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Review article

Critical review: Injectability of calcium phosphate pastes and cements

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ABSTRACT

Calcium phosphate cements (CPC) have seen clinical success in many dental and orthopaedic applications in recent years. The properties of CPC essential for clinical success are reviewed in this article, which includes properties of the set cement (e.g. bioresorbability, biocompatibility, porosity and mechanical properties) and unset cement (e.g. setting time, cohesion, flow properties and ease of delivery to the surgical site). Emphasis is on the delivery of calcium phosphate (CaP) pastes and CPC, in particular the occurrence of separation of the liquid and solid components of the pastes and cements during injection; and established methods to reduce this phase separation. In addition a review of phase separation mechanisms observed during the extrusion of other biphasic paste systems and the theoretical models used to describe these mechanisms are discussed.

Statement of Significance

Occurrence of phase separation of calcium phosphate pastes and cements during injection limits their full exploitation as a bone substitute in minimally invasive surgical applications. Due to lack of theoretical understanding of the phase separation mechanism(s), optimisation of an injectable CPC that satisfies clinical requirements has proven difficult. However, phase separation of pastes during delivery has been the focus across several research fields. Therefore in addition to a review of methods to reduce phase separation of CPC and the associated constraints, a review of phase separation mechanisms observed during extrusion of other pastes and the theoretical models used to describe these mechanisms is presented. It is anticipated this review will benefit future attempts to develop injectable calcium phosphate based systems.
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1. Introduction

Compounds of calcium phosphate (CaP) have been investigated as bone repair materials since 1920 [1]. However, they saw little use in clinical applications until the 1970s when CaP materials were used as bone substitutes in the form of porous blocks and granules [2–4]. The clinical potential of CaP materials further increased in the early 1980s with the development of self-setting calcium phosphate cement (CPC) [5]. In addition to its potential to mimic the mineral phase of bone, CPC has the ability to be moulded into bone defects and implant sites, then harden in situ to provide stability. This ability of CPC has shown great potential in percutaneous surgery whereby CPC is injected into the body to fill bone defects and stabilise fractures. Although CPC has shown clinical success in several orthopaedic applications requiring delivery by injection [6–12], it is thought that several issues currently prevent routine application in clinical applications. This has given rise to a high volume of studies aimed at improving the delivery of CPCs and broadening their clinical use [3].

Many of the studies attempting to optimise CPC for clinical applications focussed on improving the delivery of CPC to the surgical site through injection. A major issue inhibiting successful delivery of CPC is the occurrence of phase separation during injection. If phase separation occurs the extrudate has a higher liquid content than desired, which may cause extravasation from the surgical site and be detrimental to the final properties of the set CPC. The occurrence of phase separation during injection/extrusion of CaP pastes and cements, and methods to reduce it, is the principal focus of this review.

Due to the high volume of studies published concerning CPCs, review articles have proven useful in presenting a summary of recent advances, highlighting current issues and opportunities within CPC research. The focus of recent comprehensive reviews have included: processing techniques [13], mechanical performance [14], methods to reinforce CPCs [15,16], the role of polymeric additives [17], *in vivo* degradation and resorption of CaP materials [18], influence of CaP material properties on cell behaviour [19], CaP materials as drug delivery systems [20–22], stem cell delivery via CPC [23], and the synthesis and application of nanostructured CaP based materials [24–26], in addition to broader overviews of recent progress in the development of CPC materials [27–29].

In this article established methods to reduce the phase separation of CaP pastes and cements and the limits of their application are reviewed. Brief discussions relating to the other crucial properties of CPC and their influencing parameters are also included as many established methods to reduce phase separation are detrimental to the other crucial properties, as evident throughout this review. Therefore, when optimising any property of CPC, it is important to consider all the crucial properties. In addition phase separation mechanisms observed during the injection or extrusion of other biphasic paste systems and the theoretical models used to describe these mechanisms are discussed. It is anticipated that including comparisons to work from fields outside of biomaterials will give a new perspective and a greater understanding of the phase separation mechanism of CPC during injection, which will benefit researchers attempting to optimise a fully injectable CPC.

2. Types of calcium phosphate cements

Due to the high level of interest and research into CPC, many different formulations of CPC have been developed. They can be divided into two principal groups: (1) apatite (hydroxyapatite, HA, and calcium-deficient HA, CDHA) and (2) brushite cements (dicalcium phosphate dihydrate, DCPD) [30]. Both apatite and brushite CPC are produced by mixing a powder component consisting of one or more calcium orthophosphates with an aqueous solution. The mixing of these two phases induces the dissolution of the initial calcium orthophosphates. This is followed by precipitation into crystals of HA, CDHA or DCPD. During precipitation the newly formed crystals grow, and it is the entanglement of these new crystals, providing mechanical rigidity, that causes the cement to physically harden or set [29].

Hydroxyapatite (HA) can be formed via an acid-base reaction of tetra-calcium phosphate, TTCP (basic), and dicalcium phosphate anhydrous, DCPA (slightly acidic), Eq. (1).

$$Ca_4(PO_4)_2O + CaHPO_4 \rightarrow Ca_5(PO_4)_3OH \quad (1)$$

Calcium deficient HA (CDHA) can be obtained via the hydrolysis of a metastable CaP e.g. α-tricalcium phosphate (α-TCP), Eq. (2).

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