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The influence of different cellulose ethers on both the handling and mechanical properties of calcium phosphate cements for bone substitution

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ABSTRACT

The influence of cellulose ether additives (CEAs) on the performance of final calcium phosphate cement (CPC) products is thoroughly investigated. Four CEAs were added into the liquid phase of apatitic CPCs based on the hydrolysis of α-tricalcium phosphate, to investigate the influence of both molecular weight and degree of substitution on the CPCs' properties, including handling (e.g. injectability, cohesion, washout resistance and setting time), microstructure (e.g. porosity and micromorphology) and mechanical properties (e.g. fracture toughness and compressive strength). The results showed that even a small amount of CEAs modified most of these CPCs' features, depending on the structural parameters of the CEAs. The CEAs dramatically improved the injectability, cohesion and washout resistance of the pastes, prolonged the final setting time and increased the porosity of CPCs. Moreover, the CEAs had an evident toughening effect on CPCs, and this effect become more significant with increasing molecular weight and mass fraction of CEAs, inducing a significant tolerance to damage. Overall, the molecular weight of CEAs played a major role compared to their degree of substitution in CPCs' performances.

1. Introduction

Since first reported in the 1980s [1–3], calcium phosphate cements (CPCs) have attracted great interest as bone substitutes for the reconstruction of hard tissues owing to their excellent biocompatibility, bioactivity and osteoconductivity [4–6]. Compared with calcium phosphate ceramics, CPCs have the advantage that they can be easily manipulated and shaped, and, in some cases, can be injected into a defect area, thereby not only avoiding invasive surgical procedures but also providing intimate adaptation to the bone cavity even for irregular shapes [7]. The injected paste sets in situ to form apatite in an aqueous environment at body temperature. Moreover, the final composition of hardened CPCs is more similar to the calcium phosphates found in the mineralized tissues than sintered hydroxyapatite [8], with a high specific surface area and a particular microstructure, exhibiting greatly improved reactivity and providing possible application in tissue engineering or drug delivery [9–11].

However, despite the above advantages, CPCs have some critical drawbacks which limit their potential clinical application. One of them is that CPCs without any additives have a poor injectability which is normally characterized by the occurrence of phase separation between the liquid and solid [12]. Furthermore, in most cases, the injected paste tends to disintegrate upon early contact with blood or other physiological solutions due to its weak cohesion [13]. In addition to these poor handling properties, the mechanical properties of hardened CPCs, especially fracture toughness, are intrinsically low, so that cements can only be applied in non-load-bearing locations [14,15].

As a result, many biopolymers, including chitosan [16], cellulose ethers (e.g. hydroxypropyl methylcellulose) [17,18], sodium alginate [19], chondroitin sulfate [20], hyaluronic acid [21], citric acid [22], biodegradable fibers [23] and collagen [24], have been admixed either with the powder or with the liquid of the CPC paste with the aim of improving their handling and/or mechanical properties. Among these polymers, cellulose ethers are of great interest from the viewpoint of washout resistance [18,25–27].

Cellulose ethers, such as methyl cellulose (MC) and hydroxypropyl methylcellulose (HPMC), are water-soluble derivatives of cellulose, which is the most abundant polymer in nature. They have been widely used as anti-washout admixtures in civil engineering to improve the cohesion and anti-washout performance of cement-based materials (e.g. Portland cement) [28,29]. Furthermore, these versatile ethers have been widely used in pharmacology for controlled drug release systems [30,31], in injectable biphasic calcium phosphate suspensions [32,33] and in various formulations of CPCs

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for bone substitution [34,35], since they have been extensively evaluated and have proved to be biocompatible and biodegradable.

Some studies have shown that cellulose ether additives (CEAs) noticeably improve the handling properties of CPC pastes [18,25–27]. However, in most cases, the CEAs (such as HPMC or MC) were used together with other polymer additives in the formulations of CPCs, thus the influences of cellulose ethers alone on the handling and mechanical properties of CPCs are not very clear because of the interference from other additives [34,35]. Additionally, these cellulose ethers are usually considered as a whole class, regardless of their structural parameters, i.e. of their molecular weight and of their level of substitution in methoxyl (MeO) and hydroxypropyl (HPO) groups, which can be designed and adjusted during their manufacturing step. Besides, some studies on Portland cement found that the substituent groups of cellulose ethers play a significant role in terms of the retardation of cement hydration [36–38]. Therefore, it is important to understand the structure–performance relationships of cellulose ethers in CPCs in order to choose the appropriate cellulose ether product and dosage, which can be optimized for the specific application needs in CPCs.

It is worth mentioning that, although the mechanical properties of CPCs were generally evaluated, many of the studies did not relate the mechanical properties of CPCs to their microstructural features (for example porosity), which, from a material science perspective, are the intrinsic factors determining the mechanical performance of materials. On the other hand, most of the studies were conducted with compressive strength or diametrical tensile strength rather than fracture toughness, which is a real limitation for CPCs. In fact, it is the poor fracture toughness (and the brittle behavior) which prevents CPCs from wide application in load-bearing locations. Unfortunately, however, few studies in the literature report such a property, indicating that future research should begin to focus more extensively on fracture toughness, especially on the ways to improve it without sacrificing other important properties that make CPCs good bone substitutes. It has been speculated that the fracture toughness of CPCs could be improved by cellulose ethers [18], but this has never been proved until now.

The purpose of the present study is to solve the above-mentioned issues. In this work, the influence of cellulose ethers with different molecular weights and substitution levels on both handling and mechanical properties of CPCs is thoroughly investigated. Four typical cellulose ethers, namely A15, E4M, K4M and K15M, are dissolved in the cement liquid to investigate their effects on the handling properties (e.g. injectability, cohesion, washout resistance and setting time) and mechanical properties (e.g. fracture toughness and compressive strength associated with microstructure) of CPCs, using α-tricalcium phosphate (α-TCP) as the main inorganic reactive ingredient.

2. Materials and methods

2.1. Cement preparation

All of the reagents used in this experiment were of analysis grade and were used without any further purification. The α-TCP powder was synthesized using a previously described method [15]. The phase purity of the α-TCP powder was examined with X-ray diffraction (XRD, X'pert pro, PANalytical, Netherlands) and no other phase was seen (Supplementary data, Fig. S1). To prepare the solid phase of CPCs, 2 wt.% of precipitated calcium-deficient hydroxyapatite (CDHA) was added to the α-TCP powder as a seed for subsequent crystallization of apatite, and the powder mixture was milled in a Retsch RM100 Mortar Grinder for 1 h to get a fine powder. The particle size distribution of the fine powder mixture (Supplementary data, Fig. S2) was measured by laser diffraction granulometry after dispersion in ethanol in an ultrasonic bath, and the mean particle size was found to be 6 μm.

Table 1
Four typical products of METHOCEL cellulose ether.

Product	MeO (%)[a]	HPO (%)[a]	2% viscosity range (mPa s)[a]	Molecular weight range (g mol^{-1})[b]
A15	30	0	12–18	46,000–50,000
E4M	29	8.5	3000–5600	320,000–380,000
K4M	22	8.1	3000–5600	320,000–380,000
K15M	22	8.1	11,250–21,000	480,000–540,000

[a] The parameters are supplied by Dow Chemical company [39].
[b] The molecular weights of the products were measured by Keary [40].

The liquid phases of CPCs were prepared by dissolving four typical cellulose ether products – A15, E4M, K4M and K15M (METHOCEL, Dow Chemical) (Table 1) – in a 2.5 wt.% Na_2HPO_4 solution using a method provided by Dow Chemical company [39]. Specifically, a "hot/cold" technique was used. Cellulose ether powders are in fact soluble in cold water but insoluble in hot water. However, when mixed directly with cold water, the polymer powders tend to lump due to the incomplete wetting of individual powder particles. Therefore, the polymer powder was first dispersed by thoroughly mixing with the Na_2HPO_4 solution at 80 °C using a combined hot-plate magnetic stirrer until all the particles were completely wetted and evenly dispersed. Then the solution was cooled with agitation and transferred into a refrigerator to lower the temperature further, at which point polymer powder became water soluble and started to hydrate. After that, the solution was further stirred at room temperature for 3 days until hydration was complete. The first letter of the product designation specifies the chemistry of the cellulose ether: "A" indicates methylcellulose products, whereas "E" and "K" indicate hydroxypropyl methylcellulose products with different substitution levels of MeO and HPO groups. The number and/or letter following the first letter indicate the viscosity of a 2% aqueous solution at 20 °C, which increases with the molecular weight of the polymers [39,41]. A 2.5 wt.% Na_2HPO_4 solution was used as the liquid phase in the control group.

For the preparation of CPC pastes, a unique liquid-to-powder (L/P) ratio of 0.45 ml g^{-1} was used, but the polymer content in the CPC was varied by using different concentrations of polymers in the liquid phase. The different polymer solutions prepared are listed in Table 2. The numbers in the heading row indicate the proportion of polymer in the final CPC without taking water into account, i.e. the weight percentage of polymer with respect to the sum polymer + inorganic solid phase. The numbers in the other rows represent the concentrations of the polymers in the liquid phase solution to get the target mass fractions indicated in the heading row. For E4M, K4M and, above all, K15M, a homogeneous polymer solution with high concentrations could not be obtained due to the excessive viscosity.

CPC pastes were prepared by manually mixing the above-prepared solid and liquid phases in a mortar for around 1.5 min. The resulting pastes were then used for the assessment of several handling properties, as detailed in the following sections. Specimens of rhombohedral shape were then prepared by pressing the pastes

Table 2
The concentration of CEAs in solution for the preparation of CPCs.

Mass fraction, by mass of solid phase	0.25%	0.50%	0.75%	1.00%	1.25%	1.50%	2.00%
A15 (w/v%)[a]		1.12		2.23		3.34	4.45
E4 M (w/v%)	0.56	1.12	1.67	2.23	2.78		
K4 M (w/v%)	0.56	1.12	1.67	2.23	2.78		
K15 M (w/v%)	0.56	1.12	1.67				

[a] 1 w/v% = 10 g l^{-1}.