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Preparation and characterization of calcium phosphate bone cement with rapidly-generated tubular macroporous structure by incorporation of polysaccharide-based microstrips

Kannaporn Pooput*, Naruporn Monmaturapoj, Jitlada Sansatsadeekul, Somruethai Channasanon, Autcharaporn Srion

National Metal and Materials Technology Center (MTEC), 114 Paholyothin Road, Klong 1, Klongluang, Pathumthani, Thailand

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ABSTRACT

Calcium phosphate cements (CPCs) have been extensively used as bone graft substitutes for the repair of bone defect due to its biocompatibility, osteoconductivity and in-situ setting capability. They poorly degrade thus limiting their use in tissue engineering application. A possible strategy to improve the speed of CPC degradation is to add porogen to CPC to create macropores that can enhance cement resorption and can consequently be replaced by new bone. The as-generated macropores are generally not connected because of spherical shape of the porogens which can limit the extent of newly formed bone. The aim of this study was to fabricate CPCs having tubular macroporous structure by incorporating fast-dissolving maltodextrin microstrips (MDMS) and explore their properties such as setting time, mechanical property, microstructure and degradability of the cements. The results showed that after immersing MDMS-embedded composites in simulated body fluid under physiological condition for 1 d MDMS rapidly disintegrated (more than 70%), generating tubular macropores in CPCs. The disintegration of MDMS completed in 1 week. CPCs containing MDMS lower than 30% by weight had the same final setting time as those without MDMS. The average values of compressive strength of the CPC composites decreased with the disintegration of MDMS. % Porosity and pore interconnectivity increased with increasing MDMS content. In addition, MDMS-embedded CPCs were cell friendly with excellent cell adhesion, indicating a possible candidate as bone graft substitutes.

1. Introduction

Calcium phosphate cements (CPCs) with apatitic structure have been widely used as bone substitutes for several decades due to their biocompatibility, self-setting ability and osteoconductivity [1,2]. However, they are poorly resorbable and thus slowly replaced by new bone [3,4]. To enhance the speed of CPC replacement, various techniques have been employed such as introducing porogens into the cement [5,6]. After porogens dissolve, disintegrate or degrade, empty voids or pores occur in the material. These pores allow fluid to flow in, enhancing cement degradation. Speed of bone regeneration depends on how fast macropores are created in CPCs [7–9]. For being used CPCs as bone grafts, pores must be easily invaded by cells and blood vessels. In other words, pores must be larger than 50 μm and interconnected [10]. Porogens frequently used and studied in CPCs can be classified depending on their degradation rate. This includes polymeric porogens [11–13], inorganic salts [4,5] and sugar microparticles [6–9]. Poly(lactic-co-glycolic) acid (PLGA) has been extensively used as pore generator because it degrades into lactic and glycolic which are easily eliminated from the body by the Krebs cycle [14]. Even though PLGA microspheres could enhance CPC degradation and promote new bone formation, degradation rates of PLGA containing CPCs are still very slow (3–4 months) [11–13]. Many attempts have been performed to overcome this delayed degradation by incorporating fast dissolving inorganic or carbohydrate-based particulates such as salts or sugars into the CPCs [5–9]. The macroporous structure can be obtained in days, instead of weeks or months. These particles can be simply mixed with the powder and the liquid components of the cement. With their susceptible dissolution, they may dissolve in the liquid part, losing an ability to form pores in the CPCs. Furthermore, they can interrupt setting time as reported in many studies [7–9]. The as-generated macropores from those porogens are generally not interconnected because of the spherical shape of the polymeric microspheres or the non-elongated feature of the microparticles. This can

* Corresponding author.
E-mail address: kannaporn.poo@mtec.or.th (K. Pooput).

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limit the extent of newly formed bone. However, to achieve interconnected macroporous structure, high porogen content must be used. This can adversely cause cement to collapse due to very low initial strength.

Maltodextrin ($C_{6n}H_{(10n+2)}O_{(5n+1)}$, MD) is a biocompatible natural polysaccharide, derived from starch by partial hydrolysis, commonly used in food industry. MD is composed of a mixture of variable D-glucose units, represented as n in the chemical formula, less than 20. It easily dissolves in water. Its solubility depends on glucose chain length. The shorter the glucose chains, the higher the solubility. In biomedical applications, MD has been used as binder in 3D printing for tissue engineering [15–17]. From our knowledge, there is no any report using MD as porogens in CPCs. The aim of this study was to fabricate fast-dissolving porogens without compromising cement setting time to improve degradability of the apatitic CPCs and to create interconnected macroporosity by incorporating elongated MD microstrips (MDMS) into the CPCs. Compressive strength, setting time, hydroxyapatite (Ca_{10} $(PO_4)_6(OH)_2$, HAP) phase conversion, porosity and biocompatibility of the MDMS-embedded CPCs were examined.

2. Experimental section

2.1. Preparation of apatitic cement powder

Tetracalcium phosphate ($Ca_4(PO_4)_2O$, TTCP) powder was synthesized by a solid-state reaction of 0.95 mol of calcium carbonate ($CaCO_3$, Carlo Erba Reagenti, Italy) with 1.0 mol of dicalcium phosphate anhydrous ($CaHPO_4$, DCPA, Sigma Aldrich, Singapore) at 1450 °C for 6 h in a furnace, followed by quenching at room temperature. The synthesized TTCP was dry-milled in a planetary ball mill to obtain a median particle size of about 9.5 ± 0.5 μm (n=4). DCPA was commercially obtained and milled in ethanol before use. CPC powder was prepared by mixing an equivalent mass of TTCP and DCPA.

2.2. MD microstrip fabrication and embedment in CPC paste

Maltodextrin microstrips with desired diameter were prepared by mixing MD powder (Sigma-Aldrich, Germany) with deionized (DI) water and kneading with spatula and rolling pin for 10 min like kneading dough in bakery. Kneaded MD was then cut by a very sharp blade into small pieces with a desired length. In the present study, the porogen length was half the sample height. The average diameter (350 ± 35 μm) of the prepared microstrips was determined by optical and scanning electron microscopy (SEM). The morphology of the sugar strip was visualized by SEM as shown in Fig. 1.

MDMS-embedded CPCs were prepared by mixing an equimolar of TTCP and DCPA powder with desired amount of MDMS (10%, 20% and 30% w/w, MDMS to powder weight ratio) and sodium phosphate buffer composed of disodium phosphate (Na_2HPO_4, Carlo Erba Reagenti, Italy) and sodium dihydrogen phosphate (NaH_2PO_4, Carlo Erba Reagenti, Italy) as liquid for 30 s. CPC paste samples were then ready for further characterization.

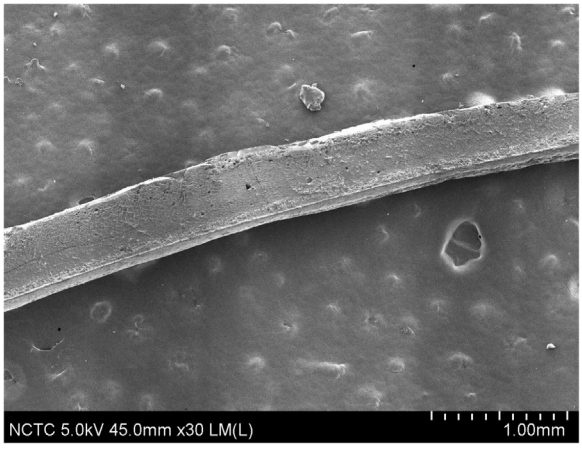

Fig. 1. Scanning electron micrograph of maltodextrin microstrip.

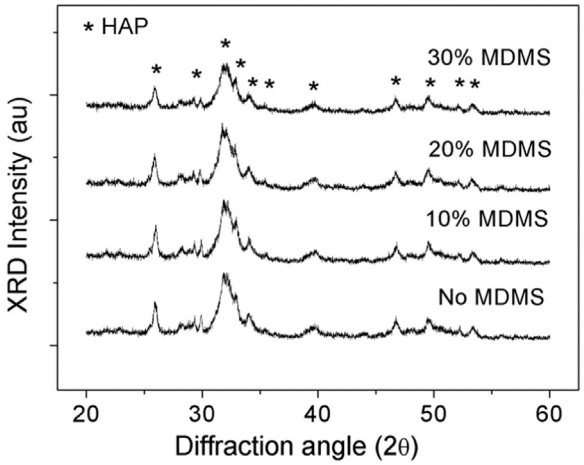

Fig. 2. X-ray Diffraction (XRD) patterns of CPCs containing different MDMS contents with 7 d SBF immersion.

Table 1
Initial and final setting times of CPCs.

Sample	Initial setting time (min)	Final setting time (min)
CPC without MDMS	4 ± 1	20 ± 2
CPC with 10% w/w MDMS	4 ± 1	20 ± 2
CPC with 20% w/w MDMS	5 ± 1	20 ± 2
CPC with 30% w/w MDMS	12 ± 2	40 ± 3

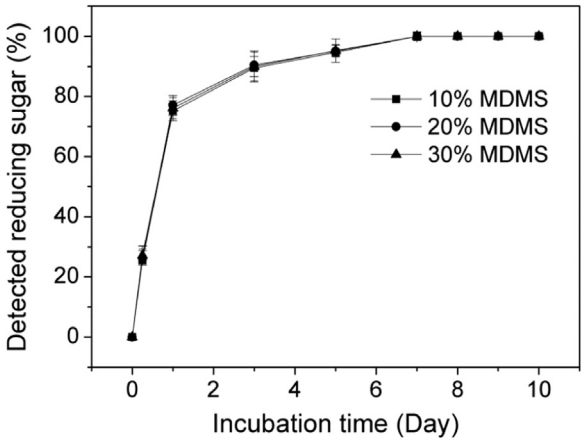

Fig. 3. Detected amount of reducing sugar of CPC materials containing 10%, 20% and 30% w/w MDMS using Benedict's solution test with different SBF incubation periods.

2.3. Setting time and compressive strength measurement

The setting time of the cement was measured using a 400 g weight loaded onto a Gillmore needle, with a tip diameter of 1 mm, according to the international standard, ISO 1566, for dental zinc phosphate cements. The initial setting time was measured when the light needle (113.4 g in mass, and 2.13 mm in diameter) failed to make perceptible indentation on the sample surface. The final setting time was determined using a heavy needle (453.6 g in mass and 1.06 mm in diameter). Each measurement was performed 4 times and the average value was calculated and presented.