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Doped calcium–aluminium–phosphate cements for biomedical applications

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Abstract Calcium–aluminium–phosphate cements (CAPCs) for biomedical applications, mainly intended for applications in the dental field as non-resorbable fillers, were obtained by reacting Ca-aluminates compounds, i.e. $CaO{\cdot}Al_2O_3$ (CA) and $CaO{\cdot}2\,Al_2O_3$ (CA_2), with $Al(H_2PO_4)_3$ aqueous solution. Hydroxyapatite was also introduced as a bioactive dispersed phase. Suitable elements like Sr and La were used to increase the radiopacity of the set yielded pastes towards X-ray wavelength used in clinical diagnostic radiographic equipments. La and Sr doped Ca-aluminates powders have been synthesized by solid state reaction at 1,400°C from a mixture of $CaCO_3$, Al_2O_3, La_2O_3 and $SrCO_3$. The characteristics of the obtained powders were analyzed and related to the starting compositions and synthesis procedures. The microstructure, setting time, radiopacity and compressive strength of the CAPCs have been investigated and discussed.

1 Introduction

A variety of bone cements have been developed being of great interest in medicine and dentistry due to their excellent biocompatibility, bone-repair properties and application functionality. Among the various formulations studied using combinations of solids and liquids reagents, high alumina cements (calcium aluminate cements, CACs) are hydraulically active cements. CACs are used as filling materials in restorative dental applications or as a mass fillers for bone voids for orthopaedic surgery applications [1–6]. During setting reaction that follows the calcium aluminate cement paste preparation, several reactions take place between solid and liquid constituents. Following a partial solvation of solid constituents, through a high water consumption the strength is enhanced [6] by the formation of the hydrate phases that fill up the initial porosity yielding a high strength in the solid mass.

The process of cement setting involves the entanglement of the precipitated crystals. For instance, if phosphate ions are present in the cement components, formation of apatite phase [3, 6] such as hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$ (HA), is desirable and expected to be formed: during setting and hydration, owing to the presence of Ca^{2+} and OH^- ions, the acidic hydrogen phosphate ions $HPO_4{}^{2-}$ and H_2PO^{4-} taken from the reactants are neutralized to $PO_4{}^{3-}$ and apatite formation occurs [6]. Although a phosphate buffer is generally used because of its neutral pH [3], acidic phosphate solutions such as H_3PO_4, $(NH_4)_2HPO_4$, $(NH_4)H_2PO_4$, $Al(H_2PO_4)_3$, or KH_2PO_4 can be used to yield chemically bonded phosphate ceramics containing apatites, and these are formed during an acid–base reaction between metals oxides and these solutions [7].

Werner et al. [8] developed calcium–aluminium–phosphate cements (CAPCs) from blends of particulate calcium aluminate species and hydroxyapatite in combination with aluminium phosphate ($Al(H_2PO_4)_3$). After in vitro tests, the Al^{3+} concentration in SBF gave no indication for potential adverse critical health effects and the very short setting time made these cements reliable for clinical applications [8].

Calcium aluminate cements have a negligible intrinsic opacity to X rays used in radiology (W radiation: $\sim$0.20 Å; E $\approx$ 95 keV). An improvement in radiopacity may ensure a safe application: during the injection, the correct in situ application and the penetration of the paste

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in bone tissue can be screened avoiding any possible leakage of the cement out in the surrounding tissues [6]. Barium sulphate, zirconium dioxide and high-density glasses are commonly use as X-ray absorbers, as well as bismuth oxide, tantalum oxide and lanthania [6, 9–11]; recently strontium carbonate, with its high solubility, (and consequently readsorbability) close to that of calcium carbonate has been also used [12, 13]. Moreover Sr^{2+} has beneficial effects on diseases and health of bone tissue [14].

In this study, cements CAPCs have been obtained by reacting Ca-aluminates compounds, i.e. $CaO \cdot Al_2O_3$ (CA) and $CaO \cdot 2\ Al_2O_3$ (CA_2), with $Al(H_2PO_4)_3$ solution. Hydroxyapatite was also introduced as a bioactive dispersed phase with the aim to improve biointegration of the cements in the biological environment. The overall behaviour of the yielded calcium-aluminate cement pastes, in term of properties and technological advantages have been taken into account during this feasibility study.

The first goal was the improvement and modification of the radiopacity of the calcium-aluminate cements. Another interesting aspect to consider was the setting behaviour. They both could be modified by changing the cements compositions, either by adding powders with high specific surface that do not form hardening phases (such as hydroxyapatite) or by introducing doping elements in the Ca–Al system.

Two different radiopacity inducing elements, lanthanum and strontium, and their behaviour in the Ca–Al system have been investigated by fixing the cation ratios in CA and CA_2 compounds. Thus, the technological advantage of setting up the production process for all the calcium-aluminate powders was exploited by varying the calcium-aluminate types and hydroxyapatite amount in the cement compositions.

The doping Sr^{2+} and La^{3+} ions were introduced during the synthesis step of the powders, instead of adding radiopaque compounds as cement fillers, as previously found in literature. The presence of these two cations in the aluminate powders could significantly enhance the radiopacity without addition of non-resorbable/inert and/or non homogenously dispersed particles. Actually, Sr^{2+} may replace Ca^{2+} in the calcium-aluminate structures because of the similar atomic radius, while La^{3+} could enter in solid solution with Ca-aluminates. In relation with their own basic characters, Sr^{2+} and La^{3+} could also modify the reactivity of the yielded calcium aluminate compounds in the acid solutions. Doped Ca-aluminates powders have been synthesized at 1,400°C from a mixture of $CaCO_3$, Al_2O_3, La_2O_3 and $SrCO_3$ and compared with undoped powders. The microstructure, setting time, radiopacity and compressive strength of the yielded cements have been investigated.

2 Experimental

2.1 Calcium aluminate powders synthesis

Ca-aluminate compounds CA ($CaO\ Al_2O_3$) and CA_2 ($CaO\ 2Al_2O_3$), were used as a reference and synthesized utilizing stoichiometric mixtures of $CaCO_3$ (RPE, Merck) and Al_2O_3 (99.99%, Almatis CT3000).

Lanthanum and strontium doped Ca-aluminate compounds were prepared by adding La_2O_3 (Merck) and $SrCO_3$ (Merck) to the basic mixtures. All powders were labelled according their $CaO{:}Al_2O_3$ M ratio while L and S indexes have been added to the label according to the eventual addition of La and Sr, as reported in Table 1.

After ball milling in water for 1 week with alumina media, all the different compositions of the powder mixtures were dried, sieved at 400 μm, pressed in 60 mm diameter discs and fired two times in a laboratory kiln at 1,400°C for 8 h.

After the first thermal treatment, the obtained solid discs were crushed in shreds and then finely ground in a planetary mill with ZrO_2 media in ethanol for 3 h, sieved at 40 μm. Following the second thermal treatment, the same loop (grinding, sieving) was repeated to obtain the powder to be utilized.

The obtained powders were characterized by X-ray-diffractometry and SEM–EDS analysis. Granulometric distribution analyses of the synthesized powders were performed by SediGraph 5100, Micromeritics Instrument Corporation, Norcross, USA.

2.2 Calcium–aluminium–phosphate-cements preparation

The cements compositions are reported in Table 2. Two typologies of cements were produced varying the amount of the liquid setting medium and of hydroxyapatite added as filler: the yielded cement pastes were labelled CM1 and CM2; for the instance 0 indicates undoped compositions, while S or L have been added to the label according to the presence of strontium or lanthanum in the above compositions.

To obtain homogeneous mixtures as the solid components of the cement pastes, the synthesized Ca-aluminates powders and commercial hydroxyapatite (Sigma-Aldrich) were dry-blended by eccentric mixing for few minutes. The hydroxyapatite (HA) powder has a high specific surface (76.50 m^2/g), small size (crystallites (c × a), 6.91 × 9.44 Å), and an intermediate degree of crystallinity (40–50%).

The powders blends were then manually mixed by a spatula with an aqueous mono-aluminium phosphate solution, $Al(H_2PO_4)_3$ (7.8 wt% Al_2O_3 and 32.8 wt% P_2O_5) (Table 2).

Table 1 Starting powders compositions by atomic ratio of the cations and wt% of oxides and carbonates

Powders label	Atomic ratio				Composition			
	Ca^{2+}	Al^{3+}	Sr^{2+}	La^{3+}	Al_2O_3 (wt%)	$CaCO_3$ (wt%)	La_2O_3 (wt%)	$SrCO_3$ (wt%)
CA	1.00	2.00	–	–	50.5	49.5	–	–
CA_2	1.00	4.00	–	–	67.1	32.9	–	–
CAS	0.67	2.00	0.23	–	50.0	33.3	–	16.7
CA_2S	0.67	4.00	0.23	–	66.7	22.2	–	11.1
CASL	1.00	2.00	0.08	0.035	45.0	45.0	5.0	5.0
CA_2SL	1.00	4.00	0.08	0.07	60	30	6.7	3.3

Table 2 Cements compositions

Cement	CA	CA_2	CALS	CA_2LS	CAS	CA_2S	HA	$Al(H_2PO_4)_3$
CM1								
0	20	20	–	–	–	–	20	40
LS	–	–	20	20	–	–	20	40
S	–	–	–	–	20	20	20	40
CM2								
0	23.5	23.5	–	–	–	–	11.8	41.2
LS	–	–	23.5	23.5	–	–	11.8	41.2
S	–	–	–	–	23.5	23.5	11.8	41.2

The amounts are in wt%

2.3 Cements characterization

Initial and final setting times of the cements were determined at room temperature, (~60% humidity) by a Gilmore's needles testing device following ASTM C266-08, with a Gilmore needle apparatus (Testing Bluhm & Feuerherdt GmbH, Berlin, Germany).

Compressive strength tests were carried out on cylindrical specimens (diameter: 10 mm, height: 20 mm) using a Zwick Z050 testing machine (Zwick GmbH, Ulm, Germany). The crosshead speed was set at 1 mm/min. Nylon cylinders (h: 20 mm; Ø: 10 mm) put over a silicon rubber slab have been used as open-base moulds to produce samples of the cements suitable for compression strength tests. The cylindrical samples were obtained by filling the moulds with fluid cement pastes. The cylindrical samples were also machined to guarantee (±0.1 mm) the opposite base faces flat and parallel. Compressive strength was measured after 24 h from the samples preparations and permanence at 37°C in physiologic solution.

A qualitative radiographic study was carried out with a standard clinical radiogenic apparatus, currently used in the odontoiatric diagnostic practice (Image X System, De Gotzen Inc., USA, anode; 70 keV and 8 mA). The samples for radiopacity evaluation tests were shaped in small plates 2.0 mm (± 0.1 mm) thick. The radiopacity was checked comparing the doped cements to the undoped ones, using image analysis [12, 15]. Image Pro Plus 6.0 (Media Cybernetics, Inc. Bethesda, MD) was used to measure the greyscale of the specimens averaged over an area of 20 × 20 pixels: the average image contrast and standard deviation were calculated.

3 Results and discussion

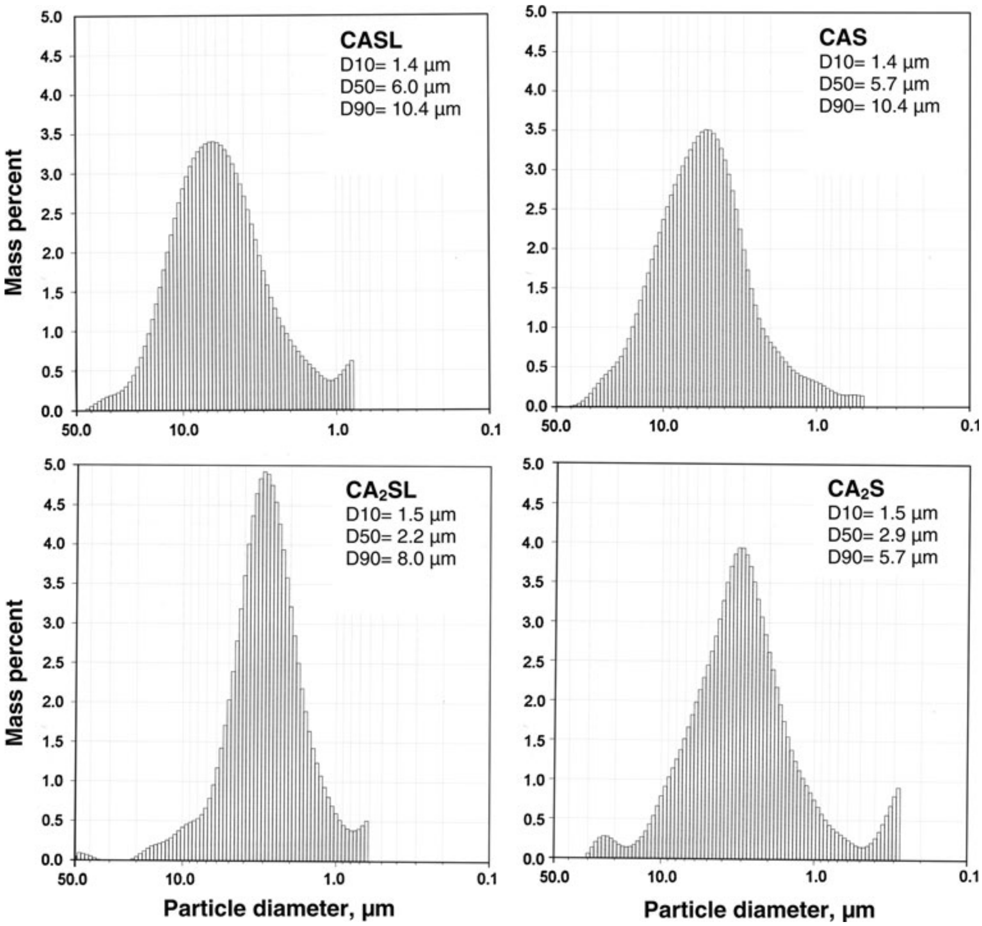
3.1 Calcium aluminate powders

Solid-state synthesis of Ca-aluminates phases requires high temperatures; by the way, incomplete reactions often occur. Calcium aluminates are formed when the appropriate proportions of calcium carbonate and aluminium oxide are heated together to allow them to react hypothetically until the mixture melts. After thermal treatments monocalcium aluminate (CA-type) billets (doped and undoped) retained shrinkages of 18–20% resulting as bulks dense and tougher to be milled in respect with CA_2-type billets. This feature is consistent with the refractory nature of the different stoichiometries [16]. Consequently, operating through the same loop conditions, the same grinding cycle for all kinds of billets, finer powder particles were obtained from CA_2-type powders, as confirmed by granulometric distribution analyses (Fig. 1).

The addition of strontium carbonate and lanthanum oxide stresses differences in the end products. The analysis on CALS billet shows the presence of two main mineralogical phases in a porphyry-like structure: a fine predominant matrix phase owing the system Ca–Al–Sr–O, and a coarser dispersed phase in the system Ca–Al–La–O as detected by EDS on mirror polished surfaces (Fig. 2). Strontium was expected to replace Ca as their atomic radii are similar and vicariant (2.15 Å for Sr and 1.97 Å for Ca), while La and Al, respectively 1.87 and 1.43 Å have too much difference in their atomic radii to be isomorphogen or allow any solid state solubility.

In CALS composition as in CA_2LS, M^{3+} cations are slightly in defect with respect to the theoretical compositions of calcium aluminates (Table 1).

Fig. 1 Granulometric analyses (mass frequency vs. particle diameter) of CA-type, CASL and CAS, and CA_2-type, CA_2SL and CA_2S, powders after milling



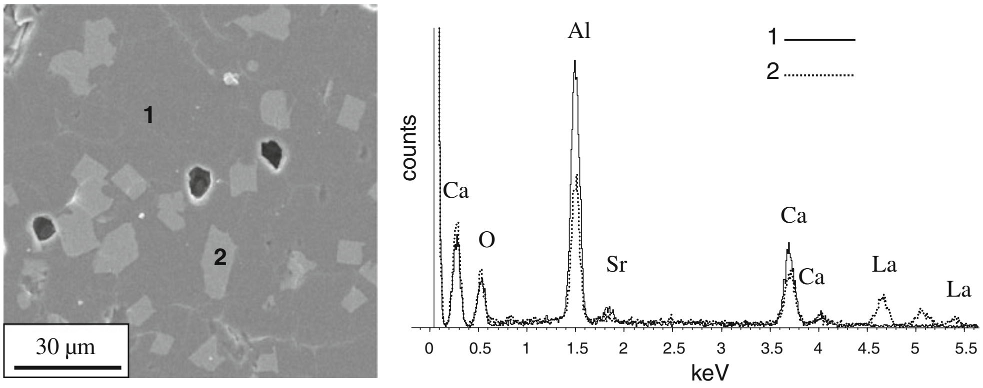


Fig. 2 SEM micrographs and EDS analysis of the mirror polished surfaces of the mono calcium aluminate billet doped with La and Sr, CALS, after thermal treatments

XRD analyses were carried out to characterize the different mono-calcium aluminate type powders (Fig. 3):

- In CA powders, according to the planned stoichiometry, the main phase was $CaAl_2O_4$ (PDF 23-1036), while Mayenite, $Ca_{12}Al_{14}O_{33}$ (PDF 09-0413), was rarely detected.
- In CALS powders the main phase was $CaAl_2O_4$. From the analysis of the diffraction pattern of this phase, it was assessed that Ca was partially replaced by Sr in the $CaAl_2O_4$ crystalline structure, as indicated by a constant small shift of the reflections of the pattern towards lower 2-theta angles (higher *d* values). Mayenite and $CaLaAl_3O_7$ (PDF 38-1251) were detected as minor phases confirming SEM–EDS analyses (Fig. 2).
- In CAS the only detected phase is $CaAl_2O_4$ where Ca was partially replaced by Sr; moreover, an oriented growth on [00l] planes seemed to be occurred.

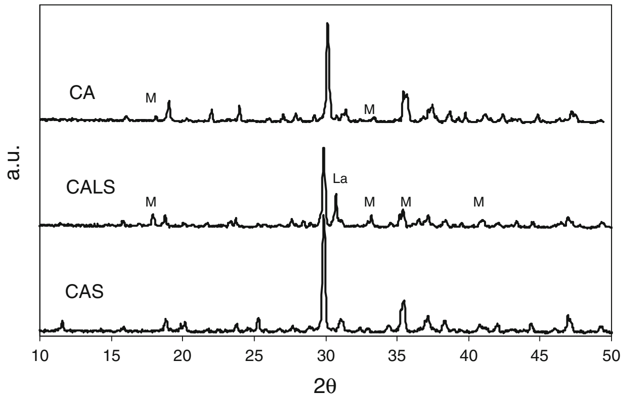


Fig. 3 XRD phase analyses on CA-type powders. The bare peaks are attributed to $CaAl_2O_4$. The labelled ones are *M* mayenite, $Ca_{12}Al_{14}O_{33}$ and *La* $CaLaAl_3O_7$

In CA_2-type powders the following features were observed (Fig. 4):

- In CA_2 powder as expected by stoichiometry, the only detected phase is Grossite $CaAl_4O_7$ (23-1037).
- In CA_2LS powders the main phases are Hibonite $CaAl_{12}O_{19}$ (PDF 38-0470) and Grossite; the minor phases are $CaLaAl_3O_7$, yet observed in CALS, and $LaAl_{11}O_{18}$ (PDF 33-0699).
- In CA_2S powders the main phase is Grossite and subordinately Hibonite.

In CA_2 series, the presence of strontium and lanthanum induces the formation of compounds with the P63/mmc (194) space group, i.e. Hibonite and $LaAl_{11}O_{18}$. Although a significant shift was not registered in the *d* parameters in XRD pattern, it could be reasonably supposed that strontium ion is present in the cell of Hibonite in substitution of calcium.

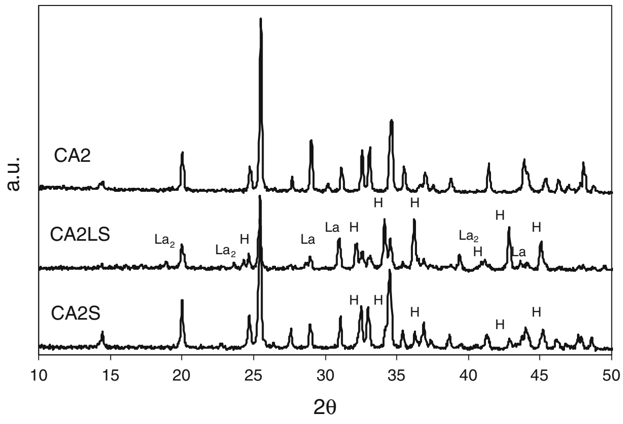


Fig. 4 XRD phase analyses on CA_2-type powders. The bare peaks belong to grossite $CaAl_4O_7$; The labelled ones are *H* hibonite, $CaAl_{12}O_{12}$; *La* $CaLaAl_3O_7$ and *La₂* $LaAl_{11}O_{18}$

3.2 Calcium–aluminium–phosphate-cements

The compositions of the yielded cements are reported in Table 2, while the setting behaviour is shown in Fig. 5. No evaluable shrinkage after setting was observed in the solid samples of the different cement compositions.

Generally, setting time is strictly correlated to powder particle size (the smaller size, the shorter setting time [13]) and mineralogical composition. Phase composition and solubility are the most important parameters stressing on the kinetics of the setting reaction, determining the overall hardening of the paste. While it was observed that the addition of strontium carbonate as radiopacifier prolonged the setting time of the calcium phosphate cements [12], it should be highlighted that Sr and/or La containing calcium-aluminate phases are much more soluble and prone to react with the acidic liquid component, because of their strong basic character (especially La containing phases). These positive features result from the studied procedure to introduce the radiopacifier elements during the powder synthesis stage. This also confirms the reasons why the compositions including CALS and CA_2LS powders exhibited the shorter setting times.

CM1-type cements were slower in setting than CM2-type, because of the higher amount of HA particles as inclusion, with a high specific surface. HA particles subtract setting solution and thus delay the wetting of Ca-aluminates phases. When HA particles came in contact with the aqueous mono-aluminium phosphate solution partially reacted forming $Ca(H_2PO_4)_2{\cdot}H_2O$, but they did not take part to the hardening process. Actually, the cement hardening is caused by an acid–base reaction [6, 7], where water or aluminium phosphate solution act as acid and the cement powder as a base. Stronger is the acid character of the setting solution or the basic character of cement powder, faster is the hardening of the cement pastes. It was observed that CM1LS and CM2LS had similar setting times. The higher leaching ability/reactivity in acidic solution of the La-containing

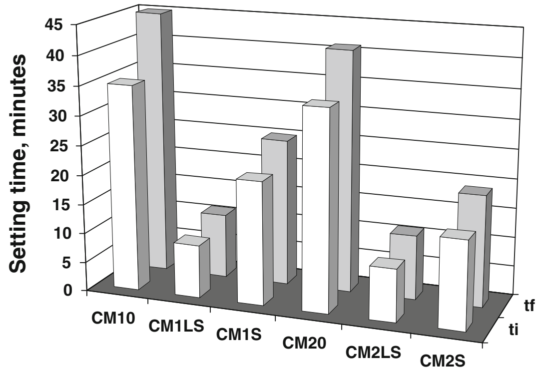


Fig. 5 Evaluation and comparison of the setting times t_i and t_f, measured through Gilmore's needles, on the different cement pastes

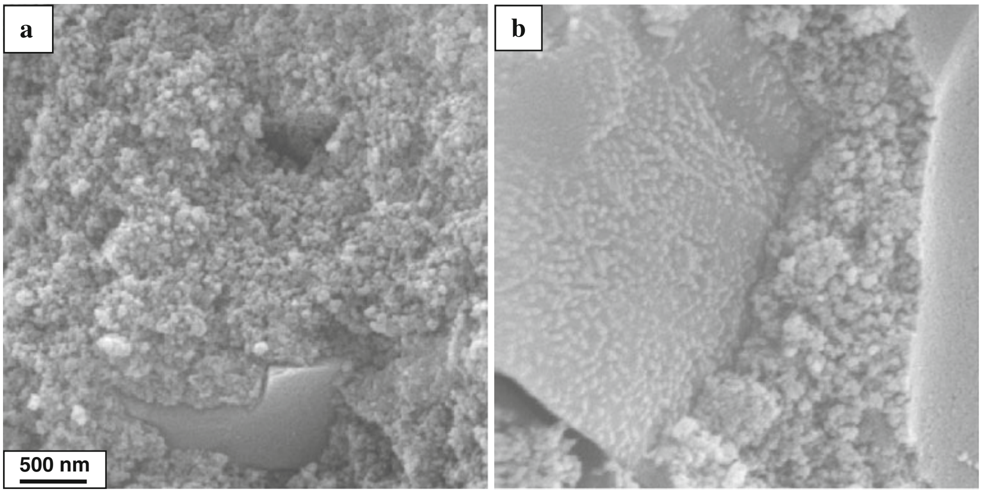


Fig. 6 SEM micrographs of the sub-micron precipitates formed in the base type cements CM10 (**a**) and the same calcium aluminate powder composition set with a $(NH_4)_2HPO_4/NH_4H_2PO_4$ buffer aqueous solution (**b**)

phases in comparison with those enriched in strontium overcame the setting delay due to the presence of HA. Chemically bonded ceramics harden through a combined dissolution and precipitation process [3], in particular chemically bonded phosphate ceramics are formed in a three-step process [7]: (i) oxides dissolve in an acid phosphate solution and metal ions are released into the solution (the rate controlling step); (ii) the aquaions formed from these cations react with phosphate anions and form a gel; (iii) the saturated gel crystallizes into a ceramic.

After setting, the cements were composed by an amorphous Ca–Al–P–O-matrix of sub-micron precipitates with embedded non reacted particles of CA- and CA_2-type powders, and partially reacted HA filler, as shown in Fig. 6a, concerning the base type cement CM10. The precipitates size is correlated to the rate of the dissolution process, i.e. to the acidity of the reacting solution. Actually, when the starting powder composition of CM10 was consolidated with a $(NH_4)_2HPO_4/NH_4H_2PO_4$ buffer aqueous solution (3.7 M of PO_4^{3-} anions), the resulting set cement had coarser precipitates than CM10 cement as the nucleation was retarded (Fig. 6b). Moreover, the cement pastes yielded with the buffer solution liquid were slow setting, as the leaching power of the buffer solution with neutral pH is lower than in the case of the acidic mono-aluminium phosphate solution.

XRD analyses on CM1S, CM1LS, CM2S and CM2LS cements are reported in Fig. 7. The peaks were attributed to CA and CA_2-type compounds (see Figs. 3, 4) and hydroxyapatite, HA. No other crystalline phases could be identified with sufficient reliability.

XRD spectra of CM1-type cements indicated the presence of an amorphous phase, while CM2-type cements had a more crystalline profile. In CM2-type cements the unreacted calcium-aluminate particles were more numerous than in CM1-type in relation with their higher amount in the starting composition. An empiric estimation of the non-crystalline fraction was done by using the amorphous hump profile between 25 and 35 2θ degrees. The total amount of amorphous phase was evaluated about 30–40 and 50–60%, respectively in CM1S and CM1LS. In both cements the amorphous phase related to HA was between 10 and 15%.

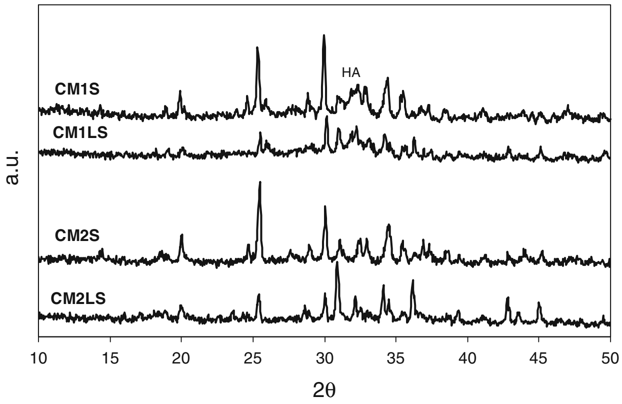


Fig. 7 XRD analyses on CM1 and CM2-type cements. The peaks are attributed to CA and CA_2-type compounds (see Figs. 3 and 4) and hydroxyapatite, HA

Calcium aluminate cements, may reach compressive strength between 100 and 200 MPa [1, 6, 17], while the calcium phosphate ones reach strength values lower than 100 MPa [6, 12] only after longer maturation period (more than 7 days). As reported by Hermansson et al. [6] mechanical strength is directly related to the consumption of water during hardening and maturation. Concerning Ca-aluminates, a consistent amount of water is involved in

Table 3 Compressive strength, σ, measured after 24 h curing at 37°C in physiological solution on the different cement compositions

Cement	σ, MPa
CM10	30 ± 3
CM1LS	55 ± 9
CM1S	71 ± 11
CM20	32 ± 4
CM2LS	73 ± 8
CM2S	58 ± 8

the hydration and formation of hydrate precipitates, as the pastes are hydraulically active, whereas for the Ca-phosphates less water is bound as hydrate phases: water is related to the rest porosity, which is the strength-controlling factor. Due to the low hydraulic activity, the CAPCs strength should be closer to calcium phosphate cements, than to CACs.

Although the quite short maturation period soaking in physiological solution (1 day), promising values in compressive strength were achieved (Table 3), as well as an increase of strength depending to the maturation time was observed in CAPC, by Werner et al. [8]. Moreover, the compressive strength of the cements obtained from Sr and/or La doped powders were doubled in respect with undoped cements CM10 and CM20. It was observed that the addition of strontium carbonate increased the compressive strength of CPCs [12] as the mechanical properties of the hydroxyapatite formed during setting increased when a small amount of Ca was substituted by Sr [12, 18]. However, it must be mentioned that the mechanical strength depends heavily on the specimens, that are not defect-free. Higher properties can be obtained by producing samples with the lowest porosity: for example, acting through a decrease of the amount of the mixing liquid, or the addition of an inert insoluble phase in the cement paste. For instance, the added HA particles do not form hardening phases, as previously reported.

Figure 8 shows the radiographic images taken through an radiological equipment on the CM1-type and CM2-type cements in the standard conditions of clinical diagnosis, while the contrast evaluations of the cements radiographies are plotted in Fig. 9. As expected, the base type cements CM10 and CM30 samples showed an almost complete radio-transparency. Doping with Sr and/or La increased sensibly the radiopacity. Moreover, the addition of radiotransparent HA influenced the overall radiopacity of the containing cements; consequently, CM2-type cements were identified as more radiopaque than CM1-type cements.

4 Conclusion

CAPCs were formulated and produced to obtain two-component cement pastes for permanent fillings in orthopaedics and dentistry, useful to be easily recognized by X radiographic analyses in situ during and after their application with surgery intervention.

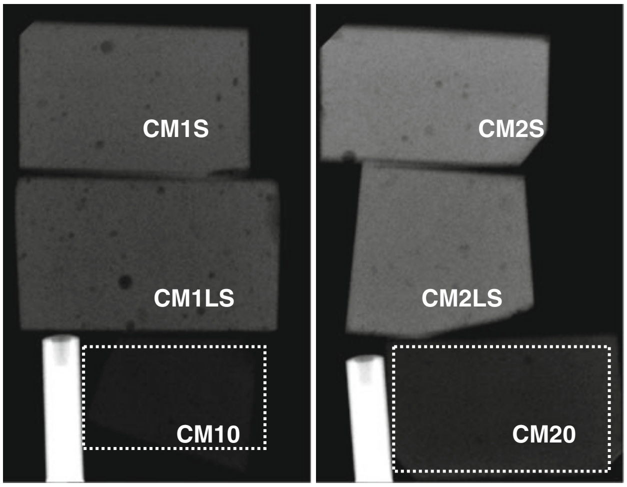


Fig. 8 RX images taken through odontoiatric radiologic equipment on the different cement compositions (standard conditions of radiographic diagnosis). As a reference marker an aluminium metallic rod was put alongside the base type cement samples, CM10 and CM20, because their almost complete radiotransparency

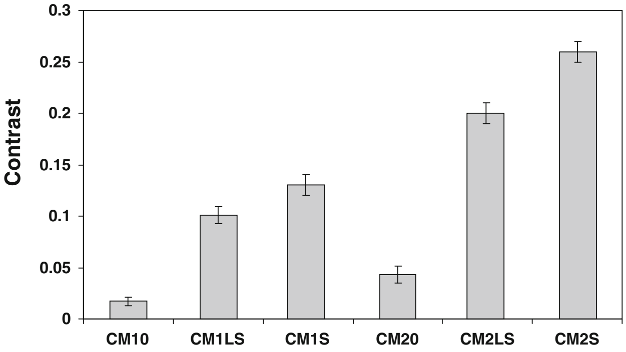


Fig. 9 Measured contrast of the cements radiographs

Ca-aluminates powders have been synthesized by solid state reaction at 1,400°C from a mixture of $CaCO_3$, Al_2O_3, La_2O_3 and $SrCO_3$. Radiopaque elements like Sr and La were introduced during the powders synthesis step, avoiding the addition of non-resorbable/inert and/or non homogenously dispersed particles as cement fillers. Highly radiopaque phases were just created as solid solutions in Ca–Al system. The radiographic tests demonstrated the achievement of a considerable RX opacity in respect of undoped cements.

Sr and/or La containing calcium-aluminate phases were much more soluble in the acidic liquid component, with consequent shortening of the setting times of the cement pastes.

Due to the low hydraulic activity, the CAPCs strength was closer to the strength of calcium phosphate cements, than to CACs ones. The strength of the Sr and/or La doped cements were higher in comparison with the undoped cements.

The overall characteristics of this kind of cements are quite promising according to the proposed use, concerning their recognized biocompatibility, bioinertness, leaching of potential toxic ions (mainly Al^{3+}), setting kinetics characteristics (times of setting, acidic/base character and interferences with chemical and biological environment) and mechanical strength.

Quantitative radiographic evaluations (comparison with radiographic standards, e.g. cortical bone), in vitro detailed analyses (swelling, secondary hydration, stability and leaching from phases containing Sr and La), as well as radiographic in vivo tests after injection/application will be surely necessary and effective to check the applicability of these radiopaque cements, likely to the similar ones already in trade.

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