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Does mixing affect the setting of injectable bone cement? An ultrasound study

M. D. Vlad · R. Torres · J. López · M. Barracó · J. A. Moreno · Enrique Fernández

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Abstract Experimental calcium sulphate bone cement has been tested by ultrasounds to characterise its progressive setting through the evolution of several acoustic properties. The acoustic impedance $z(t)$, the density $\rho(t)$ and the speed of sound $c(t)$ versus the curing time have been monitored during the viscous-to-solid transition of the cement as a function of different mixing conditions. Injectability tests were also performed and the results have been related to the acoustic properties measured previously. It has been observed that further mixing after cement's constituency, and before the initial setting time of the cement, drastically affects both the characteristic setting times and the injectability of the cement.

1 Introduction

Ceramic bone cements (CBCs), i.e. calcium phosphate and calcium sulphate based bone cements, have been used in dental and orthopaedic applications to improve the quality of life of patients affected by bone fractures, bone tumours, osteoporosis and dental and/or craniofacial affections. This success has led to the development of several commercial formulations, i.e. Norian SRS©, Cementek©, Biocement-D©, α-BSM©, chronOS Inject©, BoneSource© and/or Biopex©, which have been indicated for certain particular applications [1].

Recently, with the advent of minimally invasive surgery techniques, CBCs have been also applied to spinal surgery (vertebro- and/or kyphoplasty) [2–5]. However, surgeons have reported great difficulties in filling the vertebral bodies (bad injectability of present CBCs) and other problems, such as bone press-filtering and cement decohesion, observed during vertebral body injection, that have resulted in bone instability due to low mechanical strength and long setting times of the cement [6]. For these reasons, the clinicians have indicated that new research on injectable biomaterials is needed because the future of orthopaedic surgery also heads in the direction of minimal invasion, where clinical techniques have lower cost and patients return to their normal activities much sooner. Thus, as interest in vertebro- and kypho-plasty continues, the application of injectable cements through minimally invasive techniques in the management of skeletal defects has become popular and scientists have approached the rheological properties of these materials in several ways [6–10].

The present research aims at furthering the understanding of injectable CBCs, as those used in spinal surgery, to elucidate which rheological properties are needed to inject these biomaterials into bone cavity before their setting. This general objective has been approached by monitoring the acoustic properties of an experimental calcium sulphate CBC during its setting by ultrasounds [11]. However, as these materials have progressive setting, it is not known how the injectability can be maintained in a clinical procedure. For these reason, ultrasound monitoring and injection experiments were also investigated at different mixing conditions.

M. D. Vlad · R. Torres · J. López · M. Barracó · E. Fernández (✉)
Interdepartment Research Group for the Applied Scientific Collaboration (IRGASC), Division of Bioengineering & Biomaterials, Department of Materials Science and Metallurgy, Technical University of Catalonia (UPC), Avda. Diagonal 647, E-08028-Barcelona, Spain
e-mail: enrique.fernandez@upc.edu

J. A. Moreno
Laboratory of Non-Destructive Tests, Department of Marine Sciences, UPC

2 Materials and methods

Cements were made by mixing, by hand with a pestle in a mortar during 30 s, calcium sulphate hemihydrate (CSH) with water of pharmaceutical quality at different liquid-to-powder L/P ratios ($0.5 \leq L/P(mL/g) \leq 3.5$). The setting was monitored, 30 s later, at room temperature by ultrasounds during 1 h following the method outlined by Carlson et al. [12]. Cement made at L/P = 2 mL/g was selected for further studies. It set under static conditions to obtain, from the evolution of the speed of sound *versus* time's curve (see the results section), the ultrasound's initial and final setting times (IST, FST). Then, replicas were prepared in a glass tube and set up to resting times RT lower than the IST, where *resting time* means that time for which the cement sets without further continuous or discontinuous mixing (i.e. under static conditions). After completion of those fixed RTs, cements were mixed by agitation (*YelloLab Test Tube Shaker, Ika Works, Inc.*) at 1600 rpm during 30 s and monitored again (as above, see Ref. 12), 30 s later, by ultrasounds during 1 h. The acoustic impedance $z(t)$, the density $\rho(t)$ and the speed of sound $c(t)$ were measured with this method [12].

The injectability was approached, following the method outlined by Driessens et al. [13], by extruding syringes of 5 mL, filled with cement up to ≈4.6 mL (i.e. ≈3.7 cm), at a crosshead speed of 50 mm/min (i.e. maximum extruding time to empty the syringe ≈45 s) and up to a maximum load of 300 N, using an *MTS Insight 5* universal testing machine. Following this method, the evolution of the extrusion force was recorded against the extruding time for different mixing conditions; i.e. samples setting at rest up to different RTs and then injected, and samples mixed again at 1600 rpm for 30 s after completion of fixed RTs and then injected.

Scanning Electron Microscopy SEM was performed for some cement samples setting up to fixed resting times, before (i.e. RT = 0 min) and after (i.e. RT = 0, 1.5, 3 & 9 min) the application of further mixing during 30 s at 1600 rpm, in order to see any effect on cement's crystals distribution that could be related to cement's densification (see results). Samples were quenched in acetone immediately after both, the completion of RTs or the additional mixing protocol to stop the hydration reaction of the cement.

3 Results and discussion

Figure 1shows the evolution of the speed of sound of ultrasound pulses traversing a cement sample *versus* the curing time, and as a function of the L/P ratio. These curves are used to calculate the characteristic initial and final setting times of the curing cement reaction [11]. The speed of sound is constant for times both lower than the IST and higher than the FST; between the IST and the FST (i.e. the setting period) the speed of sound increases at constant rate. Figure 1 shows that the IST and the FST increased as the L/P ratio, indicating that high L/P ratio retards the setting. Moreover, the initial constant speed of sound before the IST decreased as the L/P ratio increased, approaching the value of 1500 m/s, characteristic of sound traversing water, i.e. the condition L/P > 2 mL/g produced very liquid cements (non useful for the present study). Similar behaviour is observed for the speed of sound at saturation after the FST, i.e. it decreased as the L/P ratio increased. In general, these results indicated that cements set faster and were more compact for lower L/P ratios.

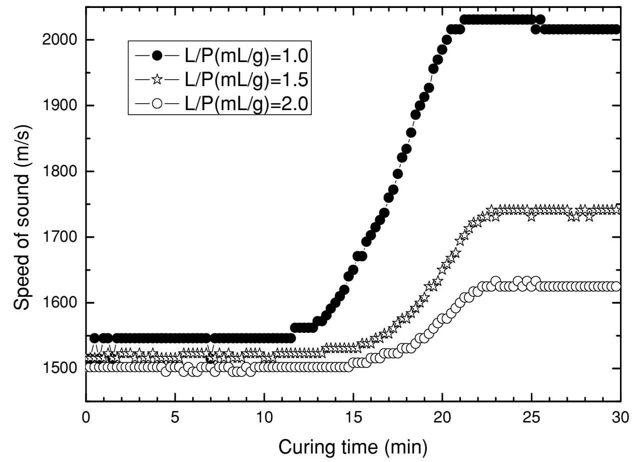

Fig. 1 Speed of sound *versus* Curing time: Effect of the liquid-to-powder ratio L/P for CS-cement

Figures 2 and 3 show the evolution of the acoustic impedance $z(t)$ and the density $\rho(t)$, respectively, *versus* the curing time for cement made at L/P = 2 mL/g, and as a function of resting times RT. This L/P ratio showed good workability, it had the highest useful IST of the series (IST ≈ 14(±1) min) and allowed for more experiments at RT < IST. Figures 2 and 3show that, if cement mixing (30 s

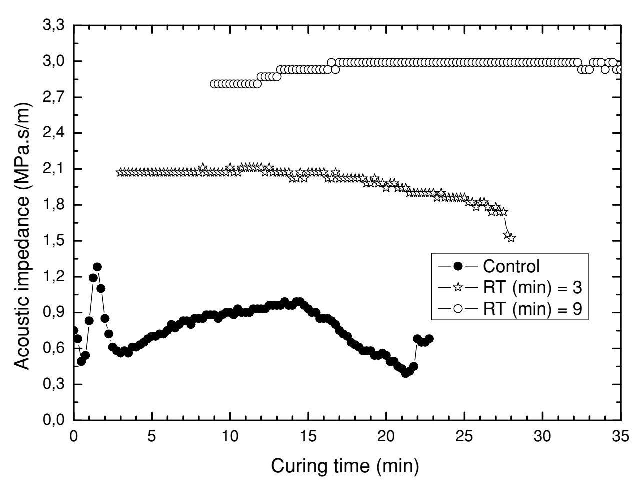

Fig. 2 Acoustic impedance *versus* Curing time: Effect of further mixing (30 s at 1600 rpm) after completion of resting times RT = 3 & 9 min of CS-cement at L/P = 2 mL/g

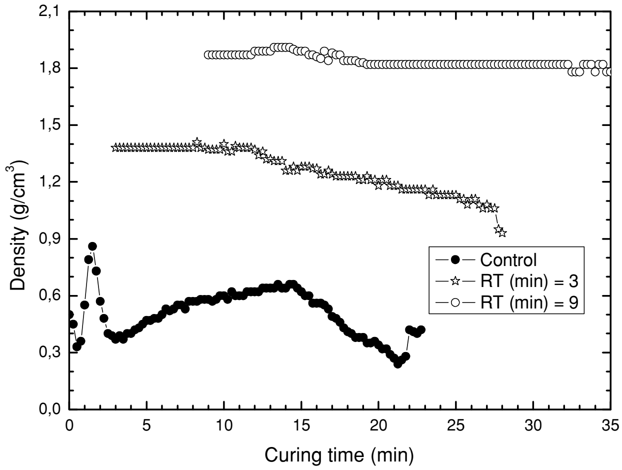

Fig. 3 Density *versus* Curing time: Effect of further mixing (30 s at 1600 rpm) after completion of resting times RT = 3 & 9 min of CS-cement at L/P = 2 mL/g

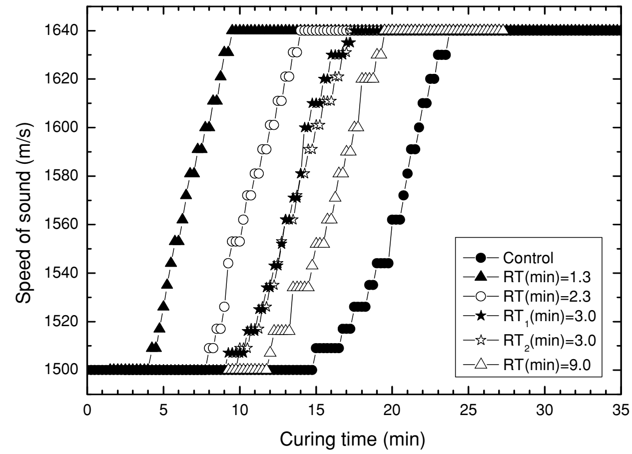

Fig. 4 Speed of sound *versus* Curing time: Effect of further mixing (30 s at 1600 rpm) after completion of resting times RT = 1.3, 2.3, 3 & 9 min of CS-cement at L/P = 2 mL/g. (Note: two curves are shown for sample RT = 3 min to show that standard deviation (not drawn for clarity) of ultrasound measurements was less than 2%)

at 1600 rpm) is again performed at some time (RT = 3 or 9 min) after the initial powder and liquid cement mixture, the acoustic impedance and the density increased with RT, as compared to the control cement for which no additional mixing is performed at any time. These results indicated that further mixing before the IST compacts and makes the cement more homogeneous (i.e. more constant $z(t)$ and $\rho(t)$ values along the whole curing period) probably by eliminating air bubbles introduced during hand mixing and also by favouring a better distribution of reactant and product crystals, i.e. CSH and CS-dihydrate (CSD) crystals. SEM results seemed to corroborate this conclusion (see later). An interesting observation is that more compact and homogenous cements are produced as RT approaches the IST, i.e. higher nearly-constant values of both $z(t)$ and $\rho(t)$. In fact, values around 0.5(± 0.1) g/cm^3 (i.e. sample at RT = 0 min) are typical of porous calcium sulphate cements while values around 1.2(±0.1) g/cm^3 (i.e. sample at RT = 3 min) and 1.8(± 0.1) g/cm^3 (i.e. sample at RT = 9 min) are also known for compact calcium sulphate cements [14]. It should be noted in Fig. 3 that data acquisition for curves RT = 3 & 9 min start at 3 & 9 min, meaning that before these times (i.e. before the application of 30 s mixing at 1600 rpm) the setting condition was exactly the same as that of the control and so the density of cements before the application of further mixing is the same as that reported by the control curve. This means that further mixing actually densifies the cement material. It should be mentioned that no thermal effect, that could accelerate the setting of the cement, was noticed with a thermometer after mixing at 1600 rpm for 30 s.

Figure 4shows the evolution of the speed of sound *versus* the curing time for cement made at L/P = 2 mL/g, and as a function of RT. It shows how setting times (IST and FST) can be drastically reduced if appropriate mixing protocols are conducted just after the initial mixture of the powder and liquid cement phases. Interestingly, when cement set at rest during 1.3 min and then was mixed during 30 s at 1600 rpm, the IST reduced from 14(±1) min (i.e. the control) to 4(±1) min, and the FST reduced from 23(±1) min to 10(±1) min. In that particular case, the setting reaction was heavily accelerated. On the other hand, when RT approached the IST the effect on the setting times reduced. Figure 4 also shows that the observed results had good reproducibility (see curves for series RT_1 and RT_2, both made at RT = 3 min), which is a characteristic of ultrasonic measurements (inherent error less than 2%; standard deviation not drawn for clarity). In fact, the differences observed between curves in Fig. 4 showed to be statistically significant at a probability level of 95% (α = 0.05).

It is thought, based of SEM observations (see later), that the results in Fig. 4 should be related with the number and size of CSD crystals which are formed at the beginning of the hydration reaction of CSH crystals and on how these crystals are distributed in volume when further mixing is applied. However, more research is needed to clarify these observations. On the other hand, Figs. 3 and 4 shows that further mixing before the IST can both accelerate the setting (i.e. fast setting cements) and improve the densification of the material (i.e. better mechanical properties). It is also important to note that the speed of sound of all samples for times lower than their IST was 1500 m/s, which is the same as that of ultrasound pulses traversing water. This means that before the IST cement behaves as a liquid phase similar to water; thus, when injection was performed before the IST, injectability was similar for all the cements tested in that condition (i.e. measured speed of sound around 1500 m/s) to that observed for sample RT(min) = 0 in Fig. 5 (see later). Moreover, the speed of sound at saturation was also the same

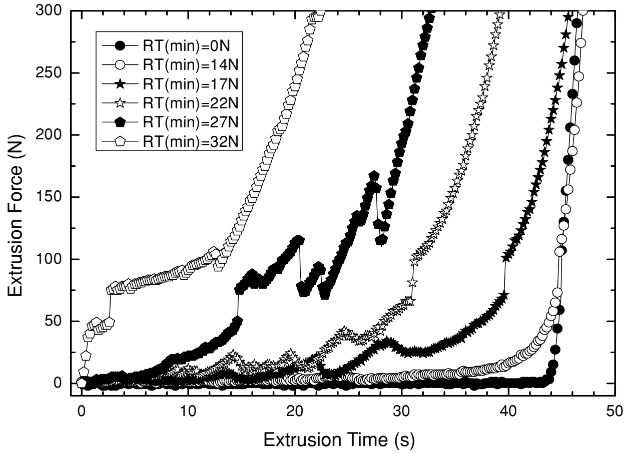

Fig. 5 Extrusion force *versus* Extrusion time: Effect of RT on CS-cement's injectability at L/P = 2 mL/g

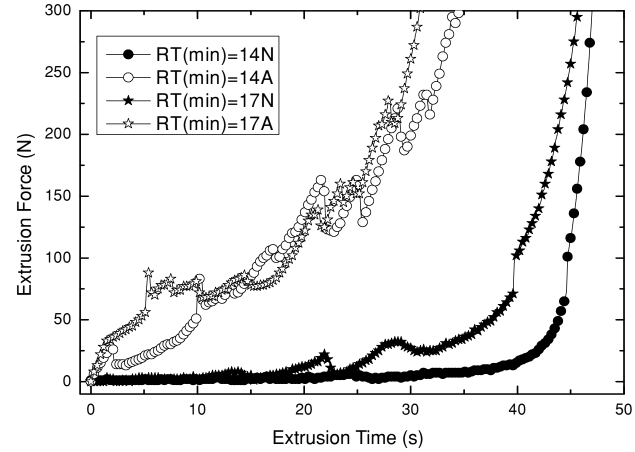

Fig. 6 Extrusion force *versus* Extrusion time: Effect of further mixing (30 s at 1600 rpm) on CS-cement's injectability at L/P = 2 mL/g, i.e. non-further agitation (N) *versus* further agitation (A) after completion of fixed resting times RT = 14 & 17 min

for all the samples, i.e. 1640 m/s. This means that the differences observed for the cement's density (see Fig. 3) are not enough to change the speed of sound traversing the cement, i.e. from the point of view of ultrasound pulses the physical properties of the crystal microstructure of the cements is the same after their FST.

Figure 5 shows the evolution of the extrusion force *versus* the extruding time during the injectability experiments of cement made at L/P = 2 mL/g. Cement samples were prepared following the same protocol. Syringes of 5 mL filled with cement were allowed to set at different resting times without further agitation (RT = 0N, 14N, 17N, 22N, 27N, 32N min; where "N" stands for "No-further agitation") and then extruded (see materials and methods). Sample at RT = 0N min was the control for the injectability experiments, i.e. sample extruded immediately after cement's constituency; RT = 14N min is a sample at the IST; RT = 17N is a sample between the IST and the FST; RT = 22N min is a sample at ≈FST; and RT = 27N & 32N min are samples at RT > FST. The general observation is that cement's injectability decreased (as expected) with the increase of RT; i.e. with the progress of the hydration setting reactions. If a force value is taken constant (200 N, for example) it is observed that this level of force was attained in shorter time for higher RTs, i.e. more set and less injectable cements. Other specific observations such as cement-water filtration and cement blockage (force step-drop variations) inside the syringe can be also observed in Fig. 5. It is worth-mentioning that the control cement (i.e. RT = 0N min) was fully injectable during the maximum allowed extruding time period, i.e. ≈ 45 s. In fact, if cements mixed at different RTs are injected before their characteristic IST (see Fig. 4) the extrusion behaviour (i.e. minimum constant extrusion force or maximum injectability) was the same as that of the control sample (i.e. RT = 0N min; in Fig. 5). This was also in agreement to the results observed in Fig. 4, where the speed of sound for times $t <$ IST was 1500 m/s, i.e. the speed of sound through water (very liquid cements). Statistic analysis performed on three series of experiments confirmed the above observations.

Figure 6shows the effect on the extrusion force *versus* the extruding time of applying further mixing of 30 s at 1600 rpm to samples setting at rest up to RT = 14N & 17N min. According to Fig. 4, it is not expected to observe any acceleration effect on the setting times IST & FST. However, Fig. 6 shows that, after completion of fixed RTs, additional mixing (i.e. samples RT = 14A & 17A in Fig. 6) significantly decreased the injectability as compared with cement samples with no additional mixing (i.e. RT = 14N & 17N). This means that, after the IST, further mixing is still able to compact the cement. In fact, from the point of view of the injectability, the additional mixing applied to samples RT = 14 & 17 was equivalent to those samples setting at rest (i.e. with no additional mixing at any time) for curing times $t > 27$ min (see Fig. 5). Moreover, the effect of compactation due to the additional mixing is so notable that liquid phase press-filtering and cement blockage inside the syringe were also noted in Fig. 6 (see force step-drop variations).

Figure 7is a survey of SEM pictures taken at different mixing conditions. Left-top picture shows the reactant powder phase of the cement, i.e. CSH crystals. These crystals are as large as 20 μm with an aspect ratio of ≈0.25. Right-top picture shows the cement after hand mixing of the powder and the liquid phases during 30 s and then quenched in acetone to stop further CSH-crystals hydration (see materials and methods). The microstructure showed a network of needle shape (aspect ratio of ≈0.08) mild entangled CSH & CSD crystals (equally oriented in all directions). Middle-left picture is the same cement as that in right-top picture but with an added mixing of 30 s at 1600 rpm. In that case, it was observed that needle-shape CSH & CSD crystals oriented preferably

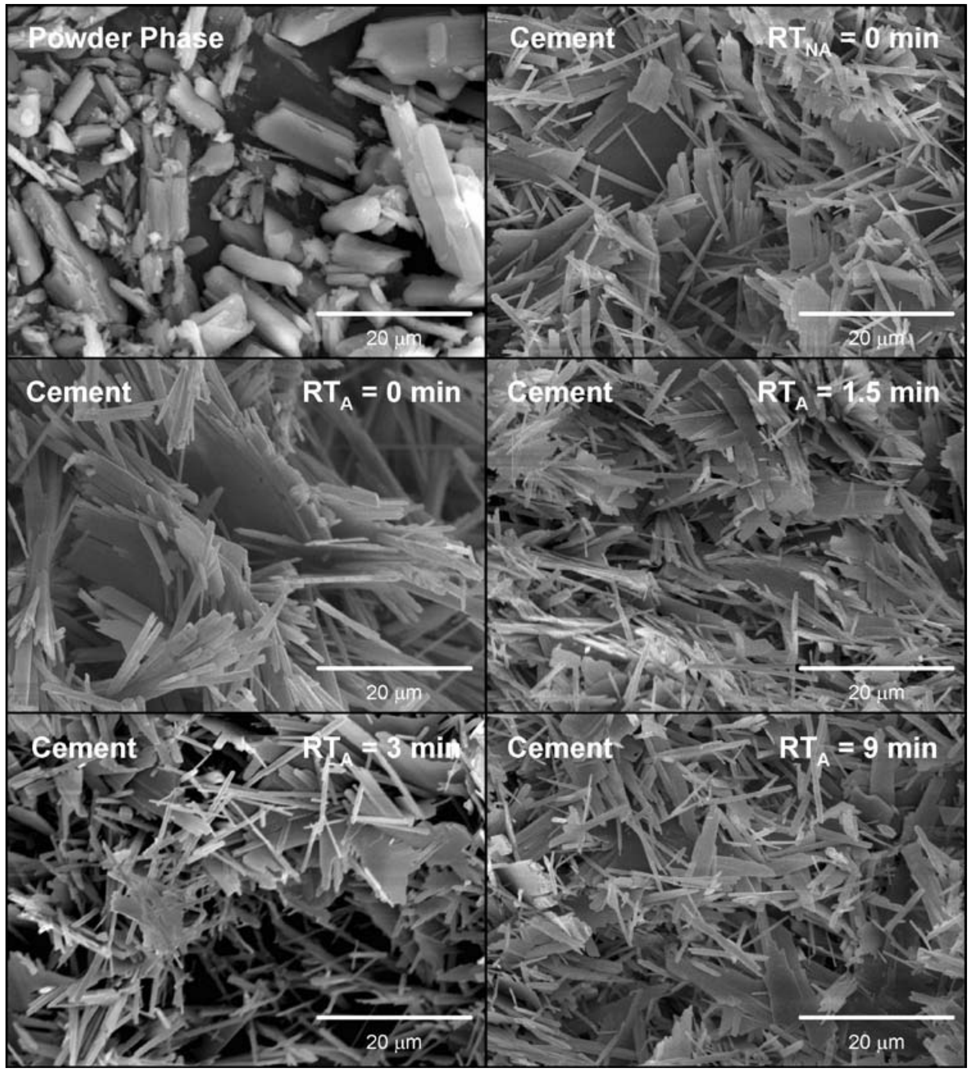

Fig. 7 SEM pictures at different mixing conditions. See the text for comprehensive description of the microstructures. (Top-left: reactant powder phase of CSH crystals; Top-right: cement control quenched without further mixing; Middle-left: cement control with further mixing of 30 s at 1600 rpm and quenched; Middle-right & bottom pictures: cement set at different times (i.e. 1.5, 3 & 9 min), mixed again for 30 s at 1600 rpm and quenched)

following centrifugal forces. Similar behaviour was observed for those samples setting at rest for 1.5 (middle-right picture) & 3 (bottom-left picture) min and mixed again for 30 s at 1600 rpm. This general effect seemed to stop as the IST of the sample was approached; see bottom-right picture for resting time of 9 min and further mixing of 30 s at 1600 rpm. Although these observations are quite subjective, these should to be at the base of a possible explanation for the acceleration (see Fig. 4) and the densification (see Figs. 3 and 6) effects observed in this study.

4 Conclusion

It has been put forward that further mixing, after cement's constituency and before the initial setting time IST, improves the setting (i.e. lower IST & FST) but reduces the injectability of calcium sulphate based cements. Ultrasound monitoring contributed with relevant information to the understanding of the curing cement's process by recording the evolution of the acoustic impedance, the density and the speed of sound during the cement's setting. The characteristics IST & FST were obtained from the evolution of the speed of sound. SEM observations helped to clarify that cement's densification was related to preferential orientation, due to agitation, of the needle-shape CSH & CSD crystals formed during the initial stages of the hydration reaction. The final conclusion is that mixing actually affects the setting of injectable calcium sulphate bone cements.

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References

1. M. BOHNER, *Eur. Spine J.* **10** (2001) S114.
2. D. C. MOORE, R. S. MAITRA, L. A. FARJO, G. P. GRAZIANO and S. A. GOLDSTEIN, *Spine* **22**(15) (1997) 1696.

3. L. E. MERMELSTEIN, R. F. MCLAIN and S. A. YERBY, *Spine* **23**(6) (1998) 664.
4. B. BAI, L. M. JAZRAWI, F. J. KUMMER and J. M. SPIVAK, *Spine* **24**(15) (1999) 1521.
5. P. F. HEINI, U. BERLEMANN, M. KAUFMANN, K. LIPPUNER, C. FANKHAUSER and P. LANDUYT, *Spine* **10** (2001) 164.
6. M. BOHNER and G. BAROUD, *Biomaterials* **26**(13) (2005) 1553.
7. U. GBURECK, J. E. BARRALET, K. SPATZ, L. M. GROVER and R. THULL, *Biomaterials* **25** (2004) 2187.
8. J. E. BARRALET, M. HOFFMAN, L. M. GROVER and U. GBURECK, *Adv. Mater.* **15**(24) (2003) 2091.
9. E. FERNÁNDEZ, S. SARDA, M. HAMCERENCU, M. D. VLAD, M. GEL, S. VALLS, R. TORRES and J. LÓPEZ, *Biomaterials* **26** (2005) 2289.
10. G. BAROUD, M. BOHNER, P. HEINI and T. STEFFEN, *Bio-Med. Mater. Eng.* **14**(4) (2004) 487.
11. A. M. VIANO, J. A. AUWARTER, J. Y. RHO and B. K. HOFFMEISTER, *J. Biomed. Mater. Res.* **56** (2001) 593.
12. J. CARLSON, M. NILSSON, E. FERNÁNDEZ and J. A. PLANELL, *Biomaterials* **24** (2003) 71.
13. I. KHAIROUN, M. G. BOLTONG, F. C. M. DRIESSENS and J. A. PLANELL, *J. Mater. Sci. Mat. Med.* **9** (1998) 425.
14. Ullmann's Encyclopedia of Industrial Chemistry. *Benzyl Alco. Calc. Sulf.* **A4** (1985) 555.