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SELF-SETTING CALCIUM ORTHOPHOSPHATE ($CaPO_4$) FORMULATIONS AND THEIR BIOMEDICAL APPLICATIONS

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***Abstract*:**

In early 1980-s, researchers discovered self-setting calcium orthophosphate ($CaPO_4$) formulations (initially known as calcium phosphate cements), which were bioactive and biodegradable grafting bioceramics in the form of a powder and a liquid. After mixing, both phases formed pastes of variable viscosity, which set and hardened forming most commonly a bone-like non-stoichiometric calcium deficient hydroxyapatite (CDHA) or brushite and rarely monetite with possible admixtures of un-reacted components. Since all these compounds were found to be biocompartible, bioresorbable and osteoconductive (therefore, *in vivo* they could be replaced with a newly forming bone), the self-setting $CaPO_4$ formulations appeared to be very promising bioceramics for bone grafting purposes. Furthermore, due to their unique properties such as an easy shaping, moldability and injectability these formulations possess both an easy manipulation and a nearly perfect adaptation to the complex shapes of bone defects, followed by gradual bioresorption and new bone formation, which are additional distinctive advantages. Moreover, their low-temperature setting reactions and intrinsic porosity allow loading them by drugs, biomolecules and even cells for tissue engineering applications. However, due to the ceramic origin, the ordinary self-setting $CaPO_4$ formulations exhibit both a brittle nature and a low bending/tensile strength, prohibiting their use in load-bearing sites; therefore, reinforced formulations have been introduced, which might be described as $CaPO_4$ concretes. Thus, the discovery of self-setting properties opened up a new era in the medical application of $CaPO_4$ and many commercial trademarks have been introduced as a result. Many more formulations are still in experimental stages. In this review, an insight into the self-setting $CaPO_4$ formulations, as excellent bioceramics suitable for both dental and bone grafting applications, has been provided.

1. Introduction

According to the statistics, approximately half of the population sustains at least one bone fracture during their lifetime [1] and, as a result, surgery might be necessary. Luckily, among the surgical procedures available, minimally invasive techniques are able to offer special benefits for patients such as fewer associated injuries, quicker recovery and less pain. In addition, shorter hospital stays are needed, often allowing outpatient treatments that cheapen the expenses [2]. However, these techniques require biomaterials able to be implanted through small (the smaller – the better) incisions *e.g.*, by means of syringes with needles and/or laparoscopic devices. To fulfill such requirements, the potential implants should be in a liquid or an injectable state, such as pastes. On the other hand, since all types of the calcified tissues are in the solid state, the bone repairing biomaterials must be solid. Therefore, potential bone grafts applicable to the minimally invasive surgery must combine injectability with solidness. Such formulations are known as self-setting (self-hardening, self-curing) formulations because, together with an initial softness and injectability, they possess an ability to solidify in the appropriate period, giving strength to the implantation sites. Since the inorganic part of the mammalian calcified tissues is composed of calcium orthophosphates (abbreviated as $CaPO_4$) of a biological origin [3], self-setting formulations based on $CaPO_4$ appear to be excellent candidates for bone repairing [4, 5]. The list of all known $CaPO_4$, including their chemical formulae, standard abbreviations and the major properties, is summarized in Table 1 [6, 7].

Although the entire subject of $CaPO_4$ has been investigated since 1770-s [8, 9], historically, Kingery appears to be the first, who contributed to their self-setting abilities. Namely, in 1950, he published a paper on the chemical interactions between oxides and/or hydroxides of various metals (CaO was among them) with H_3PO_4, in which he mentioned that some of the reaction products were set [10]. However, the $CaPO_4$ formulations were just a very small section of that study. Afterwards, self-setting abilities of some $CaPO_4$ formulations were described by Driskell *et al*., in 1975 [11], as well as Monma and Kanazawa in 1976 [12]. Namely, the latter researchers found that α-TCP was set to form CDHA when α-TCP was hydrated in water at 60 – 100 °C and pH between 8.1 and 11.4 [12]. Since the reactions took a long time and did not offer any clinical application, the results of those early studies were not noticed by coevals. Then, in early 1980-s, scientists from the American Dental Association LeGeros *et al*., [13], as well as Brown and Chow [14-17] published results of their studies. Since that, this subject became known as *calcium phosphate cements* (commonly referred to as CPC) [18], and, due to their suitability for repair, augmentation and regeneration of bones, such formulations were named as calcium phosphate *bone* cements (occasionally referred to as CPBC) [19-21]. In order to stress the fact, that these formulations consist either entirely or essentially from $CaPO_4$, this review is limited to consideration of $CaPO_4$-based ones only. The readers interested in self-setting formulations based on other types of calcium phosphates are requested to read the original publications [22, 23].

Due to a good bioresorbability, all self-setting $CaPO_4$ formulations belong to the second generation of bone substituting biomaterials [24]. These formulations represent blends of amorphous and/or crystalline $CaPO_4$ powder(s) with an aqueous solution, which might be distilled water [13-17], phosphate buffer solution (PBS) [18], aqueous solutions of sodium orthophosphates [25-43], ammonium orthophosphates [44], H_3PO_4 [45-51], $NaHSO_4$ [52], citric acid [26, 53] and its salts [54], sodium silicates [55-57], soluble magnesium orthophosphates [58], soluble $CaPO_4$ (*i.e*., $CaCO_3$ dissolved in H_3PO_4) [59], chitosan lactate in lactic acid [60], *etc*. Due to the presence of other ions in a number of the solutions, some of such formulations are set with formation of ion-substituted $CaPO_4$.

Briefly, the self-setting $CaPO_4$ formulations are used as follows. After the $CaPO_4$ powder(s) and the solution have been mixed together, a viscous and moldable paste is formed that sets to a firm mass within a few minutes. When the paste becomes sufficiently stiff, it can be placed into a defect as a substitute for the damaged part of bone, where it hardens *in situ* within the operating theatre. The proportion of solid to liquid or the powder-to-liquid (P/L) ratio is a very important characteristic because it determines both bioresorbability and rheological properties. As the paste is set and hardened at room or body temperature, direct application in healing of bone defects became a new and innovative treatment modality by the end of the XX-th century. Moreover, self-setting $CaPO_4$ formulations can be injected directly into the fractures and bone defects, where they intimately adapt to the bone cavity regardless its shape. More to the point, they were found to promote development of osteoconductive pathways, possess sufficient compressive strengths, be non-cytotoxic, create chemical bonds to the host bones, restore contour and have both the chemical composition and X-ray diffraction patterns similar to those of bone [61]. Finally, but importantly, the self-setting $CaPO_4$ formulations are osteotransductive, *i.e*., after implantation, the hardened formulations are replaced by a new bone tissue [62-64].

Table 1. Existing $CaPO_4$ and their major properties [6, 7].

Ca/P molar ratio	Compound	Formula	Solubility at 25 °C, -log(K_s)	Solubility at 25 °C, g/L	pH stability range in aqueous solutions at 25°C
0.5	Monocalcium phosphate monohydrate (MCPM)	$Ca(H_2PO_4)_2{\cdot}H_2O$	1.14	~ 18	0.0 – 2.0
0.5	Monocalcium phosphate anhydrous (MCPA or MCP)	$Ca(H_2PO_4)_2$	1.14	~ 17	[c]
1.0	Dicalcium phosphate dihydrate (DCPD), mineral brushite	$CaHPO_4{\cdot}2H_2O$	6.59	~ 0.088	2.0 – 6.0
1.0	Dicalcium phosphate anhydrous (DCPA or DCP), mineral monetite	$CaHPO_4$	6.90	~ 0.048	[c]
1.33	Octacalcium phosphate (OCP)	$Ca_8(HPO_4)_2(PO_4)_4{\cdot}5H_2O$	96.6	~ 0.0081	5.5 – 7.0
1.5	α-Tricalcium phosphate (α-TCP)	α-$Ca_3(PO_4)_2$	25.5	~ 0.0025	[a]
1.5	β-Tricalcium phosphate (β-TCP)	β-$Ca_3(PO_4)_2$	28.9	~ 0.0005	[a]
1.2 – 2.2	Amorphous calcium phosphates (ACP)	$Ca_xH_y(PO_4)_z{\cdot}nH_2O$, n = 3 – 4.5; 15 – 20% H_2O	[b]	[b]	~ 5 – 12 [d]
1.5 – 1.67	Calcium-deficient hydroxyapatite (CDHA or Ca-def HA)[e]	$Ca_{10-x}(HPO_4)_x(PO_4)_{6-x}(OH)_{2-x}$ ($0<x<1$)	~ 85	~ 0.0094	6.5 – 9.5
1.67	Hydroxyapatite (HA, HAp or OHAp)	$Ca_{10}(PO_4)_6(OH)_2$	116.8	~ 0.0003	9.5 – 12
1.67	Fluorapatite (FA or FAp)	$Ca_{10}(PO_4)_6F_2$	120.0	~ 0.0002	7 – 12
1.67	Oxyapatite (OA, OAp or OXA)[f], mineral voelckerite	$Ca_{10}(PO_4)_6O$	~ 69	~ 0.087	[a]
2.0	Tetracalcium phosphate (TTCP or TetCP), mineral hilgenstockite	$Ca_4(PO_4)_2O$	38 – 44	~ 0.0007	[a]

[a] These compounds cannot be precipitated from aqueous solutions.

[b] Cannot be measured precisely. However, the following values were found: 25.7±0.1 (pH = 7.40), 29.9±0.1 (pH = 6.00), 32.7±0.1 (pH = 5.28). The comparative extent of dissolution in acidic buffer is: ACP >> α-TCP >> β-TCP > CDHA >> HA > FA.

[c] Stable at temperatures above 100°C.

[d] Always metastable.

[e] Occasionally, it is called "precipitated HA (PHA)".

[f] Existence of OA remains questionable.

Since the hardened $CaPO_4$ intend to reproduce the composition, structure, morphology and crystallinity of bone crystals, the initial self-setting formulations might be considered as biomimetic ones [65, 66]. The aim of such formulations is to disturb bone functions and properties as little as possible and, until a new bone has been grown, to behave temporary in a manner similar to that of bone. Therefore, they provide surgeons with a unique ability of manufacturing, shaping and implanting the bioactive bone substitute biomaterials on a patient-specific base in real time in the surgery room. Implanted bone tissues also take benefits from the self-setting formulations that in an acceptable clinical time give a suitable mechanical strength for a shorter tissue functional recovery. Thus, the major advantages of the self-setting $CaPO_4$ formulations include a fast setting time, an excellent moldability, an outstanding biocompatibility and an easy manipulation; therefore, they are more versatile in handling characteristics than prefabricated $CaPO_4$ granules or blocks. Besides, like any other type of $CaPO_4$ bioceramics, the self-setting formulations provide an opportunity for bone grafting using alloplastic materials, which are unlimited in quantity and provide no risk of infectious diseases [67-69].

Since self-setting $CaPO_4$ formulations have been developed for using as implanted biomaterials for parenteral application, for their chemical composition one might employ all ionic compounds of oligoelements occurring naturally in a human body. The list of possible additives comprises (but is not limited to) the following cations: Na^+, K^+, Mg^{2+}, Ca^{2+}, Sr^{2+}, Zn^{2+}, H^+ and anions: PO_4^{3-}, HPO_4^{2-}, $H_2PO_4^-$, $P_2O_7^{4-}$, CO_3^{2-}, HCO_3^-, SO_4^{2-}, HSO_4^-, Cl^-, OH^-, F^-, silicates [62]. Therefore, mixed-type self-setting formulations consisting of $CaPO_4$ and other calcium salts, such as calcium sulfate [70-78], calcium pyrophosphate [79-81], calcium polyphosphates [82-84], calcium carbonates [18, 29, 31-36, 66, 85-88], calcium oxide [89-94], calcium hydroxide [95-97], calcium aluminates [58, 98, 99], calcium silicates [100-107], bioactive glass [108], *etc*. are available. In addition, other chemicals such as Sr-containing compounds [21, 109-113], Mg-containing compounds [113-119], Zn-containing compounds [120, 121], *etc*. may be added to $CaPO_4$ as well. Furthermore, the self-setting formulations might be prepared from various types of ion substituted $CaPO_4$ such as $Ca_2KNa(PO_4)_2$, $NaCaPO_4$, $Na_3Ca_6(PO_4)_5$ (so called "calcium alkaline orthophosphates") [122-127], magnesium substituted CDHA, strontium substituted CDHA, *etc*. [128-133]. More to the point, self-setting formulations might be prepared in the reaction-setting mixture of $Ca(OH)_2$ – KH_2PO_4 [134] and $Ca(OH)_2$ – $(NH_4)_2HPO_4$ [135] systems, as well as by treatment of calcium carbonate or calcium hydroxide with orthophosphate solutions [136, 137]. In addition, if a self-setting formulation consisting of $CaPO_4$ only is set in a chemically reactive environment (*e.g.*, in presence of CO_2), ion-substituted $CaPO_4$, such as carbonate apatite, are formed [138, 139]. Finally, self-setting $CaPO_4$-based formulations possessing special properties, such as magnetic ones due to incorporation of iron oxides [140, 141] have been developed as well. However, with a few important exceptions, the ion-substituted formulations have not been considered in this review, while the interested readers are suggested to study the aforementioned publications.

The purpose of this review is to evaluate the chemistry, physical, mechanical and biomedical properties of the available self-setting $CaPO_4$ formulations with the specific reference to their applications in surgery and dentistry.

2. General information and knowledge

According to Wikipedia, the free encyclopedia: "In the most general sense of the word, *cement* is a binder, a substance that sets and hardens independently and can bind other materials together. The name "cement" goes back to the Romans who used the term "*opus caementicium*" to describe masonry, which resembled concrete and was made from crushed rock with burnt lime as binder. The volcanic ash and pulverized brick additives, which were added to the burnt lime to obtain a hydraulic binder, were later referred to as cementum, cimentum, cäment and cement" [142]. Thus, *$CaPO_4$ cement* appears to be a generic term to describe chemical formulations in the ternary system $Ca(OH)_2$ – H_3PO_4 – H_2O which can experience a transformation from a liquid or a pasty state to a solid state and in which the end-product of the chemical reactions is a $CaPO_4$.

The first self-setting $CaPO_4$ formulation consisted of the equimolar mixture of TTCP and dicalcium phosphate (DCPA or DCPD) which was mixed with water at a P/L ratio of 4:1; the paste hardened in about 30 min and formed CDHA. These highly viscous and non-injectable pastes could be molded and, therefore, were used mainly as a contouring material in craniofacial surgery. Later studies revealed some differences between TTCP + DCPD and TTCP + DCPA formulations. Namely, due to a higher solubility of DCPD (Table 1 and Fig. 1), TTCP + DCPD mixtures set faster than TTCP + DCPA ones. Besides, injectability of TTCP + DCPD formulations is better [145-147]. In 1990-s, it was established that there were about 15 different binary combinations of $CaPO_4$ compounds, which gave self-setting pastes upon mixing with water or aqueous solutions. The list of these combinations is available in literature [148-150]. From those basic systems, secondary self-setting formulations were derived containing additional or even non-reactive compounds [19, 62, 91, 148, 145-163]. In terms of their viscosity, both pasties [164-169] and putties [170] of a very high viscosity [170-173] are known.

According to the classical solubility data of $CaPO_4$ (Fig. 1), depending upon the pH value of a self-setting paste, after hardening all formulations can form only two major end-products: a precipitated poorly crystalline HA or CDHA at pH > 4.2 and DCPD (also called "brushite") at pH < 4.2 [174]. Here one should notice, that in the vast majority cases, terms "a precipitated poorly crystalline HA" and "CDHA" are undistinguishable and might be considered as the synonyms [6, 7], while the term "brushite" was coined to honor an American mineralogist George Jarvis Brush (1831 – 1912), who was a professor at Yale University, USA. However, in the real self-setting formulations, the pH-border of 4.2 might be shifted to higher pH values. Namely, DCPD might be crystallized at the solution pH up to ~ 6, while CDHA normally is not formed at pH below 6.5 – 7 (Table 1).

In early 1990-s, depending on the type of $CaPO_4$ formed after the setting, five groups of the self-setting formulations were thought to exist: DCPD, CDHA, HA, ACP and OCP [150, 175]. However, the results of the only study on an ACP-forming formulation demonstrated that it was rapidly converted into CDHA [161]; thus, it appeared to belong to apatite-forming formulations. With the OCP-forming formulations [176-180] the situation looks as follows. Contrary to the reports of late 1980-s [176] and early 1990-s [177], in which OCP formation was claimed to be detected (however, no phase analysis was performed, just initial reagents were mixed in proportions to get the Ca/P ratio around 1.33), in recent papers either simultaneous formation of OCP and CHDA was detected [179, 180] or no phase analysis was performed [178]. Strong experimental evidences of the existence of a transient OCP phase during setting were found in still other studies; however, after a few hours, the OCP phase disappeared giving rise to the final CDHA phase [56, 181]. Therefore, OCP-forming formulations also appeared to belong to apatite-forming ones. Finally, according to the aforementioned, CDHA and HA are the synonyms. Thus, within the end of 1990-s – the beginning of the 2010-s, the amount of the groups of the self-setting formulations was shortened to just two groups: apatite-forming formulations and brushite-forming ones [182, 183]. This is a predictable situation, because in aqueous solutions HA is the least soluble $CaPO_4$ at pH > 4.2 and brushite is the least soluble one at pH < 4.2 (Fig. 1). However, in the end of the 2000-s, self-setting monetite (DCPA) forming formulations were introduced (see section *3.3. Monetite-forming formulations* below). Thus, one can claim that, depending on the type of $CaPO_4$ formed after the setting, three groups of the self-setting formulations currently exist: apatite-, brushite- and monetite-forming ones. The final hardened product of the formulations is of the paramount importance because it determines the solubility and, therefore, *in vivo* bioresorbability. Since the chemical composition of mammalian bones is similar to an ion-substituted CDHA, apatite-forming formulations have been more extensively investigated. Nevertheless, many research papers on brushite-forming formulations have been published as well, while just a few publications on monetite-forming ones are currently available.

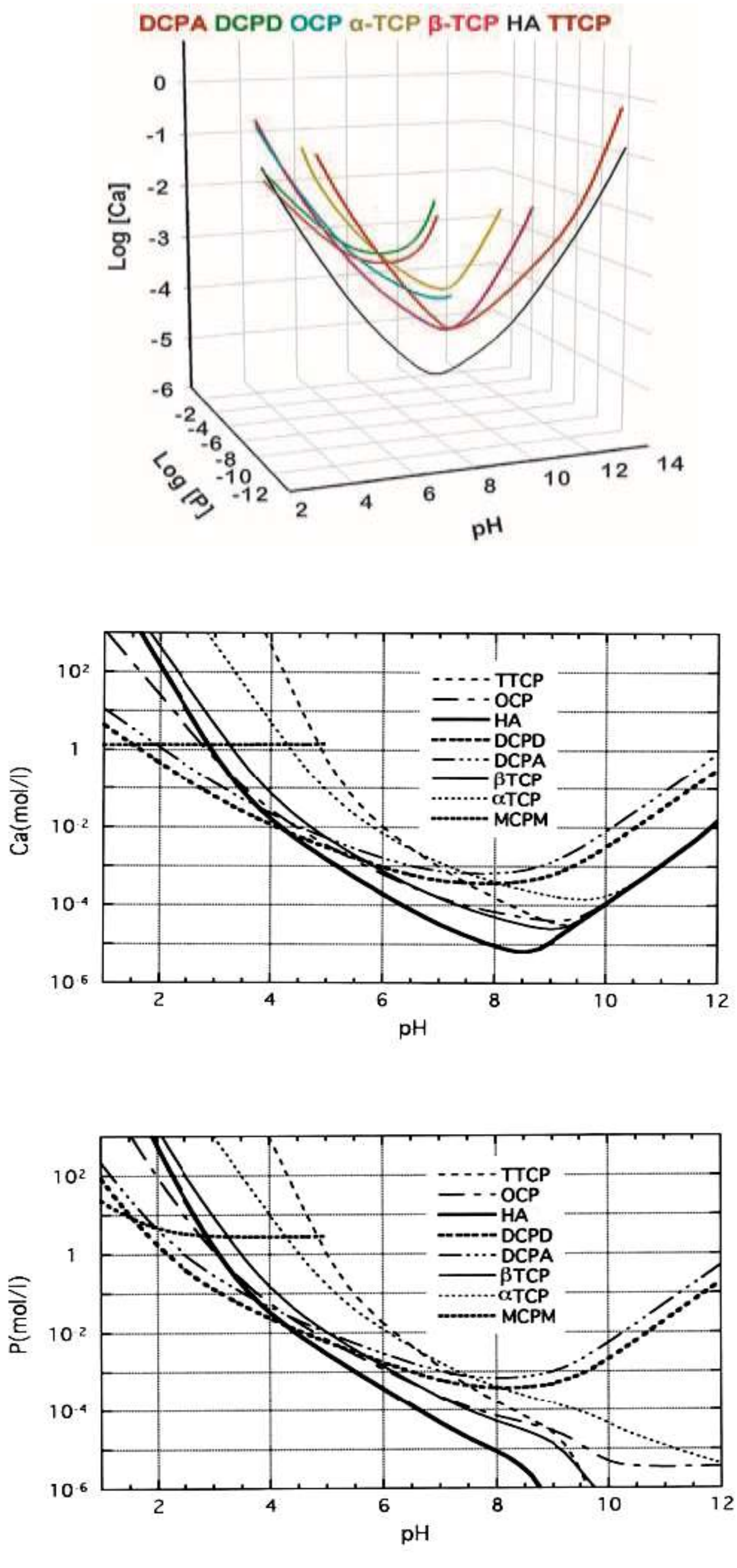

Fig. 1. Top: a 3D version of the classical solubility phase diagrams for the ternary system $Ca(OH)_2 – H_3PO_4 – H_2O$. Reprinted from Ref. [143] with permission. Middle and bottom: solubility phase diagrams in two-dimensional graphs, showing two logarithms of the concentrations of (a) calcium and (b) orthophosphate ions as a function of the pH in solutions saturated with various salts. Reprinted from Ref. [144] with permission.

All types of the self-setting $CaPO_4$ formulations are made of an aqueous solution and fine powders of one or several forms of $CaPO_4$. Here, dissolution of the initial $CaPO_4$ (quickly or slowly depending on the chemical composition and solution pH) and mass transport appear to be the primary functions of an aqueous environment, in which the dissolved reactants form a supersaturated (very far away from the equilibrium) microenvironment with regard to precipitation of the final product(s) [184, 185]. The relative stability and solubility of various types of $CaPO_4$ (see Table 1) is the major driving force for the setting reactions. Therefore, mixing of a dry powder with an aqueous solution induces various chemical transformations, in which crystals of the initial $CaPO_4$ rapidly dissolve and precipitate into crystals of CDHA (precipitated HA), DCPD or DCPA with possible formation of intermediate precursor phases such as ACP [33, 161] and OCP [44, 176-181]. During precipitation, the newly formed crystals grow and form a web of intermingling microneedles or microplatelets of CDHA, DCPD or DCPA, thus provide a mechanical rigidity to the hardened cements [186, 187]. In other words, entanglement of the newly formed crystals is the major reason of setting (Fig. 2).

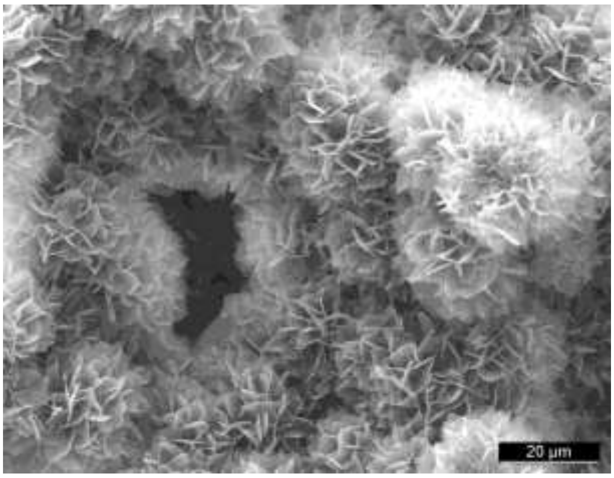

Fig. 2. A typical microstructure of a $CaPO_4$ formulation after hardening. The mechanical stability is provided by the physical entanglement of crystals. Reprinted from Ref. [186] with permission.

Setting of $CaPO_4$ formulations is a continuous process that always starts with dissolution of the initial compounds in an aqueous system. This supplies ions of calcium and orthophosphate into the solution, where they chemically interact and precipitate in the form of either the final products or precursor phases, which causes setting [15, 188, 189]. This was confirmed by Ishikawa and Asaoka, who showed that when TTCP and DCPA powders were mixed in double-distilled water, both powders were dissolved. The dissolved ions were then precipitated in the form of CDHA on the surface of un-reacted powders [190]. Since the physical state of the precipitates can be either a gel or a conglomerate of crystals, the hardening mechanism is either a sol-gel transition of ACP [33, 161] or entanglement of the precipitated crystals of the final products [62]. Thus, all types of hardened formulations possess an intrinsic porosity within the nano-/submicro-sized ranges (Fig. 2). For example, for the classical Brown-Chow formulation, after the initial setting, petal or needle-like crystals enlarge epitaxially and are responsible for the adherence and interlocking of the crystalline grains, which result in hardening. After ~ 2 hours, the newly formed crystals become rod-like, resulting from higher crystallinity with the observation of more material at the inter-particle spaces. During this period, the setting reactions proceeded at a near-constant rate, suggesting that the reaction rate was limited by factors that are unrelated to the amounts of the starting materials and the reaction products present in the system. Such factors could be related to the surface area of DCPA or TTCP or to the diffusion distances over which the ions should migrate to form CDHA [191-193]. At ~ 24 hours, the crystals were completely formed, being very compacted in some areas of high density, and well separated in areas with more porosity [155, 159, 160].

The chemical reactions occurring during hardening depend on the chemical composition of the $CaPO_4$ formulations. However, it can be stated that there are only two major chemical types of the setting reactions. The first type occurs according to the classical rules of the acid-base interaction, *i.e.* a relatively acidic (and rich in PO_4) $CaPO_4$ reacts with a relatively basic (and rich in Ca) one to produce a relatively neutral (amounts of Ca and PO_4 are in between) $CaPO_4$, which commonly appears to be less soluble if compared to the initial reactants. The first cement by Brown and Chow is a typical example of this type because TTCP (Ca/P = 2.0, basic) reacts with DCPA (Ca/P = 1.0, slightly acidic) in an aqueous suspension, forming a poorly crystalline precipitated HA (Ca/P = 1.67, slightly basic) [15, 16]:

$$2Ca_4(PO_4)_2O + 2CaHPO_4 = Ca_{10}(PO_4)_6(OH)_2 \quad (1)$$

Initially, it was believed that DCPA and TTCP reacted upon mixing with water to form the stoichiometric HA [14-17]. However, further investigations have shown that only the first nuclei consist of a nearly stoichiometric HA, whereas further growth of these nuclei occurs in the form of CDHA [194]. Besides, there is a study demonstrating that the initially formed stoichiometric HA further interacts with remaining DCPD to form CDHA [195].

According to equation (1), formation of precipitated HA releases neither acidic nor basic by-products. Thus, the liquid phase of the formulation remains at a near constant pH of ~ 7.5 for the TTCP + DCPD and ~ 8.0 for the TTCP + DCPA mixtures, respectively [191-193]. Various deviations from the stoichiometry of chemical equation (1) were studied in details and various types of CDHA with Ca/P ionic ratio within 1.5 – 1.67 were found as the final product [196]. The effect of mixing ratio and pH on the reaction between TTCP and DCPA is well described elsewhere [197]. Furthermore, the influence of Ca/P ionic ratio of TTCP on the properties of the TTCP + DCPD cement was studied as well [198].

A blend proposed by Lemaître *et al*., [199, 200] is another example of the acid-base interaction in which β-TCP (Ca/P = 1.5, almost neutral) reacts with MCPM (Ca/P = 0.5, acidic) to form DCPD (Ca/P = 1.0, slightly acidic):

$$\beta\text{-}Ca_3(PO_4)_2 + Ca(H_2PO_4)_2\cdot H_2O + 7H_2O = 4CaHPO_4\cdot 2H_2O \quad (2)$$

In chemical equation (2), MCPM may easily be substituted by H_3PO_4 [45-51], mixtures of MCPM and H_3PO_4 [201-203] or MCPA, while β-TCP may be replaced by α-TCP [202-205], CDHA [206, 207], HA [208, 209], HA + β-TCP (biphasic $CaPO_4$) [210] or even $Ca(OH)_2$ [32, 38, 48] and CaO. For example:

$$Ca_9(HPO_4)(PO_4)_5(OH) + 3H_3PO_4 + 17H_2O = 9CaHPO_4\cdot 2H_2O \quad (3)$$

Formulations such as a mixture of $Ca(OH)_2$ and $Mg(OH)_2$ as a powder component and aqueous solution of sodium orthophosphates as a hardening liquid are possible as well [211].

Furthermore, self-setting formulations based on mixtures of ACP + α-TCP [212, 213], ACP + DCPD [214, 215], DCPA + α-TCP [205], OCP + TTCP [216], OCP + α-TCP [50, 217, 218], α-TCP + TTCP [59] and unspecified "partially crystallized calcium phosphate" (presumably, ACP + CDHA) + DCPA [219-221] as the initial reagents, are also available. In addition, multiphase self-setting compositions such as α-TCP + TTCP + DCPA [222], DCPA + α-TCP + β-TCP + CDHA [223] and DCPA + α-TCP + β-TCP + CDHA + $CaCO_3$ [34, 35] have been developed as well.

The second type of the setting reaction takes advantage of the metastability of a $CaPO_4$ phase in aqueous medium and its rapid conversion into a more stable $CaPO_4$. Therefore, it might be defined as hydrolysis of a metastable $CaPO_4$ in aqueous media. As the result, both the initial components and final products have the same Ca/P ionic ratio. Due to the fact, that only one $CaPO_4$ is used, the solid part of such formulations might be called as a single-phase (or single-component) formulation [224]. Namely, self-setting formulations made of ACP + an aqueous solution [225, 226], α-TCP + an aqueous solution [25-27, 30, 39-41, 227-237], β-TCP + an aqueous solution [230, 238], DCPA + an aqueous solution [55, 239], CDHA + an aqueous solution [56], OCP + an aqueous solution [57], TTCP + an aqueous solution [58, 240, 241] or γ-radiated TTCP + an aqueous solution [242-244] are the examples; the majority of them are re-crystallized to CDHA during setting:

$$Ca_xH_y(PO_4)_z{\cdot}nH_2O + H_2O \rightarrow Ca_{10-x}(HPO_4)_x(PO_4)_{6-x}(OH)_{2-x} + nH_2O \quad (4)$$

$$3(\alpha\text{- or }\beta\text{-})Ca_3(PO_4)_2 + H_2O = Ca_9(HPO_4)(PO_4)_5(OH) \quad (5)$$

$$3Ca_4(PO_4)_2O + 3H_2O = Ca_9(HPO_4)(PO_4)_5(OH) + 3Ca(OH)_2 \quad (6)$$

As seen from the amount of publications, α-TCP appears to be the most popular compound to produce the single-phase self-setting $CaPO_4$ formulations. Moreover, the data are available that although α-TCP does not react with distilled water at 37 ºC according to reaction (5), this setting reaction occurs under the hydrothermal conditions at 200 ºC resulting in formation of porous CDHA blocks with interconnected porosity, possessing the reasonable values of the mechanical strength [245]. Therefore, one may claim on existence of self-setting properties of $CaPO_4$ formulations under elevated temperatures.

An interesting study was performed on microstructures, mechanical and setting properties of $CaPO_4$ formulations with variable Ca/P ratio within 1.29 < Ca/P < 1.77 [246]. The results showed that: (a) only the reactant with Ca/P = 1.50 was monophasic and consisted of α-TCP, which transformed during the setting into CDHA; (b) reactants with Ca/P < 1.50 were composed of calcium pyrophosphate, α-TCP and β-TCP blends, while those with Ca/P > 1.50 were composed of α-TCP, HA and TTCP blends; (c) formulations with Ca/P ratio other than 1.50 had longer setting and lower hardening properties; (d) the formulations' reactivity was clearly affected by the Ca/P ratio of the starting reactant; (e) depending on the Ca/P ratio of the starting reactant, the hardened formulations developed different crystal microstructures with specific features [246]. Furthermore, a self-setting formulation might be prepared from the thermal decomposition products of HA [247]. In addition, there is a study, in which β-TCP powders were mixed with 1.0 M $CaCl_2$ solution and 0.6 M NaH_2PO_4 solution consecutively. The ratio of β-TCP powder to $CaCl_2$ solution to NaH_2PO_4 solution was 4:1:1 (g/ml/ml), while the total P/L was 2.0 g/ml and the Ca/P ratio of the mixing liquids was 1.67 [248].

The experimental details on TTCP hydrolysis under a near-constant composition condition are available elsewhere [249]. The details on α-TCP hydrolysis are also available. The results indicated that setting of α-TCP was initially controlled by surface dissolution; therefore, it depended on the surface area of the reactants [250-253]. Hydrolysis of DCPD to CDHA was studied as well [254]. Addition of ~ 2 wt. % of a precipitated poorly crystalline HA (*i.e.*, CDHA) as a seed to α-TCP powder phase might be useful to accelerate the kinetics of reaction (5) [255]. Similar results were obtained in other studies [256, 257]. The aforementioned information is summarized in Fig. 3 [258].

Further, there is a single-phase formulation consisting of K- and Na- containing CDHA (with the Ca/P ionic ratio of 1.64 ± 0.02) that sets and hardens after mixing with an aqueous solution of sodium citrate and sodium orthophosphate [259]. After setting, this formulation gives rise to formation of a weak cement (the compressive strength of 15 ± 3 MPa) consisting of the ion-substituted CDHA again (presumably, with smaller Ca/P ionic ratio), mimicking the bone mineral. Unfortunately, neither the setting reaction nor the setting mechanism of this cement were disclosed [259].

For the majority of apatite-forming formulations, water is not a reactant in the setting reactions; it is just a medium for reactions to occur. Therefore, the quantity of water, actually needed for setting of such formulations, is very small [24, 184, 260]. Similar is valid for monetite-forming ones. However, for brushite-forming formulations, water always participates in the chemical transformations because it is necessary for DCPD formation. Using atomic weights, the mass of consumed water relative to the total mass of the $CaPO_4$ reactants in the setting reactions represented by Eq. (1), Eq. (5) and Eq. (2) was estimated at 0, 1.90 wt.% (P/L = 50) for apatite and 21.3 wt.% (P/L = 3.85) for brushite, respectively. Due to this reason, the brushite-forming formulations are always hydraulic, while this term is associated with neither apatite- nor monetite-forming ones.

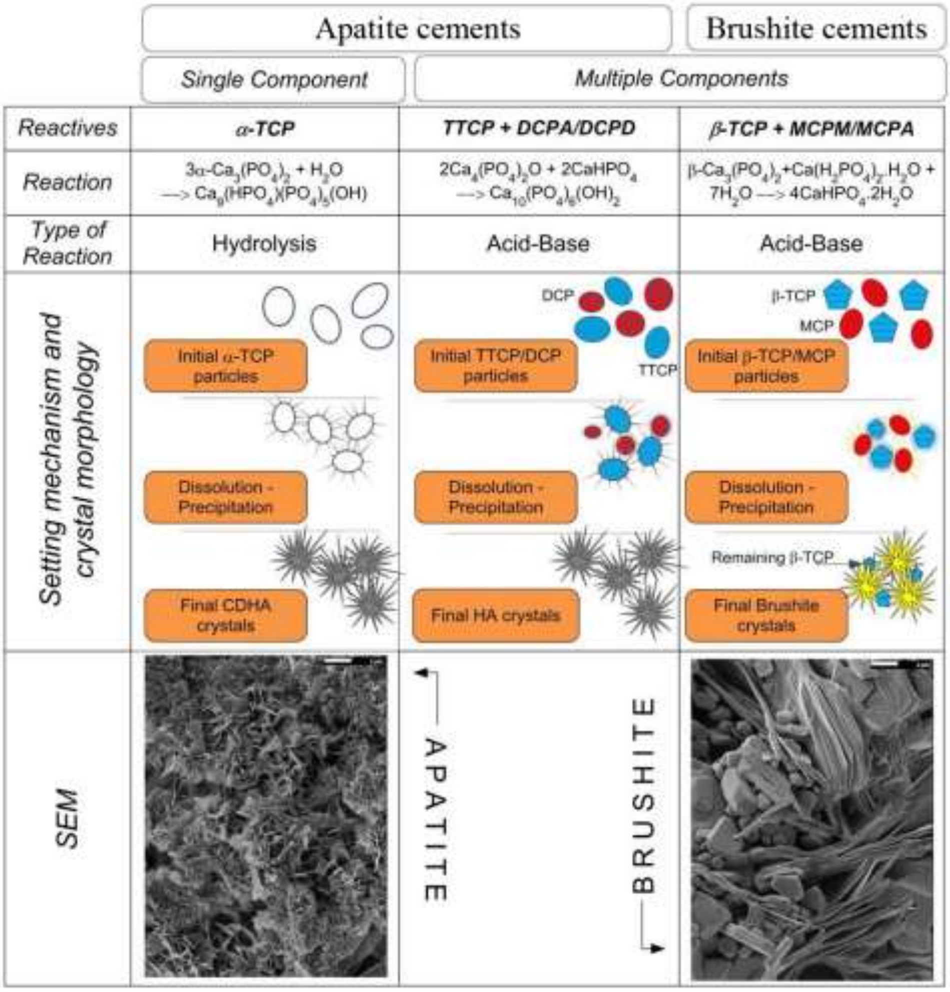

Fig. 3. Classification of $CaPO_4$ formulations with examples of the most common compositions. Scanning electron micrographs of set apatite and brushite cements obtained by the hydrolysis of α-TCP and by reaction of β-TCP with MCPM, respectively, are also shown. Reprinted from Ref. [258] with permission.

The hydration process of $CaPO_4$ formulations is slightly exothermic and undergoes five periods: initiating period, induction period, accelerating period, decelerating period and terminating period [261]. For the classical Brown-Chow formulation, the activation energy of the hydration reaction is 176 kJ/mol [262]. The rate of heat liberation during the solidification of $CaPO_4$ formulations is low. The results of adiabatic experiments showed that the temperature rise arrived at the highest value of 37 °C 3 h later, which would cause no harm to surrounding tissues [263]. The results showed that the hardening process of that formulation was initially controlled by dissolution of the reactants in a 4 h period and subsequently by diffusion through the product layer of CDHA around the grains [160]. In general, a setting process for the $CaPO_4$ formulations occurs mostly within the initial ~ 6 hours, yielding ~ 80 % conversion to the final products with the volume almost constant during setting (*i.e.*, shrinkage is small). However, after hardening, the formulations always form brittle bioceramics with the tensile strength of 5 to 20 times lower than the compression strength [263, 264]. Since this biomaterial is weak under tensile forces, such formulations can only be used either in combination with metal implants or in non-load bearing (*e.g.,* craniofacial) applications [4, 5, 260, 265]. This is confirmed by the mechanical characterization of a bone defect model filled with bioceramic cements [266].

To conclude this part, one must stress, that chemical equations (1) – (6) for setting processes are valid for the *in vitro* conditions only. There are evidences that samples of $CaPO_4$ formulations retrieved 12 h after hardening *in vivo* already contained carbonate apatite, even though the initial mixtures did not contain carbonate as one of the solid components [267]. The mass fraction of carbonate in the 12 h samples was about 1 %. The results suggest that under the *in vivo* conditions, carbonate is readily available and this allows formation of carbonate apatite in favor of carbonate-free CDHA [267].

By the end of the previous millennium, the United States Food and Drug Administration (FDA) approved several self-setting $CaPO_4$ formulations (Table 2) for clinical use [24, 268]. The same formulations also received a Conformite Europene (CE) mark for certain maxillofacial indications and for use as bone-void fillers in the specific non-load-bearing orthopedic indications [260]. The major properties of these formulations are available in literature [24]. An extended list of the available formulations is presented in Table 3 [174], while even more formulations are in experimental stages. Other lists of the commercially available injectable bone cements with their chemical composition (when obtainable) might be found elsewhere [5, 193, 269-271]. A general appearance of two randomly chosen commercial $CaPO_4$ cements is shown in Fig. 4.

Fig. 4. A presentation of two randomly chosen commercial $CaPO_4$ cements.

Table 2. Some self-setting $CaPO_4$ formulations having the 510(k) clearance from the FDA [19, 260, 268]. The technical data on these cements might be found in literature [24].

Product*	Manufacturer	Applications*
BoneSource™**	Striker Howmedica Osteonics (Rutherford, NJ)	Craniofacial
α-Bone Substitute Material (α-BSM®)***	Etex Corporation (Cambridge, MA)	Filling of bone defects and voids, dental, craniofacial
Skeletal Repair Systems (SRS®)	Norian Corporation (Cupertino, CA)	Skeletal distal radius fractures, craniofacial

* In Europe, other applications may apply, and the materials may be sold with a different commercial name.
** BoneSource™ is the original formulation of $CaPO_4$ cement developed by Brown and Chow.
*** In Europe, it is distributed by Biomet Merck (Zwijndrecht, The Netherlands) as Biobon® [166], while in North America it is marketed by Walter Lorenz Surgical (Jacksonville, FL) as Embarc® [22].

3. Three major types of the self-setting $CaPO_4$ formulations

3.1. Apatite-forming formulations

As indicated by its name, apatite-forming formulations have more or less crystallized apatite (namely, a poorly crystalline precipitated HA and/or CDHA) as the final product of the setting reactions (chemical equations (1), (4) – (6)), although traces of un-reacted starting compounds can be present [155]. Self-setting FA-forming formulations are also known; they can be prepared by the same way but in the presence of soluble F^--ions [272-274]. Due to the initial presence of carbonates, such commercial formulations as Norian SRS® and Biocement D® (Table 3) form a non-stoichiometric carbonate apatite or dahllite ($Ca_{8.8}(HPO_4)_{0.7}(PO_4)_{4.5}(CO_3)_{0.7}(OH)_{1.3}$) as the end-product [85, 275]. As both CDHA and carbonate apatite are formed in an aqueous environment and have a low crystallinity, they appear to be rather similar to the biological apatite of bones and teeth. These properties are believed to be responsible for their excellent *in vivo* resorption characteristics. Conventional apatite-forming formulations contain TCP and/or TTCP phases in their powder components [270], while a single component formulation consisting of K- and Na-containing CDHA is also available [259]. The reactivity of TCP-based apatite-forming formulations was found to vary as a function of TCP crystal phase, crystallinity and particle dimensions [276, 277]. Generally, a higher reactivity is observed with a thermodynamically less stable phase (increases in the order β-TCP < α-TCP < ACP) and with smaller particle sizes [213, 230]. Nominally, it might be stated that formation of apatites through self-setting reactions is a sort of a biomimetic process because it occurs in physiological environment and at body temperature [69]; however, both the crystallization kinetics and a driving force are very far away from the biomimeticity. A unique feature of the hardened apatite-forming formulations is that the force linking the newly formed crystals (of both CDHA and carbonate apatite) is weak; therefore, the crystals can be easily detached from the bulk of hardened formulations, especially after dissolution has partly occurred. When this happens, osteoclasts and other cells can easily ingest the apatite crystals [278].

Table 3. A list of the commercial self-setting $CaPO_4$ formulations with the producer, product name, composition (when available) and main end-product. The end-product of the reactions can be either an apatite (CDHA, carbonate apatite, *etc*…) or brushite (= DCPD) [173].

Producer	Commercial name	Composition (when available)	Product
aap Implantate (GER)	Calcifix®	Powder: calcium orthophosphates (details unknown); Solution: unknown	apatite
	OsteoCem®	Powder: calcium orthophosphates (details unknown); Solution: unknown	apatite
Berkeley Advanced Biomaterials (US)	Cem-Ostetic™	Powder: calcium orthophosphates (details unknown); Solution: water	apatite
	Tri-Ostetic™	Powder: calcium orthophosphates (details unknown); Solution: water	apatite
Biomatlante (FR)	MCPC	Powder: mainly α-TCP, ACP, BCP (HA + β-TCP); Solution: phosphate buffered solution	apatite
Biomet (US)	Calcibon®	Powder: α-TCP (61%), DCPA (26%), $CaCO_3$ (10%), CDHA (3%); Solution: H_2O, Na_2HPO_4	apatite
	Mimix™	Powder: TTCP, α-TCP, trisodium citrate; Solution: citric acid aqueous solution	apatite

	Mimix™ QC	Powder: Calcium orthophosphate powders, trisodium citrate; Solution: citric acid aqueous solution	apatite
Calcitec (US)	Osteofix	Powder: calcium orthophosphate and calcium oxide powders; Solution: phosphate buffer	apatite
CelgenTek (IR)	iN3 Cement	Powder: α-TCP, DCPA, $CaCO_3$, K_2HPO_4, Miglyol 812, Kolliphor ELP, Amphisol: Solution: 0.9% w/v EP NaCl for injection	apatite
Ceramed (PORT)	Neocement®	Powder: TTCP, β-TCP, chitosan; Solution: H_2O, citric acid, glucose	apatite
ETEX (US)	α-BSM®; Embarc; Biobon	Powder: ACP (50%), DCPD (50%); Solution: un-buffered aqueous saline solution	apatite
	β-BSM®	Composition: could not be found (it has apparently a higher compressive strength and better injectability than α-BSM®)	apatite
	γ-BSM®	Composition: could not be found (putty consistency)	apatite
	OssiPro	Composition: could not be found; the cement is claimed to be macroporous after hardening	apatite
	CarriGen	Composition: synthetic calcium orthophosphate, sodium carboxymethylcellulose, $NaHCO_3$, Na_2CO_3	apatite
FH Ortho (FR)	Eurobone 2	Composition: a mixture of calcium phosphate salts (DCPD + TTCP) and a water soluble polymer; Solution: 5 % Na_2HPO_4 at pH 8.7 aqueous solution	apatite
Graftys (FR)	Graftys® HBS	Powder: α-TCP (78%), DCPD (5%), MCPM (5%), CDHA (10%), hydroxypropylmethylcellulose (2%); Solution: 5 % Na_2HPO_4 aqueous solution	apatite
	Graftys® Quickset	Composition: calcium orthophosphate salts, hydroxypropylmethylcellulose. Solution: 0.5 % Na_2HPO_4 aqueous solution	apatite
InnoTERE (GER)	VELOX®	Powder: α-TCP (60%), DCPA (26%), $CaCO_3$ (10%), CDHA (4%); Solution: short-chain triglyceride, Tween 80, Amphisol A	apatite
Kasios (FR)	Jectos Eurobone®	Powder: β-TCP (98%), $Na_2P_2O_7$ (2%); Solution: H_2O, H_3PO_4 (3.0M), H_2SO_4 (0.1M)	brushite
	JectOS	Powder: β-TCP; Solution: H_2O, H_3PO_3	brushite (55%) + excess of β-TCP (45%)
	FixEx	Powder: β-TCP; Solution: H_2O, H_3PO_4	brushite (55%) + excess of β-TCP (45%)

Kuraray Noritake Dental (J)	Teethmate™	Powder: TTCP, DCPA, Liquid: Water, preservative	apatite
Kyphon (US)	KyphOs™	Powder: β-TCP (77%), $Mg_3(PO_4)_2$ (14%), $MgHPO_4$ (4.8%), $SrCO_3$ (3.6%); Solution: H_2O, $(NH_4)_2HPO_4$ (3.5M)	apatite
LaunchPad Medical (US)	Tetranite®	Powder: TTCP, phosphoserine; Solution: water	apatite
Merck (GER) Biomet (US)	Biocement D	Powder: 58% α-TCP, 24% DCPA, 8.5% $CaCO_3$, 8.5% CDHA; Solution: 4 wt% Na_2HPO_4 in water	apatite
Mitsubishi Materials (J)	Biopex®	Powder: α-TCP (75%), TTCP (20-18%), DCPD (5%), HA (0-2%) Solution: H_2O, Na succinate (12-13%), Na chondroitin sulfate (5-5.4%)	apatite
	Biopex®-R	Powder: α-TCP, TTCP, DCPD, HA, $Mg_3(PO_4)_2$, $NaHSO_3$; Solution: H_2O, Na succinate, Na chondroitin sulfate	apatite
NGK Spark Plug (J)	Cerapaste®	Powder: TTCP + DCPA; Solution: sodium dextran sulfate sulfur 5	apatite
	Primafix®	Powder: TTCP + DCPD; Solution: sodium dextran sulfate sulfur 5	apatite
Produits Dentaires SA (CH), CalciphOs (CH)	VitalOs®	Solution 1: β-TCP (1.34g), $Na_2H_2P_2O_7$ (0.025g), H_2O, salts (0.05M PBS solution, pH 7.4); Solution 2: MCPM (0.78g), $CaSO_4{\cdot}2H_2O$ (0.39g), H_2O, H_3PO_4 (0.05M)	brushite
Shanghai Rebone Biomaterials (CN)	Rebone	Powder: TTCP, DCPA; Solution: H_2O	apatite
Skeletal Kinetics (US)	Callos™	Powder: α-TCP, $CaCO_3$, MCPM; Solution: sodium silicate	apatite
	Callos Inject™	Composition: α-TCP and unknown compounds (likely to be close to that of Callos™)	apatite
	SKaffold™	Powder: α-TCP, CaCO3, MCPM; Solution: sodium silicate	apatite
	Skaffold ReNu™	The same as SKaffold™ but with a porogen to create macroporosity	apatite
	CAAP	Probably similar to SKaffold™	apatite
	OsteoVation EX Inject	Probably similar to Callos Inject™ (Product produced by S.K. but sold by OsteoMed)	apatite
Stryker (US) Leibinger (GER)	BoneSource™	Powder: TTCP (73%), DCPD (27%); Solution: H_2O, mixture of Na_2HPO_4 and NaH_2PO_4	apatite
Stryker (US)	HydroSet™	Powder: TTCP, DCPD, trisodium citrate; Solution: H_2O, polyvynilpyrrolidone, Na orthophosphate	apatite

Surgiwear (India)	G-Bone Cement	Powder: TCP, TTCP; Solution: sodium and calcium salts in aqueous solution	apatite
DePuy Synthes (US)	Norian® SRS Norian® CRS	Powder: α-TCP (85%), $CaCO_3$ (12%), MCPM (3%); Solution: H_2O, Na_2HPO_4	apatite
	Norian® SRS Fast Set Putty, Norian® CRS Fast Set Putty	Composition: could not be found (likely to be close to that of Norian SRS/CRS)	apatite
	Norian Drillable	Composition: calcium orthophosphate powder, bioresorbable fibers and Na hyaluronate solution	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, Na hyaluronate (0.5%)	brushite
Teknimed (FR)	Cementek®	Powder: α-TCP, TTCP, Na glycerophosphate; Solution: H_2O, $Ca(OH)_2$, H_3PO_4	apatite
	Cementek® LV	Powder: α-TCP, TTCP, Na glycerophosphate, dimethylsiloxane; Solution: H_2O, $Ca(OH)_2$, H_3PO_4	apatite

Immediately after implantation, any formulation becomes exposed to blood and other tissue fluids that delays the setting time. Intrinsic setting time for apatite-forming formulations was extensively studied and it appeared to be rather long. For example, for the original formulation by Brown and Chow it ranges from 15 to 22 min [15, 16]. This may result in procedural complications. To remedy this, the amount of liquid could be reduced to a possible minimum. In such cases, all apatite-forming formulations look like viscous and easily moldable pastes, which tend to be difficult to inject. Besides playing with the P/L ratio, the setting time also could be reduced by using additives to the liquid phase (which is distilled water in the Brown-Chow formulation [15, 16]). The list of possible additives includes H_3PO_4, MCPM and other soluble orthophosphates. These additives promote dissolution of the initial solid $CaPO_4$ by lowering the solution pH. In such cases, a setting time in the range of 10 – 15 minutes can be obtained [225-232, 279]. The influence of soluble orthophosphates (*e.g.*, Na_2HPO_4 or NaH_2PO_4) on the setting time is explained by the fact that dissolution of DCPA and formation of CDHA during setting occur in a linear fashion, thus avoiding early formation of CDHA. This is important because too early formation of CDHA might engulf un-reacted DCPA, which slows down DCPA dissolution and thus the setting kinetics becomes slower, while the presence of sodium orthophosphates prevents DCPA particles from being isolated [280]. Particle dimensions [255, 281, 282], temperature and initial presence of HA powders as seeds in the solid phase are other factors that influence the setting time [15, 16, 69, 96, 255-257, 276, 277]; however, *in vitro* studies demonstrated that these parameters did not affect significantly [155]. On the other hand, particle size reduction was found to result in a significant decrease in both initial and final setting times [255, 281, 282], an acceleration of the hardening rate [255] and hydration kinetics of the hardening formulation [282]. In general, smaller crystals or particles result in a higher supersaturation degrees achieved in the self-setting $CaPO_4$ pastes, which favors crystal nucleation and results in the precipitation of greater many and smaller needle-like crystals, instead of the larger plate-like crystals formed when bigger particles are used (Fig. 5) [258]. These different microstructures give rise to different pore size distributions in the set formulations (bottom part of Fig. 5). Besides, the crystallite dimensions of the final products can be strongly reduced by increasing the specific surface of the starting powders, which allows developing formulations with tailored structures at the micro- and nano-scale levels [255]. Unfortunately, an unclear correlation was found between the particle dimensions of the initial $CaPO_4$ and mechanical properties of the hardened products: namely, a significant increase in compressive strength and storage modulus was reported for some formulations [281, 282] but a minor effect on compressive strength was discovered for other ones [255]. This inconsistence is not surprising because the manufacturing methods used to produce test samples varied from one author to the other. Therefore, the only remaining fact is that the hardened formulations are brittle and hence worthless for load-bearing applications [4, 5].

Setting process of the most types of apatite-forming formulations occurs according to just one chemical reaction (see chemical equations (1), (4) – (6)) and at near the physiological pH, which might additionally contribute to the high biocompatibility [191-193]. Namely, for the classical formulation by Brown and Chow, the transmission electron microscopy results suggested the process for early-stage apatite formation as follows: when TTCP and DCPA powders were mixed in an orthophosphate-containing solution, TTCP powder quickly dissolved due to its higher solubility in acidic media. Then the dissolved ions of calcium and orthophosphate, along with ions already existing in the solution, were precipitated predominantly onto the surface of DCPA particles. Few apatite crystals were observed on the surface of TTCP powder. At a later stage of the reaction, an extensive growth of apatite crystals or whiskers effectively linked DCPA particles together and bridged the larger TTCP particles causing the setting [283].

However, Norian SRS® and Cementek® (Table 3) were found to set according to two chemical reactions: precipitation of DCPD, followed by precipitation of either CDHA or carbonate apatite:

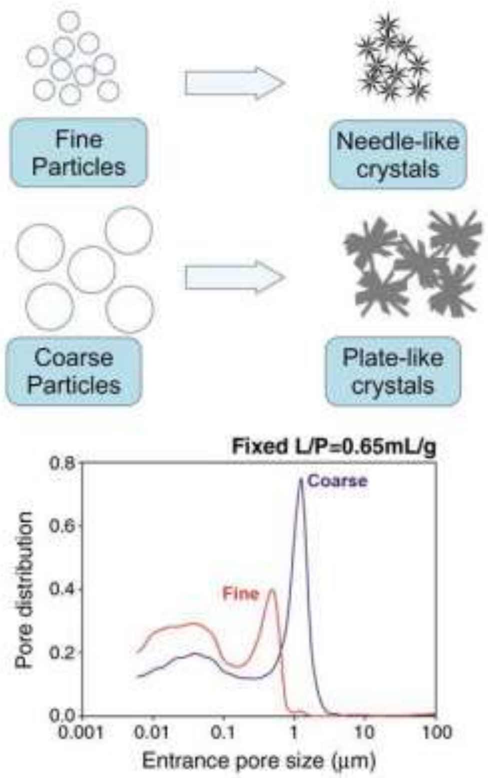

Fig. 5. A schematic drawing of the influence of the particle dimensions on the properties of self-setting formulations. Reprinted from Ref. [258] with permission

$$\alpha\text{-}Ca_3(PO_4)_2 + Ca(H_2PO_4)_2\cdot H_2O + 7H_2O = 4CaHPO_4\cdot 2H_2O \quad (7)$$

$$5.2CaHPO_4\cdot 2H_2O + 3.6CaCO_3 = Ca_{8.8}(HPO_4)_{0.7}(PO_4)_{4.5}(CO_3)_{0.7}(OH)_{1.3} + 2.9CO_2\uparrow + 12H_2O \quad (8)$$

The initial chemical reaction (7) was very fast and provoked DCPD formation and initial setting within seconds. The second step was slower: DCPD reacted completely within several hours with remaining α-$Ca_3(PO_4)_2$ and $CaCO_3$ forming carbonate apatite according to equation (8). The latter step caused the hardening. A similar two-step hardening mechanism was established for a formulation consisting of MCPM and CaO: in the first step, during the mixing time, MCPM reacted with CaO immediately to give DCPD, which, in the second step, reacted more slowly with the remaining CaO to give CDHA [91].

In addition, the setting mechanism of an apatite-forming formulation was investigated in details for a three-component mixture of TTCP, β-TCP and MCPM dry powders in convenient proportions and with the overall atomic Ca/P ratio equal to 1.67. Two liquid phases in a raw were used to damp the cement powder, initially it was water + ethanol (ethanol was added to slow down the hardening) and afterwards H_3PO_4 and sodium glycerophosphate were added to water to prepare a reactive liquid [184]. At the very beginning, DCPD was found to form according to two chemical equations:

$$Ca(H_2PO_4)_2{\cdot}H_2O + \beta\text{-}Ca_3(PO_4)_2 + 7H_2O = 4CaHPO_4{\cdot}2H_2O \quad (9)$$

$$Ca_4(PO_4)_2O + 2H_3PO_4 + 7H_2O = 4CaHPO_4{\cdot}2H_2O \quad (10)$$

The formation reactions of DCPD were fast and corresponded to the initial setting. Afterwards, TTCP reacted with the previously formed DCPD and with β-TCP to give CDHA according to the equations:

$$2Ca_4(PO_4)_2O + 2CaHPO_4{\cdot}2H_2O = Ca_{10\text{-}x}(HPO_4)_x(PO_4)_{6\text{-}x}(OH)_{2\text{-}x} + xCa(OH)_2 + (4\text{–}x)H_2O \quad (11)$$

$$2Ca_4(PO_4)_2O + 4\beta\text{-}Ca_3(PO_4)_2 + (2+2x)H_2O = 2Ca_{10\text{-}x}(HPO_4)_x(PO_4)_{6\text{-}x}(OH)_{2\text{-}x} + 2xCa(OH)_2 \quad (12)$$

The reaction kinetics of the CDHA phase formation was quite slow and corresponded to the hardening stage. Although OCP was not detected in that study, its formation as an intermediate phase was postulated [184]. A similar suggestion on the intermediate formation of OCP was made for the setting mechanism of Brown-Chow classical formulation [150, 155]; however, reliable evidences for its presence are still lacking [228, 284]. Strong experimental evidences of the existence of a transient OCP phase during setting were found in still other studies; however, that system contained sodium silicates [56, 181]. In all cases, OCP was suggested to appear as an intermediate because it was a faster forming phase than CDHA. This hypothesis is based upon the classical studies performed by Prof. W. E. Brown *et al*., about the precursor phase formation during chemical crystallization of apatites in aqueous solutions [285-287].

Solubility of the hardened apatite-forming formulations in aqueous solutions is expected to be rather similar to that of bone mineral. This means that they are relatively insoluble at neutral pH and increasingly soluble as pH drops down; this is an important characteristic of normal bone mineral that facilitates controlled dissolution by osteoclasts [275].

3.2. Brushite-forming formulations

The term "brushite" was given to DCPD in 1865 in commemoration of Prof. G. J. Brush of Yale College, USA [288]. Thus, as indicated by its name, DCPD is the major product of the setting reaction for brushite-forming formulations (chemical equations (2) and (3)), although traces of the un-reacted starting compounds can be present as well. It should be noticed that brushite is not stable in body fluids at the physiological pH and thus, being implanted, it is inevitably transformed (more or less rapidly, depending on the size of the implant) into non-stoichiometric ion-substituted CDHA. Mirtchi and Lemaître [199] and independently Bajpai *et al*., [45] introduced this type of the cements in 1987. Up to now, several formulations have been already proposed, *e.g.,* β-TCP + MCPM [199, 200], β-TCP + H_3PO_4 [45-47, 51] and TTCP + MCPM + CaO [289]. The full list of brushite-forming formulations is available in a topical review on the subject [290]. As seen from the chemical composition, all types of the brushite-forming formulations are set by the acid-base interaction only. As DCPD can only be precipitated at the solution pH < 6 (Table 1), the pastes of the self-setting brushite-forming formulations are always acidic during hardening [47, 291]. For example, during setting of a β-TCP + MCPM formulation, the formulation pH varies from very acidic pH values of ~ 2.5, to almost neutral pH values of ~ 6.0 [47]. Replacing MCPM by H_3PO_4 renders the paste very acidic for the initial ~ 30 s but then the pH profile follows that obtained with MCPM. It is important to notice, that β-TCP + H_3PO_4 formulations have several advantages over β-TCP + MCPM ones, namely: (i) easier and faster preparation, (ii) a better control of the chemical composition and reactivity, (iii) improved physico-chemical properties, such as longer setting times and larger tensile strengths due to a higher homogeneity. However, the use of H_3PO_4 might impair the biocompatibility of the formulations, due to low pH values during setting [47].

A study to elucidate the setting mechanism of β-TCP + H_3PO_4 formulations in the presence of phytic acid was performed [51]. According to the authors, at the beginning of the setting stage, H_3PO_4 rapidly reacted with a part of the available β-TCP to form MCPM:

$$\beta\text{-}Ca_3(PO_4)_2 + 4H_3PO_4 + 3H_2O = 3Ca(H_2PO_4)_2{\cdot}H_2O \quad (13)$$

Further, MCPM reacted with the remaining part of β-TCP to form monetite according to (14) and/or brushite according to (15):

$$Ca(H_2PO_4)_2{\cdot}H_2O + \beta\text{-}Ca_3(PO_4)_2 = 4CaHPO_4 + H_2O \quad (14)$$

$$Ca(H_2PO_4)_2{\cdot}H_2O + \beta\text{-}Ca_3(PO_4)_2 + 7H_2O = 4CaHPO_4{\cdot}H_2O \quad (15)$$

Formation of monetite was found to finish at approximately the same time when the dissolution of MCPM and β-TCP was completed, while brushite formation slightly continued for a few hours after the starting phases were consumed, but then its content also reached a plateau. At the end of the measurement, mixtures of brushite and monetite were formed [51].

As the solubility of $CaPO_4$ generally decreases with increasing of their basicity (Table 1 and Fig. 1), the setting time of brushite-forming formulations much depends on the solubility of a basic phase: the higher its solubility, the faster the setting time. Therefore, the setting time of formulations made of MCPM + a basic $CaPO_4$ decreases in the order: HA > β-TCP > α-TCP [4, 5]. For example, HA + MCPM mixtures have a setting time of several minutes, β-TCP + MCPM mixtures – of 30 to 60 seconds and α-TCP + MCPM mixtures – of a few seconds [199, 200]. Furthermore, if brushite-forming formulations contain an excess of a basic phase, the equilibrium pH will be given by the intersection of the solubility isotherms of the basic phase with that of DCPD. For example, the equilibrium pH values of β-TCP + MCPM, HA + MCPM and TTCP + MCPM mixtures were found to be 5.9, 4.2 and 7.6, respectively [4, 5]. Follow-up of the chemical composition by ^{31}P solid state NMR enabled to show that the chemical setting process for β-TCP + MCPM formulation reached the end after ~ 20 min [292]. Nevertheless, despite this initial high reactivity, the hardening reaction of brushite-forming formulations typically lasts one day until completion [276, 277]. Additives that inhibit the crystal growth of DCPD have been used successfully to increase the setting time of β-TCP + MCPM mixtures [293]. Interestingly that, contrary to apatite-forming formulations, the brushite-forming ones can be initially liquid and still set within a short period of time [4, 5].

By itself, brushite is remarkably biocompatible and bioresorbable [291]. Due to both a better solubility of DCPD if compared to that of CDHA (Table 1 and Fig. 1) and metastability of DCPD under the physiological conditions [294], after implantation self-setting brushite-forming formulations are faster degradable than apatite-forming ones [295-297]. They are quickly resorbed *in vivo* and suffered from a rapid decrease in strength (although the mechanical properties of the healing bone increase as bone ingrowth occurs [67]). A short setting time, a low mechanical strength and a limited injectability seem to prevent brushite-forming formulations from a broader clinical application. However, the major reason why they are not widespread is probably not related to the mechanical issues but just to a later arrival on the market. Use of sodium citrate or citric acid as setting retardants is an option to get more workable and less viscous pastes of brushite-forming formulations [53, 298-302]. Similar effect could be achieved by addition of chondroitin 4-sulfate [303] and glycolic acid [304]. For the formulations with H_3PO_4 as the initial reactant (chemical equation (3)), acid deficient formulations were also found to improve the workability. In this case, the setting reaction might be described by the following chemical equation [298]:

$$3.7\beta\text{-}Ca_3(PO_4)_2 + H_3PO_4 + 27.8H_2O = 3CaHPO_4{\cdot}2H_2O + 2.7\beta\text{-}Ca_3(PO_4)_2 + 21H_2O \quad (16)$$

Although, several studies revealed that too much of DCPD in a given volume was not detrimental to the biological properties of brushite-forming formulations [67, 275, 289], occasionally, when large quantities of them were used, a certain degree of tissue inflammation during the first weeks of *in vivo* implantation were reported [297, 298, 305]. Further investigations indicated that the inflammatory could be due to a partial transformation of DCPD into CDHA with release of orthophosphoric acid [306]:

$$(10–x)CaHPO_4{\cdot}2H_2O = Ca_{10-x}(HPO_4)_x(PO_4)_{6-x}(OH)_{2-x} + (4–x)H_3PO_4 + (18–x)H_2O \quad (17)$$

Transformation of DCPD into CDHA was found to occur via two successive processes: dissolution and precipitation [307] and could be retarded by adding magnesium ions to the formulations, thus reducing the possibility of inflammation [4, 5]. The aforementioned case of acid deficient formulations (chemical equation (16)) is the second option, because it reduces the amount of un-reacted acid [298] with an option to consume liberating in chemical equation (17) H_3PO_4 by the excess of β-TCP. Implantation of previously set brushite-forming formulations might be the third option, because a solid bioceramics was found to be better tolerated than paste implants. Besides, more bone was formed at the solid implant contact and the solid material degraded not so rapidly [308]. For the hardened brushite formulations, a linear degradation rate of 0.25 mm/week was reported [309]. This rapid degradation rate might lead to formation of an immature bone. Adding β-TCP granules to the self-setting pastes could solve this problem because the granules might act as bone anchors and encourage formation of a mature bone [309, 310].

Additional details on the self-setting brushite-forming $CaPO_4$ formulations [261], as well as their mechanical properties [311], are available in literature.

3.3. Monetite-forming formulations

The term "monetite" belongs to a $CaPO_4$ mineral, which was first described in 1882 in rock-phosphate deposits from the Moneta (now Monito) Island (archipelago of Puerto Rico) [312]. It is well known, that DCPA (monetite) is crystallized under the same conditions as DCPD (brushite) but either from aqueous solutions at elevated (t > ~ 90 °C) temperatures or at ambient conditions but in water-deficient environments [291, 313]. Therefore, self-setting monetite-forming formulations could exist. Indeed, there are several publications, in which formation of monetite instead of brushite was detected as the final product [32, 48, 51, 111, 137, 211, 302, 314-321]. For example, addition of a big amount of NaCl to a self-setting β-TCP + MCPM formulation was found to result in monetite formation at ambient conditions [318, 319]. Similarly, the same formulation mixed with glycerol, followed by injection into molds, which were immersed in deionized water to achieve full setting by diffusion of water, followed by drying and autoclaving at 120 °C also resulted in monetite formation [321]. Furthermore, solid DCPA was prepared by a chemical interaction between $Ca(OH)_2$ powder and a solution of NaH_2PO_4 dissolved in H_3PO_4 [137]. Moreover, there are self-setting $CaPO_4$ formulations, in which the final product strongly depends on the reaction temperature. Namely, setting at different temperatures showed that mainly brushite was formed at 5 °C, a mixture of brushite and monetite was formed at 21°C and mainly monetite was formed at 37 °C [316]. Interestingly, that for MCPM + β-TCP formulations, an excess of β-TCP was found to result in brushite formation, while an excess of MCPM resulted in monetite formation [302, 316]. Furthermore, the use of Sr-substituted β-TCP as an initial reactant not only induced strontium substitution in the setting products but also favored formation of monetite as setting product, whereas Sr-free cements set to brushite [111]. In addition, there are formulations, which, after setting, resulted in formation of a complicated mixture of the products, such as DCPA, DCPD, CDHA and traces of the un-reacted initial components [51, 322]. Finally, monetite might be both formed during a prolonged storage of dry powders of brushite-forming formulations in normal laboratory atmosphere (~ 60% relative humidity) [323] and by heating of the brushite-forming formulation in a microwave oven during setting [211].

3.4. Composite (apatite + brushite)-forming formulations

In 2018, a group of Russian researchers published a paper on self-setting composite (apatite + brushite)-forming formulations [324]. Briefly, the researchers just mixed unset pastes of apatite- and brushite-forming $CaPO_4$ formulations in the proportions equal to 70 wt.%/30 wt.%, 50 wt.%/50 wt.% and 30 wt.%/70 wt.%, respectively, and allowed those mixtures to set. α-TCP powders with dimensions within 1 – 10 μm were used as the source of $CaPO_4$, while a hardening liquid comprised an aqueous solution of magnesium phosphate dissolved in H_3PO_4. The P/L ratios were 4.0 g/ml for brushite- and 4.5 g/ml for apatite-forming formulations, respectively. The hardened samples were found to represent triphasic mixtures of DCPD, CDHA and un-reacted α-TCP in variable proportions starting from DCPD/CDHA/TCP = 85/10/5 wt.% for the brustite-forming formulations and ending with DCPD/CDHA/TCP = 0/90/10 wt.% for the apatite-forming ones. A uniform distribution of brushite and apatite phases without interactions between them was observed in the hardened samples. Both setting time and compressing strength were found to increase with CDHA content increasing in the hardened formulations [324].

4. Various properties

4.1. Setting and hardening

Generally, setting kinetics of the self-setting $CaPO_4$ formulations represent a process, during which the initially viscous but flowable pastes are transformed into rigid solids. This process must be slow enough to provide sufficient time to a surgeon to perform implantation but fast enough to prevent delaying the operation. Ideally, good mechanical properties should be reached within minutes after initial setting and at the initial stages these properties mainly depend on the quantity of the reaction products, the amount of contact points among them and the volume proportion of the newly formed crystals [282]. Setting time corresponds to the time needed to get a compact block; however, in no case this means that the chemical reactions are achieved by this time. Two main experimental approaches are used to study the setting process: a batch approach and a continuous approach. In the batch approach, the setting reaction is stopped at various times and the resulting samples are analyzed to determine *e.g.,* the composition and compressive strength of the samples [276, 277]. There are currently two standardized methods to apply this approach, namely, Gillmore needles method (ASTM C266-89) [325] and Vicat needle method (ASTM C191-92) [326]. The idea of both methods is to examine visually the sample surfaces to decide whether the formulation has already set, *i.e.* if no mark can be seen on the surface after indentation. Besides, the setting process might be monitored in real time by non-destructive methods (the continuous approach). The examples comprise applications of a pulse-echo ultrasound technique [327, 328], a pH meter [90, 276], an embedded fiber Bragg grating sensor [40, 43], an isothermal differential scanning calorimetry [51, 229, 230, 329-335], a rheometer [336], as well as an alternating current (AC) impedance spectroscopy [337]. For example, calorimetry measurements suggested that in equation (2) the endothermic MCPM dissolution and the highly exothermic β-TCP dissolution occurred simultaneously, followed by the exothermic crystallization of DCPD [333]. Thus, brushite-forming formulations usually warm upon final setting [329]. In addition, non-destructive methods of Fourier-transform infrared spectroscopy [55, 56, 58, 334, 338], solid state NMR [292], synchrotron X-ray diffraction [302], X-ray diffraction [51, 55, 58, 81, 204, 339] and energy dispersive X-ray diffraction [55-58, 340-342] can be applied as well. Two latter techniques proved to be powerful even though they have limitations such as the time required for each measurement (250 s for a single X-ray diffraction scan is a problem for fast setting reactions). In addition, the analysis is often located at the sample surfaces where evaporation and thermal effects can modify the reaction rates if compared to those in the bulk. Unfortunately, the continuous approaches are indirect, which markedly complicates an interpretation of the collected data, particularly for complex formulations [276].

A way to assess the hardening kinetics is to measure its setting time, which means the time required to reach a certain compressive strength, generally close to 1 MPa. The most straightforward approach is to prepare self-setting samples with a well-controlled geometry (*e.g.*, cylinders), incubating those samples for various times in the right environment (temperature, humidity) and assessing the composition and mechanical properties of the samples as a function of time [276]. An example of setting kinetics for a brushite-forming formulation coupled with a time-dependent development of its linear viscoelastic properties is schematically shown in Fig. 6 [336]. One should stress that setting time for $CaPO_4$ formulations often corresponds to an earlier stage in the overall setting reaction, typically 5 – 15 % of the overall reaction, while the end of the hardening process is typically reached after several days [155, 228]. Gillmore needles were used with the success to measure the initial (*I*) and final (*F*) setting times of $CaPO_4$ cements [148]. Namely, a light and thick needle is used to measure the initial setting time *I*, while a heavy and thin needle for the final setting time *F* [175]. The clinical meaning is that the cement paste should be implanted before time *I* and that the wound can be closed after time *F* (Fig. 7).

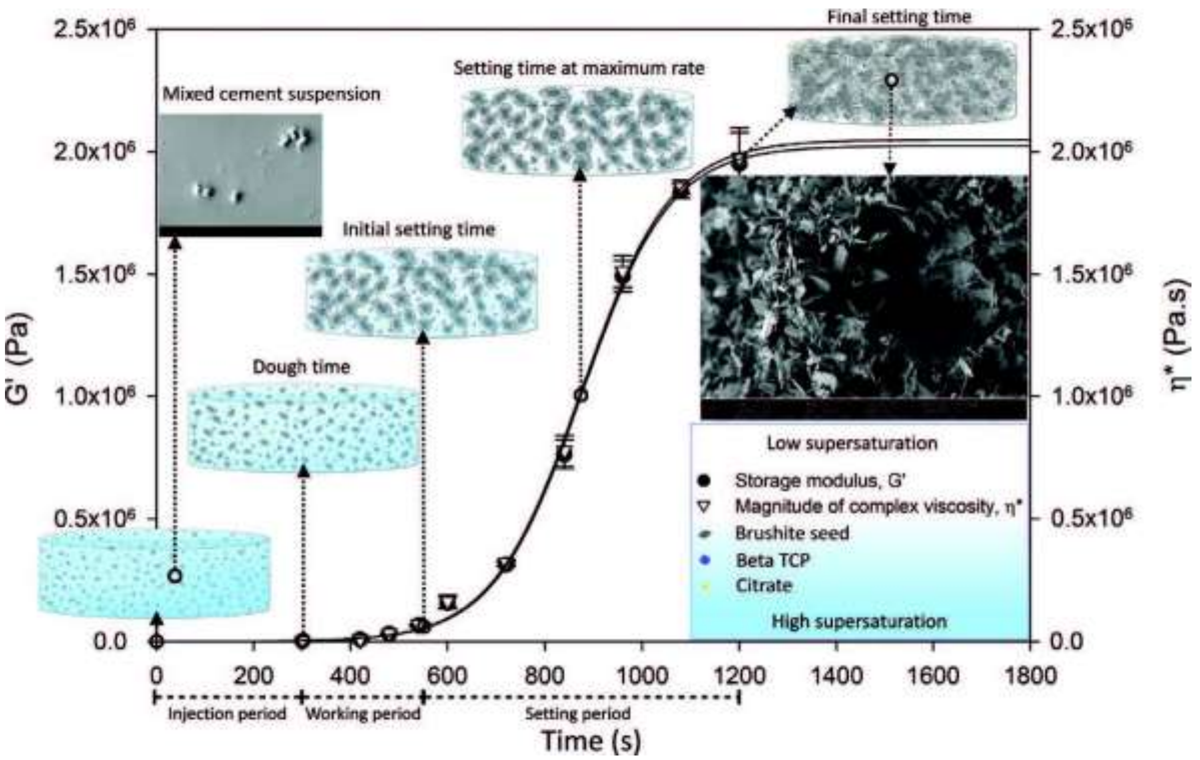

Fig. 6. A setting kinetics for a brushite-forming formulation coupled with a time-dependent development of its linear viscoelastic properties. Reprinted from Ref. [336] with permission.

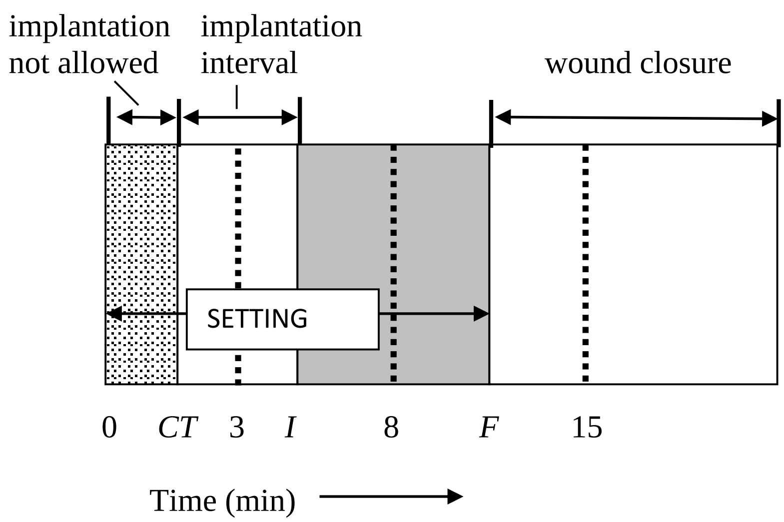

Fig. 7. A diagram of the setting parameters relevant for a self-setting $CaPO_4$ formulation: *CT* – cohesion time; *I* – initial setting time; *F* – final setting time. Adapted from Ref. [62] with permission.

The implanted formulations should not be deformed between times *I* and *F* because in that stage of the setting any deformation could induce cracks [62]. The following handling requirements have been formulated for $CaPO_4$ cements, as a result [175, 343]:

$$3 \text{ min} \le I < 8 \text{ min}$$
$$I - CT \ge 1 \text{ min}$$
$$F \le 15 \text{ min}$$

These parameters are represented schematically in Fig. 7. The second requirement means that the cohesion time (*CT*) must be at least 1 min before *I*, so that a clinician has at least 1 min to apply and to mold the material. *CT* is the time from which a formulation no longer disintegrates when immersed in Ringer's solution [175]. As the mixing in a mortar is about 1 min, the shortest *CT* that can be allowed is about 2 min, so that a clinician has at least 1 min to collect the paste from the mortar and put it on a pallet knife or into a syringe with which it is to be transferred to the wound after *CT* and before *I* [175]. For dental applications, time *I* must be close to 3 min, whereas for orthopedic applications it must be close to 8 min. However, in no case it will be tolerable for the clinicians if time *F* becomes greater than 15 min [62, 175].

However, the setting and hardening processes of the $CaPO_4$ formulations may not be so simple, as described by the aforementioned chemical equations. For example, for two-component $CaPO_4$ formulations, an influence of particle dimensions on the setting properties was discovered. Namely, in the case of the classical Brown-Chow formulation (TTCP + DCPA), to form HA, ions of Ca^{2+} and PO_4^{3-} should be supplied in the proportions equal to Ca/P = 1.67. However, dissolution rates of DCPA and TTCP appear to be different: TTCP dissolves faster than DCPA, which can be compensated by varying the particle dimensions of both reagents. Table 4 [344] summarizes the results of setting experiments for TTCP + DCPA mixtures with different particle dimensions. As shown in Table 4, apatite-forming formulations consisting of small particles of TTCP and large ones of DCPA do not set. On the other hand, mechanical strength of the hardened formulations appears to be proportional to the diameter ratio of TTCP/DCPA particles. Among 4 tested formulations, the one with the highest TTCP/DCPA diameter ratio (*i.e*. consisting of large particles of TTCP and small ones of DCPA) was found to set providing bioceramics with the highest mechanical strength. These results clearly demonstrated that the particle size regulation appears to be important. Since TTCP dissolves faster than DCPA, the proper combination of large particles of TTCP with a small specific surface area and small ones of DCPA with a large specific area appears to be necessary to decrease the dissolution rate of TTCP and increase that of DCPA [344].

Furthermore, in 2017, a nonlinear, oscillatory dynamics was detected in the evolution of phase compositions during the setting of both apatite- and brushite-forming $CaPO_4$ formulations [345]. One should stress that all these effects were discovered in the presence of additional components. Namely, Zn- and Cu-containing β-TCPs were used as the initial reagents for the brushite-forming formulations, while gelatin was present in the apatite-forming formulation. The presence of these components, on the one hand, simplified detection of the compositional fluctuations due to formation of new compounds, such as scholzite ($CaZn_2(PO_4)_2\cdot 2H_2O$), which was detected by an XRD technique, but, on the other hand, their presence might be a reason of those fluctuations. Namely, for Zn-containing β-TCP, the compositional fluctuations were found to occur throughout 80 hours (*i.e*., long after the hardening processes was over from the mechanical standpoint), while for Cu-containing β-TCP, those fluctuations fell below the detection limit after ~ 24 hours. For the case of apatite-forming formulations, the presence of gelatin was found to cause the compositional fluctuations as periodical transformations of CDHA to ACP phases during gelation and back to poorly crystalline CDHA upon hardening [345]. Obviously, the discovered compositional oscillations require further investigations, because they will help to understand the setting mechanisms.

Table 4. Effects of particle size on the diametral tensile compressive strength of self-setting $CaPO_4$ formulations consisting of TTCP and DCPA [344].

Average particle diameter (μm)		Ratio of the average particle diameter of TTCP/DCPA	Compressive strength (MPa)
TTCP	DCPA		
1.6	11.9	0.13	0 (no setting)
12.4	11.9	1.04	7.1±1.0
1.6	0.9	1.78	21.8±4.4
12.4	0.9	13.8	51.0±4.5

4.2. Phase mixing

In the clinical situation, self-setting $CaPO_4$ formulations can be either applied by the fingertips of a surgeon or injected from a syringe to the defect area of a bone. The first type of the application requires formulation of high-viscous self-setting pastes and putties, which can be applied manually as dough (there is a term "dough time", *i.e*., the time, at which a wet formulation no longer sticks to surgical gloves), while the second type requires formulation of low-viscosity compositions, which can be applied by injection from a syringe [175]. Currently, injection appears to be the preferred method between these two major options. Thus, a compromise must be found between a high viscosity leading to too high injection forces and a low viscosity increasing the risk of extravasations. Thus, viscosity values in the range of 100 – 2000 Pa·s are generally considered to be adequate [346].

In any case, before using, a surgeon needs to have a powder and a liquid be mixed properly and thoroughly (to avoid the powder/liquid encapsulation) within the prescribed time. The mixing duration is particularly critical for the fast-setting formulations. Namely, for some brushite-forming ones, mixing the paste for too long may break the growing crystals involved in the setting process, which will result in lower mechanical properties. Furthermore, the mixing stage must be performed in a sterile environment. Therefore, a mixing procedure is very important because prior to be injected, a self-setting paste must be transferred from a mixing chamber into a syringe. Ideally, this should be done without trapping air bubbles by the formulation [347]. Earlier, most $CaPO_4$ formulations were manually mixed with aqueous solutions using a mortar and either a pestle or a spatula. That time, some concerns were raised about an insufficient and inhomogeneous mixing thus compromising the implant strength, as well as on inconsistencies between operators causing unpredictable variations in graft performance [348]. Mechanical mixing (such as an electrically powered mixing machine of Norian SRS/CRS® (Fig. 8), Mini-malax® mixing system for Cementek®, produced by Teknimed S.A. or Speed-Mixer DAC 150.1 FVZ-K, produced by Hauschild Engineering) is the modern approach. It allows mixing the pastes within 60 – 80 s and enables a rapid and reliable filling of the application syringe [270]. Besides, a powder and a solution could be placed into a syringe and mixed inside a shaker to produce a consistent self-setting paste of the desired viscosity [347]. A mechanical mixing was found to decrease both the mean viscosity of the curing pastes and variability in the viscosity at a given time [349]. However, it did not improve the mechanical strength of the hardened formulations [4, 5].

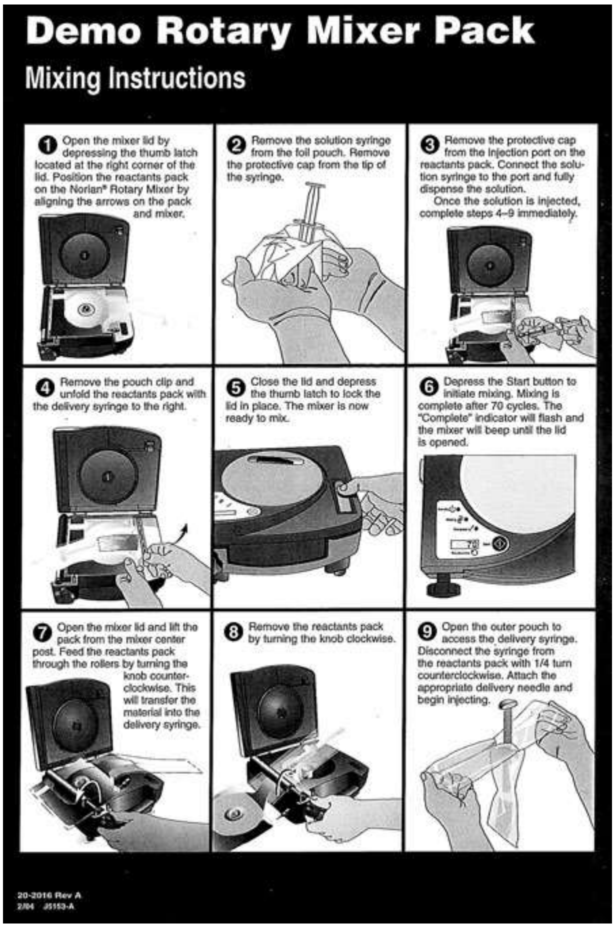

Fig. 8. Mixing instructions for a Norian rotary mixer.

Of the commercial formulations listed in Table 2, Norian SRS® is sold as a reactant pack containing two components: a mixture of dry powders (MCPM + α-TCP + $CaCO_3$) and a liquid (aqueous solution of Na_2HPO_4). The components are mixed in the operating room. The paste that is formed is malleable and injectable for ~ 5 min; it hardens within ~ 10 min after injection [24, 276]. However, data are available that out of 4.5 ml Norian SRS® cement paste ~ 3 ml is injectable only, whereas up to 1.5 ml of the paste might remain uninjectable from the syringe [62]. This phenomenon is prescribed to the formulation rheology and its interaction with the hydraulic forces of the syringe. α-BSM® (Table 2) is also a two-component system; it is prepared from a mixture of ACP and DCPD powders and a saline solution [225]. Biopex® consists of four different types of $CaPO_4$: 75 wt. % α-TCP, 18 wt. % TTCP, 5 wt. % DCPD and 2 wt. % HA (Table 3). The aqueous solution contains 12 wt. % sodium succinate and 5 wt. % sodium chondroitin sulfate [350]. Effects of liquid phase on the basic properties of Biopex® were investigated. When mixed with neutral sodium hydrogen orthophosphate or succinic acid disodium salt solution, the initial setting times of the cement were 19.4 ± 0.55 and 11.8 ± 0.45 min, respectively. These setting times were much shorter than that of distilled water, 88.4 ± 0.55 min [351]. Biopex® is mixed with a spatula inside a syringe that can be opened from the front. After mixing, the front part is closed, a needle is inserted into this front part and the cement paste can be manually injected [4, 5].

Several systematic studies on the influence of composition and concentration of the liquids used in preparing of the self-setting $CaPO_4$ formulations were performed as well [53, 299, 300]. Unfortunately, the results appeared to be rather unclear. For example, for several formulations, mixing with sodium citrate or citric acid resulted in some effects on the initial setting time [53, 300], while for other ones the effect was insignificant [299]. Concentration increasing of sodium citrate solution resulted in initial setting time increasing [53, 299], although the injectability variations of the pastes were inconsistent [53, 300].

4.3. Rheological properties

In terms of the rheological properties, all types of the self-setting $CaPO_4$ formulations belong to non-Newtonian fluids. The latter means that the viscosity of such fluids is dependent on shear rate or shear rate history. Nevertheless, good injectability, adequate viscosity and satisfactory cohesion are required for the successful biomedical applications [352, 353]. Among them, injectability was defined as an ability of a formulation to be extruded through a small hole of a long needle (*e.g.*, 2 mm diameter and 10 cm length) [354, 355] (other needles were also applied [356, 357]); and for certain applications, injectability is even a prerequisite. However, other definitions are possible. For example, injectability of a paste was also defined as its ability to stay homogeneous (without filter pressing) during injection, independently on the injection force [354]. Injectability is measured by the weight percentage of the formulation that could be injected without demixing from a standard syringe by either a hand or a force of 100 N maximum (Fig. 9). The numerical values are calculated by the following equation [358]:

$$Inj = (W_F - W_A)/(W_F - W_E) \times 100\%,$$

where *Inj* is the percentage injectability, W_E is the weight of the empty syringe, W_F is the weight of the full syringe and W_A is the weight of the syringe after the injection.

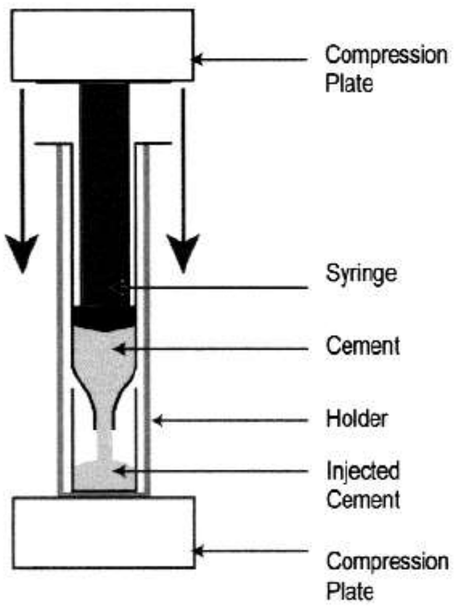

Fig. 9. A schematic representation of the experimental setup used to quantify the injectability of the $CaPO_4$ formulations. Reprinted from Ref. [359] with permission.

Usually, injectability of $CaPO_4$ formulations are varied inversely with their viscosity, the P/L ratio, as well as the time after starting the mixing of liquid and powder [89, 187, 355, 359]. In addition, powder reactivity was shown to influence the injectability. Namely, significant differences were observed between the injection behaviors of the non-hardening β-TCP pastes and self-hardening α-TCP pastes, α-TCP being less injectable than β-TCP and requiring higher injection loads. What is more, the parameters affecting powder reactivity were shown also to affect injectability. Thus, whereas powder calcination resulted in increased injectability, an addition of setting accelerants tended to reduce the injectability [358]. Furthermore, injectability is improved with smaller particle sizes, with shorter and larger diameter cannula, as well as at smaller flow rates [354]. Moreover, particle shape of the powder is also expected to have effects on the injectability. Namely, powders with spherical shape or round particles are easy to roll and thus good handling properties and injectability are found when pastes are prepared from such materials. Besides, it should be noted that the pastes could become fluid with less amount of liquid phase since no captured liquid exists in the case of spherical powder [360, 361].

Unfortunately, when a self-setting formulation, which is a biphasic blend of a finely divided ceramic (powder, granules) and a liquid, is submitted to a pressure gradient, the liquid may flow faster than the solid, resulting in local changes of the paste composition. Specifically, the paste present in the region of the highest pressure (*e.g.*, close to the plunger of a syringe) may become so depleted in liquid that the biphasic blend in this zone is no longer a paste but a wet powder [354, 356]. Contrarily, the paste in the zone of the lowest pressure (*e.g.*, at the cannula tip) is enriched in liquid. As these effects are dynamic, the size of the zone depleted in liquid (wet powder) increases during injection, eventually reaching the tip of the injection device and plugging it. The phenomenon, in which the pressure applied to the paste provokes a phase separation after a certain injection time, is generally referred as filter pressing, phase separation or phase migration [173] (see the aforementioned example for Norian SRS® [62], in which a thick mass remained inside a syringe).

Possible mechanisms underlying the limited injectability of the self-setting $CaPO_4$ formulations have been discussed in literature [187, 357, 362]. In the case of demixing, the exact composition of the extruded part of the paste becomes unknown. Moreover, due to a deviation from the initial P/L ratio, it becomes unclear whether the setting behavior and the mechanical and histological properties of the extruded part are still clinically acceptable. Therefore, a good cohesion of the paste is necessary in order to avoid these problems [363].

Cohesion (= cohesiveness, “non-decay”) is the ability of a paste to keep its geometrical integrity in an aqueous solution [173]. It is evaluated by measuring the amount of solid particles released from the formulation prior to its final setting. For the self-setting formulations, a bad cohesion may prevent setting and may lead to negative *in vivo* reactions due to the release of microparticles [364]. Since a high cohesion is the result of strong attractive forces among the particles, factors enhancing van der Waals forces (attractive) and decreasing electrostatic forces (repulsive) can be used to improve cohesion [173]. For example, an appropriate cohesion was achieved when no disintegration of the paste was observed in the fluid [175, 363]. This can be accomplished by keeping a high viscosity of the self-setting pastes [24] or using cohesion promoters (*e.g.*, 1 – 3 % aqueous solution of sodium alginate [231, 365-367], as well as other chemicals [231, 368-371]). Some $CaPO_4$ formulations fulfill both criteria, *e.g.*, Norian SRS®, but others fulfill only one or even none of these requirements. For example, BoneSource™ [152] and Cementek® (Table 3) are not injectable and blood must be kept away from the implanting site until setting [4, 5]. A poor cohesion has been associated to a poor biocompatibility that might lead to inflammatory reactions [364]. Further details on the cohesion properties of various $CaPO_4$ pastes are available in literature [363].

Viscosity is a measure of the resistance of a fluid, which is being deformed by either shear stress or tensile stress. Generally, the viscosity in the range of 100 – 1000 Pa·s appears to be ideal [372] and, if possible, a self-setting formulation should have a constant viscosity in the indicated range. Unfortunately, viscosity of the self-setting formulations is not a constant value, which, after a decrease in the first seconds after mixing, increases considerably during curing, eventually leading to hardening. Furthermore, viscosity should be high enough to prevent extravasation; therefore, it is very important to define an adequate injection window [372].

4.4. Properties improving

As written above, the properties of the existing self-setting $CaPO_4$ formulations are not ideal. Several ways can be adopted to improve them. The first approach consists of injectability improvement. There are numerous options to do this. Firstly, the injection device can be modified. For example, shorter cannulas with a larger diameter, as well as smaller injection rates favor a good injectability. The last option is not so straightforward: for example, data are available that large injection rates are not detrimental to injectability because of the shear-thinning behavior of many self-setting formulations [357]. Secondly, an external energy might be applied. For example, injectability was improved by ultrasonication, which was believed to result from a reduction in the injection force versus the filtration force as a result of a lesser reduction in the particle interaction and the paste flowability [373]. Thirdly, the composition can also be adapted. Namely, a decrease of the particle size, the P/L ratio and the plastic limit was found to contribute to a better injectability [187, 354, 359]. For example, injectability was found to be unaffected by P/L ratio within the range of 3.85 – 4.50 g/ml but dropped by nearly 100 % between P/L ratio of 4.50 and 5.00 g/ml [53]. However, a decrease in P/L ratio leads to a decrease in the mechanical properties of the self-setting formulations and cohesion might be destroyed. Furthermore, both the initial and final setting times decreased markedly with the P/L ratio increasing [299, 374]. Therefore, variations in the P/L ratio appear to be valid to a certain extent only. That is why the manufacturer of Biopex® suggests using a P/L ratio of 2.8 or 3.3 g/ml. Finally, injectability of the self-setting $CaPO_4$ formulations can be improved by additives. For example, an amount of 0.25 wt.% of sodium phytate was found to be sufficient to achieve the maximum injectability, which could be related to a decrease in zeta potential of the $CaPO_4$ particles [180].

Particle size decreasing of $CaPO_4$ crystals is one more approach of the injectability improvement. For example, α-BSM® is well injectable because it consists of small crystals. Even though small particles require a larger amount of mixing liquid to obtain a paste, injectability and cohesion of such formulations are generally very good [4, 5]. An indirect approach is to add $CaPO_4$ crystals those act as spacers between other particles. For example, DCPA is added to the formulation of Biocement D® to improve injectability [4, 5]. In addition, using of spherical $CaPO_4$ particles as initial reagents appears to be able to improve injectability [360, 361].

Using various chemical additives is the second way to improve the properties of the self-setting formulations [375]. For example, water demand can be reduced by ionically modifying the liquid component, *e.g.*, by adding nontoxic sodium salts of α-hydroxy di- and tri- acids [376, 377]. A list of additives, that have been already studied, includes fluidificants, air-entraining agents, porogens, workability-improvement agents, setting time controllers and reinforcing additives [214, 271, 378]. Besides, various radiopacifiers [379-385] and photo-luminescent additives [386] can be added to simplify an un-invasive *in vivo* monitoring of the implanted $CaPO_4$ formulations. The main role of fluidificants is to reduce a mixing time of the formulations. Citric acid is an example of this reagent; it retards the dissolution-precipitation reactions, decreases the compressive strength during initial setting, but increases its strength in the final stages of hardening [300]. Furthermore, data are available, that citric acid decreases the setting time and improves the mechanical properties of the hardened formulations [387]. Adding of surfactants to the self-setting formulations was found to have two different meanings: they might act as both air-entraining agents by lowering the surface tension [388, 389] and interaction modifiers by shifting the isoelectric point [390].

In addition, studies are available, in which the self-setting $CaPO_4$ formulations were modified by various bioorganic compounds in attempts to influence the bone healing process [391-393]. For example, there is a study, in which a self-setting formulation was set in the presence of cocarboxylase, glucuronic acid, tartaric acid, α-glucose-1-phosphate, L-arginine, L-aspartic acid and L-lysine, respectively, with the aim to influence formation and growth of CDHA crystals through the functional groups of these biomolecules [393]. Except for glucuronic acid, all these modifications were found to result in the formation of smaller and more agglomerated CDHA particles, which had a positive impact on the biological performance indicated by first experiments with the human osteoblast cell line hFOB 1.19. Moreover, an initial adhesion of human bone marrow-derived mesenchymal stem cells was improved on the formulations containing cocarboxylase, arginine and aspartic acid. Furthermore, cell proliferation was enhanced on the formulations modified with cocarboxylase and arginine whereas osteogenic differentiation remained unaffected. Besides, the formulations with arginine and aspartic acid, but not with cocarboxylase, led to a higher binding of a recombinant human bone morphogenetic protein-2 (rhBMP-2) [393]. In addition, a big variety of the functional properties of self-setting $CaPO_4$ formulations can be enhanced by polymeric additives [394].

Since a good adhesion to bones and other structures allows better transmission of forces at the implant/bone interfaces, a proper adhesion between the set formulations and bones is very important for many surgical procedures. Chemical additives might also improve adhesive properties of the self-setting $CaPO_4$ formulations. For example, it was observed that brushite-forming formulations set with pyrophosphoric acid in the liquid phase had an increased adherence to various surfaces such as bone, alumina, sintered HA and stainless steel [395]. A comparable effect can be obtained by addition of phosphoserine [396, 397]. Namely, an apatite-forming bone adhesive based on TTCP and phosphoserine was commercialized under a trade-name Tetranite® (LaunchPad Medical, USA). This formulation was measured to be ~ 10 times more adhesive than common self-setting $CaPO_4$ formulations and ~ 7.5 times more adhesive than non-resorbable polymethyl methacrylate (PMMA) bone cement. Other advantages included a high compression strength, a high adhesive shear strength of bond to both cortical and cancellous bone surfaces, as well as titanium and porous polymer surfaces, a stability of shape on setting, a rapid setting time, an excellent bioresorbability and osteoconductivity, as well as an ease of application [396]. Similar results were obtained with an apatite-forming bone adhesives based on α-TCP and phosphoserine [397].

Porosity is a very important property to provide good *in vivo* bioresorption of implanted biomaterials [398]. Thus, various air-entraining agents and porogens are commonly used to induce macroporosity of self-setting $CaPO_4$ formulations, ideally, without affecting their normal setting. For example, crystals of mannitol, $CH_2OH(CHOH)_4CH_2OH$, were tested as an air-entraining agent; however, both loss of workability during mixing and severe depreciation of mechanical properties were discovered simultaneously [399-405]. Other porogenic agents were also used to create porosity. The examples include: hydrogen peroxide in both liquid phase [406] and iced [407], crystals of $NaHCO_3$ and Na_2HPO_4 [408], calcium sulfate [71], $CaCO_3$ [289, 324], NaCl [324, 406-411], poly(D,L-lactic-*co*-glycolic acid) microparticles [412-419], glucose [418, 420], sucrose [411, 419], microspheres of pectin [421] and gelatin [422-424], vesicants [425], cetyltrimethyl ammonium bromide [426], polytrimethylene carbonate [427], as well as some immiscible liquids. In addition, mixtures of two or several porogens may be used as well. For example, multimodal porogen platforms based on sucrose porogens (for early pore formation) and poly(D,L-lactic-*co*-glycolic acid) porogens (for late pore formation) were used to enhance degradation of the self-setting $CaPO_4$ formulations [428]. All these additives could be applied on pre-set formulations only, while the solubility degree of the solid porogens during setting influences both the content and dimensions of the macroporosity. After hardening, dissolution of the remaining soluble porogens in either water or body fluids produces macropores with the dimensions and shapes of the dissolved crystals. One important limitation that can be envisaged from this route is the need to add a large amount of porogenic agents to guarantee pore interconnectivity, thus compromising not only the excellent biocompatibility and bioactivity of self-setting $CaPO_4$ formulations but also their injectability. Another shortcoming is a lack of strength of the resulting bioceramics, especially if particulates dissolve quickly, greatly limiting its applications. An innovative approach that aims at overcoming the lack of interconnectivity and initial strength consists in using bioresorbable fibers [39, 428-438]. These fibers have the function of initial reinforcing, providing the needed short-term strength and toughness, and gradually dissolving afterwards, leaving behind macropores suitable for bone ingrowth. For example, samples with the proper network (dimensions, shape and porosity) can be created from bioresorbable fibers by means of 3D plotting, followed by their infiltration with self-setting $CaPO_4$ formulations [438]. One interesting advantage of long fibers over particulates and short fibers is the fact that once resorbed they can form interconnected pores inside the solid structure facilitating bone tissue regeneration [439].

One more approach to create porosity consists in adding solid $NaHCO_3$ to the starting powder and using two different liquids: first, a basic liquid to form the paste, and later an acid liquid to obtain CO_2 bubbles to create porosity [440]. Besides, pore forming CO_2 bubbles appear at hardening of apatite-forming formulations, consisting of an acidic $CaPO_4$, such as MCPM or DCPD, and either $CaCO_3$ [33, 66, 85-87] or $NaHCO_3$ [441-443]. Furthermore, addition of an effervescent porogen formulation comprised from $NaHCO_3$ (54.52 %) and citric acid monohydrate (45.48 %) has been suggested [444]. More to the point, the liquid phase of a self-setting formulation might be initially foamed (commonly, addition of some accessory reagents, such as emulsifiers, foaming agents and/or surfactants, appear to be necessary) and subsequently mixed with $CaPO_4$ powders. In this case, the setting reactions transform the liquid foam into a solid, which ideally maintains the geometry, size and shape of the bubbles (Fig. 10). Thus, the liquid foam acts as a template for the macroporosity of the solid foam [406, 445-450]. Foaming by mixing the solid and liquid phases using a domestic hand mixer at 7000 rpm can be applied as well [451]. In addition, several other porosity creation techniques for self-setting $CaPO_4$ formulations are known and, for further details on the subject, the interested readers are referred to an excellent review [439]. Finally, there is a study devoted to evaluation of methods to determine the porosity of the self-setting $CaPO_4$ formulations [452].

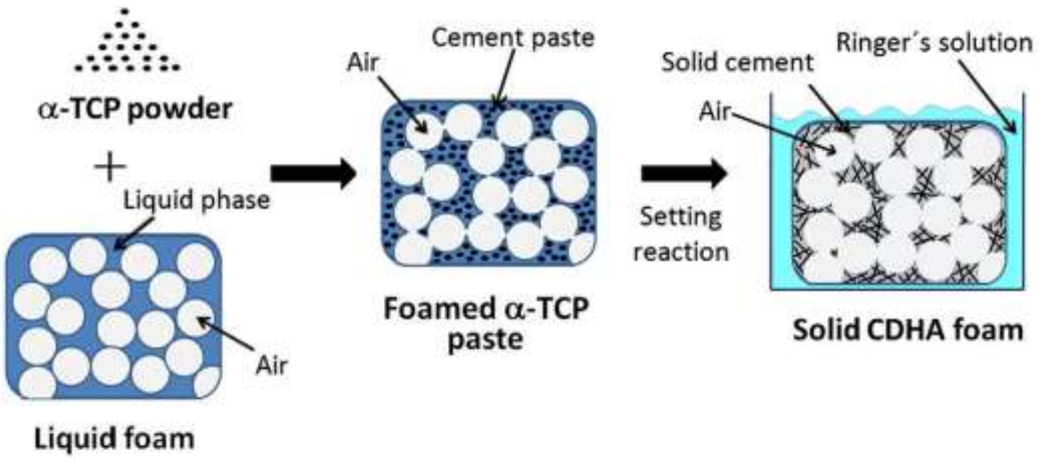

Fig. 10. A schematic drawing of CDHA foams preparation. Initially a liquid was formed by mechanical agitation of an aqueous solution of a soluble surfactant. Then, the foam was mixed with α-TCP powder, producing a foamed paste, which was either cast or directly injected into the moulds. The setting reaction produced hydrolysis of α-TCP to CDHA, which resulted in foam hardening. Reprinted from Ref. [446] with permission.

The major examples of workability-improvement agents, which are added to the self-setting formulations, include water-soluble (bio)polymers. Specifically, polysaccharides [145, 156, 453-456], gelatin [236, 374, 457-463], polyacrylic acid [464-466] and, since recently, polypeptides [467] are of an interest due to their biocompatibility and good rheological properties. Only small amounts (a few weight %) are needed to dramatically increase the viscosity of the pastes. Besides, the pastes become more cohesive and highly resistant to washout immediately after mixing. For example, a 5 wt. % sodium chondroitin sulfate solution is used as mixing liquid in Biopex® [4, 5]. In the case of gelatin, more than a 50 % improvement of the compressive strength was detected [459]. The gelatin-containing formulations after setting were found to exhibit reduced crystallinity, much smaller CDHA crystals and a more compact microstructure; all these phenomena might be accounted for the improved mechanical properties [460]. In addition, the presence of gelatin improved mechanical properties of the formulations; in particular, the formulations containing 2 wt. % gelatin were found to harden in an acceptable time and, thus, they were recommended for clinical applications [463]. In some cases, addition of a gelling agent might cause an increase in hardening time [468] but this was remedied by the use of a sodium orthophosphate solution as the liquid phase [192, 193]. Most polysaccharide solutions are thixotropic, *i.e.*, the viscosity of the solution decreases as the shear rate increases. Certain polysaccharides, such as sodium alginate, pectize in contact with calcium ions. This property can be used to make putty-like cement pastes [24]. However, only few polysaccharides are accepted for parenteral use [4, 5]. Nevertheless, the use of gelling agents widened a possible application of the self-setting $CaPO_4$ formulations because such formulations can be used even when the complete homeostasis is difficult.

Of three known groups of the self-setting formulations, monetite- and brushite-forming formulations react generally much faster than apatite-forming ones. As a result, to satisfy the clinical requirements (Fig. 7), a setting time of monetite- and brushite-forming formulations has to be prolonged, whereas that of apatite-forming ones has to be shortened [4, 5]. According to the aforementioned, setting reactions of any $CaPO_4$ formulation consists of three successive stages: (1) dissolution of reactants to saturate the mixing liquids by calcium and orthophosphate ions; (2) nucleation of crystals from the supersaturated solutions; (3) growth of the crystals. Therefore, experimental approaches to modify the setting kinetics are to be targeted to these three stages. The available approaches have been summarized in Table 5 [276]. Furthermore, seven strategies have been described to decrease the setting time of $CaPO_4$ formulations [277]. They are: (i) mean particle size decreasing of the initial powders; (ii) the P/L ratio increasing; (iii) pH drop of the mixing liquid to increase $CaPO_4$ solubility and hence accelerate the chemical transformations; (iv) adding a nucleating phase, such as a nano-sized HA powder; (v) adding orthophosphate and/or calcium ions into the mixing liquid to accelerate the setting reaction according to the common-ion effect; (vi) solubility reducing of the reaction end-product, for example, by adding fluoride ions into the mixing liquid; (vii) solubility increasing of the starting material by amorphization, *e.g.*, by prolonged milling. For further details on these strategies and approaches, as well as for application examples, the interested readers are referred to the original publications [276, 277].

Table 5. List of strategies and approaches to modify reactivity of the self-setting $CaPO_4$ formulations [280].

Strategy	Approach	Sub-approaches
1. Dissolution rate	1.1. Change contact area between reagent and mixing liquid	1.1.1. Change milling duration
		1.1.2. Use nano- or micron-sized powders
	1.2. Change solubility in the mixing liquid	1.2.1. Use more/less soluble phase
		1.2.2. Change of reaction pH
	1.3. Change saturation of the mixing liquid	
	1.4. Use dissolution inhibitors in the mixing liquid	
	1.5. Modify reagent surface	1.5.1. Chemical change (pre-reaction)
		1.5.2. Physical change (dissolution pits)
2. Nucleation rate	2.1. Use crystallization nuclei	
	2.2. Change the saturation of the reaction product in the mixing liquid	2.2.1. Change of saturation
		2.2.2. Change of end-product solubility
	2.3. Use nucleation inhibitors	
3. Growth rate	3.1. Change the saturation of the reaction product in the mixing liquid	3.1.1. Change of saturation
		3.1.2. Change of end-product solubility
	3.2. Use crystal growth inhibitors	

Since setting time can be influenced by altering the dissolution rate of the initial reactants or by slowing the nucleation and growth rates of the products and/or intermediates (precursors), various setting time controllers (accelerators and retardants) have been proposed. They comprise sodium hydrogen pyrophosphate ($Na_2H_2P_2O_7$) and magnesium sulfate, which are added in amounts < 1 wt. % [469]. According to other studies, ions of citrate, sulfate and pyrophosphate are necessary [293, 470, 471]. The molecular mechanisms of the influence for several of these ions have been discussed [472]. Combinations of citric acid with sodium alginate were found to be effective as well [473]. Application of biocompatible α-hydroxylated organic acids (glycolic, lactic, malic, tartaric and citric acids) and their calcium and sodium salts for modification of both the rheological and setting properties of $CaPO_4$ formulations is well described elsewhere [474, 475]. Besides, aqueous solutions of sodium orthophosphates [145, 280, 323, 415, 476-478], as well as silanated gelatin microspheres [479] and gelatinized starch [480] are also known as setting time accelerators. Both phytic acid [51, 481] and its salts [180] are the examples of setting retarders. An extensive list of the compounds, which might be suitable as accelerators, retarders, additives or reactants in $CaPO_4$ cement formulations, is available in literature [148]. Interestingly that in some cases a simple thermal treatment of the initial reagents (in that particular case, α-TCP powder) at ~ 500 ºC could extend the initial part of the setting reaction from a few minutes to a few hours hence providing a potential approach to better control the setting process [482, 483].

An interesting approach to adjust the setting time of apatite-based formulations by gelatin was reported [484]. The authors studied a self-setting $CaPO_4$ formulation containing 73% α-TCP, 20% TTCP, 5% DCPD and 2% HA powders on the mass basis, which was almost equal to the composition of commercial formulation Biopex-R® (Table 3). To influence the setting time, the authors divided the entire mixture of $CaPO_4$ powders into three portions: portion 1 was α-TCP (46.7%), portion 2 was TTCP (20%), while portion 3 was a mixture of DCPD (5%), α-TCP (26.3%) and HA (2%) and coated either some or all the portions of the powder components with gelatin. Afterwards, the portions were combined altogether at 7:3:5 on the mass basis to get the aforementioned composition of Biopex-R®, mixed with the proper amount of a setting liquid, kneaded for 60 s at room temperature and allowed to set at either 20 or 37 ºC. The results revealed that the gelatin coating on either TTCP- or DCPD-containing portions effectively retarded the setting reaction at 20 ºC, while it did not hinder at 37 ºC. This property implies a possibility to prepare self-setting formulations in an unhurried manner (during up to 1 hour) at 20 ºC, which will rapidly (within 1 – 3 minutes) set inside the body at 37ºC [484].

A subject of the reinforcing additives is discussed in details below in section *7. Reinforced $CaPO_4$ formulations and concretes*.

Regarding a storage stability and a shelf life, the factors, significantly influencing both properties for the initial dry powders of $CaPO_4$ formulations, were found to be temperature, humidity and a mixing regime. Various storage conditions appeared to be effective in prolonging the stability of dry brushite-forming formulations. In the order of effectiveness, they were ranged: adding solid citric acid retardant > dry argon atmosphere ≈ gentle mixing (minimal mechanical energy input) >> low temperature [323].

Finally, before a clinical use, any self-setting formulation must be sterilized [485, 486].

5. Bioresorption of the self-setting $CaPO_4$ formulations and their replacement by new bones

Due to the excellent bioresorbability of DCPA, DCPD and CDHA, a newly forming woven bone might substitute the hardened $CaPO_4$ formulations. Namely, the implants made of hardened BoneSource™ (an apatite-forming formulation) were found to be partly resorbed and replaced by natural bone, depending upon the size of the cranial defect [152]. Replacement of BoneSource™ by bone with a minimal invasion of connective tissue was detected in another study, while ChronOS™ Inject (a brushite-forming formulation) samples exhibited a higher rate of connective tissue formation and an insufficient osseointegration [487]. α-BSM® was evaluated in a canine femoral slot model. New bone was found to form in 3 weeks via an osteoconductive pathway. After 4 weeks, only ~ 1.7 % of the implanted material was observed. The hybrid bone possessed the strength of normal, un-operated bone after 12 weeks. In 26 weeks, a boundary between the old and new bones was virtually indistinguishable, with only ~ 0.36 % of the implant recognizable [225]. Neither an influence on general health, limb specific function and pain, nor associated complications with α-BSM® application were found past 2 years in another study [488]. Norian SRS® was evaluated in canine tibial and femoral metaphyseal defects. The hardened formulation appeared to be gradually remodeled over time, with blood vessels penetrating through it. However, some amounts of Norian SRS® were detected in the medullary area as long as 78 weeks after being implanted in dog femurs [65]. In one more study, *in vivo* bioresorption of the commercial injectable apatite-forming $CaPO_4$ formulations Graftys® HBS and NORIAN® SRS was compared and a critical role of the intergranular microstructure was discovered [489]. An interesting study on the *in vitro* resorption of three apatite-forming formulations (conventional, fast-setting and anti-washout) by osteoclasts if compared with a similar resorption of a sintered HA and a cortical bone revealed an intermediate behavior of the formulations: they were resorbed slower than bone but faster than HA [490]. Furthermore, bone neo-formation was seen 7 seven days after implantation of a self-setting α-TCP formulation [491]. The biodegradation rate of the formulations might be influenced by ionic substitutions in $CaPO_4$ [492]. Evidences of the direct contact of bone and a hardened $CaPO_4$ formulation without soft tissue interposition might be found in literature [493, 494].

Different studies reported on both bioresorption and the progress of bone formation around hardened $CaPO_4$ formulations which in certain cases demonstrated both osteoconductive and osteoinductive properties [495]. However, there are studies in which the osteoinductive properties of the self-setting $CaPO_4$ formulations were not confirmed [496]. Besides, inflammatory reactions were noticed when the formulation did not set [364]. Since the solubility of a non-stoichiometric CDHA is higher than that of stoichiometric HA, α- and β-TCP (Table 1), while the particle dimensions of a precipitated CDHA is smaller than those of a sintered $CaPO_4$, the biodegradability of apatite-forming formulations is always better than that of dense bioceramics made of sintered stoichiometric $CaPO_4$. For example, histologically, at 2 weeks, spicules of living bone with normal bone marrow and osteocytes in lacunae could be seen in implanted formulations. At 8 weeks, the formulation was almost totally surrounded by mature bone. At this stage, no resorption was observed [497]. Only ~ 30 % decrease of the implanted amount of Norian SRS® was reported after 24 months in a rabbit femur [498]. Moreover, several differences could be expected depending on the formulation type. For example, as the product of BoneSource™ and Cementek® is a crystalline CDHA, both commercial formulations are expected to be resorbed slower than other apatite-forming formulations. Indeed no resorption of BoneSource™ was observed after several years implantation; though some resorption of Biobon® was detected. However, porosity appears to be the main biodegradability factor at play: the more porous (for cells) hardened formulations degrade faster than the less porous ones [499, 500]. For example, as Biobon® is more porous than BoneSource™, the discovered diversity could be due to the differences in porosity [4, 5]. The latter conclusion is confirmed by the results of other studies: a positive influence of the porosity on resorption rates was found [366]. The interested readers are referred to a study on the suitability of hardened and porous $CaPO_4$ formulations as scaffolds for bone regeneration, using a rabbit model [501].

The bioresorption properties of $CaPO_4$ bioceramics are generally believed to relate to the solubility of their constitutive phases [502]. The implanted $CaPO_4$ might be bioresorbed by two possible mechanisms, namely: an active bioresorption, mediated by the cellular activity of macrophages, osteoclasts and other types of living cells (so called phagocytosis or literally “cell-eating”) [320, 503-505] and a passive bioresorption due to either dissolution [6, 7] or chemical hydrolysis (valid for brushite- and monetite-forming formulations only, because both DCPD and DCPA appear to be metastable phases at the physiological pH) [209, 298] in the body fluids. For example, a layer of OCP was found to appear on the surface of hardened brushite formulations during their incubation in various simulating media [506-508]. Probably, this transformation occurs via an intermediate formation of ACPs [507]. Sometimes, an active bioresorption is further subdivided into macrophages engulfing of $CaPO_4$ debris and osteoclast mediated bioresorption [290, 509]. Interestingly, that contrary to the brushite-forming formulations, the monetite-forming ones do not hydrolyze into a more chemically stable $CaPO_4$, such as CDHA, but conserve their chemical composition and degradability, allowing replacement by the newly formed bone tissue [411].

Dissolution might be both chemical and physical. The former occurs with $CaPO_4$ of a low solubility (those with Ca/P ratio > ~ 1.3) in acidic environments, while the latter occurs with $CaPO_4$ of a high solubility (those with Ca/P ratio < ~ 1.3). For example, for MCPM, MCPA, DCPD and DCPA the solubility product are several times higher than the corresponding ion concentrations in the surrounding body fluids; therefore, they might be physically dissolved *in vivo*, which is not the case for α-TCP, β-TCP, CDHA, HA, FA, OA and TTCP since the surrounding body fluids are already supersaturated with regard to these compounds. Therefore, biodegradation of the latter materials is only possible by osteoclastic bone remodeling and is limited to surface degradation since cells cannot penetrate the microporous ceramic structure. Osteoclastic cells resorb $CaPO_4$ with Ca/P ratio > ~ 1.3 by providing a local acidic environment which results in chemical dissolution. In order to investigate two bioresorption mechanisms separately, experiments should be performed by incubating the samples in a cell culture medium without cells to study the passive resorption, whereas the active resorption should be determined during cell culturing on the sample surfaces [509]. Unfortunately, the factors concerning the biodegradation of $CaPO_4$ biomaterials have not been completely elucidated yet. The chemical composition, physical characteristics and crystal structures certainly play an important role in their biological behavior. In addition, biodegradation may be influenced by the investigational conditions, such as experimental models, implantation sites and animal species [504].

The data are available that macrophages and giant cells decompose quickly resorbed $CaPO_4$ (*e.g.*, brushite-forming formulations) [297], while slowly (from months to years) resorbed apatite-forming formulations are decomposed by osteoclast-type cells [63, 278, 510]. Clearly, a fast resorption of brushite-forming formulations can only be achieved if this process occurs before conversion DCPD to CDHA according to equation (17) [79]. Both types of the resorption mechanisms (active + passive) might occur almost simultaneously, if a hardened formulation consists of two different types of $CaPO_4$, *e.g.*, from DCPD and β-TCP. For example, the biphasic brushite-forming ChronOS™ Inject was found to resorb by dissolution with cement disintegration and particle formation followed by the phagocytosis of the cement particles through macrophages [511]. Similar formulation was found to be degraded through a dissolution process associated with a cellular process. The observations suggested that cell activities could be influenced by a small particle size, without close correlation between the particle size and the cell activities but with a correlation between particle concentration and the cell activities [504]. To get further details on this topic, the interested readers are referred to an interesting review on the cellular degradation mechanisms of $CaPO_4$ bioceramics [512].

The summary of studies on brushite-forming formulations implantation in various animal models and defect locations is available in literature [298]. Generally, in the same animal model, a degradation rate decreases with a sample size increases, as does DCPD to CDHA conversion time. Data are available that hardened brushite-forming formulations experience an initial linear degradation rate of ~ 0.25 mm/week [309], which slightly overwhelms the bone regeneration capacity, resulting in small bone-material gaps and a reduction in mechanical properties [67]. In addition, an *in vivo* degradation was found to depend on porosity. Namely, the hardened brushite formulations of higher-porosity were found to be quantitatively transformed into crystalline OCP after 10 months of implantation, while lower-porosity ones appeared to be chemically stable with the absence of re-precipitate formation and minor bioresorption from the implant surface [513]. Additional details on the compositional changes of brushite-forming formulations after implantation in sheep are well described elsewhere [469, 514].

The kinetics of passive resorption depends on porosity of the samples, ionic substitutions in $CaPO_4$ (when applicable), crystallinity and pH at the tissue interfaces. The active resorption is due to cellular activity; however, it is also related to the passive one. Namely, the solution pH near macrophages and osteoclasts can drop to ~ 5 by excretion of lactic acid, which increases the solubility (Fig. 1), whereas near osteoblasts (bone forming cells) solution pH can become as high as 8.5 by excretion of ammonia [62]. Dissolution chemistry of CDHA (therefore, of hardened apatite-forming formulations) in acidic media ($CaPO_4$ are almost insoluble in alkaline solutions (Fig. 1)) might be described as a slightly modified sequence of four successive chemical equations [515, 516]:

$$Ca_{10-x}(HPO_4)_x(PO_4)_{6-x}(OH)_{2-x} + (2-x)H^+ = Ca_{10-x}(HPO_4)_x(PO_4)_{6-x}(H_2O)_{2-x}^{(2-x)+} \quad (18)$$

$$Ca_{10-x}(HPO_4)_x(PO_4)_{6-x}(H_2O)_{2-x}^{(2-x)+} = 3Ca_3(PO_4)_2 + (1-x)Ca^{2+} + (2-x)H_2O \quad (19)$$

$$Ca_3(PO_4)_2 + 2H^+ = Ca^{2+} + 2CaHPO_4 \quad (20)$$

$$CaHPO_4 + H^+ = Ca^{2+} + H_2PO_4^- \quad (21)$$

Obviously, the dissolution chemistry of DCPA and DCPD (therefore, of hardened monetite- and brushite-forming formulations, respectively) in acidic media is described by equation (21). One should stress, that in equation (21) water is omitted for simplicity. Therefore, dissolution of DCPA is written only.

Nevertheless, the situation with biodegradation mechanisms appears to be more difficult. Namely, in a special study brushite-forming MCPM/HA and MCPM/β-TCP formulations were compared to test the hypothesis that DCPD chemistry affected both degradation properties and cytocompatibility of the self-setting formulations [517]. Using simple *in vitro* models the authors found that brushite-forming MCPM/β-TCP formulations degraded primarily by DCPD dissolution, which was associated with a slight pH drop and relatively low mass loss. Cytocompatibility testing revealed no significant change in cell viability relative to the negative control for all of the MCPM/β-TCP formulations. In contrast, the brushite-forming MCPM/HA formulations were prone to undergo rapid conversion of DCPD to CDHA, resulting in a sharp pH drop and extensive mass loss. A stoichiometric excess of HA in the initial formulations was found to accelerate the conversion process and significant cytotoxicity was observed. Presumably, the initial excess of HA promoted DCPD → CDHA transformation. The authors concluded that, although the product of the setting reaction was the same, brushite-forming formulations produced from MCPM/HA and MCPM/β-TCP differed significantly in their degradation properties and cytocompatibility [517].

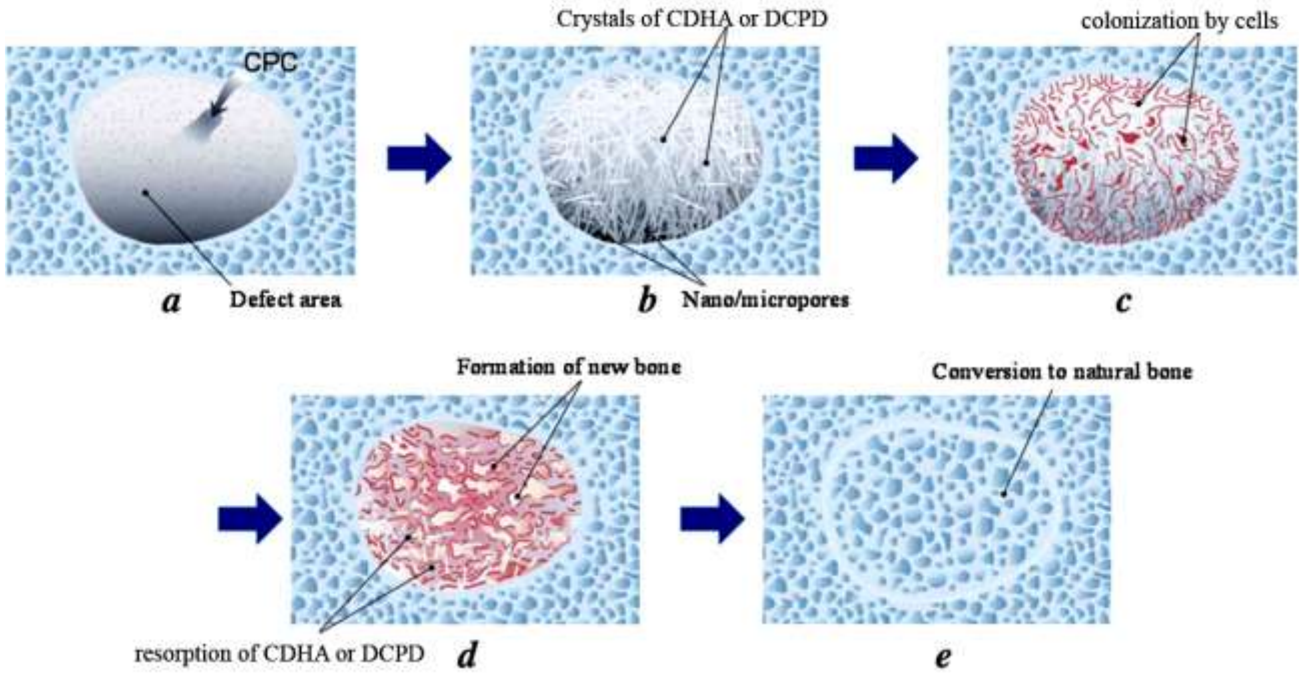

Fig. 11. A schematic drawing of bone defect regeneration by means of a self-setting $CaPO_4$ cement (CPC): (a) filling of a bone defect with a viscous formulation; (b) formulation setting with formation of the end product (CDHA or DCPD); (c) colonization by cells; (d) resorption of CDHA or DCPD by osteoclasts and bone formation by osteoblasts; (e) bone regeneration. Reprinted from Ref. [523] with permission.

The mechanism of bone healing caused by self-setting $CaPO_4$ formulations is very multifactorial because the surface of the formulations is rapidly colonized by cells. Several types of these cells degrade $CaPO_4$ by either phagocytotic mechanisms (fibroblasts, osteoblasts, monocytes/macrophages) or an acidic mechanism with a proton pump to reduce the pH of the microenvironment and resorb the hardened bioceramics (osteoclasts) [512, 518]. Various types of mesenchymal cells located at the implantation sites can induce solubilization of $CaPO_4$. Upon arrival of cells, various types of active enzymes, such as acid phosphatase, are secreted that causes dissolution of the hardened cements [519-521]. Much more biology, than chemistry and material science altogether, is involved into this very complex process and many specific details still remain unknown [522]. Nevertheless, the entire process of bone defect healing by self-setting $CaPO_4$ formulation might be schematically represented by Fig. 11 [523].

It is well known that various polypeptides and growth factors present in bone matrix might be adsorbed onto HA [524-526] and modulate the local milieu of cells. This is supported by many purification protocols of growth factors and bone morphogenetic proteins/osteogenins involving HA chromatography [527, 528]. However, osteoblasts are not found in direct contact with $CaPO_4$. A complex proteinaceous layer, usually osteoid, directly contacts the osteoblasts. After implantation of the self-setting $CaPO_4$ formulations, mitogenic events could occur either during the initial mesenchyma1 cell contact or after osteoid degradation by osteoblast collagenase. In a dense, mineralized biomaterials such as hardened $CaPO_4$ formulations, which provide a barrier to the free diffusion of circulating hormones, growth factors, and cytokines, it is questionable whether the local responses at the periphery of the material regulate osteoconduction [24]. The tissue response to injectable $CaPO_4$ formulations is well described in literature [441, 490, 510, 529, 530]. The results of histological and mechanical evaluations in a sheep vertebral bone void model are available elsewhere [531]. The interested readers are also advised to get through a paper on the *in vitro* biodegradation of hardened brushite-forming formulations by a macrophage cell-line [174].

To conclude this part, one should note that self-setting $CaPO_4$ formulations are able to provide short-term biologically desirable properties and then be replaced by a new bone, which is very important [532]. In general, the growth rate of a newly forming bone depends on age, sex and general metabolic health of the recipient as well as on the anatomic site, porosity, bulk site, crystallinity, chemical composition (monetite, brushite or apatite), particle sizes and P/L ratio of the mixture. Considering all these factors, it might take from 3 to 36 months for different formulations to be completely resorbed and replaced by bones [268]. However, additional sound scientific data to determine the exact degree of biodegradability are still needed, viz. animal studies performed in a critical-size defect model. One must stress that the bioresorption kinetics should be balanced with a rate of new bone formation to avoid collapse at the fracture site, which might occur if bioresorption is too fast. Interestingly that to advance self-setting $CaPO_4$ formulations as bioabsorbable bone replaceable materials, it is essential to utilize the patient's own blood in combination with the formulations [533, 534].

6. The mechanical properties

The mechanical properties of the hardened $CaPO_4$ formulations arise from two main conditions: (a) the end-products 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. However, investigations of their mechanical properties revealed that the hardened $CaPO_4$ formulations exhibited large sample-to-sample deviation due to the ceramic nature of samples, a presence of pores, a possibility of inhomogeneous mixing, as well as small specimen dimensions. This situation generates difficulties for obtaining accurate results and creates obstacles for testing different compositions where only a small batch size is available. In this respect, specimen shape, whether being injected, porosity ratio, surface quality, bearing support design appear to have significant matter on variability in terms of the mechanical tests [535]. In addition, the environment in which the hardened formulations are tested should also be considered. Namely, the mechanical testing is normally conducted under dry conditions at room temperature. However, testing under wet conditions at body temperature would be more representative of the *in vivo* scenario. A study is available, in which the mechanical strength of several hardened CaPO$_4$ formulations was tested in both wet and dry conditions. The strength was found to be lower when tested under the wet conditions with an exception of one formulation, which exhibited insignificant differences in compressive strength [536].

6.1. Nonporous formulations

As in most clinical applications self-setting CaPO$_4$ formulations are applied in direct contact with human trabecular bones, it may be stated as a mechanical requirement that the strength of the formulations must be at least as high as that of trabecular bones, which is close to 10 MPa [537]. Due to a combination of different forces that may include bending, torsion, tension and compression, three-dimensional (3D) complex load is normally applied to human bones. Unfortunately, ordinary CaPO$_4$ cements are strong enough at compression only [263]. In theory, after setting, they can reach the mechanical properties comparable to those of CaPO$_4$ blocks with the same porosity. However, in practice, their strength is lower than that of bones, teeth or sintered CaPO$_4$ bioceramics [193].

Two types of mechanical assessments are usually performed with the hardened self-setting CaPO$_4$ formulations: compressive strength and tensile strength tests. Compressive strength measurements are performed on cylindrical samples with an aspect ratio of 2 until fracture occurs (Fig. 12) [538]. On the other hand, direct tensile strength is difficult to measure in such brittle materials. Therefore, in many studies the alternative method of measuring the diametric tensile strength has been used, despite the fact that this technique gives results that underestimate the true tensile strength by a factor of 85% [539].

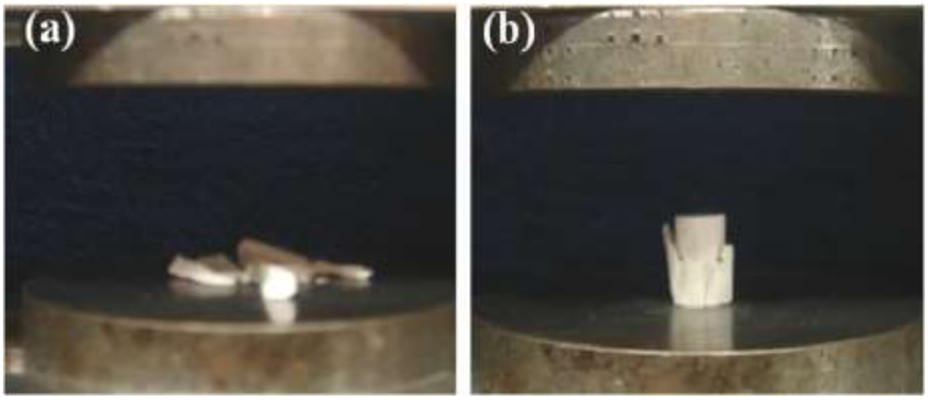

Fig. 12. Pictorial representation of specimens post critical loading for (a) the control and (b) the same formulation reinforced by 5 wt. % of bovine collagen fibers. Reprinted from Ref. [538] with permission.

Having the ceramic origin, the set products of all CaPO$_4$ formulations are brittle, have both a low impact resistance and a low tensile strength (within 1 to 10 MPa), whereas the compression strength varies within 10 to 100 MPa [190, 263, 264]. The latter value exceeds the maximum compression strength of human trabecular bones. Furthermore, at 12 weeks after implantation the compressive strength of the hardened formulations was found to be still significantly higher (60 to 70 MPa) than that of normal bone [67]. In general, hardened brushite-forming formulations are slightly weaker than hardened apatite-forming ones. Namely, a tensile strength of ~ 10 MPa and a compressive strength of ~ 60 MPa were obtained for brushite-forming formulations [540]. In comparison, apatite-forming ones can reach a tensile strength of ~ 16 MPa [541] and a compressive strength of ~ 83 MPa [542]. However, due to the inherent brittleness of ceramics, those values are close to be meaningless. Namely, the indication of a mean compressive strength of, say, 50 MPa measured on well-prepared (*e.g.*, under vibrations and pressure) and perfectly shaped samples does not inform the readers with which probability this formulation will fail *in situ* under a cyclic load of *e.g.*, 10 MPa. Furthermore, a comparison of the compressive strength of hardened formulations with that of cancellous bone is not very helpful either because cancellous bone is much less brittle than ceramics [173].

Moreover, the mechanical properties of hardened $CaPO_4$ formulations are not narrowly distributed around a mean value (as for metals), but widespread over a very large range of values, which strongly reduces their clinical application [543]. *In vivo*, the difference between the hardened apatite- and brushite-forming formulations boosts: namely, the mechanical properties of the former were found to increase [478], whereas those of the latter decreased [75]. This is attributed to a higher solubility of DCPD when compared with that of CDHA (Table 1). However, the mechanical properties of the hardened formulations may vary with implantation time. For example, animal studies indicated that the mechanical properties of apatite-forming formulations tended to increase continually [478], in contrast to those of brushite-forming ones, which initially decreased and again increased when bone was growing [67]. Furthermore, shear and tensile forces play a very important role. Thus, these parameters should also be considered, for example, using the Mohr circle approach [539]. Besides, it is difficult to compare the mechanical properties of different formulations. For example, the following numeric values of the compression strength and setting time were obtained: (i) Norian SRS® (~ 50 % porosity): 33 ± 5 MPa and 8.5 ± 0.5 min, (ii) Cementek®: 8 ± 2 MPa and 17 ± 1 min, (iii) Biocement D® (~ 40 % porosity): 83 ± 4 MPa and 6.5 ± 0.5 min, (iv) α-BSM® (~ 80 % porosity): 4 ± 1 MPa and 19 ± 1 min, respectively [542]. Among them, Biocement D® has the highest compressive strength but the lowest porosity and a high compressive strength does not necessarily mean that Biocement D® is the least breakable implant [4]. Additional details on the major properties of Norian SRS® are available elsewhere [269, 544]. Besides, the interested readers are suggested to get through the mechanical characterization of a bone defect model filled with ceramic cements [266].

To improve the mechanical properties of the self-setting $CaPO_4$ formulations, addition of water-soluble polymers might be considered. For example, in early 1990-s, a number of polymers, including polyacrylic acid and poly(vinyl alcohol) were used to improve the properties of a TTCP + DCPD formulation [545, 546]. The authors noted marked increases (up to threefold) in mechanical properties but with an unacceptable reduction of workability and setting time. Later, another research group reported similar results using sodium alginate and sodium polyacrylate [547]. Afterwards, other researchers added several polyelectrolytes, polyethylene oxide and a protein bovine serum albumin into α-BSM® cement pastes to create $CaPO_4$/polymer biocomposites [548]. Biocomposites of α-BSM® with polycations (polyethylenimine and polyallylamine hydrochloride) exhibited compressive strengths up to six times greater than that of pure α-BSM® material. Biocomposites of α-BSM® with bovine serum albumin developed compressive strengths twice that of the original α-BSM® [548]. Similar strengthening effect was achieved by addition of some commercial superplasticizers [549]. The results showed that small additions, *i.e.* 0.5 vol. %, in the aqueous liquid phase improved the maximum compressive strength (35 MPa) of Biocement-H© by 71 %, *i.e.* till ~ 60 MPa. Moreover, the addition of high amounts of superplasticizers, *i.e.* 50 vol. %, allowed for a significant increasing of the P/L ratio from 3.13 to 3.91 g/ml, without affecting the maximum strength and/or the workability [549]. This effect was explained by an inhibiting effect of the aforementioned additives on the crystal growth kinetics of newly forming $CaPO_4$ crystals, which resulted in smaller crystallites and, hence, a denser and more interdigitated microstructure. In addition, the morphology of the final crystals was changed [550]. However, the increased strength was attributed mainly to the polymer's capacity to bridge between multiple crystallites (thus forming a more cohesive composite) and to absorb energy through a plastic flow [517]. Other factors affecting strength are the materials used in the solid phase, particle sizes, incorporation of fillers (see section *7. Reinforced $CaPO_4$ formulations and concretes* for details), the P/L ratio and various additives to the liquid phase [155].

Strength of the cement-prosthesis interface might be studied by a pullout test. The details are available elsewhere [98].

6.2. Porous formulations

As a presence of pores simplifies for cracks to run throughout the ceramic mass, the mechanical properties of the hardened formulations were found to decrease exponentially with porosity increasing [235, 551]. In theory, self-setting $CaPO_4$ formulations can be made with almost any porosity. However, for most commercial formulations, the pores are of 8 – 12 µm in diameter and, after setting, porosity occupies about 40 – 50 % of the entire volume [552]. To reduce porosity of the hardened formulations, pressure can be applied [193, 553, 554]. Usually, the pore dimensions in hardened formulations are too small to allow a fast bone ingrowth. Thus, there is a lack of macroporosity. Besides, unless special efforts have been performed, the available pores are not interconnected. Due to these reasons, after injection, osteoclastic cells are able to degrade the hardened $CaPO_4$ layer-by-layer only, starting at the bone/implant interface throughout its inner part (in other words, from the outside to the inside). This is the main drawback of the classical self-setting formulations when compared to $CaPO_4$ ceramic scaffolds with an open macroporosity [4, 5].

Given that strength is reciprocally proportional to porosity [509], the former might be adjusted by varying the P/L ratio in the self-setting formulations. Since either no (apatite- and monetite-forming formulations) or not much (brushite-forming ones) water is consumed during the setting, the majority of added water acts as a dispersant medium to produce workable pastes. Therefore, for each formulation, there is a minimum amount of a liquid required to fill the voids between the $CaPO_4$ particles, while addition of a liquid in an excess of that minimum increases the particle-particle distance, resulting in porosity increasing and, therefore, strength decreasing. Considering that precipitation of new crystals takes place surrounding the initial powder particles, this leads to a more compact (less porous) structure of the crystal agglomerates (Fig. 13) [258]. Elevated compression strength would be applicable in cranioplasty for regions requiring significant soft-tissue support. For small bone defects, such as root canal fillings, formulations of low compression strength might be used [260]. Regarding a tensile strength of the self-setting $CaPO_4$ formulations, as a rule of thumb, it appears to increase two-fold with each 10 vol. % decrease of the porosity, *i.e.* 5, 10, 20, 40 and 80 MPa for 80, 70, 60, 50 and 40 % porosity, respectively [4, 5]. The effect of porosity on a compressive modulus of the self-setting $CaPO_4$ formulations is available as Fig. 4 in Ref. [554]. Ishikawa and Asaoka showed a linear relation (R^2 = 0.94) between the natural logarithm of diametral tensile strength and porosity of the self-setting $CaPO_4$ formulations, where porosity was controlled by compaction pressure (up to 173 MPa) [190]. Besides, an empirical relationship between strength, S, and porosity, P, has been introduced in another study:

$$S = S_0 e^{-bP},$$

where: S_0 is the theoretical strength at P = 0 (fully dense) and *b* is an empirical constant [555].

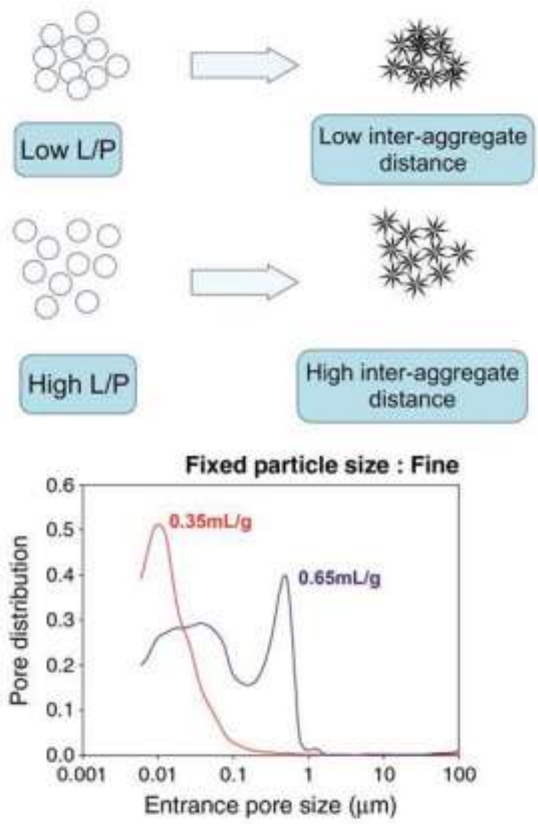

Fig. 13. A schematic drawing of the influence of the L/P ratio on the properties of self-setting formulations. Reprinted from Ref. [258] with permission.

Since porosity is mainly due to an excess of water used in the self-setting formulations, attempts were made to reduce the amount of water. However, the amount of water determines the rheological properties of self-setting pastes: a decrease in water content leads to a large increase in viscosity, eventually leading to non-flowable pastes. As $CaPO_4$ formulations are set at an almost constant volume, the final porosity can be predicted from the initial composition [4, 5]. A shrinkage degree of ~ 1 %

causes no restrictions on clinical use [261]. Studies on the *in vivo* evaluation of injectable macroporous $CaPO_4$ formulations revealed a higher bioresorption rate due to both a higher surface contact with body fluids (which increases dissolution) and enhancing cellular activity due to particle degradation [366, 441].

Besides addition of porogens [399-427], a porosity level of the self-setting $CaPO_4$ formulations might be controlled to a certain extent by adjusting particle sizes and the P/L ratio. When the P/L ratio is high, a porosity of the hardened formulations is low [4, 5]. According to calculations, the tensile strength of formulations with the zero porosity could be as high as 103 MPa [190]. However, a high density and a lack of pores decreases bioresorbability because a newly forming bone appears to be unable to grow into an implant; it might grow only simultaneously with dissolution of the hardened formulations. Thus, porosity of self-setting $CaPO_4$ formulations appears to be a very important factor for their biodegradability [4, 5].

6.3. Drillability

In a clinical context, drillability of formulation is defined as a possibility to drill holes and insert bone screws into partially and/or fully set one without fracturing the implant during processing [556]. In general, before applying grafts, bone fractures are usually stabilized by two screws positioned minimally invasively by a lateral approach. To increase stability, two additional screws with a smaller diameter can be placed across the others into the main fragment by an anterior approach. Thus, the four screws are lying across each other; that is why the operative technique is named as “jail technique” [557]. In 2012, self-setting $CaPO_4$ formulations became available, which could be drilled and set with screws after the first hardening. This option allows initially filling up a defect by a self-setting $CaPO_4$ formulation and then drilling holes in it to put the screws [558]. Norian Drillable (DePuy Synthes, USA) is a commercial example (Table 3).

A study is available, in which the authors compared two bone-healing techniques with regard to their effect on the primary stability: 1. initially setting the screws and then filling up the defect with Norian Drillable and, alternatively, 2. initially filling up the defect with Norian Drillable and subsequently setting the screws. The authors discovered that by means of a drillable formulation, the first approach significantly reduced the secondary loss of reduction of the depression fracture fragment under cyclic loading with a clinically relevant partial weight bearing [556]. In another study, researchers performed a biomechanical evaluation of 2 commercial non-drillable apatite-forming $CaPO_4$ formulations (ChronOS Inject and Graftys Quickset) and 2 newly designed bone substitutes: a magnesium orthophosphate cement and a drillable hydrogel reinforced self-setting $CaPO_4$ formulation. The authors concluded that the in-house-prepared drillable $CaPO_4$ formulation allowed an unproblematic drilling after replenishment without a negative influence on the stability [559].

7. Reinforced $CaPO_4$ formulations and concretes

Being aware on the excellent bioresorbability of DCPA, DCPD and CDHA, researchers are focused on attempts to overcome the mechanical weakness of the self-setting $CaPO_4$ formulations [560]. Among them, an approach devoted to adding of various fillers, fibers and reinforcing additives, giving rise to formation of various multiphasic biocomposite formulations, appears to be the most popular one [153, 154, 157, 263, 350, 552, 560-571]. Even nanodimensional carbon (as nanotubes [32, 572-575], graphene [576] and their combinations [577]) have been successfully tested to reinforce the self-setting $CaPO_4$ formulations. Although the biomaterials community does not use this term (just 1 paper was published [578]), a substantial amount of such formulations might be defined as $CaPO_4$ concretes. According to Wikipedia, the free encyclopedia: “Concrete is a construction material that consists of a cement (commonly Portland cement), aggregates (generally gravel and sand) and water. It solidifies and hardens after mixing and placement due to a chemical process known as hydration. The water reacts with the cement, which bonds the other components together, eventually creating a stone-like material.” [579]. The idea behind the concretes is simple: if a strong filler is present in the matrix, it might stop crack propagation. In such formulations, the load is transferred through the matrix to the fillers by shear deformation at the matrix/filler interfaces. Both fillers and matrix are assumed to work altogether providing a synergism needed to make an effective composite. However, adding fillers always reduced porosity, which negatively influenced the ability of the $CaPO_4$ concretes to allow bone ingrowth into the pores. Hence, denser formulations have slower resorption rates and thus a slower bone substitution [190]. Moreover, due to the presence of fillers, injectability and other rheological properties of the reinforced formulations and concretes frequently appear to be worse than the same properties of the ordinary formulations [580]. Thus, it is difficult to increase strength of the self-setting formulations without having a negative influence on the other properties.

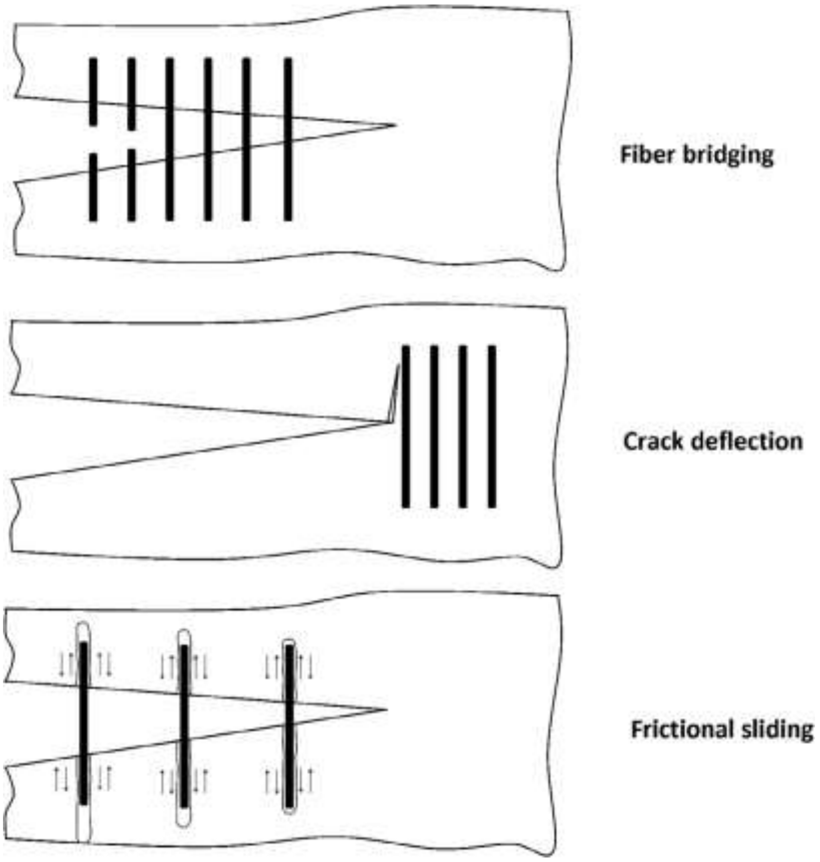

Fig. 14. A schematic illustration of three fiber reinforcement mechanisms for fiber-containing hardened formulations. Reprinted from Ref. [585] with permission.

The reinforced formulations and concretes can be prepared from any type of self-setting $CaPO_4$ formulations [560]. For example, in an attempt to improve the mechanical properties, investigators prepared concretes by adding human cadaveric femur bone chips in amounts of 25, 50 and 75 % (w/w) to α-BSM® cement [562]. The mechanical tests revealed that the specimens of pure cement exhibited a relatively high stiffness but a low ductility. However, for the concretes an increasing of bone content was found to result in the elastic modulus decreasing and the ductility increasing; however, the ultimate strength showed only small changes with no apparent trend [562]. A concrete of Biopex® cement with allografts taken from femurs and tibiae of rabbits is also available. Unfortunately, nothing is written on the mechanical properties improvement but, surprisingly, by the addition of allografts, the hydrolysis process of Biopex® was significantly changed [350]. By adding polymers, other researchers succeeded in improving the mechanical strength of the formulations up to ~ 30 MPa; however, both the kinetics of CDHA formation and, thus, the bioactivity were decreased [158, 581]. Incorporation of long carbon fibers at a volume fraction of 5.7 % increased the flexural strength about 4 times and work of fracture ~ 100 times, if compared to un-reinforced formulations [582]. In another study, DCPD-forming formulations were reinforced by poly(propylene fumarate) and, if compared with non-reinforced controls, flexural strength improved from 1.80 ± 0.19 MPa to 16.1 ± 1.7 MPa, flexural modulus increased from 1073 ± 158 MPa to 1304 ± 110 MPa, maximum displacement during testing increased from 0.11 ± 0.04 mm to 0.51 ± 0.09 mm and work of fracture improved from 2.7 ± 0.8 J/m ^{2} to 249 ± 82 J/m ^{2} [583]. The reinforcement mechanisms were found to be crack bridging and fiber pullout, while fiber length and volume fraction were key microstructural parameters that determined the concrete properties [584]. In another paper, fiber bridging, crack deflection and frictional sliding were mentioned as three main mechanisms according to how a fiber could mechanically reinforce a self-setting formulation (Fig. 14). Namely, for the case of fiber bridging, fibers keep connecting the crack sides altogether and, thus, effectively dissipate the fracture energy and delay any further propagation. For the case of crack deflection, fibers act as barriers that extend the path distance at which the crack needs to travel through the matrix. Frictional sliding occurs at the fiber/matrix interfaces when fibers begin to pull out of the hardened formulation. This leads to a stress transfer that ultimately results in increased energy dissipation and fracture toughness [585].

Although addition of polypropylene, nylon and carbon fibers was found to reduce the compression strength of a double-setting $CaPO_4$ formulation due to increased porosity, it strongly increased the fracture toughness and tensile strength, relative to the values for the un-reinforced formulations [563]. A knitted two-dimensionally oriented polyglactin fiber-mesh was found to be effective in improving load-bearing behavior of self-setting formulations for potential structural repair of bone defects [265]. To make the material stronger, fast setting and anti-washout, chitosan was added [137, 233, 405, 462, 545, 586-592]. Furthermore, anti-washout properties might appear by adding sodium alginate [593], chitosan-alginate complex [594], inositol phosphate [595] and a konjac glucomannan/κ-carrageenan blend [596]. $CaPO_4$ concretes containing SiO_2 and TiO_2 particles showed a significant (~ 80 – 100 MPa) increase in the compressive strength, whilst no change in the mechanical behavior was observed when ZrO_2 particles were added [597]. Additional examples of the properties improving comprise incorporation of silica [38], silk fibroin [88], calcium silicates [100, 569], calcium carbonate [87, 597], carbon [598], basalt [599] and poly(vinyl alcohol) [600] fibers, polypeptide copolymers [601], gelatinized starches [602], fibrin glue [603], magnesium wires [604] and collagen [538, 605-612]. Fig. 12 shows specimens of a hardened unreinforced $CaPO_4$ formulation (a) and the same formulation reinforced by 5 wt. % of bovine collagen fibers (b) after compression loading up to ~ 15% level of strain. The characteristic brittle behavior of the set unreinforced formulation can be observed, as the specimen exhibited catastrophic failure after critical loading and subsequently broke into fragments. Observing a typical compression specimen of the set reinforced formulation after testing clearly displays that the failure mechanism was very different, as the specimen maintains a degree of cohesive structure and remains capable of supporting a load [538]. Additionally, strength improvement was found when DCPA and TiO_2 crystals were used as fillers for mechanically activated α-TCP formulations [613]. Moreover, some reinforcements can also provide additional properties. For example, $BaTiO_3$ powder is added to the self-setting $CaPO_4$ formulations to take the advantage of its piezoelectric properties, because an electromechanical effect plays a vital role in fracture healing at the defect site and bone integration with the implant [211].

Blending of fibers with the self-setting pastes or precursor powders can be carried out using different structures of the fibrous materials, as shown in Fig. 15 [614] and the effects of varying fiber type, fiber length and volume fraction of fiber-reinforced $CaPO_4$ formulations were investigated [586, 615]. Four fiber types were studied: aramid, carbon, E-glass and polyglactin. Fiber length ranged within 3 – 200 mm and fiber volume fraction ranged within 1.9 – 9.5 %. The results indicated that the self-setting formulations were substantially strengthened via fiber reinforcement. Aramid contributed to the largest increase in strength, followed by carbon, E-glass and polyglactin. Fiber length, fiber volume fraction and fiber strength were found to be key microstructural parameters that controlled the mechanical properties of the concretes [586, 615, 616]. For example, two different fiber reinforcement strategies were discussed [616]. Among them, the first one represented an introduction of short fibers with lengths much shorter than the matrix dimensions. These fibers were randomly distributed within the matrix (Fig. 15a), resulting in composites with relatively isotropic properties. An incorporation of continuous fibers in which the fibers were nearly as long as the specimen size and were aligned inside the matrix in certain directions (Fig. 15e) was another strategy. In the latter case, the fracture resistance of the composite appeared to be anisotropic: it was highly enhanced in the direction perpendicular to the fibers, while the cracks propagated easily in the direction parallel to the fibers [616]. Fiber length also plays an important role [615]. Namely, for each of the aforementioned type of fibers, increasing their length generally increased both the ultimate strength and work-of-fracture of the hardened formulations. Namely, for concretes containing 5.7% aramid fibers, the ultimate strength was 24 ± 3 MPa for 3 mm fibers, 36 ± 13 MPa for 8 mm fibers, 48 ± 14 MPa for 25 mm fibers and 62 ± 16 MPa for 75 mm fibers. In addition, at 25 mm fiber length, the ultimate strength of the hardened formulations was found to be linearly proportional to the fiber strength [615].

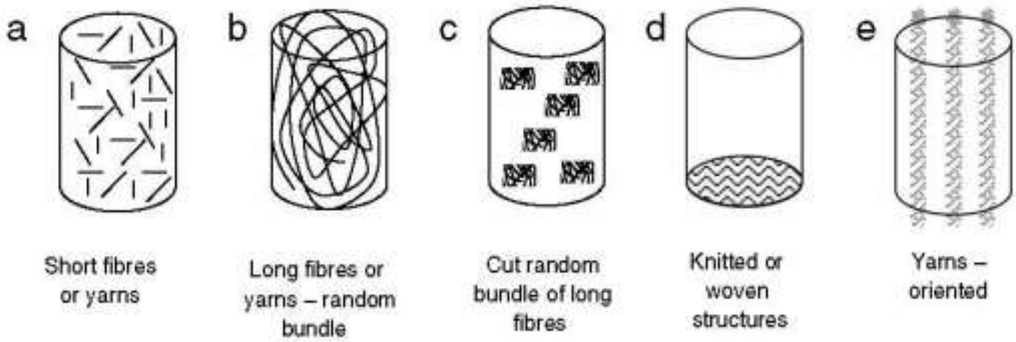

Fig. 15. Different ways of fiber disposition in the fiber-reinforced $CaPO_4$ self-setting formulations. As seen from this figure, fibers can be introduced as short staple ones (a) or as long fibers forming a random bundle (b). The random bundles can also be cut into small pieces and dispersed inside the self-setting matrix (c). If fibers are spun into yarns, the latter can also be cut and introduced randomly into the formulation ((a) and (b)), oriented (e) or may be woven or knitted into laminar textile structures (d). Reprinted from Ref. [614] with permission.

Fiber reinforcement of porous formulations (mannitol was used as a porogen) was performed as well [616]. Namely, reinforcement by aramid fibers (volume fraction of 6 %) was found to improve the properties of a $CaPO_4$ concrete with the strength increasing threefold at 0 % mannitol, sevenfold at 30 % mannitol and nearly fourfold at 40 % mannitol. Simultaneously, the work of fracture increased by nearly 200 times, however the modulus was not changed as a result of fiber reinforcement [616]. A positive influence of polyamide fibers [617], polyhydroxyalkanoate fibers [618] and bioactive glass [619-623] is also known. In addition, a reinforcement of the self-setting formulations could be performed by infiltration of a preset composition with a reactive polymer followed by cross-linking the polymer *in situ* [624].

The reinforcement level of any filler strongly depends on the presence or absence of mutual interactions between the filler and the matrix. Such interactions comprise adsorption, adhesion, chemical bonding, *etc*., and all of them appear to be a function of a chemical affinity between the components [625, 626]. In the case of great differences between the surface properties of fillers and matrixes (*e.g.*, one is hydrophilic, while another is hydrophobic), additional reagents may be added to diminish the differences. Namely, a study is available, in which the authors improved the interfacial adhesion between water insoluble chitosan fibers and $CaPO_4$ matrix to obtain tougher fiber-reinforced concretes [625]. This was done by adding an aqueous solution of trimethyl chitosan, which both was a better soluble chitosan derivative and had a chemical affinity to the reinforcing chitosan fibers. The improved wettability and chemical affinity of the chitosan fibers in the presence of trimethyl chitosan caused an enhancement of the interfacial adhesion. This resulted in a work of fracture increasing (several hundred-fold increase) of the concretes, while the elastic modulus and bending strength were maintained similar to the materials without additives

[625]. The interfacial properties and bond-slip response between the CaPO$_4$ matrix and embedded poly(vinyl alcohol) fibers were investigated in another publication [626].

The reinforcement of self-setting CaPO$_4$ formulations by bioresorbable and/or biodegradable fillers responds to a different strategy. In this case, the rationale is to provide strength augmentation at the initial stages and, subsequently to filler degradation, to facilitate bone ingrowth into the macropores [39, 429-438, 604]. For example, the initial strength of a concrete was threefold higher than that of the unreinforced control [429]. The work of fracture (toughness) was found to increase by two orders of magnitude for other biocomposites of CaPO$_4$ with bioresorbable fibers, such as Vicryl polyglactin 910 (Ethicon, Somerville, NJ) [430] and a mesh of copolymer of polyglycolic and polylactic acids [434]. The addition of fillers with higher bioresorption rate than the hardened CaPO$_4$ matrix allows creating macropores to favor cell colonization, angiogenesis and eventually fostering bone regeneration. Ideally, the loss of strength produced by filler degradation should be compensated by the formation of new bone. One important advantage of long fibers over particulates and short fibers is the fact that once resorbed they form a network of interconnected channels inside the set structures, which could facilitate bone ingrowth into implants [192, 193, 429, 434]. For example, interconnected macropores were formed in a hardened formulation at 84 days' immersion in a physiological solution [434]. One should note that, apart from the mechanical properties of the reinforcing materials, the structure of the incorporated fibers, regular or random, appears to be crucial for the resulting flexural strength and modulus of elasticity [432]. A higher strength might help extending the use of CaPO$_4$ formulations to larger stress-bearing repairs, while the macropores might facilitate tissue ingrowth and integration of the hardened formulations with adjacent bones. To extend this idea further, several types of fibers with different rates of bioresorbability might be simultaneously incorporated into the self-setting formulations. Excellent reviews detailing how various parameters of fibers (*i.e.*, type, their orientation, aspect ratio, volume fraction, tensile modulus and fiber/matrix interface properties) can influence the mechanical properties of self-setting CaPO$_4$ formulations are available elsewhere [560, 614, 627].

Besides the aforementioned, it is important to mention on the reinforced formulations and concretes, after hardening consisting of CaPO$_4$ only [309, 310, 511, 628-636]. The first biphasic concrete consisting of a hardened DCPD matrix filled with β-TCP granules was introduced in 1992 [629]. Further development of this formulation was well described in other papers [309, 511]; unfortunately, neither mechanical nor rheological properties of that concrete were disclosed. Nevertheless, the results of still another study showed that, by addition of 20 wt. % the as-prepared β-TCP aggregates, the compressive strength of the self-setting concrete was increased by about 70 %, while the paste itself still maintained injectable, while the heat release in the hydration process decreased by ~ 25% [632]. In addition, HA/collagen biocomposites were also used as reinforcements for the self-setting CaPO$_4$ formulations [637].

At physiological pH, the *in vitro* solubility of DCPD is approximately 100 times higher than that of β-TCP (Table 1 and Fig. 1); roughly, the same order of magnitude applies for the *in vivo* bioresorption kinetics of these types of CaPO$_4$. Thus, a new bone is formed in the space left after bioresorption of the DCPD matrix, while β-TCP granules act as guiding structures. This feature of the cement can be considered an inverse scaffolding effect [638]. Another research group invented a formulation that incorporated as major powder components α-TCP, ACP and biphasic CaPO$_4$ (BCP = HA + β-TCP in various HA/β-TCP ratios) [561]. It was believed that after setting such formulation could create a porous bioceramics *in vivo* due to preferential dissolution of a better soluble ACP component compared to the other CaPO$_4$ in the matrix. Further, this combination was extended to a multiphase concrete composition consisting of 70 % w/w settable matrix (mixture of 45 % α-TCP, 5 % MCPM and 25 % of ion-substituted ACP) with the average particle dimensions of 15 µm and 30 % BCP granules (ranging between 80 and 200 µm) as a filler [628]. The role of BCP granules is quite interesting: after implantation of a formulation without BCP granules, the quality of newly formed bone was not identical to the host bone, while implantation of a concrete with BCP granules resulted in formation of a new bone identical to the host bone. The reason of this phenomenon is not clear yet; but, perhaps, it correlates with the similar results for β-TCP granules, which act as bone anchors and encourage formation of a mature bone [309, 310]. Other ACP-containing formulations were elaborated as well [639].

Effects of added α-TCP and β-TCP were investigated to shed light on the setting reactions of apatite-forming formulations consisting of TTCP and DCPA [631]. Added β-TCP showed no reactivity, and thus resulted in extended setting time and decreased mechanical strength. Similar results were obtained in another study [635]. In contrast, α-TCP dissolved to supply calcium and orthophosphate ions after initial apatite crystal formation by the chemical reaction (1). Although setting time was delayed because α-TCP was involved only in the latter reaction of apatite cement, larger apatite crystals were formed due to its addition. Due to larger apatite crystal formation, the mechanical strength of the α-TCP-added formulations increased by approximately 30 %, as compared to α-TCP-free ones [631]. In another study, HA whiskers were used as the reinforcement phase to prepare concretes and the maximum strength was achieved when HA whiskers were added in amount of 4% (wt.) [633]. Besides, self-setting $CaPO_4$ formulations might be reinforced by calcium polyphosphate fibers [640, 641]. Finally, the properties of self-setting formulations based on magnesium orthophosphates might be improved by addition of $CaPO_4$ [642].

To conclude this part, one should briefly mention on the reverse situation: there are bone concretes made of various polymeric cements, reinforced by $CaPO_4$ powders or granules to establish a compromise between the desired mechanical and biological properties [643-649]. The $CaPO_4$ presented in such formulations act as fillers, which are necessary to both improve the mechanical properties and impart bioactivity; however, they do not participate in the hardening mechanisms. For example, the higher the amount of HA was in bioactive acrylic bone cements, the higher were the compressive and tensile moduli. Furthermore, as the percentage of HA increased to 20 wt. %, the heterogeneity of the material was higher [644]. Polymerization of monomers is primarily responsible for setting of such types of biocomposites and concretes. However, that is another story.

8. Biomedical and clinical applications

Injectable and self-setting $CaPO_4$ formulations have been introduced as adjuncts to internal fixation for treating selected fractures. Various studies have already shown that they are highly biocompatible and osteoconductive materials, which can stimulate tissue regeneration [24, 650]. The main purpose of such formulations is to fill voids in metaphyseal bones, thereby reducing the need for bone graft, although such formulations might also improve the holding strength around metal devices in osteoporotic bone. Bone augmentation (*i.e.*, a reinforcement of osteoporotic bone through injection) appears to be a very promising application field of the self-setting $CaPO_4$ formulations. Such procedures ease the fixation of screws in mechanically poor bone (for example for osteosynthesis) and decrease pains associated with unstable vertebrae. The combination of a self-setting nature, a biocompatibility, a lack of any by-products and a great potential for replacement by bones make the $CaPO_4$ formulations very promising materials for clinical and medical applications. In addition, they can easily be used by bone remodeling cells for reconstruction of damaged parts of bones [151, 152, 297, 530, 651-653]. An ability to be molded in place also is a very important property because these formulations can easily be delivered into the desired place and can be fitted perfectly with bone defects [152]. Besides, some formulations were found to possess an antimicrobial activity [89, 92, 94, 101, 654], as well as promote osteoblast cell adhesion and gene expression *in vitro* [655].

Numerous studies reported optimistic results on the clinical application of the self-setting $CaPO_4$ formulations. For example, the data on cytocompatibility and early osteogenic characteristics are available in literature [656]. The ratio of the cases determined to be “effective” or “better” among the 74 cases we found to be 97.3 % [657]. Besides, the results of intra-articular degradation and bioresorption kinetics of these formulations revealed no signs of pronounced acute or chronic inflammation [658]. Injected Norian SRS® cement was mainly found as a single particle, anterior to the cruciate ligaments. Synovial tissues surrounded the cement within 4 weeks and signs of superficial bioresorption were found [658]. However, several cases of disintegration and/or washout of the self-setting $CaPO_4$ formulations were reported as a potential clinical problem [190, 279]. Perhaps, this problem could be solved by putting pressure on the paste during the setting period. In addition, sodium alginate could be added; however, the mechanical properties (strength) of this formulation are still poor [156].

According to the available information, the earliest attempts for biomedical applications of the self-setting $CaPO_4$ formulations occurred in 1984 and were related to dentistry [659, 660]. However, those were *in vitro* studies, while the earliest animal studies were performed in 1987 [45]. Afterwards, in 1991, a TTCP + DCPA cement was investigated histologically by implanting disks within the heads of nine cats [661]. Simultaneously, another research group evaluated the tissue reactions to this cement in the teeth of monkeys [662]. Some important examples of biomedical applications of the self-setting $CaPO_4$ formulations are given below.

8.1. Dental applications

A group of investigators extracted all mandibular premolar teeth from beagles [663]. After one month of healing, alveolar bone was reduced to make space for a previously fabricated $CaPO_4$ cement block. One more month later, 8-mm HA implants were placed in such a manner that the apical half was embedded into alveolar bone and the coronal half in the $CaPO_4$ cement block. The investigators observed that the cement block was gradually replaced by bone and histopathologic features of the cement area were similar to that of natural bone. Moreover, the coronal half of the implants, previously surrounded by the $CaPO_4$ cement, was firmly attached by natural bone [663]. In another study, the same researchers used fluorescent labeling analysis and electron microanalysis to measure the extent of new bone formation and elemental (Ca, P, Mg) distribution [664]. The results indicated the presence of newly formed bone at ~ 1 month after surgery and similar elemental distributions in the $CaPO_4$ cement and natural bone areas at ~ 6 months after the surgery [268].

A self-setting $CaPO_4$ was injected as a bone filler for gaps around oral implants placed on the medial femoral condyles of six goats and found excellent bone formation around the graft material. Unfortunately, the degradation rate of the formulation appeared to be very slow and no resorption was observed [665]. In another study, a self-setting formulation was placed on artificially created periodontal defects but no significant difference was found between the hardened formulation and control. However, the formulation acted as a scaffold for bone formation and provided histocompatible healing of periodontal tissues [666]. Still other investigators used a self-setting formulation for direct pulp capping [667, 668] and compared it to calcium hydroxide. Both materials were found to be equally capable of producing a secondary dentin at ~ 24 weeks [668]. Positive results were obtained in other studies [178, 669, 670]. A commercially available TTCP + DCPA formulation Teethmate™ Desensitizer (Kuraray Noritake Dental, Japan) after mixing with an aqueous solution can be directly applied onto the teeth to seal open dentinal tubules or enamel cracks. Besides, self-setting $CaPO_4$ formulations were tried as root canal fillers [92, 671, 672], for pulpotomy [673] and restoration of enamel carious cavities [274]. Namely, a high alkaline pH value of the setting reaction of single-phase TTCP formulations provides a strong antimicrobial potency which is of interest for dental applications, *e.g.*, as pulp capping agents or root canal fillers. The studies demonstrated a higher potency compared to commercial $Ca(OH)_2$/salicylate formulations against various oral microbial strains, *e.g.*, *streptococcus salvarius*, *staphylococcus epidermidis* or a clinically isolated plaque mixture [654]. Finally, the self-setting $CaPO_4$ formulations can be used as adjunctive supportive agents for dental implants [674]. Further details on the dental applications of $CaPO_4$ are available in a topical review [675].

8.2. Oral, maxillofacial and craniofacial applications

Bone regeneration in oral, maxillofacial and craniofacial surgery can be divided in two main types of procedures: bone augmentation and bone defect healing. An application of the self-setting $CaPO_4$ formulations for such purposes seems logical, as there is little or no stress generated under these conditions. Moreover, the ability to mold the material at placement is an enormous advantage from a cosmetics standpoint [268]. For example, BoneSource™ is indicated for the repair of neurosurgical burr holes, contiguous craniotomy cuts and other cranial defects with a surface area no larger than 25 cm^2 per a defect. In addition, it may be used in the sinus region for facial augmentation [152, 676] and the formulation can be supported by metal hardware [152]. In dogs, BoneSource™ was employed to supplement the supraorbital ridge and to augment skull base defects [677]. Another group performed trials to ascertain the inflammation around the site and the degree of loss of the implanted BoneSource™. The material was found to be osteoconductive with both periosteal and endosteal bone formation [678]. Still another group presented excellent results using the material combined with an underlying resorbable mesh in calvarian defects of Yorkshire pigs. They found progressive bone ingrowths in all defects at 180 days, with nearly complete replacement by host bone [435]. Besides, excellent results for over 100 human patients were reported when a self-setting $CaPO_4$ formulation was used in cranial defects. The success rate after 6 years was 97 % [141]. Furthermore, self-setting $CaPO_4$ formulations are used in orbital reconstructions [165, 167, 679]. The results of still other medical trials are available elsewhere [59, 290, 680-692].

To conclude this part, one should stress that complications still occur [693-695]. Namely, two cases of apatite-forming cement bioresorption and subsequent seroma formation were reported for patients who had undergone retrosigmoid craniotomy [693]. Furthermore, another study describes complications occurred with 17 patients who underwent the secondary forehead cranioplasty with Norian® CRS [694]. Of 17 patients, 10 (59%) ultimately had infectious complications. Infection occurred on a mean of 17.3 months after surgery and of the 10 patients with complications, 9 required surgical debridement and subsequent delayed reconstruction. The authors concluded that although apatite-forming cements could yield excellent aesthetic results, their use in secondary reconstruction yielded unacceptably high infection rates leading to discontinuation of their use in this patient population [694]. The next study was devoted to a case of foreign body reaction following frontal reconstruction with the commercial product JectOS, followed by a literature review on complications of this material after craniofacial reconstruction from 2002 to 2017. All complications were categorized into two groups: immunologic reactions (consisting of seroma collection, chronic sinus mucosa swelling and foreign body reactions) and non-immune events (infection, fragmentation and ejection). The authors suggested using self-setting $CaPO_4$ formulations only in selected cases with small defects, while long-term follow-ups would be necessary to observe their consequences [695].

8.3. Orthopedic applications

Self-setting $CaPO_4$ formulations have successfully been used for treatment of distal radius fractures [275, 696-698]. Besides, other successful attempts have been made to use these formulations for calcaneal fractures [699], hip fractures [700, 701], augmentation of osteoporotic vertebral bodies [702, 703], tibial plateau fractures [66, 698, 704-708], restoration of pedicle screw fixation [709, 710], reinforcement of thoracolumbar burst fractures [711], cancellous bone screws [712, 713], vertebral body fillings [714], in wrist arthrodesis [715] and for fixation of titanium implants [716]. A study on a cement augmentation of the femoral neck defect might be found elsewhere [717]. Considering their properties, the self-setting $CaPO_4$ formulations might potentially be applied to reinforce osteoporotic vertebral bodies [702, 718]. Further details and additional examples on this topic are available elsewhere [290, 719-721]. Besides, the self-setting formulations appear to be a reliable subchondral replacement biomaterial when the bone defect is adjacent to the articular cartilage [722].

8.4. Vertebroplasty and kyphoplasty

Vertebroplasty and kyphoplasty are two surgical procedures that have been introduced to medically manage of osteoporosis-induced vertebral compression fractures by augmenting, stabilizing, and restoring weakened vertebra to their normal functional state and height as best as possible. Vertebroplasty involves a direct injection of the self-setting formulations into the fractured vertebral body, whereas an inflatable balloon tamp is used for kyphoplasty to create a cavity in the vertebral body into which self-setting formulations can then be injected to fill the cavity. Particularly, both procedures involve injection of the self-setting $CaPO_4$ formulations into the fractured vertebral body, which resulted in a faster healing [141, 271, 722-730]. Furthermore, prophylactic injections of such formulations also have been performed.

8.5. Drug delivery

In general, a potential substrate to be used as a drug carrier must have an ability to incorporate a drug, retain it in a specific target site and deliver it progressively with time in the surrounding tissues. Therefore, a certain level of porosity is mandatory. Luckily, during setting, liquids are trapped within micro-reservoirs inside the formulations, while release of incorporated ions enables continuous hardening for several days and causes formation of pores (so called intrinsic porosity). Thus, the micro-reservoirs are beneficial for incorporation of drugs and other biomedically important components. Additional advantages are provided if a biomaterial is injectable, biodegradable, sets at ambient temperature, has both near neutral pH values and a large surface area [68, 69]. These properties make self-setting $CaPO_4$ formulations to be very attractive candidates as drug carriers for therapeutic peptides [731], antibiotics [29, 449, 732-742], anticancer [43-748] and anti-inflammatory [749, 750] agents, cytokines [751], hormones [752], bone morphogenetic proteins [590, 753-757] and other biologically active compounds [451, 758-771]. For example, a “growth factor cement” was reported [768]. In that study, a combination of a recombinant human bone morphogenetic protein-2 (rhBMP-2), transforming growth factor-beta (TGF-β1), platelet-derived growth factor and basic fibroblast growth factor (bFGF) was used in a $CaPO_4$ cement for treatment of peri-implant defects in a dog model. The findings indicated a significant effect of the “growth factor cement” on increased bone-to-implant contact and amount of bone per surface area if compared with both the cement-only and no-cement treatment groups [768]. Similar data were found for a combination of a self-setting formulation with an exogenous nerve growth factor [769]. Even more complicated combination of deproteinized osteoarticular allografts integrated with a $CaPO_4$ cement and recombinant human vascular endothelial cell growth factor plus rhBMP-2 has been studied as well [770]. The drug delivery properties of the self-setting $CaPO_4$ formulations might be influenced by crystal morphology, porosity and microstructure [771]. However, one must admit that, in the vast majority of the cases, loading with drugs at dosages necessary to combat infections, bone disorders and diseases, reduces the mechanical properties of the self-setting $CaPO_4$ formulations.

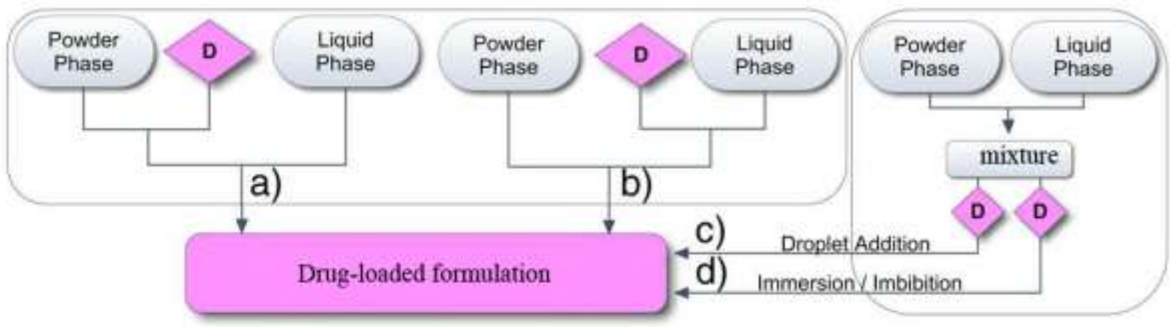

Fig. 16. A schematic drawing of the possible ways of drug (denoted as D) incorporation into the self-setting formulations. Prior phase mixing a drug can either be distributed within the powder phase (a) or solubilized in the liquid phase (b). Drug loading can also be made after setting by droplet addition (c) or by imbibition (immersion) in the drug-containing solution (d). The procedures (c) and (d) do not allow injection since they require formulation pre-setting. Reprinted from Ref. [258] with permission.

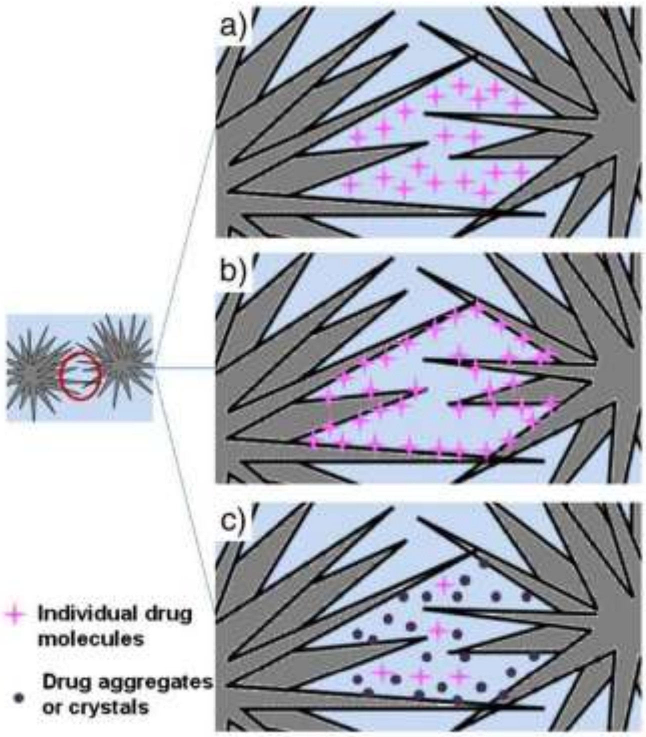

Fig. 17. A schematic drawing of the different ways a drug can be found within a solid matrix: (a) as individual molecules dissolved in the remaining liquid within the pores; (b) adsorbed or chemically bound to the crystals surface; (c) in a solid form, as drug crystals or aggregates. Reprinted from Ref. [258] with permission.

For the self-setting formulations, the first issue that has to be considered and which will determine a drug distribution and its interaction with the matrix is the incorporation method of the drug. In principle, drugs (as well as hormones, cells and other biomedical or biological compounds) might be incorporated into both a liquid and a powder phases before phase mixing, as well as into the self-setting formulations obtained after both phases have been mixed. This process is schematically shown in Fig. 16 [258]. After setting, the drugs appear to be distributed within a porous solid matrix. According to a topical review on the subject [258], there are 3 options of drug existence inside the matrix: a) dissolved in the remaining liquid phase within the existing pores among the newly formed inorganic crystals, b) adsorbed or chemically bound on the surface of the crystals, or c) in a solid form inside pores (Fig. 17).

Studies on drug release are the second most important topic on drugs incorporation into the self-setting formulations [279, 550, 733-736, 772-774]. This process is regulated by the microstructure of the set formulations (*i.e.*, porosity), as well as by presence or absence of additives able to influence the movement of drug molecules within the solid matrix. For example, it was observed that hardened formulations with a very low porosity showed much slower drug release patterns than those with higher porosities [734]. Moreover, drugs that inhibit the setting reactions and reduce the porosity have a slower rate of release. This phenomenon has been observed with gentamicin sulfate. The presence of sulfate ions in this drug inhibits brushite crystal growth, resulting in a finer solid microstructure with lower porosity that slows down drug release [732]. In another study, investigators added sodium flomoxef to a self-setting formulation and found that the release of antibiotic could be easily controlled *in vivo* by adjusting the content of sodium alginate [279]. *In vitro* elution of vancomycin from a hardened cement has been studied as well [773]. Regarding the possible mechanisms of drug releases, a topical review on the subject [258] describes 3 reasonable scenario: (a) if the rate of the matrix degradation is slower than drug diffusion, drug release is controlled by diffusion of the drug through the liquid permeating the set formulation (might be valid for apatite-forming formulations), (b) if the rate of matrix degradation is faster than drug diffusion, the former controls drug release (might be valid for monetite- and brushite-forming formulations) and (c) in some cases, an apatite layer can be formed on the surface after implantation, this hindering the diffusion of the drug to the surrounding tissue (Fig. 18). In addition, both the kinetics and the mechanism of drug release from apatite-forming formulations was found to be tuned by controlling the kinetics of crystallization (the history of formation) of their HA precursor powders during synthesis [774]. Finally, various types of surface coatings might be applied as well to slow down the kinetics of drug release.

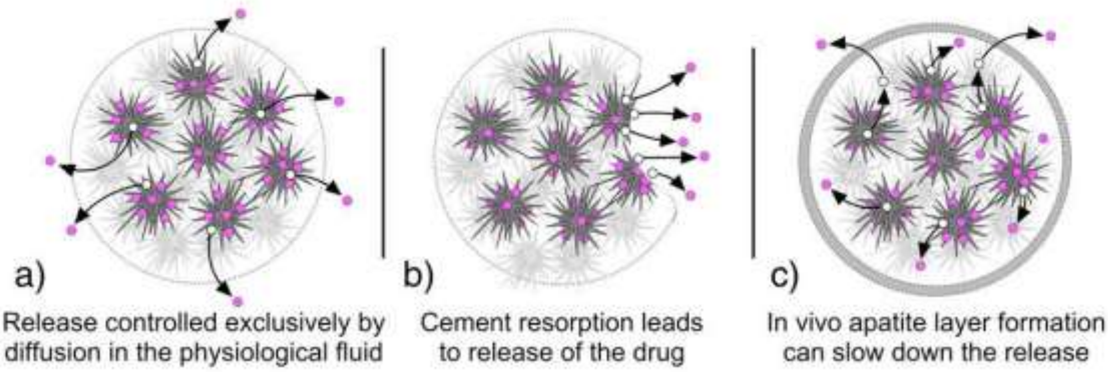

Fig. 18. A schematic drawing of the different ways a drug release from hardened formulations. Reprinted from Ref. [258] with permission.

Studies on drug adsorption appear to be the third most important topic. In general, adsorption of any type of bioorganic molecules is related to chemical interactions between their functional groups and the $CaPO_4$ matrix and the strength of this interaction influences the release pattern of drugs. Accordingly, bioorganic substances with adherent functional groups show a slow release pattern, whereas those that do not adhere well to $CaPO_4$ matrices will be more rapidly released. For instance, vancomycin release from 3D printed brushite matrices is complete within 1 – 2 days, while only 25% of tetracycline loaded on the same matrix is released after 5 days incubation [775]. Therefore, in order to obtain adequate release patterns, adsorption of bioorganic molecules to the self-setting matrix needs to be tuned. This can be done by either selecting the most appropriate drug for the matrix or modifying the self-setting matrix itself. For instance, doping brushite-forming formulations with Sr was found to reduce the antibiotic adsorption capacity, resulting in an increase in the fraction of drug released and in a faster release rate [776].

The laboratory studies on incorporation of drugs into the self-setting $CaPO_4$ formulations cover different aspects. Firstly, it is necessary to verify that addition of a drug does not influence the setting reaction not only in terms of the setting and hardening mechanisms but also with respect to the rheological behavior and injectability. Secondly, it is necessary to determine the *in vitro* kinetics of drug release. Thirdly, the drug delivery properties of the formulation must be studied *in vivo*. Finally, but still importantly, the clinical performance of the drug delivery system must be evaluated as well [68, 69]. For example, recombinant human transforming growth factor β1 (rhTGF-β1) was added to a $CaPO_4$ cement [777-780]. This resulted in formation of a bioactivated formulation that could be used as a bone filler and for the replacement of bone [777]. It appeared that after 8 weeks the addition of growth factors stimulated and increased bone formation (50 % volume) and bone contact (65 %) in comparison to control calvarian defects in an animal study. Besides, the growth factor group reduced the remaining volume of the cement by 20 % [778]. Examples of rhBMP-2 release from a loaded porous $CaPO_4$ cement might be found elsewhere [780, 781], while an experimental study on a self-setting formulation impregnated with dideoxy-kanamycin B is also available [782]. In addition, the self-setting $CaPO_4$ formulations could be loaded by other bioactive and/or biological compounds, such as ascorbic [783] and nucleic [784] acids. Further details and additional examples are well described elsewhere [62, 68, 69, 258]. Thus, the possibility of using injectable and self-setting $CaPO_4$ formulations as drug-delivery systems offers an attractive and an efficient solution for the treatment of various bone diseases, *e.g.*, tumours, osteoporosis and osteomyelitis, which normally require long and painful therapies.

Additional details on this topic are available in literature [785].

8.6. Brief conclusions on the biomedical applications

To conclude the biomedical part, one should stress that despite several encouraging results, not every surgeon' expectation has been met yet [782]. First, the self-setting $CaPO_4$ formulations are not superior to autografts, despite offering primary stability against compressive loading [786, 787]. One of the main concerns of clinicians is to reach higher bioresorption rates, an improvement of bone reconstruction and to a lesser extent, higher mechanical resistance [66]. Besides, clinical application of the self-setting formulations in comminuted fractures revealed penetration of the viscous paste into the joint space [788-790]. The interested readers are referred to a paper on cement leakage during vertebroplasty [791]. To date, cadaveric studies have already shown that using of the self-setting $CaPO_4$ formulations with conventional metal fixation in certain fractures of the distal radius, tibial plateau, proximal femur and calcaneus can produce a better stability, stiffness and strength than metal fixation alone. Early clinical results have revealed a reduced time to full load bearing when the formulations were used for augmentation of tibial plateau and calcaneal fractures, more rapid gain of strength and range of motion when used in distal radius fractures and improved stability in certain hip fractures [652, 696]. However, surgeons reported on difficulties in filling the vertebral bodies (a bad injectability of present formulations) and other problems, such as filter pressing and decohesion, observed during vertebral body injection that resulted in bone instability due to low mechanical strength as well as long setting times of the cements [792]. This happens due to not only poor mechanical properties of the self-setting formulations but also some difficulties of filling vertebral bodies. In order to maintain a good cohesion and reduce filter pressing, the $CaPO_4$ formulations need to be more viscous (hence, less injectable) [4, 5]. For example, they might be modified by addition of polysaccharides [145, 156, 453-456] and/or gelatin [236, 374, 457-462].

Another type of concerns has been raised that the use of self-setting $CaPO_4$ formulations for the augmentation of fractured and osteoporotic bones might aggravate cardiovascular deterioration in the event of pulmonary cement embolism by stimulating coagulation [793]. To investigate these potential problems, 2.0 ml of either $CaPO_4$ or PMMA cement were injected intravenously in 14 sheep. Intravenous injection of $CaPO_4$ cement resulted in a more severe increase in pulmonary arterial pressure and decrease in arterial blood pressure compared to the PMMA cement. Disintegration of the $CaPO_4$ cement seemed to be the reason for more severe reaction that represents a risk of cardiovascular complications. The authors concluded that further research efforts should aim at improving cohesion of self-setting $CaPO_4$ formulations in an aqueous environment for future clinical applications such as vertebral body augmentation [793].

The third type of concerns is related to an inflammation and other adverse reactions from the surrounding tissues. Although such cases are rare, all of them must be considered in differential diagnosis of the side effects [693-695, 794-797]. For example, there was a patient, who experienced an allergic reaction to Biopex® [796]. A patch test was performed and a positive reaction to magnesium orthophosphate was obtained. Since Biopex® contains magnesium orthophosphate, that case was diagnosed as an allergic reaction. Three publications [693-695] have been described above in section *8.2. Oral, maxillofacial and craniofacial applications*. In addition, there are cases, such as cochlear implantation surgery [797], in which self-setting $CaPO_4$ formulations appear to be unsuitable.

To conclude the biomedical part of this review, one should mention that, although the long-term outcomes are still poorly documented, currently there are no doubts regarding a very great potential of clinical applications of the self-setting $CaPO_4$ formulations for healing of bone and dental defects. For example, a bioresorbable $CaPO_4$ cement was once found to be a better choice, at least in terms of the prevention of subsidence, than autogenous iliac bone graft for the treatment of subarticular defects associated with unstable tibial plateau fractures [798]. Furthermore, BoneSource™ was found to be safe and effective when used to fill traumatic metaphyseal bone voids and appeared to be at least as good as autograft for treatment of these defects [799]. However, in other studies, autologous cancellous grafts were demonstrated to lead to a significantly better bone regeneration compared to the application of $CaPO_4$ granules produced from a self-setting $CaPO_4$ formulation after 6 weeks [800]. Since this manuscript is intended to be read mainly by chemists and materials researchers, the biological, medical and clinical aspects of the self-setting $CaPO_4$ formulations have not been discussed in many details. For additional biomedical details, the interested readers are referred to other papers and reviews [24, 62, 68, 69, 260, 652, 657, 785, 786, 801, 802].

9. Non-biomedical applications

Since a non-biomedical topic is beyond the general subject of current review, this section is brief. In literature, there are some reports on brushite cement-based biosensors, one for phenol detection by combing the cement with the enzyme tyrosinase [803] and another for the detection of glucose using the enzyme glucose oxidase [804]. Both biosensors have faster signaling and higher sensitivity than traditional biosensor systems based on polymeric or clay matrices, opening up many possibilities for the future development of these devices.

10. Recent achievements and future developments

Since the self-setting $CaPO_4$ formulations represent an intriguing group of new biomaterials for bone augmentation and reconstruction, there is a great potential for further improvement of their properties, in which the ideal characteristics (Table 6) should be approached by manipulations with the chemical composition, powder particle sizes and distribution, as well as by means of various additives. Many commercial formulations have been already approved for the clinical applications (Tables 2 and 3). New compositions are expected to appear in the market soon. The forthcoming commercial products will need to be improved in order to take the advantage of a variety of possibilities offered by the self-setting properties. New formulations will include: (i) injectable and open macroporous compositions to optimize their osteoconduction [374], (ii) formulations containing only one $CaPO_4$ (single-phase powders) [259] and (iii) drug-loaded and hormone-loaded formulations for the treatment of bone diseases [62, 68, 69]. Furthermore, incorporation of autologous or allogenic osteo-progenitor cells into the self-setting formulations will be favorable [805-807]. Obviously, the first two directions deal with both chemistry and material science, while the last two directions are more related to biology and medicine.

Regarding the material point of view, an innovative approach of so-called ready-to-use self-setting formulations was introduced relatively recently. The concept was shown to work with both single-phase $CaPO_4$ powders and mixtures of several components. For example, the ready-to-use formulations can be obtained by stabilizing the $CaPO_4$ reactants as separated liquid or pasty components, with at least one of them containing an aqueous liquid, which is needed to initiate the setting reactions after mixing. Such formulations consist of two injectable pastes to be mixed together and injected at the time of implantation [808, 809]. The preparation process is fast and reproducible since two liquid phases can be mixed more homogeneously than powder with liquid as performed for conventional self-setting formulations. This strategy allows usage of dual chamber syringes equipped with a mixing device (*e.g.*, by a static twin-chambered mixer incorporated in the injection cannula that allows injection of the paste immediately after mixing), meaning reduced paste processing/handling time, lesser contamination risks, enhanced reproducibility and immediate injection of the mixture into the bone defects [810]. In such formulations, a wide range of possibilities appears by changing the $CaPO_4$ components. Furthermore, such formulations can also be modulated by adjoining different additives as setting retardants, polymeric adjuvants, visco-enhancing agents, suspension stabilizers, osteoinductive agents, radio-opaque fillers and/or macropore-forming agents [439, 523]. For example, aqueous pastes of α-TCP powder were found to be stabilized for up to a year at room temperature by using of 0.1 M $MgCl_2$ solution (it was believed that chemical reaction (5) was suppressed by sorption of Mg cations on the α-TCP surface; therefore, wet α-TCP formulations were not set). Then, adding of a $CaCl_2$ solution in a 1:4 volume ratio activated wet α-TCP pastes and the formulations were set. This was explained by displacement of adsorbed Mg cations from the surface of α-TCP particles by Ca cations, which initiated α-TCP transformation to CDHA according to reaction (5) [811].

Table 6. Major advantages and disadvantages of the self-setting $CaPO_4$ formulations [68, 69, 268].

Advantages	Disadvantages
1. Self-setting ability *in vivo*. 2. Good injectability that allows cement implantation by minimally invasive surgical techniques, which are less damageable than the traditional surgical techniques. 3. Good osteoconductivity and occasional osteoinductivity: the initial biological properties of the hardened cements are similar to those of CDHA or brushite. 4. Can be replaced by newly formed bone after a period of time (osteotransductivity). 5. Moldability: the perfect fit to the implant site, which assures good bone-material contact, even in geometrically complex defects. 6. Excellent biocompatibility and bioactivity. 7. No toxicity. 8. Low cost. 9. Ease of preparation and handling. 10. Setting at body temperature. 11. Form chemical bonds to the host bone. 12. Clinically safe materials in their powder components. 13. Can be used to deliver antibiotics, anti-inflammatory drugs, growth factors, morphogenic proteins, *etc*. at local sites, which are able to stimulate certain biological responses.*	1. Mechanical weakness: limited use due to potential collapse of material followed by soft tissue formation instead of bone formation (loaded areas). Until cements with adequate shear strength are available, most complex fractures that can be repaired with cement also will require metal supports. 2. Can be washed out from surgical defect if excess of blood. 3. Lack of macroporosity (especially interconnected pores), which prevents fast bone ingrowth and the cements degrade layer-by-layer from the outside to the inside only. 4. The *in vivo* biodegradation of many formulations is slower than the growth rate of a newly forming bone.

*Further studies are necessary.

Another preparation approach of the ready-to-use self-setting $CaPO_4$ formulations comprises a water-reactive paste such as a mixture of TTCP and DCPD powders dispersed in a non-aqueous but water-miscible liquid (*e.g.*, glycerol, polyethylene glycol, N-methyl-2-pyrrolidone) + a gelling agent (*e.g.*, hydroxylpropylmethylcellulose, carboxymethyl-cellulose, chitosan, sodium alginate) + a hardening accelerator (*e.g*., MCPM, Na_2HPO_4, K_2HPO_4, tartaric, malic, malonic, citric and/or glycolic acids) to form a stable paste that can be directly injected into bone defects [316, 738, 812-820]. More complicated formulations for water-miscible liquid are also possible: for example, $CaPO_4$-containing precursor powders "were mixed with 2.5 wt-% finely ground K_2HPO_4 and subsequently dispersed in a carrier liquid consisting of Miglyol 812 with 14.7 wt-% Cremophor ELP (BASF) and 4.9 wt-% Amphisol A (Brenntag AG) to obtain a cement paste with a final solid content of 86 wt-%" [821, page 476]. In literature, this type of self-setting pastes is called "premixed calcium phosphate cements" (occasionally referred to as PCPC), in which the paste preparation is done under defined conditions, while the pastes remain stable during storage and harden only after placement into the defect. The pastes can be obtained of different consistencies, from low viscosity ones to putty-like plastic pastes [170-172]. Setting occurs *in vivo* upon a contact with body fluids or *in vitro* in a physiological solution. Since hardening occurs solely after the paste has been injected into a bone defect, this approach works with any formulation. In addition, premixed $CaPO_4$ formulations eliminate the powder-liquid mixing stage during surgery, which might improve their performance and allow shortening the surgical time. Besides, a risk of operator-induced error is considerably reduced. On the negative side, the setting reaction of the premixed formulations is difficult to control and the mechanical properties of the hardened $CaPO_4$ are poor. Commonly, a hardening process is both slow and volume-dependent because it relies on the exchange or replacement of a non-aqueous liquid by water. Furthermore, the use of additional components makes both production and certification more difficult, while the release of large amounts of a foreign liquid during injection may result in adverse biological reactions. In addition, premixed $CaPO_4$ formulations must be protected from the environmental moisture during storage [822, 823]. Besides, little attention has been paid to the problem that the presence of water impurities in the non-aqueous liquid and/or the powdered solid can compromise the stability of the paste. The compositions of some premixed $CaPO_4$ formulations are available in literature [439].

The earliest premixed self-setting $CaPO_4$ formulations were formed apatite as the final product, had a setting time of longer than 1 h and a low mechanical strength [812]. Afterwards, improved formulations were developed. They exhibited a rapid setting when immersed in a physiological solution, yielding a hardened $CaPO_4$ bioceramics with a higher mechanical strength, approached the reported strengths of sintered porous HA implants and cancellous bone [813-815]. Such formulations are produced commercially, *e.g.*, VELOX® (InnoTERE GmbH, (Radebeul, Germany). Brushite-forming premixed self-setting formulations have been introduced as well [808, 809, 822, 824-828]; they have shorter setting times then the aforementioned apatite-forming ones. In addition, studies appeared on preparation of the premixed monetite-forming formulations [314-317], as well as on premixed macroporous $CaPO_4$ scaffolds reinforced by slow-dissolving fibers (in other words, premixed macroporous concretes) [436]. Similarly to the common self-setting $CaPO_4$ formulations, the premixed ones could be also used for drug delivery applications [829]. Furthermore, antimicrobial properties could be created by means of additives [830, 831].

The third approach to manufacture the ready-to-use self-setting $CaPO_4$ formulations applies very low temperatures [49, 832]. According to this approach, powder and liquid components of the self-setting formulations are mixed and the prepared pastes are immediately frozen. Thus, premixed frozen $CaPO_4$ “slabs” are obtained, which are stored in freezers or even in liquid nitrogen. By freezing, the setting reactions are slowed down or even inhibited (this depends on the temperature) but when the formulations have to be applied, the “slabs” are defrosted and the softened pastes are molded by hands at ambient temperatures. When frozen and stored at $t = -80$ ºC or less, significant degradation in compression strength did not occur for the duration of the study (28 days [49] and 18 months [832]). Interestingly, that in the case of the brushite-forming formulations prepared from a combination of β-TCP with 2 M H_3PO_4 solution, freezing the paste had the effect of increasing mean compressive strength fivefold (from 4 to 20 MPa), which was accompanied by a reduction in the setting rate of the cement. This strength improvement was attributed to a modification of crystal morphology and a reduction in damage caused to the cement matrix during manipulation [49].

A dual setting approach appears to be one more direction of further development of the self-setting $CaPO_4$ formulations [833-840]. This approach is based on an addition of monomeric but polymerizable organic and/or bioorganic compounds to the $CaPO_4$ formulations, which results in preparation of $CaPO_4$-based biocomposites and hybrid formulations [841]. In such formulations, these monomers are simultaneously cross-linked during setting of the $CaPO_4$ components. For example, addition of 20 wt. % of acrylamide and 1 wt. % ammonium polyacrylate to the liquid was found to increase the compressive and tensile strength of α-TCP formulation by 149 % and 69 % (55 and 21 MPa), respectively due to a dual setting mechanism. In another study, a dual setting system based on simultaneous setting of brushite-forming β-TCP/MCPA formulation and formation of lactide modified poly(ethylene glycol) dimethacrylate-based hydrogels was developed. After radical polymerization, the gels formed a continuous phase within the $CaPO_4$ matrixes with a strong reduction of cement brittleness [839]. Other types of the dual setting $CaPO_4$-containing formulations are known as well [834-840]. The advantages of the dual setting strategy comprise the possibility of a high polymer loading into the $CaPO_4$ matrixes without compromising the rheological properties of the freshly prepared pastes. This is related to the fact that the dissolved monomers represent water miscible liquids of a low viscosity; therefore, even high monomer concentrations are not strongly altering the initial rheology [560]. This approach enables the possibility of adding a high amount of polymer to the cement, which translates to a potentially significant increase in its strength and toughness. Furthermore, one should mention that dual setting $CaPO_4$-containing formulations consisting solely of inorganic compounds are known as well. The examples comprise $CaPO_4/CaSO_4$ [70-78] and $CaPO_4$/tetraethyl orthosilicate [842] formulations; after hardening, the latter resulted in formation of interpenetrating phase composite $CaPO_4$/silica gel products, in which macropores $CaPO_4$ matrixes were infiltrated by microporous silica gels, leading to both a higher density and a compressive strength ~ 5-10 times higher than the $CaPO_4$ references alone [842]. A schematic drawing of the dual setting mechanism is shown in Fig. 19 [560].

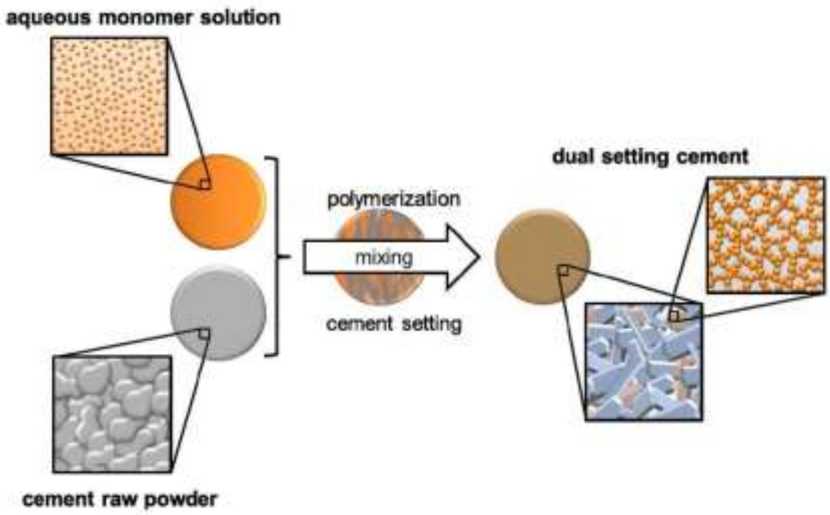

Fig. 19. A schematic drawing of the hardening mechanism of a dual-setting formulation with the formation of interconnected matrices of a polymer and the precipitated $CaPO_4$ crystals. Reprinted from Ref. [560] with permission.

According to section *4.4. Properties improving*, the major examples of liquid phase thickeners being added to the self-setting formulations include water-soluble (bio)polymers, such as polysaccharides [145, 156, 453-456], gelatin [236, 374, 457-463] and polyacrylic acid [464-466]. However, all of them form hydrogels, which exhibit viscosity decreasing with temperature increasing. The differences in temperature between the room (~ 25 °C) and the body (~ 37 °C), makes the self-setting formulations more likely to undergo extravasation from the bone defect after being injected. Thus, the preferred situation appears to be the opposite: whereas a low viscosity is convenient for mixing and injection, an instantaneous increase of viscosity is beneficial once the formulation fills the bone defect, because the latter ensures both stability and washout resistance to the blood flow. Hence, application of polymeric additives featuring an inverse thermal gelling is of particular interest for controlling the properties of injectable formulations and pluronic F127 appears to be a good example of such compound [832]. The pluronic-containing self-setting formulations were found to exhibit temperature-dependent properties. Namely, addition of pluronic enhanced the injectability and allowed the rheological properties of the formulations to be tuned with the injection force decreasing with the temperature decreasing of the paste. In addition, due to gelling, the cohesion was found to increase as the temperature of the host medium increased [832].

Using biphasic $CaPO_4$ formulations (such as mixtures of α-TCP + β-TCP powders) [34, 35, 37, 41, 42, 223] instead of α- or β-TCP alone or those containing 2 types of CDHA (one of which was precipitated abruptly, retaining the amorphous nature longer, while the other one was precipitated at a slower rate, more rapidly transitioning to the crystalline structure) [741] as the initial component of the self-setting formulation appears to be the next innovative approach. In the case of α-TCP + β-TCP formulations, due to the differences between them in both the reaction kinetics and reactivity in interactions with other chemicals, depending on the α-TCP/β-TCP ratio in the precursor blends, the variability of the handling behavior, physicochemical properties and degradation characteristics of the hardened formulations were observed. Namely, after hydrolysis of α-TCP phase according to equation (5), the α-TCP + β-TCP blend transforms to a partially non-absorbable CDHA and a completely resorbable β-TCP phase, providing new properties. In general, biphasic α-TCP + β-TCP formulations revealed longer setting and injectability times as compared to monophasic ones. During hardening, the amount of apatite formation was found to be inversely proportional to the extent of β-TCP, whereas the predominant morphology of the precipitated crystals changed from platelets to needles with increasing of the β-TCP content. The hardening process appeared to be controlled by the transformation reaction of α-TCP into a mixed matrix consisting of CDHA and β-TCP. *In vitro* degradation studies indicated that the degradation rates of biphasic α-TCP + β-TCP formulations containing sufficient amounts of β-TCP were more than twice as high if compared to just α-TCP-containing formulations [34, 35, 37, 41, 42, 223]. Furthermore, if α-TCP + β-TCP blend is used as a single-phase (or single-component) cement powder, hydrolysis of α-TCP phase into CDHA and stability of β-TCP phase results in formation of solid BCP (CDHA + β-TCP) formulations [37, 41]. Therefore, this approach could be considered as a new preparation technique of multiphasic $CaPO_4$ formulations [843]. In the case of the biphasic CDHA formulations, the weight ratio between 2 types of CDHA in the self-setting formulations was found to determine both the setting rate and the drug release kinetics for two different antibiotics. Namely, the greater the content of CDHA precipitated at a slower rate, both the faster the setting and the slower antibiotic release were found. In contrast, the greater the content of CDHA precipitated abruptly, both the slower the setting and the faster antibiotic release were found. The authors concluded that the antibiotic release profiles could be predicted and easily tuned to the desired properties using a set of equations empirically derived to fit the experimental release patterns [741].

A lack of macropores is a substantial disadvantage of many current self-setting $CaPO_4$ formulations [366]. As a result, biodegradation takes place layer-by-layer on the surface, from outside to inside. To solve this problem, various types of porogens are used [399-427]. Using a hydrophobic liquid instead of soluble particles could be an alternative. At the turn of the millennium, an open macroporous structure was obtained using a mixture of oil and a self-setting paste [844]; however, since than no research papers on this subject have been published. Besides, by means of surfactants, air bubbles might be incorporated into the bulk of the formulations [389]. Unfortunately, the mechanical strength and porosity are conflicting requirements. As porosity of the $CaPO_4$ formulations appears to be of the paramount importance to achieve an excellent bioresorbability, other experimental approaches have to be developed [845].

In the case of $CaPO_4$ reinforced formulations and concretes, one innovative approach represents a surface functionalization of the reinforced phases [846, 847]. For example, a study is available, in which the authors functionalized a surface of poly(vinyl alcohol) fibers with thermoresponsive poly(N-isopropylacrylamide) brushes of tunable thickness to improve simultaneously fiber dispersion and fiber-matrix affinity. These brushes shifted from hydrophilic to hydrophobic behavior at temperatures above their lower critical solution temperature of 32 °C. This dual thermoresponsive shift was found to favor fiber dispersion throughout the hydrophilic $CaPO_4$ formulations (at 21 °C) and toughens them when reached their hydrophobic state (at 37 °C). The reinforcement efficacy of these surface-modified fibers was almost double at 37 versus 21 °C [847].

In addition, the future studies could combine in one formulation porogens and biodegradable fibers of different shapes and dissolution rates to form after *in vivo* hardening scaffolds with sustained strength. In such a system, one porogen is quickly dissolved, which creates macropores to start a bone ingrowth process, while the second type of fibers provides the required strength to the implant. After significant bone ingrowth into the initial pores increased the implant strength, the second set of fibers would then be dissolved to create additional macropores for bone ingrowth [429]. Such complicated formulations have already been developed. For example, chitosan, sodium orthophosphate and hydroxypropylmethylcellulose were used to render $CaPO_4$ formulations fast setting and resistant to washout, while absorbable fibers and mannitol as a porogen were incorporated for strength and macropores, respectively. Both strength and fracture resistance of this concrete were substantially increased and approached those values for sintered porous HA implants [848]. Turning on a bit of imagination, one might predict development of polymeric forms of drugs (already available [849, 850]), hormones, growth factors, *etc*. (*e.g.*, prepared by either incorporation into or cross-linking with either water-soluble or bioresorbable polymers). Coupled with reinforcing biodegradable fibers and porogens, such types of "healing fibers" might be added to self-setting $CaPO_4$ formulations, which not only will accelerate the remedial process, but also will allow simultaneous improvement in both their strength and injectability. In addition, graded structures are possible. For example, a layered structure was designed by combining a macroporous layer of $CaPO_4$ cement with a strong fiber-reinforced $CaPO_4$ concrete layer. The rationale for such construction was for the macroporous layer to accept tissue ingrowth, while the fiber-reinforced strong layer would provide the needed early-strength [851].

Stability (insolubility) in normal physiological fluid environment and resorbability under acidic conditions produced by osteoclasts appears to be among the most important *in vivo* characteristics of the modern types of $CaPO_4$ bioceramics. For some clinical applications, such as cranioplasty, a relatively slow bioresorption and replacement by bone is quite acceptable, whereas in other applications, such as periodontal bone defects repair, sinus lift, *etc*., the ability of the hardened formulations to be replaced quickly by bone is crucial. Experimental results suggest that a number of parameters of the self-setting $CaPO_4$ formulations, such as the Ca/P ionic ratio, carbonate content, ionic substitution, crystallinity, *etc*. might affect the dissolution characteristics in slightly acidic solutions. This gives an opportunity to formulate compositions, possessing different resorption rates, which is suited for different biomedical applications [192, 193].

Furthermore, the discovery of self-setting $CaPO_4$ formulations has already opened up new perspectives in synthesis of bioceramic scaffolds, possessing sufficient mechanical properties and suitable for tissue engineering purposes [401, 406, 407, 555]. In the past, strong scaffolds could only be manufactured by the sintering route at elevated temperatures [852]. Therefore, until recently, it was impossible to produce resorbable preset low-temperature hydrated 3D bioceramics for various applications, *e.g.*, porous scaffolds and granules, from low-temperature $CaPO_4$, such as ACP, DCPA, DCPD, OCP and CDHA. Currently, using the appropriate techniques (*e.g.*, 3D powder printing [775, 853, 854], plotting [767, 855-857] or robocasting [236]), open macroporous 3D scaffolds [221, 400, 439, 445-450, 555, 767, 855-860] and/or other objects [862, 862] consisting of the aforementioned low-temperature phases (currently, excluding ACP and OCP) can be produced via cementitious reactions; thus, dramatically widening the biomedical applications of low-temperature $CaPO_4$. Furthermore, the data are available, that bulk porous bioceramics consisting of mutually connected $CaPO_4$ spheres can be prepared by setting reaction (5) [201-203, 863]. It is important to stress, that bulk $CaPO_4$ materials produced at or close to room temperature commonly have the specific surface areas that are often close to the ones of bone mineral (~ 80 m^2/g) which is up to two orders of magnitude higher than the values exhibited by sintered $CaPO_4$ bioceramics (typically below 1 m^2/g). Such high values of the specific surface are believed to stimulate protein adsorption, which is a very important event in bone healing. Therefore, the low-temperature $CaPO_4$ bioceramics could be very promising for tissue engineering applications and, among them, CDHA is of a special interest due to its chemical similarity to bone material.

Nevertheless, one should stress, that the most promising direction of the future developments of the self-setting $CaPO_4$ formulations is obviously seen in their functionalization by incorporation of (or impregnation by) various hormones, growth factors, drugs, other bioorganic compounds, as well as incorporation of living cells and/or other tiny biological objects [864-879]. For example, silk fibroin can regular the mineralization process and bond with HA to form fibroin/HA nanodimensional biocomposites with increased gelation properties and, thus, it can be used as an additive to improve cohesion of $CaPO_4$ formulations and decrease a risk of cardiovascular complications in its application in veterbroplasty and kyphoplasty [871].

While the simplicity in processing of the self-setting formulations encourages the incorporation of cells, the principal difficulty remains to ensure cell survival. The harsh environment in terms of pH and high ionic strength together with the high stiffness achieved upon hardening can be thought as the principal threats for cell endurance. The initial attempts have already been performed but without a great success yet. For example, researchers have already found that unset $CaPO_4$ formulations might have toxic effects when placed on cell monolayers, while the set formulations are biocompatible for the same type of cells (MC3T3-E1 osteoblast-like cells were tested). A gel encapsulation in alginate beads was found to be a possible solution to protect living cells for seeding into self-setting pastes [806, 880]. *In vitro* cytotoxic effect of α-TCP-based self-setting formulation was also observed [881]. In light of these results, the encapsulation approach [414] could potentially be used to seed a patient's *ex vivo* expanded stem cells into the formulations to create osteoinductive bone grafts those could be used to treat that patient. However, this becomes more related to tissue engineering and biology, rather than to chemistry and material science. A first possibility would be designing self-setting formulations that have setting reactions close to the physiological pH or by adding additives into the self-setting pastes able to neutralize the acidic or basic ions released during the chemical reactions.

In addition, besides the aforementioned chemical, material and biomedical improvements of the self-setting $CaPO_4$ formulations, one should not forget on a better design of both the mixing equipment and delivery (injection) techniques. As an example, the interested readers are referred to a new cannula to ease cement injection during vertebroplasty [882]; however, this subject is beyond the scope of current review.

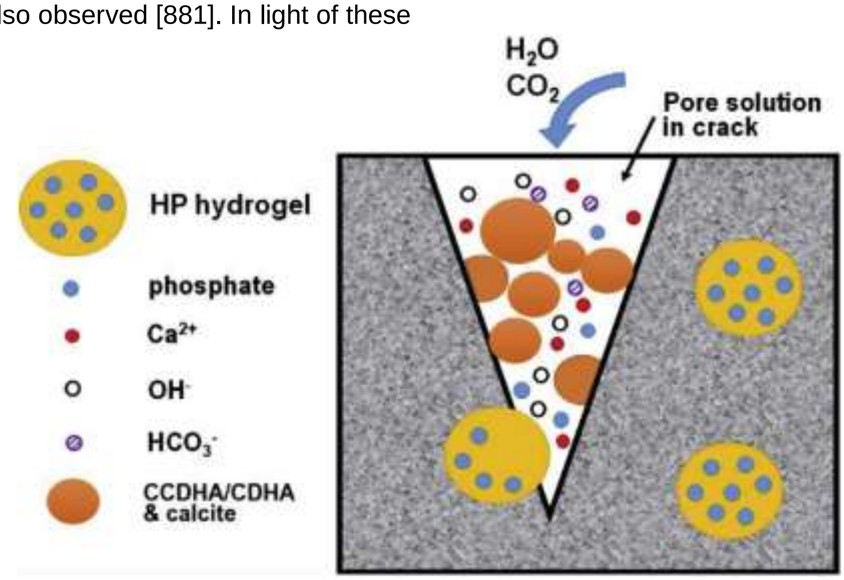

Fig. 20. A schematic illustration of a self-healing process in a bone-mimic Portland cement formulation. After formation of cracks in a hardened formulation, water and CO_2 from the atmosphere penetrate into the cracks, resulting in swelling of a phosphate-containing hydrogel and releasing of orthophosphate ions from hydrogel into a pore solution, where it reacts with Ca^{2+}, OH^- and HCO_3^- ions to form carbonated CDHA and calcite within the cracks, resulting in self-healing. Abbreviations: HP hydrogel – phosphate-containing hydrogel, CCDHA – carbonated CDHA. Reprinted from Ref. [887] with permission.

Finally, one should not forget on the recent progress in silica-based self-setting formulations used as construction materials (Portland cements). Due to the ceramic nature, industrial concretes are very sensitive to crack formation due to their limited tensile strength. Therefore, self-healing Portland cement formulations are developed [883-886]. In 2019, a study was published, in which the authors proposed a novel bio-inspired and bone-mimic formulation based on Portland cement, which resulted in CDHA formation during self-healing [887]. Briefly, the authors prepared a phosphate (Na_2HPO_4)-containing hydrogel and added it to an ordinary Portland cement. The phosphate-containing hydrogel was found to release orthophosphate ions into the Portland cement cracks at controlled rates. Carbonated CDHA particles with dimensions ~ 30 μm intermixed with minor amounts of calcite were found to be precipitated within the cracks during the self-healing process. The healing products grew from the surfaces of both sides of cracks to their centers. The compressive strength and impermeability of the self-healing formulations containing the phosphate hydrogel were fully restored after being cured for 28 days. Schematically, the self-healing process is shown in Fig. 20 [887]. This paper may be considered as the first portent of a self-setting $CaPO_4$-containing formulation, which possesses the self-healing properties.

11. Conclusions

To conclude, self-setting $CaPO_4$ formulations appear to be relatively simple biomaterials, formed by combining $CaPO_4$ powders with an aqueous solution. Their major advantages arise from their ability to set at ambient temperatures inside the body. Therefore, due to the initial plasticity of unset formulations, bone defects can be filled without leaving gaps between $CaPO_4$ and surrounding bones, forming continuity between them. Second, their injectability through a syringe meets the major requirements of minimum invasive surgery [888]. In addition, these formulations may be used to fabricate (*e.g.*, by 3D printing) porous $CaPO_4$ scaffolds with complex shapes, which become stiff after hardening. Thus, among the diverse range of bone replacing biomaterials, the self-setting $CaPO_4$ formulations undoubtedly represent a distinct group because they are relatively simple biomaterials formed by combining of a $CaPO_4$ mixture with an aqueous solution [585]. However, they symbolize an important breakthrough in the field of bone repair bioceramics, since they offer the possibility of obtaining thermally unstable $CaPO_4$ in a monolithic form at room or body temperature by means of a cementation reaction. This particular fabrication technique implies that the self-setting formulations are moldable and therefore can adapt easily to the bone cavity providing a good fixation and the optimum tissue-biomaterial contact, necessary for stimulating bone ingrowth into them and their subsequent osteotransduction [62].

Unfortunately, the perfect grafting material does not exist. The self-setting $CaPO_4$ formulations are not an exception to this statement. While possessing excellent biological properties (osteoconduction and, occasionally, osteoinduction), adequate setting time, excellent moldability and the capability to deliver different bone-enhancing proteins/antibiotics at a local level, these biomaterials lack the adequate mechanical properties for applications other than non-loaded surgical sites (see Table 6 for other details). Nevertheless, even in its present state, the self-setting $CaPO_4$ formulations appear to be suitable for a number of applications. They can be injected into osteoporotic bones to reinforce them or can be used to make granules and blocks out of low-temperature $CaPO_4$. Several types of the self-setting formulations are now on the market (Tables 2 and 3), while scaffolds made of low-temperature $CaPO_4$ are being tested. The use of slightly different chemical compositions and various dopants affects both the setting time and tensile strength that enables further improvements. In addition, new trials are conducted with the reinforced formulations and concretes, which represent additional attempts to improve the existing products.

It is anticipated that the use of self-setting $CaPO_4$ formulations will enable a faster and more aggressive rehabilitation, as the strength of the hardened concretes makes it possible to allow the full weight-bearing earlier than when bone graft is used. Although, preliminary clinical trials have already confirmed the great potential of this novel therapeutic product, the self-setting $CaPO_4$ formulations need to be improved further; in particular, their bioresorption needs to be accelerated as well as their injectability and mechanical properties need to get better. Besides, extra clinical studies are required to define the most appropriate indications and limitations of the $CaPO_4$ formulations for fracture repair.

To finalize this paper, one should mention on a recently published book on the subject [785], which is highly recommended for everybody, who wishes to get additional information and knowledge on the self-setting $CaPO_4$ formulations.

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