Acta Biomaterialia 6 (2010) 2863–2873

Contents lists available at ScienceDirect

Acta Biomaterialia

journal homepage: www.elsevier.com/locate/actabiomat

Review

New processing approaches in calcium phosphate cements and their applications in regenerative medicine

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ARTICLE INFO

Article history:
Received 15 November 2009
Received in revised form 22 January 2010
Accepted 25 January 2010
Available online 01 February 2010

Keywords:
Calcium phosphate cements
Scaffolds
Microcarriers
Granules
Bone regeneration

ABSTRACT

The key feature of calcium phosphate cements (CPCs) lies in the setting reaction triggered by mixing one or more solid calcium phosphate salts with an aqueous solution. Upon mixture, the reaction takes place through a dissolution–precipitation process which is macroscopically observed by a gradual hardening of the cement paste. The precipitation of hydroxyapatite nanocrystals at body or room temperature, and the fact that those materials can be used as self-setting pastes, have for many years been the most attractive features of CPCs. However, the need to develop materials able to sustain bone tissue ingrowth and be capable of delivering drugs and bioactive molecules, together with the continuous requirement from surgeons to develop more easily handling cements, has pushed the development of new processing routes that can accommodate all these requirements, taking advantage of the possibility of manipulating the self-setting CPC paste. It is the goal of this paper to provide a brief overview of the new processing developments in the area of CPCs and to identify the most significant achievements.

1. Introduction

When calcium phosphate cements (CPCs) were introduced more than two decades ago, they represented a real breakthrough in the field of bioceramics. The possibility of having a mouldable calcium phosphate (CaP) paste able to self-set in vivo reported significant benefits for several clinical situations such as the treatment of osteoporosis related fractures, unstable fractures, maxillofacial defects and deformities, and more recently for other specific applications such as vertebroplasty [1,2].

In general, CPCs are hydraulic cements, formed by a combination of one or more calcium orthophosphates, which upon mixing with the liquid phase, form a paste that is able to set and harden after being implanted within the body. The cement setting reaction is a dissolution and precipitation process, and the entanglement of the precipitated crystals is the mechanism responsible for cement hardening.

The reaction product of CPCs can theoretically be any of those calcium orthophosphates that can precipitate at low temperature in aqueous systems. However, despite the large number of possible formulations, most of the CPCs give as the end-product either precipitated hydroxyapatite (pHA) or brushite (dicalcium phosphate dihydrate, DCPD), which in fact are the most stable calcium orthophosphate phases at pH >4.2 and pH <4.2, respectively.

CPCs represent an alternative to the traditional high temperature crystalline CaP ceramics, namely sintered hydroxyapatite (HA), which is hardly resorbable, or the more resorbable β-TCP (tricalcium phosphate). Some of the salient features of CPCs are their excellent biocompatibility, bioactivity and osteoconductivity. However, there are still some aspects to be improved, crucial issues such as the control of the resorption rate, the enhancement of the osteogenic potential, or the compliance with clinical requirements and surgeon's needs [3].

On the other hand, in recent years, new strategies that exploit the intrinsic properties of CPCs have been envisaged, and the possibility to use them for the fabrication of scaffolds or pre-set granules through various processing techniques has been put forward. In fact, the versatility of this family of materials and their ability to harden at low temperature make them very attractive materials to be used in combination with different techniques. The benefits of using CPCs in pre-set solid blocks or granules, when injectability is not an issue anymore, are still numerous when compared to conventional ceramic sintering techniques. These advantages are related mainly to the fact that the consolidation of the material is

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doi:10.1016/j.actbio.2010.01.036

achieved through a low-temperature dissolution–precipitation reaction that, somehow, mimics the processes taking place in the biomineralization phenomena. This allows obtaining hydrated compounds with morphologies and compositions very similar to the CaP found in the mineralized tissues, with high specific surface area and a particular microtexture that can play a significant role in osteoinduction related phenomena [4]. Furthermore, the low temperature setting renders CPCs an ideal platform for delivering drugs or bioactive molecules that can be used to increase the bone regeneration capacity of the material [5].

All these issues have triggered considerable research efforts, resulting in a large number of publications in recent years. The goal of this paper is to give a brief overview of the new developments in CPCs for regenerative medicine and to identify the most significant achievements.

2. Synthesis of CPC-based scaffolds

2.1. General strategy

While one of the greatest advantages of CPCs lies on the consolidation reaction of those materials, i.e. gradual hardening of a viscous paste onto a solid body, allowing their use as both injectable pastes and pre-set materials, cements per se cannot be used as scaffolds in tissue engineering applications because their lack of macroporosity. In fact, macroporosity has emerged as one of the key requirements for the materials design to act as substrates for tissue engineering and regenerative medicine. The role of macroporosity is to guide and support tissue ingrowth within the material so that colonization and angiogenesis events can take place along with the progressive bioresorption of the scaffold. Thus, the purpose of this section is to review the different strategies adopted for the fabrication of macroporous scaffolds from CPCs while maintaining the inherent properties of cements. The different methods being used to create macroporosity are summarized in Table 1, and the main properties of the obtained CPC-based scaffolds are shown in Table 2. Some of the methods allow maintaining the injectability of the CPCs, while others pre-set macroporous blocks or scaffolds are obtained.

2.2. Leaching/degradation of a second phase

A classical method of introducing macroporosity is through a leaching process. Particulates are introduced as porogens during the preparation of the cement paste. Depending on the solubility of the sacrificial material these are dissolved before implantation or gradually degraded in vivo. Along this line are the works by Markovic et al. [6], Takagi and Chow [7], Barralet et al. [8], Fernández et al. [9], and Cama et al. [10], among others, that employed soluble particulates of sucrose, mannitol, $NaHCO_3$, $CaSO_4{\cdot}2H_2O$ or Na_2HPO_4 to create the macroporosity. The degree of solubility of the particulates during the setting reaction of the cement is responsible for the content and dimension of the macroporosity. One important limitation that can be envisaged from this route is the need to add a large amount of porogenic agent to guarantee interconnectivity of the porosity, thus compromising not only the excellent biocompatibility and bioactivity of CPCs but also the cements' injectability. Another shortcoming is the lack of strength of the resulting material, especially if particulates dissolve quickly, greatly limiting its applications. An innovative approach that aims at overcoming the lack of interconnectivity and initial strength consists in using resorbable fibers. Xu and Quinn [11] and Zuo et al. [12] added resorbable polyglactin or poly(ε-caprolactone) and poly(L-lactic acid) fibers in CPC. These fibers had the function of reinforcing the cement, providing the needed short-term strength and toughness, and gradually dissolving afterwards, leaving behind macropores suitable for bone ingrowth. They also investigated [13,14] the effects of fiber length, fiber volume fraction and the type of fiber mixed with the CPC. One interesting advantage of long fibers over particulates and short fibers is the fact that, once resorbed, they can form interconnected pores inside the CPC structure facilitating bone tissue regeneration. The same authors underwent similar studies using resorbable meshes instead of fibers and confirmed once more the superior strength of these composites [15,16], although obviously, these materials were not injectable. In a more recent work by Xu et al., injectable cements were prepared combining the use of a fast dissolving porogen with the reinforcing effect of fibers. To guarantee the cement paste injectability, Xu incorporated chitosan [17] or hydroxypropyl methylcellulose [18] in the cement formulation.

Table 1
Processing techniques for the preparation of CPC-based scaffolds.

Method	Via	Advantages	Disadvantages
Leaching	Particulates Fibers Meshes	Easy process Versatile Degradability and initial strength tailorable Can be made injectable	Poor reproducibility Residual porogens Scarce or null pore interconnectivity (in the case of particles)
Foaming	Gas generation from acid–base and decomposition reactions	Easy process	Scaffolds with low initial strength Poor reproducibility Risk of embolism
	Surface active foaming agents	Easy process Injectable pastes	Scaffolds with low initial strength
Emulsion	Oil–water mixtures	Tailorable size and content of porosities	In some cases may require a cleaning step to remove oil Risk of embolism
Freeze drying	Water freezing + sublimation	Highly porous structures	Energy and time consuming
Templates	Polymeric foams (*positive replica*)	High interconnectivity and porosity	Very low strength Residual components from firing step Sintering and crystal growth from the firing step
	Indirect rapid prototyping (*negative replica*)	Higher strength	Limited porosity and connectivity Problems with residual solvents
Rapid prototyping	Direct rapid prototyping (3D-P)	Accurate control of the scaffold's architecture Reproducible and fast	Microarchitecture limited by the particle's size