Setting Behavior and in Vitro Bioactivity of Hydroxyapatite/Calcium Sulfate Cements

M. V. Cabañas, L. M. Rodríguez-Lorenzo, and M. Vallet-Regí*

Departamento de Química Inorgánica y Bioinorgánica, Facultad de Farmacia, Universidad Complutense, 28040 Madrid, Spain

Received January 16, 2002. Revised Manuscript Received May 13, 2002

The transformation of calcium sulfate hemihydrate into gypsum via reaction with water has been used for many years to produce materials for bone augmentation. In this work, a mixture of $CaSO_4{\cdot}{}^1/_2H_2O$ and hydroxyapatite was prepared, and its behavior as cement was studied and compared with that of pure calcium sulfate hemihydrate. The setting process was monitored with Gillmore needles, X-ray diffraction, and differential scanning calorimetry. The utilization of the mixture allows one to prepare homogeneous pastes with better manipulation characteristics than pure calcium sulfate hemihydrate. The workability and setting time of the hydroxyapatite-containing cements are higher than those of pure $CaSO_4{\cdot}{}^1/_2H_2O$. The different techniques employed allow us to relate the initial setting time with the chemical transformation of the calcium sulfate hemihydrate into calcium sulfate dihydrate. The biphasic specimens show an improved bioactivity response compared to pure hydroxyapatite or gypsum when soaked in a simulated body fluid.

Introduction

The transformation of $CaSO_4{\cdot}{}^1/_2H_2O$ (calcium sulfate hemihydrate) into $CaSO_4{\cdot}2H_2O$ (gypsum) via reaction with water has been used for many years to produce materials for bone augmentation,[1,2] and it continues to be the object of interest and research.[3,4] The ability of setting "in situ" after filling the defect, the lack of an inflammatory response, and the promotion of bone healing are the main reasons for this long history. One of the main drawbacks of this material is its vivo resorption rate, which is too fast for appropriate tissue regeneration.[2]

Hydroxyapatite (OHAp) is another material frequently used for bone augmentation. It has been applied in two forms, as blocks and in particulate form.[5,6] The OHAp blocks are inconvenient to use because they cannot be accurately shaped into the defect site, while the particles' main disadvantage is that they may easily migrate into surrounding tissues.

The combination of the two mentioned materials, $CaSO_4{\cdot}2H_2O$ and OHAp, can overcome the individual drawbacks and extend their applications. First, it enables one to control the rate of resorption, keeping the integrity of the graft during bone healing, and, second, to avoid the migration of the OHAp particles. Consequently, the past few years have seen an increase in clinical and in vivo studies using this biphasic material.[7,8] Similar approaches have been assayed to produce "in situ" calcium phosphates via a paste formation, as has been done by Driessens et al.[9] or Chow and Takagi.[10] However, there are no known publications on how the addition of OHAp particles affects the cementing behavior of calcium sulfate hemihydrate, which is necessary for a better understanding and optimization of these materials. These cements are usually injected percutaneously using a syringe or implanted operatively like putty. Therefore, it is important to control parameters such as working time, setting time, or thermodynamic behavior. The adequate management of the cements can be crucial for the success of a clinical procedure.

The aim of this work is to study the behavior as cement of a biphasic mixture of calcium sulfate hemihydrate and OHAp, with different liquid/powder (L/P) ratios. The working and setting times of the paste, apparent density, microstructure, and bioactivity behavior of the resulting cement are studied, and comparisons are made between pure calcium sulfate and a biphasic mixture.

Experimental Section

OHAp has been synthesized and characterized as described elsewhere.[11,12] Calcium sulfate hemihydrate of commercial

---

* Corresponding author. Phone: 34 91 3941861. Fax: 34 91 3941786. E-mail: vallet@farm.ucm.es.

(1) Coetzee, A. S. *Arch. Otolaryngol.* **1980**, *106*, 405.

(2) Costantino, P. D.; Friedman, C. D. *Otolaryngol. Clin. N. Am.* **1994**, *27*, 1037.

(3) Pecora, G.; De Leonardis, D.; Ibrahim, N.; Bovi, M.; Cornelini, R. *Int. Endod. J.* **2001**, *34*, 184.

(4) Pietrzak, W. S.; Ronk, R. *J. Craniofac. Surg.* **2001**, *11*, 327.

(5) Jarcho, M. *Clin. Orthop.* **1981**, *157*, 259.

(6) Byrd, H. S.; Hobar, P. C.; Shewmake, K. *Plast. Reconstr. Surg.* **1993**, *91*, 15.

(7) Rawlings, C. E., III; Wilkins, R. H.; Hanker, J. S.; Georgiade, N. G.; Harrelson, J. M. *J. Neurosurg.* **1988**, *69*, 269.

(8) Sato, S.; Koshino, T.; Saito, T. *Biomaterials* **1998**, *19*, 1895.

(9) Driessens, F. C. M.; Planell, J. A.; Boltong, M. G.; Khairoum, I.; Ginegra, M. P. *Proc. Inst. Mech. Eng., Part H: J. Eng. Med.* **1988**, *212*, 427.

(10) Chow, L. C.; Takagi, S. *J. Res. Natl. Inst. Stand. Technol.* **2001**, *106*, 1029.

(11) Rodríguez-Lorenzo, L. M.; Vallet-Regí, M. *Chem. Mater.* **2000**, *12*, 2460.

10.1021/cm021121w CCC: $22.00

grade has been used. X-ray diffraction (XRD) patterns were obtained using a Philips X'Pert diffractometer with Cu Kα radiation in order to check the presence of secondary phases.

Recently, materials containing 60 wt % of a stable component and 40 wt % of a resorbable component have been developed, and it seems to be an appropriate mixture to induce osseous regeneration.[13] The use of this ratio for a system consisting of OHAp, as a stable discrete phase, and gypsum, as a resorbable matrix, led to very long setting times; therefore, the maximum amount of the stable component (40 wt %) that maintained the handling properties of the gypsum matrix was selected. Calcium sulfate hemihydrate and OHAp (in a 60/40 wt % ratio) were mixed in an agate container by soft grinding for 24 h. Slurries were prepared by pouring portions of the powder over deionized water in different L/P ratios.

For the preparation of biphasic pieces, the slurries were injected into stainless steel molds by using a 27 mm syringe with an opening of 2 mm. The molds (12 × 6 and 6 × 12 mm, width × height) were placed in an oven at physiological temperature (37 °C) for setting. The obtained specimens were extracted from the molds and dried at 37 °C for 24 h. A total of 8−10 specimens were obtained for each preparation, and at least four preparations were done per L/P ratio. Samples of pure calcium sulfate were also prepared for comparison purposes.

The setting time was studied by Gillmore needles. The initial setting time (t_0) is the time elapsed between the start of the mix and the moment when the small Gillmore needle (2.12 mm diameter and 113.4 g by weight) fails to indent the surface of a piece. The final setting time (t_f) is determined when the large Gillmore needle (1.06 mm diameter and 453.6 g by weight) fails to indent the surface of a specimen.

XRD was used for monitoring the in situ transformation of calcium sulfate hemihydrate into gypsum. For this purpose, XRD patterns of the slurry between 10 and 16° (2θ) were registered every 1 min. We have termed these experiments as time-dependent XRD (TDXRD). The heat generated during the setting reaction of the slurry was evaluated by differential scanning calorimetry (DSC). For this purpose, a Seiko SSI/SSC/5200 instrument fixed at 37 °C was employed.

The apparent density of the specimens was determined by Archimedes' method by immersion in mercury. Results are the average of four measurements. The distribution and morphology of the phases in the set specimens were studied by scanning electron microscopy (SEM) by using a JEOL JSM 6400 microscope.

In vitro degradation/bioactivy tests were carried out by soaking the pieces, vertically held over platinum holders in simulated body fluid (SBF), at pH = 7.4 and 37 °C. The SBF is an acellular solution with an ionic composition similar to that of human plasma.[14] The ionic concentration of SBF (mM) is as follows: Na^+, 142.0; K^+, 5.0; Ca^{2+}, 2.5; Mg^{2+}, 1.5; Cl^-, 148.8; HCO_3^-, 4.2; HPO_4^{2-}, 1.0; SO_4^{2-}, 0.5. A fixed mass/liquid ratio, 0.01 g/cm^3, was selected. The fluid was previously filtered with a Millipore 0.23 μm system, and all operations were carried out in a laminar flux cabin (Telstar AV-100), avoiding bacterial contamination. The Ca^{2+} concentration and pH change produced in the solution after different times of soaking were determined with an Ilyte Na^+, K^+, and Ca^{2+} pH system, whereas the phosphorus change was determined by UV−vis spectroscopy by complex formation in a Beckman DU-7 spectrophotometer. After the degradation/bioactivity test, the specimens were studied by glancing-angle incidence XRD and SEM.

Results

The initial and final setting times obtained with the Gillmore needles are shown in Figure 1. A higher setting time with the increase of the L/P ratio was obtained for both series. When the same L/P ratios are compared, the setting time values are greater for biphasic specimens than for pure calcium sulfate specimens. For high L/P ratios the final setting time exceeds 1 h.

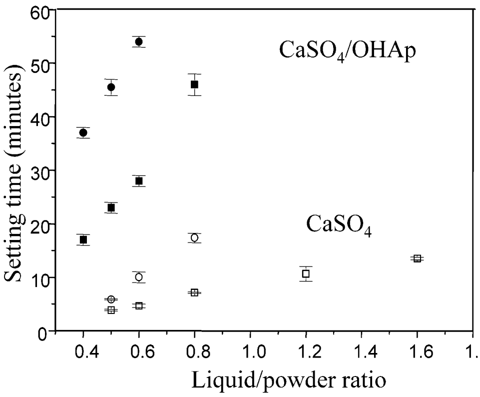

Figure 1. Initial (□) and final (○) setting time obtained by Gillmore needles for biphasic and pure calcium sulfate slurries.

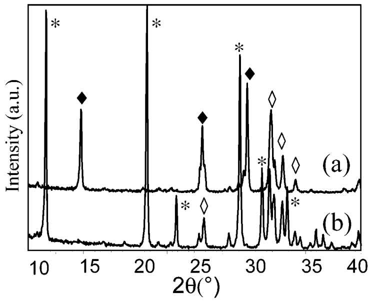

Figure 2. XRD patterns for (a) the initial biphasic mixture and (b) biphasic set cements. Diffraction maxima: ◆, $CaSO_4 \cdot {}^1/_2H_2O$; *, $CaSO_4 \cdot 2H_2O$; ◇, OHAp.

The XRD patterns of the starting mixture and the final set specimen are displayed in Figure 2. The diffraction maxima of the starting material can be attributed to $CaSO_4 \cdot {}^1/_2H_2O$[15] plus OHAp[16] (Figure 2a), whereas a mixture of $CaSO_4 \cdot 2H_2O$[17] and OHAp is observed for the specimens after the setting reaction (Figure 2b).

The evolution of the XRD maxima corresponding to the $CaSO_4 \cdot {}^1/_2H_2O$ ($2\theta = 14.7°$) and $CaSO_4 \cdot 2H_2O$ ($2\theta = 11.6°$) over time, for a pure calcium sulfate slurry with a L/P = 0.8, is displayed in Figure 3. Initially, only the diffraction maximum corresponding to $CaSO_4 \cdot {}^1/_2H_2O$ is observed; the intensity of this maximum decreases with time, and simultaneously the diffraction maximum corresponding to gypsum appears and its intensity increases. The study applied to different slurries shows that the moment of appearance of the $CaSO_4 \cdot 2H_2O$ maximum is delayed with increasing L/P ratio as well as in the presence of OHAp. As an example, for a L/P ratio of 0.6, the maximum was delayed from 2 to 11 min. In addition, the total transformation of hemihydrate into gypsum, that is, when no hemihydrate maximum is observed in the XRD pattern, is delayed when the

---

(12) Rodríguez-Lorenzo, L. M.; Vallet-Regí, M.; Ferreira, J. M. F. *Biomaterials* **2001**, *22*, 583.

(13) Rohanizadeh, R.; Padrines, M.; Bouler, J. M.; Couchourel, D.; Fortun, Y.; Daculsi, G. *J. Biomed. Mater. Res.* **1998**, *42*, 530.

(14) Kokubo, T.; Kushitani, H.; Sakka, S.; Kitsugi, T.; Yamamuro, T. *J. Biomed. Mater. Res.* **1990**, *24*, 721.

(15) Powder diffraction file no. 41-0224 of the International Center for Diffraction Data.

(16) Powder diffraction file no. 9-0432 of the International Center for Diffraction Data.

(17) Powder diffraction file no. 33-0311 of the International Center for Diffraction Data.

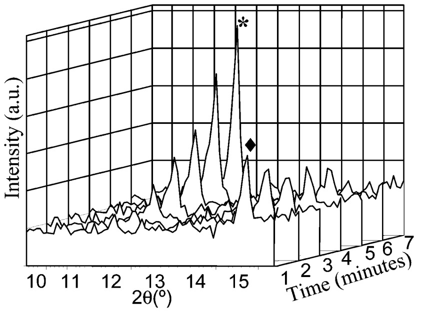

Figure 3. TDXRD patterns for a calcium sulfate slurry with a L/P ratio equal to 0.8. Diffraction maxima: ◆, $CaSO_4\cdot{}^1/_2H_2O$; *, $CaSO_4\cdot 2H_2O$.

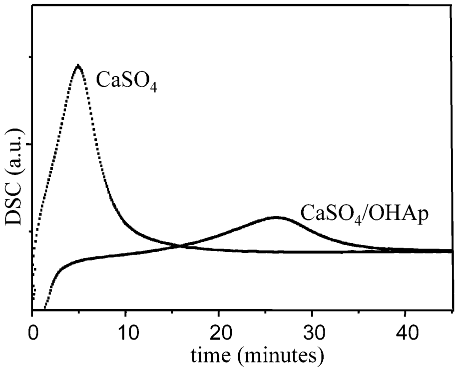

Figure 4. DSC isothermal diagram at 37 °C versus time for a pure calcium sulfate and biphasic slurries with a L/P ratio equal to 0.6.

L/P ratio is increased. For a L/P ratio of 0.8, the reaction lasted 7 min, whereas for a L/P ratio of 1.2, it lasted 10 min, in a pure calcium sulfate slurry. On the TDXRD experiments, the total transformation of hemihydrate into gypsum could not be observed in the presence of OHAp: in such a case, the $CaSO_4\cdot{}^1/_2H_2O$ maximum is still noticeable in the XRD pattern after 24 h.

Figure 4 shows a DSC isothermal analysis at 37 °C for a biphasic mixture and pure calcium sulfate slurries with a L/P ratio equal to 0.6. For both series, an exothermic peak is observed. The time passed from the beginning of the reaction up to the appearance of this exothermic peak is higher for the biphasic slurry than for the pure calcium sulfate cement. The maximum value of this peak appeared after 5 min for pure calcium sulfate, whereas it took 27 min for the OHAp−sulfate mixture. The same trend was observed for all higher water content assays. Besides, the addition of OHAp into the slurry has resulted in a decrease of the heat released.

The apparent density of the pieces determined by Archimedes' method is shown in Figure 5. A density decrease can be observed as the water/powder ratio increases for both series studied. The apparent densities obtained for pure calcium sulfate specimens are similar to those observed by other authors.[18] The biphasic $OHAp/CaSO_4\cdot 2H_2O$ set specimens show apparent densities slightly higher than those of pure calcium sulfate dihydrate.

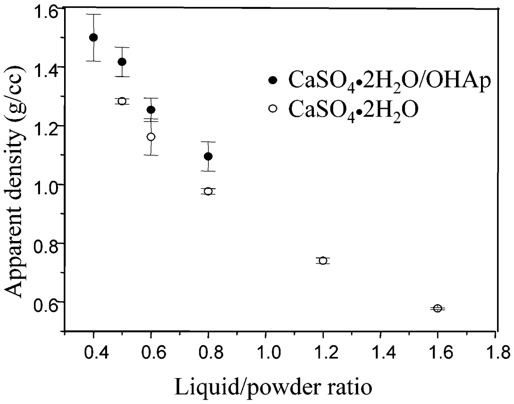

Figure 5. Apparent density of specimens as a function of the L/P ratio.

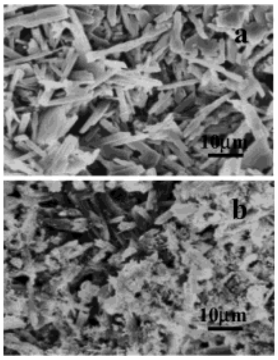

Figure 6. SEM micrographs of a cross section of (a) pure calcium sulfate dihydrate and (b) OHAp/calcium sulfate dihydrate specimens.

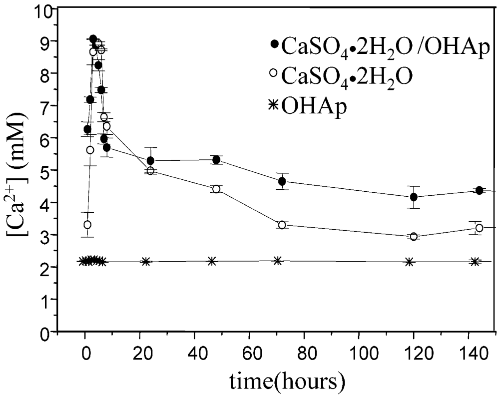

Figure 7. Variations of calcium content (mM) in a SBF solution as a function of soaking time, for biphasic and pure calcium sulfate set specimens (L/P = 0.6). Data of a pellet of pure OHAp are also included.

SEM micrographs on a fracture surface of both biphasic and pure calcium sulfate set specimens are collected in Figure 6. The pure $CaSO_4\cdot 2H_2O$ specimens (Figure 6a) are constituted by large and elongated crystals, which are typical of gypsum,[19] while small particles of OHAp filling spaces between gypsum crystals can be seen in the biphasic cements (Figure 6b).

In Vitro Degradation/Bioactivity. Figure 7 shows the variation of the Ca^{2+} concentration in solution with soaking time for a biphasic mixture and pure calcium sulfate set specimens with a L/P ratio of 0.6. Data of a pellet of pure OHAp are also included. Initially, rapid Ca^{2+} release from the specimens to the solution is observed for the set specimens. After 5 h, the calcium

---

(18) Lautenschlager, E. P.; Corbin, F. *J. Dent. Res.* **1969**, *48*, 206.

(19) Shen, C.; Mohammed, H.; Kamar, A. *J. Dent. Res.* **1981**, *60*, 1410.

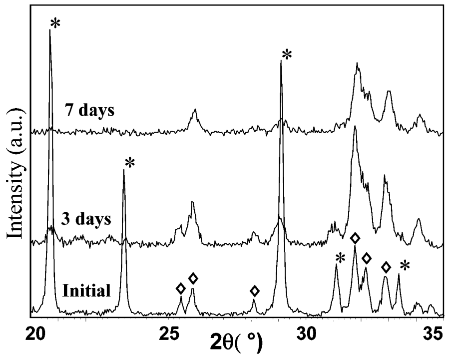

Figure 8. Glancing-angle incidence XRD patterns of a biphasic set specimen before and after soaking in SBF for different time periods. Diffraction maxima: *, $CaSO_4{\cdot}2H_2O$; ◇, OHAp.

concentration decreases rapidly, and after 3 days, it reaches a plateau up to the end of the experiment (7 days). On the other hand, the phosphorus concentration of the SBF solution initially does not vary and it decreases after 5 h of soaking. No phosphorus is detected in the solution after 3 days of soaking. No changes in pH were observed for the duration of these experiments. The specimens showed no signs of disintegration after being soaked in the fluid for 7 days. The different specimens prepared with different L/P ratios show a similar behavior to that depicted in Figure 7.

Glancing-angle incidence XRD patterns obtained from the surface of the biphasic set samples before and after soaking in SBF are shown in Figure 8. After 3 days of soaking, the intensity of gypsum maxima decreases, and after 7 days, no gypsum is detected. After this soaking time, only diffraction maxima corresponding to OHAp can be detected, although a broadening and a decrease of intensity in these maxima can be observed. SEM pictures obtained from specimens after soaking in SBF show that the surface of the specimens is covered by a new layer of material: after soaking for 3 days, this layer is constituted by small particles of 100−200 nm (Figure 9a); the size of these particles kept growing for 7 days (Figure 9b).

For gypsum specimens, no XRD maxima attributable to an apatite-like structure were observed after different soaking times. The SEM analysis does not show the presence of a layer over the pure $CaSO_4{\cdot}2H_2O$ specimen surface, although the crystals corresponding to gypsum seem to be thinner than those before soaking (Figure 9c).

Discussion

The introduction of OHAp into the cement composition was advantageous from a technological point of view. As can be observed in Figure 1, it enabled us to prepare pastes with a lower L/P ratio than that for pure calcium sulfate. When a L/P ratio of 0.4 was assayed for $CaSO_4{\cdot}{}^1/_2H_2O$, it was impossible to form a paste that could be considered homogeneous. The paste partially dried before the liquid soaked all of the powder. On the contrary, a homogeneous and workable paste was effectively achieved when OHAp was added to plaster, $CaSO_4{\cdot}{}^1/_2H_2O$. This different behavior can be related to the different solubilities of OHAp and the plaster. OHAp is insoluble in water, and therefore it has no interaction with it, leading to a higher effective water/plaster ratio. Consequently, the addition of OHAp to $CaSO_4{\cdot}{}^1/_2H_2O$ allows one to prepare cements with lower L/P ratios, which, in turn, would yield greater compressive strength and hardness for the final specimens.[20]

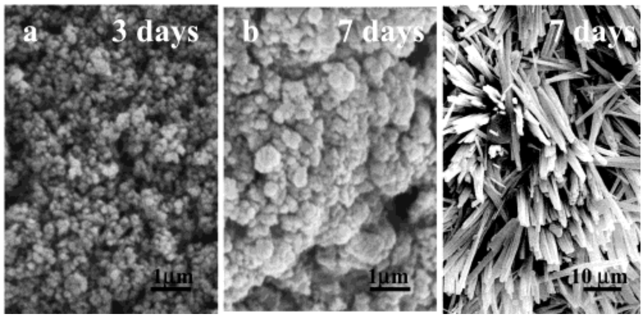

Figure 9. SEM micrographs of biphasic (a and b) and pure calcium sulfate dihydrate (c) specimens soaked in SBF for different time periods.

Another remarkable consequence of the OHAp presence was the significant increase in the initial setting time in comparison with pure calcium sulfate. In biphasic specimens, t_0 varied from 17 to 45 min depending on the L/P ratio. This is the time elapsed between the mixing of water and powder and when the small Gillmore needle fails to indent the surface of a piece. However, before t_0 is reached, the biphasic paste is easily manipulated, and it is possible to mold and handle for at least 10 or 30 min, again, depending on the L/P ratio, before the paste dries. On the contrary, when OHAp had not been added to the $CaSO_4{\cdot}{}^1/_2H_2O$, the paste dried just 2 min after the mixing. Taking into account that in clinical applications the cement must be applied before t_0, the extra time obtained by adding OHAp results in an obvious advantage for surgeons or dentists who will have a comfortable time to work with the paste before it dries, keeping the effective setting time lower than 15 min.

The delayed hardening was confirmed by the TDXRD experiments, which showed higher times for the appearance of the $CaSO_4{\cdot}2H_2O$ maximum in the presence of OHAp. The total transformation of $CaSO_4{\cdot}{}^1/_2H_2O$ into gypsum could also be observed in these experiments, showing that it is delayed when the L/P ratio was increased. The total transformation could not be observed in the presence of OHAp: the partial reaction could be due to the energy supplied by the X-ray radiation used for monitoring the experiment; taking into account the higher exposition time needed, it could dry the paste before the reaction was completed. To check this deduction, an independent XRD pattern was taken for slurries whose hardening had been completed prior to X-ray radiation. The total disappearance of the $CaSO_4{\cdot}{}^1/_2H_2O$ maximum, which confirms the prediction, can be observed in Figure 2b.

The exothermic peak displayed in the DSC diagrams can also be related with the transformation of calcium sulfate hemihydrate into dihydrate. The crystallization of gypsum is an exothermic process.[21] The appearance of the dihydrate maximum in the XRD pattern coin-

---

(20) Prombonas, A.; Vlissidis, D. *J. Prosthet. Dent.* **1994**, *72*, 95.

(21) Winkler, M. M.; Monaghan, P.; Gilbert, J. L.; Lautenschlager, E. P. *J. Prosthet. Dent.* **1998**, *79*, 532.

cides, approximately, with that moment in which it began to release heat in the DSC diagram. The amount of heat released increases with the amount of dihydrate being crystallized. Therefore, a correlation can be established between the maximum heat of the DSC diagram and the total transformation of hemihydrate into gypsum. Once more DSC proved that the presence of OHAp delayed the total transformation of hemihydrate–dihydrate.

It is noteworthy that the t_0 obtained with the Gillmore needles is quite similar to the time needed for the total disappearance of the $CaSO_4 \cdot {}^1/_2H_2O$ maximum on the TDXRD patterns. Besides, the time at which the maximum heat release takes place, as observed in the DSC diagram, is also around the t_0 obtained with the Gillmore needles. Therefore, it can be concluded that XRD and DSC are appropriate techniques to monitor the setting time of the cements, allowing, in addition, the observation of the changes that occur while the slurry is setting.

The combined use of the three techniques enables one to relate the initial setting time with the total transformation of plaster into gypsum. During this process, heat is released until the total transformation is reached. Because the total transformation of hemihydrate into gypsum is correlated to t_0, the difference between t_f and t_0, hardening of the paste, has to be correlated only to the growth of the calcium sulfate dihydrate crystals.

The dissolution of $CaSO_4 \cdot {}^1/_2H_2O$ and subsequent recrystallization to form $CaSO_4 \cdot 2H_2O$ is generally accepted as a setting mechanism for calcium sulfate cements.[19,22] According to our experiments, it can be considered that the introduction of OHAp particles and/or higher amounts of water delays the second step of the mechanism. This fact could be related with the increase in the amount of calcium sulfate hemihydrate which has to be dissolved before achieving the supersaturation level required for the subsequent precipitation of gypsum. Because OHAp seems not to interact with water, it may play a simple role as a barrier, physically hindering the contact between calcium sulfate and water, delaying in that way the reaction. It should also be noted that the presence of this stable phase led to an effective higher percentage of water and, therefore, to an increase of the time required to nucleate gypsum.

The greater density observed for the specimens containing OHAp is due to the distribution of OHAp particles into the spaces left by calcium sulfate upon setting, as observed by SEM. Consequently, the addition of OHAp is advantageous not only in terms of the workability of the materials but also for the reliability of the set specimens because a greater density implies a better mechanical performance.[23,24]

The stability of these biphasic materials in a wet environment was tested as described above. The Ca^{2+} ions released into the solution observed for the first 5 h had to be mainly attributed to the dissolution of $CaSO_4 \cdot 2H_2O$ because no appreciable increase was observed for the P concentration. A OHAp pellet was immersed in SBF to check this point. No dissolution was observed, confirming the former appreciation (Figure 7). After 5 h, calcium and phosphorus concentrations in the solution decreased. This effect could be explained by the precipitation of a calcium phosphate. According to SEM images (Figure 9a,b), a new layer of material was formed on the surface of the soaked specimens, and according to XRD patterns (Figure 8), it is made of an apatite-like phase. The broadening of the reflections observed by XRD allows one to distinguish the new layer from the original OHAp. The XRD patterns of biphasic samples soaked for 7 days are similar to those observed for synthetic or biological apatites of poor crystallinity.[25]

Specimens of pure $CaSO_4 \cdot 2H_2O$ cement showed no extra diffraction maxima after being immersed. Therefore, no apatite phase was formed on the surface of these specimens. Indeed, no layer was observed on the surface of the pure calcium sulfate cement specimens after soaking in SBF (Figure 9c). The smaller size of the crystal can be explained as caused by the dissolution process of $CaSO_4 \cdot 2H_2O$.

The formation of a new apatite-like phase on the surface of biphasic cement and not on the surface of pure $CaSO_4 \cdot 2H_2O$ can be explained as the combination of two effects: (i) the partial dissolution of calcium sulfate which causes an increase in the local supersaturation of Ca^{2+} ions and (ii) the OHAp particles which act as crystallization nuclei. When OHAp particles are lacking, the increase in the supersaturation seems not to be enough to promote the formation of new crystals of OHAp on the material surface, at least for the time assayed.

According to the above results, biphasic materials, $OHAp-CaSO_4 \cdot 2H_2O$, are more bioactive (faster kinetics of formation of an apatite-like layer on soaking) than pure calcium sulfate dihydrate or OHAp.

Conclusions

The incorporation of a 40 wt % of OHAp particles into calcium sulfate hemihydrate powders allowed one to prepare cement pastes with improved manipulation characteristics in comparison to pure calcium sulfate cements.

TDXRD and DSC enabled one to understand the mechanism of setting of calcium sulfate cements. The initial setting time of the cements can be related to the total conversion of calcium sulfate hemihydrate into gypsum.

The OHAp particles act as an element that disturbs the setting reaction, delaying the crystallization of gypsum, increasing the setting time, and decreasing the heat generated during the setting of these cements. This means that the biphasic $OHAp/CaSO_4$ paste increases the working time of the cement, being moldable and easily manipulated for longer times than pure calcium sulfate and resulting in an obvious advantage for the clinician who will have extra time to work with the paste before it dries.

The biphasic OHAp/gypsum set specimens show apparent densities slightly higher than those of pure

---

(22) Solberg, C.; Hansen, S. *Cem. Concr. Res.* **2001**, *31*, 641.

(23) Xu, H. H. K.; Quinn, J. B.; Takagi, S.; Chow, L. C.; Eichmiller, F. C. *J. Biomed. Mater. Res.* **2001**, *57*, 457.

(24) Rodríguez-Lorenzo, L. M.; Vallet-Regí, M.; Ferreira, J. M. F.; Ginebra, M. P.; Aparicio, C.; Planell, J. A. *J. Biomed. Mater. Res.* **2002**, *60*, 159.

(25) LeGeros, R. Z. Calcium Phosphates in enamel, dentin and bone. In *Calcium Phosphates in Oral Biology in Medicine*; Myers, H. M., Ed.; Monographs in oral science; Karge: Zurich, Switzerland, 1991; pp 108–29.

gypsum and an improved bioactivity response compared to pure OHAp or gypsum when soaked in a SBF.

Acknowledgment. Financial support of CICYT, Spain, through Research Project MAT99-0466 is acknowledged. We also thank C.A.I. Difracción de rayos X and C.A.I. Centro de Microscopia Electrónica, Universidad Complutense, Madrid (Spain), for valuable technical assistance.

CM021121W