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The rheological behavior of a fast-setting calcium phosphate bone cement and its dependence on deformation conditions

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ABSTRACT

Calcium phosphate cements are osteoconductive biomaterials that are widely used for bone repair and regeneration applications, including spinal fusion, vertebroplasty, khyphoplasty, cranioplasty and periodontal surgeries. The flow and deformation behavior (rheology) and injectability of the calcium phosphate bone cements to the treatment site are governed by the setting kinetics of the cement during which the initially flowable, viscous cement paste transforms into a rigid elastic solid. Here time-dependent development of the linear viscoelastic properties of a brushite-forming calcium phosphate cement are characterized and linked to the mechanism and kinetics of the setting reaction and to the injectability window available during the surgical applications of the cement. The setting kinetics is shown to be a function of the deformation conditions that are utilized in rheological characterization, emphasizing the intimate relationships between setting kinetics, particle to particle network formation and deformation history. Furthermore, the preshearing of the calcium phosphate cement prior to injection and temperature are shown to alter the kinetics of the setting reaction and thus to provide additional degrees of freedom for the tailoring of the rheological behavior and injectability of the calcium phosphate cement.

1. Introduction

Calcium phosphate ceramics (Ca-P), are biocompatible and osteoconductive biomaterials that are available as granules, blocks or cements and are widely used in dentistry, orthopedic and reconstructive surgeries (Ooms et al., 2002; Jarcho, 1986; Jarcho, 1981; Costantino and Friedman, 1994). Highly crystalline and dense Ca-P ceramic blocks or granules can be obtained by sintering at temperatures ≥ 1000 °C. Ca-P ceramics can also be employed as flowable bone cements which can be injected to the treatment site to set, i.e., to transform into a rigid solid in situ., Such CaP cements are highly filled suspensions, which consist of a powder containing one or more calcium phosphate compounds and a liquid phase that can consist of water, saline or sodium phosphate solutions (Ooms et al., 2002). One drawback of the CaP cements is the possible migration of CaP particles into tissues which surround the application location. This can give rise to Ca-ion levels which are locally increased to above the physiological level and result in cellular dysfunction in vital organs (Castilla-Guerra et al., 2006; Iacovelli et al., 2011). For this reason CaP cements are generally not used at locations that are in the vicinity of brain which is especially sensitive to Ca^{2+} ion fluctuations.

Freshly prepared Ca-P cement suspensions exhibit relatively low shear viscosity and elasticity (ability to hold their shape) and can be readily injected from a syringe into a bone defect site under manual pressure. Ideally the Ca-P cement needs to be injected to fill the defect cavity prior to its “dough time” (the time at which the Ca-P cement no longer sticks to surgical gloves). The time window over which the Ca-P cement remains injectable is limited by the kinetics of its setting reaction and the entanglements of the crystals that precipitate and form particle-to-particle networks (Ooms et al., 2002; Ginebra et al., 1995a; Fernandez et al., 1996, 1998a, 1998b; Sarda et al., 2001). During the setting reaction the shear viscosity of the Ca-P cement increases exponentially and the cement gains elasticity and hardness. Generally freshly-prepared Ca-P cement formulations remain injectable for about 3 min in dentistry and 8 minutes in orthopedic surgeries (Jansen et al., 2005).

The analysis of the setting kinetics and the characterization of the changes in the rheological behavior of calcium phosphate cements during setting are more urgent tasks for brushite-forming cements in comparison to hydroxyapatite-forming Ca-P cements. This is because brushite-forming cements gel (gain elasticity) and set considerably faster than hydroxyapatite-forming cements due to the fast dissolution

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of their acidic phase and the water consuming reaction between the acidic and basic precursors (Bohner, 2000). A typical brushite forming cement formulation sets in a few minutes and this period can increase or decrease depending on its water content. However, changing the concentration of the aqueous phase is generally not an option for the control of the setting kinetics of brushite-forming cements. The presence and consumption of excess water leads to the formation of micropores, which reduce the mechanical properties (Hofmann et al., 2009). On the other hand, reducing the water content to a concentration that is lower than optimum increases packing inhomogeneities, shear viscosity and adversely affects the workability and injectability of brushite-forming cements during surgery (Bohner and Baroud, 2005).

The setting kinetics of a calcium phosphate cement is conventionally described by various critical times ("setting times") at which the setting reaction is initiated, reaches a maximum rate and is completed. The setting times of Ca-P bone cements are determined according to two standard test methods (Standard test method for time of setting of hydraulic-cement paste by Gillmore needles, 1993; Standard test method for time of setting of hydraulic cement by Vicat needle, 2002). Both tests are based on the measurement of the surface hardness of the Ca-P cement against an indenting needle as a representation of its resistance to deformation and flow during the surgical operation. In the former method, the initial and final setting times are defined as the times necessary for the setting cement to support static pressures of 0.3 MPa and 5 MPa, respectively. The final setting time of a Ca-P cement is generally aimed to be less than 15 minutes. It is obvious that the kinetics of the setting reaction cannot be described using setting times alone. However, in various previous investigations it was only the setting times that were determined and related to myriad variables that affect dissolution and crystallization, such as the powder/liquid ratio, temperature, pH, seed material content, precursor particle size and crystallinity, calcium and phosphate ion concentrations, ionic strength and chemical retarding reagent concentrations (Bermudez et al., 1994a, 1994b, 1994c; Ginebra et al., 1994; Fernandez et al., 1999a, 1999b; Driessens et al., 1993; Ginebra et al., 1995b). Furthermore, the time and deformation rate dependent changes in the shear viscosity and elasticity of the Ca-P cement during its transformation from a readily flowable suspension to a rigid solid have also not been well-documented. Such data have the potential to facilitate the accurate characterization of the setting kinetics of individual Ca-P cement formulations, to establish flowability versus structure correlations, to provide more precise definitions of injectability windows, and to enable the probing of deformation history based methods for the control of the flowability and injectability of Ca-P cements.

In this study the dynamic properties, i.e., the storage modulus, $G'(\omega)$, loss modulus, $G''(\omega)$, and the magnitude of the complex viscosity,$\eta^*(\omega)$, of brushite-forming Ca-P cement are characterized during its setting reaction. To our knowledge this is the first investigation of the dynamics of the setting reaction of brushite-forming Ca-P cements via the characterization of their linear viscoelastic material functions that reflect the development of elasticity and the viscosity of the brushite-forming cements during the setting reaction. The use of a rotational rheometer to characterize the setting kinetics further provides the capability to apply different shearing histories prior to or during the setting reaction. This capability has the potential to provide additional mechanisms to independently control the setting rate and thus the injectability and mechanical properties of the Ca-P bone cement during surgery.

2. Materials and methods

Brushite-forming calcium phosphate cement consisting of stoichiometric amounts of β-tricalcium phosphate (obtained from Sigma Aldridge with purity of 96%) and monocalcium phosphate monohydrate (obtained from J.T. Baker with purity of 99.5%) were mixed with 1 wt% of brushite seeds (obtained from Sigma Aldridge with purity of 98%). The powder mixture batch was prepared daily and stored in a desiccator. The setting kinetics of the brushite-forming cement was regulated by the addition of citrate-containing salts or acid (Hofmann et al., 2006a, 2006b). The citrate groups are adsorbed at the surfaces of calcium phosphate crystals and introduce a high electrostatic charge (Barralet et al., 2005), resulting in the retardation of both the dissolution and crystallization of calcium phosphates by chelating free ions, stabilizing the suspension and blocking crystal growth sites. In our investigation a 0.5 M aqueous citric acid solution was prepared using citric acid with purity of 99.5% (Sigma Aldridge). Typically, 1 g of cement powder was mixed with 1 ml of citric acid solution (0.5 M) to set as brushite according to the following reaction:

$$\beta\text{-}Ca_3(PO_4)_2 + Ca(HPO_4)_2.H_2O + 7H_2O \rightarrow 4CaHPO_4{\cdot}2H_2O \quad (1)$$

For the mixing process a Misonix XL2020 ultrasonic processor was used. The sonicator generates liquid jet streams as a result of ultrasonic cavitation to overcome the attractive van der Waals forces between the particles. Sonication can give rise to significant temperature increases that can be detrimental to the integrity of the suspension. The power input to the sonicator was kept at a low 30 W so that the bulk temperature of the cement suspension could be kept in the vicinity of ambient temperature.

2.1. Characterization of the setting kinetics and rheological behavior

The kinetics of the setting reaction and the associated time-dependent changes in viscous and elastic behavior were characterized using a rotational rheometer, i.e., an Advanced Rheometric Expansion System (ARES) Rheometer (available from TA Instruments) employing small-amplitude oscillatory shearing. During oscillatory shearing the cement specimen was sandwiched in between two Al disks (25 mm diameter), one of which oscillates at constant angular velocity while the second disk remains stationary. The free surfaces of the specimens in between the parallel plate fixtures were always sealed via coating with a low molecular weight silicone oil. The silicone polymer established a diffusion barrier and prevented the evaporation of the liquid phase.

Two different procedures were followed for the characterization of the time-dependent development of elasticity and viscosity during setting. In both procedures the freshly-mixed Ca-P cement samples were transferred from the mixing vessel to the rheometer (a process that took less than three minutes) and were loaded into the gap between the parallel plate fixtures of the rheometer. The first set of freshly-prepared Ca-P cement suspensions were kept without shearing (under quiescent conditions) for various durations of time, prior to the characterization of their dynamic properties. In these experiments the principal parameter was the duration of time that elapsed between the preparation of the Ca-P cement and the initiation of the rheological characterization. In other words, this first group of Ca-P cement samples were allowed to rest for various durations under quiescent conditions (no shearing) and then subjected to time-dependent oscillatory shear at a frequency of 1 rad/s and strain amplitude of 0.04 at 25 °C. These experiments represent the baseline behavior of the Ca-P cement suspensions when they are kept under quiescent and ambient conditions, akin to a surgeon keeping the Ca-P cement within a syringe prior to starting to use it.

In a second set of experiments the freshly prepared Ca-P cement suspension samples were subjected to continuous shearing (without a quiescent waiting period). This constitutes a "preshearing" step and was applied at various frequencies for different durations. This preshearing step was followed by oscillatory shearing under the same conditions as applied to the first set of samples which were kept under quiescent conditions ($\omega = 1$ rad/s and $\gamma_0 = 0.04$ at 25 °C). The objective of this second set of experiments was to investigate the role preshearing would play in the development of the subsequent rheological behavior and the setting kinetics. Although the actual injection tests for the CaP cements were not carried out, the comprehensive viscoelastic properties that are