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Injectability of calcium phosphate pastes

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Abstract

A theoretical model was developed to assess ways to improve the injectability of calcium phosphate pastes. The theoretical results were then compared to experimental data obtained on calcium phosphate slips. The theoretical approach predicted that the injectability of a cement paste could be improved by an increase of the liquid-to-powder ratio, and a decrease of the particle size and the plastic limit (PL) of the powder. The theoretical results were confirmed by experimental data. Interestingly, an increase of the viscosity of the mixing liquid with small additions of xanthan had a positive effect on the paste injectability. This effect could be due to a change of the PL of the powder or to the lubricating effect of the polymer.

Keywords: Model; Injectability; Calcium phosphate; Cement; Plastic limit

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1. Introduction

Calcium phosphate (CaP) hydraulic cements have been in clinical use for the last 10 years. Most of these materials have been claimed to be injectable. However, most surgeons complain that CaP cements are poorly injectable [1]. This discrepancy stems from the fact that the injectability of a cement is not clearly defined. In principle, any cement paste can be claimed to be injectable. The question is how injectable it really is.

Khairoun et al. [2,3] measured the injectability of a cement paste by measuring the percentage of a paste that could be extruded from a syringe fitted with a needle. They characterized a bad injectability by the occurrence of phase separation between the solid and the liquid, that resulted in plugging, and hence partial extrusion. According to these authors the more cement could be extruded, the more injectable the cement was. In all their experiments, the authors used the same injection system and the same load, i.e. 100 N. It makes sense to keep the same geometry because a change of geometry is expected to provoke a change of injectability. However, it is questionable to always use the same force. Indeed, when polysaccharides such as chondroitin sulfate or hyaluronic acid are added to a solution, they can form very viscous solutions at very small concentrations [4]. As a result, the force required to extrude a cement paste containing a polymer gel in mixing liquid might reach values larger than 100 N, and hence be declared ‘‘non-injectable’’.

Based on these remarks, it appears that the device used by Khairoun et al. [2,3] does not measure the injectability of a paste, but rather its ease at injection. The latter property is only important if the cement paste is meant to be injected by hand, i.e. when the applied force is limited (typically about 200 N). In surgical practice, many cements are applied under high pressures by means of injection guns. Moreover various geometries are used. Based on these remarks, it appears to be important to define the injectability of a paste independently of the injection force. Therefore, the injectability of a paste is defined here as its capacity to stay homogeneous during injection, independently of the injection force.

The injectability of CaP cements has been investigated by several groups. Ishikawa [1] observed that cements based on tetracalcium phosphate (TetCP)—dicalcium phosphate—water mixtures were more injectable when TetCP particles were round and not irregular in shape. Moreover, a higher injectability was measured with

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Nomenclature

Q_i	flow rate of the injected paste
ΔP_i	pressure drop in the injected paste
ΔP_c	pressure drop in the filtration cake
μ_l	viscosity of the liquid
μ_p	viscosity of the paste (particles + liquid)
D_n	diameter of the needle (or cannula)
L_n	length of the needle (or cannula)
d_e	diameter of the particles
m_S	initial amount of solid/powder in the paste
ρ_S	theoretical density of the particles
th	thickness of the cake
ε	volume fraction of the liquid in the paste
ε_m	volume fraction of the liquid in the packed cake
Φ	volume fraction of the mixing liquid
x	maximum particle volume fraction
V_L	volume fraction of the liquid in the cement paste
$V_{L,min}$	minimum volume fraction of the liquid in the cement paste
V_S	volume fraction of the solid in the cement paste
LPR	liquid-to-powder ratio
PL	plastic limit
k	(solid volume fraction of the cake)/(solid volume fraction of the filtrate)
α_c	resistance of the cake
α_m	resistance of the filter
$f(\text{PL}, \text{LPR})$	function of PL and LPR
t	time

larger liquid-to-powder ratios, LPR. Khairoun et al. [2,3] measured the injectability of cement formulations based on α-tricalcium phosphate (α-TCP)—water mixtures. Measurements were made as a function of time [2], LPR [2] and the presence of polymeric additives [3]. The injectability was strongly improved with an increase of LPR and at earlier times after cement mixing. However, the addition of soluble polymers did not significantly improve or worsen the cement injectability [3]. A slightly different result was obtained by Ginebra et al. [5], who observed that the injectability of α-TCP—water mixtures could be improved by adding a polymeric drug (poly(4-HMA)), but only at short times. At longer times, the injectability worsened. Andrianjatovo and Lemaître [6] observed that the injectability of a brushite CPC was strongly improved by adding polysaccharides. However, this improvement was not quantified and not well described. Leroux et al. [7] used sodium glycerophosphate, lactic acid, glycerol and chitosan to improve the injectability of another type of CPC. These authors measured the pressure required to extrude the paste and observed that all additives decreased the extrusion force. The use of a small amount of chitosan ($<0.5\%$) led to a “good fluidity and good injectability”. However, a larger amount ($>0.5\%$) decreased both the setting time and the injectability. More recently, Belkoff et al. [8] added hydroxymethylcellulose solutions to a calcium phosphate cement to improve its injectability. Borzacchiello et al. [9] added polyvinyl alcohol (PVA) into a cement paste and observed that the cement injectability was strongly improved. Sarda et al. [10] found that the injectability of α-TCP—water mixtures were increased by 50–100% with the addition of citrate ions. A similar result was obtained recently by the groups of Barralet and co-workers [11,12] for brushite and apatite cements. These authors also observed an increase of the injectability with an increase of LPR. To summarize, the injectability of CaP cements is generally improved by an increase of LPR, the use of round particles, the addition of citrate ions, and the addition of viscous polymer solutions.

Despite these various experimental studies on CaP cement injectability, there is no theoretical work explaining the presented results. For example, why would polymeric gels or a change of LPR improve the cement injectability? The absence of model describing the injectability of CaP cement pastes reduces the possibility of designing truly injectable cements. So, the goal of this study was to develop an injectability model based on simple theoretical considerations. This model was meant to be able to discriminate between physical and chemical factors affecting the cement injectability. Furthermore, the theoretical results were validated experimentally. Finally, based on the theoretical and experimental results, recommendations were put forward to improve the injectability of CaP pastes in general (for which the viscosity is constant), and the injectability of CaP cement pastes in particular (for which the viscosity varies very rapidly with time [13]).

To test the injectability of CaP cement pastes, two aspects should be considered. First, a suitable experimental setup has to be defined. Second, adequate compositions and parameters should be investigated. Looking at the literature, the common strategy to test CaP cement pastes was to modify the cement composition with an additive and to measure the injectability at a given time after cement mixing [2,3]. This method might lead to confusion and should be used with caution. For example, Borzacchiello et al. [9] added PVA into a cement paste and observed that the cement injectability was strongly enhanced. However, along with the increase of injectability, the addition of PVA induced a very large increase of the setting time. The same is true for the work of Barralet and co-workers [11,12]. Another study [2] showed that the injectability strongly decreases with an increase of the time after mixing. Therefore, the increase of cement injectability provoked by the addition of PVA might be due to the increase of setting time only. This implies that: (i) injectability studies should not be done independently of setting time studies, and (ii) injectability of a cement should be measured after a time interval related to the setting time, e.g. after a time interval corresponding to 50% of the setting time. So a cement with a setting time of 5 min would be tested after 2.5 min, and a cement with a setting time of 20 min would be tested after 10 min. In some studies, the setting time is not measured [1], whereas in other studies, the time of injectability testing is not indicated [11,12].

In the present study, the goal was to identify some factors affecting the injectability of a paste. Therefore, non-setting pastes were used. Moreover, considering our definition of injectability, it would be limiting to test the injectability of a cement paste at constant force, as proposed by Khairoun et al. [2,3]. So, the injectability was tested here at constant deformation rate, as proposed by some other authors [1,11,12].

From the experimental results discussed earlier, it appears that apart from a change of the geometry of the injection system, there are two ways to modify the cement injectability: physically and chemically. For example, the use of a different LPR has mostly a physical influence (e.g. dilution). The same is true with polymeric gels as long as there is no chemical interaction between the gel and the calcium phosphate particles. When citrate ions [11,12] are added to a cement paste, there is a chemical interaction between the additive, i.e. carboxyl groups, and the calcium phosphate particles, i.e. calcium ions. This interaction can modify the particle interactions and hence the physico-chemical properties of the cement, in particular the injectability. For example, Sarda et al. [10] observed that the injectability of α-TCP—water mixtures increased by 50–100% with the addition of citrate ions. Citrate ions modified the setting reaction and postponed the full completion of the hydrolysis of α-TCP. Similar results were obtained by the groups of Barralet and co-workers [11,12]. The experiments presented in this study looked at the effect of geometry, physics and chemistry on the paste injectability. In this article, the terms "injection" and "extrusion" are used as synonyms.

2. Theoretical aspects

There are two competitive phenomena occurring during the injection of a CPC paste through a needle: paste flow and filtering. If the pressure required to filter the liquid through the cement particles is lower than the pressure required to inject the paste, phase separation occurs. This phenomenon is often referred to as "filter-pressing". The approach used in this study was to estimate the ease at "filtering" a cement and the ease of "injecting" a cement. The latter results were then compared and parameters favorizing injectability were identified.

2.1. Approach

2.1.1. Injection

Calcium phosphate cement pastes are non-Newtonian fluids, but the Hagen–Poiseuille relationship was used as a first approximation. This relationship relates the flow rate Q_i of a Newtonian liquid running through a cylinder, in this case a needle, to the pressure drop ΔP_i that has to be applied on the fluid to obtain a flow rate

$$Q_\mathrm{i} = \frac{\Delta P_\mathrm{i} \pi D_\mathrm{n}^4}{128 \mu_\mathrm{p} L_\mathrm{n}}, \tag{1}$$

where μ_p is the viscosity of the fluid, D_n is the diameter of the cannula (or needle) and L_n is the length of the cannula (it is assumed that the pressure drop in the syringe bulk is negligible compared to the pressure drop in the cannula).

2.1.2. Filtration

During filtration, particles are packed on the filter while the liquid flows through the particles and the filter. The packed particles form a dense layer called "cake" whose thickness, th, increases with time. From the law of Darcy, the cake thickness, th, can be written as [14]

$$\mathrm{th}^2 = \left(\frac{k \Delta P_\mathrm{c}}{\mu_\mathrm{l}(\alpha_\mathrm{c} + \alpha_\mathrm{m})(1 - \varepsilon_\mathrm{m})} \right) t, \tag{2}$$

where ε_m is the void fraction of the cake, k is the ratio of the solid volume fraction of the cake divided by the solid volume fraction of the filtrate (see also below), α_c is the resistance of the cake, α_m is the resistance of the filter, t is the time, ΔP_c is the pressure drop through the cake and μ_l is the viscosity of the liquid. For cement injection, there is no filter, so the resistance of the filter, $\alpha_\mathrm{m} = 0$.

The ratio of the solid volume fraction of the cake divided by the solid volume fraction of the filtrate, k, is expressed by

$$k = \left(\frac{1 - \varepsilon_\mathrm{m}}{1 - \varepsilon} \right), \tag{3}$$

where ε is the volume fraction of the liquid in the paste, and ε_m is the volume fraction of the liquid in the packed cake. When the particles are round, the cake resistance is a function of ε_m and the diameter of the particles, d_e, [14]

$$\alpha_c = \frac{150}{d_e^2}\frac{(1-\varepsilon_m)^2}{\varepsilon_m^3}. \tag{4}$$

Combining Eqs. (2)–(4) and neglecting α_m gives

$$th^2 = \left(\frac{d_e^2}{150\mu_l}\frac{\varepsilon_m^3}{(1-\varepsilon_m)^2(1-\varepsilon)}\Delta P_c\right)t. \tag{5}$$

2.1.3. Filter-pressing

In Eq. (5), the applied pressure, ΔP_c, is equal to the pressure used to inject the cement paste, ΔP_i (Eq. (1)). Therefore, Eqs. (1) and (5) can be combined

$$th^2 = \left(d_e^2\frac{128}{150\pi}\frac{\mu_p}{\mu_l}\frac{\varepsilon_m^3}{(1-\varepsilon_m)^2(1-\varepsilon)}\frac{L_n}{D_n^4}Q_i\right)t. \tag{6}$$

In this relationship, there is clearly a relationship between the viscosity of the paste and the mixing liquid. De Kruif et al. [15] analyzed the change of the viscosity of a slip as a function of its particle volume fraction, Φ, and found that their results followed the Krieger–Dougherty equation:

$$\mu_p = \mu_l\left(1-\frac{\Phi}{x}\right)^{-2}, \tag{7}$$

where x is the maximum particle volume fraction. This value varied from 0.63 to 0.71 depending on the shear rate (from low to high shear, respectively). The solid volume fraction, Φ, is related to the liquid volume fraction of the paste, ε:

$$\Phi = 1-\varepsilon. \tag{8}$$

Combining Eqs. (6)–(8) leads to

$$th^2 = \left(d_e^2\frac{128}{150\pi}\left(1-\frac{1-\varepsilon}{x}\right)^{-2}\frac{\varepsilon_m^3}{(1-\varepsilon_m)^2(1-\varepsilon)}\frac{L_n}{D_n^4}Q_i\right)t. \tag{9}$$

What is the physical signification of x? Eq. (7) indicates that the paste viscosity increases dramatically when the solid volume fraction reaches x. Therefore, x is related to the minimum void fraction:

$$x = 1-\varepsilon_m. \tag{10}$$

Combining Eqs. (9) and (10), and rearranging the resulting equation gives

$$th^2 = \left(d_e^2\frac{128}{150\pi}\frac{\varepsilon_m^3}{(\varepsilon-\varepsilon_m)^2(1-\varepsilon)}\frac{L_n}{D_n^4}Q_i\right)t. \tag{11}$$

In Eq. (11), ε and ε_m are related to entities that are known, i.e. LPR and PL. The liquid volume fraction of the paste, ε, is given by

$$\varepsilon = \left(\frac{V_S}{V_S+V_P}\right), \tag{12}$$

where V_S and V_P are the initial volume fraction of the liquid and the powder (or solid). The LPR is given by

$$\mathrm{LPR} = \left(\frac{V_S}{m_S}\right), \tag{13}$$

where m_S is the initial amount of solid (=powder). Therefore

$$\varepsilon = \left(\frac{\rho_S\mathrm{LPR}}{1+\rho_S\mathrm{LPR}}\right), \tag{14}$$

where ρ_S is the theoretical solid density. The plastic limit, PL, of a powder–liquid mixture is defined as the minimum amount of liquid that has to be added to the powder to form a paste [16]. PL is normally expressed by the ratio between the volume of the liquid, $V_{L,min}$, and the mass of the powder, m_S.

$$\mathrm{PL} = \left(\frac{V_{L,min}}{m_S}\right). \tag{15}$$

Below PL, the powder–liquid mixture is dry and its "viscosity" is very high. Therefore, considering the physical analogy of x and PL, the parameter x corresponds to the solid volume fraction of PL:

$$x = \left(\frac{1}{1+\rho_S\mathrm{PL}}\right). \tag{16}$$

Therefore, combining Eqs. (10) and (16) gives

$$\varepsilon_m = \left(\frac{\rho_S\mathrm{PL}}{1+\rho_S\mathrm{PL}}\right). \tag{17}$$

Combining Eqs. (11), (14) and (17) leads to

$$th^2 = \left(d_e^2\frac{128}{150\pi}f(\mathrm{PL},\mathrm{LPR})\frac{L_n}{D_n^4}Q_i\right)t, \tag{18}$$

where

$$f(\mathrm{PL},\mathrm{LPR}) = \frac{\rho_S\mathrm{PL}^3}{(1+\rho_S\mathrm{PL})}\frac{(1+\rho_S\mathrm{LPR})^3}{(\mathrm{LPR}-\mathrm{PL})^2}. \tag{19}$$

2.2. Theoretical results and discussion

It is clear that injectability is favored if the rate of cake formation is slow. As a result, Eq. (18) indicates that injectability is improved with smaller particle size, with shorter and larger diameter cannula, and at a smaller flow rate. The effect of LPR and PL is slightly more difficult to understand, but a plot of $f(\mathrm{PL},\mathrm{LPR})$ indicates that injectability is favored when the cement LPR is significantly larger than the LPR corresponding to PL (Fig. 1).

The diameter and the length of the cannula, as well as the paste flow rate, are parameters independent of the cement and related only to the experimental setup. Therefore, the injectability of any paste can be found to be good if an appropriate setup is used, hence rendering the definition and the use of the word "injectability" difficult.

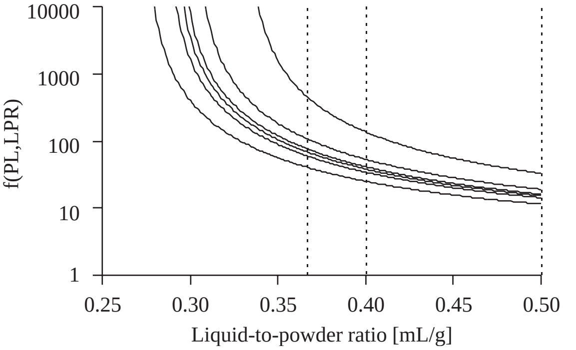


Fig. 1. Variation of $f(\mathrm{PL};\mathrm{LPR})$ as a function of the liquid-to-powder ratio, LPR, and the plastic limit, PL. Six curves are represented corresponding to the six pastes tested in this study. From bottom to top: (i) milled β-TCP, PAA solution; (ii) Unmilled β-TCP, PAA solution; (iii) milled β-TCP, xanthan solution; (iv) milled β-TCP, water; (v) unmilled β-TCP, xanthan solution; (vi) unmilled β-TCP, water.

However, a well injectable paste should be injectable almost independently of the experimental setup. To reach this goal, our theoretical model shows that the composition of the cement can be modified according to two main strategies: (i) decrease the average particle size (physical approach), and (ii) increase the difference between LPR and PL (physical or chemical approach).

The first approach is difficult to apply since the particle size distribution of a cement paste varies continuously. Therefore, milling the cement components can perhaps improve temporarily/initially the cement injectability, but certainly not during the whole injection period. The second general approach appears more promising because it is easy to increase the cement LPR so that it is significantly higher than the LPR corresponding to PL. However, the ability of the cement paste to harden in an aqueous environment is reduced accordingly [3,17] due to a decrease of cement viscosity. This reduced stability can even lead to a total degradation of the cement paste. The same is true for a slightly different approach, which consists in decreasing PL while keeping the same LPR. This can be achieved by using (i) round rather than irregular particles [1,18], (ii) perfectly disagglomerated powder [19], or (iii) a powder with a broad particle size distribution [20]. A chemical route is also possible. Indeed, a decrease of the particle interactions via a change of the particle surface charge or the adsorption of a polymer (steric stabilization) can lower PL. Considering the good complexation of calcium ions with carboxyl groups, carboxylated compounds such as citrate ions or poly(acrylic acid) could be used [10–12]. However, only very few additives can be used for in vivo applications.

3. Experimental

In the previous section, a theoretical approach was used to determine the factors influencing the injectability of a paste. In this section, experiments were performed to verify the theoretical predictions.

3.1. Materials and methods

3.1.1. Materials

β-Tricalcium phosphate powder (β-TCP; $Ca_3(PO_4)_2$; Fluka No. 21218, Buchs, Switzerland) was used as a model powder to investigate the injectability of calcium phosphate pastes. β-TCP is rather inert in water (solubility $\approx 10^{-4}$ M at pH 7–10) [21], so β-TCP can be mixed with water without provoking time-changes of the paste viscosity. Part of the β-TCP powder was milled for 15 min in a planetary mill (400 RPM; 100 g of powder; 100 1-cm ZrO_2 beads; Pulverisette 5, Fritsch). The general morphology of both powders was observed by scanning electron microscopy (SEM) (Hitachi S-3000 N) after coating the powder with gold/palladium (Fig. 2). The particle size distribution was determined with a laser granulometer (Mastersizer 2000, Malvern, USA). Three measurements were done in isopropanol and in water. The average of the three measurements obtained in water is represented in Fig. 3. Clearly, milling leads to the formation of a large amount of small particles (see also Fig. 2). Surprisingly, milling provokes a shift of the distribution toward larger particle sizes. Considering the fact that this shift was observed in both liquids, and that the results were reproducible, it is believed that particle agglomeration occurs during milling. SEM photos show indeed that large agglomerates are present in the milled powder (Fig. 2). The specific surface area (SSA) of the powder was determined by nitrogen adsorption using the BET model (Gemini 2360, Micromeritics, USA). The SSA was increased from 1.16 ± 0.02 to $4.85 \pm 0.05\ \mathrm{m^2/g}$ during milling (95% confidence interval on the mean). The purity of the β-TCP powder was assessed by X-ray diffraction (XRD). Small amounts (7–8%) of β-calcium pyrophosphate ($Ca_2P_2O_7$) were detected. Xanthan gum (Jungbunzlauer—Austria) was the polysaccharide chosen to modify the liquid viscosity. As xanthan gum does not possess any reactive groups such as carboxyl groups, it was assumed that xanthan gum gel had only a physical effect on the paste injectability. Poly(acrylic acid) sodium salt (PAA 170 kDa; Art 81138; Fluka, Buchs, Switzerland) was used to modify the injectability via a chemical interaction. PAA is indeed known to interact with calcium ions [22] and is very often used in the production of ceramic slips [23]. However, small amounts of PAA do not modify markedly the viscosity of the solution.

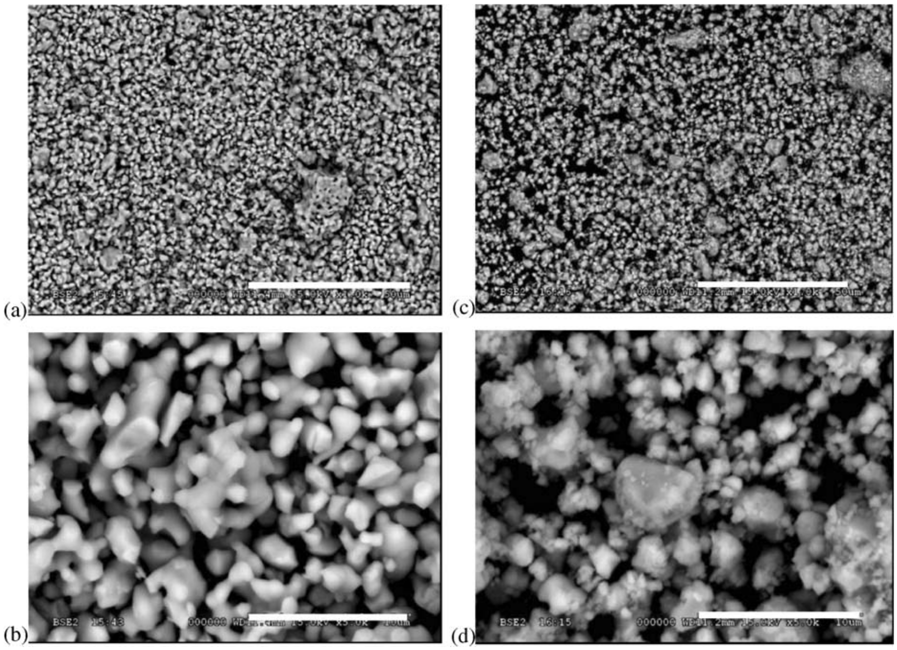


Fig. 2. SEM photos of (a, b) unmilled powder and (c, d) milled powder. The error bars (white line) correspond to a size of (a, c) 50 μm and (b, d) 10 μm.

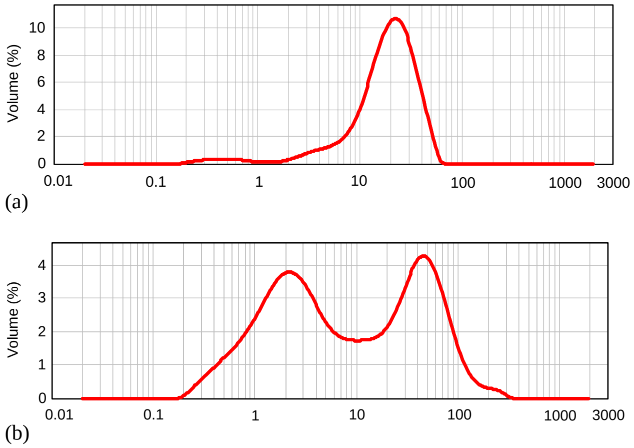


Fig. 3. Particle size volume distribution of (a) unmilled and (b) milled β-TCP powder as measured by laser granulometry in water. The size (x-axis) is given in micrometers. A similar result is obtained in isopropanol.

3.1.2. *Plastic limit*

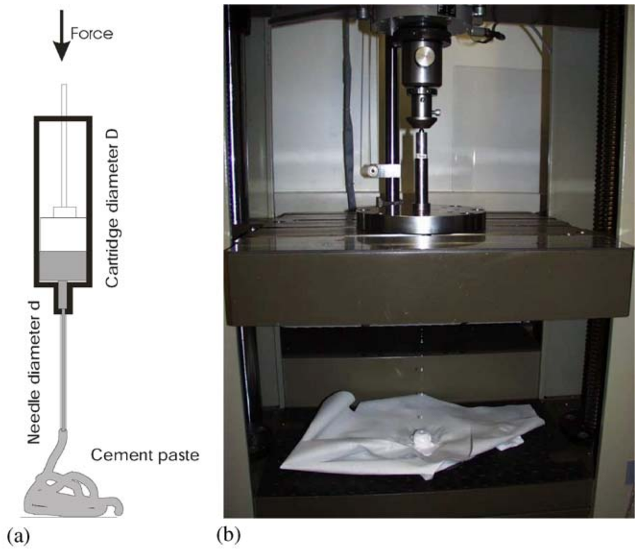
The PL of both β-TCP powders was determined as follows. One gram of powder was weighed in a glass beaker. In all, 0.2 ml of solution was added to the powder and the mixture was kneaded with a metallic spatula until a homogeneous mixture was obtained. Additional solution was added dropwise. After each drop, the mixture was kneaded. When the mixture stuck together, hence forming a single pasty block, the material present on the spatula was scratched off and placed in the beaker. The beaker weight was determined. PL was defined as the minimum amount of liquid that had to be added to a powder to form a paste. PL was expressed in milliliters per gram, and was determined for all combinations of powder and solution (water, 1% PAA, 0.2% xanthan, milled and unmilled β-TCP powder).

3.1.3. *Mixing cartridge and cannulas*

The mixing cartridge used for the extrusion experiments consisted of several elements: (i) the metallic cartridge itself; (ii) a hollow piston closing the rear of the cartridge; (iii) a pierced and round mixing plate linked to a long cylindrical arm that could pass through the hollow piston; (iv) a handle; (v) a tip to close the front part of the cartridge. The powder–aqueous solution mixtures could be mixed through the rotational and longitudinal displacements of the round mixing plate inside of the cartridge. The cartridge had an inner diameter of 24 mm. Two different cannulas (Norian Corporation, Cupertino, CA, USA) were used. The first one was a gauge 14 cannula with an inner diameter of 1.71 mm and a length of 80 mm. The second one was a gauge 10 cannula with an inner diameter of 2.90 mm and a length of 82 mm. Those sizes correspond to an inner volume of 184 and 541 mm^3, respectively. The experimental setup is shown in Fig. 4.

3.1.4. *Pastes*

In all, 15 g of β-TCP powder and an aqueous solution were mixed in the metallic cartridge with a spatula for 30 s. The paste was then extruded through a cannula placed at the tip of the syringe. The extrusion rate was kept constant, while the force was recorded. The



(a) (b)

Fig. 4. Experimental setup showing (a) a scheme of the mixing and injection device, and (b) the paste falling down.

fraction of paste that could be extruded was determined by measuring the weight of the metallic cartridge before and after extrusion. Therefore, the maximum fraction could never reach 100% since residual cement was always left in the cannula (see under "factorial designs"). The extrusion force was measured after the plunger has moved 5 mm to avoid transient effects.

3.1.5. Factorial designs

The experiments were performed according to three factorial designs. The first two designs were repeated once (i.e. each composition was tested once) and had four factors (i.e. 16 experiments per factorial design): (A) cannula diameter (gauge 14 or 10); (B) volume of mixing liquid (5.5 and 6.0 ml in the first design, 6.0 or 7.5 ml in the second design); (C) solution (demineralized water or 0.2% xanthan solution); (D) extrusion speed (0.4 or 2.0 mm/s). The third design was repeated twice (i.e. each composition was tested twice) and contained three factors: (A) particle diameter (low/high); (B) volume of mixing liquid (5.5, 6.0 and 7.5 ml); (C) type of liquid (demineralized water or 1.0% PAA solution). All experiments were performed with a gauge 10 cannula at an injection rate of 2 mm/s. These various formulations corresponded to a total paste volume of 10.3, 10.8 and 12.3 ml for 5.5, 6.0 and 7.5 ml of liquid, respectively. For comparison purposes, the inner volume of a gauge 10 cannula was 0.54 ml, hence corresponding to 5.3%, 5.0% and 4.4% (respectively) of the various volumes of paste. Therefore, the maximum extruded fraction could not reach values larger than 94.7%, 95.0% and 95.6% with a gauge 10 cannula (for 5.5, 6.0 and 7.5 ml of liquid, respectively). The values for a gauge 14 needle could be calculated similarly: 98.2%, 98.3% and 98.5% for 5.5, 6.0 and 7.5 ml of liquid, respectively. Actually, the maximum values were even lower since the holes of the mixing plates had also a certain volume.

3.2. Results

3.2.1. Plastic limit

PL depended not only on the type of liquid used to measure it, but also on milling (Table 1). The values were lower for the milled powder and for the 1% PAA solution ($p<0.01$). For the unmilled powder, the 0.2% xanthan solution gave slightly lower results than pure water ($p<0.01$). Interestingly, all amounts of liquid used in the injection/extrusion experiments (5.5, 6.0 and 7.5 ml) were much higher than the values corresponding to the PL values (Unmilled powder: 5.0, 4.3 and 4.5 ml for water, PAA and xanthan; milled powder: 4.4, 4.1 and 4.4 ml for water, PAA and xanthan).

3.2.2. Extrusion curves

Extrusion curves were normally characterized by a very rapid increase of the force followed by a plateau

Table 1
Plastic limit of the two β-TCP powders when measured with water, 1% PAA solution and 0.2% xanthan solution

β-TCP powder	Water	PAA	Xanthan
Unmilled	0.332 (0.011)	0.287 (0.010)	0.303 (0.010)
Milled	0.294 (0.012)	0.275 (0.012)	0.291 (0.003)

Note: The numbers given within brackets correspond to the 95% confidence interval on the mean. Significant differences ($p<0.01$) were observed between all values obtained with the unmilled powder. Significant differences were also measured with the milled powder, i.e. between the result obtained with the 1% PAA solution and the results obtained with pure water or xanthan gel. The results obtained with the milled powder were significantly lower ($p<0.01$) than those obtained with the unmilled powder.

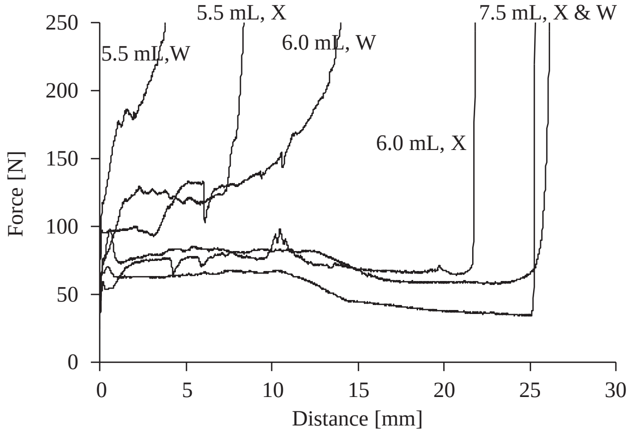


Fig. 5. Typical extrusion curves obtained with various amounts of mixing liquid (5.5, 6.0 and 7.5 ml) and various liquids (water (W) or 0.2% xanthan solution (X)).

and a final very rapid increase (Fig. 5). However, the plateau disappeared in samples where filter-pressing occurred (see curves obtained with 5.5 ml water and xanthan). In the latter case, there was only a sharp increase of force leading to phase separation. In most cases, the plateau was divided in two parts, the first part being slightly higher than the second part. From these curves, it is also apparent that the extrusion force at the plateau increased with a decrease of the amount of mixing liquid (Fig. 5).

The statistical results obtained in all three designs are summarized in Tables 2 and 3. The injection force was significantly decreased by an increase of the amount of mixing liquid. The injection rate increased with the injection force. These effects, however, were observed for a low amount of mixing liquid. More complex results were obtained in the third design (Table 3). However, they showed similar trends: an increase of the mixing liquid generally increased the injectability and decreased the injection force. Nevertheless, these results were modified by the values of the other factors.

Table 2
Statistical analysis of the two first factorial designs

	Extruded fraction	Applied force
First design	B (+17.7%; $p<0.0001$) C (+14.0%; $p<0.0002$) Average: 50.6%	B (−77 N; $p=0.011$) D (+53 N; $p=0.063$) Average: 214 N
Second design	B (+10.1%; $p<0.0001$) C (+9.9%; $p<0.0001$) BC (−8.9%; $p<0.0001$) Average: 78.4%	No significant effects Average: 87 N

Note: The factors were: (A) cannula diameter (gauge 14 or 10); (B) volume of mixing liquid (5.5 or 6.0 ml in the first design, 6.0 and 7.5 ml in the second design); (C) solution (demineralized water or 0.2% xanthan solution); (D) extrusion speed (0.4 or 2.0 mm/s).

Table 3
Statistical analysis of the third factorial design

	Extruded fraction	Applied force
Third design—first part (5.5 and 6.0 ml)	A (−16.6%; $p<0.0001$)	A (+18.7 N; $p<0.003$)
	B (+7.8%; $p<0.003$)	B (−26.0 N; $p<0.0003$)
	AB (−8.0%; $p<0.003$)	AB (−17.3 N; $p<0.005$)
	C (+10.8%; $p<0.0001$)	C (−20.1 N; $p<0.002$)
	AC (+8.7%; $p<0.002$)	
	Average: 67.6%	Average: 65.0 N
Third design—second part (6.0 and 7.5 ml)	A (−3.2%; $p<0.0006$)	
	B (+9.3%; $p<0.0001$)	
	AB (+5.4%; $p<0.0001$)	
	C (+5.6%; $p<0.0001$)	C (−13.8 N; $p<0.0001$)
	AC (+5.4%; $p<0.0001$)	
	BC (−6.9%; $p<0.0001$)	
	ABC (−3.7%; $p<0.0003$)	
	Average: 84.6%%	Average: 35.0 N

Note: The factors were: (A) particle diameter (small/large); (B) volume of mixing liquid (5.5, 6.0 and 7.5 ml); (C) type of liquid (demineralized water or 1.0% PAA solution). The results were analyzed as two separate factorial designs of experiments containing three factors at two levels.

3.2.3. Extruded fraction

The injectability expressed here as the extruded fraction was increased by an increase of the amount of mixing liquid and the replacement of water with the xanthan solution (Table 2). It was not, however, affected by the cannula diameter or the extrusion speed in a detectable way. In the third factorial design (Table 3), more complex results were observed, but the general trends were confirmed: a higher LPR and smaller particles led to a better injectability. Noteworthy, the use of a PAA solution improved the cement injectability.

When all results were summarized they became clearer. It can be seen that the extruded fraction was

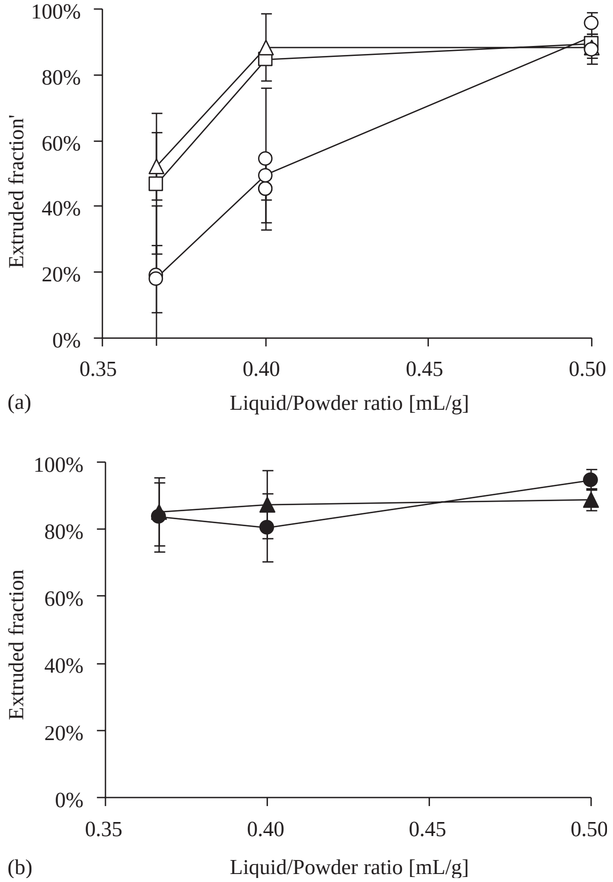


Fig. 6. Extruded fraction of the paste as a function of the LPR and the composition of the mixing liquid. (a) Unmilled β-TCP powder: (○) water; (△) PAA 1% solution; (□) xanthan 0.2% solution; and (b) milled β-TCP powder: (●) water; (▲) PAA 1% solution. The error bars indicate the 95% confidence interval on the mean.

increased by an increase of LPR and by the addition of xanthan and PAA (Fig. 6a). Moreover, the extruded fraction was increased by a decrease of the particle size (Fig. 6b).

3.3. Discussion

3.3.1. Plastic limit

Within the investigated range of parameters, only small variations of PL were observed. These variations can stem from several causes: (i) a decrease of the average particle size is generally associated with an increase of PL, due to the increased surface area to wet; (ii) a broader particle size distribution is also expected to decrease PL, because small particles can fill the pores between larger particles [20]. For example, a bimodal distribution (as in Fig. 3) is expected to have a much lower PL than a monomodal distribution. More generally, a multimodal particle size distribution, where the size ratio between the diameter of adjacent size fraction is $\sqrt{2}$, is the most efficient way to minimize the PL [20]: (iii) agglomerates contribute to larger PL values [19]; (iv) a decrease of the particle interactions, e.g. via citrate ions, decreases PL. In the present study, the effect of PAA is clearly associated to the fourth explanation. However, the reason why powder milling provokes a change of PL is not clear. It could be due to the second or third explanation. Finally, the effect of xanthan is unclear, because xanthan is not meant to interact chemically with the particles. It could be related to the slight stickiness of the xanthan solution.

3.3.2. Extrusion force

The measured extrusion force decreased with an increase of the LPR, as predicted by the model. From Eqs. (7), (8) and (14), it can be seen indeed that an increase of the LPR should decrease the paste viscosity, and hence the extrusion pressure (Eq. (1)). Eq. (1) predicts an increase of the injection pressure when the flow rate is increased, as measured in the first factorial design (Table 2). The positive effect of a decrease of the particle size or the addition of PAA (Table 3) is not directly predicted by Eqs. (1)–(19) but could be attributed to a decrease of PL (Eq. (19), Table 1 and Fig. 1). The absence of effect of the cannula diameter on the injection force is puzzling, but could perhaps come from the limited number of data and the large standard deviation. Additionally, the decrease of the injection force after 10–15 mm is puzzling (Fig. 5). Further experiments are certainly required.

3.3.3. Extruded fraction

The positive effects of an increase of LPR (Fig. 6) and a decrease of particle size (Table 3) were predicted by our model (Fig. 1). However, the model implied that a change of particle size would not provoke any change of PL. Here, a change was observed (Table 1) which means that it is not clear if the improved injectability was due to the decrease of the average particle size or a decrease of PL (Table 1). Alternatively, the model did not predict the positive effect of xanthan on the paste injectability (Table 2, Fig. 6), but this effect could be due to the decrease of PL (Table 1). In fact, it appears that most of the results can be explained by the value of the function $f(\mathrm{PL}, \mathrm{LPR})$, since above a value of $f(\mathrm{PL}, \mathrm{LPR}) = 50$, all pastes but one are only partially injectable (Fig. 7). Therefore, the determination of PL appears to be a very important step in the interpretation of the injectability of a CaP paste.

Many studies mentioned in Section 1 [5–9] showed a positive effect of polymers on the injectability of cements. As none of these authors measured the PL, it is difficult to know whether this effect comes from the viscosity of the polymer, or from a change of the particle interaction expressed by a decrease of the PL. Interestingly, the use of hydrogels is a well-known experimental way to improve the injectability of concrete cements [24]. Assuming that the positive effect of polymers stems from their high viscosity, several explanations could be proposed to explain why our model does not predict it.

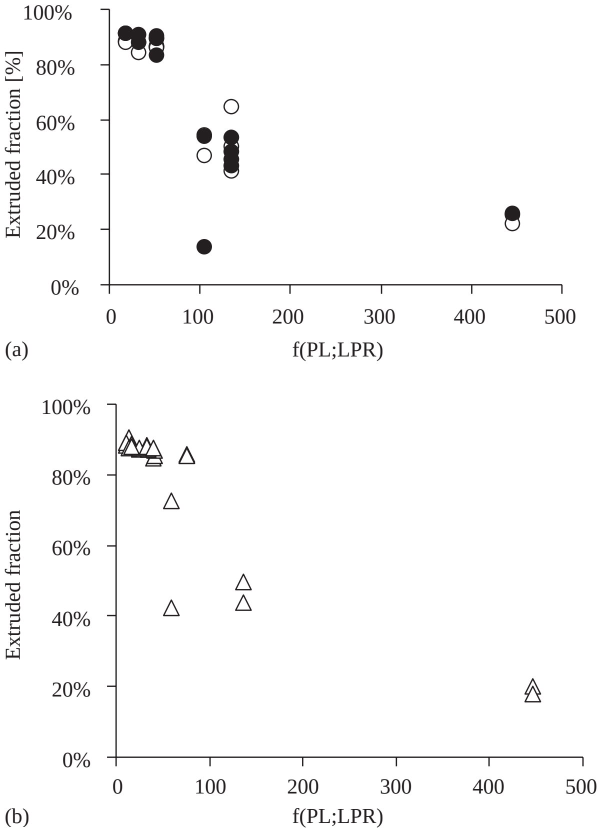


Fig. 7. Relationship between the extruded fraction and the function $f(\mathrm{PL}, \mathrm{LPR})$. (a) Results obtained in the first and second factorial design; (○) gauge 10 and (●) gauge 14. (b) Results obtained in the third factorial design.

The first and main reason could be that the model is too simple to predict the effect of viscosity. For example, the model assumed that the mixing liquid and the CaP paste were Newtonian fluids, which is by far not the case. PAA solution—CaP powder mixtures were strongly shear-thickening. In other words, the paste rapidly flew under gravity but behaved like a very viscous paste when mixed with a spatula. Additionally, xanthan gum formed strongly shear-thinning gels, as previously shown in the literature [25]. Pearson and Tardy [26] reviewed the different mathematical approaches used to describe non-Newtonian flow in porous media. They concluded that none of the present continuum models give accurate estimates of macroscopic transport properties. In fact, both the description of the flow of wet granular materials and the flow of a liquid in a porous structure are extremely complex and require complicated computational approaches [27–29]. Another over-simplification is to assume that particles are spherical and that the Krieger–Dougherty equation is valid. Lombois et al. [30] have recently shown that the addition of a polymer into the mixing liquid of a solid–liquid paste can sometimes lead to a decrease of the viscosity of the paste due to lubricating effects. This effect is observed in the so-called "granular regime" where the flow behavior is mostly controlled by direct interparticular contact [31]. In that case, the paste cannot be sheared without volume expansion, and hence intergrain friction occurs. The presence of a polymer between the grains can in some conditions reduce the friction coefficient between the grains, and hence improve the paste injectability. This explanation would have to be confirmed with rheological measurements of the various tested pastes.

3.3.4. Possible strategies to improve the injectability of CaP cements

The goal of the present study was to better understand which factors control and affect the injectability of a CaP cement paste. Experimentally, a few factors affecting the injectability of CaP pastes were determined, and a few conclusions were drawn. However, there is an important difference between a CaP paste and CaP cement paste: in the first case, the viscosity is constant with time, whereas in the second case, it varies very rapidly [13]. So, not all conclusions drawn from the experimental and theoretical data can be applied to a CaP cement paste, as mentioned in Section 2.2. Generally, the following strategies to improve the cement injectability are:

- decrease the average particle size,
- increase LPR,
- use round particles,
- use deagglomerated particles,
- use a broad particle size distribution,
- add ions or polymers decreasing particle interactions,
- increase the viscosity of the mixing liquid.

Among all these factors, only two do not lower the viscosity of the CaP paste (unpublished data), i.e. a decrease of the average particle size, and an increase of the viscosity of the mixing liquid. Considering the negative effect of a low viscosity on the erosion of the cement [3], it appears that the latter two strategies are the most adequate ways to improve the cement injectability. However, as the particle size of a cement paste is a transient value, the most adequate and applicable strategy is to increase the viscosity of the mixing liquid.

4. Conclusion

The present experimental and theoretical results show that the injectability of a paste can mainly be improved in two ways. First, the injection device can be modified. Shorter cannulas with a larger diameter, as well as smaller injection rates favor a good injectability. Second, the cement composition can also be adapted. A decrease of the particle size, an increase of the liquid-to-powder ratio and a decrease of plastic limit contribute to a better injectability. Interestingly, the theoretical model did not predict any effect of the viscosity of the mixing liquid. Experimentally, an effect was observed (xanthan gel), but this effect was attributed to a change of plastic limit. Considering the fact that CaP cements must be able to set in an aqueous environment, it appears that the most adequate and applicable way to improve the injectability of CaP cements is to replace the mixing liquid with a hydrogel.

Finally, it must be mentioned that the results obtained in this study suggest that there is a very strong correlation between the plastic limit of a CaP paste and its injectability. As the plastic limit of a CaP paste is much easier to measure as its injectability, such measurements could be used to evaluate possible changes of CaP injectability following a change of composition.

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