder used in this study was prepared by mixing partially crystallized calcium phosphate (PCCP) and dicalcium phosphate anhydrous (DCPA) at a mass ratio of 1:1, as described in our previous work [26,27]. The precursor of PCCP was synthesized from an aqueous solution of  $\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$  ( $0.36 \text{ mol l}^{-1}$ ) and  $(\text{NH}_4)_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$  ( $0.15 \text{ mol l}^{-1}$ ) by chemical precipitation method in our laboratory. Then the deposit was centrifugally separated, freeze-dried and calcined at  $450^\circ\text{C}$  for 2 h in a furnace to attain PCCP. The PCCP powders were milled in a planetary ball mill using  $\text{ZrO}_2$  balls at 400 rpm for 2 h. DCPA of analytical grade purity was commercially obtained from Shanghai No. 4 Reagent & H.V. Chemical Co. Inc., China. Sodium citrate was obtained from Tianjin Y.H. Chemical Reagent Co. Inc., China.

PLGA (50/50 lactide to glycolide ratio, mol. wt. = 30,000) was purchased from Jinan M.K. Biotechnology Co., Ltd., China. PLGA microspheres were made by a solvent evaporation method. PLGA (1.5 g) was dissolved in 10 ml methylene chloride ( $\text{CH}_2\text{Cl}_2$ ) to form a homogeneous solution, which was subsequently poured into 80 ml of 0.5% methyl cellulose (M20, Sinopharm Chemical

Reagent Co., Ltd.) solution. The solution was stirred at 450 rpm with an overhead stirrer for 8 h at room temperature, allowing the solvent to evaporate. After stirring, the solution was allowed to stand for 4 h and the liquid was decanted. The microspheres were then washed three times with deionized water, centrifuged and lyophilized. Microspheres with a diameter ranging in 100–300  $\mu\text{m}$  were separated by sieving for use in this study.

The PLGA microspheres were uniformly mixed with CPC powder at a PLGA to CPC weight ratio of 30/70. Sodium citrate solution was used as the liquid phase in this study and deionized water without sodium citrate (0%) was used as the control. Sodium citrate solutions with concentrations of 5, 10, 15 and 20 wt.% were made by dissolving the sodium citrate to deionized water. Then the PLGA/CPC mixture was homogeneously mixed with sodium citrate solution at a liquid to CPC ratio of  $0.4 \text{ ml g}^{-1}$ . All processes were carried out at  $25 \pm 2^\circ\text{C}$  and 50–60% humidity.

### 2.2. Setting time measurements

The setting time of the CPC containing PLGA microspheres was measured according to ASTM C191-03 [28]. The samples were tested using a Vicat apparatus which had a movable rod of  $300 \pm 0.5 \text{ g}$  mass and a removable needle of  $1 \pm 0.05 \text{ mm}$  diameter, fixed at the end of the rod. The Vicat needle was carefully lowered vertically onto the surface of the newly shaped cement samples and kept there for 5 s, applying an equivalent static pressure of 3.7 MPa. The indentation was repeated at intervals of 30 s until the cement was hardened. The initial setting time was calculated as the difference between the time when the needle penetrated 25 mm into the cement paste and the time of the initial contact between the powder and the liquid phase. The final set occurred when there was no visible penetration. The setting times of the cements were measured in a humidity chamber at  $37^\circ\text{C}$  and >90% humidity and in normal laboratory atmosphere ( $25 \pm 2^\circ\text{C}$  and 50–60% humidity), respectively. Each measurement was performed six times and the average value was calculated.

### 2.3. Injectability tests

The injectability of the CPC containing PLGA microspheres was tested with a syringe of 14.5 mm inner diameter, which was fitted with a needle of 1.6 mm inner diameter. After mixing the PLGA/CPC mixture with sodium citrate solution (0, 5, 10, 15 and 20 wt.%) for 1 min, the as-prepared paste was poured into the syringe. A 5 kg compressive load was then mounted vertically on the top of the plunger for 2 min. The entire process totally took about 4 min, which was much shorter than the initial and final setting time. The mass of the paste before and after injecting was measured and the injectability was calculated according to Eq. (1). Each test was performed six times and the average value was calculated.

ID	Title	Pages
1757	Improved injectability and in vitro degradation of a calcium phosphate cement containing poly(lactide-co-glycolide) microspheres	9

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