

# Poly(propylene fumarate)/(calcium sulphate/ $\beta$ -tricalcium phosphate) composites: Preparation, characterization and in vitro degradation

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## Abstract

This study aimed to prepare a poly(propylene fumarate)/(calcium sulphate/ $\beta$ -tricalcium phosphate) (PPF/(CaSO<sub>4</sub>/ $\beta$ -TCP)) composite. We first examined the effects of varying the molecular weight of PPF and the *N*-vinyl pyrrolidinone (NVP) to PPF ratio on the maximum cross-linking temperature and the composite compressive strength and modulus. Then the in vitro biodegradation behaviour of PPF/(CaSO<sub>4</sub>/ $\beta$ -TCP) composites was investigated. The effects of varying the molecular weight of PPF, the NVP/PPF ratio and the CaSO<sub>4</sub>/ $\beta$ -TCP molar ratio on the weight loss and the composite compressive strength and modulus were examined. The cross-linking temperature, which increased with increasing molecular weight of PPF and NVP/PPF ratio, ranged from 41 to 43 °C for all formulations. The mechanical properties were increased by a decrease in the NVP/PPF ratio. For all formulations, the compressive strength values fell between 12 and 62 MPa, while the compressive modulus values fell between 290 and 1149 MPa. The weight loss decreased either with increasing molecular weight of PPF or with decreasing NVP/PPF ratio and CaSO<sub>4</sub>/ $\beta$ -TCP molar ratio during degradation. The compressive strength and modulus increased with decreasing NVP/PPF ratio or decreasing CaSO<sub>4</sub>/ $\beta$ -TCP ratio. The greatest weight loss over 6 weeks was 14.72%. For all formulations, the compressive modulus values fell between 57 and 712 MPa and the compressive strength fell between 0.5 and 21 MPa throughout 6 weeks degradation. Scanning electron microscopy and X-ray diffraction analysis of the PPF/(CaSO<sub>4</sub>/ $\beta$ -TCP) composites demonstrated that hydroxyapatite was deposited on the surface of CaSO<sub>4</sub>/ $\beta$ -TCP granules during degradation.

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## 1. Introduction

Poly(propylene fumarate) (PPF) is a synthetic material that has recently been explored for use as a degradable scaffold for bone tissue engineering [1]. PPF consists of repeating units that contain one unsaturated double bond, which permits covalent cross-linking, and two ester groups, which allow for hydrolysis of the polymer into the nontoxic degradation products of fumaric acid and propylene glycol [2–4]. PPF is often combined with particles of ceramic

materials such as  $\beta$ -tricalcium phosphate ( $\beta$ -TCP), calcium carbonate or calcium sulphate to improve their properties [5–8]. These composite materials exhibit compressive strengths from 2 to 30 MPa, which is appropriate for replacement of cancellous bone. Most importantly, the rate of degradation and mechanical behaviour of PPF composites scaffolds can be altered by varying parameters, such as the cross-linking density, the inorganic content and the molecular weight of PPF [9–12].

PPF can be cross-linked by *N*-vinyl pyrrolidinone (NVP) [1,12], poly(propylene fumarate)-diacrylate (PPF-DA) macromers [3,9] and methylmethacrylate (MMA) [7]. These studies showed that decreasing the *N*-VP/PPF or PPF/PPF-DA ratio, or increasing the MMA content

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increased the compressive strength and compressive modulus and decreased the weight loss over the degradation time. Peter et al. [5] proved that increasing molecular weight led to an increase in both compressive strength and compressive modulus and a decrease in weight loss. However, a threshold molecular weight exists above which the number of cross-linked double bonds per PPF chain is independent of the chain length, and any end effects due to steric hindrances diminish, so the molecular weight of PPF does not affect the mechanical properties of the composite significantly [1]. Ceramic fillers play a crucial role in composite reinforcement, and have been utilized in degradable polymer systems as internal buffers to neutralize the local pH and inhibit any autocatalytic degradation [9,12]. According to early *in vitro* studies, the time needed to reach 20% original weight ranged from near 84 days (PPF/ $\beta$ -TCP composite) to over 200 days (PPF/ $\text{CaSO}_4$  composite) [5,8]. In another degradation study sodium chloride (NaCl) porogen content appeared to have the greatest effect upon physical degradation at 32 weeks. Water absorption capacity, porosity and compressive modulus were maintained at constant values following NaCl leaching in this study [13]. These investigations all demonstrated that PPF-based scaffolds can maintain their structure for 12 months.

$\text{CaSO}_4$  and  $\beta$ -TCP are more biodegradable and biocompatible than PPF. A  $\text{CaSO}_4/\beta$ -TCP composite has been prepared in our laboratory, and the rate of its degradation can be adjusted by varying its composition and sintering temperature [14]. Therefore, filling a certain size of  $\text{CaSO}_4/\beta$ -TCP spherical granules into PPF networks not only improves the mechanical property and biocompatibility of the composite, but also makes its degradation more controllable. To our knowledge, no research work on PPF/( $\text{CaSO}_4/\beta$ -TCP) biomaterial has been published before.

In this study, we aimed to develop a biodegradable PPF/( $\text{CaSO}_4/\beta$ -TCP) composite which may be suitable for bone replacement. In the composite, the spherical  $\text{CaSO}_4/\beta$ -TCP granules were expected to degrade faster than the surrounding PPF/NVP, leading to an increase in the porosity of the composites. The effects of different components on the handling properties and mechanical properties of this composite are also investigated. We then assessed the factors that influence PPF/( $\text{CaSO}_4/\beta$ -TCP) degradation. In particular, we investigate the effects of the molecular weight of PPF, the NVP/PPF ratio and the  $\text{CaSO}_4/\beta$ -TCP molar ratio on the *in vitro* degradation behaviour of PPF/( $\text{CaSO}_4/\beta$ -TCP) composites.

## 2. Materials and methods

### 2.1. Materials

*N,N*-Dimethyl-*p*-toluidine (DMT) was purchased from Acros Organics (New Jersey, USA). Fumaryl chloride and NVP were purchased from Shanghai Hao Chemical

Co., Ltd. (Shanghai, China). BP was purchased from Shanghai Zhongli Chemical Co., Ltd. (Shanghai, China).  $\text{CaSO}_4$ ,  $\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$  and  $(\text{NH}_4)_2\text{HPO}_4$  were purchased from Bodi Chemical Co., Ltd. (Tianjin, China). Propylene glycol, potassium carbonate, sodium sulphate, NaCl, sodium dihydrogen phosphate dodecahydrate, sodium hydroxide, disodium hydrogen phosphate, phosphoric acid and all other organic solvents, such as methylene chloride and petroleum ether, were purchased from Tianjin Jiangtian Chemical Co., Ltd. (Tianjin, China), and used as received. Fumaryl chloride was purified by distillation at 1 atm pressure under nitrogen.

### 2.2. PPF synthesis

PPF was synthesized by a two-step reaction process [15]. Briefly, fumaryl chloride was added dropwise to a solution of propylene glycol in methylene chloride at 0 °C under nitrogen in the presence of  $\text{K}_2\text{CO}_3$ . Fumaryl chloride, propylene glycol and potassium carbonate were measured out in a 1:3:1.5 molar ratio. After addition of fumaryl chloride, the reaction mixture was stirred for an additional 2 h at 0 °C and then water was added to dissolve the inorganic salt. The organic layer was separated and dried with  $\text{Na}_2\text{SO}_4$ . After filtration and evaporation of the solvent, the formed di-(2-hydroxypropyl) fumarate underwent a transesterification reaction to produce PPF at 160 °C and 0.5 mm Hg for 12 h (PPF (1)), 16 h (PPF (2)) or 20 h (PPF (3)). PPF was purified through solution precipitation in chloroform and petroleum ether.

### 2.3. Spherical $\text{CaSO}_4/\beta$ -TCP granule preparation

$\beta$ -TCP powder was prepared by adding diammonium phosphate ( $(\text{NH}_4)_2\text{HPO}_4$ ) solution into a reactor containing a calcium nitrate tetrahydrate ( $\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$ ) solution at room temperature with a molar ratio of 1:1.5. The suspension was stirred (at 200 rpm) at 37 °C for 2 h. The pH value of the suspension was maintained at 8–10 by adding ammonia solution. The suspension was filtered via a Buechner funnel, washed with distilled water, dried at 90 °C for 12 h in air and then calcined at 900 °C for 2 h to obtain  $\beta$ -TCP powder. The powders of  $\text{CaSO}_4$  and  $\beta$ -TCP were mixed at molar ratios of 1:1, 1:4 and 2:1, respectively, and then ball milled for 4 h.

The spherical  $\text{CaSO}_4/\beta$ -TCP granules were prepared by the method of Komlev et al. [16]. In brief, 30 g of gelatin was dissolved in 100 ml of distilled water at 39 °C. Fine  $\text{CaSO}_4/\beta$ -TCP powder was then added at an amount of 1.0 g of  $\text{CaSO}_4/\beta$ -TCP powder per 2.0 ml of gelatin solution. After that, the  $\text{CaSO}_4/\beta$ -TCP/gelatin slurry was dispersed in oil in a reaction flask by stirring with a glass paddle stirrer at 250–300 rpm. The oil temperature was between 10 and 15 °C. The stirring resulted in the formation of beads due to the surface tension forces. The beads were filtered, washed in acetone followed by ethanol and dried in air. These gelatin-bonded beads were heated at

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