



Injectability of calcium phosphate pastes: Effects of particle size and state of aggregation of β -tricalcium phosphate powders



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ABSTRACT

The present study discloses a systematic study about the influence of some relevant experimental variables on injectability of calcium phosphate cements. Non-reactive and reactive pastes were prepared, based on tricalcium phosphate doped with 5 mol% (Sr-TCP) that was synthesised by co-precipitation. The varied experimental parameters included: (i) the heat treatment temperature within the range of 800–1100 °C; (ii) different milling extents of calcined powders; (iii) the liquid-to-powder ratio (LPR); (iv) the use of powder blends with different particle sizes (PS) and particle size distributions (PSD); (v) the partial replacement of fine powders by large spherical dense granules prepared via freeze granulation method to simulate coarse individual particles. The aim was contributing to better understanding of the effects of PS, PSD, morphology and state of aggregation of the starting powders on injectability of pastes produced thereof. Powders heat treated at 800 and 1000 °C with different morphologies but with similar apparent PSD curves obtained by milling/blending originated completely injectable reactive cement pastes at low LPR. This contrasted with non-reactive systems prepared thereof under the same conditions. Hypotheses were put forward to explain why the injectability results collected upon extruding non-reactive pastes cannot be directly transposed to reactive systems. The results obtained underline the interdependent roles of the different powder features and ionic strength in the liquid media on determining the flow and injectability behaviours.

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1. Introduction

Calcium phosphate bone cements (CPC) have attracted much attention in recent years opening up a new era in the medical applications since early 1980s [1,2]. CPC offer numerous attractive advantages including resorbability, osteoconductivity, resemblance with chemical bone composition, capability to establish chemical bonds with the hard tissues, fast setting time, excellent mouldability, outstanding biocompatibility, etc. [3–7]. CPC also provide the opportunity for bone grafting using alloplastic materials, which are unlimited in quantity and provide no risk for infectious diseases [7]. Injectability and the practically isothermal *in situ* setting offer great opportunities to decrease the invasiveness and painfulness of surgeries, reduced recovery time and increase the overall benefits for the patient and the medical system [8,9]. However, the commercially available CPC formulations are not completely satisfactory [10,11]. The main shortcomings include

insufficient mechanical strength and poor injectability. These properties are crucial for bone graft applications in surgical procedures for the correction of vertebral compression fractures, usually caused by osteoporosis. The currently used polymethylmethacrylate (PMMA) based cements injected into the vertebra offer good compressive strength but unsatisfactory fatigue resistance [12] and the high exothermicity of the polymerisation reactions might cause extensive necrosis [4,5,7,13]. The monomer toxicity and the inability to participate in the biological processes of bone remodelling constitute other weak points of PMMA based cements [3,6]. These concerns drove the search for CPC with improved flow and mechanical properties in the recent years. But achieving CPC pastes with good injectability still remains a major challenge as flow properties are affected by several factors such as: (i) average particle size (PS) and particle size distributions (PSD) of the starting powders; (ii) fraction and nature of the phases presented; (iii) the presence of strongly bonded particles (aggregates); (iv) particles shape; (v) liquid-to-powder ratio (LPR); (vi) the presence of rheological modifiers and/or additives with specific roles [4–6,14–27].

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Injectability is expressed as the percentage of paste that can be extruded from a syringe, ideally in a homogeneous way under an applied force [17]. The eventual occurrence of solid/liquid segregation (also known as filter pressing effect) during injection worsens or even hinders injectability [14,17,24]. In such circumstances the firstly extruded paste contains more liquid than the initial mixture. This paste heterogeneity increases extrusion load and might clog the cannula and block the process, leaving retained paste in the syringe that contains less amount of liquid than the initial mixture.

Narrow PSD and the presence of aggregates (strongly bonded particles) tend to confer a shear thickening behaviour to the pastes and increase their tendency to segregate upon extrusion. Increasing the viscosity of mixing liquid is a common strategy to decrease the filter pressing effect and enhance injectability, but further work is required to better understand how to control the flow behaviour [15,17,23,24]. Therefore, drawing firm conclusions about the effects of each experimental variable is difficult when several factors are concomitantly changed, as it happens in a complex reactive CPC paste made of ill characterised powders. Simplifications were attempted in studies carried out with non-reactive systems (aqueous suspensions of tricalcium phosphate, β -Ca₃(PO₄)₂- β -TCP) [14,17,28], but no systematic efforts were made towards discriminating between the size of particles and the size of aggregates. The main limitations towards evaluating the specific effects of each experimental variable on injectability are: (i) the lack of well characterised powders in what concerns PS and PSD; (ii) the frequent confusion between PS and aggregates size; and (iii) the limited size range of the practically achievable non-aggregates particles.

Therefore, the main goal of this study is to contribute to a better clarification about the effects of particle size and particle size distribution and state of aggregation on the injectability and filter pressing effect of CPC pastes. For that, non-setting and setting pastes from strontium-doped tricalcium phosphate (Sr-TCP) powders calcined at different temperatures (800–1100 °C) and milled for different times (0, 6 and 12 min), as well as some powder blends, were considered. Furthermore, relatively large individual particles (spherical granules) of the same material were prepared and added in controlled amounts to the previous formulations to enlarge the PS scope.

2. Materials and methods

2.1. Powders preparation and characterisation

The powder selected for the present study was β -TCP doped with 5 mol% of strontium (Sr-TCP). Improvements in thermal stability of β -TCP powders [29] as well as high performance of CPC derived from Sr-doped TCP [30] were the reasons for selecting the strontium-doped powders. The Sr-TCP in the present work was prepared by a precipitation method described by Kannan et al. [31] with a few minor modifications reported recently [32]. The precipitated powder was vacuum filtered, dried, ground and sieved through a mesh size of 200 μ m, divided into four batches and each portion was then heat-treated at one of the following temperatures (800, 900, 1000 and 1100 °C) in air (Thermolab furnace, Pt30%Rh/Pt6%Rh-thermocouple). The heat treatment schedule included a heating rate of 5 °C min⁻¹, a dwelling time for 2 h at the maximum temperature, followed by natural cooling to room temperature [31]. Each of these powders was submitted to dry milling for different times (6 and 12 min) in a 250 mL planetary agate mill (weight ratio of balls to powder of 3:1). For each calcination temperature, the following sub-lots of powders were obtained: (i) non-milled; (ii) milled for 6 min; and (iii) milled for 12 min. The codes for powder samples consist of two parts

separated by a hyphen, the first one relative to temperature (800, 900, 1000, 1100 °C) and the other to milling time (0, 6, 12 min). For example, 800-0 refers to a non-milled powder sample calcined at 800 °C, while 1100-12 refers to a powder sample calcined at 1100 °C and milled for 12 min. All investigated powders were passed through a 40 μ m sieve.

The qualitative analyses of crystalline phases presented in the powders heat-treated at different temperatures were performed by X-ray powder diffraction (XRD) using a high-resolution Rigaku Geigerflex D/Mac, C Series, diffractometer with Cu K α radiation ($\lambda = 1.54096$ Å). Data sets were recorded in the 2θ range 20–50° with a step size of 0.02° 2θ s⁻¹. Elemental analyses of the powders for Ca, Sr and P were determined using inductively coupled plasma (ICP) spectrometry (ICP-OES Jobin Yvon Activa M., USA). Particle size distributions of the Sr-TCP powders were measured in a laser scattering instrument (Coulter LS230, Buckinghamshire, UK, Fraunhofer optical model). Specific surface area (SSA) of powders were obtained according to the BET method using a Micromeritics Gemini 2370 V5.00 (Norcross, USA) through the gas adsorption measurements, after degassing the powders in a Micromeritics Flow Prep 060 (Norcross, USA). The morphology and microstructure of the powders heat-treated at different temperatures, before and after milling at different times, were observed by Scanning Electron Microscopy (SEM, Hitachi S-4100, Tokyo, Japan).

2.2. Granules preparation and characterisation

Spherical dense granules might be regarded as individual large particles, thus enabling enlarging the range of available particle sizes and extending the scope of the studies aiming at assessing the effects of PS and PSD on the flow behaviour and injectability. With this purpose, a high concentrated (47 vol.% solids) aqueous suspension was prepared from the Sr-TCP powder calcined at 800 °C in presence of 0.4 wt.% ammonium salt of polyacrylate dispersant (BK Ladenburg, Germany). The suspension was ball milled for several days in order to obtain a well deagglomerated system using a weight ratio of zirconia balls to powder of 3:1. The as deagglomerated powder exhibited a narrow particle size distribution with two particle populations centred at 2.5 μ m and 0.05 μ m, and an overall $D_{50} \approx 0.51$ μ m. The suspension was then sprayed into liquid nitrogen (Power Pro freeze granulator LS-2, Gothenburg, Sweden) and the frozen granules were then lyophilised (Labconco, LYPH Lock 4.5, Kansas City, MO) [33]. The dried granules were subsequently sintered at 1150 °C in air atmosphere for 2 h at 5 °C min⁻¹ heating rate, and finally separated by size to obtain a size range between 20 and 40 μ m. Differential thermal analysis (DTA, Setaram Labsys, Setaram Instrumentation, Caluire, France) was used to determine the maximum sintering temperature in order to obtain Sr-TCP granules of β -TCP phase (without α -TCP phase). The evolution of powder morphology with milling time and the microstructure of the sintered granules were observed by Scanning Electron Microscopy (SEM, Hitachi S-4100, Tokyo, Japan). The density of the granules was determined by helium gas pycnometry (Accupyc Quantachrome apparatus, Florida, USA) and complemented by SEM observation.

2.3. Injectability evaluation

2.3.1. Preparation of the pastes

Non-setting pastes (non-reactive systems that do not harden over time) were prepared by mixing 6 g of each Sr-TCP powder sample with an aqueous solution of 3 wt.% of polyvinylpyrrolidone (PVP, Sigma-Aldrich, Germany) using liquid to powder ratios (LPR) of 0.28, 0.34, 0.4 and 0.6 g mL⁻¹. Setting pastes (reactive systems) were also prepared by mixing in a 1:1 wt. ratio, Sr-TCP powders and monocalcium phosphate monohydrate (MCPM,

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