Rheological properties of an apatitic bone cement during initial setting

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One scientific and technological aspect of main importance to the medical profession is to develop injectable calcium phosphate cements (CPCs) to be used through minimally invasive surgery techniques with still suitable mechanical and biodegradable properties. The objective of this research was to study the influence of several technological factors on the injectability of CPCs. This was performed by studying the rheological behavior of the cement pastes during their initial setting. Cement rheology was approached by looking at the creep response of apatitic cements as a function of the shear stress, the liquid-to-solid (L/S) ratio, the temperature and the addition of organic admixtures. Results showed creep experiments to be a finer method to detect characteristic setting times than other established subjective procedures. However, of all transition times detected none but the dough time seems to be of relevant importance when injectability of cement is concerned. Creep experiments also showed that the addition of organic admixtures such as citric acid increased injectability by retarding the hydration time.

1. Introduction

Medical engineering of calcium phosphate cements (CPCs) is considered to have started with the work of Brown and Chow [1]. After nearly 15 years of serious research by different groups, CPCs have finally arrived to the market. However, one scientific aspect of main importance to the medical profession is still to be needed, i.e. to develop injectable CPCs for minimally invasive surgery techniques. As there is no common procedure to measure injectability, different methods have been tried [2, 3].

The setting and hardening properties of α-$Ca_3(PO_4)_2$ (α-TCP) based cements are due to the progressive dissolution of the α-TCP phase and the formation of an entangled network of calcium-deficient hydroxyapatite (CDHA) crystals [4, 5]. Studies have shown the existence of two rate-controlling mechanisms during α-TCP hydration [6]. Initially, the controlling mechanism is dissolution–precipitation and the surface area of the reactant shows a key-role during the process. After a certain time, a diffusion controlling mechanism through an hydrated layer of crystals covering the α-TCP particles takes place.

From the point of view of injectability or even workability, the first initial setting period, where the cement losses gradually its plasticity, is not well known. However, this is the critical period where studies should be performed to understand and clarify which technological factors can affect workability and injectability without affecting drastically the final mechanical properties of the cement after injection. In a previous paper [7], the study of the rheological behavior of α-TCP slurries using a viscosimeter gave the possibility of looking at the effect on cement viscosity of various parameters during the initial setting, such as the particle size of the α-TCP powder, the (liquid-to-solid) L/S ratio and the addition of dispersants. Although those results were used to qualitatively consider the rheological behavior of the cements, the L/S ratio used in the slurries was higher than that used in normal CPCs. In the present study, the rheological behavior of CPCs has been approached at real L/S ratios using a rheometer. Creep and viscosity of bone cements have been studied as a function of the shear stress, the L/S ratio, the temperature and the addition of admixtures.

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2. Materials and methods

2.1. Calcium phosphate cements

The apatitic cement was composed of α-$Ca_3(PO_4)_2$ (α-TCP) and a liquid phase containing 2.5% by weight of Na_2HPO_4 (Merck-Ref. 1-06586), used as an accelerator. The liquid phase also contained 1.5% by weight of citric acid (Panreac-Ref. 141808) used as a fluidifying additive. α-TCP was synthesized at 1300 °C by mixing calcium hydrogen phosphate $CaHPO_4$ (DCP, Sigma-Ref. C-7263) and calcium carbonate $CaCO_3$ (CC, Sigma-Ref. C-4830) [8]. α-TCP powder was milled (Pulverisette 6, by Fritsch GmbH) to obtain a medium diameter $d(0.5)$ of 7 µm. The L/S ratio of the cement was 0.32 ml/g.

2.2. Setting times

Initial (I) and Final (F) setting times were measured according to ASTM-C266-89 standard by Gillmore needles. The initial setting time I is defined as the time necessary so that the light needle (113.4 g, $\varnothing = 2.13$ mm) does no longer leave a visible print on the cement paste, i.e. to support a static pressure of 0.3 MPa. The final setting time F is defined as the time necessary so that the heavy needle (453.6 g, $\varnothing = 1.06$ mm) does no longer leave a visible print on the surface of the cement, i.e. to support a static pressure of 5 MPa.

2.3. Creep testing

The dough-, the working- and the curing-periods of time as well as the I and F setting times were also determined by creep testing. These experiments were performed using a Haake RheoStress RS-100 with parallel-disks sensor system controlling constant stress and temperature. Creep testing performed at sufficient low shear stress is a non-destructive method that consists in applying a prescribed constant shear stress (τ) and monitoring the resulting shear strain (γ) and viscosity (η) as a function of time during the first period of setting. The resulting deformation of the sample placed into the sensor system is detected with a digital encoder processing one million impulses per revolution. The amount of cement needed to perform the experiments was as small as 2.0–4.0 g. Creep and viscosity measurements were recorded 1.0 min after starting mixing the powder and the liquid cement phases.

2.4. Injectability

Injectability property was approximated by extruding a certain amount of cement paste through a commercial syringe (Ico) following an established method [2]. Injectability is reported as a weight loss percentage (Inj%) between the cement paste extruded from the syringe to the cement paste remaining inside the syringe. Extrusion was performed using a Universal Testing Machine (MTS-Bionix) at 15 mm · mm^{-1} crosshead speed. Extrusion was initiated 1.5 min after starting mixing the powder and the liquid cement phases and stopped when the maximum force detected during the process attained 100 N. At this moment, the weight loss percentage and so the injectability was measured. Syringes (14 mm in diameter) had a capacity of 5 ml with a nozzle diameter of 2.0 mm. The amount of cement used for extrusion ranged from 2 to 4 g and measurements were repeated three times for reproducibility.

3. Results

3.1. Citric acid influence

The I and F setting times for the cement without citric acid additive were $I(\text{min}) = 17 \pm 3$ and $F(\text{min}) > 60$, according to the Gillmore needles. Injectability gave the value of $\text{Inj}(\%) = 46 \pm 2$. The cement with 1.5 % wt of citric acid additive showed values of $I(\text{min}) = 22 \pm 3$, $F(\text{min}) > 60$ and $\text{Inj}(\%) = 66 \pm 4$.

Figs 1 and 2 show Creep-strain fraction (γ/γ_s; γ = creep-strain at any time; γ_s = maximum attainable creep-strain) and viscosity (η) variation against time for both cements, with and without citric acid, at 25 °C. From these figures, several characteristic times, or transition times, of the cement setting can directly be defined:

a. There is a first period of time, the dough period, corresponding to the observation of a relative maximum value in the viscosity vs. time curve. The time where viscosity is maximum can be defined as the dough time (D), i.e. the time the cement mixture needs to be

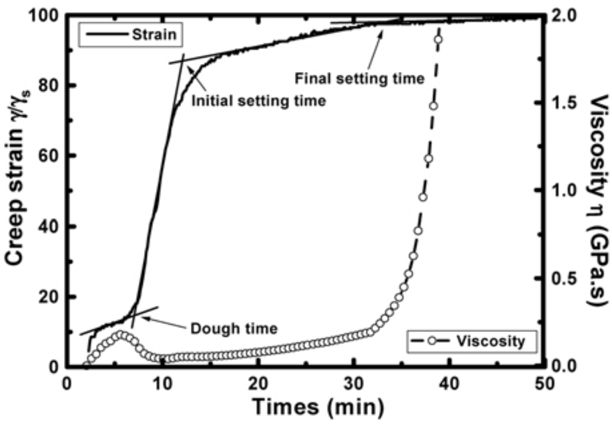

Figure 1 Creep-strain and viscosity variation vs. time at 25 °C (L/S = 0.32 ml/g, τ = 500 Pa). Time-of-setting for apatitic cement without citric acid.

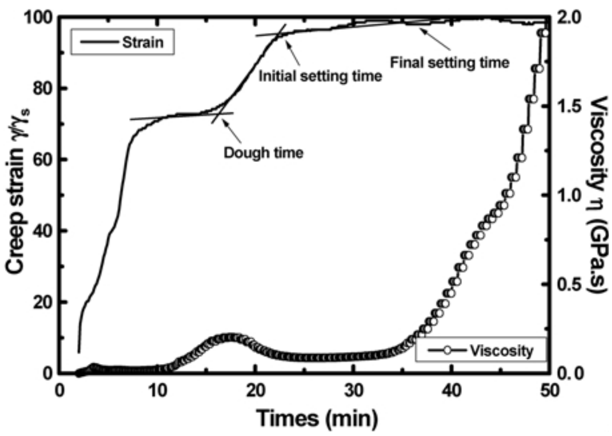

Figure 2 Creep-strain and viscosity variation vs. time at 25 °C (L/S = 0.32 ml/g, τ = 500 Pa). Time-of-setting for apatitic cement with citric acid.

homogeneous (approx. 6 and 18 min for both cements with and without citric acid, respectively).

b. There is a second period of time, the working period, of quasi-constant viscosity where the creep-strain increases linearly. The time where linearity is lost is the time where the curing of cement theoretically starts. This time agrees (approx. 12 and 22 min) with the initial setting time *I* measured by the Gillmore needles (approx. 17 and 22 min). The working time, defined as the difference between the initial setting- and the dough-time, is the time available for working the cement paste without affecting the structure (approx. 6 and 4 min). During this period, the viscosity is constant and low.

c. There is a third period of time, the curing period, starting at the *I* setting time, defined above, and ending at the *F* setting time, where the viscosity increases drastically and finally creep-strain stops. The *F* setting time is however much shorter ($\approx$ 35 min) than the one measured by the Gillmore needles ($\approx$ 60 min). Considering that *F* has been defined as the time the surgeon needs to wait until a certain pressure can be applied to close the wound without distracting the cement microstructure, the measure of *F* obtained by the Gillmore needles is more restrictive.

3.2. Stress influence

Fig. 3 shows creep-strain fraction (γ/γ_s) and viscosity (η) variation against time for two different values of shear stress (τ), at 25 °C. The maximum stress allowed by the instrument was 1000 Pa and no deformation was detected for stress values below 500 Pa. Creep-strain fraction increased for higher values of stress, especially at the initial period of setting where viscosity was lower. However, the same characteristic dough time (approx. 6 min) and initial setting time (approx. 12 min) were observed. The shear stress did not retard or accelerate the cement setting. Rather, the viscous material accommodated higher values of shear stress with higher shear rates.

3.3. L/S ratio influence

Experiments were performed to evaluate the influence of L/S ratio on cement setting. Fig. 4 shows the variation against time of creep-strain and viscosity for different L/S ratio cement pastes (0.30 and 0.32 ml/g), at 25 °C.

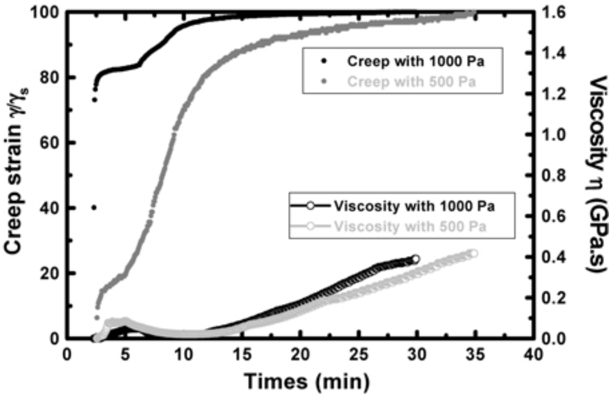

Figure 3 Creep-strain and viscosity variation vs. time and stress applied at 25 °C (L/S = 0.32 ml/g).

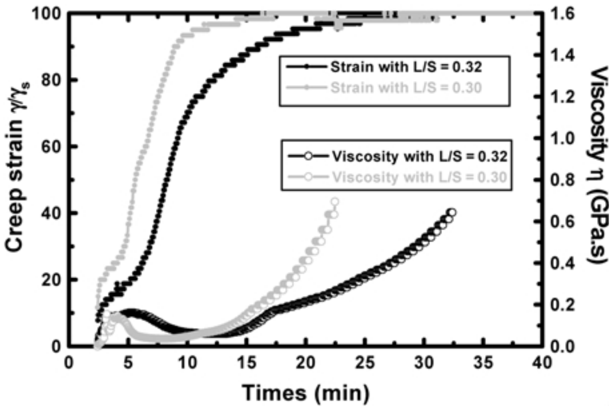

Figure 4 Creep-strain and viscosity variation vs. time and L/S ratio at 25 °C ($\tau = 500$ Pa).

It was observed, as expected, that when the L/S ratio was increased from 0.30 to 0.32 ml/g, the transition times also increased (I = 10 to 12 min; F = 15 to 32 min; D = 4 to 6 min, respectively).

3.4. Temperature influence

In order to show the influence of temperature on cement rheology behavior, creep-strain vs. time is reported on Fig. 5 at different temperatures going from 15 to 35 °C. When the temperature was increased, the characteristic times of cement setting decreased, as expected. The *I* setting time decreased from 20 to 5 min at 15 and 35 °C, respectively. The Dough time decreased from 9 min at 15 °C to practically zero at 35 °C.

3.5. Influence of citric acid on injectability

Fig. 6 shows the variation of injectability against time as a function of the additive for a cement paste made at a L/S ratio of 0.32 ml/g. Injectability was higher for the cement with citric acid only during the first 5 min of setting. After this time, the cement without citric additive showed to be more injectable. However, injectability showed to decrease slowly in both cements rather than drastically after a certain time, time which some authors also have defined as a dough time [2].

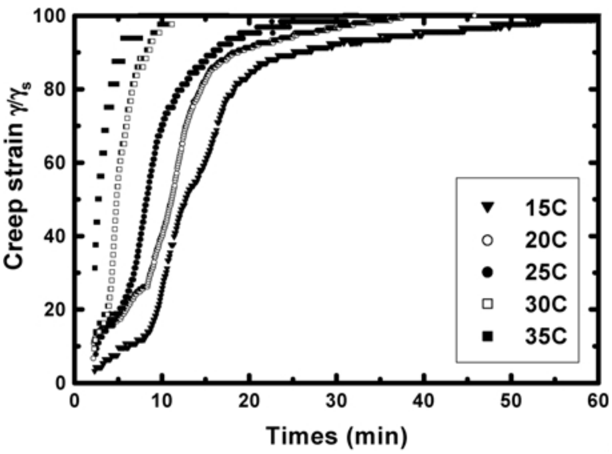

Figure 5 Creep-strain variation vs. time and temperature (L/S = 0.32 ml/g, $\tau = 500$ Pa).

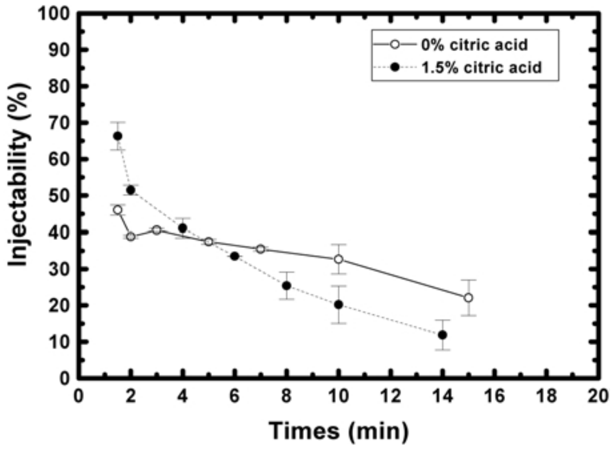

Figure 6 Injectability of cement paste as a function of time after the start of mixing at 25 °C and L/S = 0.32 ml/g ($\tau = 500$ Pa) with and without citric acid.

4. Discussion

CPC were developed as bone-substitute materials and in the past direct applications were found in the dental and maxilofacial areas. During that period different parameters were defined operatively in order to standardize the production and the use of the cement in the operation theater. In that sense, an I and an F were naturally defined. The I-time was defined as the time after which the cement paste cannot be deformed without damaging the structure of the solidifying cement. The F-time was defined as the time when the cement paste can be touched without damaging the structure. These definitions meant the cement had to be applied before the I-time and the wound might be closed after the F-time. In between, the cement paste should not be deformed, as this would induce cracks in the material during its setting. In order to facilitate the quantification of these times several standards have been defined as for example ASTM-C266-89 which gives I- and F-times as the ones the cement needs to withstand, without leaving a print on its surface, static pressures of 0.3 and 5 MPa, respectively.

Nevertheless, a natural question comes when the cement has to be injected through minimally invasive surgery techniques. Are I- and F-times really important when the cement is placed through a syringe? As far as we are concerned, the cement has to be injected at shorter times than the D-time. It has been observed that injectability, measured as a weight percentage of cement mass extruded through a syringe, drastically decreased [2] after several minutes after the start of mixing but still far from the I-time (see also Fig. 6).

In order to approach workability and injectability properties, it should be considered other technological factors different from the ones used to optimize mechanical properties after setting. Temperature during injection was thought to be one of them and creep (see Fig. 5) performed an approximation to this effect. It was observed that the times defined in Fig. 1 (D-, I- and F-time) became longer as the temperature decreased ($D = 0$, $I = 5$ min at 35 °C; $D = 9$, $I = 20$ min at 15 °C). This is due to the acceleration of the dissolution–precipitation processes when temperature is increased. In fact, the effect of temperature on the acceleration of setting has already been reported for α-TCP cements [9, 10]. What is relevant from results in Fig. 5 is that the working period ($WP \equiv I - D$) was increased 50% when temperature during creep was reduced from 35 °C ($WP = 5$ min) to 15 °C ($WP \approx 10$ min). Despite those results, no improvement was found in the cement injectability using the syringe extrusion method [2]. So, it seems that a D-time of 9 min was not enough to make the cement more injectable. The value of the D-time should be increased even further in order to improve injectability. Temperature alone does not seem to be the parameter to attain this objective.

Similar conclusions are obtained from the analysis of Fig. 4. An increase of the L/S ratio from 0.30 to 0.32 ml/g increased the D-time from 4 to 6 min, and the I-time from 10 to 12 min, thus giving the same working period ($WP = 6$ min). It is well known that α-TCP cement injectability increases with L/S ratio [2]. However, an increase of the D-time from 4 to 6 min by increasing the L/S ratio was not enough to drastically increase the injectability. Moreover, this approach will negatively affect mechanical properties of the cement after setting due to an increase of porosity.

Finally, Figs 1 and 2 confirm the importance of the D-time in relation to injectability. When the liquid phase of the cement was modified with additions of citric acid from 0% to 1.5% by weight, the D-time was increased from 6 to 18 min and the I-time from 17 to 22 min. This shows that citric acid modification practically did not affect the I-time. However, the working period was significantly reduced (from ≈ 10 to ≈ 5 min). Thus, with citric acid there is less time to work the cement without distracting the structure. However, the increase of the D-time from 6 to 18 min resulted in a clear increase, from 46% to 66%, of the injectability.

Some authors have defined a ''dough-time D'' as the time when injectability decreases drastically as a function of the injection time [2]. This definition is more restrictive than the one we have proposed and is more practical. However, it does not give any information about the physical processes controlling injectability. The creep method used to measure the D-time and the I-time seems to be a better way to find how several factors affect injectability and workability.

5. Conclusion

The study of the rheological behavior of calcium phosphate cements using a rheometer allows understanding which technological factors can affect workability and injectability. This method gave the possibility of looking at the effect of various factors on the initial setting, such as the temperature, the L/S ratio and the addition of organic additives. It showed various periods of time characteristic of the cement setting, comparable with those measured with traditional methods. When developing injectable cements, only the D-time seems to be of importance. Cements are injectable at shorter times than the D-time. Nevertheless, injectability of calcium phosphate bone cements needs a direct approach and in that sense even the concept of injectability needs a critical revision.

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