Available online at www.sciencedirect.com
ScienceDirect
Acta Biomaterialia 5 (2009) 3165–3177
Acta BIOMATERIALIA
www.elsevier.com/locate/actabiomat

β-TCP/MCPM-based premixed calcium phosphate cements

Bing Han [a], Peng-Wei Ma [a], Li-Li Zhang [a], Yu-Ji Yin [a,*], Kang-De Yao [a], Fu-Jiang Zhang [b], Yong-Dong Zhang [b], Xiu-Lan Li [b], Wei Nie [c]

[a] School of Materials Science and Engineering, Tianjin University, Tianjin 300072, China
[b] Tianjin Hospital, Tianjin 300211, China
[c] Tianjin Institute of Medical and Pharmaceutical Sciences, Tianjin 300020, China

Received 26 October 2008; received in revised form 4 March 2009; accepted 7 April 2009
Available online 3 May 2009

Abstract

Novel premixed calcium phosphate cements (CPCs) were prepared by combining cement liquids comprised of glycerol or polyethylene glycol with CPC powders that consisted of β-tricalcium phosphate (β-TCP) and monocalcium phosphate monohydrate (MCPM). Changing the powder to liquid mass ratio enabled the setting time to be regulated, and improved the compressive strength of the CPCs. Although some ratios of the new premixed CPCs had long setting times, these ranged from 12.4 to 27.8 min which is much shorter than the hour or more reported previously for a premixed CPC. The premixed CPCs had tolerable washout resistance before final setting, and the cements had strengths matching that of cancellous bone (5–10 MPa); their maximum compressive strength was up to 12 MPa. The inflammatory response around the premixed CPCs implanted in the subcutaneous tissue in rabbits was more prominent than that of apatite cement. These differences might be due to the much faster resorption rate of the premixed CPCs.

Keywords: Premixed calcium phosphate cement; β-Tricalcium phosphate; Monocalcium phosphate monohydrate; Washout resistance; Biocompatibility

1. Introduction

Bone defects and damage due to disease, accident and aging have long been challenging surgeons and affecting human health and quality of life. Since its first report in the 1980s [1,2], calcium phosphate cement (CPC) has attracted much attention world wide because of its excellent self-setting ability, biocompatibility, osteoconductivity, bioresorbability and moldability [3–6]. CPCs typically set at low temperature following the combination of a solid component containing one or several calcium orthophosphate salts and an aqueous solution, and form a solid calcium phosphate in situ. Several different cement compositions have been developed, the most common of which are based on tetracalcium (TTCP, $Ca_4(PO4)_2O$)–dicalcium phosphate anhydrous (DCPA, $CaHPO_4$), α-tricalcium phosphate (α-TCP, α-$Ca_3(PO4)_2$)-based and β-TCP [7–9]. Based on the differing pH-dependent solubility, thermodynamic stability and kinetic performance of the various calcium phosphate systems, the final product of the setting reaction may be either dicalcium phosphate dehydrate (DCPD, $CaHPO_4{\cdot}2H_2O$) (pH $\leqslant$4.2) or hydroxyapatite (HA, $Ca_5(PO4)_3OH$) (pH >4.2) [10,11]. Although HA-based cements have been more frequently studied because their setting conditions, i.e. pH and reaction product, are closer to the in vivo environment, DCPD is more soluble than HA under physiological conditions and can be resorbed following implantation [12].

Clinical use of CPCs requires the surgeon to have the CPC powder and liquid mixed thoroughly and then to place the paste into the defect within a prescribed time before the paste hardens [13,14]. The operation of on-site powder–liquid mixing not only increases surgical time, but also may compromise the implant performance due to insufficient and inhomogeneous mixing resulting from the limited mixing time [14].

* Corresponding author. Tel.: +86 22 27401902.
E-mail addresses: yinyuji@tju.edu.cn, yinyuji@yahoo.com.cn (Y.-J. Yin).

1742-7061/$ - see front matter © 2009 Acta Materialia Inc. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.actbio.2009.04.024

To avoid these problems, a premixed CPC containing TTCP–DCPA powders, non-aqueous but water-miscible liquid, gelling agent and setting accelerator was developed [13]. This water-free paste was stable and set only when exposed to an aqueous environment through the exchange of the non-aqueous liquid and aqueous solution. However, this premixed CPC had a long setting time (>1 h), and could not provide geometrical integrity and support strength from the initial stage after placement in a defect site. Recently, improved new premixed CPCs with shorter setting times have been developed [14]. However, the addition of certain acidic accelerators or other functional agents may affect their performance in vivo [14,15], and also complicate the preparation of cement.

Compared to TTCP, β-TCP is more stable and cheaper, and most importantly, β-TCP/monocalcium phosphate monohydrate (MCPM)-based cement, known as brushite cement, has a much shorter setting time than TTCP/DCPA-based cement. When mixed with water, β-TCP/MCPM-based cement can set in 30 s [16,17]; in contrast, TTCP/DCPA-based cement needs more than 30 min to harden without setting accelerator [18,19]. The objective of the present study is to develop novel β-TCP/MCPM-based premixed CPCs. Puttied premixed CPC pastes were prepared by combining cement liquids comprised of glycerol or polyethylene glycol with CPC powers that consisted of β-TCP and MCPM. These novel premixed CPCs were capable of rapid setting without accelerator, resisted washout, hardened while being immersed in a physiological solution, and formed DCPD/DCPA. These premixed CPCs: (i) avoid powder–liquid mixing during surgery thereby shortening the surgical time; (ii) allow the paste to be mixed in advance under well-controlled conditions thus avoiding insufficient and inhomogeneous mixing; (iii) will not harden in the package or in a syringe, and will harden rapidly in an aqueous environment with physiological solution; and (iv) eliminate the requirement for the surgeon to mix and finish the placement into the defect within a prescribed time before the paste hardens [14]. The premixed CPCs possessed strength approaching those of cancellous bone and sintered porous HA or β-TCP implants. The inflammatory response around the premixed CPCs implanted in the subcutaneous tissue in rabbits was more prominent than apatite cement due to the much faster resorption rate of the premixed CPCs.

2. Materials and methods

2.1. CPC powder phase

The CPC powder consisted of β-TCP (55% mass fraction) and MCPM (45% mass fraction) at a molar ratio of 1:1. The commercially obtained β-TCP powder (Sichuan University, Sichuan, China) was ball milled in ethanol for 4 h and sieved, giving an average particle size of 9 μm. MCPM was analytical-grade reagent and used as supplied.

2.2. CPC liquid phases

The CPC liquid consisted entirely of a non-aqueous liquid. The non-aqueous liquid was glycerol (Sigma Chemical Co., St. Louis, MO, USA) and poly(ethylene glycol) (PEG 600, Sigma), which were selected because they are non-toxic, biocompatible and have been applied in the food and biomedical fields. For example, the glycerol is known as a lubricant and has been used in chewing gum, beverage and gelatine-containing foods [14]. PEG is used in drug production and in some biomaterials [20,21].

2.3. Preparation of premixed pastes

Premixed CPC pastes were prepared by mixing CPC powder with non-aqueous liquids, i.e. glycerol or PEG, at powder to liquid mass ratio (P/L) of 2.5–3.5 and 2.7–3.7, respectively. These P/Ls were chosen in order to produce pastes that exhibited workable consistencies and were convenient for clinical use. The powder and liquid of each premixed CPC were mixed using a spatula to form a cohesive paste. The pastes were quickly packed into flexible plastic tubes, tightly sealed to isolate them from moisture and stored in a desiccator at room temperature. The premixed CPCs mixed with PEG and glycerol are denoted PP-CPC and PG-CPC, respectively. For the washout resistance test, microstructure analysis and biocompatibility evaluation, specimens with P/Ls of 3.5 and 3.7 for PG-CPC and PP-CPC, respectively, were prepared, since for these P/Ls both premixed CPCs exhibited compromised handling properties and mechanical strength.

Conventional β-TCP/MCPM-based cement (denoted as C-CPC) was prepared as described elsewhere [9]. The C-CPC liquid phase was made by dissolving tetrasodium pyrophosphate (0.2 M) in deionized water.

2.4. Washout resistance test

The washout resistance was tested by manually shaping the premixed CPC paste into an 8 mm diameter ball within 3 min, and then immediately placing this ball into phosphate-buffered solution (PBS, pH 7.4) at 37 °C. According to Refs. [13,14], the material was considered to pass the washout resistance test if the paste ball did not visibly disintegrate in aqueous solution after 10 min. In terms of mimicking the flow situation in vivo, a method was introduced to test the washout resistance in a dynamic situation. In this method, the paste balls were placed in circulating flow generated by the rotation of a magnetic rotor, and the washout resistance of the premixed CPCs was evaluated visibly by the extent of disintegration of the paste balls. Quantitative measurements, e.g. weighing, were not done because of the exchange of the solutions.

2.5. Setting time (ST) measurement

The premixed CPC paste was shaped within 3 min by a stainless steel mold into a cylindrical sample 6 mm diame-

ID	Title	Pages
1128	β-TCP/MCPM-based premixed calcium phosphate cements	13