Chapter 12

Calcium Phosphate Bone Cements

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Additional information is available at the end of the chapter

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Abstract

Biomaterials utilized in biomedical applications are of various characteristics and cements are unique in their *in situ*, biomimetic formation ability. They present the most topographically complex surfaces that usually elicit a favorable cellular response for tissue regeneration. In addition their composition may provide an effective chemical gradient around the resorbing implant to induce desired cellular activity that leads to rapid wound healing and regeneration. These are the main reasons for many cement systems to function well in the body, especially as hard tissue replacements. The properties and the setting mechanisms of the clinically most relevant cement system, calcium phosphate cements have been elucidated in this chapter.

Keywords: calcium phosphate cement, calcium orthophosphates, inorganic bone cement, cement injectability, cement setting kinetics, cement biocompatibility, orthopaedic cements

1. Introduction

In the simplest sense cement is a binder of functional solid materials. Biomedical materials that necessitate combination with a binder are usually strong, inert metals and ceramics that are implanted in order to augment defects in hard tissues such as bone and dentin. For a long time since the Second World War, this binding function had been fulfilled by organic cements that gain elasticity by crosslinking *in situ*. Polymethylmethacrylate and various other resins that display a rapid rise in viscosity and elasticity upon addition of chemicals or exposure to light have been widely accepted as effective cements despite their commonly encountered biocompatibility issues due to the release of irritating monomers and inflammatory heat of setting. Inorganic cements emerged later thanks to the advances in materials characterization techniques and understanding of the molecular mechanisms of bioactivity. Calcium sulfate,

zinc phosphate, zinc polycarboxylate, magnesium phosphate, calcium phosphate, calcium silicate and glass polyalkenoate cements all proved to be biocompatible and to some degree osteoconductive. Particularly the effectiveness of calcium phosphate cements (CPC) as biomaterials has been attributed largely to their similar composition to hard tissues, aqueous setting solutions and tailorable viscosity. In addition constant improvements in cement properties have been realized due to their biomimetic setting reactions at ambient conditions that enabled experimenting with a wide variety of chemical and biological additives. As a result, inorganic cements led in quantity by calcium phosphate cements have been applied as bulk materials to fill defects in bone and teeth, support, induce and conduct bone regeneration rather than just bind more effective biomaterials in isolation. As highlighted in the subsequent parts of this chapter, biological interaction of calcium phosphate cements with human cells have been tested extensively and provides the basis for various modification approaches to extend their applications and facilitate their evolution toward the ideal biomaterial.

Inherent solubility of most calcium compounds in water has been a major motivation for material scientists to research and discover novel cementitious systems of these materials. So was the discovery of the major class of inorganic biomedical cements, calcium phosphate cements, realized. CPCs were discovered by LeGeros, Brown and Chow in early 1980s as an alternative to bulky bone graft bioceramics to set in situ and fill bone or dental defects [1, 2]. According to Chow, the discovery of the first CPC was in fact a result of basic studies on calcium phosphate solubility behaviors for the purpose of development of a tooth remineralizing suspension similar to contemporary toothpaste formulations. Based on solubility phase diagrams, material scientists were aware of the fact that both tetracalcium phosphate (TTCP) and dicalcium phosphate anhydrate (DCP) are much more soluble than hydroxyapatite (HA) under neutral pH conditions. Further, a slurry containing appropriate amounts of these compounds can produce continuous HA precipitation while maintaining the solution composition relatively constant. Brown and Chow observed that some of the TTCP + DCP aqueous pastes became a hardened mass when left in test tubes for a few hours. Thus unaware of the beneficial biomedical consequences, they discovered a new type of bioactive, self-hardening cement that consisted of only calcium phosphates and formed HA as the product. Rigorous subsequent in vivo research on the same cement system led to the conclusion that implanted CPC was gradually replaced by new bone. This CPC composition received approval by the US Food and Drug Administration in 1996, thus becoming the first commercially available CPC for use in humans [3]. Since then, many compositions have been proposed, most of which are given in the following sections.

2. Applications

Compared to sintered calcium phosphate ceramics which are the most commonly applied materials in orthopedic surgery, calcium phosphate cements have three major advantages. Firstly, CPCs are nanocrystalline and hence have a very high specific surface area. Values as high as 100 m^2/g can be reached. In comparison, sintered ceramics have surface areas close to or below 1 m^2/g. Secondly, CPCs enable the synthesis of granules and blocks of low-temperature calcium phosphates such as dicalcium phosphate dihydrate (DCPD), dicalcium phosphate anhydrate,

octacalcium phosphate (OCP), or precipitated apatite (PHA) [4]. In addition, initial flowability of CPCs enable their convenient conveying to the surgical site by means of a pressurization equipment and easy shaping by hand to conform to the defect perfectly. Injectability and sufficient compressive strength of CPCs has expanded their use to minimally invasive surgeries like percutaneous vertebroplasty and balloon kyphoplasty where organic polymethylmethacrylate (PMMA) cements had previously been the only choice for the surgeon to fill bone defects or fix bulk implants to the defect site [5, 6]. Due to the superiority of CPCs to PMMA in many aspects including bioactivity [7–9], dimensional stability [10], and biomimetic hardening, these materials are gradually replacing the organic bone cements especially in minimally invasive operations.

Calcium phosphate bone cement pastes typically exhibit relatively low shear viscosity and elastic modulus, then gain elasticity and shear viscosity with time. The rates of growths of the elasticity and viscosity of calcium phosphate based cements are generally higher than those of conventional cements as a result of the rapid dissolution and crystallization of calcium phosphate particles in water. Their initial flowability and workability are exploited most commonly in biomedical applications for bone repair and regeneration due to their exceptional osteoconductivity especially following cancerous bone removal and for minimally invasive surgeries. The minimally invasive clinical applications of bone cement pastes include spinal fusion, vertebroplasty, khyphoplasty, cranioplasty and periodontal surgery. During surgical applications the precise placement of the bone cement paste by the surgeon is very important. Various means are available for the placement of the cement paste into the repair site. Generally a syringe with a needle can be used. Calcium phosphate cements must react slowly enough to provide enough time for the surgeon to inject and work the paste into the implantation site, and fast enough to prevent washing-out or delaying the wound closure. Also its setting time and extent of reaction should be balanced to impart strength to the final product. The initial setting time is critical as it should allow sufficient time for shaping and filling. After the filling, it is not advisable to disturb the set cement until its hardening because any mechanical strain during this period will produce cracks and adversely affect the strength. Therefore it requires the shortest possible final setting time so that the wound closure is not delayed. The initial setting time denotes the end of workability of the paste after wetting, and the final setting time indicates the hardening of the set mass [11]. An initial setting time of about 8 minutes and a final setting time of less than 15 minutes are recommended for orthopedic applications.

Typically after setting of calcium phosphate cements, aqueous setting liquid is trapped in micro-reservoirs. The release of incorporated ions enable continuous hardening for days after setting. This reservoir effect is beneficial for many aqueous inorganic cements but especially for biomedical applications because of the contribution of the material to the dynamic tissue remodeling processes. Inorganic bone cements are required to provide a temporary support for the activity of the bone microenvironment consisting of cells, proteins, growth factors and ions while simultaneously facilitating the natural remodeling process by providing a preferentially alkaline environment and an abundance of relevant ions of calcium, phosphate, carbonate, etc. An excellent explanation of the bone remodeling process from a materials scientist's perspective by Driessens *et al*. is recommended for more information [12]. Exceptional bioactivity of apatite forming CPCs is due to the alkaline microenvironment rich in calcium and phosphate

ions in ratio similar to those in the bone extracellular matrix. In addition, the inherent microporosity of these materials is beneficial for the release of drugs, and biomolecules that are proven to direct cellular activity so as to facilitate a wound healing and remodeling process close to natural as possible [13]. However macroporosity is also needed to be able to make use of these macromolecule osteoinductive factors like bone morphogenetic protein, transforming growth factor, platelet-derived growth factor, basic fibroblast growth factor and enable invasion of the material by osteoblasts [14]. Generally interconnected pores of sizes in excess of 300 μm are recommended to enhance new bone formation and the formation of capillaries [15]. Various macropore induction techniques have been applied to these biomimetically setting pastes with ease but those that work *in situ* are the most suitable for orthopedic applications [16–19]. Precise control on the porous architecture of calcium phosphate cement based scaffolds have been realized in a number of recent studies by indirect 3D printing techniques [20, 21]. The dimensional accuracy and bioactivity of such custom-fit forms of the material were found outstanding.

3. Properties

3.1. Bioactivity

As the chemical composition of the mammalian bone mineral is similar to ion-substituted, calcium-deficient hydroxyapatite (CDHA), apatite forming calcium phosphate cements have been more extensively investigated as bioactive implant materials than brushite forming CPCs. All apatite CPC formulations have precipitated hydroxyapatite (PHA) as the end-product of the reaction which has a much finer crystal structure than its sintered counterparts or other CPC setting products including brushite and monetite. High surface area and roughness are the physical requisites for osteoconduction as bone bonding is achieved by micro-mechanical interdigitation of the cement line (a thick apatite layer secreted by osteoblasts) with the material surface [22]. Also micro-topographically complex surfaces promote osteoconduction by both increasing the available surface area for fibrin attachment and providing surface features with which fibrin becomes entangled; and potentiating the activation of platelets, which produce density gradients of cytokines and growth factors that guide leukocytes and osteogenic cells during the healing process [23]. Furthermore Davies demonstrated that platelet activation on calcium phosphate surfaces is a function of the surface topography of the calcium phosphate, rather than the composition.

According to Davies, the formation of bone requires not only the recruitment and migration of a potentially osteogenic cell population but also the differentiation of this population into mature secretory cells [24]. The potentially osteogenic population migrates through the wound site and reaches the surface of bone fragments, or the implant within the wound site. This stage termed osteoconduction is the most important aspect of peri-implant healing. The implant surface design can have a profound influence on osteoconduction not only by modulating the levels of platelet activation, but also by maintaining the anchorage of the temporary scaffold of fibrin and proteins through which these cells reach the implant surface. Cells that reach the solid surface will initiate matrix synthesis by secreting the first collagenous matrix of the cement line directly on the implant surface. This new bone formation stage is generally considered as a separate and distinct phenomenon and is followed by remodeling of the bone. The bone bonding theory of Davies helps one understand how calcium phosphate and

most other inorganic cements provide the advantages of accelerating early healing and bone bonding over most other biomaterials. Calcium phosphates are known to readily adsorb proteins to their surfaces. Potentiating protein adsorption on calcium phosphate surfaces can be expected to increase the binding of fibrinogen that may lead to increased platelet adhesion and, possibly result in increased platelet activation that may accelerate healing. Increasing protein adsorption can also include an improvement in fibrin binding to the implant surface resulting in an earlier establishment of the three-dimensional matrix through which osteogenic cells have to migrate to reach the implant surface. Therefore surface micro-topography and chemistry of calcium phosphates are critical for both the osteoconduction, and also the bonding of the elaborated bone matrix to that surface.

Aside from osteoconductivity, the most important requirement for a bone substitute implant material is biocompatibility. It is defined by Williams as [25]: "The ability of a biomaterial to perform its desired function with respect to a medical therapy, without eliciting any undesirable local or systemic effects in the recipient or beneficiary of that therapy, but generating the most appropriate beneficial cellular or tissue response in that specific situation, and optimizing the clinically relevant performance of that therapy." Orthopedic and maxillofacial implants are designed for non-sustained, short-term contact meaning that the implant should degrade in time. Therefore the implant material is required to have a level of degradability in the body in addition to the appropriate beneficial cellular response to be biocompatible. The physical presence of particulate or ionic degradation products are able to stimulate inflammatory cells, especially macrophages and giant cells that may elicit a systematic response and lead to a foreign body reaction to the biomaterial. Therefore biomaterial and its degradation products have to be devoid of any potential for mutagenicity, genotoxicity, carcinogenicity, reproductive toxicity and other adverse systematic effects in order to be considered biocompatible.

In this context apatite and brushite CPCs are biocompatible and osteoconductive. Calcium phosphate cements form an apatite layer on the surface shortly after implantation in bone. However, a unique feature of cements is that the particles are mixed with each other and the force linking them is weak; therefore, these particles can easily detach from the cement body, especially after some dissolution has occurred. When this happens, the particles are easily ingested by osteoclast-like cells or by giant cells [26]. However, inflammatory reactions and cytotoxicity have been reported when large brushite CPC volumes were used, primarily due to the transformation to precipitated HA and the resultant release of phosphoric acid [27, 28]. The transformation of DCPD into PHA can be prevented by adding magnesium ions to the cement paste [29] and converting brushite to the more stable anhydrous form, monetite [30]. The latter has been achieved by various techniques including heating [31], water deficient setting [32], acidic setting [33] and high ionic strength [34]. Some inflammatory reactions due to the initial acidity of brushite cement precursors may also apparently occur when the CPC does not set since the pH gradually increases close to the physiological level upon setting. The addition of collagen to brushite cement at different powder-to-liquid ratios resulted in an up to ninefold reduction in the amount of particles released from the cement when compared to the control cement without collagen. Collagen effectively prevented particle loss from the submerged cement paste during setting. In addition brushite-collagen cement composites had a three-fold increased cell adhesion capacity [35]. Numerous other in vivo and in vitro assessments have reported that calcium phosphates always support the attachment, differentiation, and proliferation of osteoblasts and mesenchymal cells, with hydroxyapatites being

the most efficient among them [36, 37]. CPCs are not generally considered to be osteoinductive. However their drug delivery capability has been effectively exploited to impart osteoinductivity to various CPC formulations [16, 38].

3.2. Mechanical properties

The mechanical properties of calcium phosphate cements depend on two conditions: (a) the precipitate should grow in the form of clusters of crystals which have a high degree of rigidity, (b) the morphology of the crystals should enable entanglement of the clusters. In Driessen's study of 450 different CPC formulations, about 40% set in a time shorter than 60 minutes [39]. However, only part of these formulations led to cement bodies having a considerable strength. It was found that both compressive and diametral tensile strength were maximum for stoichiometric compositions with respect to the reaction products. Strength is also related to pore structure due to the size distribution of all the particles and the pressure applied to compact the particle network. Thus, the early compressive strength of the cement is mainly dependent on the quantity of the hydration products, the amount of contact points among hydrated grains, and the volume proportion of hydration product crystals [40]. In addition to the above-mentioned factors, the final compressive strength is obviously dependent on the degree of dissolution, recrystallization, growth and intergrowth of cement precursor and product crystals [41].

Both the extent of CPC conversion and the compressive strength of the cement increase drastically with time in the form of a sigmoidal function [42, 43]. In common practice, the observation of the initial plateau strength values is prevented by the requirement of sample rigidity and the finite time period of strength measurements, so that an exponential rise with time and an end plateau is reported in mechanical characterization results. The complete variation of cement strength and modulus as a function setting time can be conveniently observed using a mechanical spectrometer that is able to probe the viscoelastic character of the cement suspension [44, 45]. The compressive strength is highly correlated with the extent of conversion of the reactants to the products. After setting, CPCs can reach mechanical properties comparable to those of calcium phosphate blocks with the same porosity. Having the ceramic origin, the set products of all calcium orthophosphate cements are brittle, have both a low impact resistance and a low tensile strength within 1–10 MPa, whereas the compressive strength varies within 10–100 MPa. Brushite cements are slightly weaker than apatite cements. However their innovative modification methods result in exceptional strength because of the water consuming setting reaction of brushite cements [46]. Unlike apatite cements, which consume little (1 mole per 3 moles of powder reactant in β-tricalcium phosphate (β-TCP) systems) or no water (TTCP/DCP systems) during setting, the brushite cement system consumes a lot of water during setting reaction (up to 6 moles per 1 mole of powder reactant), theoretically allowing for the formation of cements with low or almost zero porosities. Some excellent reviews on the mechanical properties of both apatite and brushite cements are recommended for additional information [26, 47, 48]. In macroporous form apatite cement has adequate strength to replace trabecular bone. In vivo, the mechanical properties of apatite cements were found to increase, whereas those of brushite cements decreased [49, 50]. This is generally attributed to a higher bioresorbability of DCPD when compared with that of CDHA which not only depends on the inherent solubility but also on various physiological processes occurring around the implant site [51].

One of the main reasons for the weakness of CPCs is their inherent microporosity, which makes it easier for micro- and macro-cracks to run throughout the mass [14]. The pores that typically account for about 40% of hardened cement volume, originate from water reservoirs that form due to packing imperfections, shrinkage, drying and water consuming setting reaction. Porosity may be controlled to a certain extent by precompaction [52], adjusting the particle size [53, 54] and the powder/liquid (P/L) ratio [46], addition of porogens [55] and rheology enhancing chemical [56]. Combination of precompaction with citric acid due to its liquefying effect results in outstanding strength values. Unusually high strengths can also be obtained when cement P/L ratio is maximized to the limiting level of insufficient wetting. This is possible by either efficient dispersion of particle agglomerates through a liquefying effect due to electrostatic repulsion of particles or by using bimodal particle size distribution in the setting cement. Various organic and inorganic chemicals including alpha-hydroxylic acids (a.k.a. carboxylic acids), and vinylic superplasticizers have been utilized for increasing the surface charge by binding to the active surface sites [56, 57]. Bimodal particle size distributions have been shown to decrease the water demand in an α-tricalcium phosphate (α-TCP) single-component, HA-forming system where the addition of an $CaCO_3$ filler of much smaller particle size enabled higher workable P/L [58]. In the case of macropore introduction to the cement matrix by incorporation of porogens, the microporosity is simply decreased because the sample contains less CPC per unit volume due to more macroporosity. Although this is beneficial for the resorbability of the cement, mechanical properties of macroporous cement are greatly reduced compared to macropore free cements. According to Rice, strength of ceramics vary as an exponential function of porosity as given below and so does the strength of CPCs [59]:

$$\sigma = \sigma_0 \, exp(-KP) \tag{1}$$

where σ_0 is the strength of the material with zero porosity and K is a constant. This equation is modified by Le Huec to take pore size into account accordingly [60]:

$$\sigma = \left(E_0 \, R/(\pi c)\right)^{0.5} \exp(-KP) \tag{2}$$

where E_0 is the modulus of zero porosity, c is the average pore size and R is fracture surface energy.

Fiber reinforcement is one of the most convenient methods to compensate for the induced macroporosity in CPCs [61, 62]. Certain fibers like aramid have the property of bonding with hydroxyapatite and providing nucleation sites for set crystals. This property of aramid was made use of in the study by Xu *et al*. where fiber reinforcement imparted a substantial improvement of mechanical properties over those of fiber free porous cement, with strength increasing 3–7 times and toughness by 2 orders of magnitude [55]. The porosity values of the fiber composites were slightly less than those without fibers because the 6% mass imparted by the reinforcing fibers was fully dense.

Other factors affecting strength are the materials used in the solid phase, incorporation and particle size/shape of filler materials in the solid phase. Several researchers attempted to add

filler materials to increase the mechanical properties as in a composite matrix [63, 64]. The idea behind the use of filler particles is that if a tough filler is present in the matrix, it may stop crack Propagation. However by adding fillers porosity decreases, as does the ability of the material to allow bone ingrowth into the pores. Using bioresorbable polymers as fillers provides an effective solution to this problem [65, 66].

3.3. Injectability

Injectability of CPCs is of crucial importance for surgical procedures utilizing minimally invasive procedures such as in vertebraplasty and kyphoplasty or for delivery of the cement into a very narrow space as in root canal obturation. During the injection of the cement paste a pressure drop of the ceramic paste is developed as the paste flows out of the syringe and the needle and as it is forced into the treatment site. This pressure drop represents the bottle neck to injection and is overcome by the surgeon applying a higher pressure on the ram of the syringe that holds the cement. The applicability and the injectability of the cement suspension are governed by the time-dependent shear viscosity and elasticity of the ceramic paste (functions of all parameters affecting the setting kinetics). Once the ceramic suspension attains certain upper thresholds of viscosity and elasticity the injection of the cement paste to the treatment site is no longer possible. A rapid increase in the shear viscosity of the cement paste (transition from flowable suspension to a gel and then to a rigid solid) that is associated with the cement reaching its setting time, restricts the duration of time that the cement remains viable for injection during surgery. Usual practice for the orthopedic surgeon is to change cement formulations that include various setting retarder or promoter chemicals in addition to the setting precursors, according to the time limitations of the task. Alternatively, the setting time and flowability of calcium phosphate cements are adjustable *in situ* by the novel preshearing technology through application of oscillatory and torsional shear strains prior to pressurization and delivery to the surgical site which gives the surgeon freedom to use a wide range of cement formulations that set at various times [44].

At the initial period after mixing with the setting liquid, cements consist of dissolving particles in an aqueous solution that is gradually enriching in precursor ions. This dynamic microstructure with constantly changing maximum packing ratio and solid content typically exhibits concomitant slow alterations in the cement flow behavior according to the Krieger-Dougherty model:

$$\eta^r = \left(1 - \frac{\phi}{\phi_{max}}\right)^{-n} \tag{3}$$

where η^r is the relative viscosity (the ratio between the cement and the setting liquid viscosities), ϕ and ϕ_{max} are the volume fraction of particles in suspension and the volume fraction at which viscosity approaches infinity, respectively, and n is the intrinsic viscosity, an experimentally determinable constant (2.5 for spherical particles). Calcium phosphate cements show a shear-thinning behavior by a significant yield stress that increases with time. They are viscoplastic and can be described as Herschel-Bulkley fluids at any instant but lose their plasticity with time [67]. Furthermore, these materials are thixotropic [68]. The rheological behavior of the cement pastes are strongly influenced by the change of the surface charge during setting. The formation of agglomerates upon mixing the cement powder with the setting liquid can be minimized by taking advantage of the electrostatic repulsion between highly charged surfaces.

The Zeta potential is an important property of cement particles influencing not just particle coagulation but also ion exchange between the hydrate layer around the ceramic particle and the particle surface itself as well as the net precipitation of new material [69].

CPC injectability depends on many factors and may be quite poor in certain cases which results in liquid-solid phase separation called filter-pressing. Their capillary flow has been analyzed extensively in order to understand their injectability behavior [70, 71]. The common observation has been the overshot pressure that is needed to extrude the whole cement sample out, in other words clogging. Highly filled suspensions stably flowing inside a barrel exhibit a constant pressure vs. time curve as seen in **Figure 1a**. Binder phase migrates toward the direction of applied pressure starting at time t_0 and leaves a percolated particle network termed mat behind as shown in **Figure 1b**. Filtration of the low viscosity binder is caused by weak adhesion between the particles and the binder that may originate from improper dispersion in addition to low binder viscosity, low particle surface area and high difference between the densities of the two phases [72]. Further increasing the pressure either thickens the mat layer or discharges it (**Figure 1c**) depending on the propensity of the system to wall-slip [73–76]. The viscoplasticity of complex fluids, including gels and concentrated suspensions and cements is always accompanied by slip at the wall [77–81]. The wall-slip behavior of concentrated suspensions always occurs on the basis of the apparent slip behavior which is generated by the formation of a slip layer consisting of pure binder (which is typically 1/16th to 1/8th of particle diameter) [82–84]: Understanding the conditions necessary for the development of a contiguous slip layer at the wall is the key to prevent mat layer formation and the resulting flow instabilities including filter-pressing and clogging [85]. The development of the apparent slip layer as well as the shear viscosity of the suspension as a function of time is affected by the role that entrained air plays. Wall-slip and shear viscosity of the suspension are both intimately linked to the amount of air that is entrained during mixing and processing [86–90]. Another important factor which affects the flow and deformation behavior of concentrated suspensions is linked directly to the efficacy of the distributive and dispersive mixing of the ingredients of the formulation and the possible shear-induced migration of particles during flow [91–95].

The solid mat layer in a cement is thickened as filtration progresses, setting continues, the liquid content decreases or the solid packing increases, as a result of which the pressure required

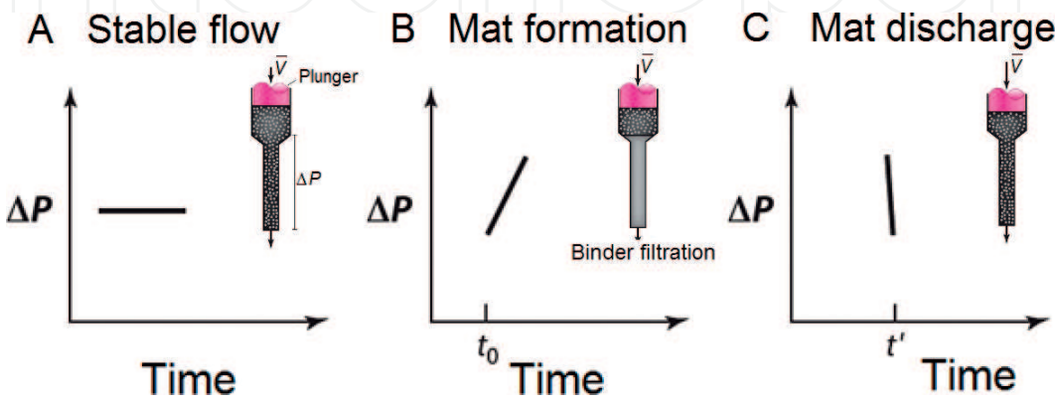

Figure 1. Stable flow (a), destabilized flow due to mat formation (b), stabilized flow due to mat formation (c) in capillary and the associated variation in the pressure drop (adapted with permission from Kalyon and Aktas et al. [72]).

to induce both liquid flow and mat discharge increases. This self-feeding loop gradually transforms the suspension to a packed bed at an increasing rate as evidenced by the exponential nature of the pressure vs. time curves of unstably flowing suspensions. Empirical attempts to tackle the filter-pressing issue shows that the injectability of CPCs is generally improved by decreasing the P/L ratio, the use of finer, round particles, the addition of electrically stabilizing groups, and the addition of viscous polymer solutions [96–101]. In addition to a large number of parameters relating to CPC composition, the injectability of a setting cement depends strongly on the post-mixing time interval relative to the cement setting time. In this regard, premixed CPCs that do not harden until being placed into the defect constitutes an advantage in that the viscoelastic properties are independent of time prior to injection [102].

3.4. Bioresorbability

Calcium phosphate cements are able to provide short-term biologically desirable properties and then be replaced by a new bone. In order to achieve optimum clinical results, an appropriate CPC resorption rate is an important parameter that may vary with the intended clinical applications. For critical applications close to vital organs like cranioplasty, rapid implant resorption and replacement by bone may not be an as important factor as implant stability and integrity, and even may not be desirable due to the sensitivity of the brain to local ionic concentration gradients. For other applications, such as periodontal bone defect repairs or sinus lift, the ability of the implant cement to be replaced quickly by bone is highly desirable. Studies on the in vivo evaluation of macroporous calcium phosphate cements revealed a higher bioresorption rate due to both a higher contact with body fluids and enhanced cellular activity due to particle degradation. When the bioresorbability of dense and macroporous α-tricalcium phosphate cement were compared, it was seen that pores formed by albumin foaming promoted bone ingrowth and replacement [103]. Introduction of macroporosity to the CPC causes a trade-off between strength and bioresorbability which should be compensated by some means of strength reinforcement such as incorporation of polymeric fibers.

The overall bioresorption behavior of calcium phosphate cement is a combination of a solution-mediated passive resorption process and a cell-mediated active resorption process. The resorption properties of bioceramics are generally believed to relate to the solubility of their constitutive phases. The much higher (3 orders of magnitude) solubility of brushite compared to hydroxyapatite translates as the much quicker resorption of brushite cements. An important in vivo characteristic of HA-forming CPC is that it does not dissolve spontaneously in a normal physiological fluid environment, yet is resorbable under cell-mediated acidic conditions. Although brushite is soluble in normal physiological fluids, studies have shown that resorption of brushite CPC was also essentially cell-mediated [3]. Phase changes often occur in brushite cements in vivo by a dissolution-reprecipitation reaction, which results in stable phases with lower solubility, thus slowing down degradation and hence bone regeneration kinetics. The kinetics of passive resorption depends on porosity of the samples, ionic substitutions, Ca:P ratio, crystallinity and pH of the cement-tissue interface. The active resorption is due to cellular activity; however, it is also related to the passive one. Serum pH near macrophages and osteoclasts can drop to 5 by the excretion of lactic acid, whereas near osteoblasts pH can become as high as 8.5 by the excretion of ammonia [12]. The micropores in hardened cements do not allow fast bone ingrowth and they are not interconnected unless special

efforts have been performed. Due to these reasons osteoclastic cells are able to degrade the hardened cements layer-by-layer only, starting at the bone cement interface. This is the main drawback of the classical cement formulations without controlled macroporous architecture. Bone substitution rate also depends on the anatomic site, age, sex, and general metabolic health of the recipient. Considering these factors, it may take 3–36 months for the cement to be completely resorbed and replaced by bone [26]. A linear degradation rate of 0.25 mm/week has been reported in literature [104].

Various ions of zinc, magnesium, fluoride and pyrophosphate have been observed to inhibit β-TCP and HA dissolution [105–107]. HA dissolution is also inhibited by the presence of compounds such as bisphosphonates, polyphosphates or pyrophosphoric acid [108]. Bisphosphonates which are metabolically stable analogs of pyrophosphate, bind strongly to hydroxyapatite crystals and suppress osteoclast-mediated bone resorption and crystal growth. The oxygen atom that binds the two phosphate groups of pyrophosphate (P—O—P) is substituted by a carbon atom (P—C—P) in bisphosphonates. Bisphosphonates are characterized by the two covalently bonded sidechains attached to the central carbon atom, termed R1 and R2. Binding to bone is enhanced when R1 is a hydroxyl group, whereas the R2 side group has some effect on binding but predominantly determines the antiresorptive potency of the bisphosphonates. Bisphosphonates with an R2 side chain containing a basic primary nitrogen atom in an alkyl chain like pamidronate and alendronate are more potent antiresorptive agents than either etidronate or clodronate, whereas compounds with more highly substituted nitrogen moieties in R2 such as ibandronate can display further increases in antiresorptive potency [109].

Resorption of calcium phosphate cements is not desired at the onset of hardening in vivo due to washout of loose calcium phosphate particles by the surrounding body fluid before maintaining mechanical rigidity. The implant should be placed into the wound site between the initial and final setting times therefore washout constitutes a problem for the cement formulations with long setting time. Besides improving the setting times, it is possible to have a coherent cement prior to implantation that sets in contact with body fluids. These are called premixed cements and are essentially pastes formed by calcium phosphate particles mixed with non-aqueous but water-miscible liquids like glycerol [100]. Also several studies show that incorporation of a gelling agent such as hydroxypropyl methylcellulose, carboxymethyl cellulose, alginate, chitosan, into CPC provides good washout resistance [110, 111]. However, generally premixed CPC have lower mechanical properties probably related to the volume initially taken up by the non-aqueous liquid [3].

4. Thermochemistry and setting kinetics

Dissolution of the initial calcium phosphates and mass transport are the primary functions of the aqueous CPC setting solution, in which the dissolved reactants form a supersaturated microenvironment with regard to precipitation of the final product. The relative stability and solubility of various calcium phosphates is the major driving force for the setting reactions that occur in various cement formulations. Mixing of calcium phosphate precursors with aqueous setting solution induces various chemical transformations, where crystals of the initial

calcium phosphates dissolve and precipitate into crystals of HA or brushite. When powders of calcium oxides are mixed with an acid-phosphate solution, they dissolve at various rates in the solvent and release calcium cations in the solution. These cations react with the phosphate anions at various rates within the solvent and form a precipitate of salt molecules. Thus, CPC setting is a result of the following three steps [112]:

I. The acid phosphates dissolve in water, release phosphate anions, and form an acid-phosphate solution of low pH.

II. The calcium oxides dissolve gradually in the low pH solution and release Ca^{2+} cations.

III. The phosphate anions react with the newly released cations and form a coordinated network and consolidate into a CPC

The conditions to form a CPC are governed by the rate of reactions that control each of these three steps. The growth kinetics is mainly controlled by phosphate incorporation step, and additives interfering with this step regulate precipitation and crystal growth. Adsorbed atoms from the solution have to be removed during crystal growth to accommodate the competing HPO_2^{4-} ion; hence, dehydration or impurity de-adsorption is an important part of the activation barrier for growth and dissolution [113]. Since acid-phosphate reactants such as DCP, monocalcium phosphate monohydrate (MCPM), or orthophosphoric acid (PA) are generally soluble, their dissolutions rates are comparatively high, hence uncontrollable. The phosphate reaction between dissolved cations and anions described in step III is also inherently fast and may be kinetically constrained to the formation of intermediate precursor phases according to the Ostwald's rule of stages. Thus, the only reaction that can be controlled is the dissolution of calcium oxides given in step II. Particle size [114, 115], crystallinity [116], powder/liquid ratio [117], precursor chemistry [105], Ca:P ratio [118], temperature [44], surface charge [69], liquid pH [119], ionic strength [34], and concentration of stabilizing, setting promoting or retarding chemicals [120–122] may significantly affect the rate of dissolution and the consequent setting time of CPC. α-TCP is a calcium oxide that dissolves fast and also reacts fast. On the other hand β-TCP dissolution rate is too low in neutral water, so that it remains mostly unreacted in a solution with a slightly acidic phosphate source. For this reason appropriate calcium oxides, based on their solubility, should be selected in combination with suitable acid-phosphate counterparts to synthesize CPCs [123].

Relative stability of different calcium phosphate salts in equilibrium with their saturated solution for different pH values can be understood from **Figure 2** showing the solubility isotherms for the ternary system $Ca(OH)_2$-H_3PO_4-H_2O at 25°C according to the solubility constants given in literature [124]. These isotherms have a negative slope in the neutral and acid regions of the solubility diagrams which point to the fact that calcium phosphates become more soluble as the pH decreases. The gradient of the slopes indicates the solubility increase of the salt as the pH decreases. Therefore the isotherm slope is considered as a measure of the salt basicity and DCPD and DCP are acid salts in comparison to OCP, α-TCP, β-TCP, HA and TTCP because they have lower negative slopes [125]. The isotherms show that the amount dissolved at equilibrium depends on the pH of the solution and the thermodynamic solubility product of the compound which is a function of both crystal and solution chemistry and physical properties.

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Accordingly, HA is the least soluble salt down to a pH of 4.2; for pH values lower than this, DCP is the least soluble salt. Also, it can be observed for pH values lower than 8.5 that the most soluble salt is TTCP; and for pH values higher than 8.5 that the most soluble salt is DCPD. TTCP and DCP were used as the precursors in the first apatite CPC not fully coincidentally because these are the most soluble salts and thus would provide the greatest driving force for the HA-forming reaction. Since at a pH above 4.2, all other calcium phosphate compounds are more soluble than HA, they can be used as precursors for apatite cements. Although several calcium phosphate phases, such as OCP and whitlockite (not shown in figure), are more soluble than HA under neutral pH conditions, they have been found as the major phase in the cement products [126, 127]. This is because these metastable phases precipitate in preference to HA according to the Ostwald's rule of stages [128], and finally convert to HA. Homogeneous formation of HA at low concentrations is almost never observed due to the activation energy barrier for nucleation that should be overcome with high supersaturation. At the onset of precipitation, initial supersaturation is the thermodynamic driving force. It is demonstrated by Song *et al*. for a batch system that after the fast precipitation in the early stage, the following precipitation becomes very slow due to the decrease of supersaturation of the solution with the depletion of calcium and phosphate ions [129]. The fast precipitation cannot continue because there is no supply of extra calcium and phosphate ions. However at a semi-batch system such as that of a CPC, where time dependent dissolution of precursor calcium phosphates supplies ions for supersaturation, the fast precipitation can be kept provided that suitable pH value and concentrations of calcium and phosphate are present.

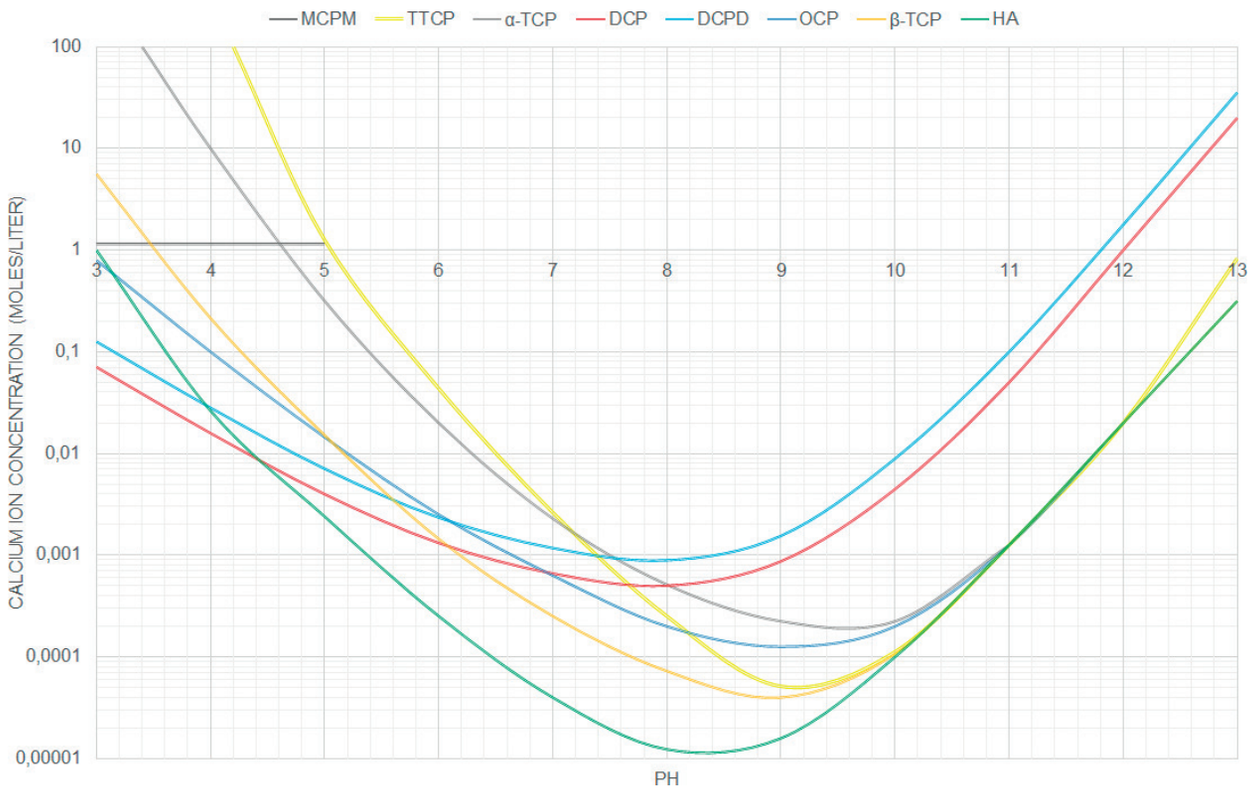

Figure 2. Calcium ion concentration of various calcium phosphate compounds as functions of solution pH.

Although the likelihood of precipitation of a particular calcium phosphate phase is ultimately determined by the thermodynamic driving force of formation, kinetic factors may be considerably more important in controlling the nature of the solids formed. Ostwald's Rule of Stages postulated in 1897 states that the crystal phase that nucleates in a supersaturated solution is not the phase that is thermodynamically stable at that temperature and pressure but rather another metastable phase that is closest in free energy to the parent phase [130]. There are also examples of phase transformations where a metastable phase exists but does not form due to immediate transformation into another phase. It is possible to observe the metastable intermediate by slowing down the kinetics of the reaction. According to the Ostwald's rule of stages, the nucleated phase is the phase that has the lowest free-energy barrier of formation of a critical radius R_c (having the lowest critical radius), rather than the phase that is thermodynamically stable (having the highest supersaturation). In classical nucleation theory [131], the free energy of formation ΔG, and the activation energy for nucleation ΔG^* are related to the surface energy γ, density ρ, and the difference between the chemical potentials of the products and the reactants $\Delta\mu$ which is basically a function of the supersaturation S with respect to the precipitating phase, which is the driving force for nucleation:

$$\Delta G = 4\pi R^2 \gamma + \frac{4}{3}\pi R^3 \rho \, \Delta\mu \tag{4}$$

$$R_c = \frac{-2\gamma}{\rho \, \Delta\mu} \tag{5}$$

where

$$\Delta\mu = -kTlnS \tag{6}$$

and

$$S = \frac{Ionic\ activity\ product}{Solubility\ product\ \left(K_{sp}\right)} \tag{7}$$

The ionic activity product of a calcium phosphate phase is the product of the concentration of the constituent ions and their activity coefficients. The activity coefficients are also complex functions of the interactions between ions in the solution as expressed by the Pitzer's thermodynamical model for electrolytes [132], hence ionic strength. Brown and Chow have shown that the thermodynamic solubility product depends on the purity of the calcium phosphate, which in turn, depends on the method of preparation [133]. Substitute ions like fluoride, carbonate and magnesium influence the structure of the calcium phosphates and therefore have specific effects on their solubilities [134].

Generally two types of CPC setting reactions are observed, the most common one is the setting reaction that occurs according to an acid-base reaction, i.e., a relatively acidic calcium phosphate phase reacts with a relatively basic one to produce a more or less neutral calcium phosphate salt [135]. Typical examples are the cement of Brown and Chow, where TTCP (basic) reacts with DCP (slightly acidic) to form PHA (slightly basic), the cement of Lemaitre where β-TCP, (slightly basic) reacts with MCPM (acidic) to form DCPD (neutral), and a variation of Lemaitre's formulation where MCPM is substituted by PA while β-TCP is replaced by CDHA according to the reactions:

$$Ca_4(PO_4)_2O + CaHPO_4 \rightarrow Ca_5(PO_4)_3OH \quad (8)$$

$$\beta - Ca_3(PO_4)_2 + Ca(H_2PO_4)_2.H_2O + 7H_2O \rightarrow 4\ CaHPO_4.2H_2O \quad (9)$$

$$Ca_9(HPO_4)(PO_4)_5OH + 3H_3PO_4 + 17\ H_2O \rightarrow 9\ CaHPO_4.2H_2O \quad (10)$$

The TTCP + DCPD and TTCP + DCP combinations have been the most studied [136]. They offer hardening at a suitable time at body or room temperature within a neutral pH range. From a theoretical standpoint, any calcium phosphate that is more acidic than HA can react directly with TTCP to form PHA or CDHA according to the following reactions:

$$7\ Ca_4(PO_4)_2O + 2\ Ca(H_2PO_4)_2.H_2O \rightarrow 6\ Ca_5(PO_4)_3OH + 3\ H_2O \quad (11)$$

$$2\ Ca_4(PO_4)_2O + Ca(H_2PO_4)_2.H_2O \rightarrow Ca_9(HPO_4)(PO_4)_5OH + 2\ H_2O \quad (12)$$

$$Ca_4(PO_4)_2O + CaHPO_4.2H_2O \rightarrow Ca_5(PO_4)_3OH + 2\ H_2O \quad (13)$$

$$3\ Ca_4(PO_4)_2O + 6\ CaHPO_4.2H_2O \rightarrow 2\ Ca_9(HPO_4)(PO_4)_5OH + 13\ H_2O \quad (14)$$

$$Ca_4(PO_4)_2O + CaHPO_4 \rightarrow Ca_5(PO_4)_3OH \quad (15)$$

$$3\ Ca_4(PO_4)_2O + 6\ CaHPO_4 \rightarrow 2\ Ca_9(HPO_4)(PO_4)_5OH + H_2O \quad (16)$$

$$3\ Ca_4(PO_4)_2O + Ca_8H_2(PO_4)_6.5H_2O \rightarrow 4\ Ca_5(PO_4)_3OH + 4\ H_2O \quad (17)$$

$$3\ Ca_4(PO_4)_2O + 3\ Ca_8H_2(PO_4)_6.5H_2O \rightarrow 4\ Ca_9(HPO_4)(PO_4)_5OH + 14\ H_2O \quad (18)$$

$$Ca_4(PO_4)_2O + 2\ Ca_3(PO_4)_2 + H_2O \rightarrow 2Ca_5(PO_4)_3OH \quad (19)$$

It is also possible to form HA from acid-base mixtures of calcium phosphates with a Ca/P lower than that of HA when an additional source of calcium ions instead of TTCP is present such as $CaCO_3$ or $Ca(OH)_2$. [137, 138] Takagi *et al*. were the first to propose a calcium phosphate cement formulation without TTCP. Different combinations of DCP and DCPD, α-TCP, amorphous calcium phosphate (ACP), calcium hydroxide and calcium carbonate have been prepared to obtain improvements in the setting time to as low as 5 minutes and tensile strengths as high as 7.5 MPa [139].

All brushite CPCs are obtained by an acid–base reaction. Because DCPD and DCP are the least soluble calcium phosphates under acidic pH (<4.2), they are the products formed by acidic CPC formulations. All other calcium phosphate phases being more soluble under these

pH conditions, can be used as precursors for the DCPD- or DCP-forming cements. Although DCP is the more stable of the two phases, it is kinetically constrained to have a higher nucleation activation energy and can only form under certain conditions as explained earlier. After setting, the pH of the cement paste slowly changes towards the equilibrium pH [140]. Up to now, several formulations have been proposed, including β-TCP + MCPM, β-TCP + H_3PO_4, and TTCP + MCPM + CaO [51, 99, 141].

The second type of setting reaction is defined as hydrolysis of a metastable calcium phosphate when the reactant and the product have the same Ca/P molar ratio. Typical examples are ACP, α-TCP, and TTCP which form CDHA upon contact with an aqueous solution:

$$Ca_x H_y (PO_4)_z.nH_2O + H_2O \rightarrow Ca_{10-x}(HPO_4)_x (PO_4)_{6-x} (OH)_{2-x} + nH_2O \quad (20)$$

$$3\,\alpha - Ca_3 (PO_4)_2 + H_2O \rightarrow Ca_9(HPO_4)(PO_4)_5 OH \quad (21)$$

$$3\,Ca_4 (PO_4)_2 O + 3\,H_2O \rightarrow Ca_9(HPO_4)(PO_4)_5 OH + 3Ca(OH)_2 \quad (22)$$

Chemical composition of calcium phosphate cements may include all ionic compounds of naturally occurring minerals in human body. The list of possible additives includes the following cations: Na^+, K^+, Mg^{2+}, Ca^{2+}, H^+, Sr^{2+}, Si^{4+}, Fe^{2+}, Ag^+, and anions: PO_4^{3-}, HPO_4^{2-}, H_2PO^{4-}, CO_3^{2-}, HCO_3^-, SO_4^{2-}, HSO_4^-, Cl^-, F^-, SiO_4^{4-}. Therefore, mixed-type cements consisting of calcium phosphates and other calcium salts like gypsum, calcium sulfate hemihydrate, calcium pyrophosphate, calcium polyphosphates, calcium carbonate, calcium oxide, calcium hydroxide, calcium aluminate, calcium silicate, strontium phosphate, as well as cements made of ion substituted calcium phosphates such as $Ca_2KNa(PO_4)_2$, $NaCaPO_4$, $Na_3Ca_6(PO_4)_5$, magnesium-substituted calcium deficient hydroxyapatite (CDHA), strontium-substituted CDHA are possible [142].

CO_3^{2-} ions have the most significant effect on CPC microstructure such that incorporation of carbonate in the apatite cement causes a decrease in the precipitated crystallite size and reduces the setting rate as well as the attained compressive strength. According to the study by Khairoun *et al*. $CaCO_3$ addition extended the initial setting times but significantly shortened the final setting times of single component HA cement. Furthermore its accelerating effect was more pronounced at higher concentrations [137]. Morphological studies reveal that the size and shape of the crystallites change from long needles to smaller rods to tiny spheroids [18, 102]. Carbonate ions can incorporate into apatite and substitute for PO_4^{3-} or OH^- in the apatite crystal structure and subsequently change its properties. It is reported that the supersaturation required for precipitation of slightly carbonated apatite was higher than that of apatite in simulated body fluid [143]. Carbonate ions disturb the crystallization of the growing apatite crystallites to such an extent that, depending upon the amount of carbonate added, the material may give an amorphous X-ray diffraction pattern. A submicron structure of interconnected microcrystals are responsible for the improved final mechanical properties of the cement formulation with addition of calcium carbonate. Moreover, carbonate ions cause the bonding in the apatite to become weaker and more isotropic, which results in the small spheroidal crystals and in faster dissolution rates [42].

Similarly, many carboxyl group containing acids and salts have significant effect on hydroxyapatite microstructure and in general setting kinetics of calcium phosphate cements. A number of α-hydroxylated carboxylic acids and salts readily form calcium complexes as well as relatively insoluble and often amorphous Ca-carboxylate compounds [56]. These include glycolic, citric, tartaric, malonic, malic, succinic, lactic and maleic acids. Upon application of precompaction, compressive strength of TTCP-DCP cement increased fourfold to 184 MPa with sodium citrate concentration up to 500 mM compared to plain water and citric acid cement liquid [144]. Sodium citrate addition changed the surface zeta potentials of TTCP and DCP to −50.6 and −50.1 mV with 50 mM sodium citrate from −15.0 and −18.4 mV with water.

5. Phase evolution during setting

The powder of the original calcium phosphate cement formulation proposed by Brown and Chow consists of an equimolar mixture of TTCP and DCP. The setting reaction of calcium phosphate cements starts with ordered dissolution of the salts in the aqueous system. This supplies Ca^{2+} and PO_4^{3-} ions, which precipitate in the form of HA. Epitaxial enlargement of petal or needle-like crystals after initial setting is responsible for the adherence and interlocking of the crystalline grains, which result in hardening [26]. Detailed investigations of the setting of various CPC formulation using various molar ratios, particle sizes, P/L ratios reveal that the reaction proceeds by complete dissolution of the acidic phases DCP or MCPM and partial dissolution of the basic TTCP or β-TCP particles. The specific surface area and the resulting solubility of the basic phase has a much greater effect on the setting rate as increasing its specific surface area leads to an increase in pH, and results in a sharp rise in the solubility of the acidic particles and the supersaturation of HA in the solution [40]. For apatite cement setting is controlled by the dissolution of reactant particles in the first 4-h period, and since the rate of dissolution is proportional to the surface area of the particles which is basically constant in CPC specimens in the earlier stage, the precipitation rate of HA is linear with time. HA forms among the reactant particles which enhances the joint of solids, or around the particles which reduces the distance between grains [42]. Setting is controlled by diffusion through the HA layer at later stages. At 24 hours, the crystals are completely formed, being highly compacted in some areas of high density and well separated in areas with more porosity. Precipitated HA either in stoichiometric or calcium deficient form, nucleate and grow on TTCP particles, thereby reducing their dissolution rate at the final stages [145]. When such a shell is formed around the reactants, the rate of HA formation is controlled by the transport of water and ions through the shell and decrease with an increase of its thickness. Since the densities of DCP and HA are different, the hydration of the residual DCP engulfed by the shell to HA leads to volume expansion and internal stress which is harmful to the compressive strength.

Liu *et al*. describes the thermodynamics of apatite cement setting clearly [118]. Calcium phosphate cement setting reactions are generally exothermic reactions consisting of several steps. In the short initiating period, water is absorbed and wets the surface of the grains upon mixing calcium phosphate powder with water. This is a physical exothermic process. In the inducing

period or latency, the particle dissolution which is also exothermic contributes to a rise in concentration of the calcium and phosphate ions in the solution. With the different dissolution rates of the basic and acidic precursors and the latter being faster, initially acidic pH translates toward the neutral or basic region until the solution is supersaturated, and then DCPD or HA crystallizes from the solution. The accelerating period is a fast, reaction controlled region. In the decelerating period, setting reaction decreases and the reaction process converts from surface reaction-controlled to diffusion-controlled after the setting product grows around the particle surface of the raw materials. Finally, the precipitate product layer may be destroyed by osmotic pressure and crystallization interior stress, which may lead to the increase of the reaction rate and another slight exothermic peak.

The phase evolution of brushite forming β-TCP—MCPM system has been monitored by various techniques including FTIR spectroscopy [146], DS calorimetry [117], pH-stat base titration [33, 34] and small amplitude oscillatory rheometry [44]. The observations confirm the above-mentioned general thermodynamic changes in the state of the CPC. Upon mixing the cement precursors with excess setting liquid, MCPM instantly dissolves and supplies $H_2PO_4^-$ and Ca^{2+} ions to the solution. A small fraction of $H_2PO_4^-$ is expected to dissociate into H^+ and HPO_4^{2-} ions due to its relative stability among phosphoric acid species in water at room temperature [83]. β-TCP dissolves simultaneously to release $3Ca^{2+}$ and $2PO_4^{3-}$ that can form brushite $CaHPO_4{\cdot}2H_2O$ provided that stoichiometric H^+ ions are removed from the solution to first form HPO_4^{2-}groups, resulting in an initial rise in solution pH that is an indication of supersaturation build-up. At this stage cement injectability is maximum. Subsequent to this period, the injectability of CPC gradually diminishes as crystal domains start to expand and intergrow with increasing β-TCP dissolution. Built-up supersaturation can quickly relax by crystal growth in the presence of brushite seeds. As crystals intergrow into small domains, cements gain dough consistency and elasticity develops as seen in **Figure 3**. With increasing intergrowth of the crystalline phase the suspension becomes thicker, i.e., more viscous and more elastic as defined by the increases of the storage modulus, G′ and the magnitude of complex viscosity, η* occurring between the dough time and the initial setting time. CPC is workable by hand prior to the dough time as it lacks stiffness and rigidity. Subsequent precipitation and β-TCP dissolution act to balance the supersaturation and pH until the rate of one weakens relative to the other [147]. This interplay between dissolution and precipitation continues indefinitely until the consumption of precursors.

After the working period a particle to particle network develops and the injectability of the doughy cement suspension becomes modestly more difficult as the initial setting time is approached [148]. Bone cements with various solid contents have been reported to be injectable well beyond their dough time [67] which is most likely due to the active wall-slip mechanism that enables stable flow of doughy pastes. Cement suspension can be shaped by hand at this working period when it has a dough consistency and does not stick to surgical gloves. At the initial setting time a solid network structure or gelling starts to develop in cement microstructure when elasticity and viscosity starts to overshoot asymptotically. The viscoelastic properties change abruptly during this setting period with a sudden transition from

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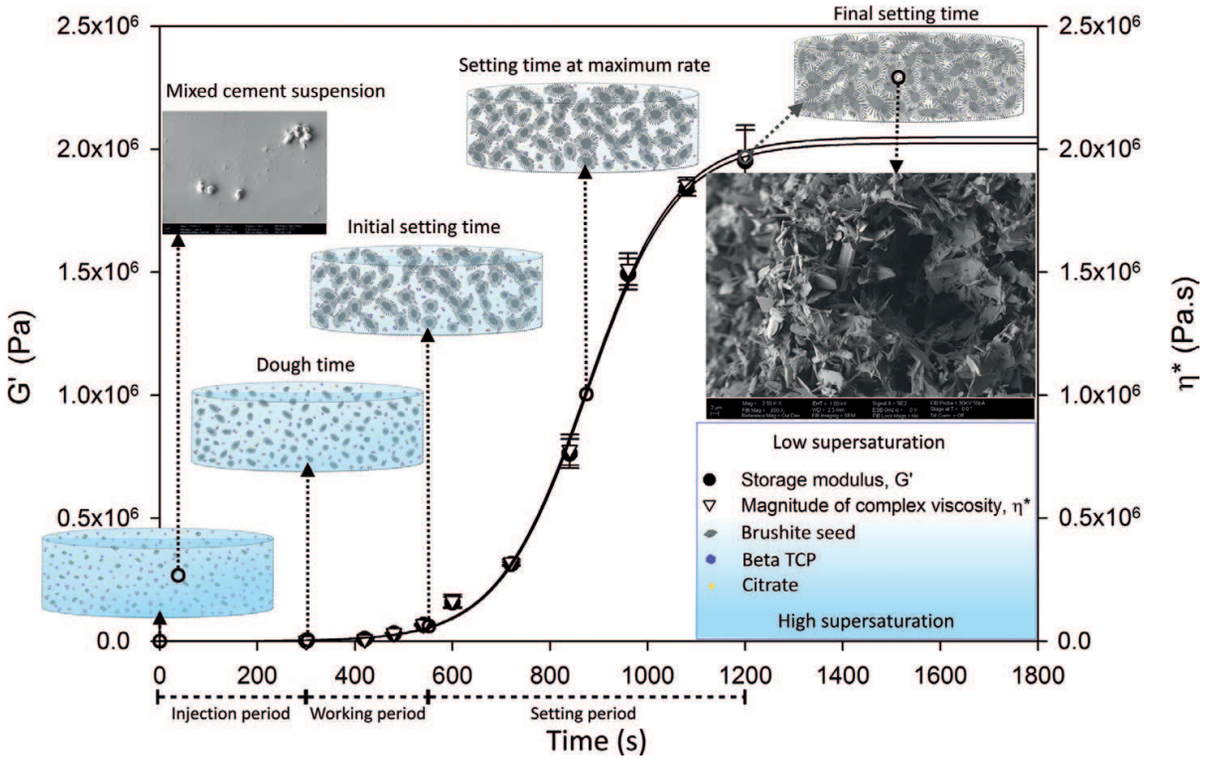

Figure 3. Schematics of calcium phosphate cement setting as represented by the dynamic rheological properties (Şahin and Kalyon [44]).

viscous to elastic flow behavior and elasticity increases at a decreasing rate as a function of the dissolution rate which depends on the β-TCP and water content. Flow instabilities naturally build pressure drop up constantly beyond that point as a result of which injection becomes impractical.

A recent development on improvement of injectability or extrudability of calcium phosphate cements was introduced by our research group so that the inherent injectability problem can be solved by conditioning the cement prior to injection by preshearing. [44]. Our observation that application of oscillatory and steady shear strains i.e. preshearing alters both the setting kinetics and the microstructure, enables tailoring of the cement viscosity and the injection, working and setting periods. The rheology of fast-setting brushite cement was also characterized (**Figure 3**) including the linear viscoelastic strain limit which was characterized for inorganic cements as a function of setting time for the first time. A preshearing apparatus akin to a syringe with the capability to not only pressurize but also mix, preshear and dispense cements *in situ* is designed to facilitate their effective handling and injection. This novel mechanical modification technique is applicable to most inorganic cements and opens an avenue for further research on modification of cement properties, especially rheology without resorting to chemical additives that may compromise the bioactivity and other favorable properties. The beneficial effects of preshearing on workability and extrudability of inorganic cements promise exciting new applications for them such as direct 3D printing of micro- and macroporous scaffolds for bone regeneration.

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