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Leading Opinion

Technological issues for the development of more efficient calcium phosphate bone cements: A critical assessment ☆

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Abstract

The first calcium phosphate cements (CPCs) were discovered in the 1980s. Two decades later, the interest for these materials is still rising. The goal of the present document is to review the most recent achievements in the field and to analyze future directions in research and development.

Keywords: Calcium phosphate cement; Vertebroplasty; Delivery; In vivo

1. Introduction

Calcium phosphate cements (CPCs) are obtained by mixing one or several reactive calcium phosphate powders with an aqueous solution to form a paste that hardens within a restricted period of time (e.g. 15 min). In that respect, CPCs are different from traditionally used bone substitutes such as granules and blocks which are not in a paste form and do not sustain a rapid phase transition.

CPCs were proposed 2 decades ago by LeGeros et al. [1], and Brown and Chow [2]. The first commercial CPC products were introduced a decade ago for the treatment of maxillo-facial defects and deformities [3] as well as for the treatment of fracture defects [4]. Now, companies are introducing second-generation cements and are also widening their portfolio to fulfil the various requirements of their customers (Table 1). For example, brushite cements which have proved to be faster resorbing than apatite cements in animal studies [5] have entered the clinics. Other cements are designed for one very specific application, i.e. cranioplasty or vertebroplasty.

These achievements have been possible due to the considerable effort and large number of studies devoted to CPCs. In fact, a few thousand papers have been published so far and the publication rate increases almost every year (Fig 1). The goal of the present article is not to review most of the literature as has been done by several authors in the past [6–9], but to give a brief overview of the present achievements and to pinpoint newest developments and trends.

2. Brief overview

Many discoveries and developments made in the field of CPCs stem from calcium silicate and sulphate-based cements in the construction industry or from

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Table 1
List of commercial calcium phosphate cements with their composition (when available)

Company	Cement name	Components	End-product
ETEX	α-BSM Embarc Biobon	*Powder*: ACP (50%), DCPD (50%) *Solution*: H_2O (unbuffered saline solution) [46,47]	Apatite
Stryker-Leibinger Corp.	BoneSource	*Powder*: TetCP (73%), DCP (27%) *Solution*: H_2O, mixture of Na_2HPO_4 and NaH_2PO_4 [48,49]	Apatite
Teknimed	Cementek®	*Powder*: α-TCP, TetCP, Na Glycerophosphate *Solution*: H_2O, $Ca(OH)_2$, H_3PO_4 [50]	Apatite
	Cementek® LV	*Powder*: α-TCP, TetCP, Na Glycerophosphate, dimethylsiloxane *Solution*: H_2O, $Ca(OH)_2$, H_3PO_4 [50]	Apatite
Biomet	Calcibon® (previously called "Biocement D")	*Powder*: α-TCP (61%), DCP (26%), $CaCO_3$ (10%), PHA (3%) *Solution*: H_2O, Na_2HPO_4 [51]	Apatite
	Mimix™	*Powder*: TetCP, α-TCP, $C_6H_5O_7Na_3 \cdot 2H_2O$ *Solution*: H_2O, $C_6H_8O_7$	Apatite
	QuickSet Mimix™	*Powder*: nf[a] *Solution*: nf[a]	Apatite
Mitsubishi materials	Biopex®	*Powder*: α-TCP (75%), TetCP (20–18%), DCPD (5%), HA (0–2%) *Solution*: H_2O, sodium succinate (12–13%), sodium chondroitin sulphate (5–5.4%) (when two values are indicated, the first value stems from Ref. [52] and the second value from Ref. [53])	Apatite
	Biopex®-R	*Powder*: α-TCP, TetCP, DCPD, HA, $Mg_3(PO_4)_2$, $NaHSO_3$ *Solution*: H_2O, sodium succinate, sodium chondroitin sulphate [53]	Apatite
Kyphon	KyphOs™	*Powder*: α-TCP (77%), $Mg_3(PO_4)_2$ (14%), $MgHPO_4$ (4.8%), $SrCO_3$ (3.6%) *Solution*: H_2O, $(NH_4)_2HPO_4$ (3.5 M) [54]	Apatite
Skeletal Kinetics	Callos™ [55]	*Powder*: nf[a] *Solution*: nf[a]	Apatite
Shanghai Rebone Biomaterials Co, Ltd	Rebone	*Powder*: TetCP, DCP *Solution*: H_2O [56][b]	Apatite
Synthes-Norian	Norian® SRS Norian® CRS	*Powder*: α-TCP (85%), $CaCO_3$ (12%) MCPM (3%) *Solution*: H_2O, Na_2HPO_4 [4,57][c]	Apatite
	Norian® SRS Fast Set Putty Norian® CRS Fast Set Putty	*Powder*: nf[a] *Solution*: nf[a]	Apatite
	chronOS™ Inject	*Powder*: β-TCP (73%), MCPM (21%), $MgHPO_4 \cdot 3H_2O$ (5%), $MgSO_4$ (<1%), $Na_2H_2P_2O_7$ (<1%) *Solution*: H_2O, sodium hyaluronate (0.5%) [43]	Brushite
Kasios	Eurobone®	*Powder*: β-TCP (98%), $Na_4P_2O_7$ (2%) *Solution*: H_2O, H_3PO_4 (3.0 M), H_2SO_4 (0.1 M) [58]	Brushite
CalciphOs	VitalOs	*Component 1*: β-TCP (1.34 g), $Na_2H_2P_2O_7$ (0.025 g), H_2O, salts (0.05 M pH 7.4 PBS solution) *Component 2*: MCPM (0.78 g), $CaSO_4 \cdot 2H_2O$ (0.39 g), H_2O, H_3PO_4 (0.05 M) [59][d]	Brushite

The end-product of the reaction can be either an apatite (calcium-deficient, carbonated, etc.) or brushite.
[a]Not found in the literature or on the web.
[b]Assumed composition based on the scientific literature.
[c]Estimated composition.
[d]The cement consists of two liquids in which the various powder components are dispersed.

poly(methyl methacrylate) medical cements. For example, it is well-known that the setting time of a cement can be modified (i) with a change of the powder size (smaller size → shorter setting time), (ii) with a change of the amount of mixing liquid (smaller amount → shorter setting time), (iii) by adding rapidly available calcium

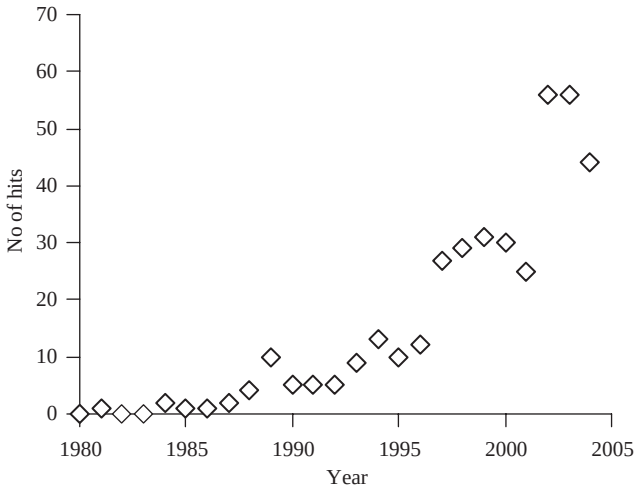

Fig. 1. Number of hits for "calcium phosphate cements" in Pubmed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD=&DB=PubMed; January 4, 2005) as a function of publication year. Some hits were found before 1982–1983, the year of discovery. Additional hits could be found with another search, for example "hydroxyapatite cement". Additionally, these hits are only related to one database (in this case a medical database). More hits can be found in an engineering database such as Thomson ISI, but the evolution is the same.

and/or phosphate ions (either pre-dissolved in the mixing liquid or as freely soluble salt; higher salt concentration → shorter setting time), (iv) by adding crystal nucleii (e.g. apatite nanocrystals for apatite cements; more nucleii → shorter setting time), or (v) by adding crystal growth inhibitors (more inhibitor → longer setting time). Mechanically, higher properties can be obtained with a decrease of the cement porosity, for example via a decrease of the amount of mixing liquid, or the addition of dense granules. Another strategy is to add reinforcing fibers [10] or to try to modify the average crystal size. However, aspects additional to those relevant to construction and PMMA cements must also be considered. For example, the biological response of CPC can only be assessed by implantating CPCs. Furthermore, strict requirements are set on CPC composition due to their medical use and the fact that CPC are resorbable: not only the cement, but its resorption products should be biocompatible.

Testing methods of PMMA and construction cements have been applied to CPCs, for example the use of Vicat tests for setting time measurements, or the so-called Brasilian test for the determination of the diametral tensile strength. However, not all testing methods can be applied to CPCs. The Vicat-test used to measure the setting time of construction cement or the diametral tensile strength cannot be applied for CPCs with low mechanical properties. Moreover, specifics of CPCs evaluation require new testing methods. For example, CPCs (i.e. aqueous pastes) must harden in an aqueous environment, which implies that the cement should not disintegrate upon contact with body fluids.

Despite the large number of information collected in the past 2 decades on CPCs, the question might be raised to know whether additional research is needed, particularly from materials science. In fact, the previous paragraph has already given some hints that the answer is positive. Despite the numerous publications, some very basic aspects of the cements such as setting time, fracture mechanics (effect of microporosity, fatigue properties), or cohesion (among others) are not well understood. Additionally, a new synthesis method for amorphous calcium phosphates via milling has been recently proposed [11,12] which opens up new perspectives in terms of more controlled setting reactions and perhaps better drug delivery systems. Furthermore, CPCs can be used to synthesise calcium phosphate granules and porous blocks with very high surface areas that might be potent drug carriers or biologically very reactive. Last but not least, there is a large gap between cement development and clinical use: the needs of clinicians have to be recognised, considered and integrated in future research. A look at the number of publications devoted to CPCs confirms the assertion that much needs to be done in the field: the number of publications has increased very rapidly, almost exponentially in fact (Fig 1). Interestingly, CPCs are being more investigated than calcium phosphate ceramics (i.e. those obtained by sintering).

3. New trends

As previously mentioned, there are several directions that require more research: (i) studies on basic properties of CPCs (setting time, injectability, cohesion); (ii) amorphous calcium phosphates e.g. via milling; (iii) synthesis of granules and blocks; (iv) surgeons' needs (or clinical requirements). The goal of the present section is to discuss these various aspects in more details.

3.1. Basic properties

Despite the long history of CPCs, there is presently very little known about some basic properties of CPCs, such as setting time, fracture mechanics (e.g. fatigue [13], tenacity [14]), or cohesion. This is very surprising because these properties are of large importance for the cement application. In the present section, two aspects will be discussed: setting time and cohesion.

Setting time: The traditional method to characterise the setting reaction of a cement uses a mechanical approach: the cement is considered to be set when it can resist a given mechanical load applied onto its surface. This method is excellent when the applied load is low (i.e. 10–20%) compared to the maximum compressive strength of the cement and when the compressive strength of the cement increases steadily during setting.

Obviously, this method is not adequate to compare cements with widely different compressive strengths. Moreover, it has been reported that cements can have sometimes two hardening reactions: thus only one setting measurement is inadequate. Two measurements corresponding to the so-called initial and final setting times have been proposed by Driessens et al. [15], but the information is still scarce and might be inadequate if the applied loads are not appropriate for the setting properties of the cement (e.g. too low or too high loads applied to determine the initial and final setting time).

Therefore, more chemistry-based approaches may be more appropriate, for example to interpret thermal analysis data during setting. This approach that has been extensively used by Brown et al. [16] enables a better understanding of the kinetics of the setting reaction as a whole and not of single points in time. Unfortunately, there is still too little known about setting kinetics in order to design a "perfect" CPC paste that would have a constant viscosity for a given time and then hardens very rapidly. To reach this goal, setting kinetics (and viscosity changes) have to be determined and well understood, for example by combining the very precise information retrieved from calorimetric studies [16,17] with the less precise information retrieved from mechanical evaluations [18].

Cohesion: Presently, there are a few studies devoted to this topic (e.g. [19–22]), but no agreement on the definition: some authors talk about "non-decay" [19], whereas other authors used the term "compliance" [20,21] and "stability" [22]. Here, "cohesion" (i.e. the ability of a cement to stay in one piece during setting) is used. The approach in all the latter studies has been to test the "cohesion" of the cement during setting in an aqueous solution, typically in water [19] or in Ringer's solution [20–22]. Basically, it appears that an increase of the cement viscosity, e.g. with the addition of a gel-forming polymer into the mixing solution, increases the cement cohesion [19,21,22]. However, recent results obtained in Robert Mathys Foundation laboratories contradict this finding: an increase of the sodium hyaluronate concentration in the mixing liquid of a cement from 1.0% to 1.5% led to a dramatic decrease of the cohesion. Moreover, the type of solution used to test the cohesion, strongly affects the results: the amount of released particles was reduced 70 fold when water was replaced with 150 mM pH 7.4 phosphate buffer solution. So it is clear that there is presently a great need for more understanding concerning cohesion. The extreme importance of this topic is illustrated by recent findings that CPCs used for vertebroplasty have been associated with an increased risk of blood clotting [23,24]. Considering the facts that (i) CPCs would be very appropriate for vertebroplasty, (ii) vertebral bodies are intensively irrigated by blood, and (iii) the distance from the spine to the lungs and heart is short, it is of high importance to understand the reason why blood clotting occurs. A most likely explanation is that clotting is provoked by interfacial reactions between solid particles and blood. So, the release of calcium phosphate particles from the cement into the blood stream should be prevented and/or controlled. Therefore, cement cohesion and blood–calcium phosphate interactions should be better understood.

3.2. ACP-based cements

Two main approaches can be used to make a CPC: (i) via an acid–base reaction [2], or via a conversion reaction of a metastable compound, either α-tricalcium phosphate [25] or a so-called amorphous calcium phosphate [26]. Initially, amorphous calcium phosphate was obtained by precipitation and had a Ca/P molar ratio close to 1.5 [26]. Recently, several authors [11,12] synthesised amorphous calcium phosphate powders by mechanical activation after high energy ball milling (called "micronisation" in the pharmaceutical field; "amorphous" means in this context that X-ray diffraction pattern of "amorphous" calcium phosphate powders are practically peakless). As a result, it is in principle possible to "amorphise" or "micronise" many calcium phosphate compounds and hence synthesise any cement formulation, e.g. a brushite cement based on an amorphous calcium phosphate obtained from milling brushite [11]. The advantage of this new technique compared to the traditional precipitation technique is twofold: firstly, these new "amorphous" calcium phosphate powders require less mixing liquid than CPCs based on precipitated amorphous calcium phosphate powders [11] hence leading to higher mechanical properties, and secondly their synthesis is more reproducible and mechanically activated calcium phosphate powders seem to be more stable against ageing effects and recrystallisation than precipitated ACPs. However, there is a much larger risk of incorporating wear particles. Additionally, it is difficult to prevent agglomeration during dry milling or to prevent the presence of organic residues during wet milling. Nevertheless, the possibility of using amorphous calcium phosphates opens up new perspectives in terms of faster setting or incorporation of foreign ions in the structure. A recent unpublished study performed in RMF laboratories has shown that it is very easy to incorporate very large amounts of sulphate ions in an apatite structure provided the sulphate ions (here in the form of Gypsum, 9 w%) are present during the conversion of an amorphous α-tricalcium phosphate in an aqueous solution.

3.3. Synthesis of granules and blocks

Until recently, CPCs have not been used for the synthesis of granules or blocks despite two unique features of CPC compared to sintered calcium

phosphate materials. Firstly, apatite CPCs are nanocrystalline and hence have a very high specific surface area. Values as high as $100\,m^2/g$ can be reached. By comparison, sintered ceramics have surface areas close to or below $1\,m^2/g$. As the first reaction occurring during cement implantation is protein adsorption from blood and as these reactions control further biological events, it appears logical to think that CPC granules would behave differently than sintered β-tricalcium phosphate granules, even though their solubility is similar. Secondly, CPCs enable the synthesis of granules and blocks of low-temperature calcium phosphates such as dicalcium phosphate dihydrate, octacalcium phosphate (e.g. by chemically converting in a solution granules made of brushite cement), or precipitated apatite. These hydrated compounds can all be found in the body, contrary to traditional bone substitute ceramics such as sintered hydroxyapatite, β-tricalcium phosphate and biphasic calcium phosphates. Initial studies have been carried out to synthesise granules and macroporous blocks from CPC [27–30], and in vitro cell culture tests [31–33] and in vivo implantations have been performed [34,35]. However, there is presently no in vivo study clearly demonstrating the anything other than equivalence of CPC granules/blocks to sintered ceramics granules/blocks. There is also no study linking the surface properties of CPC (e.g. specific surface area) and their in vivo performance. Last but not least, characterizing the surface properties of nanocrystalline and nanoporous structures is very complex, and relating these properties to a biological performance when simultaneously the surface and bulk chemistry vary might be futile. Nevertheless, CPCs have a large potential as drug carriers due to their high specific surface area [36].

3.4. Surgeons' requirements

There is a large difference between the interests of engineers or CPC researchers and the needs of clinicians. Whereas the former group are interested in improving performance via an understanding of the chemistry and physics of CPC, the second are interested in a CPC that "works", regardless of the composition. A "working" cement must have several features, such as low price, easy and reliable mixing and delivery, good visualisation during injection (e.g. for vertebroplasty) and good clinical outcome, in particular fast replacement with bone or rapid bone apposition.

Price: The increasingly large requirements set by authorities for the launch of cements give little hope for lower cement costs.

Handling and mixing: Better cement handling can certainly be achieved. One approach to control mixing and handling is to use a mixing machine where the human factor only plays a minor role, hence reducing failure risks. For example, the new electrically powered mixing machine of Norian SRS/CRS mixes the cement paste within 70–80 s, and enables a rapid and reliable filling of the application syringe. A more innovative approach is proposed by Takagi et al. [37] who combine a water-reactive calcium phosphate such as a mixture of tetracalcium- and dicalcium-phosphate with glycerol to form a stable paste that can be directly injected into the defect. Setting occurs upon contact with body fluids. Another very innovative approach is proposed by Lemaître et al. [38] who provision CPCs in the form of two injectable pastes that can be mixed together and injected at the time of implantation (with a static mixer incorporated in the injection cannula). The first commercial formulation based on this principle is available in the dental field (VitalOS, Table 1). However, this approach appears to be limited to acid–base cement reactions.

Injectability: One important drawback of CPC compared to PMMA cements has been their poor injectability. Liquid–solid phase separation (so-called filter-pressing) has often been observed in commercial formulations. Recent efforts in the field of cement injectability have enabled a better understanding of CPC injectability [39] and also provided innovative solutions [40,41]. As a result, cheaper alternatives to the use of rheological agents such as sodium hyaluronate (as in "chronOS Inject"; Table 1) or chondroitin sulphate (as in "Biopex"; Table 1) might be developed.

Faster resorption: Recent work shows that brushite CPC can have a faster resorption than apatite CPC [5]. However, in vivo transformation of brushite into apatite has been observed [42], which impairs its resorption rate. This transformation can be postponed by the addition of a soluble magnesium salt. Another approach to accelerate CPC resorption, particularly for apatite CPC, is to incorporate macropores in the structure which enable faster cement resorption and a high volume of bone ingrowth. Three main approaches can be used. The pores are produced by solid particles or fibers that dissolve after setting [43], by liquid droplets, e.g. oil, that can diffuse out and/or be consumed by cells after implantation [27], or by air bubbles [44]. Unfortunately, injectability, mechanical properties and cohesion during setting are usually compromised during setting, another drawback is that most of these methods do not lead to an open macroporous structure.

Remaining problems: Despite these achievements, other problems remain. For example, the rheological behaviour of CPC is largely unknown. To our knowledge, there is only one study partly devoted to the topic [45]. Moreover, the large effect of temperature on the setting properties of CPC, particularly apatite CPC is a huge challenge for cement producers: the setting time of apatite is typically reduced three- to fourfold when temperature increases from 20 to 37 °C. This implies

that compositions and/or mixing systems should be optimised. Addition of radio-opacifiers into CPC might provide a better visualization during injection, particularly for vertebroplasty. However, solutions are not trivial. For example, iodide-based organic contrasting agents can be incorporated in a powder or liquid form, but their slow release from the cement and the occurrence of deadly allergic reactions strongly impairs their use. Moreover, their medical status (pharmaceutical product) complicates certification procedures. Radio-opaque powders such as barium sulphate, or zirconium oxide do not present the same problem, but it is a concern to implant billions of non-resorbable particles in a matrix that is likely to be resorbed over time. Presently, the use of strontium carbonate appears to be the most suitable choice because the powder has a solubility close to that of calcium carbonate, so the powder should be resorbable. Moreover, strontium ions have a good biocompatibility as indicated by the high LD50 for $SrCl_2$ (147.6 mg/kg i.v. in mice; Merck Index).

4. Conclusion

Despite the numerous scientific articles on CPCs, there is still a lot to be done to reach a better understanding of the physical, chemical and biological properties of CPC. Additionally, the gap between CPC research and clinical use should be decreased, for example by studying and defining the needs of specific applications (e.g. vertebroplasty: injectability, radio-opacity, viscosity, absence of clotting) in terms of cement properties and by finding adequate solutions. Recent and future developments will enable the commercialisation of better and more differentiated products that should improve the clinical outcome and hence the patient life quality. Further, CPCs await a major role as model cold setting systems for the study of inorganic/organic molecule interactions as interest in hard tissue mimetics grows in materials science. Main trends are in the field of drug delivery (e.g. bone morphogenetic proteins), synthesis of granules and blocks with improved biological properties, more resorbable cements (e.g. via macropores or using brushite CPC), better handling (e.g. mixing, injection) and novel organic–inorganic hybrid materials with properties yet to be evaluated.

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