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Review

Calcium phosphate cements for bone substitution: Chemistry, handling and mechanical properties

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ABSTRACT

Since their initial formulation in the 1980s, calcium phosphate cements (CPCs) have been increasingly used as bone substitutes. This article provides an overview on the chemistry, kinetics of setting and handling properties (setting time, cohesion and injectability) of CPCs for bone substitution, with a focus on their mechanical properties. Many processing parameters, such as particle size, composition of cement reactants and additives, can be adjusted to control the setting process of CPCs, concomitantly influencing their handling and mechanical performance. Moreover, this review shows that, although the mechanical strength of CPCs is generally low, it is not a critical issue for their application for bone repair – an observation not often realized by researchers and clinicians. CPCs with compressive strengths comparable to those of cortical bones can be produced through densification and/or homogenization of the cement matrix. The real limitation for CPCs appears to be their low fracture toughness and poor mechanical reliability (Weibull modulus), which have so far been only rarely studied.

1. Introduction

Owing to diseases and traumatic events, a few million patients worldwide need to undertake bone grafting operations each year [1]. Bone grafting, first established two centuries ago, is the procedure of replacing missing or damaged bones with materials from either the patients themselves (autograft) or donors (allograft) [2,3].

Currently, autograft is still considered the gold standard, since the bone harvested from the patients themselves contains living cells and growth factors. Nevertheless, autograft has a number of limitations, such as an additional operation on a second surgical site with associated donor site pain and morbidity, as well as the obvious short supply of bone sources. Alternatively, modern allograft using donor bone from a regular bone bank might partly overcome the limitation of bone supply; however, after sterilization treatments, the bone will lose the biological factors and have impaired strength [4]. Furthermore, there are still concerns regarding immunological reaction between the patient and the donor bone, as well as disease transmission [5]; thus healing can in some cases be unpredictable [6].

Because of the above drawbacks, there is an increasing demand for synthetic bone substitutes, which are free from the limitations of bone supply, inconsistency and disease [7]. Moreover, there is the potential to use these substitutes in conjunction with the own cells of the patient or recombinant growth factors to speed up or improve the quality of bone regeneration; this process is known as "tissue engineering" [8]. A wide range of synthetic materials, including metals [7], ceramics [9,10], polymers [11,12] and cements [13–18]m have been proposed and developed as bone substitutes [7]. Among them, calcium phosphate cements (CPCs) have been attracting great attention due to their excellent biological behavior (e.g. biocompatibility, bioactivity and osteoconductivity) [19–23].

CPCs were first created in the 1980s, by Brown and Chow [24,25]. Since then, many CPCs with varying compositions have been investigated and are available commercially [26,27]. CPCs are produced by a chemical reaction between two phases – a solid and a liquid – which, when mixed, form a paste which progressively sets and hardens into a solid mass; this is similar to the cements used in civil engineering. The solid phase comprises one or several calcium phosphate (CaP) compounds. Water or a calcium- or phosphate-containing solution is used as the liquid and may contain chitosan [28,29], alginate [30,31], hyaluronate [32,33], gelatin [34,35], chondroitin sulfate [36,37], succinate [37] or citric acid [38,39] to allow the dissolution of the initial CaP compounds until the oversaturation of the solution, thus inducing the reprecipitation of crystals. The hardening of the cement takes place through entanglement of the reprecipitated needle-like or plate-like

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crystals (Fig. 1). Currently, despite numerous CPC formulations, there are only two possible final products for the CPC reaction: brushite (dicalcium phosphate dihydrate, DCPD) or apatite, such as hydroxyapatite or calcium-deficient hydroxyapatite (CDHA) [40]. Moreover, these two final products are mostly obtained though two types of chemical reaction: hydrolysis and acid–base [23,40,41]. The major difference between the two final CPC products is their solubility: brushite is 1-2 orders of magnitude more soluble than apatite at physiological pH [42]. However, as brushite is a metastable phase, in vivo transformation of brushite to apatite may happen [40]. Moreover, apatite is similar to the calcium phosphates found in mammalian bones. In this review, without specific notification, CPCs are mainly referred to as apatite.

In addition to their excellent biological behavior, the main advantages of CPCs are that they can be injected and have the ability to harden in vivo at body temperature [22,43]. After mixing of the solid and liquid phases, CPCs form a viscous paste, which can be easily manipulated and shaped, and, in some cases, can be injected into a defect area, not only avoiding invasive surgical procedures but also providing intimate adaptation to the surrounding bone even for irregularly shaped cavities, representing a unique advantage over bioceramics, which are difficult to machine and shape [44]. The characteristics of being injectable and of hardening in vivo can also be found in acrylic bone cements (e.g. poly(methyl methacrylate), PMMA), which find wide applications in arthroplasty fixation and vertebroplasty [45]. However, the hardening process (also called polymerization) of PMMA is highly exothermic, causing necrosis of the surrounding tissue [46]. In contrast, the hardening of CPCs is only slightly exothermic, if at all, which is important for biomedical applications as well as for incorporation of different biological molecules and drugs [22,43,47–49].

Another important feature of CPCs is that they are intrinsically microporous [50]. The micropores are left by extra aqueous solution after hardening of CPCs and/or due to intergranular spaces, with pore size in the range of submicro/micrometers [50]. Such micropores are useful for the impregnation of biological fluids into CPCs, and help resorption and replacement of CPCs by bone. However, it would also be desirable to create macropores of at least tens of micrometers in CPCs to favor bone colonization in the implant, accelerating the overall process of replacement of CPCs by bone, like in CaP bioceramics [51,52]. The pores (micro or macro) are not only critical for the above biological behaviors in CPCs, but also increase the CPCs' surface area available for reaction, enhancing their ability to load growth factors or drugs, thus making them good candidates for bone tissue engineering.

Although CPCs appear highly promising for bone regeneration, it is widely accepted that there are still some crucial issues that need to be solved to satisfy clinical requirements [26,27]. Specifically, CPCs without any additives normally have poor injectability due to the liquid – solid phase separation [53,54]. Moreover, the CPC pastes tend to disintegrate upon early contact with blood or biological fluids due to their weak cohesion [55]. Another main challenge facing CPCs is that in general they have poor mechanical properties, not only in terms of strength, which has been widely studied, but especially in terms of toughness, brittleness and reliability, which have been rarely reported, limiting their application to non- or moderate load-bearing places [56,57].

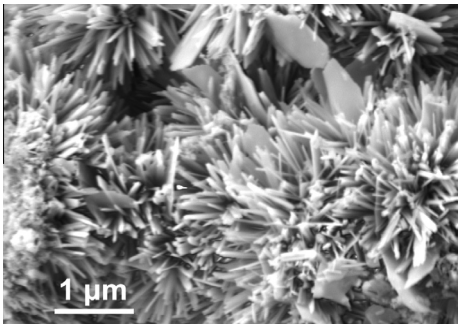

Fig. 1. SEM micrograph of a CPC fracture surface showing needle-like and plate-like crystals.

In the last few decades, considerable effort and many studies have been devoted to exploring and understanding the mechanisms under the aforementioned problems in CPCs and to try to solve them, with varying degrees of success. The purpose of this article is to provide an overview of the chemistry, kinetics of setting and handling properties of CPCs for bone substitution, with a focus on their mechanical properties, and to identify the most significant achievements.

2. Chemistry and kinetics of CPC setting

The cement setting reaction is perhaps the most important feature of CPCs because it not only directly controls cement hardening time and other setting properties, but also determines the nature of the cement products, and therefore most of the physical and biological properties of the hardened cement [58].

At present, there are numerous combinations of calcium- and phosphate-containing compounds in CPCs. However, the chemistry of the setting reaction in these cement systems is similar, and can be explained and understood by analyzing the solubility behavior of the compounds involved [13,58,59]. The chemical process during the setting reaction mainly involves two mechanisms: dissolution and reprecipitation [60]. During dissolution, the starting powders release calcium and phosphate ions, generating a supersaturation in the solution. Once the ionic concentration reaches a critical value, the nucleation of the new phase occurs, generally surrounding the powder particles. Afterwards, the new phase keeps growing as the dissolution of the reagents continues [43]. In the above dissolution/reprecipitation process, the final composition of precipitates depends on the relative stability of the various calcium phosphate salts in the system, and can be predicted by using the solubility phase diagram, which describes the evolution of solubility of a compound – in the form of the logarithm of the total calcium (or phosphate) concentration – as a function of the pH [13,58,59]. Specifically, a less stable (more soluble) calcium phosphate phase would dissolve to form a more stable (less soluble) one [13,58]. Since apatite is the most stable calcium phosphate at pH > 4.2 (37 °C) and brushite is the most stable one at pH < 4.2 (37 °C), this can explain why, despite numerous CPC formulations, there are only two main final products for the CPC reaction [13].

Solubility phase diagrams can be used to predict the thermodynamic behavior of CPCs, but they cannot always explain the observed setting and hardening behavior, and kinetics must also be considered. Understanding the mechanisms controlling the setting process of CPCs will help to gain a comprehensive knowledge about their setting kinetics and then to better control their microstructure, which determines their applications for different purposes. Currently, many CPC substitutes are based on the hydrolysis of an α-tricalcium phosphate (α-TCP) powder, which is used in most commercial cement formulations, so the following section will focus mainly on the setting kinetics of α-TCP-based CPCs. Many studies have focused on the effects of particle size [61–64], crystallinity [65–67], temperature [68–70] and various constituents [71–73]. Many methods, such as X-ray diffraction (XRD) [62,65,74–76], isothermal calorimetry [61,63,64,66,69,77,78], strength measurement [62,74,75], ^{31}P solid-state nuclear magnetic resonance imaging (NMR) [79,80], impedance spectroscopy [80–82] and attenuated total

reflectance–Fourier transform infrared spectroscopy [83,84] have been used to study the evolution of setting reaction with time.

Fernandez et al. [74] estimated the extent of conversion of α-TCP to CDHA by using the height of several selected peaks obtained by XRD, assuming a quasi-constant ratio between peak height and peak area. Ginebra et al. [75] calculated the relative amounts of different phases existing in the specimen by using an external standard method. Both groups of authors found that the extent of conversion of α-TCP to CDHA could be exponentially fitted as a function of hardening time.

Moreover, these two groups of authors also surveyed the evolution of compressive strength of CPCs with hardening time and described it with exponential equations. Furthermore, they found a linear correlation between the compressive strength and the extent of conversion [74,75]. Ginebra et al. [76] further established a relationship between depth of reaction evolution and reaction time, and proposed an α-TCP hydrolysis kinetics with two rate-limiting mechanisms. The first mechanism, "surface area of reactants", controls the reaction in the initial stage; in contrast, after 16 h, the other mechanism, "diffusion through the hydrated layer", leads the rest of the reaction.

Ginebra et al. [62] investigated the effect of different particle sizes of α-TCP on the kinetics of the setting reaction by combining data from XRD and strength measurements. The results showed that fine particles have a much faster rate of hydrolysis than coarse ones. This could easily be explained by considering the fact that a higher specific area accelerates the process of dissolution.

Despite its simplicity to use, XRD has limited ability for quantitative phase analysis, especially for poorly crystallized or amorphous phases, so a more accurate method is required to interpret the rate of hydrolysis and reaction mechanisms. Solid-state NMR, especially ^{31}P NMR, appears to be an innovative approach to overcome the difficulties met in using XRD, since this technology allows the quantification of both amorphous and well crystallized compounds [79,80].

AC impedance spectroscopy has been used to monitor the cement setting reaction. Unlike the aforementioned mechanical (measuring strength) and compositional (XRD or NMR) approaches, which usually inspect cement setting intermittently, AC impedance spectroscopy is an effective method to study the hydration process with no interval by reflecting the microstructure development through continuous detection of the AC impedance parameters [85]. Liu and Shen [81] used AC impedance spectroscopy to investigate the effect of apatite seeding on the hydration of CPC, finding that, with increasing seed content, the mean diameter and porosity of CPC decrease at the beginning of hydration, but increase at the end of hydration. Using this technology at high frequencies allows for focusing on the interfacial changes; Despas et al. [80] revealed that the setting of CPC was retarded by the addition of alendronate, and was sensitive to the way in which the latter was introduced to the cement formulation.

Isothermal calorimetry is a commonly used technique for the study of reaction kinetics. Durucan and Brown [61] surveyed the setting kinetics of CPC based on α-TCP with three particle sizes by means of isothermal calorimetry. Their result is consistent with the conclusion deduced from XRD that the setting reaction shows a strong dependence on particle size. Moreover, by comparison to the model suggested by Ginebra et al. [76], the authors proposed a slightly different kinetic model whereby the α-TCP hydrolysis reaction was considered to be initially controlled by a surface mechanism, and subsequently by a nucleation and growth mechanism. Brunner et al. [63] analyzed the reactivity of three amorphous α-TCP nanoparticles synthesized by spray flame, as well as that of microsized α-TCP. The authors observed a pronounced increase in reactivity for these nanoparticles, while the total energy release during hardening was constant.

Gbureck et al. [65] reported that prolonged high-energy milling of α-TCP provokes a pronounced increase in thermodynamic and kinetic solubility which could be attributed to the formation of amorphous α-TCP. Camire et al. [66] related milling time and reactivity by means of isothermal calorimetry. It is noted that the total energy release during the hardening reaction is two- to threefold higher for α-TCP milled with prolonged time than without any milling. The authors verified that the improved reactivity is due not only to a decrease in particle size and a concomitant increase in specific surface area, but mainly to amorphous α-TCP resulting from a longer milling time.

Bohner et al. [78] calcined microsized α-TCP at different temperatures for various durations and assessed its reactivity as measured by isothermal calorimetry. No pronounced changes in composition, particle size or crystal size are observed; nevertheless, the calorimetric data show that the induction time (time to start the reaction) increases from several minutes for α-TCP without calcination to 2-3 h for α-TCP with calcination, which is speculated to be due to the disappearance of surface defects during the calcination process.

It is well known that temperature has a significant effect on the kinetics of chemical reactions. In general, a high temperature accelerates the reaction rate while a low temperature plays the opposite role, which is the same for the hydrolysis of α-TCP. Ginebra et al. [68] found that, with the temperature increasing from 22 to 37 °C, the time to reach a certain extent of conversion is sharply reduced and the compressive strength is pronouncedly improved. TenHuisen and Brown [69] used isothermal calorimetry to study the effect of different temperatures on the hydrolysis of α-TCP. Their result shows that temperature has a significant effect on reactivity, as demonstrated by the increasing heat release rate, and on the growth rate, as indicated by a decrease in surface area of the CDHA with increasing temperature from 30 °C up to 75 °C.

The kinetics of CPC setting also depends on the composition of both the solid and liquid phases. Durucan and Brown [73] assessed the reactivity of α-TCP associated with several calcium salt additives, including DCPA (dicalcium phosphate anhydrous), DCPD, $CaCO_3$ and $CaSO_4{\cdot}½H_2O$ by means of isothermal calorimetry. The authors reported that all the additives delay the formation of HA in an ascending order: DCPA < DCPD < $CaSO_4{\cdot}½H_2O$ < $CaCO_3$. Different liquid phases also influence the reaction rate of CPCs. TenHuisen and Brown [71] surveyed the effects of acetic and citric acids on the formation of HA. They noted that the kinetics of hardening strongly depends on both the concentration and the type of acid. Acetic acid accelerates the reaction due to the increased solubilities of the reactant phases at lower pH. Conversely, retardation by citric acid is related to the complexing and adsorbing ability of citrate ions which are adsorbed onto α-TCP crystals and apatite nuclei, thus retarding both the formation of crystal nuclei and their further growth and entanglement.

To sum up, there are many factors, such as particle size, crystallinity, temperature, composition and even physical modification of the reactant surface [78], influencing the kinetics of α-TCP setting. Due to chemical similarity, it is expected that these factors should also play an important role in the kinetics of the setting reactions of other cement systems [40]. Furthermore, besides the methods mentioned above, other methods (e.g. measurement of rheological properties, pH and calcium (phosphate) ion concentration) might be desirable to characterize the kinetics of CPC setting [40].

3. Handling properties of CPC

Besides having excellent biological behavior, being injectable and self-setting in vivo at body temperature are the two main advantages of CPCs as bone substitutes. However, without any

improvement, CPCs normally have a relatively long setting time, poor injectability and poor cohesion [26,86,87]. A CPC paste with a long setting time can cause problems. For instance, a severe inflammatory response occurred when a CPC was unable to set and disintegrated [88]. A CPC with weak cohesion can also cause serious problems. For example, a study [89] showed that, when in contact with blood, a CPC used for vertebroplasty caused blood clotting, which was provoked by interfacial reactions between blood and solid particles released from the CPC. All of the above drawbacks are considered to be challenges that must be overcome for the wide application of CPCs. To this end, the above handling properties will be detailed and the methods used to improve them will be introduced in the following subsections.

3.1. Setting time

The setting time of a CPC is often defined as the time needed for the CPC to become strong enough to resist an applied force. Currently, the Gillmore needles method [90] is the most prevalent method used to measure the setting time of CPCs. This is the time from the initial setting time (the time when the cement can withstand a small fixed pressure exerted by a thick Gillmore needle) and the final setting time (the time when the cement can withstand a high fixed pressure exerted by a thin Gillmore needle) [91]. There is a clinical meaning to the two setting times: between them, the cement should not be deformed because it would interfere in the setting process and create potential cracks [92]. Many strategies have been used to reduce the setting time of CPCs. It is worth mentioning that the setting time, generally of the order of minutes or hours, is just the starting period of the whole hardening process of CPCs, which may last for several days or longer. Thus, as discussed in Section 2, all of the factors which promote fast kinetics could reduce the setting time of CPCs: (i) smaller particle size (high specific surface); (ii) low crystallinity; (iii) accelerators in the liquid and solid compositions; (iv) higher setting temperature; and (v) a low liquid-to-powder ratio (L/P ratio) [40]. Nevertheless, it does not mean that the shorter the setting time, the better: a setting time that is too short may cause the cement to be unworkable before the surgeon finishes performing implantation. Thus it is critical to prepare a cement with a suitable setting time (a few minutes) so that it can set slowly enough to provide sufficient time for the surgeon to perform implantation but fast enough to prevent delaying the operation or causing the aforementioned problems [41].

3.2. Cohesion and anti-washout ability

Cohesion is defined as the ability of a CPC to harden in a static aqueous environment without disintegrating into small particles [55]. The definition of the "anti-washout ability" (hereinafter "anti-washout") is similar to that of cohesion, except that the former is evaluated in a dynamic aqueous environment. Because of their similarity, cohesion time and anti-washout time are usually examined as a whole, even though the latter is longer. Great efforts have been made to enhance the cohesion of CPCs. In fact, the cohesion of a CPC paste can be viewed as a competition between forces acting on the particles and forces acting between the paste and the surrounding fluid, the latter forces being mainly governed by the difference in osmotic pressure between the cement interstitial fluid and the surrounding liquid [86]. Thus, methods which lead to strong attractive forces between CPC particles or weaken osmotic pressure can be used to improve cohesion. Similar to the methods used to decrease setting time, the same strategies, such as using a smaller particle size and decreasing the L/P ratio, can be applied to strengthen particles' interactions, thus enhancing cohesion. Moreover, increasing the viscosity of the mixing liquid has proved to be another effective approach to improve cohesion. Numerous biopolymers, such as sodium alginate [30], hydroxypropyl methylcellulose (HPMC) [93,94], hyaluronic acid [32], chitosan [95,96] and modified starch [97], have been admixed either to the powder or to the liquid of CPCs. Small amounts of these biopolymers can significantly improve the cohesion and anti-washout of CPCs. Based on these studies, Bohner et al. [86] performed a theoretical and experimental study to test the effect of various parameters potentially affecting the cohesion of cement pastes. Their results suggested that the two best methods to increase the cohesion of a cement paste are to decrease the particle size of the starting powders and to use a viscous solution. However, despite the prominent effect of these viscous solutions on the improvement of the cohesion of pastes, they may in some cases compromise the setting time and mechanical properties [55].

3.3. Injectability

There is presently no common understanding in the biocement community about the meaning of injectability. For many authors, injectability is related to the injection force that has to be applied to a syringe so as to deliver the cement paste [27]. However, this definition appears not to measure the injectability of a paste but, rather, its ease of injection, which is strongly dependent on the injection system (e.g. type of syringe, needle size, injection speed) [27,53,98,99]. Moreover, this definition does not consider the quality of the extruded paste, in which phase separation (also called filter-pressing) may happen, probably causing a deviation of the actual composition of the extruded paste from the initial one [97,100]. Due to this deviation, it becomes unclear whether the setting, mechanical and biological behaviors of the extruded cement are still clinically acceptable [41]. In fact, it is the filter-pressing which has been shown to be the mechanism underlying the limited injectability of a CPC paste [54]. Thus Bohner and Baroud [27,53] redefined the injectability of a paste as the ability to stay homogeneous (without filter-pressing) during injection, independent of the injection force.

Many methods have been used to reduce or eliminate filter-pressing in order to improve the injectability of CPC pastes. Khairoun et al. [100] surveyed the factors which control injectability, and found that the injectability was significantly enhanced by increasing the L/P ratio and injecting soon after cement mixing. Ishikawa [101] observed that a CPC paste made of round particles was more injectable than one made of irregular particles. Furthermore, various additives have been added to CPCs, either in the powder or in solution, to try to improve injectability. Andrianjatovo and Lemaitre [102] observed an obvious improvement in injectability by adding polysaccharides. Burguera et al. [103] and Liu et al. [94] added different methylcellulose or HPMC solutions to CPCs and obtained a strongly improved injectability. Sarda et al. [39] found that, with the addition of citrate ions, the injectability of a CPC paste was increased by 50–100%. According to various observations, Bohner and Baroud [53] conducted a theoretical and experimental study on the injectability of CPCs. They found that, of all the parameters (including decreasing particle size, increasing L/P ratio, using round particles, using deagglomerated particles, using particles with a broad size distribution, adding ions or polymers decreasing particle interactions and increasing the viscosity of the mixing liquid) that could be used to improve injectability, the best strategy is to increase the viscosity of the mixing liquid.

In summary, according to the above review, it can be concluded that the best way to improve cohesion and injectability of CPCs is to use a viscous solution as the liquid phase. However, these viscous solutions may compromise the setting time or the strength.

4. Mechanical properties of CPC

For most surgical applications, the two most important properties of materials are mechanical properties (“strength”) and chemical properties (reactivity). Thus, both mechanical properties and reactivity should be taken into account when developing a new biomaterial. As for the former, it is well known that, from a material science point of view, the mechanical properties of a material are determined by its microstructure. Different fabrication routes and processing parameters result in a variety of microstructural features. Thus, microstructure is the crucial connecting link between fabrication and mechanical properties. Any attempt to directly relate mechanical properties to fabrication without relating both to microstructure will be completely impractical and meaningless for a theoretical understanding and the effective design of targeted properties. Therefore, microstructure–mechanical

Table 1
Composition and mechanical properties of CPCs prepared with different processing parameters.

Composition matrix/additive/fiber (or porogen)	Porosity (%)	CS (MPa)	FS (MPa)	E_b (GPa)	K_{Ic} (MPa.m$^{1/2}$)	WOF (kJ/m^2)	Ref.
HA (α-TCP)/-/-		9–38					[104]
HA (α-TCP + pHA)/-/-	45–67	1–34	1–6[a]				[105]
HA (α-TCP + pHA)/-/-	34–51	39–103		4.5–9	0.15–0.5		[106]
HA (α-TCP + β-TCP + pHA)/-/-		1–40					[62,68,75]
HA (α-TCP + DCPA + $CaCO_3$ + pHA + $NaHCO_3$)/-/-	39–60	1–15					[107]
HA (milled β-TCP)/-/-	40–45	7–52	1.4–6[a]				[108]
HA (TTCP + DCPA)/-/-	31–50	4–37		0.5–3[c]			[109]
HA (TTCP + DCPA)/-/-		34–49					[110]
HA (TTCP + DCPA)/-/-		58–66	7–13[a]				[111]
HA (TTCP + DCPA)/-/-	27–39	129–174	11–18	4–6			[112]
HA (TTCP + DCPA)/-/-		10–37					[113]
HA (TTCP + DCPA)/-/-			1.5–12[a]				[114]
HA (TTCP + DCPA + pHA or β-TCP)/-/-		43–60					[81]
HA (α-TCP + DCPD)/-/-		20–65					[115]
HA (MCPM + $CaCO_3$ + pHA)/-/-	59–79	0.5–2	2–15[a]				[116]
HA (MCPM + $Ca(OH)_2$ + pHA)/-/-	45–47	5–17					[117]
HA (β-TCP + $CaCO_3$ + MCPM)/-/-	~50		0.5–1.3	0.7–2.6	<0.2		[118]
Brushite (β-TCP + MCPM + $Na_2H_2P_2O_7$)/-/-	37	10.7	1.3[b]	7.9[c]			[119]
Brushite (β-TCP + MCPM)/-/-	26–42	8–25	2–4.5[a] 4.4–8.5[b]				[120]
HA (α-TCP)/citric acid/-		3–60					[39]
HA (α-TCP)/citric acid, chitosan, glucose/-		2–23					[95]
HA (α-TCP + pHA)/HPMC or MC/-	49–53	24–31			0.22–0.24		[94]
HA (α-TCP + pHA)/polysorbate 80/-	51–79	0.1–17					[121]
HA (α-TCP + pHA)/albumen/-	47–77	0.6–38					[122]
HA (α-TCP + pHA)/poly(4-HMA)/-		5–40	5–9				[123]
HA (α-TCP + DCP + pHA)/$CaCO_3$/-		2–70					[124]
HA (TTCP + DCPA)/chitosan lactate/-			8–20	4–6	0.18 –0.23		[125]
HA (TTCP + DCPA)/trisodium citrate or citric acid/-	16–34	62–180					[126,127]
HA (TTCP + DCPA)/chitosan, chitosan-malate, chitosan-lactate/-		8–66	4.5–17	2.5–6.5			[96]
HA (TTCP + DCPA)/sodium alginate/-			0.5–13.5[a]				[30]
HA (DCPA + $CaCO_3$ + pHA)/polyacrylic acid/-	44	75	3.5[b]	13.5[c]			[119]
Brushite (β-TCP + MCPM)/citric acid/-	11–34	18–52					[128]
Brushite (β-TCP + MCPM)/sodium citrate or citric acid/-	15–32	10–26					[129]
HA (α-TCP + pHA)/-/mannitol	41–77	2–50	1–16.5	0.5–9.7	0.05–0.3		[130]
HA (TTCP + DCPA)/-/NaCl particles	~74	1.5–4.5					[131]
HA (TTCP + DCPA)/-/NaCl particles	54–81	1.8–6.5					[132]
HA (TTCP + DCPA)/-/Na_2HPO_4 ice flakes	31–63	0.4–37		0.018–2.9[c]			[133]
HA (TTCP + DCPA)/-/sucrose, $NaHCO_3$, Na_2HPO_4 particles	38–70		0.4–10[a]				[134]
HA (TTCP + DCPA)/-/gelatin microsphere	65–70	2–6					[135]
HA (PCCP + DCPA)/-/PLGA microsphere		10–23		0.4–1.8[c]			[136]
HA (α-TCP + DCPA + pHA)/-/PLGA microsphere	58–84	4–30		0.4–3.4[c]			[137]
HA (α-TCP + DCPA + $CaCO_3$ + pHA)/-/ PTMC microsphere	40–70	15–64		0.5–5.5[c]			[138]
HA (α-TCP)/-/polyamide fiber	52–55	9.5–13					[139]
HA (TTCP + DCPA)/-/HA whiskers	41–44		4.7–7.4			0.04–0.1	[140]
HA (TTCP + DCPA)/-/PLGA fibers		36–82	11–17			0.02–0.95	[141]
HA (TTCP + DCPA)/-/aramid, carbon, E-glass, polyglactin fibers			13–62	2–7		0.01–10	[142]
HA (TTCP + DCPD)/-/glass fibers		0.6–3.7		0.097–0.14[c]		0.09–0.54	[143]
HA (PCCP + DCPA)/-/CNT		26–59					[144]
HA (α-TCP + DCPA + $CaCO_3$ + pHA)/-/PCL and PLLA	56–71		2.5–7.5	14–49		0.01–0.5	[145]
HA (TTCP + DCPA)/-/aramid fibers (mannitol)	46–71		2–43	0.8–8.5		0.005–6.6	[146]
HA (β-TCP + DCPA)/BSA/MWCNT		1–16					[147]
HA (PCCP + DCPA)/sodium citrate/PLGA microspheres		2–32					[148]
HA (TTCP + DCPA)/chitosan lactate/mannitol	35–83		1–24	0.1–5.5	0.01–0.32		[149]
HA (TTCP + DCPA)/chitosan lactate + $NaHCO_3$ + citric acid/PLGA	47–79		2–20	0.3–1.8		0.2–4.4	[150]
Brushite (β-TCP + MCPM)/sodium citrate/mannitol		17–46		2.5–5.5[c]			[151]

CS: Compressive Strength; FS: Flexural Strength; E_b: Effective elastic modulus in bending; K_{Ic}: Fracture toughness, WOF: Work Of Fracture; pHA: precipitated hydroxyapatite; TTCP: tetracalcium phosphate; MCPM: monocalcium phosphate monohydrate; PCCP: partially crystallized calcium phosphate; 4-HMA: 2-hydroxy-4-N-methacrylamidobenzoic acid; PLGA: poly(lactic-co-glycolic acid); PTMC: poly(trimethylene carbonate); PCL: poly(ε-caprolactone); PLLA: poly(L-lactic acid); BSA: bovine serum albumin; CNT: carbon nanotubes; MWCNT: multi-walled carbon nanotubes.

[a] Diametrical tensile strength.

[b] Tensile strength.

[c] Effective elastic modulus in compression.

properties relations will be taken into account throughout the following subsections.

Unlike bioceramics, which need sintering at a high temperature, CPCs are formed through a dissolution–reprecipitation process at room or body temperature. During this process, an entangled network of apatite crystals is formed, which is responsible for the mechanical properties of CPCs. With time, apatite crystals continue to grow and the entangled network becomes denser until the cement achieves its maximal mechanical properties. A complete list of data of mechanical properties is given in Table 1, along with the cement system (matrix/additives/fiber or porogen) used. The data are listed to give an idea of the variety of mechanical properties of CPCs prepared with different processing parameters. Care should be taken in comparing the absolute values.

Most mechanical properties were assessed using compressive or tensile loading, giving values of the compressive or tensile strength and, sometimes, the corresponding effective elastic modulus. It is worth noting that, due to the difficulty of directly measuring the tensile strength of CPCs, in most studies alternative methods (indirect tensile tests) of measuring flexural strength or diametral tensile strength (DTS) were used, although normally a bending test gives higher values and the DTS test gives lower values compared to the true tensile strength [120]. In contrast, few studies about toughness [94,106,118,125,130,149,152] and reliability [109,130,133,153] have been reported. The mechanical properties of CPCs are strongly dependent on their microstructural features, such as porosity (pore fraction and size), amount, size, morphology and distribution of formed apatite crystals. Furthermore, these microstructural features are related to all the technological factors involved in the fabrication of CPCs. Therefore it is imaginable that all the factors, such as the chemical composition of the cement, the relative proportions of the reactants in the mixture, powder or liquid additives acting as accelerators or retarders, particle size, L/P ratio, pressure applied during sample preparation and aging conditions, will affect its mechanical properties.

Porosity is one of the main parameters influencing both the biological activity and the mechanical properties of biomaterials. As mentioned previously, one special feature of CPCs is that they are intrinsically microporous. The microporosity of CPCs, which usually varies between 30 and 55%, is significantly dependent on the L/P ratio: the higher the L/P ratio, the higher the microporosity [106]. As well as intrinsic micropores that allow for impregnation of biological fluids, macropores are also desirable to enable bone ingrowth into the CPC, concomitantly improving its bioresorption and accelerating its replacement by new bone. The most common techniques used to create macropores in CPCs are porogen leaching, which produces macropores after setting [106,132–135,146,151,154–157], and gas foaming, which creates macropores before setting [105,107,150,157,158]. However, neither method is exempt from drawbacks. On the one hand, for porogen leaching, it is necessary to add a large amount of a porogenic agent to guarantee interconnectivity, which often compromises the injectability of the CPC paste [136]. On the other hand, for gas foaming, the liberation of gas after the implantation of the cement paste could have harmful effects on the organism [122]. In order to avoid these problems, Ginebra et al. [122] proposed a new method to fabricate macroporous CPCs by mixing the cement paste with a pre-prepared foam.

4.1. Strength

Despite the different functions of micropores and macropores in biological activity, it is widely accepted that both types of pores are detrimental to strength. In Fig. 2, data from studies extracted from Table 1 are compiled to illustrate the range of compressive strength for CPCs over a wide range of porosity, resulting from

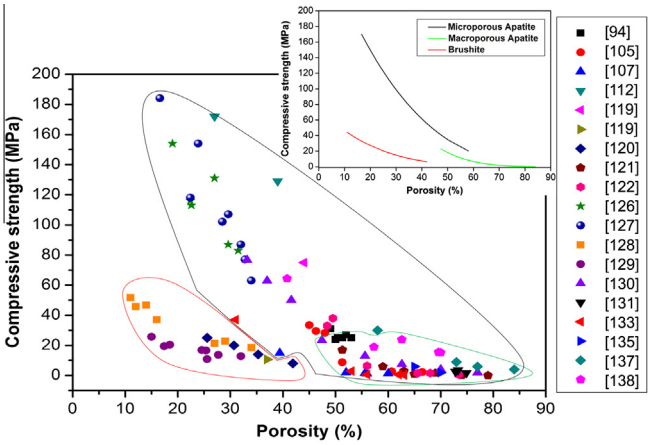

Fig. 2. Compressive strength of CPCs compiled from different studies as a function of total porosity. The red line includes strength data of brushite CPCs. The black line includes strength data of apatite CPCs. The green line demonstrates the strength data of apatite CPCs containing macropores. The insert in the up-right corner shows the power law fittings of all the data points of compressive strength of brushite, microporous apatite and macroporous apatite respectively.

different fabrication routes and processing parameters. It is worth mentioning that, besides the effect of the pore itself, the sample testing conditions (dry and wet samples) also have a great influence on the compressive strength values measured. In Fig. 2, most of the data points are values of compressive strength measured using wet samples; the few exceptions will be detailed later. Moreover, considering the testing conditions, it should be noted that, similar to most brittle materials, the tensile or bending strength of CPCs is usually much lower than their compressive strength, as seen in Table 1, where in some cases both tests were performed. Indeed, brittle fracture proceeds by crack propagation from pre-existing flaws like microcracks, and it is normally easier to propagate a crack in tension than in compression [159].

Several trends can be observed in Fig. 2. First, the compressive strength spans almost three orders of magnitude across studies, from 0.2 to 184 MPa for porosities of 11-84%. The data show that CPCs can be prepared with compressive strengths comparable to those reported for human cancellous bone (4-12 MPa) [160] or cortical bone (130-180 MPa) [160]. This result may be surprising to many researchers, who usually presume that CPCs are not suitable candidates to be used in load-bearing places. This point will be further detailed in Section 4.4. Secondly, regardless of the CPC composition (apatite or brushite), the strength decreases globally with increasing porosity, which is a common occurrence in materials science and has been widely observed in other porous materials used for bone substitution [160–163]. Moreover, with comparable porosities, apatite cements generally have higher strengths than brushite cements, which is also consistent with other reported facts [41]. Finally, it can be observed that the introduction of macropores into CPCs usually (though not always) provokes a sharp decrease in strength within a narrow range of porosity. For example, Liu et al. [94] found a 23% decrease in strength, from 31 to 24 MPa, with just a 1% increase in porosity, from 49% porosity for a microporous cement to 50% porosity for a microporous and macroporous cement. A similar phenomenon was also observed in Almirall et al.'s study [105]: a 69% reduction in strength, from 28 to 8.8 MPa, with a 3% increase in porosity, from 48 to 51%. In order to further demonstrate this trend (a steep decrease in strength for macroporous cements), a power law [164] was used to fit all of the data points of the compressive strengths of brushite, microporous apatite and macroporous apatite cements. The inset in Fig. 2 shows the fittings of the three types of cement. As seen in the inset, once

macropores are introduced into microporous cements, the compressive strength decreases by a factor of ~2 (compare, for instance, both of the fitted trends in the range 50-60% total porosity in the inset of Fig. 2). This obvious variation in strength, resulting from the addition of macropores, has been observed in other brittle biomaterials, like bioceramics; for instance, Pecqueux et al. [162] considered the introduced macropores as large critical flaws provoking fracture. The steep decrease in strength is not observed in all of the macroporous CPCs shown in Fig. 2, which may be because these macroporous CPCs have no strength data available with a porosity adjacent to control cements without macropores. Overall, however, the detrimental effect of macropores on the strength of CPCs is significant. The strength is reduced drastically by increasing the amount of macroporosity, being several times or even orders of magnitude lower than that without macropores. Moreover, the strength of macroporous CPCs is less variable at high porosities (60–85%). The strengths of macroporous CPC in Habraken et al.'s study [138] are generally higher than those in other studies with comparable porosities. This may be attributed to the fact that their strength tests were conducted on dry samples. Indeed, it has been reported that in similar conditions dry samples have a higher strength than wet samples, which seems to be a general feature [120,127,130], although it has been rarely reported explicitly.

Besides the effect of pore fraction, pore size also significantly affects the strength of CPCs. Bai et al. [131] fabricated macroporous CPCs with equivalent total porosity but with different macropore sizes, finding that the compressive strength is inversely proportional to macropore size. This result is in accordance with other studies on ceramics [162,165], and can be explained by the classic Griffith theory [166], which relates strength to critical flaw size; in this case, macropores can be considered to act as large critical flaws, hence reducing strength.

The characteristics of apatite crystals (amount, size, morphology and distribution) also have important effects on the strength of CPCs. These characteristics are dependent on the cement dissolution–precipitation process, the kinetics of which can be controlled by many factors, as discussed in Section 2.2. It is therefore expected that these factors will affect the characteristics of apatite crystals, which in turn influence the strength of CPCs.

Particle size significantly affects the kinetics of CPC setting. The smaller the particle size of the starting materials, the faster they will convert into apatite and the smaller the apatite crystals formed, which, in turn, will lead to more and dense crystal entanglement and thus to an increase in strength [110]. A similar trend has been reported by Zhang et al. [106], but was attributed to the presence of larger flaws in the case of cements prepared with a coarse powder. Otsuka et al. [167] reported an increase in the compressive strength of a CPC when the specific surface of the precipitated phase increased. However, Ginebra et al. [62] argued that there was no improvement in the final strength of a CPC prepared from a fine powder. They explained that a fine initial powder could lead to a more compact microstructure, but with a smaller fraction of empty space between crystals and some cavities where initial particles were located, which had a weakening effect; in contrast, a coarse initial powder could result in a less densely packed but more homogeneous microstructure.

The aging condition is another main factor influencing the kinetics of apatite formation, although in most cases it is undertaken in Ringer's solution at 37 °C. At higher temperatures the starting particles transform into apatite more quickly, and the microstructure of CPCs is more homogeneous and dense, leading to a higher strength, which is clearly apparent in the early stage of hardening [68]. However, with increasing hardening temperature, the growth rate of precipitated apatite crystals is also faster, resulting in a larger crystal size [69], which might have a detrimental effect on the final strength.

Different additives functioning as accelerators or retarders, and mixed with the powder or liquid phase of the cement, also have important effects on the strength of CPCs by controlling their kinetics of setting and ultimately their microstructure. Apatite particles are solid-phase additives that are frequently employed as seeds to promote the formation of apatite in CPCs [40,73,81,117,168–171]. Brown and Fulmer [170] indicated that apatite seeds accelerated the initial setting reactions but did not appear to have major long-term effects on the extent of reaction or on microstructural development. Both Bermudez et al. [169] and Yang et al. [117] observed that, by adding certain amounts of apatite seeds, the setting time of CPCs decreased and the compressive strength concomitantly increased; conversely, however, excess apatite prolonged the setting time and decreased the compressive strength. Yang et al. [117] attributed the evolution in strength to variation in the morphology of the precipitated apatite crystals with the amount of apatite seeds. Furthermore, in contrast to these studies, Liu and Shen [81] argued that both setting time and compressive strength decreased with increasing amount of apatite seeds. Besides the addition of accelerators to the solid phase, adding accelerators to the liquid phase has been reported. Ishikawa et al. [114] used a cement liquid containing PO_4^{3-} anions in apatite cements, and found that formation of both apatite and DTS during the first 3 h was significantly increased by the presence of phosphate ions. However, the phosphate produced no significant effects on the properties of the cement after 24 h. Phosphate anions used as accelerators in the cement liquid have also been widely studied in other CPC systems [40,172,173]. Unlike cement accelerators, cement retardants delay setting, which is nevertheless positively correlated with a higher final strength [73,124,174]. Fernandez et al. [124] found that incorporation of 10 wt.% $CaCO_3$ improved compressive strength by a maximum of 40% compared to samples free of $CaCO_3$. Similarly, Bohner et al. [174] demonstrated that the addition of SO_4^{2-} improved the DTS of a β-TCP-based cement pronouncedly. These improvements in strength are mainly attributed to a refinement of the cement microstructure (for instance, the incorporation of carbonate in the apatite causes a decrease in crystallite size). Other major cement retardants that have been tested to increase the cement mechanical properties are α-hydroxyl acids (citric acid or glycolic acid) and their salts (sodium citrate), which allow easier mixing of the cement and processing with a decreased L/P ratio (relating to a decreased porosity), thus resulting in improved strength [16,39,126,127,129,148,175]. However, these additives generally have optimal concentrations that can be used in the cement, whereas a higher concentration of such additives can decrease strength [148]. The aforementioned strengthening effects, through refinement of microstructure and reduction of porosity, can also be realized in CPCs simultaneously [123]. Moreover, the addition of free ions (Sr^{2+}, Mg^{2+}, Si^{4+}) to the cement system usually has a retardant effect on setting. Nevertheless, they do not always have a beneficial effect on cement strength. Lilley et al. [176] found that the compressive strength of Mg-substituted CPCs decreased with an increasing amount of added Mg. The authors attributed this to an increased porosity which was related to the addition of Mg. Similarly, Saint-Jean et al. [104] revealed that the substitution of calcium by strontium in HA was detrimental to its compressive strength. The authors suggested that this inferior strength was related to the presence of larger voids between the crystals.

In summary, the mechanical properties of CPCs, and in particular strength, depend strongly on the microstructure, which is related to all of the technological factors involved in the fabrication, such as chemical composition, powder or liquid additives acting as accelerators or retarders, particle size, L/P ratio

and aging conditions. Moreover, a general conclusion is obtained: crystalline structures that are more compact and homogeneous, with smaller crystals, seem to give better mechanical properties than less compact or less homogeneous ones with larger crystals.

4.2. Fracture toughness

Strength, especially compressive strength, has been widely tested in studies of CPCs as a criterion (often the only criterion) evaluating their mechanical performance. However, this notion appears to be inadequate in many cases. For example, CPCs implanted in bone defects are usually subject to cyclic loading. The value of strength alone cannot suitably represent the CPC's ability to resist fracture in such loading conditions. Moreover, strength is not an intrinsic property, but depends both on the number and size of defects (e.g. pores) and on the fracture toughness, which is a real limitation for CPCs. In fact, it is the poor fracture toughness, which describes the resistance of a material to crack propagation, and low reliability (characteristics of brittle behavior) that prevent CPCs from widespread use in load-bearing locations. Unfortunately, however, unlike the abundant reports on strength, the literature is sparse on the fracture toughness and reliability of CPCs. The present section and the next are dedicated to toughness and mechanical reliability, respectively.

Fracture toughness, K_{Ic}, also called the critical stress intensity factor, is a property which is used to describe the ability of a material containing cracks or notches to resist crack propagation [177,178]. The fracture toughness of a material depends on the nature of its nano/microstructure (e.g. bond strength), and also on the activation of several possible toughening (or reinforcement) mechanisms, which are mainly due to microstructural features [179,180]. Without the activation of significant toughening mechanisms, the basic fracture toughness of CPCs is very low (typically $K_{Ic} < 0.5$ MPa.m$^{1/2}$). Because of their low fracture toughness, CPCs are very sensitive to the presence of defects and flaws (e.g. pores), which can cause catastrophic failure, as mentioned in Section 4.1. However, the low fracture toughness of CPCs can be improved by a number of toughening mechanisms, which will be detailed in Section 4.4.

A number of techniques have been used to determine the fracture toughness of CPCs. Xu and co-workers [125,149] investigated the fracture toughness of apatite cements by using the single-edge V-notched beam (SEVNB) method. The authors found that the K_{Ic} values are in the range of 0.01-0.32 MPa.m$^{1/2}$ for CPCs with porosities of 35-83%. However, in order to get accurate measurements, the SEVNB method requires the crack to be very sharp (small notch root radius), which is a difficult task in brittle materials [177]. In contrast, the chevron-notched beam fracture toughness (CN) method has the advantage of not requiring such a sharp crack and not needing the actual crack length to be measured, and has been widely used for brittle materials [177]. Zhang et al. [106,130] and Liu et al. [94] used the CN method to measure the fracture toughness of apatite cements, getting K_{Ic} values in the range of 0.05-0.5 MPa.m$^{1/2}$ for samples with porosities of 31-77%. By using the CN method, Morgan et al. [118] found that carbonated apatite cements with a porosity of 50% can have a fracture toughness as high as 0.1 MPa.m$^{1/2}$. O'Hara et al. [152] introduced chevron notches into short rods of CPCs and measured their fracture toughness, getting values between 0.1 and 0.26 MPa.m$^{1/2}$. All of the above studies show K_{Ic} values comparable to the reported values for cancellous bone (0.1-0.8 MPa.m$^{1/2}$) [163] but much lower than those for cortical bone (2-12 MPa.m$^{1/2}$) [163], indicating that more effort is still required to increase the fracture toughness of CPCs for their application in load-bearing locations.

Despite the crucial importance of fracture toughness, in many studies the work of fracture, γ_{wof}, has been used instead of fracture toughness to characterize the resistance to crack propagation because of its ease of measurement [57]. γ_{wof} is the total energy consumed to produce a unit area of fracture surface during complete fracture [181]. It is calculated from the load – displacement integral divided by the nominal specimen cross-section [182]. Some groups have used work of fracture to assess the ability of CPCs to resist crack propagation (see Table 1). However, γ_{wof} can only be used for comparison within a given study because it is not an intrinsic material property but is strongly linked to specimen geometry and to other experimental factors [160,163].

4.3. Mechanical reliability

Besides poor fracture toughness, low reliability is another prominent factor limiting the wide applicability of CPCs in load-bearing places. The reliability or the probability of failure of brittle materials can be characterized using Weibull statistics. The basic Weibull probability function [183,184] using the strength data ranked in ascending order is usually written as

$$P_f = 1 - \exp\left[-\left(\frac{\sigma_r - \sigma_u}{\sigma_0}\right)^m\right] \quad (1\text{-}1)$$

where P_f is the probability of failure, σ_r is the fracture strength, σ_u is the threshold stress below which no failure occurs in the material (for most brittle materials, $\sigma_u = 0$ can be taken as a safe stress level [185]), σ_0 is a normalizing parameter determined from the stress at which 1/e of the population survive and m is the Weibull modulus.

The Weibull modulus, m, is a dimensionless number used to characterize the variability in measured strength of components made from brittle materials, which arises from the presence of flaws having a distribution in size and orientation [186]. A high value of m indicates a sharp distribution of strength data (high reliability), while a low value represents a large scatter (low reliability). It should be noted, however, that the Weibull model is based on an empirical description of the probability of failure of individual volume elements of the material (i.e. not relying on fracture mechanics). Nevertheless, because of its practical applicability, it has become the most widely used model to describe fracture statistics in brittle materials.

The Weibull modulus has been used to evaluate the reliability of ceramics [187–189] and dental cements [190,191], but the evaluation of CPCs has received little attention [109,130,133,153]. Morgan and Dauskardt [153] evaluated the reliability of an apatite cement in four-point bending, getting a value of 5.6 for the Weibull modulus. Barralet et al. [109] investigated the reliability under compression of CPCs prepared using different compaction pressures, finding that the value of the Weibull modulus increases with increasing compaction pressure. The authors attributed the increase in Weibull modulus to the decreased range of flaw sizes. Moreover, Barralet et al. [133] found that the addition of frozen sodium phosphate solution particles, which are used as porogen to create macropores, is detrimental to the reliability of CPCs. Compared to macropore-free CPCs, the reduced reliability (Weibull modulus) of the macroporous CPCs is mainly due to its wider flaw size distribution resulting from the addition of sodium phosphate particles. Zhang [130] investigated the reliability of micro- and macroporus CPCs, and found that the Weibull modulus of macroporous CPCs is higher and/or less variable than that of microporous CPCs. Zhang attributed this result to the fact that, because macropores act as critical flaws, either alone or as interacting groups, because they are introduced in large numbers in each specimen and because the porogenic particles are calibrated in size, the strength of macroporous CPCs becomes more "deterministic", making their Weibull modulus higher. While the Weibull modulus provides useful information for assessing the reliability of CPCs, the

requirement of a large number of testing samples may be impractical for some studies.

While the strength of CPCs has been widely investigated, fracture toughness and reliability, which are actually the real limitations for CPCs, have received little attention. Future studies should focus more on these fields to promote applications in load-bearing places.

4.4. Reinforcement of CPC

Despite numerous advantages, it is widely accepted that CPCs need further improvements to their mechanical properties, especially fracture toughness, to broaden their potential clinical applications. As discussed in Section 4.1, the mechanical properties of CPCs are affected by many factors. It is expected that these factors can be adjusted to improve the mechanical properties. Among them, porosity is the factor that is most detrimental to the mechanical properties. Thus, one simple and effective way to improve the mechanical properties is to reduce the volume fraction of the pores in CPCs to get a denser matrix. This should be the case for both toughness and strength [106,149], although in what follows most of the references on the subject deal with strength only. Uniaxially, biaxially or isostatically compacting the cement paste prior to hydration has proved to be an effective method to achieve this goal. Chow et al. [111] demonstrated that compaction pressure rather than compaction time could pronouncedly increase DTS as compared to CPCs obtained by simple mixing, even though the pressure is very low (2.8 MPa). Barralet et al. [109] showed that with increasing compaction pressure between 18 and 106 MPa, the porosity decreased from 50 to 31%, which resulted in an increase in the wet compressive strength from 4 to 37 MPa. Ishikawa and Asaoka [192] applied compaction pressures up to 173 MPa, reducing the porosity down to approximately 26-28%. However, they found that, when compaction pressures above 100 MPa were applied, only a slight decrease in porosity was achieved and the DTS was not pronouncedly improved.

Although the above approaches to increase the strength of CPCs by improving the particle packing of powder reactants with a pressurizing technique work effectively, they have the same function as decreasing the L/P ratio, which would influence the workability and injectability of the cement pastes and might prohibit application in minimally invasive surgery. In this sense, further improvement should be considered to balance handling properties and mechanical properties, or to improve them both at the same time.

Sarda et al. [39] added certain amounts of citric acid to the cement liquid to study its effect on the injectability and setting properties of apatite cements. It was found that citric acid can improve injectability and strength at the same time. One of the reasons for this improvement in strength is the reduced porosity that can be achieved from the decreased L/P ratio that can result from the improved mixing behavior. However, another strengthening mechanism is also proposed. It is known that the more homogeneous and denser the microstructure, the higher the strength. As mentioned previously, the mechanical properties of CPCs come from an entangled network of apatite crystals. Citrate ions adsorb onto the surface of reactants and of newly formed apatite nuclei, providing Coulomb repulsion, which counterbalances the Van der Waals attraction between them [193]. In this way, the particles, instead of agglomerating in the liquid, slide along each other easily and disperse homogeneously (Fig. 3). Then growth and entanglement of apatite crystals are based on these initially more homogeneous microstructures of small apatite nuclei, and thus produces a stronger matrix.

According to this prominent effect of citric acid on the improvement of strength, Barralet et al. [127] and Gbureck et al. [126] added sodium citrate to the cement liquid and compacted the resulting cement paste, achieving compressive strengths of up to 180 and 154 MPa, respectively, which are in the strength range of cortical bone, demonstrating the potential of this CPC system for application in load-bearing places. It is worth noting that the high applied pressure (e.g. 200 MPa) generally decreases the formation rate of HA, indicating that an even higher strength could be achieved with a longer hardening time [127]. Except for the aforementioned synergistic effects of adding sodium citrate and exerting an external pressure to significantly improve strength, Hofmann et al. [128] found that a high strength can also be achieved by adjusting the particle size and distribution of the powder reactants, as well as by adding citric acid but without external pressure. The effect of citric acid combined with other additives, such as chitosan or glucose, on mechanical properties have also been reported [95,194]. The authors [95,194] also noted that adding different amounts of citric acid increased the strength of CPCs to different degrees. Unlike the previous strengthening mechanism proposed by Sarda et al. [39] and Barralet et al. [129], they suggested that there is a chelate reaction between citric acid and calcium, which might make crystals interlock tightly and could thus account for the increase in strength.

Recently, Liu et al. [94] investigated the influence of four cellulose ethers on the mechanical properties of CPCs and found that the cellulose ethers studied have an evident toughening effect, which becomes more significant with increasing molecular weight and mass fraction of cellulose ethers. In addition to the effect of

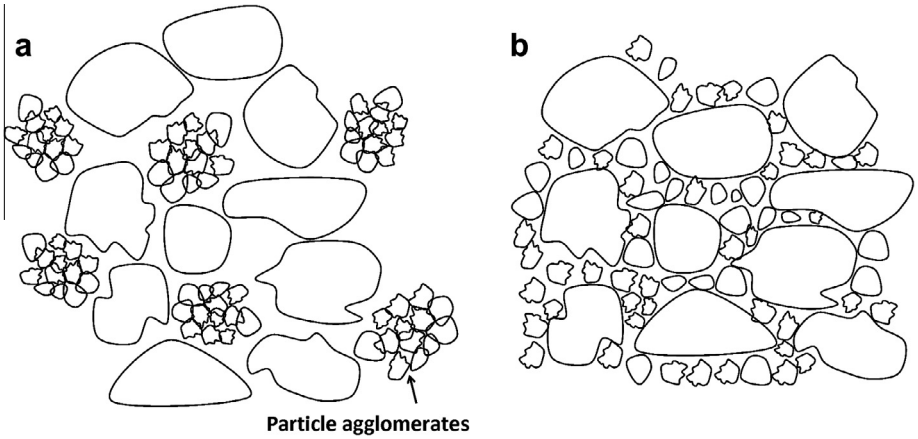

Fig. 3. Schematic illustration showing the distribution of starting powders (e.g. α-TCP, TTCP, DCPA, DCPD. . .) in cement pastes formed without (a) and with citrate ions (b). In the latter case powders are dispersed more homogeneously due to their higher surface charge. Inspired from Fig. 4 of [126].

homogenization of the cement matrix, as discussed previously, the authors [94] also ascribed the increase in toughness to the effect of crack bridging by polymer ligaments. This was also associated with a less brittle fracture and with a sort of tolerance to damage, the material becoming able to withstand a certain extent of deformation before complete failure, as in the case of some fiber composites. The above-mentioned effects will be described and discussed later. However, despite the significant toughening effect endowed by adding cellulose ethers, a decrease in compressive strength was observed in the composite CPCs as soon as some polymer was added. This is due to the fact that, as mentioned previously, strength is dependent on both fracture toughness and defect (pore) size. Although adding cellulose ethers can improve the fracture toughness of CPCs, the concomitant sudden increase in pore size decreases the strength. Then, as more polymer is added, the strength increases with increasing polymer mass fraction in comparison with control CPCs with identical porosities, which is attributed to the increase in toughness [94,130].

Besides the aforementioned effect of densification and homogenization of the cement matrix, another main strategy to improve the mechanical properties (especially fracture toughness) of CPCs is to add fibers to their matrix. This notion of improving mechanical performance by producing fiber composites has been widely studied in materials engineering and has been realized in industrial applications. For instance, reinforcement with fibers has been extensively developed in the field of hydraulic cements and concretes for civil engineering and building applications. The incorporation of fibers into a brittle cement matrix has been proved to be an effective method to improve fracture toughness as well as tensile and flexural strength [195].

In the fiber-added composite cements for civil engineering, three mechanisms of fiber reinforcement (fiber bridging, crack deflection and frictional sliding) appear to be operative (Fig. 4). Specifically, first, when the matrix starts to crack, the fibers bridge the crack to resist its further opening and propagation. Secondly, crack deflection by the fibers prolongs the distance over which the crack propagates, consuming more energy in newly formed surfaces. These two mechanisms have also been reported to be the major contributors to the fracture toughness of human bone, which is a hierarchical composite consisting of hard mineral nanoparticles (carbonated apatite) and a fibrous polymer (collagen) [179,180]. Finally, the frictional sliding of fibers against the matrix during pullout further consumes the applied energy and increases the fracture resistance of the composite [146]. Due to the chemical similarity between CPCs and cements for civil engineering, it is strongly expected that, by adding fibers, the above toughening mechanisms can also be achieved in CPCs.

Choosing the proper fibers is the premise of successful reinforcement of CPC composites. Generally speaking, a fiber with a high tensile strength is essential. However, it is not only the fiber type that is important: other factors, such as fiber length, volume fraction, orientation and fiber/matrix adhesion, are also critical for the final properties of the composite [57]. Cement pastes or precursor powders can be mixed with fibrous materials having different spatial organizations (short fibers, random long fibers, woven structures, oriented yarns...), hence producing various composite microstructures [56].

Moreover, to be used in CPCs, specific requirements must be taken into account in the selection of the fibers. First of all, they must be biocompatible. Furthermore, in some cases, they can be used not only as a reinforcement for the cement matrix at the early stage of hardening but also as a porogen to create pores after complete hardening. Then, in addition to being biocompatible, they must also be biodegradable. Various fibers have been employed in the reinforcement of CPCs to date. These can be classified into two categories: (i) non-resorbable fibers, including collagen fibers

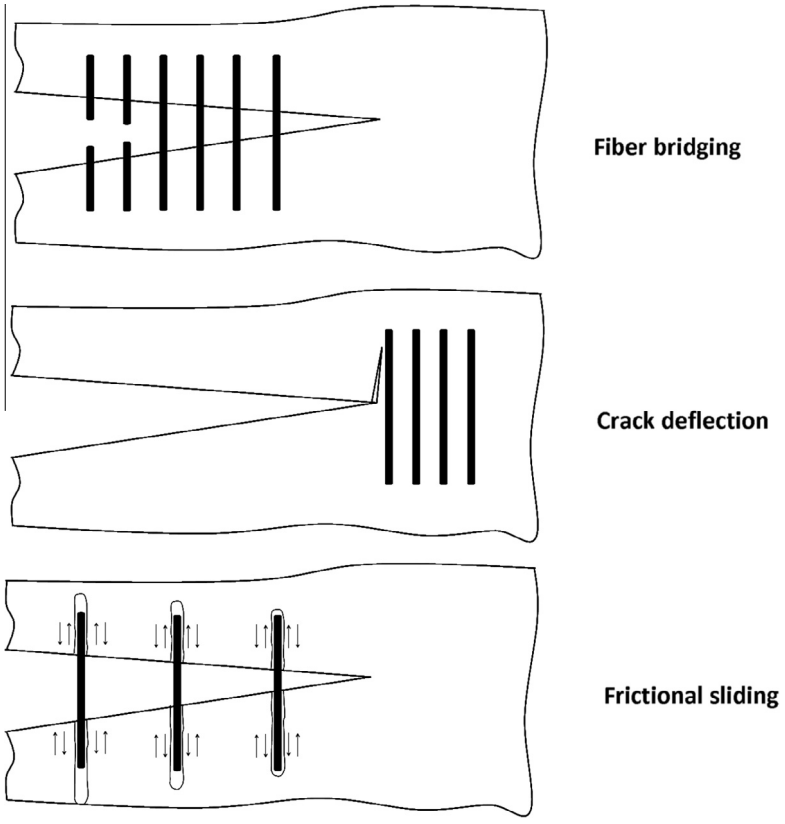

Fig. 4. Schematic illustration showing three mechanisms of fiber reinforcement (fiber bridging, crack deflection and frictional sliding) in fiber-added composite cements.

[152], polyamides [139,142], carbon fibers [142,144,147] and glass fibers [142,143]; and (ii) resorbable fibers, which are mainly natural or synthetic polyesters such as polylactide (PLA) [145], poly(lactic-co-glycolic acid) (PLGA) [141,150,196–199] and poly ε-caprolactone (PCL) [145] or chitosan [200].

Xu et al. [142] investigated CPC reinforcement by adding polyamides, carbon, glass and polyglactin fibers with different lengths and volume fractions. They found that both the volume fraction (with fixed fiber length) and the length (at constant fiber volume fraction) of these fibers have significant effects on the mechanical properties (flexural strength, Young's modulus and work of fracture). The mechanical properties gradually increased with increasing fiber volume fraction. However, a plateau or a decrease following the increase was often observed in the mechanical properties at high fiber volume. This is mainly because the high volume of fibers may compromise their workability, making it difficult for them to be mixed and wetted by the CPC paste, leaving space between fibers and matrix [142,143]. A similar evolution in mechanical properties was also found in CPCs with increasing fiber length. The authors ascribed the decrease in mechanical properties to the heterogeneous distribution of the long fibers [142]. This negative effect of heterogeneous fiber distribution was also observed in Dos Santos et al.'s study [139], where the compressive strength of composite CPCs showed great variability. Being considered as the shortest "fibers", carbon nanotubes (CNT) and multi-walled carbon nanotubes (MWCNT), which find wide applications in sintered HA–CNT composites [201], have also been used as reinforcing agents in CPCs [144,147]. Wang et al. [144] mineralized CNT with an HA nanoparticle layer to improve their wettability towards CPC. Compared to pristine CNT, which only slightly improved the compressive strength of the CPC, the mineralized CNT significantly improved the mechanical properties of the CPC due to the enhanced interfacial bonding between them. Similarly, Chew et al. [147] used hydroxyl functionalized MWCNT (MWCNT-OH) to increase the strength of CPC. The authors found that a further increase in the strength of CPC/MWCNT composites cold be achieved by adding an appropriate amount of bovine serum albumin (BSA), which promotes CPC crystal growth. Due to their compositional similarity to apatite cement matrix and bone mineral, Muller et al. [140] used hydrothermally synthesized HA whiskers to reinforce CPCs, reporting maximal increases of 60 and 122% in flexural strength and work of fracture, respectively. However, the addition of non-resorbable fibers could be a meaningful strategy only for non-resorbable CPCs. The incorporation of these non-resorbable fibers into resorbable CPCs could cause fiber release into the surrounding tissues, with the subsequent biocompatibility risks [56].

Unlike non-resorbable fibers, the reinforcement of CPCs with resorbable or biodegradable fibers relies on a different strategy. On the one hand, the addition of resorbable fibers can provide early temporary reinforcement at the implant site. On the other hand, after fiber degradation, the resulting macropores can facilitate bone ingrowth. Xu and Quinn [198] investigated the evolution of the mechanical properties (flexural strength, Young's modulus and work of fracture) of CPCs reinforced with 8 mm long PLGA fibers at 25% fiber volume. Their results showed a threefold increase in flexural strength and a 100-fold increase in work of fracture; in contrast, no prominent differences were observed in the Young's modulus. With increasing immersion time, the mechanical properties of the composite CPCs progressively decreased at different rates with fiber degradation. A laminar-like mesh consisting of knitted fibers was also used to improve mechanical properties of CPCs [199]. Similar to their previous study [198], by adding mesh, the authors observed a threefold increase in flexural strength and a 150-fold increase in work of fracture. After 84 days of immersion and mesh dissolution, interconnected macropores suitable for bone ingrowth were created in the CPCs. Zuo et al. [145] tried to improve the mechanical properties of CPCs by using ultrafine PLA fibers with a controllable diameter, made using an electrospinning technique. However, due to their hydrophobic properties, most of the fibers displayed an obvious separation from the CPC matrix. The flexural strength and Young's modulus decreased gradually with the addition of fibers. Conversely, the work of fracture progressively increased with increasing fiber content, which was attributed to an increased flexibility of the CPCs. Recently, Kruger et al. [202] used degradable magnesium wire to reinforce CPCs, reaching a maximal flexural strength of 140 MPa, which is in the range of the reported values for cortical bone.

As for resorbable fibers, macropores produced from fiber degradation can promote bone ingrowth. However, these macropores are detrimental to the mechanical stability of CPCs before new bone grows into the pores. To solve this problem, several types of fibers having different resorption rates could be used simultaneously [41]. The fast degradable fibers create pores for bone ingrowth, while fibers with a low degradation rate provide strength to the implant. Once new bone has grown into the macropores created by the fast degradable fibers (thereby increasing strength), the fibers with a low degradation rate start to dissolve to create macroporous channels for continuous tissue ingrowth. Similarly, a layered CPC structure was developed by combining a macroporous CPC layer with a fiber-reinforced strong layer, enabling fast bone ingrowth into the macroporous layer and continuous bone ingrowth into the fiber-reinforced layer after fiber degradation [203].

Moreover, in conjunction with fibers, various additives such as chitosan lactate or HPMC have been incorporated into CPC to attempt to improve different properties. Zhang and Xu [204] incorporated chitosan lactate into CPC–fiber composites as an additional reinforcing agent. Their results show significantly improved mechanical properties with respect to the separate contributions of fibers or polymer alone. The synergistic reinforcement can be explained as follows: the addition of chitosan lactate into the CPCs produced a stronger matrix to support the fibers to better resist crack propagation, with the strong matrix amplifying the fiber effect. Moreover, the matrix/fiber adhesion may also have been improved by the addition of chitosan lactate. Xu et al. [205] added HPMC at a mass fraction of 1% to a macro-CPC–fiber composite, as a gelling agent. The incorporation of HPMC maintains the injection force of the CPC–fiber composites with different fiber volume fractions within a low range (6–10 N), which greatly facilitates injection. Recently, with regard to stem-cell-based tissue engineering, the addition of stem cells into fiber-reinforced CPCs is starting to attract attention [206–208].

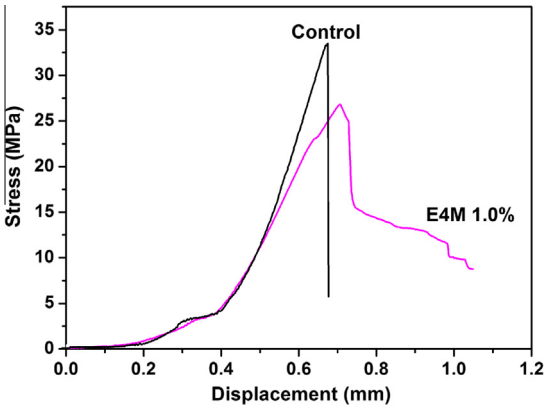

Fig. 5. Stress vs. displacement curves of control CPC and CPC with 1% of HPMC (E4M). The addition of E4M appears to make composite CPC less brittle, endowing it a sort of tolerance to damage.

The addition of fibers generally has a positive effect on the fracture behavior of CPCs, endowing the latter with some degree of tolerance to damage, as in the case of composite CPCs prepared by adding polymers to the paste (Fig. 5). This tolerance to damage is very interesting for biological applications, since the material, in the case of an overload, will nevertheless retain some degree of mechanical integrity, which will both prevent debris from escaping the implant site and allow the material to withstand further (reduced) loading.

In summary, based on the above review, two main strategies can be proposed for enhancing the mechanical properties of CPCs. First, under the premise of keeping critical factors for bone ingrowth or other biological performance, a denser and more homogeneous matrix consisting of smaller crystals would be desirable to improve the "intrinsic" mechanical properties. Second, incorporation of fibers and/or of polymers into CPCs could supply extra enhancement of mechanical properties. However, deliberate selection of the second phase (fibers with proper type, length and volume fraction, or polymers with appropriate structure, molecular weight and volume fraction) should be taken into account.

5. Conclusion

The chemistry and kinetics of the setting, handling properties and mechanical properties of CPCs for bone substitution were reviewed with emphasis on their mechanical performance. Many processing parameters, such as powder particle size and composition, can be adjusted to control the setting process, concomitantly influencing the handling and mechanical performance. The methods used to improve injectability may nevertheless often compromise cohesion, and vice versa. Increasing the viscosity of the mixing liquid seems to be the most suitable strategy to improve both cohesion and injectability at the same time. In general, CPCs have a poor to moderate mechanical performance, with compressive strengths comparable to those of cancellous bone, showing a potential for the repair of non-load-bearing defects. However, under the effect of densification and/or homogenization of the cement matrix, CPCs with strengths comparable to those of cortical bone can be formed, and these cements may have potential for the repair of load-bearing defects. Fracture toughness, tolerance to damage and mechanical reliability appear to be the real limiting factors for CPCs' applications in load-bearing bone repair, and we believe they have received too little attention so far. The addition of fibers to CPC matrix is shown to be an effective method to improve fracture toughness through crack-bridging and crack deflection toughening mechanisms. Future research should focus more on fracture toughness, tolerance to damage and reliability, and especially on ways to improve them without sacrificing the other important properties that make CPCs good bone substitutes. Moreover, since complex tridimensional and cyclic loads are often applied, shear and fatigue properties of CPCs, which have been rarely reported [119,209], should also merit investigation which, together with compressive, tensile (bending) properties, fracture toughness and reliability, will bring a more complete understanding of the mechanical performance of CPCs. Finally, it will also be desirable, from the viewpoint of surgical application (e.g. vertebroplasty, trauma surgical procedures), to develop a CPC combining good handling properties, better mechanical performance and faster bone replacement. To achieve this, it seems that the fabrication of composite cements by adding some natural polymers or their derivatives (e.g. HPMC [94]) into the starting powder or in solution into the cement paste, could be an interesting option. However, these new generations of composite cements would still present a limited porous structure that hampers both interactions with biological fluids and cell colonization. Thus, another challenge would be to develop composite CPCs where the added organic component would allow the formation of a foam structure that might present some adhesive and plastic properties that could be of interest for surgical applications. A balance would then have to be found between the biological performance and the changes in mechanical behavior provoked by both the macroporosity and the composite effect. However, a complete study of the chemical, handling, mechanical and biological performances is still pending. Such future research should also consider the ability of the material to withstand stresses over time, i.e. until the load bearing can be assumed by newly formed bone.

Appendix A. Figures with essential color discrimination

Certain figures in this article, particularly Figs. 2 and 5, are difficult to interpret in black and white. The full color images can be found in the on-line version, at http://dx.doi.org/10.1016/j.actbio.2013.11.001.

References

[1] Giannoudis PV, Dinopoulos H, Tsiridis E. Bone substitutes: an update. Injury 2005;363:S20–7.
[2] Hing KA. Bioceramic bone graft substitutes: influence of porosity and chemistry. Int J Appl Ceram Technol 2005;2:184–99.
[3] Meeder PJ, Eggers C. The history of autogenous bone grafting. Injury 1994;25(Suppl 1):A2–3.
[4] Hing KA, Annaz B, Saeed S, Revell PA, Buckland T. Microporosity enhances bioactivity of synthetic bone graft substitutes. J Mater Sci-Mater M 2005;16:467–75.
[5] Barriga A, Diaz-de-Rada P, Barroso JL, Alfonso M, Lamata M, Hernaez S, et al. Frozen cancellous bone allografts: positive cultures of implanted grafts in posterior fusions of the spine. Eur Spine J 2004;13:152–6.
[6] Togawa D, Bauer TW, Lieberman IH, Sakai H. Lumbar intervertebral body fusion cages: histological evaluation of clinically failed cages retrieved from humans. J Bone Joint Surg Am 2004;86-A:70–9.
[7] Navarro M, Michiardi A, Castano O, Planell JA. Biomaterials in orthopaedics. J R Soc Interface 2008;5:1137–58.
[8] Reddi AH. Morphogenesis and tissue engineering of bone and cartilage: inductive signals, stem cells, and biomimetic biomaterials. Tissue Eng 2000;6:351–9.
[9] Bohner M, Galea L, Doebelin N. Calcium phosphate bone graft substitutes: failures and hopes. J Eur Ceram Soc 2012;32:2663–71.
[10] Dorozhkin SV. Bioceramics of calcium orthophosphates. Biomaterials 2010;31:1465–85.
[11] Nair LS, Laurencin CT. Biodegradable polymers as biomaterials. Prog Polym Sci 2007;32:762–98.
[12] Zhou H, Lawrence JG, Bhaduri SB. Fabrication aspects of PLA–CaP/PLGA–CaP composites for orthopedic applications: a review. Acta Biomater 2012;8:1999–2016.
[13] Chow LC, Eanes ED. Calcium phosphate cement. Octacalcium phosphate. Basel: Karger; 2001. p. 148–163.
[14] Dorozhkin SV, Epple M. Biological and medical significance of calcium phosphates. Angew Chem Int Ed 2002;41:3130–46.
[15] Vallet-Regi M, Gonzalez-Calbet JM. Calcium phosphates as substitution of bone tissues. Prog Solid State Chem 2004;32:1–31.
[16] Tamimi F, Sheikh Z, Barralet J. Dicalcium phosphate cements: brushite and monetite. Acta Biomater 2012;8:474–87.
[17] Carrodeguas RG, De Aza S. -Tricalcium phosphate: synthesis, properties and biomedical applications. Acta Biomater 2011;7:3536–46.
[18] Moseke C, Gbureck U. Tetracalcium phosphate: synthesis, properties and biomedical applications. Acta Biomater 2010;6:3815–23.
[19] Bucholz RW. Nonallograft osteoconductive bone graft substitutes. Clin Orthop Relat Res 2002:44–52.
[20] Ambard AJ, Mueninghoff L. Calcium phosphate cement: review of mechanical and biological properties. Malden, MA: Blackwell Publishing Inc.; 2006. p. 321–328.
[21] LeGeros RZ. Calcium phosphate-based osteoinductive materials. Chem Rev 2008;108:4742–53.
[22] Ginebra MP, Traykova T, Planell JA. Calcium phosphate cements as bone drug delivery systems: a review. J Control Release 2006;113:102–10.
[23] Ginebra MP, Espanol M, Montufar EB, Perez RA, Mestres G. New processing approaches in calcium phosphate cements and their applications in regenerative medicine. Acta Biomater 2010;6:2863–73.
[24] Brown WE, Chow LC. A new calcium phosphate setting cement. J Dent Res 1983;62:672–9.
[25] LeGeros RZ, Chohayeb A, Shulman A. Apatitic calcium phosphates: possible dental restorative materials. J Dent Res 1982;61:343–7.

[26] Bohner M, Gbureck U, Barralet JE. Technological issues for the development of more efficient calcium phosphate bone cements: a critical assessment. Biomaterials 2005;26:6423–9.
[27] Bohner M. Design of ceramic-based cements and putties for bone graft substitution. Eur Cell Mater 2010;20:1–12.
[28] Xu H, Quinn JB, Takagi S, Chow LC. Processing and properties of strong and non-rigid calcium phosphate cement. J Dent Res 2002;81:219–24.
[29] Wang XH, Ma JB, Wang YN, He BL. Structural characterization of phosphorylated chitosan and their applications as effective additives of calcium phosphate cements. Biomaterials 2001;22:2247–55.
[30] Ishikawa K, Miyamoto Y, Kon M, Nagayama M, Asaoka K. Non-decay type fast-setting calcium phosphate cement: composite with sodium alginate. Biomaterials 1995;16:527–32.
[31] Dos Santos LA, De Oliveira LC, Rigo ECS, Carrodeguas RG, Boschi AO, De Arruda ACF. Influence of polymeric additives on the mechanical properties of α-tricalcium phosphate cement. Bone 1999;25:99S–102S.
[32] Alkhraisat MH, Rueda C, Marino FT, Torres J, Jerez LB, Gbureck U, et al. The effect of hyaluronic acid on brushite cement cohesion. Acta Biomater 2009;5:3150–6.
[33] Kai D, Li DX, Zhu XD, Zhang L, Fan HS, Zhang XD. Addition of sodium hyaluronate and the effect on performance of the injectable calcium phosphate cement. J Mater Sci-Mater M 2009;20:1595–602.
[34] Bigi A, Bracci B, Panzavolta S. Effect of added gelatin on the properties of calcium phosphate cement. Biomaterials 2004;25:2893–9.
[35] Montufar EB, Traykova T, Planell JA, Ginebra MP. Comparison of a low molecular weight and a macromolecular surfactant as foaming agents for injectable self setting hydroxyapatite foams: polysorbate 80 versus gelatine. Mater Sci Eng C Mater Biol Appl 2011;31:1498–504.
[36] Tamimi-Marino F, Mastio J, Rueda C, Blanco L, Lopez-Cabarcos E. Increase of the final setting time of brushite cements by using chondroitin 4-sulfate and silica gel. J Mater Sci-Mater M 2007;18:1195–201.
[37] Tanaka S, Kishi T, Shimogoryo R, Matsuya S, Ishikawa K. Biopex((r)) acquires anti-washout properties by adding sodium alginate into its liquid phase. Dent Mater J 2003;22:301–12.
[38] Barralet JE, Tremayne M, Lilley KJ, Gbureck U. Modification of calcium phosphate cement with α-hydroxy acids and their salts. Chem Mater 2005;17:1313–9.
[39] Sarda S, Fernandez E, Nilsson M, Balcells M, Planell JA. Kinetic study of citric acid influence on calcium phosphate bone cements as water-reducing agent. J Biomed Mater Res 2002;61:653–9.
[40] Bohner M. Reactivity of calcium phosphate cements. J Mater Chem 2007;17:3980–6.
[41] Dorozhkin SV. Calcium orthophosphate cements for biomedical application. J Mater Sci 2008;43:3028–57.
[42] Vereecke G, Lemaître J. Calculation of the solubility diagrams in the system $Ca(OH)_2$–H_3PO_4–KOH–HNO_3–CO_2–H_2O. J Cryst Growth 1990;104:820–32.
[43] Ginebra MP, Canal C, Espanol M, Pastorino D, Montufar EB. Calcium phosphate cements as drug delivery materials. Adv Drug Deliv Rev 2012;64:1090–110.
[44] Khairoun I, Magne D, Gauthier O, Bouler JM, Aguado E, Daculsi G, et al. In vitro characterization and in vivo properties of a carbonated apatite bone cement. J Biomed Mater Res 2002;60:633–42.
[45] Lewis G. Injectable bone cements for use in vertebroplasty and kyphoplasty: state-of-the-art review. J Biomed Mater Res 2006;76B:456–68.
[46] Ormsby R, McNally T, Mitchell C, Dunne N. Incorporation of multiwalled carbon nanotubes to acrylic based bone cements: effects on mechanical and thermal properties. J Mech Behav Biomed Mater 2010;3:136–45.
[47] Bohner M. Physical and chemical aspects of calcium phosphates used in spinal surgery. Eur Spine J 2001;10:S114–21.
[48] Verron E, Khairoun I, Guicheux J, Bouler JM. Calcium phosphate biomaterials as bone drug delivery systems: a review. Drug Discov Today 2010;15:547–52.
[49] Verron E, Bouler JM, Guicheux J. Controlling the biological function of calcium phosphate bone substitutes with drugs. Acta Biomater 2012;8:3541–51.
[50] Espanol M, Perez RA, Montufar EB, Marichal C, Sacco A, Ginebra MP. Intrinsic porosity of calcium phosphate cements and its significance for drug delivery and tissue engineering applications. Acta Biomater 2009;5:2752–62.
[51] Gauthier O, Bouler JM, Aguado E, Pilet P, Daculsi G. Macroporous biphasic calcium phosphate ceramics: influence of macropore diameter and macroporosity percentage on bone ingrowth. Biomaterials 1998;19:133–9.
[52] von Doernberg MC, von Rechenberg B, Bohner M, Grunenfelder S, van Lenthe GH, Muller R, et al. In vivo behavior of calcium phosphate scaffolds with four different pore sizes. Biomaterials 2006;27:5186–98.
[53] Bohner M, Baroud G. Injectability of calcium phosphate pastes. Biomaterials 2005;26:1553–63.
[54] Habib M, Baroud G, Gitzhofer F, Bohner M. Mechanisms underlying the limited injectability of hydraulic calcium phosphate paste. Acta Biomater 2008;4:1465–71.
[55] Khairoun I, Driessens F, Boltong MG, Planell JA, Wenz R. Addition of cohesion promoters to calcium phosphate cements. Biomaterials 1999;20:393–8.
[56] Canal C, Ginebra MP. Fibre-reinforced calcium phosphate cements: a review. J Mech Behav Biomed Mater 2011;4:1658–71.
[57] Kruger R, Groll J. Fiber reinforced calcium phosphate cements – on the way to degradable load bearing bone substitutes? Biomaterials 2012;33:5887–900.
[58] Chow LC. Next generation calcium phosphate-based biomaterials. Dent Mater J 2009;28:1–10.
[59] Fernandez E, Gil FJ, Ginebra MP, Driessens F, Planell JA, Best SM. Calcium phosphate bone cements for clinical applications. Part I. Solution chemistry. J Mater Sci-Mater M 1999;10:169–76.
[60] Chen WC, Lin JH, Ju CP. Transmission electron microscopic study on setting mechanism of tetracalcium phosphate/dicalcium phosphate anhydrous-based calcium phosphate cement. J Biomed Mater Res A 2003;64:664–71.
[61] Durucan C, Brown PW. Kinetic model for α-tricalcium phosphate hydrolysis. J Am Ceram Soc 2002;85:2013–8.
[62] Ginebra MP, Driessens F, Planell JA. Effect of the particle size on the micro and nanostructural features of a calcium phosphate cement: a kinetic analysis. Biomaterials 2004;25:3453–62.
[63] Brunner TJ, Grass RN, Bohner M, Stark WJ. Effect of particle size, crystal phase and crystallinity on the reactivity of tricalcium phosphate cements for bone reconstruction. J Mater Chem 2007;17:4072–8.
[64] Bohner M, Brunner TJ, Stark WJ. Controlling the reactivity of calcium phosphate cements. J Mater Chem 2008;18:5669–75.
[65] Gbureck U, Barralet JE, Radu L, Klinger HG, Thull R. Amorphous α-tricalcium phosphate: preparation and aqueous setting reaction. J Am Ceram Soc 2004;87:1126–32.
[66] Camire CL, Gbureck U, Hirsiger W, Bohner M. Correlating crystallinity and reactivity in an α-tricalcium phosphate. Biomaterials 2005;26:2787–94.
[67] Brunner TJ, Bohner M, Dora C, Gerber C, Stark WJ. Comparison of amorphous TCP nanoparticles to micron-sized α-TCP as starting materials for calcium phosphate cements. J Biomed Mater Res 2007;83B:400–7.
[68] Ginebra MP, Fernandez E, Driessens F, Boltong MG, Muntasell J, Font J, et al. The effects of temperature on the behaviour of an apatitic calcium phosphate cement. J Mater Sci-Mater M 1995;6:857–60.
[69] TenHuisen KS, Brown PW. Formation of calcium-deficient hydroxyapatite from α-tricalcium phosphate. Biomaterials 1998;19:2209–17.
[70] Durucan C, Brown PW. -tricalcium phosphate hydrolysis to hydroxyapatite at and near physiological temperature. J Mater Sci-Mater M 2000;11:365–71.
[71] TenHuisen KS, Brown PW. The effects of citric and acetic-acids on the formation of calcium-deficient hydroxyapatite at 38 °C. J Mater Sci-Mater M 1994;5:291–8.
[72] TenHuisen KS, Brown PW. Hydrolysis of α-tricalcium phosphate in NaF solutions. Biomaterials 1999;20:427–34.
[73] Durucan C, Brown PW. Reactivity of α-tricalcium phosphate. J Mater Sci 2002;37:963–9.
[74] Fernandez E, Ginebra MP, Boltong MG, Driessens F, Ginebra J, DeMaeyer E, et al. Kinetic study of the setting reaction of a calcium phosphate bone cement. J Biomed Mater Res 1996;32:367–74.
[75] Ginebra MP, Fernandez E, DeMaeyer E, Verbeeck R, Boltong MG, Ginebra J, et al. Setting reaction and hardening of an apatitic calcium phosphate cement. J Dent Res 1997;76:905–12.
[76] Ginebra MP, Fernandez E, Driessens F, Planell JA. Modeling of the hydrolysis of α-tricalcium phosphate. J Am Ceram Soc 1999;82:2808–12.
[77] Bohner M, Malsy AK, Camire CL, Gbureck U. Combining particle size distribution and isothermal calorimetry data to determine the reaction kinetics of α-tricalcium phosphate–water mixtures. Acta Biomater 2006;2:343–8.
[78] Bohner M, Luginbuhl R, Reber C, Doebelin N, Baroud G, Conforto E. A physical approach to modify the hydraulic reactivity of α-tricalcium phosphate powder. Acta Biomater 2009;5:3524–35.
[79] Schnitzler V, Fayon F, Despas C, Khairoun I, Mellier C, Rouillon T, et al. Investigation of alendronate-doped apatitic cements as a potential technology for the prevention of osteoporotic hip fractures: critical influence of the drug introduction mode on the in vitro cement properties. Acta Biomater 2011;7:759–70.
[80] Despas C, Schnitzler V, Janvier P, Fayon F, Massiot D, Bouler JM, Bujoli B, Walcarius A. High frequency impedance measurement as a relevant tool to monitor apatitic cement setting reaction. Acta Biomater 2014;10:940–50.
[81] Liu CS, Shen W. Effect of crystal seeding on the hydration of calcium phosphate cement. J Mater Sci-Mater M 1997;8:803–7.
[82] Liu CS, Huang Y, Zheng HY. Study of the hydration process of calcium phosphate cement by ac impedance spectroscopy. J Am Ceram Soc 1999;82:1052–7.
[83] Hofmann MP, Young AM, Gbureck U, Nazhat SN, Barralet JE. FTIR-monitoring of a fast setting brushite bone cement: effect of intermediate phases. J Mater Chem 2006;16:3199–206.
[84] Tadier S, Le Bolay N, Rey C, Combes C. Co-grinding significance for calcium carbonate-calcium phosphate mixed cement. Part I. Effect of particle size and mixing on solid phase reactivity. Acta Biomater 2011;7:1817–26.
[85] Liu CS, Shao HF, Chen FY, Zheng HY. Rheological properties of concentrated aqueous injectable calcium phosphate cement slurry. Biomaterials 2006;27:5003–13.
[86] Bohner M, Doebelin N, Baroud G. Theoretical and experimental approach to test the cohesion of calcium phosphate pastes. Eur Cell Mater 2006;12:26–35.
[87] Perez RA, Kim H, Ginebra M. Polymeric additives to enhance the functional properties of calcium phosphate cements. J Tissue Eng 2012;3:204–8.
[88] Ueyama Y, Ishikawa K, Mano T, Koyama T, Nagatsuka H, Matsumura T, et al. Initial tissue response to anti-washout apatite cement in the rat palatal region: comparison with conventional apatite cement. J Biomed Mater Res 2001;55:652–60.
[89] Bernards CM, Chapman JR, Mirza SK. Lethality of embolized norian bone cement varies with the time between mixing and embolization. In:

Proceedingz of the 50th annual meeting of the orthopaedic research society (ORS), San Francisco, USA, 2004, p. 254.
[90] ASTM. Standard test method for time of setting of hydraulic-cement paste by Gillmore needles. ASTM C266–08, 2008.
[91] Driessens F, Boltong MG, Bermudez O, Planell JA, Ginebra MP, Fernandez E. Effectvie formulations for the preparation of calcium-phosphate bone cements. J Mater Sci-Mater M 1994;5:164–70.
[92] Driessens F, Planell JA, Boltong MG, Khairoun I, Ginebra MP. Osteotransductive bone cements. Proc Inst Mech Eng [H] 1998;212:427–35.
[93] Cherng A, Takagi S, Chow LC. Effects of hydroxypropyl methylcellulose and other gelling agents on the handling properties of calcium phosphate cement. J Biomed Mater Res 1997;35:273–7.
[94] Liu W, Zhang J, Weiss P, Tancret F, Bouler JM. The influence of different cellulose ethers on both the handling and mechanical properties of calcium phosphate cements for bone substitution. Acta Biomater 2013;9:5740–50.
[95] Liu H, Li H, Cheng W, Yang Y, Zhu M, Zhou C. Novel injectable calcium phosphate/chitosan composites for bone substitute materials. Acta Biomater 2006;2:557–65.
[96] Takagi S, Chow LC, Hirayama S, Eichmiller FC. Properties of elastomeric calcium phosphate cement–chitosan composites. Dent Mater 2003;19:797–804.
[97] Wang XP, Chen L, Xiang H, Ye JD. Influence of anti-washout agents on the rheological properties and injectability of a calcium phosphate cement. J Biomed Mater Res 2007;81B:410–8.
[98] Habib M, Baroud G, Galea L, Bohner M. Evaluation of the ultrasonication process for injectability of hydraulic calcium phosphate pastes. Acta Biomater 2012;8:1164–8.
[99] Burguera EF, Xu H, Sun LM. Injectable calcium phosphate cement: effects of powder-to-liquid ratio and needle size. J Biomed Mater Res 2008;84B:493–502.
[100] Khairoun I, Boltong MG, Driessens F, Planell JA. Some factors controlling the injectability of calcium phosphate bone cements. J Mater Sci-Mater M 1998;9:425–8.
[101] Ishikawa K. Effects of spherical tetracalcium phosphate on injectability and basic properties of apatitic cement. Key Eng Mater 2003;240–242:369–72.
[102] Andrianjatovo H, Lemaitre J. Effects of polysaccharides on the cement properties in the monocalcium phosphate β-tricalcium phosphate system. Innovation et technologie en biologie et medecine 1995;16:140–7.
[103] Burguera EF, Xu H, Weir MD. Injectable and rapid-setting calcium phosphate bone cement with dicalcium phosphate dihydrate. J Biomed Mater Res 2006;77B:126–34.
[104] Saint-Jean SJ, Camire CL, Nevsten P, Hansen S, Ginebra MP. Study of the reactivity and in vitro bioactivity of Sr-substituted α-TCP cements. J Mater Sci-Mater M 2005;16:993–1001.
[105] Almirall A, Larrecq G, Delgado JA, Martinez S, Planell JA, Ginebra MP. Fabrication of low temperature macroporous hydroxyapatite scaffolds by foaming and hydrolysis of an α-TCP paste. Biomaterials 2004;25:3671–80.
[106] Zhang JT, Tancret F, Bouler JM. Fabrication and mechanical properties of calcium phosphate cements (CPC) for bone substitution. Mater Sci Eng C Mater Biol Appl 2011;31:740–7.
[107] Del Real RP, Wolke J, Vallet-Regi M, Jansen JA. A new method to produce macropores in calcium phosphate cements. Biomaterials 2002;23:3673–80.
[108] Gbureck U, Grolms O, Barralet JE, Grover LM, Thull R. Mechanical activation and cement formation of β-tricalcium phosphate. Biomaterials 2003;24:4123–31.
[109] Barralet JE, Gaunt T, Wright AJ, Gibson IR, Knowles JC. Effect of porosity reduction by compaction on compressive strength and microstructure of calcium phosphate cement. J Biomed Mater Res 2002;63:1–9.
[110] Liu CS, Shao HF, Chen FY, Zheng HY. Effects of the granularity of raw materials on the hydration and hardening process of calcium phosphate cement. Biomaterials 2003;24:4103–13.
[111] Chow LC, Hirayama S, Takagi S, Parry E. Diametral tensile strength and compressive strength of a calcium phosphate cement: effect of applied pressure. J Biomed Mater Res 2000;53:511–7.
[112] Martin RI, Brown PW. Mechanical properties of hydroxyapatite formed at physiological temperature. J Mater Sci Mater Med 1995;6:138–43.
[113] Fukase Y, Eanes ED, Takagi S, Chow LC, Brown WE. Setting reactions and compressive strengths of calcium phosphate cements. J Dent Res 1990;69:1852–6.
[114] Ishikawa K, Takagi S, Chow LC, Suzuki K, Ishikawa Y. Properties and mechanisms of fast-setting calcium-phosphate cements. J Mater Sci-Mater M 1995;6:528–33.
[115] Yamamoto H, Niwa S, Hori M, Hattori T, Sawai K, Aoki S, et al. Mechanical strength of calcium phosphate cement in vivo and in vitro. Biomaterials 1998;19:1587–91.
[116] Calafiori AR, Di Marco G, Martino G, Marotta M. Preparation and characterization of calcium phosphate biomaterials. J Mater Sci-Mater M 2007;18:2331–8.
[117] Yang QZ, Troczynski T, Liu DM. Influence of apatite seeds on the synthesis of calcium phosphate cement. Biomaterials 2002;23:2751–60.
[118] Morgan EF, Yetkinler DN, Constantz BR, Dauskardt RH. Mechanical properties of carbonated apatite bone mineral substitute: strength, fracture and fatigue behaviour. J Mater Sci-Mater M 1997;8:559–70.
[119] Charriere E, Terrazzoni S, Pittet C, Mordasini P, Dutoit M, Lemaitre J, et al. Mechanical characterization of brushite and hydroxyapatite cements. Biomaterials 2001;22:2937–45.
[120] Pittet C, Lemaitre J. Mechanical characterization of brushite cements: a Mohr circles' approach. J Biomed Mater Res 2000;53:769–80.
[121] Montufar EB, Traykova T, Gil C, Harr I, Almirall A, Aguirre A, et al. Foamed surfactant solution as a template for self-setting injectable hydroxyapatite scaffolds for bone regeneration. Acta Biomater 2010;6:876–85.
[122] Ginebra M, Delgado J, Harr I, Almirall A, Del Valle S, Planell JA. Factors affecting the structure and properties of an injectable self-setting calcium phosphate foam. J Biomed Mater Res A 2007;80A:351–61.
[123] Ginebra MP, Rilliard A, Fernandez E, Elvira C, San Roman J, Planell JA. Mechanical and rheological improvement of a calcium phosphate cement by the addition of a polymeric drug. J Biomed Mater Res 2001;57:113–8.
[124] Fernandez E, Gil FJ, Best SM, Ginebra MP, Driessens FCM, Planell JA. Improvement of the mechanical properties of new calcium phosphate bone cements in the $CaHPO_4$–α-$Ca_3(PO_4)_2$ system: compressive strength and microstructural development. J Biomed Mater Res 1998;41:560–7.
[125] Weir MD, Xu HHK. Osteoblastic induction on calcium phosphate cement–chitosan constructs for bone tissue engineering. J Biomed Mater Res A 2010;94:223–33.
[126] Gbureck U, Barralet JE, Spatz K, Grover LM, Thull R. Ionic modification of calcium phosphate cement viscosity. Part I. Hypodermic injection and strength improvement of apatite cement. Biomaterials 2004;25:2187–95.
[127] Barralet JE, Hofmann M, Grover LM, Gbureck U. High-strength apatitic cement by modification with α-hydroxy acid salts. Adv Mater 2003;15:2091–4.
[128] Hofmann MP, Mohammed AR, Perrie Y, Gbureck U, Barralet JE. High-strength resorbable brushite bone cement with controlled drug-releasing capabilities. Acta Biomater 2009;5:43–9.
[129] Barralet JE, Grover LM, Gbureck U. Ionic modification of calcium phosphate cement viscosity. Part II. Hypodermic injection and strength improvement of brushite cement. Biomaterials 2004;25:2197–203.
[130] Zhang JT. Fabrication et propriétiés mécaniques de ciments phosphocalciques poreux pour la substitution osseuse. [PhD thesis]. Université de Nantes, 2012.
[131] Bai F, Meng GL, Yuan YA, Liu CS, Wang Z, Liu JA. Role of macropore size in the mechanical properties and in vitro degradation of porous calcium phosphate cements. Mater Lett 2010;64:2028–31.
[132] Guo H, Su JC, Wei J, Kong H, Liu CS. Biocompatibility and osteogenicity of degradable Ca-deficient hydroxyapatite scaffolds from calcium phosphate cement for bone tissue engineering. Acta Biomater 2009;5:268–78.
[133] Barralet JE, Grover L, Gaunt T, Wright AJ, Gibson IR. Preparation of macroporous calcium phosphate cement tissue engineering scaffold. Biomaterials 2002;23:3063–72.
[134] Takagi S, Chow LC. Formation of macropores in calcium phosphate cement implants. J Mater Sci-Mater M 2001;12:135–9.
[135] Li M, Liu XY, Liu XD, Ge BF, Chen KM. Creation of macroporous calcium phosphate cements as bone substitutes by using genipin-crosslinked gelatin microspheres. J Mater Sci-Mater M 2009;20:925–34.
[136] Qi XP, Ye JD. Mechanical and rheological properties and injectability of calcium phosphate cement containing poly (lactic-co-glycolic acid) microspheres. Mater Sci Eng C Mater Biol Appl 2009;29:1901–6.
[137] Lopez-Heredia MA, Sariibrahimoglu K, Yang W, Bohner M, Yamashita D, Kunstar A, et al. Influence of the pore generator on the evolution of the mechanical properties and the porosity and interconnectivity of a calcium phosphate cement. Acta Biomater 2012;8:404–14.
[138] Habraken W, Zhang Z, Wolke J, Grijpma DW, Mikos AG, Feijen J, et al. Introduction of enzymatically degradable poly(trimethylene carbonate) microspheres into an injectable calcium phosphate cement. Biomaterials 2008;29:2464–76.
[139] Dos Santos LA, de Oliveira LC, Rigo E, Carrodeguas RG, Boschi AO, de Arruda A. Fiber reinforced calcium phosphate cement. Artif Organs 2000;24:212–6.
[140] Muller FA, Gbureck U, Kasuga T, Mizutani Y, Barralet JE, Lohbauer U. Whisker-reinforced calcium phosphate cements. J Am Ceram Soc 2007;90:3694–7.
[141] Guo DG, Sun HL, Xu KW, Han Y. Long-term variations in mechanical properties and in vivo degradability of CPC/PLGA composite. J Biomed Mater Res 2007;82B:533–44.
[142] Xu H, Eichmiller FC, Giuseppetti AA. Reinforcement of a self-setting calcium phosphate cement with different fibers. J Biomed Mater Res 2000;52:107–14.
[143] Nezafati N, Moztarzadeh F, Hesaraki S, Mozafari M. Synergistically reinforcement of a self-setting calcium phosphate cement with bioactive glass fibers. Ceram Int 2011;37:927–34.
[144] Wang X, Ye J, Wang Y, Chen L. Reinforcement of calcium phosphate cement by bio-mineralized carbon nanotube. J Am Ceram Soc 2007;90:962–4.
[145] Zuo Y, Yang F, Wolke J, Li YB, Jansen JA. Incorporation of biodegradable electrospun fibers into calcium phosphate cement for bone regeneration. Acta Biomater 2010;6:1238–47.
[146] Xu H, Quinn JB, Takagi S, Chow LC, Eichmiller FC. Strong and macroporous calcium phosphate cement: effects of porosity and fiber reinforcement on mechanical properties. J Biomed Mater Res 2001;57:457–66.
[147] Chew KK, Low KL, Zein S, McPhail DS, Gerhardt LC, Roether JA, et al. Reinforcement of calcium phosphate cement with multi-walled carbon nanotubes and bovine serum albumin for injectable bone substitute applications. J Mech Behav Biomed Mater 2011;4:331–9.
[148] Qi XP, Ye JD, Wang YJ. Improved injectability and in vitro degradation of a calcium phosphate cement containing poly(lactide-co-glycolide) microspheres. Acta Biomater 2008;4:1837–45.
[149] Zhang Y, Xu H, Takagi S, Chow LC. In situ hardening hydroxyapatite-based scaffold for bone repair. J Mater Sci-Mater M 2006;17:437–45.

[150] Chen WC, Zhou HZ, Tang MH, Weir MD, Bao CY, Xu H. Gas-foaming calcium phosphate cement scaffold encapsulating human umbilical cord stem cells. Tissue Eng Part A 2012;18:816–27.
[151] Cama G, Barberis F, Botter R, Cirillo P, Capurro M, Quarto R, et al. Preparation and properties of macroporous brushite bone cements. Acta Biomater 2009;5:2161–8.
[152] O'Hara RM, Orr JF, Buchanan FJ, Wilcox RK, Barton DC, Dunne NJ. Development of a bovine collagen–apatitic calcium phosphate cement for potential fracture treatment through vertebroplasty. Acta Biomater 2012;8:4043–52.
[153] Morgan JP, Dauskardt RH. Notch strength insensitivity of self-setting hydroxyapatite bone cements. J Mater Sci-Mater M 2003;14:647–53.
[154] Félix Lanao RP, Leeuwenburgh SCG, Wolke JGC, Jansen JA. In vitro degradation rate of apatitic calcium phosphate cement with incorporated PLGA microspheres. Acta Biomater 2011;7:3459–68.
[155] Habraken WJEM, Liao HB, Zhang Z, Wolke JGC, Grijpma DW, Mikos AG, et al. In vivo degradation of calcium phosphate cement incorporated into biodegradable microspheres. Acta Biomater 2010;6:2200–11.
[156] Link DP, van den Dolder J, van den Beucken JJ, Habraken W, Soede A, Boerman OC, et al. Evaluation of an orthotopically implanted calcium phosphate cement containing gelatin microparticles. J Biomed Mater Res A 2009;90:372–9.
[157] Klijn RJ, van den Beucken J, Lanao R, Veldhuis G, Leeuwenburgh SC, Wolke J, et al. Three different strategies to obtain porous calcium phosphate cements: comparison of performance in a rat skull bone augmentation model. Tissue Eng Part A 2012;18:1171–82.
[158] Hesaraki S, Moztarzadeh F, Sharifi D. Formation of interconnected macropores in apatitic calcium phosphate bone cement with the use of an effervescent additive. J Biomed Mater Res A 2007;83A:80–7.
[159] Ashby MF, Jones DRH. Engineering materials. 1. An introduction to properties, applications and design. Oxford: Butterworth-Heinemann; 2011.
[160] Wagoner-Johnson A, Herschler BA. A review of the mechanical behavior of CaP and CaP/polymer composites for applications in bone replacement and repair. Acta Biomater 2011;7:16–30.
[161] Tancret F, Bouler JM, Chamousset J, Minois LM. Modelling the mechanical properties of microporous and macroporous biphasic calcium phosphate bioceramics. J Eur Ceram Soc 2006;26:3647–56.
[162] Pecqueux F, Tancret F, Payraudeau N, Bouler JM. Influence of microporosity and macroporosity on the mechanical properties of biphasic calcium phosphate bioceramics: modelling and experiment. J Eur Ceram Soc 2010;30:819–29.
[163] Fu Q, Saiz E, Rahaman MN, Tomsia AP. Bioactive glass scaffolds for bone tissue engineering: state of the art and future perspectives. Mater Sci Eng C Mater Biol Appl 2011;31:1245–56.
[164] Wagh AS, Singh JP, Poeppel RB. Dependence of ceramic fracture properties on porosity. J Mater Sci 1993;28:3589–93.
[165] Liu DM. Influence of porosity and pore size on the compressive strength of porous hydroxyapatite ceramic. Ceram Int 1997;23:135–9.
[166] Griffith AA. The phenomenon of rupture and flow in solids. Philos Trans R Soc Lond A 1921;221:163–98.
[167] Otsuka M, Matsuda Y, Suwa Y, Fox JL, Higuchi WI. Effect of particle size of metastable calcium phosphates on mechanical strength of a novel self-setting bioactive calcium phosphate cement. J Biomed Mater Res 1995;29:25–32.
[168] Bermudez O, Boltong MG, Driessens FCM, Planell JA. Compressive strength and diametral tensile-strength of some calcium-orthophosphate cements – a pilot-study. J Mater Sci-Mater M 1993;4:389–93.
[169] Bermudez O, Boltong MG, Driessens FCM, Planell JA. Development of some calcium-phosphate cements from combinations of α-TCP, MCPM and CaO. J Mater Sci-Mater M 1994;5:160–3.
[170] Brown PW, Fulmer M. Kinetics of hydroxyapatite formation at low temperature. J Am Ceram Soc 1991;74:934–40.
[171] Liu CS, Shen W, Gu YF, Hu LM. Mechanism of the hardening process for a hydroxyapatite cement. J Biomed Mater Res 1997;35:75–80.
[172] Fernandez E, Boltong MG, Ginebra MP, Bermudez O, Driessens FCM, Planell JA. Common ion effect on some calcium phosphate cements. Clin Mater 1994;16:99–103.
[173] Khairoun I, Boltong MG, Driessens FCM, Planell JA. Effect of calcium carbonate on clinical compliance of apatitic calcium phosphate bone cement. J Biomed Mater Res 1997;38:356–60.
[174] Bohner M, Merkle HP, Landuyt PV, Trophardy G, Lemaitre J. Effect of several additives and their admixtures on the physico-chemical properties of a calcium phosphate cement. J Mater Sci-Mater M 2000;11:111–6.
[175] Marino FT, Torres J, Hamdan M, Rodriguez CR, Cabarcos EL. Advantages of using glycolic acid as a retardant in a brushite forming cement. J Biomed Mater Res 2007;83B:571–9.
[176] Lilley KJ, Gbureck U, Knowles JC, Farrar DF, Barralet JE. Cement from magnesium substituted hydroxyapatite. J Mater Sci-Mater M 2005;16:455–60.
[177] Munz D, Fett D. Ceramics: mechanical properties, failure behavior, materials selection. Springer; 2001.
[178] Munz D. What can we learn from r-curve measurements? J Am Ceram Soc 2007;90:1–15.
[179] Ritchie RO. The conflicts between strength and toughness. Nat Mater 2011;10:817–22.
[180] Launey ME, Ritchie RO. On the fracture toughness of advanced materials. Adv Mater 2009;21:2103–10.
[181] Ritchie RO, Koester KJ, Ionova S, Yao W, Lane NE, Ager JW. Measurement of the toughness of bone: a tutorial with special reference to small animal studies. Bone 2008;43:798–812.
[182] Tattersall HG, Tappin G. The work of fracture and its measurement in metals, ceramics and other materials. J Mater Sci 1966;1:296–301.
[183] Weibull W. A statistical theory of the strength of materials. Ingeniörs Vetenskaps Akademiens–Handlingar 1939;151:1–45.
[184] Weibull W. A statistical distribution function of wide applicability. J Appl Mech 1951;18:293–305.
[185] Davies DGS. The statistical approach to engineering design in ceramics. Proc Br Ceram Soc 1973;22:429–52.
[186] Karageorgiou V, Kaplan D. Porosity of 3D biornaterial scaffolds and osteogenesis. Biomaterials 2005;26:5474–91.
[187] Fan X, Case ED, Ren F, Shu Y, Baumann MJ. Part i: porosity dependence of the weibull modulus for hydroxyapatite and other brittle materials. J Mech Behav Biomed Mater 2012;8:21–36.
[188] Martinez-Vazquez FJ, Perera FH, Miranda P, Pajares A, Guiberteau F. Improving the compressive strength of bioceramic robocast scaffolds by polymer infiltration. Acta Biomater 2010;6:4361–8.
[189] Cordell JM, Vogl ML, Johnson A. The influence of micropore size on the mechanical properties of bulk hydroxyapatite and hydroxyapatite scaffolds. J Mech Behav Biomed Mater 2009;2:560–70.
[190] Fleming G, Farooq AA, Barralet JE. Influence of powder/liquid mixing ratio on the performance of a restorative glass-ionomer dental cement. Biomaterials 2003;24:4173–9.
[191] Dowling AH, Fleming GJP. Is encapsulation of posterior glass-ionomer restoratives the solution to clinically induced variability introduced on mixing? Dent Mater 2008;24:957–66.
[192] Ishikawa K, Asaoka K. Estimation of ideal mechanical strength and critical porosity of calcium-phosphate cement. J Biomed Mater Res 1995;29:1537–43.
[193] Leeuwenburgh SC, Ana ID, Jansen JA. Sodium citrate as an effective dispersant for the synthesis of inorganic–organic composites with a nanodispersed mineral phase. Acta Biomater 2010;6:836–44.
[194] Yokoyama A, Yamamoto S, Kawasaki T, Kohgo T, Nakasu M. Development of calcium phosphate cement using chitosan and citric acid for bone substitute materials. Biomaterials 2002;23:1091–101.
[195] Beaudoin JJ. Handbook of fiber-reinforced concrete: principles, properties, developments and applications. Park Ridge, NJ: Noyes Publications; 1990.
[196] Burguera EF, Xu H, Takagi S, Chow LC. High early strength calcium phosphate bone cement: effects of dicalcium phosphate dihydrate and absorbable fibers. J Biomed Mater Res A 2005;75A:966–75.
[197] Gorst N, Perrie Y, Gbureck U, Hutton AL, Hofmann MP, Grover LM, et al. Effects of fibre reinforcement on the mechanical properties of brushite cement. Acta Biomater 2006;2:95–102.
[198] Xu H, Quinn JB. Calcium phosphate cement containing resorbable fibers for short-term reinforcement and macroporosity. Biomaterials 2002;23:193–202.
[199] Xu H, Simon CG. Self-hardening calcium phosphate cement-mesh composite: reinforcement, macropores, and cell response. J Biomed Mater Res A 2004;69A:267–78.
[200] Lian Q, Li DC, He JK, Wang Z. Mechanical properties and in-vivo performance of calcium phosphate cement–chitosan fibre composite. Proc Inst Mech Eng [H] 2008;222:347–53.
[201] Lahiri D, Ghosh S, Agarwal A. Carbon nanotube reinforced hydroxyapatite composite for orthopedic application: a review. Mater Sci Eng C Mater Biol Appl 2012;32:1727–58.
[202] Kruger R, Seitz JM, Ewald A, Bach FW, Groll J. Strong and tough magnesium wire reinforced phosphate cement composites for load-bearing bone replacement. J Mech Behav Biomed Mater 2013;20:36–44.
[203] Xu H, Burguera EF, Carey LE. Strong, macroporous, and in situ-setting calcium phosphate cement-layered structures. Biomaterials 2007;28:3786–96.
[204] Zhang Y, Xu H. Effects of synergistic reinforcement and absorbable fiber strength on hydroxyapatite bone cement. J Biomed Mater Res A 2005;75A:832–40.
[205] Xu H, Weir MD, Burguera EF, Fraser AM. Injectable and macroporous calcium phosphate cement scaffold. Biomaterials 2006;27:4279–87.
[206] Weir MD, Xu HHK. Human bone marrow stem cell-encapsulating calcium phosphate scaffolds for bone repair. Acta Biomater 2010;6:4118–26.
[207] Zhao L, Weir MD, Xu H. Human umbilical cord stem cell encapsulation in calcium phosphate scaffolds for bone engineering. Biomaterials 2010;31:3848–57.
[208] Chen WC, Zhou HZ, Weir MD, Bao CY, Xu H. Umbilical cord stem cells released from alginate–fibrin microbeads inside macroporous and biofunctionalized calcium phosphate cement for bone regeneration. Acta Biomater 2012;8:2297–306.
[209] Gisep A, Kugler S, Wahl D, Rahn B. Mechanical characterisation of a bone defect model filled with ceramic cements. J Mater Sci-Mater M 2004;15:1065–71.