Acta Biomaterialia 66 (2018) 23–43

Contents lists available at ScienceDirect

Acta Biomaterialia

journal homepage: www.elsevier.com/locate/actabiomat

Review article

Magnesium-based bioceramics in orthopedic applications

Maryam Nabiyouni [a,1,2], Theresa Brückner [b,1], Huan Zhou [c], Uwe Gbureck [b,*], Sarit B. Bhaduri [d,e]

[a] Department of Bioengineering, University of Toledo, Toledo, OH, USA
[b] Department for Functional Materials in Medicine and Dentistry, University Hospital of Würzburg, Würzburg, Germany
[c] School of Mechanical Engineering, Jiangsu University of Technology, Changzhou, Jiangsu, China
[d] Department of Mechanical, Industrial and Manufacturing Engineering, University of Toledo, Toledo, OH, USA
[e] Department of Surgery (Dentistry), University of Toledo, Toledo, OH, USA

ARTICLE INFO

Article history:
Received 4 September 2017
Received in revised form 17 November 2017
Accepted 20 November 2017
Available online 2 December 2017

Keywords:
Magnesium containing cement
Bioscaffold
Implant coating

ABSTRACT

Magnesium ions are directly involved in numerous biological mechanisms; for example, they play an important part in the regulation of ion channels, DNA stabilization, enzyme activation and stimulation of cell growth and proliferation. This alkaline earth metal has gained great popularity in orthopedic applications in recent years. Magnesium-based bioceramics include a large group of magnesium containing compounds such as oxides, phosphates and silicates, that are involved in orthopedic applications like bone cements, bone scaffolds or implant coatings. This article aims to give a comprehensive review on different magnesium-based bioceramics, e.g. magnesium phosphates (MgO-P_2O_5), calcium magnesium phosphates (CaO-MgO-P_2O_5), and magnesium glasses (SiO_2-MgO) with a strong focus on the chemistry and properties of magnesium phosphate containing cements as the main application form. In addition, the processing of magnesium phosphate minerals into macroporous scaffolds for tissue engineering applications by either using traditional porogens or by additive manufacturing approaches are reflected. Finally, the biological *in vitro* and *in vivo* properties of magnesium phosphates for bone regeneration are summarized, which show promising results regarding the application as bone replacement material, but still lack in terms of testing in large animal models, load-bearing application sites and clinical data.

Statement of Significance

Though bone substitutes from calcium phosphates have been investigated for a long time, a new trend is visible in the biomaterials sector: magnesium based bioceramics from magnesium phosphates and silicates due to the special biological significance of magnesium ions in enzymatic activation, cell growth and proliferation, etc. In contrast to pure magnesium implants, such formulations do not release hydrogen during degradation. As with calcium based bioceramics, magnesium based bioceramics are used for the development of diverse applications such as cements, macroporous scaffolds and coatings. From this perspective, we present a systematic overview on diverse kinds of magnesium based bioceramics, their processing regimes for different clinical purposes and their behavior both *in vitro* and *in vivo*.

Contents

---

[*] Corresponding author.
E-mail address: uwe.gbureck@fmz.uni-wuerzburg.de (U. Gbureck).

[1] Joint first authorship.

[2] Currently at: Progenity, Inc., Ann Arbor, MI, USA.

https://doi.org/10.1016/j.actbio.2017.11.033

1. Introduction

Although human bones as crucial components of the skeleton are capable of physiological remodeling and self-healing, they are unable to cope with the negative effects of extensive defects such as "critical-sized defects (CSDs)". Currently, autografts, allografts and xenografts are the most common methods of treatment for orthopedic ailments including CSDs [1,2]. Even though these methods are reasonably effective in many cases, they are associated with certain limitations. For instance, providing adequate autografts is challenging in large defective areas such as in the case of spinal arthrodesis [3]. Allografts are alternatives in some procedures; however, they are associated with other issues like the immunologic problems, low osteogenicity and higher rate of resorption compared to the autogenous bone [4]. The invasive nature of these methods makes them susceptible to possible infection, rejection, and disease transmission [3,5]. The high cost of graft supply and surgery procedures are some of the financial burdens limiting their use in the orthopedic applications [3,6].

A great need for bone substitutes and the aforementioned limitations of already existing materials encourage scientists in their quest for more reliable bone substitutes with biological and physical properties comparable to human bones. In general, recently developed artificial bone substitutes consist of metals, ceramics, biological and synthetic polymers and their composites, whereas the majority of commercially available ceramic products is based on a few calcium phosphate (CaP) phases such as hydroxyapatite or tricalcium phosphate. In addressing the "Grand Challenge" in biomaterials research, three different generations are identified: bio-inert materials (first generation, e.g. titanium, alumina, polyethylene), bioactive and biodegradable materials (second generation, e.g. hydroxyapatite or bioactive glasses) and materials designed to stimulate specific cellular responses at the molecular level (third generation, e.g. peptide or protein modified, degradable polymers) [7]. Among bone substitute materials, long-term stable materials based on sintered calcium phosphates (e.g. hydroxyapatite, tricalcium phosphate) are still successfully used in a wide range of applications. The third-generation materials can open up newer possibilities of treatments and applications, but they are not meant to replace materials from previous generations [8]. The basic premise is that ideal materials will be resorbed and replaced over time by the body's own regenerated biological tissues [9]. The resorption process is triggered by both passive dissolution as well as by osteoclastic cells, whereas the low solubility of tertiary, sintered calcium phosphates commonly results in a low resorption kinetics such that those materials often remain over years at the implantation site. An attempt to overcome this problem is the use of protonated calcium phosphates such as brushite or monetite, which should degrade faster by their higher solubility. However, especially for brushite cements, phase changes often occur *in vivo* by a dissolution–reprecipitation reaction, which results in CaP phases with lower solubility, thus slowing down degradation and hence bone regeneration kinetics [10,11].

Magnesium phosphate (MgP) materials are being currently investigated as alternatives to the above described calcium phosphates. The rationale behind this is the sufficient solubility of MgP phases under *in vivo* conditions and the fact that Mg^{2+} is a potent inhibitor of hydroxyapatite crystal growth thereby suppressing unwanted crystallization *in vivo.* In contrast to the *in vivo* dissolution of Mg-alloys, which produces large amounts of hydrogen gas and an alkaline environment [12,13], the dissolution of magnesium phosphates only results in the release of biocompatible Mg^{2+} and HPO_4^{2-} ions. A recent article by Ostrowski et al. [14] reviewed the applications of magnesium phosphates for bone replacement with a strong focus on cement formulations, their material and biological properties. Here, we attempt a more comprehensive review of Mg-containing bioceramics by including not only cement formulations in the $MgO\text{-}P_2O_5$ binary system but also calcium magnesium phosphates in the $CaO\text{-}MgO\text{-}P_2O_5$ ternary system, as well as magnesium silicate glasses in the $MgO\text{-}SiO_2$ binary system. In addition, we highlight the use of these materials in further application forms such as 3D printed scaffolds and implant coatings as well as for drug and gene delivery purpose.

2. Role of magnesium in bone metabolism

In order to emphasize the potential of magnesium containing ceramics in orthopedic applications, a thorough understanding of the physiological roles that magnesium plays in bone metabolism is addressed first. Magnesium ions are the fourth most abundant cations in mammalians behind sodium, potassium, and calcium, and also the second most prevalent intracellular cation [15,16]. Magnesium plays multiple essential roles within the mammalian cells including: regulation of calcium and sodium ion channels, stabilizing DNA, cofactor and catalyzer for many enzymes, and stimulating cell growth and proliferation [16-18].

Adult human bodies contain 1000 mmol [15] or about 24.00 g [20] of magnesium on the average, with more than half of Mg^{2+} stored in the bones [13,15,21] (Table 1), although this number decreases by age [20]. Magnesium content is 0.44 wt% of enamel, 1.24 wt% of dentin and 0.72 wt% of bone in an adult human [22]. The concentration of magnesium in the serum varies. It normally ranges between 0.75 and 0.95 mmol/L [15]. Inside the cell, magne-

Table 1
Total distribution of magnesium in the human body [19,20].

Location	Percent of total	Magnesium content* (mg)
Bone	53	12,720
Muscle	27	6480
Soft tissue	19.2	4608
Erythrocyte	0.5	120
Serum	0.3	72
Total	100	24,000

* Data for 70 kg adult humans

sium cations are mostly found in Mg-ATPase complexes, bound to the mitochondria and the extracellular membrane, bound to a variety of proteins and enzymes, in the endoplasmic reticulum, and even inside the nucleus [18]. Although the concentration of magnesium is not regulated by specific hormones as opposed to calcium and sodium, it is tightly regulated *via* the gastro-intestinal tract and the kidneys [23,24]. Magnesium can be released from bones and muscles, in case of deficiency [21], which might be due to decreased intake or increased loss *via* thiazide diuretics [25].

The deficiency of magnesium in the body leads to numerous health problems. According to the U.S. Food and Nutrition Board, the Recommended Dietary Allowance (RDA) for magnesium is 420 mg/day for adult males and 320 mg/day for adult females [26]. Magnesium deficiency is linked to low bone mass, reduced bone growth, osteoporosis, and increased skeletal fragility [26]. Studies in humans and rat models demonstrated that magnesium deficiency can cause three phenomena: 1) low serum parathyroid hormone (PTH) and calcitriol, the hormonally active form of vitamin D levels, which may contribute to reduced bone formation; 2) an increase in substance P, a neuropeptide, which in turn stimulates production of cytokines to intensify osteoclastic bone resorption; 3) a decrease in osteoprotegerin (*OPG*) and an increase in receptor activator of nuclear factor *kB* ligand (*RANKL*) favoring an increase in bone resorption [27]. On the contrary, enhanced bone regeneration was observed around degradable magnesium alloys [13,28,29] which corresponds to an additional Mg^{2+} ion supply. Thus, some *in vitro* studies explicitly analyzed the effect of Mg^{2+} ions on different bone cells to simulate magnesium alloy degradation [30–32]. This shows another key role of magnesium in bone which is related to adhesion and growth of osteoblastic cells [20]. The interactions between osteoblast cells and biomaterial surfaces are thought to be mediated primarily by membrane-associated adhesion receptors belonging to the integrin superfamily, which are transmembrane proteins consisting of non-covalently associated α- and β-subunits [33]. The extracellular domain of the α-subunit needs to bond to divalent cations such as Mg^{2+} and Ca^{2+} and the change of extracellular ions can modify the integrin affinity to their respective ligands [34,35]. Yoshizawa et al. [30] cultured human bone marrow stromal cells in Mg^{2+} supplemented medium. At concentrations of 10 mM $MgSO_4$, mineralization of the extracellular matrix (ECM) was enhanced and an increased expression of the collagen type X protein as well as the vascular endothelial growth factor (VEGF) and other osteogenic ECM proteins and transcription factors was evenly observed. At higher concentrations of >20 mM, Mg^{2+} ions appeared being cytotoxic [30]. This concentration dependency of the metabolic activity was likewise observed by Wu et al. [32] for human osteoclasts as cell proliferation and differentiation was increased at low and decreased at rather high Mg^{2+} concentrations. They further recognized the significance of the Mg^{2+} origin (magnesium chloride solutions v. magnesium extracts) [32]. Using co-cultures of bone forming and bone resorbing cells, the susceptibility of monocytes towards high Mg^{2+} concentrations is eased [31]. Thus, magnesium is not only an essential element in human body, but its incorporation in bioceramics can play an important role in the bone-substitute/bone interaction, leading to *de novo* tissue development.

3. MgO-P_2O_5 binary system

As compared to the CaO-P_2O_5 (Ca-P) binary system, the MgO-P_2O_5 (Mg-P) binary system has been studied to a much lesser extent in biomedical applications, although the compounds of the Mg-P system have been extensively used in agricultural, environmental, and civil engineering fields [36–41]. Unlike their Ca-P counterpart, Mg-P did not receive their well-deserved attention in the biomedical fields, perhaps due to the overwhelming attention given to Ca-P and lesser appreciation of the role of magnesium in the human body. Consequently, the development of research on magnesium phosphate cements (MPCs) is also less mature as opposed to that related to CPCs. A summary of important MgP compounds including important raw materials for MPC generation is given in Table 2. It is seen that most compounds in the Mg-P system have Mg/P ratios of 1 and 1.5, which correspond to important compounds of orthopedic significance in the Ca-P system, such as dicalcium phosphate anhydrous (DCPA, monetite, $CaHPO_4$), dicalcium phosphate dihydrate (DCPD, brushite, $CaHPO_4{\cdot}2H_2O$), and tricalcium phosphate (TCP, $Ca_3(PO_4)_2$). An important compound in the Ca-P binary system, hydroxyapatite (HA), with a Ca/P ratio of 1.67, does not occur in the Mg-P binary system. In contrast to brushite and octacalcium phosphate (OCP, $Ca_8(HPO_4)_2(PO_4)_4{\cdot}5H_2O$), other Ca-P compounds do not have crystallization water in their structures [42], whereas most of the magnesium phosphates are hydrated at low temperature. These compounds ($Mg(H_2PO_4)_2{\cdot}xH_2O$ with $x = 4, 2, 0$; $MgHPO_4{\cdot}yH_2O$ with $y = 3, 7$; and $Mg_3(PO_4)_2{\cdot}zH_2O$ with $z = 8, 22$) can be synthesized *via* precipitation in aqueous solutions [43,44]. The complex phase relationship between these hydrated phases has been reported by Brown et al. [43], as shown in Fig. 1. This reference is the most comprehensive phase diagram and mostly agrees with previous results from Belposky et al. [45] and Shpunt et al. [46], respectively.

The diagram is drawn according to the convention devised in the construction of previously complied CaO-P_2O_5-H_2O phase diagram [53]. An important conclusion is that, with the exception of newberyite ($MgHPO_4{\cdot}3H_2O$), most of the MgPs have incongruent solubility. The diagram shows six different hydrated MgPs with different amounts of water of crystallization. The data reveal greater solubility range for $x = 2$ as opposed to $y = 3$, an important piece of information for the setting reactions in cements. As an example, the dissolution of cattiite ($Mg_3(PO_4)_2{\cdot}22H_2O$) yields a solution saturated with newberyite but unsaturated with cattiite and hence results in the precipitation of newberyite. The diagram also proves that incongruent dissolution of bobierrite ($Mg_3(PO_4)_2{\cdot}8H_2O$) to cattiite is not possible.

The high-temperature calcination can convert these materials into either magnesium pyrophosphate ($Mg_2P_2O_7$) or magnesium orthophosphate ($Mg_3(PO_4)_2$) [54,55]. Like the CaP compounds, compounds in the MgP system can accept other cations such as NH_4^+, Na^+, and K^+ to result in new materials with modified physical properties [54,56–59]. Finally, all of the MgP compounds listed in Table 2 are resorbable and therefore are very important for orthopedic applications. Newberyite is as reactive as monetite and brushite, while bobierrite and cattiite have solubility similar to that of TCP [42,47,48]. Thus, the Mg-P compounds can be as effective as their Ca-P counterparts and provide additional benefits such as ability to achieve high strength. Further, the minerals of the Mg-P system have a superior degradation potential to Ca-P [14]. The dissolution rates are higher compared to HA [60,61] and their advantage over brushite are the Mg^{2+} ions which should avoid

Table 2
MgP compounds, their corresponding chemical formula and solubility product constants and calculated solubilities at 25 °C. The * labeled Mg-P is metastable in water [47-52].

MgP compound	Chemical formula	Solubility $-\log(K_{sp})$	Solubility in mg/L	Mg/P ratio
Bobierrite (trimagnesium phosphate octahydrate)	$Mg_3(PO_4)_2{\cdot}8H_2O$	25.2	1.46	1.5
Brucite (magnesium hydroxide)	$Mg(OH)_2$	11.2	6.79	/
Cattiite (trimagnesium phosphate hydrate) *	$Mg_3(PO_4)_2{\cdot}22H_2O$	23.1	6.20	1.5
Dittmarite	$NH_4MgPO_4{\cdot}H_2O$	Unknown	Unknown	1
Farringtonite (trimagnesium phosphate)	$Mg_3(PO_4)_2$	23.4	2.15	1.5
Hannayite	$(NH_4)_2Mg_3(HPO_4)_4{\cdot}8H_2O$	Unknown	Unknown	0.75
K-struvite (magnesium potassium phosphate hexahydrate)	$KMgPO_4{\cdot}6H_2O$	10.6	78.0	1
Magnesia (magnesium oxide)	MgO	25.0	$1.27{\cdot}10^{-8}$	/
Newberyite (magnesium phosphate dibasic trihydrate)	$MgHPO_4{\cdot}3H_2O$	5.51–5.82	$(1.69–2.54){\cdot}10^3$	1
Schertelite	$(NH_4)_2Mg(HPO_4)_2{\cdot}4H_2O$	unknown	unknown	0.5
Struvite (magnesium ammonium phosphate hexahydrate)	$NH_4MgPO_4{\cdot}6H_2O$	9.94–13.4	8.38–119	1

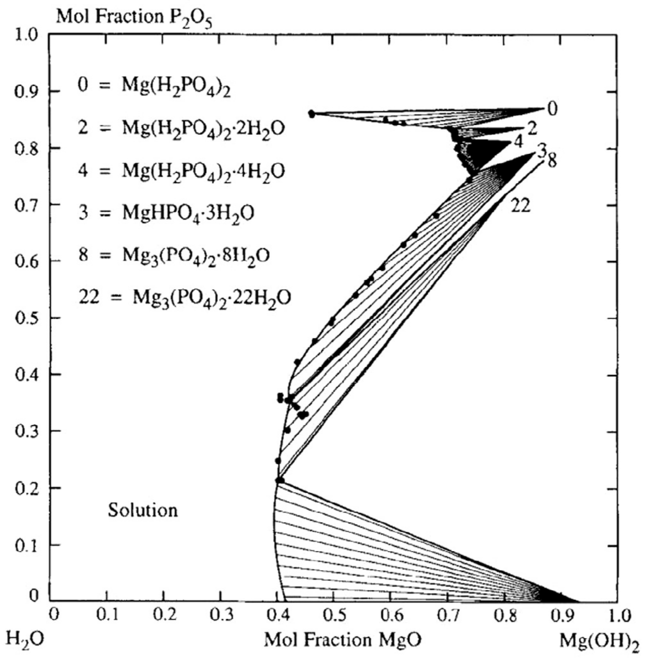

Fig. 1. Ternary System $MgO\text{-}P_2O_5\text{-}H_2O$ at 25 °C [43]. Copyright (1993), with permission from Wiley.

recrystallization into less soluble mineral phases (e.g. apatitic reprecipitates). This could be confirmed *in vivo* [11]. Indeed, magnesium salts are added to brushite on purpose to avoid crystallization [10,62].

Unlike in the CaP system, compounds containing NH_4^+ occur in the MgP system, and their uniqueness has been noted in literature. Such compounds include dittmarite (dimagnesium ammonium phosphate monohydrate, $MgNH_4PO_4{\cdot}6H_2O$), schertelite (dimagnesium ammonium phosphate tetrahydrate, $MgNH_4PO_4{\cdot}4H_2O$), struvite (dimagnesium ammonium phosphate hexahydrate, $MgNH_4PO4{\cdot}6H_2O$) [63] and hannayite ($(NH_4)_2Mg_3(HPO_4)_4{\cdot}8H_2O$) [64]. Some of these phases result in better mechanical properties e.g., struvite-containing compositions. There is no equivalent phase in the Ca-P system [57].

Including ammonium containing compounds into the above mentioned context reveals the following relationships (Fig. 2): Dittmarite can be found as an early intermediate product of struvite formation or when the reaction is very fast [65,66]. Besides, Sarkar [67] showed that struvite is unstable at temperatures >55 °C and forms dittmarite at ~60 °C in excess water wherein hydration at room temperature regains struvite [67]. Thus, low amounts of water as well as the high heat development, followed by dehydration might trigger dittmarite setting [63]. Through precipitation, Frazier et al. [64] obtained schertelite and hannayite. Schertelite was highly soluble in water and formed struvite. Similar results were observed after aging in air for several months [64]. Schertelite was further assumed to be an intermediate mineral in struvite formation [66]. Hannayite would also dissolve in water - but more steadily compared to schertelite – and form a mixture of struvite and newberyite. It further represents an intermediate mineral phase during the formation of schertelite when struvite (or newberyite) is immersed in saturated $(NH_4)_2HPO_4$ solution [64]. Conditions, such as heating struvite in dry air results in the loss of water of crystallization and ammonia and might lead to the formation of amorphous MgP (e.g. $MgHPO_4$). This phase can be rehydrated to form newberyite or struvite which depends on the remaining ammonium quantity [66,67]. Using a primary

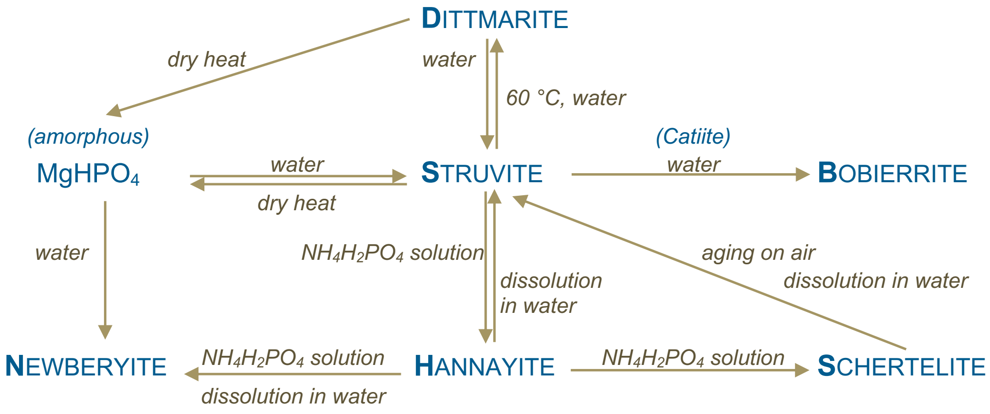

Fig. 2. Scheme of the correlations between different Mg-P within the $MgO\text{-}H_3PO_4\text{-}(NH_3)\text{-}H_2O$ system.

sodium phosphate as reactant is an alternative approach to generate amorphous MgP phases as shown by Mestres et al. [68–70]. According to Frazier et al. [64], bobierrite is the product of the slow transformation from struvite in water *via* cattiite [64].

4. CaO-MgO-P_2O_5 ternary system

Important materials in the CaO-MgO-P_2O_5 system mainly refer to magnesium doped (substituted) calcium phosphates. In bone structure, the amount of magnesium associated with apatite minerals is higher at the beginning and decreases with increasing calcification [71,72] leading to an increase in crystallinity and stability. Therefore, it is logical to assume that the more Mg^{2+} is contained, the higher is the probability to achieve amorphous or nanocrystalline structures with lesser stability and greater solubility. This section simultaneously addresses the effects of Mg^{2+} substitution into the lattice of diverse calcium phosphates and their synthesis *via* aqueous media which is most common in literature.

In many cases, the substitution with Mg^{2+} can be disruptive to the crystalline lattice resulting in amorphous phases. It is believed that the presence of Mg^{2+} ions initially retards the nucleation and growth of HA in the biological mineralization process from its precursors (amorphous and OCP). This is because the active growth sides are blocked through the adsorption of Mg^{2+} ions at the crystal surface [73–79]. On the other hand, Abbona et al. [80] suggested that magnesium ions can either be incorporated into amorphous calcium phosphate clusters and HA pre-nuclei [80].

With excessive magnesium in aqueous Ca^{2+}, Mg^{2+}, and PO_4^{3-} containing solutions, brushite and whitlockite can also form as end products of precipitation. Boistelle et al. [81] studied precipitation of calcium phosphates at 37 °C in urine or aqueous solutions with comparable Ca^{2+} and Mg^{2+} concentration. They found that initially, only an amorphous phase and brushite precipitated, although the solutions were supersaturated with respect to all calcium phosphates. Later, the amorphous calcium phosphates transform either into whitlockite or apatite depending on the solution composition [81]. Cheng et al. [82] kept neutral aqueous solutions (1 or 3 mM $CaCl_2$, 0 to 9 mM $MgCl_2$, 0.1 to 90 mM Na_2HPO_4 and 300 mM NaCl) at 37 °C for 21 days. In all solutions with 1 mM Ca^{2+} ions and 3 mM Ca^{2+} with<10 mM PO_4^{3-}, heterogeneous nucleation of OCP ($Mg/Ca \leq 1$) or brushite ($Mg/Ca > 1$) was observed; the former transforming into apatite with time. In contrast, homogeneous nucleation of an unstable amorphous calcium magnesium phosphate occurred in solutions with 3 mM Ca^{2+} and $\geq$10 mM PO_4^{3-}, transforming into apatite, brushite, whitlockite (and newberyite) depending on Mg/Ca and PO_4^{3-} values [82].

In HA, up to 10 at.% of calcium can be substituted with magnesium [83,84]. In line with its smaller ionic radius (0.065 nm), Mg^{2+} substitution causes a reduction of the lattice parameters [85] and crystallinity of HA [83,84]. Such ionic substitutions also have an effect on the microscopic structure of the precipitated minerals. In contrast to pure amorphous magnesium phosphate dense nanospheres, calcium magnesium phosphates produced at similar conditions with a Ca^{2+}:Mg^{2+} ratio of 1:1 are mostly less dense and have an elongated nanorod morphology, while pure HA forms less dense nanospheres [86]. Furthermore, it was shown that the ratio of Mg^{2+}:Ca^{2+} during mineral precipitation is directing the precipitation of either amorphous or crystalline phases [87].

The total concentration of magnesium can amount to up to 30 at.%, with the excess being stored in the amorphous phase and/or on the crystal surface [83–85]. Magnesium doped HA displays increased solubility with respect to stoichiometric HA which may be related to reduced crystallinity and/or an increased surface hydration [85,88]. Near-infrared and medium-infrared spectroscopic data indicated that the samples enriched with Mg^{2+} ions retained more water at their surface [89]. Additionally, the H-bonding network in defective subsurface layers was also noticeably modified, indicating that the Mg^{2+}/Ca^{2+} exchange was not limited to the surface. After calcination, the magnesium doped HA can be converted into HA (e.g., Mg < 1 mol% Ca) or biphasic calcium phosphate (BCP) phases from both HA and β-TCP (e.g., Mg > 1 mol% Ca). In the latter case, the β-TCP structure type increased with the amount of magnesium [90,91]. The doping Mg^{2+} can either be incorporated into BCP phases, or segregated as free MgO [90].

The substitution of TCP with Mg^{2+} can stabilize β-TCP at high temperature, suppressing the transformation into α-TCP, which is of interest for the fabrication of dense ß-TCP ceramic monoliths at temperatures >1125 °C [92,93]. ß-TCP can incorporate up to 14 mol% Mg^{2+} corresponding to a molar Mg:Ca ratio of 0.16, which forms whitlockite as a bioceramic with decreased solubility [94,95]. Magnesium containing β-TCP is formed by sintering or *via* precipitation or hydrolysis of monetite in aqueous systems. Kumta et al. [96] precipitated magnesium doped β-TCP by dropwise adding of Ca^{2+} and Mg^{2+} containing solutions into acidic NaH_2PO_4 at 95–100 °C [96]. The same result was obtained by hydrolyzing monetite in a stirred Ca^{2+} and Mg^{2+} containing solution under similar conditions [97]. Furthermore, doping with Mg^{2+} improved the densification and mechanical behavior of TCP but reduced its solubility [98].

Magnesium substitution can also stabilize brushite, which is normally unstable under physiological conditions and converts into HA over time. As an example, Lee et al. [99] synthesized magnesium doped brushite through the reaction of Na_2HPO_4, $CaCl_2$, and $MgCl_2$ in an aqueous solution with different Mg/(Ca + Mg) ratios (0, 14%, 50%) [99]. However, similar to HA, the substitution of brushite with magnesium is limited and excessive Mg^{2+} is likely to remain in the interstitial sites of the brushite structure. Mg^{2+} substitution distorts the lattice to be weakly crystalline rather than exhibiting other phases. It is also possible that an excess of magnesium results in the formation of some amorphous phase. In this case, magnesium would distort the structure considerably and inhibits the crystallization of the hexagonal shaped brushite platelets, lowering their surface energy and thus intensifying the formation of nanospherical particles. Additionally, bobierrite appears to crystallize from the brushite phase during the 12 h aging period.

5. SiO_2-MgO binary system

Glasses in the SiO_2-MgO binary system are bioactive and a list of MgO containing silicate glasses was provided by Diba et al. [20,100]. MgO is reported to have different roles in the glass network such as acting as modifier [101,102], intermediate oxide [103] or exhibiting of anomalous properties [104]. For example, MgO is added as an intermediate oxide in the $49.5SiO_2$–$1.1P_2O_5$–(23.0(1-*x*))CaO-*x*MgO-$26.4Na_2O$ (mol%) system wherein tetrahedral MgO_4 structures formed in case of $0 \leq \times \leq 1$ [104]. The addition of MgO to SiO_2–Na_2O–CaO–MgO, SiO_2–K_2O-MgO-BaO or SiO_2-CaO-K_2O-MgO system caused a decrease in hardness, elastic modulus and brittleness and showed an improved fracture toughness with increasing MgO content [105]. In addition, the Mg^{2+} ions can create a tighter glass network due to their high Dietzel's ionic field strength [20]. MgO containing silicate glasses have lower transition temperatures which is caused by the formation of Si-O-Mg instead of Si-O-Si bonds [104]. Further, crystallization is inhibited with the elevation of crystallization temperatures [106]. Consequently, MgO containing glasses have a larger processing window which enables processing without crystals formation [104]. Besides, beneficial effects of Mg^{2+} addition include a higher thermal stability, surface reactivity [106], and glass dissolution

Table 3
Examples of MgO containing glasses with potentials in biomedical applications.

Chemical formula	Biomedical application of Mg^{2+}	Refs.
MgO-CaO-P_2O_5-SiO_2	Glass degradation rate, apatite formation	[108]
MgO-CaO-P_2O_5-SiO_2-Na_2O-K_2O	Higher expression of collagen type I, and alkaline phosphatase in human fibroblasts	[106,109]
MgO-CaO-P_2O_5-SiO_2-K_2O	Glass stability	[106]
MgO-CaO-P_2O_5-SiO_2-Na_2O-K_2O-B_2O_3	Antibacterial properties	[110]
SiO_2-CaO-P_2O_5-MgO-K_2O-$Na_2OAl_2O_3$	Higher expression of collagen type I, II, and V in human osteoblasts	[111]

via disruption of silica glass network [107]. Common magnesium containing glasses for biomedical applications are listed in Table 3.

6. Application forms of magnesium phosphates

6.1. Cements

Magnesium based cements have a long history as construction materials in civil engineering [66]. Cement chemistry is based on the formation of either magnesium carbonate, phosphate, silicate-hydrate, oxychloride or oxysulfate salts. The chemistry of such cements was reviewed in detail including relevant material properties but excluding their application in biomedical engineering [66]. The latter topic was recently covered for magnesium phosphate cements (MPCs) by an article by Ostrowski et al. [14] giving an overview about both the principal setting reactions, the material properties of the cements including rheology, mechanical properties, as well as their *in vivo* performance. In addition to their high early strength [68], the following characteristics make them superior (or at least equal) to classic CPCs:

- Detailed *in vitro* studies proved the ability of Mg^{2+} ions to stimulate osteoblast differentiation [30,31] and to inhibit osteoclast formation [31,32] in a dose-dependent manner.
- The products of MPCs have a superior degradation potential to CPCs [14]. The dissolution rates of hardened MPCs are higher compared to HA forming CPC [60,61] and their advantage over brushite forming CPC are the Mg^{2+} ions which should avoid recrystallization into less soluble mineral phases (e.g. apatitic reprecipitates).
- Antibiotics are usually incorporated into CPC to provide them with antibacterial properties [112]. In contrast, specific sodium containing MPC formulations were shown to be intrinsically antimicrobial against variable bacterial strains that are related to implant infections (e.g. *Escherichia coli*) [69] or dental plaque (e.g. *Streptococcus sanguinis*) [68].
- CPCs are not known for their bonding ability to bone [113]. In fact, there is only one research article published which deals with promoting the adhesive potential of brushite CPC *via* substitution of orthophosphoric with pyrophosphoric acid [114]. Indeed, MPC were successfully used *in vivo* as adhesives for bone-implant interfaces [115] and tendon-to-bone healing [116]. These results seem quite promising.

6.1.1. Cement formulations and setting principles

So far, most of the raw materials for successful MPC compositions are crystalline, such as, magnesia (magnesium oxide, MgO) [68–70,117–119] and farringtonite (trimagnesium phosphate, $Mg_3(PO_4)_2$) [11,120–123]. More recently, the use of brucite (magnesium hydroxide, $Mg(OH)_2$) has also been reported (see Table 2) [124,125]. For the first time, Babaie et al. [126] described the only use of amorphous magnesium phosphate (AMP) raw material in forming a viable MPC composition [126]. Usually, the crystalline compounds react *via* an exothermal acid-base reaction [127] which is comparable to that of brushite forming CPCs [14]. Diammonium hydrogen phosphate (DAHP, $(NH_4)_2HPO_4$) [120–123,128], ammonium dihydrogen phosphate (ADHP, $NH_4H_2PO_4$) [11,60,68–70,119,128], sodium dihydrogen phosphate (NDHP, NaH_2PO_4) [68–70], potassium dihydrogen phosphate (KDHP, KH_2PO_4) [118,129,130] and phosphoric acid (H_3PO_4) [125] among others have already been used as possible reactants for MPC in biomedical applications. The phosphate salts can either be dissolved in the aqueous phase [11,120–123,128] or supplemented as solids to the powdery phase [60,68–70,118,119,129].

Wagh and Jeong [131] clarified the acid-base reaction mechanism of MPC with magnesia as raw powder *via* an intermediate aquosol and gel formation [131]. The dissolution of the phosphate salt results in an initial decrease in pH [132]. Thereupon, MgO dissolves in the acid aqueous environment to form Mg^{2+} and OH^- ions [131], in turn, elevating the MPC paste pH value [132]. This dissolution step is either proposed as dissociation of an intermediate brucite mineral as a consequence of the stepwise adsorption of water molecules (Eqs. (1)–(3)) [127]. Subsequently, the magnesium cations interact with water and generate positively charged aquosols which further react with the dissolved phosphate ions from the acidic reacting agent to hydrophosphate salts (Eqs. (4) and (5)) and form a gel. With the progress of the reaction, the gel gains viscosity and precipitates as a layer of the final hydration product on the surface of undissolved MgO grains [131] which was confirmed by Ding et al. [130] through microscopic observations [130] (Fig. 3). The hydration product introduced *via* Eq. (5) is newberyite [14].

$$MgO + H_2O \rightarrow MgOH^+ + OH^- \tag{1}$$

$$MgOH^+ + 2H_2O \rightarrow Mg(OH)_2 + H_3O^+ \tag{2}$$

$$Mg(OH)_2 \rightarrow Mg^{2+} + 2OH^- \tag{3}$$

$$Mg^{2+} + H_2O \rightarrow [Mg \leftarrow OH_2]^{2+} \tag{4}$$

$$[Mg \leftarrow OH_2]^{2+} + HPO_4^{2-} + 2H_2O \rightarrow MgHPO_4 \cdot 3H_2O \tag{5}$$

The setting mechanism of MPC is not yet completely understood, but most researchers agree with a dissolution and precipitation reaction as described above [127] including the work of Neiman and Sarma [133]. The mechanical stability of the hardened cement is provided *via* mechanical interlocking of the hydration products [127].

Using an ammonium phosphate salt (DAHP, ADHP), hydrated ammonium magnesium phosphates such as struvite [11,60,68–70,119–123,134], dittmarite [134], schertelite [68–70] and more seldom hannayite [128,134] are formed, among which struvite is the most frequent product [65,127]. Possible reaction routes for the struvite generation on the basis of either MgO or farringtonite and DAHP are proposed as follows wherein magnesia causes the vaporization of ammonia and farringtonite releases phosphoric acid (Eq. (6) and (7)) [14,137]:

$$\underset{magnesia}{MgO} + \underset{DAHP}{(NH_4)_2HPO_4} + 5H_2O \rightarrow \underset{struvite}{NH_4MgPO_4 \cdot 6H_2O} + \underset{ammonia}{NH_3 \uparrow} \tag{6}$$

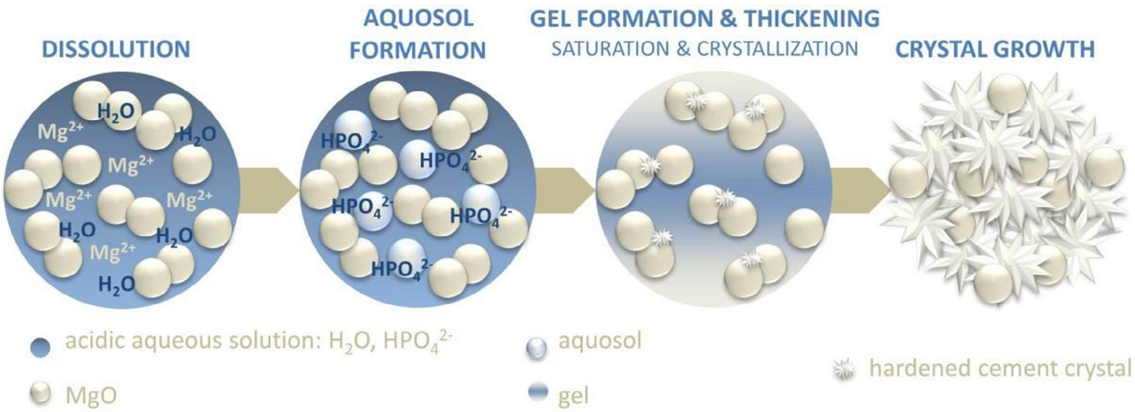

Fig. 3. Scheme of the acid-base reaction which underlies the setting mechanism of MPC sytems on the basis of MgO and contains intermediate aquosol and gel formation as proposed by [131].

$$\underset{Farringtonite}{2Mg_3(PO_4)_2} + 3(NH_4)_2HPO_4 + 36H_2O \rightarrow 6NH_4MgPO_4 \cdot 6H_2O + \underset{phosphoric\ acid}{H_3PO_4} \tag{7}$$

The utilization of the corresponding primary phosphate slightly alters the above out-pointed stoichiometry [119], whereby with MgO (Eq. (6)) no ammonia will be formed and with farringtonite the amount of phosphoric acid (Eq. (7)) will increase. The substitution of DAHP with the potassium containing equivalent KDHP leads to the formation of K-struvite (magnesium potassium phosphate hexahydrate, $KMgPO_4{\cdot}6H_2O$) [118,129,130,136]. While magnesia based MPC typically show an initial pH drop (phosphate dissolution) with successive pH increase (OH^- release) [132], farringtonite based cements exhibit a continuous pH decrease because of the phosphoric acid side product [11].

As already mentioned, struvite is the most frequent setting product of MPC [65,127], which has mainly to do with the fact that struvite – among all possible products within the MgO-H_3PO_4-NH_3-H_2O system has the lowest solubility product constant [127]. However, (reciprocal) transformations are possible as already mentioned in Section 3 (Fig. 2).

Ammonium- and potassium-free hydrated products of MPC comprise mainly of newberyite and to a lesser extent bobierrite. Both can be found as side products in the MgO-H_3PO_4-NH_3-H_2O system [127,134]. However, a selected precipitation of newberyite is possible when using phosphoric acid as a reactant with MgO [131,137] or brucite [125] (Eqs. (8) and (9)) [133,126].

$$\underset{magnesia}{MgO} + \underset{phosphoric\ acid}{H_3PO_4} + 2H_2O \rightarrow \underset{newberyite}{MgHPO_4 \cdot 3H_2O} \quad [133] \tag{8}$$

$$\underset{brucite}{Mg(OH)_2} + H_3PO_4 \rightarrow MgHPO_4 \cdot 3H_2O + H_2O \quad [126] \tag{9}$$

Apart from MPC, magnesium oxychloride cements (MOC) – also called Sorel cements after their discoverer Stanislas Sorel [138] – were evenly proposed as biomaterial by Tan et al. [139,140] in 2014 [139]. MOC were used in diverse applications like stucco or flooring, as they have a high strength and resilience when properly filled [141] and they are considered for niche applications such as nuclear waste immobilization [66]. Basically, MOC describe all formulations within the MgO-$MgCl_2$-H_2O system [138] whereas the resulting hydrate phase and its properties depend on factors such as precursor molar ratio [142–145], MgO reactivity [142,143,146,147] and temperature [138]. Examples of possible reaction routes are given by Eqs. (10) and (11) [66]. Similar to the acid-base mechanism described above for MPC the magnesia raw powder dissolves in an acid ~1.5–3.0 M solution of magnesium chloride ($MgCl_2$) [66] *via* neutralization reactions, followed by hydrolysis of the resulting Mg^{2+} ions with free OH^- and subsequent bridging of the as-formed mononuclear to form polynuclear complexes $[Mg_x(OH)_y\text{-}(H_2O)_z]^{2x-y}$ with unknown composition. The resulting amorphous gel consists of polynuclear complexes, Cl^- and water and quantitatively precipitates [148] to form a basic crystalline hydrated magnesium chloride salt with the general formula $xMg(OH)_2{\cdot}yMgCl_2{\cdot}zH_2O$ [66]. The research of Lukens [149] in 1932 for example revealed the formation of the 5-phase ($x/y = 5$) precipitate and its gradual transformation into the 3-phase ($x/y = 3$) modification in $MgCl_2$ solution [149]. Both are considered being the main reaction products that are responsible for the mechanical rigidity of hardened MOC [148].

$$\underset{magnesia}{3MgO} + \underset{magnesium\ chloride}{MgCl_2} + 11H_2O \rightarrow \underset{\text{“3–phase”},\ 3-1-8}{3Mg(OH)_2 \cdot MgCl_2 \cdot 8H_2O} \tag{10}$$

$$5MgO + MgCl_2 + 13H_2O \rightarrow \underset{\text{“5–phase”},\ 5-1-8}{5Mg(OH)_2 \cdot MgCl_2 \cdot 8H_2O} \tag{11}$$

Because of their poor water resistance, the MOCs experienced degradation, which is not desirable in construction [66]. However, this degradability actually makes them interesting for biomedical applications, as MOCs dissolve to form brucite under moist conditions [139]. Tan et al. [139,140] used a 5-phase forming MOC system in combination with phosphoric acid to promote its water resistance and to have a better control over its degradability [139,140]. The addition of phosphoric acid decreased the concentration of Mg^{2+} ions being necessary for a longer-term stable 5-phase-formation [150] and it stimulated the precipitation of the less soluble magnesium phosphate hydrate bobierrite on the cement surfaces after deposition in phosphate buffered saline (PBS) for 50 d [139,140].

6.1.2. Setting kinetics

MPCs are generally known for their fast setting character which was the main reason for their use in diverse civil engineering applications such as rapid repair concretes since the 1970′s [66]. Depending on the exact cement formulation, the initial setting times of MPC with biomedical purpose range between <1 min and >90 min [14,120,128]. Many factors which concern setting kinetics are comparable to the findings of CPC research (e.g. particle size, PLR, setting solution, reacting salt concentration etc.), but the most crucial parameter seems to be the dissolution step of the MgO and farringtonite, respectively [14]. The corresponding synthesis routes affect properties like crystal size, surface area and thus reactivity [66]. For example, MgO can be synthesized by grinding calcined magnesite ($MgCO_3$) [151,152]. Alternatively, it can also be synthesized through the precipitation of $Mg(OH)_2$ from hydrolyzed limestone ($Ca(OH)_2$) in a $MgCl_2$-rich brine with subsequent calcination [66]. For farringtonite as raw material, researchers mostly chose the high-temperature solid reaction route of commercial $MgHPO_4{\cdot}3H_2O$ and $Mg(OH)_2$ [11,120–123], but precipitation is evenly possible [128]. Corresponding reaction equations are recapped in Table 4.

With increase in duration [153–155] as well as height of the temperature treatment [146,153–157] the surface area [146,154,157] and thus reactivity [154–157] of MgO is decreased, while crystal size increases [153,155,156]. Hence, magnesia which has been calcined at comparably low temperatures between 600 and 1300 °C (700–1000 °C) is called reactive or caustic-calcined (light-burned), respectively. Caustic-calcined magnesia might be too reactive for its use in MPC, but it is acceptable for MOC, as less reactive MgO requires lesser amount of water, which alters the ionic strength of the $MgCl_2$ solution [66]. Bates and Young [143] showed that a calcination temperature of 800 °C provided the best results in terms of setting time and mechanical properties in a MOC system [143]. In case of MPC, calcination at 1500 °C which is called dead-burning [66] is a current method to decelerate setting [68–70,119] to comply with clinical requirements. In contrast, farringtonite which is mostly produced *via* sintering [11,120–123], is intrinsically less reactive and might be additionally grounded to regain reactivity and ensure short setting times [158].

As already known for CPC [159–161], an increase in temperature evenly accelerates the setting of MPC [14,66,127,134]. According to Yang and Wu [134] setting of a MPC at −10 °C was still possible within <30 min [134] and autogenous heating occurs due to the exothermic reaction [66]. The heat release might be reduced by the addition of setting retarding agents [68], but controversial effects were equally observed [120]. For example, Mestres and Ginebra [68] found a temperature decay from 110 to 42 °C using 3 wt% sodium borate decahydrate (borax, $Na_2B_4O_7{\cdot}10H_2O$) as a setting retarder [68], while Moseke et al. [120] found the reaction to be more exothermic when adding 1.5 M diammonium citrate ($(NH_4)_2C_6H_6O_7$) [120]. In MPC research with biomedical purpose, only the as-mentioned compounds were used as setting retarders, so far [68–70,120]. While citrates are known from CPC chemistry [162,163], borates and boric acid were frequently used in MPC of civil engineering applications [134,164].

As opposed to conventional raw materials of magnesia and farringtonite, the use of non-conventional raw materials presents some interesting scenarios. For example, brucite-derived MPC compositions do not need to undergo any initial high-temperature processing [124,125]. However, such formulations require that retardants such as boric acid and borax need to be added to the compositions [124]. Even though the mechanism is not absolutely clear yet, borax and boric acid seem to be very effective in retarding of MPC setting [66]. Also, AMP-based MPC compositions have very slow setting kinetics such that promoters need to be used to develop clinically relevant compositions [126].

Finally, strategies to alter setting kinetics, which are well-known from CPC research and have already been positively evaluated *in vivo* can also be considered. These strategies include parameters like raw material particle size [68,122,158], surface area [118,128], composition [68,122], powder to liquid ratio (PLR) [11,118,120,122,128] and P/Mg ratio [134]. In these situations, additives are generally not necessary, but might help in handling and workability related properties such as injectability [120].

6.1.3. Mechanical properties

MPCs are likewise not suitable for load-bearing applications due to their brittle mechanical fracture behavior [14]. Some authors observed that MPC were superior from the perspective of their mechanical performance when directly compared to CPC [11,60,68,125]. Indeed, maximum compressive strengths of 85 MPa [165] are reported in the literature on MPCs with biomedical context. However, the fact which really points out MPC in direct comparison to CPC is that they are gaining those high values quite fast after initiating the setting reaction. Mestres and Ginebra [68] showed that 60% of the final compressive strength of a struvite forming MPC was already reached after 1 h under physiological conditions while the final strength of ~50 MPa was obtained 1 h later [68]. Other groups only analyzed the mechanical properties after 24 h of setting or after longer periods to observe degradation in an aqueous environment [11,60,118–120,123,125,128,136,165], but the phenomenon of high early strength is well-known in MPC research for civil engineering applications [66,134,164] and constitutes one of the main reasons for their use as rapid repair concretes [127]. The wet compressive strengths after 24 h observed for different MPC and MOC with biomedical purpose is shown in Table 5.

However, it has to be kept in mind that different experimental approaches were performed to obtain the results of the as-mentioned examples and that the shown trend is not definite. To be annotated, most research actually focused on compressive strength while bending or (diametric) tensile strength of biomedical MPC were barely explored. The systematic study of Meininger et al. [166] about the strength reliability of 3D-printed MgP represents an exception. The compressive strength of MPC can be influenced by different parameters such as P/Mg ratio, particle size, PLR and curing conditions [127].

In magnesia based cement systems it was found to be beneficial in concerns of compressive strength when an excess of MgO is available [127,134,164]. In theory, a 1:1 M ratio from MgO and ADHP would be sufficient for a quantitative conversion, but from a practical standpoint, this does not quite work out [127]. On the one hand, it is known that hydrated MgP precipitate on the surfaces of magnesia grains [130,131] which are blocked for further reaction. An excess of MgO thus provides more reactant for the present phosphates [66] and residual MgO might serve as a ceramic filler in the gaps of the hydrated products [127]. However, MgO slowly degrades to form $Mg(OH)_2$ on heat release followed

Table 4
Reaction equations of possible dry and wet routes for the synthesis of MPC raw powders magnesia and farringtonite.

Magnesia	
Dry route	Wet route
$MgCO_3 \xrightarrow{630-710^\circ C} MgO + CO_2$[152]	$MgCl_2 + Ca(OH)_2 \longrightarrow CaCl_2 + Mg(OH)_2$[66] $Mg(OH)_2 \xrightarrow{T} MgO + H_2O$[152]
Farringtonite	
Dry route	Wet route
$2MgHPO_4 \cdot 3H_2O + Mg(OH)_2 \xrightarrow{>1000^\circ C, >5h} Mg_3(PO_4)_2 + 7H_2O + H_2$	$3MgCl_2 + 2Na_3PO_4 \rightarrow Mg_3(PO_4)_2 + 3NaCl_2$

Table 5

Rating of the wet compressive strengths of different MPC and MOC with selective examples from literature with biomedical purpose. * Bi_2O_3 is a radiopaque supplement. **High compressive strengths after 24 h were achieved without phosphoric acid which resulted in cements with low water-resistance and would not be suitable for biomedical applications. ***No details about hardening conditions were revealed.

Compressive strength after 24 h under moist conditions at 37 °C			
Struvite MPC	Amorphous MPC	MOC	Newberyite MPC
Examples from literature with biomedical context			
Mestres, 2011: ~50 MPa solid phase: MgO, ADHP, borax liquid phase: water PLR: 7.7 g/mL, cylindrical specimens stored in Ringer's solution [68]	Mestres, 2011: ~50 MPa solid phase: MgO, NaH_2PO_4, borax liquid phase: water PLR: 7.7 g/mL, cylindrical specimens stored in Ringer's solution [68]	Tan, 2014: 20–66** MPa solid phase: MgO liquid phase: $MgCl_2$ with or without H_3PO_4 PLR: 1.0 g/mL, cylindrical specimens*** [139]	Zhou, 2013: ~30 MPa solid phase: $MgHPO_4{\cdot}3H_2O$ liquid phase: water PLR: 2.5 g/mL, cylindrical specimens stored at 100% humidity [125]
Kanter, 2014: 58–66 MPa solid phase: $Mg_3(PO_4)_2$ liquid phase: ADHP/DAHP PLR: 2.0–3.0 g/mL, rectangular specimens stored in PBS [11]	Mestres, 2014: ~40 MPa solid phase: MgO, NaH_2PO_4, borax, Bi_2O_3* liquid phase: water PLR: 7.7 g/mL, cylindrical specimens stored in Ringer's solution [70] Babaie, 2016: ~25 MPa solid phase: AMP liquid phase: water (with PVA added) PLR: 0.5 g/mL, cylindrical specimens after soaking in SBF [126]	Tan, 2015: 20–66** MPa solid phase: MgO liquid phase: $MgCl_2$ with or without H_3PO_4 PLR: 1.0–1.7 g/mL, cylindrical specimens stored in PBS [140]	Rostami, 2015: ~45 MPa solid phase: $MgHPO_4{\cdot}3H_2O$, borax/boric acid liquid phase: water PLR: 3.0 g/mL (optimum), cylindrical specimens soaked in SBF [124]

by crack formation which again deteriorates the mechanical performance [66,127]. This is not the case, when brucite ($Mg(OH)_2$) is directly used as the raw material, as shown by Rostami [124] with strength values comparable to some of the struvite based compositions [124]. On the other hand, an excess of unreacted soluble phosphate would disturb the mechanical integrity of the hardened cement specimen as well [127]. Yang and Wu [134] depicted that decreasing the P/Mg ratio from 1:2 (35.5 MPa) to 1:5 (74.4 MPa) more than doubled the resulting compressive strength after 24 h in a struvite forming MPC [134]. Similar results were obtained for K-struvite systems with an optimum P/Mg ratio of 1:4. In this context, the major conversion to K-struvite (~85%) using a 1:1 ratio did not result in the best mechanical properties [136] for the above defined reasons. Le Rouzic et al. [167] confirmed the negative impact of a KDHP excess in K-struvite systems [167]. According to the knowledge about MPC for civil engineering, most magnesia-based research with biomedical purpose deals with MgO excesses [60,68–70,118,119,165]. The used primary phosphate/MgO ratio ranged between 1:3.4 [118] and 1:4 [165]. Concerning farringtonite as a raw material, a systematic study with regard to the influence of the P/Mg ratio on the mechanical properties of the hardened specimens was not found in current literature. However, currently available farringtonite based formulations have used an excess of the raw material. For instance, Vorndran et al. [122] used a molar DAHP/farringtonite ratio of approximately 1:3.3 when mixing farringtonite with 3.5 M DAHP solution at a PLR of 3.0 g/mL [122] and compositions of related publications reported similar ratios [120]. In theory, a molar DAHP/farringtonite ratio of 1:0.7 should be sufficient for a quantitative reaction (Eq. (7)).

The particle size or surface area of the used raw materials not only affects setting kinetics, but additionally has an impact on the strength properties of the hardened cement [11,127]. This was indeed shown frequently in farringtonite based cement systems either by applying different calcination temperatures on the precipitated raw powder with subsequent milling [128] or by differently grinding the uniformly sintered raw powder [122,158]. Ostrowski et al. [128] generated hannayite cements with a 15-fold increase of the wet compressive strength to ~30 MPa after 48 h by decreasing the surface area from 81.19 m^2/g (amorphous) to 0.65 m^2/g (crystalline). This behavior is contrary to the common wisdom. It has to be mentioned that the used PLR are not comparable because of handling reasons [128]. Generally, the common wisdom in CPC research points out to an increase in compressive strength with increasing reactivity [168,169]. Vorndran et al. [122] and Klammert et al. [158] reported that smaller-sized raw materials led to increased compressive strengths in both struvite- and newberyite-based MPC formulations [122,158]. Yang and Wu [134] found an almost 4-fold increase in compressive strength to 36.5 MPa after a hardening time of 1 h when they used a MgO with an higher surface area of 0.35 m^2/g instead of 0.13 m^2/g. However, with longer hardening periods, the compressive strengths approximated each other [134].

When the reactants of MPCs are split in both the solid and the liquid phase, a change in the PLR results in an altered amount of the liquid component which causes opposite effects: A decrease in PLR increases the water amount which promotes the product formation, as water is consumed during reaction [63,118]. Simultaneously, the amount of second retardant is increased as well evenly supporting the formation of hydrated MgP [136]. An excess of water would have the same effect as in CPC which is to serve as a pore builder [118,170,171]. In this regard, MPC are less susceptible to PLR alterations [11,120]. However, in reality, the influence of porosity increase with decreasing PLR seems to predominate the effect of product quantity [11,63,118,120,122,134,136,164]. This was clearly shown by Kanter et al. [11], who observed an increase in compressive strength from 58 to 66 MPa when increasing the PLR from 2.0 to 3.0 g/mL. In this case, the change in the liquid amount accompanied a decrease in porosity from 7 to 5% with a simultaneous decrease in struvite content from 41 to 34% [11]. Similar results were obtained by Wang et al. [136] for K-struvite on the basis of magnesia [136]. A minor compressive strength at a definite PLR is also possible due to handling reasons. When the cements set too fast, they cannot be molded properly and do not result in cohesive specimens with suitable mechanical rigidity and resilience [128]. In literature with biomedical context, a porosity range between 4.2% [70] and 22% [118] is reported, which is mostly below the values known for CPC [172,173]. Finally, the use of single raw material such as brucite or AMP ensures that the PLR calculations can be accurate [124–126].

As already described, the environmental temperature alters the setting kinetics of MPC [127,134]. At high temperatures, the early strength characteristic is reached faster, but there is no impact on the final strength. In contrast, setting in dry atmosphere seems to be more effective in terms of long-term stability compared to setting in water due to degradation processes [127]. However, most MPC researchers with biomedical applications analyzed the compressive strength of their cement formulations at 37 °C under wet or at least moist conditions. This practice to simulate biological setting conditions is highly recommended. This should also be considered for the analysis of MOC for biological applications: It was found that the 3-phase modification tends to form a chlorocarbonate phase with atmospheric CO_2 which serves as a less soluble layer on top of the MOC [174,175]. In addition, Sugimoto et al. [176] revealed the susceptibility of this phase towards changes of humidity which leads to crystal water exchange and density alterations followed by a possible damage to the matrix [176].

The incorporation of high concentrations of kinetics retarding agents mostly led to a deterioration of the mechanical properties in both MPC as well as MOC systems [120,134,139,177], while little amounts can improve them [120,177]. A consistent increase of the flexural strength with a borax content of up to 10 wt% was observed by Yang and Qian [129]. In this case, the adjustment of the PLR for workability reasons is probably the main cause of the monitored strength development [129].

The aforementioned parameters have a detrimental or enhancing impact on the strength properties of the hardened MPC. However, addressing the problem of brittle mechanical fracture behavior actually would require the use of composite systems either by fiber reinforcement or by an interpenetrating polymeric phase [172]. This area of research is highly "under-explored", but offers a lot of possibilities according to the know-how from CPC research [14]. Indeed, fiber reinforcement has already been investigated for rapid repair concrete applications [178,179] and a report about cement-polymer-composites with an initial rubber-like behavior followed by a gain in stiffness while setting in an aqueous environment for sealing applications was evenly found in current concrete literature [180]. To the best of our knowledge, solely Krüger et al. [181] published their results about the mechanical improvement of a biomedical MPC. They successfully improved the fracture behavior by the implementation of degradable magnesium alloy wires. Beside an enhancement of the bending strength with up to ~140 MPa, an increase in non-linear behavior was observed [181].

6.1.4. Rheological properties

In MPC research, only few publications deal with cement characteristics such as cement paste injectability or cohesion. In terms of injectability, most publications give rather a statement of the cement system used being injectable [116,182] or they provide a subjective and qualitative evaluation of the cements' handling properties [61,69,128]. In general, it seems that the workability becomes better by decreasing the PLR [61,120,128], by increasing the raw material crystallinity [128], when amorphous products are formed [69,70], or by adding liquefying agents [120]. Mestres et al. [70] improved the injectability of their struvite forming MPC system from 36 to 90% by substituting half of the ADHP salt with the sodium containing equivalent to promote the formation of an amorphous product together with the crystalline struvite precipitate [70]. Moseke et al. [120] even obtained injectabilities of up to 99% when adding adequately high concentrations of diammonium citrate which maintained a negative Zeta potential of the raw material particles while reaction leading to the electrostatic repulsion of those particles [120]. The performance of this liquefying effect can be easily evaluated considering that the first study used needles with a 14 mm inner diameter [70] while the latter used needles with a smaller inner diameter of 0.8 mm [120]. According to the Hagen-Poiseuille relationship, the flow rate of the paste goes along with the fourth power of the needle diameter [183]. With respect to cohesion of MPC, it was solely investigated by Mestres et al. [69] who found cohesion times of <7 min [69]. This lies exactly within the given range for clinical requirements [184].

6.1.5. Combinations of MPC and CPC

As already mentioned, research on MPCs with biomedical applications is much less mature as compared to that on CPC. It is, therefore, well-worth the effort to develop formulations with controllable properties by combining CPCs with their well-proven clinical track records with MPCs with superior characteristics (e.g., high early strength, higher degradation kinetics etc.).

In the past, certain amounts of magnesium containing compounds have already been incorporated in CPC to affect setting kinetics [160,185,186], to eliminate the crystallization of insoluble precipitates in brushite cements [10] or to enhance the degradation and biological outcome [187]. Ginebra et al. [182] were the first to investigate a vast spectrum of different cement formulations on the basis of newberyite and/or MgO with regard to their suitability as bone substitution materials. Among all CaP compounds used (e.g. moncalcium phosphate monohydrate (MCPM), dicalcium phosphate anhydrous (DCPA), dicalcium phosphate dihydrate (DCPD), α-/β-TCP, tetracalcium phosphate (TTCP)), DCPA together with a combination of MgO and newberyite seemed to be the most promising reaction partners leading to cements with adequate setting kinetics (4–7 min) and mechanical properties (~11 MPa compressive and ~2 MPa tensile strength) [182].

Regarding formulations of combinatory systems, there generally exist two different preparation methods: raw materials known from both CPC and MPC research are mixed to a certain extent (2–4 components) [60,119,158,187-191,193] as was the case in the previously mentioned publication of Ginebra et al. [182]. Alternatively, calcium containing compounds (e.g. calcium carbonate, $CaCO_3$ and DCPA) are added to magnesium containing ones (e.g. newberyite, brucite) prior to high-temperature treatment leading to a calcium and magnesium containing sintering cake (e.g. mixtures of farringtonite and stanfieldite, $Ca_3Mg_3(PO_4)_6$, generally described as $Ca_xMg_{(3-x)}(PO_4)_2$) before cement reaction is applied [122,158]. In the latter case, the resulting calcium doped MgP might be handled as a conventional MgP and can be mixed with DAHP solution to result in struvite as the main setting product [122] (Table 6).

Some researchers systematically studied the properties of combinatory cements in comparison to the single components and partially found synergistic effects depending on the exact cement preparation. Klammert et al. [158] mixed $Ca_xMg_{(3-x)}(PO_4)_2$ with MCPA and 0.5 M citric acid as equivalent to brushite forming CPC. For x = 0.75 and at a defined milling time and PLR, the combination showed the best mechanical properties [158]. Similar results were obtained by Yang et al. [119] who mixed CSH with different amounts of MPC consisting of MgO and ADHP and water whereat CSD and struvite were the main reaction products [119]. At small amounts, sulfates are known to be applied as setting retardener in brushite forming CPC [162,194-196]. Here, concentrations not exceeding 50% CSH likewise led to hardened cements with better compressive strengths of ~70 MPa after 4 weeks as compared to the pure CSH or MPC (~30 MPa). Simultaneously, the slow setting of the CSH (25 min) and the fast setting of the MPC control (3 min) were balanced and reached proper setting times between 7 and 12 min [119]. Yet another paper dealing with mixtures of TTCP, DCPA (CPC), MgO and ADHP (MPC) arrived at similar conclusions [60]. Pijocha et al. [190] found positive effects on the heat evolution during setting using combinatory systems of MgO, ADHP, HA and CSH [190]. Besides the setting characteristics and mechanical performance, the biological outcome and degradability

Table 6
List of exemplified formulations from literature where up to four components known from MPC and CPC research were used to fabricate a combined cement system (CSH: calcium sulfate hydrate).

2-Component systems	3-Component systems	4-Component systems
MgO + MCPM [187–189]	MgO + ADHP + HA [190]	MgO + ADHP + TTCP + DCPA [60,191]
$Mg_3(PO_4)_2$ + MCPM [158]	MgO + ADHP + CSH [119]	MgO + MCPM + TTCP + DCPA [187]
$Ca_xMg_{(3-x)}(PO_4)_2$ + DAHP [122,192]	MgO + $MgHPO_4{\cdot}3H_2O$ + DCPA [188,193]	MgO + ADHP + HA + CSH [190]
$Ca_xMg_{(3-x)}(PO_4)_2$ + MCPM [158]	MgO + $MgHPO_4{\cdot}3H_2O$ + DCPD [188]	

are other properties that seem to be well controllable by adjusting the composition of combinatory cement formulations [60,119,122,187,189,191] (see "Biological performance").

MPC can also be formed by the addition of MgO-containing bioactive glasses. This is aimed at stimulating integration between the implants and their surrounding tissues. Bioactive glass cements have been produced in different forms such as powder and beads with diverse compositions in the $MgO\text{-}CaO\text{-}P_2O_5\text{-}SiO_2$ and $MgO\text{-}CaO\text{-}P_2O_5\text{-}SiO_2\text{-}CaF_2$ systems with or without additives like starch, cellulose, acetate, poly(methyl methacrylate) (PMMA), phosphoric ester, and N,N dimethyl-P-toluidine [197–200]. In general, the MgO-containing bioactive glass cements are meant to set in a few minutes and have high compressive strength while getting bonded to the surrounding osseous tissue. Addition of MgO in the $MgO\text{-}CaO\text{-}P_2O_5\text{-}SiO_2\text{-}CaF_2$ system seems to decrease the compressive strength *via* formation of crystalline struvite and inhibiting HA formation in simulated body fluid (SBF) [201]. However, MgO-containing bioglasses possess high compressive strength in the presence of polyacrylic acid (PAA) as a cross-linker. The change in the compressive strength depends on the crosslinking of the PAA carboxyl groups with Ca^{2+} and Mg^{2+} ions present in the glass powder [202]. Even though the mechanical properties of glass containing cement composites are improved by the addition of polymers like PAA, the bioactivity of these materials can limit their biomedical applications.

6.2. Scaffolds

Magnesium phosphates have additional applications as tissue engineering micro/macroporous scaffolds. Such scaffolds show bone regeneration, biocompatibility, and often higher physical and mechanical properties compared to their magnesium-free counterparts. Methods for scaffold fabrication include the foam replica technique [203], granulation of self-setting cements in an oil phase [204], the use of leachable salt particles in cements [205], dispense plotting (Robocasting) of MgP containing pastes [206] or 3D powder printing of suitable cement/binder combinations [135,166,207]. The general requirements for these scaffolds are suitable surface chemistry, biocompatibility, biodegradability, porosity, physical and thermal stability, reproducibility, and scalability in order to be applicable in bone tissue engineering [208–211]. The following section gives an overview about the studies applying either traditional scaffold preparation techniques as well as CAD/CAM procedures.

6.2.1. Traditional techniques for scaffold fabrication

Wei et al. [191] introduced a hierarchically structured 3D microporous/macroporous magnesium–calcium phosphate scaffold fabricated *via* the setting of struvite and HA as reactants with sodium chloride added as a space holder for creating porosity by leaching. In a different study, Wu et al. observed an increased degradation rate in magnesium containing calcium phosphate scaffolds in Tris-HCl solution compared with the magnesium-free scaffolds [117]. Macropores in MPC scaffolds may also be created by gas bubbles formed during cement setting [212]. Here, magnesium metal powder was added to an amorphous magnesium phosphate cement powder dispersed in 15% polyvinylalcohol (PVA) solution. The rapid corrosion of Mg resulted in hydrogen bubbles, which were entrapped in the cement paste until a hardened matrix of crystalline bobierrite was formed. Such scaffolds provided up to 91% total porosity with a compressive strength of ~2 MPa. While the macroporous network formed by porogens is usually only to a minor part interconnective, fabrication regimes using the foam replica technique results in a high interconnectivity of pores. The latter technique was used to fabricate both farringtonite [203] and Mg-containing glass in the $MgO\text{-}CaO\text{-}P_2O_5\text{-}SiO_2$ system [213] and led to products with chemical and physical stability and cell proliferation properties.

Pore formation in MgP scaffolds can also be created by controlled solvent evaporation, e.g. freeze-drying. Hussain et al. [214] reported magnesium calcium phosphate containing gelatin scaffolds fabricated by dissolving up to 90 wt% of a 2:1 mixture of $CaHPO_4$ and MgO in 3% gelatin solution. After freeze drying, these composite scaffolds showed a porosity between 34 and 50%, a medium pore diameter of ~150 μm and enhanced physical and mechanical properties when compared to the pure gelatin scaffolds. Mechanical testing such as the resistance to the volume change indicated that there is significant improvement of MPC containing gelatin scaffolds compared with their Mg-free counterparts.

To the best of our knowledge, there is only one report of magnesium phosphate-polymer composite electrospun scaffold for bone tissue engineering [215]. Zhou et al. reported that it is possible to uniformly disperse particles of amorphous magnesium phosphate (AMP) in poly-lactic acid (PLA), there by creating a suspension. Under suitable conditions of pumping rate (e.g., 1 mL/hr), needle diameter (e.g., 22 gauge), applied high voltage (e.g., 20 kV), and needle tip to collector distance (e.g., 20 cm), composite PLA-AMP scaffolds could be fabricated. *In vitro* testing for cell attachment and proliferation indicated that the scaffolds are bioactive [215].

6.2.2. CAD/CAM based fabrication techniques

Robocasting and sintering of ground glasses has been used in the $MgO\text{-}CaO\text{-}P_2O_5\text{-}SiO_2\text{-}Na_2O\text{-}K_2O$ and in $MgO\text{-}CaO\text{-}P_2O_5\text{-}SiO_2\text{-}Na_2O\text{-}B_2O_3$ systems to fabricate biodegradable MgO containing scaffolds [216,217]. MgO presence in silicate-based bioactive glass scaffolds gives them a manufacturing advantage since glasses which contain 5 wt% MgO can be used to fabricate porous structures without crystallization [218]. Furthermore, Fu et al. [218] showed that MgO-containing glass scaffolds are able to promote HA formation on bioglasses and stimulate bone-implant interactions, although the HA layer formation is slower when it is compared to the traditional 45S5 bioglasses. Addition of zinc, copper, and biopolymers like poly(D, L lactic) acid (PDLLA) as coating materials can enhance the mechanical properties of MgO-containing bioglass, and improve their fracture toughness. A more comprehensive section on bioglass scaffolds is presented by Diba et al. [20]. The fabrication of macroporous MPC scaffolds composed of a mixture of struvite and newberyite in a two-step process was demonstrated by Lee at al. [206]. Here, a green ceramic paste was produced in a first step, which contained water, trimagnesium phosphate powder as well as hydroxypropylmethyl cellulose for adjusting a suitable viscosity. The paste was processed into 3D scaffolds by a paste extrusion system and in a second step hardened by immersion in an diammonium hydrogenphosphate solution. This avoids sintering of the scaffolds and enables a simultaneous drug modification of the scaffolds during fabrication. A similar technique was used by Kim et al. [205], who added sodium chloride particles to the magnesium phosphate paste to introduce various micropore sizes (<25 μm and 25–53 μm) into the scaffold. This was done to increase the speed and rate of biodegradation and bone regeneration compared to micropore-free scaffolds, which could be demonstrated by an orthotopic implantation into 4–6 mm rabbit calvarial defects over 4–8 weeks [205].

3D powder printing is another technique, which has been applied to fabricate MgP ceramics and scaffolds for bone regeneration. This was done by using farringtonite powder (particle size ~27 μm) blended with 20% diammonium hydrogenphosphate) [135] in combination with ammonium phosphate binder solutions. Strength of the printed structures were initially in the range of ~ 2 MPa under compressive load, which increased to a maximum of 6–7 MPa following scaffold immersion in the binder solution for 24 h. This was mainly caused by an increase in the degree of reaction as indicated by X-ray diffraction analysis [135]. Vorndran et al. [207] extended this printing concept by using different binder liquids (ammonium and potassium phosphates, phosphoric acid) to produce a range of scaffold materials by hydraulic cement setting reactions during 3D printing. While the formation of K-struvite during printing was too slow to achieve structures with high dimensional accuracy, both ammonium phosphate (forming struvite) and phosphoric acid (forming newberyite) were applicable to the printing procedure. After a post-hardening regime following repeated binder immersion, compressive strength ranged from 10 MPa (struvite) to 35 MPa for newberyite. Apart from using the materials for bone regeneration, the authors also demonstrated an application of the materials for an indirect manufacturing of metal casting molds by 3D printing [207]. A more recent work by Meininger et al. [166] applied strontium modified magnesium phosphates to 3D powder printing since Sr^{2+} ions are known to prevent osteoporosis and to encourage bone formation. The fabrication regime included blending of Sr-MgP powders with hydroxypropylmethyl cellulose, followed by printing with water and subsequent sintering of the samples. A post sintering immersion in ammonium phosphate solution resulted in a partial conversion of the structures into struvite with a simultaneous strong increase of their mechanical performance to 36.7 MPa (compression), 24.2 MPa (bending) and 10.7 MPa (tension), together with a reasonably modest Weibull modulus of up to 8.8. Micro-computed tomography (μ-CT) analysis demonstrated the formation of a highly interconnected porous architecture with a median pore size in the range of 17–26 μm [166].

6.3. Implant coatings

Protection against corrosion, interaction between implant and surrounding tissues, and induction of bioactivity are three main purposes for production of coating materials [219]. In recent years, doping with magnesium ions has become very popular for bioceramic coatings made of hydroxyapatite, tricalcium phosphate, octacalcium phosphate [220,221] or bioactive MgO containing bioglasses. Currently, most MgP-containing coatings are produced in $MgO\text{-}CaO\text{-}P_2O_5\text{-}SiO_2\text{-}Na_2O$ systems via enameling, pulsed laser deposition, magnetron sputtering, plasma spraying and sol-gel methods with K_2O, CaF_2, B_2O_3, ZnO, or SrO additives [222–226]. Resulting coating materials have been tested for their mechanical and thermal properties along with *in vitro* and *in vivo* bioactivity. Pazo et al. [227] showed that SiO_2 and MgO content of bioactive glasses enhance the resistance against temperature change in glasses by reducing their thermal expansion coefficient (TEC). This might be due to the role SiO_2 plays as a site for creation of new networks [227]. It has also been argued that magnesium has the ability to strengthen the coating/substrate interface in experimental materials. Also, magnesium ions present in the $CaO\text{-}MgO\text{-}P_2O_5$ system slow down the dissolution of calcium ions from the Mg/Ca coatings [226]. Magnesium incorporation on the surface of implants increases osteoconductivity [228] and magnesium bound integrin positively affects the adhesion ability of cells to the orthopedic or dental implants [34].

In contrast to using MgO-containing bioglasses, the deposition of crystalline magnesium phosphate coatings on substrates is insignificant and in contrast to CaP based ceramic coatings, only few studies have been performed. The very few publications that are available in the literature report successful coating of different crystalline MgP phases on corroding Mg-alloys (e.g., AZ31) for biomedical and other purposes. Ishizaki et al. reported the formation of single phase newberyite coatings on AZ31 using a chemical treatment, followed by low-temperature heat-treatments [229]. While the coating provided corrosion resistance, the ultimate use was not in the biomedical field. Zhao et al. reported a phosphate conversion technique to produce layered MgP coatings with an inner layer of newberyite and outer layers of newberyite and struvite [230]. The intended use was in the orthopedic field and the coatings provided bioactive surfaces with immediate near-term corrosion protection of the AZ31 alloy. Ren et al. used a microwave assisted technique to coat AZ31 with different crystalline phases such as newberyite and trimagnesium phosphate hydrate (TMP). Preosteoblasts were quite viable in contact with these cytocompatible coatings [231]. Meininger et al. [232] used an electrochemically assisted deposition technique to deposit strontium substituted magnesium phosphate coatings on titanium. While at low Sr:Mg ratios of the electrolyte (Sr:Mg = 0–0.26) crystalline struvite was deposited, a higher Sr:Mg ratio of 0.51 resulted in the formation of a mainly amorphous coating. Immersion of the coatings in SBF (with or without 10% fetal calf serum) over a course of 28 days revealed the release of up to 44% Sr^{2+} from the coating.

Finally, to the best of our knowledge, the report of Ren et al. [231] is the only example of using AMP (along with polylactic acid, PLA) on AZ31 as a protectant of the substrate while simultaneously enhancing osseointegration. The basic raw material being amorphous, the coating can be made from a suspension of the two components using a simple spin-coating technique. The coating was able to perform the aforementioned protective and osseointegrative activities.

7. Biological performance

7.1. In vitro cytocompatibility

In semi-biological systems like SBF solution, Mg^{2+} ions were shown to form complexes with OH^- and result into weak buffers [106]. In cell studies, the cytocompatibility and positive effects of MPC on cell proliferation were frequently shown for bone-linked cells such as murine osteoblast-like cell line MC3T3-E1 [125,158] and human osteoblast cell line MG-63 [60,119,122,123,189,191]. However, Burmester et al. [233] emphasized the importance to use bone-derived primary cells or at least more suitable cell lines during examinations of the osteoinductivity of magnesium containing implant materials as MG-63 behaved completely different to primary osteoblasts when exposed to Mg^{2+} extracts [233]. This

Table 7
List of MPC and combinatory systems that have already been implanted in animal models.

Source	Cement paste composition	Set cement composition	Application form	Animal model	Defect model	Examination time point
Magnesium phosphate cements – implantation in bone						
Yu, [165]	*powder*: MgO, $NH_4H_2PO_4$, unknown retarder *liquid:* unknown	Unknown probably struvite	pre-hardened cylinders	New Zealand white rabbits (∼3 kg)	distal condyle of the femur; hole defect of Ø 3.2 mm, 10 mm depth	0.5, 1, 2, 3 and 6 months
	Outcome: no inflammatory response or fibrous tissue growth, degradation with simultaneous new bone ingrowth within 6 months, osteoblast layer at the interface					
Zeng [189,245]	*Powder:* MgO *liquid:* phosphoric acid (+bone marrow stromal cells)	Unknown probably newberyite	Granules	New Zealand white rabbits (2–2.5 kg)	Maxillary sinus floor elevation	2 and 8 weeks
	Outcome: amount of newly formed bone less, when no cells were used; 7(14) % new bone formation within 8 weeks (with cells); 22(14) % residual material (with cells)					
Kanter, [11]	*Powder:* farringtonite *liquid:* $(NH_4)_2HPO_4$, $NH_4H_2PO_4$ solution	Struvite, farringtonite	Paste	Merino sheep (∼94 kg)	Medial condyle of the femur; hole defect of Ø 10 mm, 15 mm depth	3, 7 and 10 months
	Outcome: no inflammation or rejection, nearly quantitative cement degradation (<2 mm in diameter) and new bone formation after 10 months, loss of mechanical performance, increase in porosity and pore size and apatite formation					
Kim [205]	*Paste*: farringtonite, NaCl, cellulose, ethanol *post-hardening liquid:* $(NH_4)_2HPO_4$ solution	struvite, farringtonite, cellulose	3D printed post-hardened micro-porous discs	white rabbits	cranial bone defect à Ø 4 and 6 mm	4 and 8 weeks
	Outcome: faster dissolution in the smaller defect and new bone formation, better bone regeneration and blood vessel formation in micro-porous structures depending on the pore size with maximum 85(50) % regenerated bone within 8 weeks for the 4(6) mm defect					
Magnesium phosphate cements – heterotopic implantation						
Yu [165]	*Powder:* MgO, $NH_4H_2PO_4$, unknown retarder *liquid*: unknown	Unknown probably struvite	Pre-hardened cylinders	New Zealand white rabbits (∼3 kg)	Subcutaneously, dorsal muscle pouch implant size of Ø 3.2 mm, 10 mm length	1, 2 and 3 months
	Outcome: no toxicity, degradation indicated by increasing surface roughness and decreasing compressive strength					
Kim [205]	*Paste:* farringtonite, NaCl, cellulose, ethanol post-hardening liquid: $(NH_4)_2HPO_4$ solution	Struvite, farringtonite, cellulose	3D printed post-hardened micro-porous blocks	Sprague-Dawley rats	femoral extensor muscle, implant size of 4x4x8 mm	1 and 6 weeks
	Outcome: faster dissolution for micro-pores containing scaffolds					
Magnesium calcium phosphate cements - implantation in bone						
Wu, [60]	*Powder:* MgO, $(NH_4)_2HPO_4$ / $CaHPO_4$, $Ca_4(PO_4)_2O$ *Liquid:* water	Struvite, MgO, hydroxy-apatite, $Ca_4(PO_4)_2O$	pre-hardened cylinders	New Zealand white rabbits (∼3 kg)	Distal part of the femur, hole defect of Ø 4 mm, 3 mm depth	1, 2, 3 and 6 months
	Outcome: no inflammatory or foreign-body response, nearly quantitative cement degradation and new bone formation after 6 months, good biocompatibility and osteoconductivity					
Schendel [244]	OsteoCrete®	Unknown	paste	New Zealand white rabbits	cranial bone defect à 1.5 cm^2; bone flap repositioned with cement paste	2, 12 and 24 weeks
	Outcome: no adverse effects, 50% replaced after 12 weeks with new bone ingrowth, good adhesion to the bone surface and good bone flap position and apparent stability					
Zeng, [189,245]	*Powder*: MgO, $Ca(H_2PO_2)_2$ *liquid:* water (+bone marrow stromal cells)	Farringtonite	Granules	New Zealand white rabbits (2–2.5 kg)	Maxillary sinus floor elevation	2 and 8 weeks
	Outcome: amount of newly formed bone less, when no cells were used; 26(31) % new bone formation within 8 weeks (with cells); 30(22) % residual material (with cells); moderate biodegradability and excellent osteoconductivity					
Magnesium calcium phosphate cements - heterotopic implantation						
Driessens, [193]	*Powder:* MgO, newberyite, $CaHPO_4$ *liquid*: unknown	Bobierrite, brucite, monetite	pre-hardened cylinders	Wistar rats (150–200 g)	subcutaneously, implant size of Ø 6 mm, 12 mm length	1, 2, 4 or 8 weeks
	Outcome: slow dissolution of the magnesium phosphate with decrease in mechanical performance and apatite formation					
Klammert [192]	*Powder:* $Ca_{0.75}Mg_{2.25}(PO_4)_2$ *liquid:* $(NH_4)_2HPO_4$ solution	Struvite, farringtonite	Pre-hardened cylinders	Sprague-Dawley rats (∼318 g)	Femoral extensor muscle implant size of Ø 5 mm, 10 mm length	1, 2, 6, 10 and 15 months
	Outcome: no indication for infection, inflammation or rejection; chemical dissolution by surface, changes of the phase composition into whitlockite and decrease in mechanical performance					
Klammert [192]	*Powder:* $Ca_{0.75}Mg_{2.25}(PO_4)_2$, $Ca(H_2PO_2)_2{\cdot}H_2O$ *liquid:* citric acid	newberyite, brushite	pre-hardened cylinders	Sprague-Dawley rats (∼318 g)	femoral extensor muscle implant size of Ø 5 mm, 10 mm length	1, 2, 6, 10 and 15 months
	Outcome: no indication for infection, inflammation or rejection; chemical dissolution by volume, changes of the phase composition into whitlockite and decrease in mechanical performance					

was carried out by Hussain et al. [234] using bone marrow mesenchymal stem cells from Fisher 344 rat femurs whereat proliferation and osteogenic differentiation on MCPC were additionally improved using MCPC containing gelatin sponges [234]. The *in vitro* biocompatibility was further evidenced by Yu et al. [165] who evaluated the toxicology of MPC, including a gene mutation assay (Ames test), chromosome aberration assay (micronucleus test), and DNA damage assay (unscheduled DNA synthesis test) [165].

MCPCs were shown to be degradable in Tris-HCl solution and the degradation was significantly improved when compared to magnesium-free CPC due to the fast dissolution rate of MCPCs

[189]. According to Großardt et al. [121] the chemical dissolution of struvite MPC dominates the active resorption by murine monocytic cell line RAW 264.7 derived osteoclasts at a factor of 3. Simultaneously, the total resorption was almost 20-times higher compared to calcium phosphate formulation monetite ($CaHPO_4$) and at least 8-times higher compared to brushite [121]. In contrast, Blum et al. [235] found the active resorption to be the predominant degradation mechanism of struvite wherein the amount of released Mg^{2+} and PO_4^{3-} ions could additionally be enhanced through calcium doping of the cement raw material [235].

Zhou et al. evaluated the important cell-differentiation markers for MC3T3 cells in contact with AMP/PLA scaffolds. Relevant genes such as osteocalcin (OCN), osteopontin (OPN), alkaline phosphatase (ALP), collagen-1 (Col 1), with beta actin as the house keeping gene were monitored via RT-PCR. They reported that that there was 80% increase in OCN, and more than three times higher in OPN expression when the cells were in contact with AMP-PLA scaffold. Col1 expression also increased under a similar situation [215]. Babaie et al. monitored the expressions of ALP on various AMP cement compositions. All compositions showed that ALP expressions are quite viable for the cells to proliferate on the cement surface [87,126].

Multiple studies on MgO-containing glass scaffolds reported all or some of these properties in previously investigated systems. For instance, the bioactive glass which was prepared *via* glass sintering and slip casting in $MgO\text{-}CaO\text{-}P_2O_5\text{-}SiO_2\text{-}Na_2O\text{-}K_2O$ system showed mechanical, physical and thermal stability, *in vitro* bioactivity and degradation when compared to the control groups. *In vivo* studies of the same composition revealed enhanced cell proliferation in different cell lines [218,236–241].

Interestingly, specific amorphous, sodium containing MPC were shown to have intrinsic antimicrobial properties due to the alkaline pH development while setting. Those were shown to be antimicrobial against variable bacterial strains that are related to implant infections (e.g. *Escherichia coli*) or dental plaque (e.g. *Streptococcus sanguinis*) by Mestres et al. [68,69]. For bioactive, MgO containing SiO_2-glasses, higher antibacterial activities resulting from the increased pH caused by MgO content [110], and stimulation of bone cell proliferation [242,243] was revealed.

7.2. In vivo degradation

The biological applications of magnesium raised the interest MPCs for the similar applications as well. However, relatively lower maturity of the research in this field is probably the reason for the limited number of published animal studies concerning both MPC and combinatory systems (Table 7). Nevertheless, their biocompatibility was affirmed *in vivo*, as no inflammatory reactions [11,60,165,192], formation of fibrous tissue [165], foreign-body response [60], inflammation [192], rejection [11,192] or toxic [165] and adverse effects in general [244] were reported. Besides, all non-heterotopic animal models indicated the osteoconductive character of MPCs and the combinatory systems [60,165,205,244–246]. Interestingly, mixtures of MPC and CPC often showed superior biological properties compared to the single components *in vitro* [60,189] and *in vivo*. For example, MCPCs exhibited high biodegradability and osteoconductivity in rabbit bone tissues without any inflammation and necrosis. Two months of monitoring of implanted rabbits further indicated that MCPCs were capable of forming direct bonds with the host bone without interrupting the surrounding connective tissues, and they exhibited higher osteogenesis in comparison to CPCs [60]. In terms of biocompatibility, the pH and temperature development while setting have also to be considered. While the pH exemplarily depends on the chosen raw powder and might be controlled over a wide pH range [132], the commonly high heat release during the reaction of MPC was shown to be confined by adding setting retarding agents [68].

The products of MPC have a superior degradation potential to CPC [14] and their dissolution rates are higher compared to HA [60,61] (Fig. 4). For example, the chemical dissolution was shown by Klammert et al. [192] who implanted pre-hardened cylinders of struvite and newberyite in the absence of bone cells. After 15 months, struvite presented the highest loss of mechanical performance (95%), followed by newberyite (67%). This work demonstrated that such magnesium phosphate compounds do not only chemically dissolve in a physiological environment, but also present remarkable changes of their phase composition, in which both converted into low-crystalline whitlockite ($Ca_3(PO_4)_2$) [192]. In two other cases, the formation of nanocrystalline apatite was reported, but as a nearly quantitative implant degradation within 10 months took place, the detected apatite probably was due to the attended new bone growth. In some *in vivo* studies, presence of osteoclasts was detected at the MPC implantation sites, leading to the conclusion that active resorption mechanism might be the principal degradation mechanism [205,245].

Porosity is another parameter which affects biodegradability in addition to the pure chemical solubility. Increasing the initial porosity from 5 to 7% by varying the PLR in a struvite forming cement, Kanter et al. [11] observed a drop in implant diameter by 60 to 80% within 10 months. In both cases, the early pore diameter was below 1 μm. The reason for this effect was likely a higher degree of cement conversion into the final product struvite (with higher solubility than the cement raw material farringtonite) at lower PLR [11]. By introducing differently sized micropores *via* soluble salt leaching on purpose, Kim et al. [205] observed a faster degradation in rabbit calvarial defects, while forming a better quality of the regenerated bone and numerous blood vessels [205].

Possible biological limitations for an application of MgP cements and minerals in bone replacement might be due to the release of a large amount of Mg^{2+} during degradation. While it is unlikely that this systemically influences Mg^{2+} homeostasis for usual implant sizes (< 10 g, daily magnesium uptake ∼300–400 mg for adults [26]), a large local release of Mg^{2+} might affect crystallization and properties of HA bone mineral during remodeling since Mg^{2+} is a potent inhibitor of HA crystal growth. In addition, many MPC use further setting regulating compounds (e.g. borates), whereby it is unclear whether these compounds influence osteoblast and osteoclast activity and hence may reduce implant degradation and bone remodeling. Finally, the initially high strength of most MPC will likely decrease during cement dissolution. Again, it is unknown if this strength loss is compensated by new tissue formation and how this will influence bone remodeling, especially in larger defects with partial mechanical loading. Clearly, all these points have to be addressed in future, preferably by using large *in vivo* models with a good transferability of the results to humans.

As an additional feature, MPC seem to have a certain bone bonding potential [113] as Revell et al. [247] confirmed that magnesium-substituted CaP coating on titanium alloy implants enhanced the bone bonding in *in vivo* systems [247]. Further, they were already used in an adhesive manner *in vivo* for a successfully improved tendon-to-bone-healing [116] and it was shown that MPC are more effective in stabilizing bone fragments to native bone compared to CPC [248]. Gulotta et al. [116] used a commercially available MPC [249] which was composed of reactive MgO, potassium as well as sodium phosphate and tricalcium phosphate. However, this formulation has not been approved as bone adhesive so far [113]. Waselau et al. [248] compared biocompatibility and bone adhesive characteristics of MPC, CPC, and sham samples in horses. Seven weeks after implantation, it was observed that MPC secured fragments significantly closer to parent bone, com-

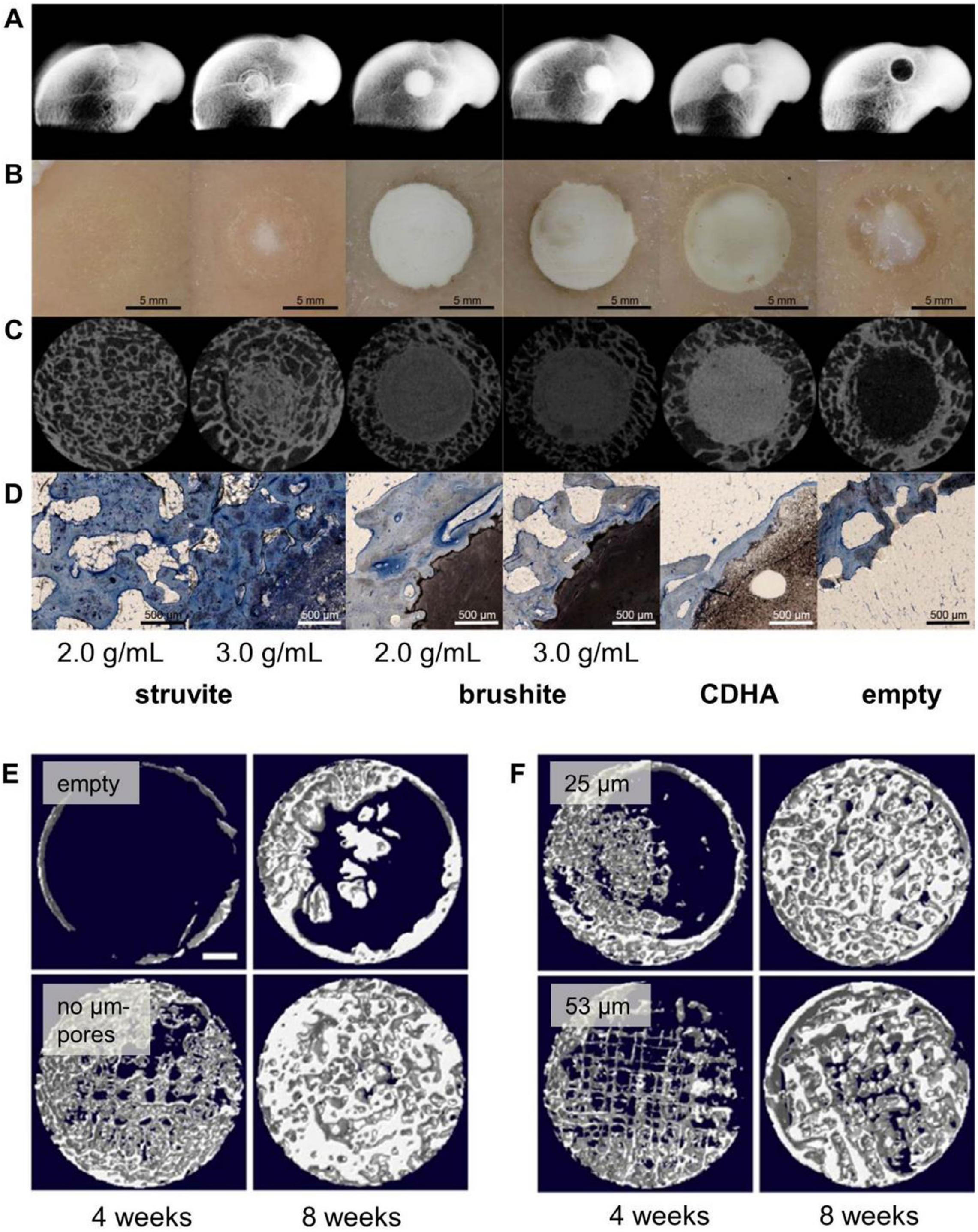

Fig. 4. X-ray (A), macroscopic images (B), μ-CT slices (C) and histological sections (D) of ovine femoral condyle defects filled with struvite, brushite or calcium deficient hydroxyapatite (CDHA) cement paste of different powder-to-liquid ratios (PLR) after 10 months of implantation. Figures reveal the higher degradation potential of magnesium phosphate especially at lower PLR i.e. slightly higher porosity. μ-CT images of macroporous prehardened struvite scaffolds in turn show the dependence of the degradation behavior on the pore size (no micropores (E) and 25/53 μm pores (F)) after 4 and 8 weeks implantation in 6 mm calvarial defects in rabbits. Figures A-D were reused from [11] and figures E-F from [205]. Copyright (2014, 2016), with permission from Elsevier.

pared with a CPC. Callus amount and bone remodeling and healing were significantly greater with MPC than with CPC [248].

To equip them with special biological properties, biologically active ions like strontium [166,232], enzymes like lysozyme [206], radio-opaque additives like bismuth oxide [70] and even bone marrow stromal cells [245] have already been incorporated in MgP scaffolds and cement systems. Another potential application of magnesium phosphates is drug [206] and gene delivery. Currently, there are two approaches for gene delivery: viral and non-viral [250].

The biological effectiveness of MgO-containing bioactive glasses comprises the induced formation of HA and interaction with bone tissue (Table 8) and can be compressed as follows [251,252]: Cations present in bioactive glasses rapidly become replaced by

Table 8
Suggested steps for bioactive glasses-bone interaction [252].

1	Formation of silanol groups (Si-OH)
2	Formation of silica-rich layer by polycondensation of silanols
3	Amorphous HA layer formed by adsorption of Ca^{2+} and PO_4^{3-}
4	Crystallization of carbonated HA layer by incorporation of CO_3^{2-}
5	Adsorption of biological moieties on carbonated HA surface
6	Action of macrophages
7	Attachment of stem cells
8	Differentiation of stem cells
9	Generation of bony matrix
10	Crystallization of matrix

the hydrogen ions from the body, leading to the formation of silanol groups. These sites later become adsorption sites for growth factors and lead to *de novo* bone generation [252]. This effect might be caused by the electrical stimulation initiated by the presence of Mg^{2+} ions [253].

Biocompatibility is a crucial characteristic of any of the reported bioactive glasses. *In vivo* studies were conducted in different SiO_2-MgO systems to demonstrate the potential of these compositions in orthopedics. For example, *in vivo* studies of 26 different bioactive glasses in MgO-CaO-P_2O_5-SiO_2-Na_2O-B_2O_3 system showed no inflammatory responses and formation of new bones in intramuscular and intraosseus implants [254]. Higher MgO content of the bioactive glasses in MgO-SiO_2-P_2O_5-CaO system was shown to increase the glass surface and decrease the pore sizes. Consequently, MgO accelerated the formation of HA on the glasses, making them more biocompatible by providing more sites for cell attachment [255]. The same results were observed in the MgO-SiO_2-CaO-P_2O_5-Na_2O-K_2O where the implanted materials stimulated osteoconductivity and bone colonization through the macroporous structure of bioactive glasses [256]. Osseous tissue proliferation, implant disaggregation and reabsorption are some of the other effects which are provided by the addition of magnesium to the bioactive glasses. The lower bonding interfaces in systems like CaO-P_2O_5-SiO_2-MgO and higher glass degradation rate can lead to lower bioactivity [257]. However, higher MgO content of bioactive glass cements can be beneficial in biological systems since it releases alkaline-earth ions like Mg^{2+} that can act as a buffer as it interacts with the H^+ and H_3O^+ products of acidic agents like polyacrylic acid [258]. MgO-containing bioglass coating materials, especially those with higher Mg content, have limitations in biomedical applications due to their lower bioactivity when compared to other available materials like 45S5 bioglasses®. However, the bioactivity issues can be overcome by maintaining the SiO_2 level of MgO-containing glasses at values <60 wt% since higher ratios inhibit the formation of HA layer on bioglass surfaces which results in lower bioactivity [259].

8. Future directions

Understanding applications of magnesium phosphates in orthopedics is still in an early stage, though the materials have been known for decades. In cement related applications, compared to the well-developed CPC system, there is still much room for improving the properties of MPCs. Some possibilities are: 1) composition modification such as removal of NH_4^+ and optimizing MgO content; 2) preparation of composite cements such as adding porogens to create porosity and improve biological responses; 3) improving handling properties and setting behavior; 4) evaluation as a drug delivery vehicle. Especially the latter is practically unexplored compared to the well-investigated drug delivery possibilities with CaP ceramics and cements [112]. Here, the unusual low porosity of struvite forming MPC is thought to offer the possibility of a physically entrapment of drugs within the dense ceramic matrix, which are only released upon cement degradation. In addition, the beneficial role of Mg^{2+} in gene delivery is rarely studied and magnesium phosphates' potential applications in gene delivery have not been compared to their calcium phosphates counterpart. MgP scaffolds for tissue engineering applications (e.g. prepared by 3D printing) have been studied far less than their CaP counterpart [260], although magnesium phosphates exhibit much higher mechanical strength and dissolution rate than calcium phosphates. There is also still room for further material development in the CaO-MgO-P_2O_5 system. First, the effects of Mg^{2+} substitution in several CaP phases such as monetite and calcium pyrophosphate are not clear. Second, though Mg^{2+} is supposed to accelerate calcium phosphate dissolution rate and improve substance biocompatibility, the potential of using such compounds in the MgO-CaO-P_2O_5 ternary system is not well studied yet. Lastly, there has not been much effort in understanding the synergistic relationship between Ca^{2+} and Mg^{2+} and even the interaction of other possible dopants on tissue response and material properties. A recent study is one of a few that mentioned that Mg^{2+} can buffer the toxicity of excessive Sr^{2+}, while Ca^{2+} has no impact at all [261]. However, despite of these promising aspects, there is still a relative lack of clinical and *in vivo* data for Mg-based formulations. Although a range of MPC have been tested *in vivo* and there is already one commercial MPC available for bone replacement, the majority of *in vivo* experiments were performed in small animal models and the transfer of these results to humans to estimate their bone regeneration capacity is difficult. Here, further experimental work in large animal models (preferably also at partially load bearing application sites) is necessary to predict whether MgP based ceramics have indeed a superior bone regeneration capacity compared with their well-established calcium phosphate counterparts. Testing may include not only the effect of different mineral compositions, but also focus on the biological influence of setting retarders (e.g. borates). This for example has been underestimated in CPC chemistry, where it was recently shown that the addition of citric acid as retarder for brushite cements strongly inhibits osteoclast activity and hence cement resorption [11,262]. Future research on MgO containing glasses may be directed toward evaluating the effects of MgO additions on the behavior of newly-developed borate-based bioglasses. Since many of MgO containing bioglasses have been used as coatings on Ti and Ti-alloys, it will be interesting to study if any MgO containing bioglass can protect biodegradable Mg-alloys and simultaneously make them osteoconductive. Finally, more "structure-property-processing" correlations can be made on MgO containing glass-ceramics, paying attention to phases such as akermanite ($Ca_2MgSi_2O_7$) or diopside ($CaMgSi_2O_6$).

Acknowledgement

SBB acknowledges partial support from NSF Grant no. 1706513.

References

[1] H. Zhou, J.G. Lawrence, S.B. Bhaduri, Fabrication aspects of PLA-CaP/PLGA-CaP composites for orthopedic applications: a review, Acta Biomater. 8 (2012) 1999–2016.
[2] M.M. Stevens, Biomaterials for bone tissue engineering, Mater. Today 11 (2008) 18–25.
[3] J.F. Keating, M.M. McQueen, Substitutes for autologous bone graft in orthopaedic trauma, J. Bone & Joint Surg. Brit. 83-B (2001) 3–8.
[4] C.J. Damien, J.R. Parsons, Bone graft and bone graft substitutes: a review of current technology and applications, J. Appl. Biomat. 2 (1991) 187–208.
[5] C.F. Lord, M.C. Gebhardt, W.W. Tomford, H.J. Mankin, Infection in bone allografts. Incidence, nature, and treatment, J. Bone Joint Surg. Ser. A 70 (1988) 369–376.
[6] D. Logeart-Avramoglou, F. Anagnostou, R. Bizios, H. Petite, Engineering bone: challenges and obstacles, J. Cell Mol. Med. 9 (2005) 72–84.

[7] L.L. Hench, J.M. Polak, Third-generation biomedical materials, Science 295 (2002) 1014.

[8] M. Navarro, A. Michiardi, O. Castaño, J.A. Planell, Biomaterials in orthopaedics, J. R. Soc. Interface 5 (2008) 1137–1158.

[9] R. Langer, J.P. Vacanti, Tissue engineering, Science 14 (1993) 920–926.

[10] M. Bohner, F. Theiss, D. Apelt, W. Hirsiger, R. Houriet, G. Rizzoli, E. Gnos, C. Frei, J.A. Auer, B. von Rechenberg, Compositional changes of a dicalcium phosphate dihydrate cement after implantation in sheep, Biomaterials 24 (2003) 3463–3474.

[11] B. Kanter, M. Geffers, A. Ignatius, U. Gbureck, Control of in vivo mineral bone cement degradation, Acta Biomater 10 (2014) 3279–3287.

[12] J. Walker, S. Shadanbaz, T.B. Woodfield, M.P. Staiger, G.J. Dias, Magnesium biomaterials for orthopedic application: a review from a biological perspective, J. Biomed. Mater. Res. B 102 (2014) 1316–1331.

[13] M.P. Staiger, A.M. Pietak, J. Huadmai, G. Dias, Magnesium and its alloys as orthopedic biomaterials: a review, Biomaterials 27 (2006) 1728–1734.

[14] N. Ostrowski, A. Roy, P.N. Kumta, Magnesium phosphate cement systems for hard tissue applications: a review, ACS Biomater. Sci. Eng. 2 (2016) 1067–1083.

[15] J.R. Weisinger, E. Bellorín-Font, Magnesium and phosphorus, Lancet 352 (1998) 391–396.

[16] F.I. Wolf, A. Cittadini, Chemistry and biochemistry of magnesium, Mol. Asp. Med. 24 (2003) 3–9.

[17] F.I. Wolf, V. Trapani, Cell (patho)physiology of magnesium, Clin. Sci. 114 (2008) 27–35.

[18] M.E. Maguire, J.A. Cowan, Magnesium chemistry and biochemistry, Biometals 15 (2002) 203–210.

[19] R.W. Schrier, Atlas of disease of the kidney, Philadelphia, 1999.

[20] M. Diba, F. Tapia, A. Boccaccini, L. Strobel, Magnesium-containing bioactive glasses for biomedical applications, Int. J. Appl. Glass Sci. 3 (2012) 221–253.

[21] J. Vormann, Magnesium: nutrition and metabolism, Mol. Asp. Med. 24 (2003) 27–37.

[22] S.V. Dorozhkin, M. Epple, Biological and medical significance of calcium phosphates, Angew. Chem. Int. Ed. 41 (2002) 3130–3146.

[23] P.W. Flatman, Magnesium transport across cell membranes, J. Membr. Biol. 80 (1984) 1–14.

[24] D.B. Simon, Y. Lu, K.A. Choate, H. Velazquez, E. Al-Sabban, M. Praga, G. Casari, A. Bettinelli, G. Colussi, J. Rodriguez-Soriano, D. McCredie, D. Milford, S. Sanjad, R.P. Lifton, Paracellin-1, a renal tight junction protein required for paracellular Mg^{2+} resorption, Science 285 (1999) 103–106.

[25] S.B. Baker, L.I. Worthley, The essentials of calcium, magnesium and phosphate metabolism: part II. Disorders, Crit. Care Resusc 4 (2002) 307–315.

[26] R.K. Rude, H.E. Gruber, L.Y. Wei, A. Frausto, B.G. Mills, Magnesium deficiency: effect on bone and mineral metabolism in the mouse, Calcif. Tissue Int. 72 (2003) 32–41.

[27] R.K. Rude, F.R. Singer, H.E. Gruber, Skeletal and hormonal effects of magnesium deficiency, J. Am. Coll. Nutr. 28 (2009) 131–141.

[28] F. Witte, V. Kaese, H. Haferkamp, E. Switzer, A. Meyer-Lindenberg, C.J. Wirth, H. Windhagen, In vivo corrosion of four magnesium alloys and the associated bone response, Biomaterials 26 (2005) 3557–3563.

[29] F. Witte, H. Ulrich, C. Palm, E. Willbold, Biodegradable magnesium scaffolds: part II: Peri-implant bone remodeling, J. Biomed. Mater. Res. A 81A (2007) 757–765.

[30] S. Yoshizawa, A. Brown, A. Barchowsky, C. Sfeir, Magnesium ion stimulation of bone marrow stromal cells enhances osteogenic activity, simulating the effect of magnesium alloy degradation, Acta Biomater. 10 (2014) 2834–2842.

[31] L. Wu, F. Feyerabend, A.F. Schilling, R. Willumeit-Römer, B.J.C. Luthringer, Effects of extracellular magnesium extract on the proliferation and differentiation of human osteoblasts and osteoclasts in coculture, Acta Biomater. 27 (2015) 294–304.

[32] L. Wu, B.J.C. Luthringer, F. Feyerabend, A.F. Schilling, R. Willumeit, Effects of extracellular magnesium on the differentiation and function of human osteoclasts, Acta Biomater. 10 (2014) 2843–2854.

[33] G. Gronowicz, M.B. McCarthy, Response of human osteoblasts to implant materials: Integrin-mediated adhesion, J. Orthop. Res. 14 (1996) 878–887.

[34] H. Zreiqat, C.R. Howlett, A. Zannettino, P. Evans, G. Schulze-Tanzil, C. Knabe, M. Shakibaei, Mechanisms of magnesium-stimulated adhesion of osteoblastic cells to commonly used orthopaedic implants, J. Biomed. Mater. Res. 62 (2002) 175–184.

[35] J. Gailit, E. Ruoslahti, Regulation of the fibronectin receptor affinity by divalent cations, J. Biol. Chem. 263 (1988) 12927–12932.

[36] I.L. Shashkova, N.V. Kitikova, A.I. Rat'ko, A.G. D'yachenko, Preparation of calcium and magnesium hydrogen phosphates from natural dolomite and their sorptive properties, Inorg. Mater. 36 (2000) 826–829.

[37] M.a.A. Aramendía V. Borau C. Jiménez J.M.a. Marinas F.J. Romero Synthesis and characterization of magnesium phosphates and their catalytic properties in the conversion of 2-hexanol J. Colloid Interf. Sci. 217 1999 288 298

[38] S. Sugiyama, J.B. Moffat, Oxidative coupling of methane on salts of magnesium doped by alkali carbonates, Energy Fuels 8 (1994) 463–469.

[39] J.W. Park, K.H. Kim, K.Y. Ann, Fundamental properties of magnesium phosphate cement mortar for rapid repair of concrete, Adv. Mater. Sci. Eng. 7179403 (2016).

[40] S.S. Seehra, S. Gupta, S. Kumar, Rapid setting magnesium phosphate cement for quick repair of concrete pavements – characterization and durability aspects, Cement Concr. Res. 23 (1993) 254–266.

[41] Q. Yang, B. Zhu, X. Wu, Characteristics and durability test of magnesium phosphate cement-based material for rapid repair of concrete, Mater. Struct. 33 (2000) 229–234.

[42] S. Dorozhkin, Calcium orthophosphate cements for biomedical application, J. Mater. Sci. 43 (2008) 3028–3057.

[43] P.W. Brown, J. Gulick, J. Dumm, The System $MgO—P_2O_5—H_2O$ at 25°C, J. Am. Ceram. Soc. 76 (1993) 1558–1562.

[44] C.K. Chau, F. Qiao, Z. Li, Potentiometric study of the formation of magnesium potassium phosphate hexahydrate, J. Mater. Civil Eng. 24 (2012) 586–591.

[45] A. Belposky, S. Shpunt, M. Shulgina, Physiochemical researches in the field of magnesium phosphates, J. Appl. Chem. 23 (1950) 873–884.

[46] S. Shpunt, A. Belposky, M. Shulgina, The polytherm of the $MgO-P_2O_5-H_2O$, J. Appl. Chem. 24 (1951) 439–447.

[47] A.W. Taylor, A.W. Frazier, E.L. Gurney, J.P. Smith, Solubility products of di- and trimagnesium phosphates and the dissociation of magnesium phosphate solutions, Trans. Faraday Soc. 59 (1963) 1585–1589.

[48] M.I.H. Bhuiyan, D.S. Mavinic, F.A. Koch, Thermal decomposition of struvite and its phase transition, Chemosphere 70 (2008) 1347–1356.

[49] S.V. Golubev, O.S. Pokrovsky, V.S. Savenko, Homogeneous precipitation of magnesium phosphates from seawater solutions, J. Cryst. Growth 223 (2001) 550–556.

[50] A.W. Taylor, A.W. Frazier, E.L. Gurney, Solubility products of magnesium ammonium and magnesium potassium phosphates, Trans. Faraday Soc. 59 (1963) 1580–1584.

[51] C.K. Chau, Z. Li, Accelerated reactivity assessment of light burnt magnesium oxide, J. Am. Ceram. Soc. 91 (2008) 1640–1645.

[52] F. Abbona, H.E. Lundager Madsen, R. Boistelle, Crystallization of two magnesium phosphates, struvite and newberyite: effect of pH and concentration, J. Cryst. Growth 57 (1982) 6–14.

[53] P.W. Brown, Phase relationships in the ternary system $CaO—P_2O_5—H_2O$ at 25°C, J. Am. Ceram. Soc. 75 (1992) 17–22.

[54] S. Mousa, Study on synthesis of magnesium phosphate materials phosphorus, Res. Bull. 24 (2010) 16–21.

[55] B.C. Sales, B.C. Chakoumakos, L.A. Boatner, J.O. Ramey, Structural properties of the amorphous phases produced by heating crystalline $MgHPO_4{\cdot}3H_2O$, J. Non-Cryst. Solids 159 (1993) 121–139.

[56] M. Mathew, P. Kingsbury, S. Takagi, W.E. Brown, A new struvite-type compound, magnesium sodium phosphate heptahydrate, Acta Crystallogr. Sect. B 38 (1982) 40–44.

[57] C.K. Chau, F. Qiao, Z. Li, Microstructure of magnesium potassium phosphate cement, Constr. Build. Mater. 25 (2011) 2911–2917.

[58] S.E. Vinokurov, Y.M. Kulyako, O.M. Slyunchev, S.I. Rovnyi, A.S. Wagh, M.D. Maloney, B.F. Myasoedov, Magnesium potassium phosphate matrices for immobilization of high-level liquid wastes, Radiochemistry 51 (2009) 65–72.

[59] B.E.I. Abdelrazig, J.H. Sharp, Phase changes on heating ammonium magnesium phosphate hydrates, Thermochim. Acta 129 (1988) 197–215.

[60] F. Wu, J. Wei, H. Guo, F. Chen, H. Hong, C. Liu, Self-setting bioactive calcium–magnesium phosphate cement with high strength and degradability for bone regeneration, Acta Biomater. 4 (2008) 1873–1884.

[61] W. Fan, S. Jiacan, W. Jie, G. Han, L. Changsheng, Injectable bioactive calcium–magnesium phosphate cement for bone regeneration, Biomed. Mater. 3 (2008) 044105.

[62] K.J. Lilley, U. Gbureck, J.C. Knowles, D.F. Farrar, J.E. Barralet, Cement from magnesium substituted hydroxyapatite, J. Mater. Sci. – Mater. Med. 16 (2005) 455–460.

[63] D.A. Hall, R. Stevens, B.E. Jazairi, Effect of water content on the structure and mechanical properties of magnesia-phosphate cement mortar, J. Am. Ceram. Soc. 81 (1998) 1550–1556.

[64] A.W. Frazier, J.R. Lehr, J.P. Smith, The magnesium phosphates hannayite, schertelite and bobierrite, Am. Mineral. 48 (1963) 635–641.

[65] D.V. Ribeiro, M.R. Morelli, Performance analysis of magnesium phosphate cement mortar containing grinding dust, Mater. Res. 12 (2009) 51–56.

[66] S.A. Walling, J.L. Provis, Magnesia-based cements: a journey of 150 years, and cements for the future?, Chem Rev. 116 (2016) 4170–4204.

[67] A.K. Sarkar, Hydration/dehydration characteristics of struvite and dittmarite pertaining to magnesium ammonium phosphate cement systems, J. Mater. Sci. 26 (1991) 2514–2518.

[68] G. Mestres, M.P. Ginebra, Novel magnesium phosphate cements with high early strength and antibacterial properties, Acta Biomater. 7 (2011) 1853–1861.

[69] G. Mestres, M. Abdolhosseini, W. Bowles, S.H. Huang, C. Aparicio, S.U. Gorr, M. P. Ginebra, Antimicrobial properties and dentin bonding strength of magnesium phosphate cements, Acta Biomater. 9 (2013) 8384–8393.

[70] G. Mestres, F.S. Aguilera, N. Manzanares, S. Sauro, R. Osorio, M. Toledano, M.P. Ginebra, Magnesium phosphate cements for endodontic applications with improved long-term sealing ability, Int. Endod. J. 47 (2014) 127–139.

[71] J.M. Burnell, E.J. Teubner, A.G. Miller, Normal maturational changes in bone matrix, mineral, and crystal size in the rat, Calcif. Tissue Int. 31 (1980) 13–19.

[72] A. Bigi, E. Foresti, R. Gregorini, A. Ripamonti, N. Roveri, J.S. Shah, The role of magnesium on the structure of biological apatites, Calcif. Tissue Int. 50 (1992) 439–444.

[73] Z. Amjad, P.G. Koutsoukos, G.H. Nancollas, The crystallization of hydroxyapatite and fluorapatite in the presence of magnesium ions, J. Colloid Interf. Sci. 101 (1984) 250–256.

[74] E.D. Eanes, S.L. Rattner, The effect of magnesium on apatite formation in seeded supersaturated solutions at pH 7.4, J. Dent. Res. 60 (1981) 1719–1723.

[75] M.H. Salimi, J.C. Heughebaert, G.H. Nancollas, Crystal growth of calcium phosphates in the presence of magnesium ions, Langmuir 1 (1985) 119–122.
[76] A.L. Boskey, A.S. Posner, Magnesium stabilization of amorphous calcium phosphate: a kinetic study, Mater. Res. Bull. 9 (1974) 907–916.
[77] H. Zhou, S. Bhaduri, Novel microwave synthesis of amorphous calcium phosphate nanospheres, J. Biomed. Mater. Res. B: Appl. Biomat. 100B (2012) 1142–1150.
[78] H. Zhou, T.J.F. Luchini, S.B. Bhaduri, Microwave assisted synthesis of amorphous magnesium phosphate nanospheres, J. Mater. Sci. Mater. Med. 23 (2012) 2831–2837.
[79] M.S. Tung, B. Tomazic, W.E. Brown, The effects of magnesium and fluoride on the hydrolysis of octacalcium phosphate, Arch. Oral Biol. 37 (1992) 585–591.
[80] F. Abbona, A. Baronnet, A XRD and TEM study on the transformation of amorphous calcium phosphate in the presence of magnesium, J. Cryst. Growth 165 (1996) 98–105.
[81] R. Boistelle, I. ILopez-Valero, F. Abbona, Crystallization of calcium phosphate in the presence of magnesium, Nephrologie 14 (1993) 265–269.
[82] P. Cheng, J. Grabher, R. LeGeros, Effects of magnesium on calcium phosphate formation, Magnesium 7 (1988) 123–132.
[83] A. Bigi, G. Falini, E. Foresti, M. Gazzano, A. Ripmonti, N. Roveri, Rietveld structure refinements of calcium hydroxylapatite containing magnesium, Acta Crystallogr. B 52 (1996) 87–92.
[84] A. Yasukawa, S. Ouchi, K. Kandori, T. Ishikawa, Preparation and characterization of magnesium-calcium hydroxyapatites, J. Mater. Chem. 6 (1996) 1401–1405.
[85] E. Boanini, M. Gazzano, A. Bigi, Ionic substitutions in calcium phosphates synthesized at low temperature, Acta Biomater. 6 (2010) 1882–1894.
[86] M. Nabiyouni, Y.F. Ren, S.B. Bhaduri, Magnesium substitution in the structure of orthopedic nanoparticles: a comparison between amorphous magnesium phosphates, calcium magnesium phosphates, and hydroxyapatites, Mater. Sci. Eng. C 52 (2015) 11–17.
[87] E. Babaie, H. Zhou, B. Lin, S.B. Bhaduri, Influence of ethanol content in the precipitation medium on the composition, structure and reactivity of magnesium-calcium phosphate, Mater. Sci. Eng. C 53 (2015) 204–211.
[88] E. Landi, G. Logroscino, L. Proietti, A. Tampieri, M. Sandri, S. Sprio, Biomimetic Mg-substituted hydroxyapatite: from synthesis to in vivo behaviour, J. Mater. Sci. Mater. Med. 19 (2008) 239–247.
[89] L. Bertinetti, C. Drouet, C. Combes, C. Rey, A. Tampieri, S. Coluccia, G. Martra, Surface characteristics of nanocrystalline apatites: effect of mg surface enrichment on morphology Surface hydration species, and cationic environments, Langmuir 25 (2009) 5647–5654.
[90] V. Aina, G. Lusvardi, B. Annaz, I.R. Gibson, F.E. Imrie, G. Malavasi, L. Menabue, G. Cerrato, G. Martra, Magnesium- and strontium-co-substituted hydroxyapatite: the effects of doped-ions on the structure and chemico-physical properties, J Mater Sci. Mater. Med. 23 (2012) 2867–2879.
[91] I. Cacciotti, A. Bianco, M. Lombardi, L. Montanaro, Mg-substituted hydroxyapatite nanopowders: synthesis, thermal stability and sintering behaviour, J. Eur. Ceram. Soc. 29 (2009) 2969–2978.
[92] I. Cacciotti, A. Bianco, High thermally stable Mg-substituted tricalcium phosphate via precipitation, Ceram. Int. 37 (2011) 127–137.
[93] H.-S. Ryu, K.S. Hong, J.-K. Lee, D.J. Kim, Variations of structure and composition in magnesium incorporated hydroxyapatite/β-tricalcium phosphate, J. Mater. Res. 21 (2006) 428–436.
[94] X. Zhang, F. Jiang, T. Groth, K.S. Vecchio, Preparation, characterization and mechanical performance of dense beta-TCP ceramics with/without magnesium substitution, J. Mater. Sci.-Mater. Med. 19 (2008) 3063–3070.
[95] R. Enderle, F. Gotz-Neunhoeffer, M. Gobbels, F.A. Muller, P. Greil, Influence of magnesium doping on the phase transformation temperature of beta-TCP ceramics examined by Rietveld refinement, Biomaterials 26 (2005) 3379–3384.
[96] P.N. Kumta, C. Sfeir, D.-H. Lee, D. Olton, D. Choi, Nanostructured calcium phosphates for biomedical applications: novel synthesis and characterization, Acta Biomater. 1 (2005) 65–83.
[97] R. Legeros, Calcium Phosphates in Oral Biology and Medicine, Karger, Basel, 1991.
[98] W. Xue, K. Dahlquist, A. Banerjee, A. Bandyopadhyay, S. Bose, Synthesis and characterization of tricalcium phosphate with Zn and Mg based dopants, J. Mater. Sci. Mater. Med. 19 (2008) 2669–2677.
[99] D. Lee, P.N. Kumta, Chemical synthesis and stabilization of magnesium substituted brushite, Mater. Sci. Eng. C 30 (2010) 934–943.
[100] M. Diba, O.-M. Goudouri, F. Tapia, A.R. Boccaccini, Magnesium-containing bioactive polycrystalline silicate-based ceramics and glass-ceramics for biomedical applications, Curr. Opin. Solid St. M 18 (2014) 147–167.
[101] A.M. George, J.F. Stebbins, Structure and dynamics of magnesium in silicate melts; a high-temperature ^{25}Mg NMR study, Am. Mineral. 83 (1998) 1022–1029.
[102] J.M. Oliveira, R.N. Correia, M.H. Fernandes, Effects of Si speciation on the in vitro bioactivity of glasses, Biomaterials 23 (2002) 371–379.
[103] K. Shimoda, Y. Tobu, M. Hatakeyama, T. Nemoto, K. Saito, Structural investigation of Mg local environments in silicate glasses by ultra-high field Mg-25 3QMAS NMR spectroscopy, Am. Mineral. 92 (2007) 695–698.
[104] S.J. Watts, R.G. Hill, M.D. O'Donnell, R.V. Law, Influence of magnesia on the structure and properties of bioactive glasses, J. Non-Cryst. Solids 356 (2010) 517–524.
[105] R.J. Hand, D.R. Tadjiev, Mechanical properties of silicate glasses as a function of composition, J. Non-Cryst. Solids 356 (2010) 2417–2423.
[106] E. Verné, O. Bretcanu, C. Balagna, C.L. Bianchi, M. Cannas, S. Gatti, C. Vitale-Brovarone, Early stage reactivity and in vitro behavior of silica-based bioactive glasses and glass-ceramics, J. Mater. Sci. Mater. Med. 20 (2009) 75–87.
[107] E. Dietrich, H. Oudadesse, A. Lucas-Girot, Y. Le Gal, S. Jeanne, G. Cathelineau, Effects of Mg and Zn on the surface of doped melt-derived glass for biomaterials applications, Appl. Surf. Sci. 255 (2008) 391–395.
[108] J. Ma, C.Z. Chen, D.G. Wang, Y. Jiao, J.Z. Shi, Effect of magnesia on the degradability and bioactivity of sol–gel derived SiO_2–CaO–MgO–P_2O_5 system glasses, Colloids Surf. B Biointerf. 81 (2010) 87–95.
[109] V.G. Varanasi, J.B. Owyoung, E. Saiz, S.J. Marshall, G.W. Marshall, P.M. Loomer, The ionic products of bioactive glass particle dissolution enhance periodontal ligament fibroblast osteocalcin expression and enhance early mineralized tissue development, J. Biomed. Mater. Res. A 98A (2011) 177–184.
[110] D. Zhang, O. Leppäranta, E. Munukka, H. Ylänen, M.K. Viljanen, E. Eerola, M. Hupa, L. Hupa, Antibacterial effects and dissolution behavior of six bioactive glasses, J. Biomed. Mater. Res. A 93A (2010) 475–483.
[111] Y. Josset, F. Nasrallah, E. Jallot, M. Lorenzato, O. Dufour-Mallet, G. Balossier, D. Laurent-Maquin, Influence of physicochemical reactions of bioactive glass on the behavior and activity of human osteoblasts in vitro, J. Biomed. Mater. Res. A 67A (2003) 1205–1218.
[112] M.-P. Ginebra, C. Canal, M. Espanol, D. Pastorino, E.B. Montufar, Calcium phosphate cements as drug delivery materials, Adv. Drug Deliv. Rev. 64 (2012) 1090–1110.
[113] D.F. Farrar, Bone adhesives for trauma surgery: a review of challenges and developments, Int J Adhes Adhes 33 (2012) 89–97.
[114] L.M. Grover, U. Gbureck, D. Farrar, J.E. Barralet, Adhesion of a novel calcium phosphate cement to cortical bone and several common biomaterials key eng, Mater. 309–311 (2006) 859. 852.
[115] L.J.M. Hirvinen, A.S. Litsky, V.F. Samii, S.E. Weisbrode, A.L. Bertone, Influence of bone cements on bone-screw interfaces in the third metacarpal and third metatarsal bones of horses, Am. J. Vet. Res. 70 (2009) 964–972.
[116] L.V. Gulotta, D. Kovacevic, L. Ying, J.R. Ehteshami, S. Montgomery, S.A. Rodeo, Augmentation of tendon-to-bone healing with a magnesium-based bone adhesive, Am. J. Sport Med. 36 (2008) 1290–1297.
[117] F. Wu, J. Wei, H. Guo, F.P. Chen, H. Hong, C.S. Liu, Self-setting bioactive calcium-magnesium phosphate cement with high strength and degradability for bone regeneration, Acta Biomater. 4 (2008) 1873–1884.
[118] A. Wang, J. Zhang, J. Li, A. Ma, L. Liu, Effect of liquid-to-solid ratios on the properties of magnesium phosphate chemically bonded ceramics, Mater. Sci. Eng. C 33 (2013) 2508–2512.
[119] G.Y. Yang, J.L. Liu, F. Li, Z.Y. Pan, X. Ni, Y. Shen, H.Z. Xu, Q. Huang, Bioactive calcium sulfate/magnesium phosphate cement for bone substitute applications, Mater. Sci. Eng. C 35 (2014) 70–76.
[120] C. Moseke, V. Saratsis, U. Gbureck, Injectability and mechanical properties of magnesium phosphate cements, J. Mater. Sci. Mater. Med. 22 (2011) 2591–2598.
[121] C. Großardt, A. Ewald, L.M. Grover, J.E. Barralet, U. Gbureck, Passive and active in vitro resorption of calcium and magnesium phosphate cements by osteoclastic cells, Tissue. Eng. Part A 16 (2010) 3687–3695.
[122] E. Vorndran, A. Ewald, F. Müller, K. Zorn, A. Kufner, U. Gbureck, Formation and properties of magnesium–ammonium–phosphate hexahydrate biocements in the Ca–Mg–PO4 system, J. Mater. Sci. Mater. Med. 22 (2011) 429–436.
[123] A. Ewald, K. Helmschrott, G. Knebl, N. Mehrban, L.M. Grover, U. Gbureck, Effect of cold-setting calcium- and magnesium phosphate matrices on protein expression in osteoblastic cells, J. Biomed. Mater. Res. B: Appl. Biomat. 96B (2011) 326–332.
[124] N. Rostami, Development of Novel Magnesium Phosphate Bone Cement, University of Toledo, 2014.
[125] H. Zhou, A.K. Agarwal, V.K. Goel, S.B. Bhaduri, Microwave assisted preparation of magnesium phosphate cement (MPC) for orthopedic applications: a novel solution to the exothermicity problem, Mater. Sci. Eng. C 33 (2013) 4288–4294.
[126] E. Babaie, B. Lin, V.K. Goel, S.B. Bhaduri, Evaluation of amorphous magnesium phosphate (AMP) based non-exothermic orthopedic cements, Biomed. Mater. 11 (2016) 00551.
[127] N. Yang, C. Shi, Y. Chang, Research progresses in magnesium phosphate cement based materials, J. Mater. Civil Eng. 26 (2014).
[128] N. Ostrowski, V. Sharma, A. Roy, P.N. Kumta, Systematic assessment of synthesized tri-magnesium phosphate powders (amorphous, semi-crystalline and crystalline) and cements for ceramic bone cement applications, J. Mater. Sci. Tech. 31 (2015) 437–444.
[129] J. Yang, C. Qian, Effect of borax on hydration and hardening properties of magnesium and potassium phosphate cement pastes, J. Wuhan Univ. Technol. Mater. Sci. Ed. 25 (2010) 613.
[130] Z. Ding, B. Dong, F. Xing, N. Han, Z. Li, Cementing mechanism of potassium phosphate based magnesium phosphate cement, Ceram. Int. 38 (2012) 6281–6288.
[131] A.S. Wagh, S.Y. Jeong, Chemically bonded phosphate ceramics: I, a dissolution model of formation, J. Am. Ceram. Soc. 86 (2003) 1838–1844.
[132] E. Soudée, J. Péra, Mechanism of setting reaction in magnesia-phosphate cements, Cement Concrete Res. 30 (2000) 315–321.
[133] R. Neiman, A.C. Sarma, Setting and thermal reactions of phosphate investments, J. Dent. Res. 59 (1980) 1478–1485.
[134] Q. Yang, X. Wu, Factors influencing properties of phosphate cement-based binder for rapid repair of concrete, Cem. Concr. Res. 29 (1999) 389–396.

[135] U. Klammert, E. Vorndran, T. Reuther, F.A. Muller, K. Zorn, U. Gbureck, Low temperature fabrication of magnesium phosphate cement scaffolds by 3D powder printing, J. Mater. Sci. Mater. Med. 21 (2010) 2947–2953.

[136] A. Wang, Z. Yuan, J. Zhang, L. Liu, J. Li, Z. Liu, Effect of raw material ratios on the compressive strength of magnesium potassium phosphate chemically bonded ceramics, Mater. Sci. Eng. C 33 (2013) 5058–5063.

[137] T. Finch, J.H. Sharp, Chemical reactions between magnesia and aluminium orthophosphate to form magnesia-phosphate cements, J. Mater. Sci. 24 (1989) 4379–4386.

[138] R.E. Dinnebier, D. Freyer, S. Bette, M. Oestreich, $9Mg(OH)_2\cdot MgCl_2\cdot 4H_2O$, a High Temperature phase of the magnesia binder system, Inorg. Chem. 49 (2010) 9770–9776.

[139] Y. Tan, Y. Liu, L. Grover, Effect of phosphoric acid on the properties of magnesium oxychloride cement as a biomaterial, Cem. Concr. Res. 56 (2014) 69–74.

[140] Y. Tan, Y. Liu, Z. Zhao, J.Z. Paxton, L.M. Grover, Synthesis and in vitro degradation of a novel magnesium oxychloride cement, J. Biomed. Mater. Res. A 103 (2015) 194–202.

[141] J.B. Shaw, G.A. Bole, New developments in oxychloride stucco and flooring, J. Am. Ceram. Soc. 5 (1922) 311–321.

[142] H. Bilinski, B. Matkovic, C. Mazuranic, T.B. Zunic, The formation of magnesium oxychloride phases in the systems $MgO\text{-}MgCl_2\text{-}H_2O$ and $NaOH\text{-}MgCl_2\text{-}H_2O$, J. Am. Ceram. Soc. 67 (1984) 266–269.

[143] P.H. Bates, R.K. Young, Plastic magnesia cements, J. Am. Ceram. Soc. 4 (1921) 570–596.

[144] Z. Li, C.K. Chau, Influence of molar ratios on properties of magnesium oxychloride cement, Cement Concrete Res. 37 (2007) 866–870.

[145] H. Ba, H. Guan, Influence of $MgO/MgCl_2$ molar ratio on phase stability of magnesium oxychloride cement, J. Wuhan Univ. Techn.-Mater. Sci. Ed 24 (2009) 476–481.

[146] F.C. Harper, Effect of calcination temperature on the properties of magnesium oxides for use in magnesium oxychloride cements, J. Appl. Chem. 17 (1967) 5–10.

[147] S. Alegret, M. Blanco, R. Subirats, Potentiometric study of the reactivity of calcined magnesites for use in magnesium oxychloride cements, J. Am. Ceram. Soc. 67 (1984) 579–582.

[148] D. Dehua, Z. Chuanmei, The formation mechanism of the hydrate phases in magnesium oxychloride cement, Cem. Concr. Res. 29 (1999) 1365–1371.

[149] H.S. Lukens, The composition of magnesium oxychloride, J. Am. Chem. Soc. 54 (1932) 2372–2380.

[150] D. Deng, The mechanism for soluble phosphates to improve the water resistance of magnesium oxychloride cement, Cem. Concr. Res. 33 (2003) 1311–1317.

[151] M. Krähenbühl, B. Etter, K.M. Udert, Pretreated magnesite as a source of low-cost magnesium for producing struvite from urine in Nepal, Sci. Total Environ. 542 (2016) 1155–1161.

[152] J.H. Canterford, Magnesia—an important industrial mineral: a review of processing options and uses, Min. Proces. Extract. Metal Rev. 2 (1985) 57–104.

[153] Y. Kotera, T. Saito, M. Terada, Crystal growth of magnesium oxide prepared by the thermal decomposition of magnesium hydroxide, B. Chem. Soc. Jpn. 36 (1963) 195–199.

[154] C.A. Strydom, E.M. van der Merwe, M.E. Aphane, The effect of calcining conditions on the rehydration of dead burnt magnesium oxide using magnesium acetate as a hydrating agent, J. Therm. Anal. Cal. 80 (2005) 659–662.

[155] W.R. Eubank, Calcination studies of magnesium oxides, J. Am. Ceram. Soc. 34 (1951) 225–229.

[156] X. Zhang, Y. Zheng, X. Feng, X. Han, Z. Bai, Z. Zhang, Calcination temperature-dependent surface structure and physicochemical properties of magnesium oxide, RSC Adv. 5 (2015) 86102–86112.

[157] E. Soudée, J. Péra, Influence of magnesia surface on the setting time of magnesia–phosphate cement, Cem. Concr. Res. 32 (2002) 153–157.

[158] U. Klammert, T. Reuther, M. Blank, I. Reske, J.E. Barralet, L.M. Grover, A.C. Kübler, U. Gbureck, Phase composition, mechanical performance and in vitro biocompatibility of hydraulic setting calcium magnesium phosphate cement, Acta Biomater. 6 (2010) 1529–1535.

[159] M.P. Ginebra, E. Fernández, M.G. Boltong, O. Bermúdez, J.A. Planell, F.C.M. Driessens, Compliance of an apatitic calcium phosphate cement with the short-term clinical requirements in bone surgery, orthopaedics and dentistry, Clin. Mater. 17 (1994) 99–104.

[160] M.P. Ginebra, M.G. Boltong, E. FernÁndez, J.A. Planell, F.C.M. Driessens, Effect of various additives and temperature on some properties of an apatitic calcium phosphate cement, J. Mater. Sci. Mater. Med. 6 (1995) 612–616.

[161] M.T. Fulmer, P.W. Brown, Effects of Na_2HPO_4 and NaH_2PO_4 on hydroxyapatite formation, J. Biomed. Mater. Res. 27 (1993) 1095–1102.

[162] M. Bohner, J. Lemaitre, T.A. Ring, Effects of sulfate, pyrophosphate, and citrate ions on the physicochemical properties of cements made of β-tricalcium phosphate-phosphoric acid-water mixtures, J. Am. Ceram. Soc. 79 (1996) 1427–1434.

[163] J.E. Barralet, L.M. Grover, U. Gbureck, Ionic modification of calcium phosphate cement viscosity Part II: hypodermic injection and strength improvement of brushite cement, Biomaterials 25 (2004) 2197–2203.

[164] Q. Yang, B. Zhu, S. Zhang, X. Wu, Properties and applications of magnesia–phosphate cement mortar for rapid repair of concrete, Cem. Concr. Res. 30 (2000) 1807–1813.

[165] Y. Yu, J. Wang, C. Liu, B. Zhang, H. Chen, H. Guo, G. Zhong, W. Qu, S. Jiang, H. Huang, Evaluation of inherent toxicology and biocompatibility of magnesium phosphate bone cement, Colloids Surf. B Biointerfaces 76 (2010) 496–504.

[166] S. Meininger, S. Mandal, A. Kumar, J. Groll, B. Basu, U. Gbureck, Strength reliability and in vitro degradation of three-dimensional powder printed strontium-substituted magnesium phosphate scaffolds, Acta Biomater. 31 (2016) 401–411.

[167] M. Le Rouzic, T. Chaussadent, L. Stefan, M. Saillio, On the influence of Mg/P ratio on the properties and durability of magnesium potassium phosphate cement pastes, Cem. Concr. Res. 96 (2017) 27–41.

[168] U. Gbureck, O. Grolms, J.E. Barralet, L.M. Grover, R. Thull, Mechanical activation and cement formation of β-tricalcium phosphate, Biomaterials 24 (2003) 4123–4131.

[169] J. Bae, Y. Ida, K. Sekine, F. Kawano, K. Hamada, Effects of high-energy ball-milling on injectability and strength of β-tricalcium-phosphate cement, J. Mech. Behav. Biomed. Mater. 47 (2015) 77–86.

[170] M.P. Hofmann, A.R. Mohammed, Y. Perrie, U. Gbureck, J.E. Barralet, High-strength resorbable brushite bone cement with controlled drug-releasing capabilities, Acta Biomater. 5 (2009) 43–49.

[171] J.E. Barralet, M. Hofmann, L.M. Grover, U. Gbureck, High-strength apatitic cement by modification with α-hydroxy acid salts, Adv. Mater. 15 (2003) 2091–2094.

[172] M. Geffers, J. Groll, U. Gbureck, Reinforcement strategies for load-bearing calcium phosphate biocements, Materials 8 (2015) 2700–2717.

[173] J. Zhang, W. Liu, V. Schnitzler, F. Tancret, J.-M. Bouler, Calcium phosphate cements for bone substitution: chemistry, handling and mechanical properties, Acta Biomater. 10 (2014) 1035–1049.

[174] C.A. Sorre, C.R. Armstrong, Reactions and equilibria in magnesium oxychloride cements, J. Am. Ceram. Soc. 59 (1976) 51–54.

[175] L. Urwongse, C.A. Sorrell, The system $MgO\text{-}MgCl_2\text{-}H_2O$ at 23 °C, J. Am. Ceram. Soc. 63 (1980) 501–504.

[176] K. Sugimoto, R.E. Dinnebier, T. Schlecht, Chlorartinite, a volcanic exhalation product also found in industrial magnesia screed, J. Appl. Crystal. 39 (2006) 739–744.

[177] D.A. Hall, R. Stevens, B. El-Jazairi, The effect of retarders on the microstructure and mechanical properties of magnesia–phosphate cement mortar, Cem. Concr. Res. 31 (2001) 455.

[178] J. Péra, J. Ambroise, Fiber-reinforced magnesia-phosphate cement composites for rapid repair, Cem. Concr. Comp. 20 (1998) 31–39.

[179] P. Frantzis, R. Baggott, Bond between reinforcing steel fibres and magnesium phosphate/calcium aluminate binders, Cem. Concr. Comp. 22 (2000) 187–192.

[180] A. Robisson, S. Maheshwari, S. Musso, J.J. Thomas, F.M. Auzerais, D. Han, M. Qu, F.-J. Ulm, Reactive elastomeric composites: when rubber meets cement, Comp. Sci. Tech. 75 (2013) 77–83.

[181] R. Krüger, J.-M. Seitz, A. Ewald, F.-W. Bach, J. Groll, Strong and tough magnesium wire reinforced phosphate cement composites for load-bearing bone replacement, J. Mech. Behav. Biomed. Mater. 20 (2013) 36–44.

[182] M.P. Ginebra, M.G. Boltong, F.C.M. Driessens, O. Bermúdez, E. Fernández, J.A. Planell, Preparation and properties of some magnesium-containing calcium phosphate cements, J. Mater. Sci. Mater. Med. 5 (1994) 103–107.

[183] M. Bohner, G. Baroud, Injectability of calcium phosphate pastes, Biomaterials 26 (2005) 1553–1563.

[184] I. Khairoun, M.G. Boltong, F.C.M. Driessens, J.A. Planell, Limited compliance of some apatitic calcium phosphate bone cements with clinical requirements, J. Mater. Sci. Mater. Med. 9 (1998) 667–671.

[185] P.W. Brown, N. Hocker, S. Hoyle, Variations in solution chemistry during the low-temperature formation of hydroxyapatite, J. Am. Ceram. Soc. 74 (1991) 1848–1854.

[186] K.S. TenHuisen, P.W. Brown, Effects of magnesium on the formation of calcium-deficient hydroxyapatite from $CaHPO_4\cdot 2H_2O$ and $Ca_4(PO_4)_2O$, J. Biomed. Mater. Res. 36 (1997) 306–314.

[187] J. Lu J. Wei Y. Yan H. Li J. Jia S. Wei H. Guo T. Xiao C. Liu Preparation and preliminary cytocompatibility of magnesium doped apatite cement with degradability for bone regeneration J. Mater. Sci. Mater. Med. 22 2011 607 615

[188] F.C.M. Driessens, M.G. Boltong, O. Bermúdez, J.A. Planell, M.P. Ginebra, E. Fernández, Effective formulations for the preparation of calcium phosphate bone cements, J. Mater. Sci. Mater. Med. 5 (1994) 164–170.

[189] J. Jia, H. Zhou, J. Wei, X. Jiang, H. Hua, F. Chen, S. Wei, J.-W. Shin, C. Liu, Development of magnesium calcium phosphate biocement for bone regeneration, J. R. Soc. Interface 7 (2010) 1171–1180.

[190] D. Pijocha, G. Lói, W. Nocun-Wczelik, A. Slósarczyk, Effect of retardants on the heat release during setting of bone cement-type composites, J. Achiev. Mater. Manufact. Eng. 49 (2011) 204–209.

[191] J. Wei, J. Jia, F. Wu, S. Wei, H. Zhou, H. Zhang, J.-W. Shin, C. Liu, Hierarchically microporous/macroporous scaffold of magnesium–calcium phosphate for bone tissue regeneration, Biomaterials 31 (2010) 1260–1269.

[192] U. Klammert, A. Ignatius, U. Wolfram, T. Reuther, U. Gbureck, In vivo degradation of low temperature calcium and magnesium phosphate ceramics in a heterotopic model, Acta Biomater. 7 (2011) 3469–3475.

[193] F.C.M. Driessens, M.G. Boltong, M.I. Zapatero, R.M.H. Verbeeck, W. Bonfield, O. Bérmúdez, E. Fernández, M.P. Ginebra, J.A. Planell, In vivo behaviour of three calcium phosphate cements and a magnesium phosphate cement, J. Mater. Sci. Mater. Med. 6 (1995) 272–278.

[194] A.A. Mirtchi, J. Lemaître, E. Hunting, Calcium phosphate cements: action of setting regulators on the properties of the β-tricalcium phosphate-monocalcium phosphate cements, Biomaterials 10 (1989) 634–638.

[195] F. Tamimi-Mariño, J. Mastio, C. Rueda, L. Blanco, E. López-Cabarcos, Increase of the final setting time of brushite cements by using chondroitin 4-sulfate and silica gel, J. Mater. Sci. Mater. Med. 18 (2007) 1195–1201.

[196] M. Bohner, J. Lemaître, P.V. Landuyt, P.-Y. Zambelli, H.P. Merkle, B. Gander, Gentamicin-loaded hydraulic calcium phosphate bone cement as antibiotic delivery system, J. Pharm. Sci. 86 (1997) 565–572.

[197] J. Tamura, Mechanical and biological properties of two types of bioactive bone cements containing MgO–CaO–SiO2–P2O5–CaF2 glass and glass-ceramic powder, J. Biomed. Mater. Res. 30 (1996) 89–94.

[198] S. Shinzato, T. Nakamura, J. Tamura, T. Kokubo, Y. Kitamura, Bioactive bone cement: effects of phosphoric ester monomer on mechanical properties and osteoconductivity, J. Biomed. Mater. Res. 56 (2001) 571–577.

[199] L. Boesel, M. Fernandes, R. Reis, The behavior of novel hydrophilic composite bone cements in simulated body fluids, J. Biomed. Mater. Res. B 70 (2004) 368–377.

[200] S. Shinzato, T. Nakamura, K. Kawanabe, T. Kokubo, PMMA-based bioactive cement: Effect of caf2 on osteoconductivity and histological change with time, J. Biomed. Mater. Res. B 65 (2003) 262–271.

[201] S. Yoshihara, T. Kokubo, N. Nishimura, T. Yamamuro, T. Nakamura, Effects of glass composition on compressive strength of bioactive cement-based on Cao–Sio2–P2o5 glass powders, J. Mater. Sci. Mater. Med. 5 (1994) 123–129.

[202] S. Matsuya, Y. Matsuya, M. Ohta, Structure of bioactive glass and its application to glass ionomer cement, Dent. Mater. J. 18 (1999) 155–166.

[203] R. Kruger, D. Joklitschke, U. Gbureck, A. Ewald, Development and cytocompatibility testing of trimagnesium phosphate and struvite foams, Tissue Eng. Part A 17 (2011) 562. 562.

[204] T. Christel, M. Geffers, U. Klammert, B. Nies, A. Hoess, J. Groll, A.C. Kuebler, U. Gbureck, Fabrication and cytocompatibility of spherical magnesium ammonium phosphate granules, Mater. Sci. Eng. C 42 (2014) 130–136.

[205] J.A. Kim, J. Lim, R. Naren, H.S. Yun, E.K. Park, Effect of the biodegradation rate controlled by pore structures in magnesium phosphate ceramic scaffolds on bone tissue regeneration in vivo, Acta Biomater. 44 (2016) 155–167.

[206] J. Lee, M.M. Farag, E.K. Park, J. Lim, H.S. Yun, A simultaneous process of 3D magnesium phosphate scaffold fabrication and bioactive substance loading for hard tissue regeneration, Mater. Sci. Eng. C 36 (2014) 252–260.

[207] E. Vorndran, K. Wunder, C. Moseke, I. Biermann, F.A. Muller, K. Zorn, U. Gbureck, Hydraulic setting $Mg_3(PO_4)_2$ powders for 3D printing technology, Adv. Appl. Ceram. 110 (2011) 476–481.

[208] G. Chen, T. Ushida, T. Tateishi, Scaffold design for tissue engineering, Macromolec. Biosci. 2 (2002) 67–77.

[209] R. Murugan, S. Ramakrishna, Design strategies of tissue engineering scaffolds with controlled fiber orientation, Tissue Eng. 13 (2007) 1845–1866.

[210] K. Rezwan, Q. Chen, J. Blaker, A. Boccaccini, Biodegradable and bioactive porous polymer/inorganic composite scaffolds for bone tissue engineering, Biomaterials 27 (2006) 3413–3431.

[211] O. Bretcanu, X. Chatzistavrou, K. Paraskevopoulos, R. Conradt, I. Thompson, A. Boccaccini, Sintering and crystallisation of 45S5 Bioglass (R) Powder, J. Eur. Ceram. Soc. 29 (2009) 3299–3306.

[212] E. Babaie, B. Lin, S.B. Bhaduri, A new method to produce macroporous Mg-phosphate bone growth substitutes, Mater. Sci. Eng. C 75 (2017) 602–609.

[213] X. Wang, X. Li, A. Ito, Y. Sogo, Synthesis and characterization of hierarchically macroporous and mesoporous CaO-MO-SiO_2-P_2O_5 (M=Mg, Zn, Sr) bioactive glass scaffolds, Acta Biomater. 7 (2011) 3638–3644.

[214] A. Hussain, K. Bessho, K. Takahashi, Y. Tabata, Magnesium calcium phosphate as a novel component enhances mechanical/physical properties of gelatin scaffold and osteogenic differentiation of bone marrow mesenchymal stem cells, Tissue Eng. Part A 18 (2012) 768–774.

[215] H. Zhou, M. Nabiyouni, B. Lin, S.B. Bhaduri, Fabrication of novel poly(lactic acid)/amorphous magnesium phosphate bionanocomposite fibers for tissue engineering applications via electrospinning, Mater. Sci. Eng. C 33 (2013) 2302–2310.

[216] J. Russias, Fabrication and in vitro characterization of three-dimensional organic/inorganic scaffolds by robocasting, J. Biomed. Mater. Res. A 83 (2007) 434–445.

[217] L. Moimas, G. De Rosa, V. Sergo, C. Schmid, Bioactive porous scaffolds for tissue engineering applications: investigation on the degradation process by Raman Spectroscopy and scanning electron microscopy, J. Appl. Biomater. Biomech. 4 (2006) 102–109.

[218] Q. Fu, M. Rahaman, B. Bal, W. Huang, D. Day, Preparation and bioactive characteristics of a porous 13–93 glass, and fabrication into the articulating surface of a proximal tibia, J. Biomed. Mater. Res. A 82 (2007) 222–229.

[219] L. Hench, O. Anderson, Bioactive glass coatings, in: L.L. Hench, J. Wilson (Eds.), An Introduction to Bioceramics, World Scientific, London, 1993, pp. 239–260.

[220] W. Mroz, B. Budner, R. Syroka, K. Niedzielski, G. Golanski, A. Slosarczyk, D. Schwarze, T. Douglas, In vivo implantation of porous titanium alloy implants coated with magnesium-doped octacalcium phosphate and hydroxyapatite thin films using pulsed laser depostion, J. Biomed. Mater. Res. B (2014).

[221] R. Borges, S. Ribeiro, J. Marchi, H. Yoshimura, Mechanical characterization of tricalcium phosphate ceramics doped with magnesium, in: S.M. Castanho, W. Acchar, D. Hotza (Eds.) Brazil Ceram. Conf. 57, Material Science Forum, 2014, pp. 454–459.

[222] S. Lopez-Esteban, E. Saiz, S. Fujino, T. Oku, K. Suganuma, A. Tomsia, Bioactive Glass Coatings for Orthopedic Metallic Implants, J. Eur. Ceram. Soc. 23 (2003) 2921–2930.

[223] P. Keranen, N. Moritz, J. Alm, H. Ylanen, B. Kommonen, H. Aro, Bioactive glass microspheres as osteopromotive inlays in macrotextured surfaces of Ti and CoCr alloy bone implants: trapezoidal surface grooves without inlay most efficient in resisting torsional forces, J. Mech. Behav. Biomed. Mater. 4 (2011) 1483–1491.

[224] N. Lotfibakhshaiesh, D. Brauer, R. Hill, Bioactive glass engineered coatings for Ti6Al4V alloys: influence of strontium substitution for calcium on sintering behaviour, J. Non-Cryst. Solids 356 (2010) 2583–2590.

[225] Y. Zhao, M. Song, J. Liu, Characteristics of bioactive glass coatings obtained by pulsed laser deposition, Surf. Interface Anal. 40 (2008) 1463–1468.

[226] G. Qi, S. Zhang, K. Khor, S. Lye, X. Zeng, W. Weng, C. Liu, S. Venkatraman, L. Ma, Osteoblastic cell response on magnesium-incorporated apatite coatings, Appl. Surf. Sci. 225 (2008) 304–307.

[227] A. Pazo, E. Saiz, A.P. Tomsia, Silicate glass coatings on Ti-based implants, Acta Mater. 46 (1998) 2551–2558.

[228] J. Park, H. Ko, J. Jang, H. Kang, J. Suh, Increased new bone formation with a surface magnesium-incorporated deproteinized porcine bone substitute in rabbit calvarial defects, J. Biomed. Mater. Res. 100 (2012) 834–840.

[229] T. Ishizaki, I. Shigematsu, N. Saito, Anticorrosive magnesium phosphate coating on AZ31 magnesium alloy, Surf. Coat. Tech. 203 (2009) 2288–2291.

[230] H. Zhao, S. Cai, Z. Ding, M. Zhang, Y. Li, G. Xu, A simple method for the preparation of magnesium phosphate conversion coatings on a AZ31 magnesium alloy with improved corrosion resistance, RSC Adv. 5 (2015) 24586–24590.

[231] Y. Ren, E. Babaie, B. Lin, S.B. Bhaduri, Microwave-assisted magnesium phosphate coating on the AZ31 magnesium alloy, Biomed. Mater. 12 (2017) 045026.

[232] M. Meininger, C. Wolf-Brandstetter, J. Zerweck, F. Wenninger, U. Gbureck, J. Groll, C. Moseke, Electrochemically assisted deposition of strontium modified magnesium phosphate on titanium surfaces, Mater. Sci. Eng. C 67 (2016) 65–71.

[233] A. Burmester, R. Willumeit-Römer, F. Feyerabend, Behavior of bone cells in contact with magnesium implant material, J. Biomed. Mater. Res. B 105 (2015) 165–179.

[234] A. Hussain, K. Bessho, K. Takahashi, Y. Tabata, Magnesium calcium phosphate as a novel component enhances mechanical/physical properties of gelatin scaffold and osteogenic differentiation of bone marrow mesenchymal stem cells, Tissue Eng. Part A 18 (2011) 768–774.

[235] C. Blum, T. Brückner, A. Ewald, A. Ignatius, U. Gbureck, Mg: Ca ratio as regulating factor for osteoclastic in vitro resorption of struvite biocements, Mater. Sci. Eng. C 73 (2017) 111–119.

[236] K. Kolan, M. Leu, G. Hilmas, R. Brown, M. Velez, Fabrication of 13–93 bioactive glass scaffolds for bone tissue engineering using indirect selective laser sintering, Biofabrication 3 (2011) 025004.

[237] R. Brown, D. Day, T. Day, S. Jung, M. Rahaman, Q. Fu, Growth and differentiation of osteoblastic cells on 13–93 bioactive glass fibers and scaffolds, Acta Biomater. 4 (2008) 387–396.

[238] Q. Fu, M. Rahaman, H. Fu, X. Liu, Silicate, borosilicate, and borate bioactive glass scaffolds with controllable degradation rate for bone tissue engineering applications. I. Preparation and in vitro degradation, J. Biomed. Mater. Res. A 95 (2010) 164–171.

[239] Q. Fu, M. Rahaman, B. Bal, K. Kuroki, R. Brown, In vivo evaluation of 13–93 bioactive glass scaffolds with trabecular and oriented microstructures in a subcutaneous rat Implantation model, J. Biomed. Mater. Res. A 95 (2010) 235–244.

[240] N. Doiphode, T. Huang, M. Leu, M. Rahaman, D. Day, Freeze extrusion fabrication of 13–93 bioactive glass scaffolds for bone repair, J Mater Sci: Mater. Med. 22 (2011) 515–523.

[241] X. Liu, M. Rahaman, Q. Fu, A. Tomsia, Porous and strong bioactive glass (13–93) scaffolds prepared by unidirectional freezing of camphene-based suspensions, Acta Biomater. 8 (2012) 415–423.

[242] Y. Rezaei, F. Moztarzadeh, S. Shahabi, M. Tahriri, Synthesis, Characterization, and In Vitro Bioactivity of Sol-Gel-Derived SiO_2–CaO–P_2O_5–MgO-SrO Bioactive Glass, Taylor & Francis, 2014.

[243] M. Erol, A. Özyuguran, Ö. Çelebican, Synthesis, characterization, and in vitro bioactivity of sol-gel-derived Zn, Mg, and Zn-Mg Co-doped bioactive glasses, Chem. Eng. Tech. 33 (2010) 1066–1074.

[244] S.A. Schendel, J. Peauroi, Magnesium-based bone cement and bone void filler: preliminary experimental studies, J. Craniofac. Surg. 20 (2009) 461–464.

[245] D. Zeng, L. Xia, W. Zhang, H. Huang, B. Wei, Q. Huang, J. Wei, C. Liu, X. Jiang, Maxillary sinus floor elevation using a tissue-engineered bone with calcium-magnesium phosphate cement and bone marrow stromal cells in rabbits, Tissue Eng. Part A 18 (2011) 870–881.

[246] B. Flautre, J. Lemaître, C. Maynou, P. Van Landuyt, P. Hardouin, Influence of polymeric additives on the biological properties of brushite cements: an experimental study in rabbit, J. Biomed. Mater. Res. A 66A (2003) 214–223.

[247] P.A. Revell, E. Damien, X.S. Zhang, P. Evans, C.R. Howlett, The Effect of Magnesium Ions on Bone Bonding to Hydroxyapatite Coating on Titanium Alloy Implants, Key Eng. Mater. 254–256 (2004) 447–450.

[248] M. Waselau, V.F. Samii, S.E. Weisbrode, A.S. Litsky, A.L. Bertone, Effects of a magnesium adhesive cement on bone stability and healing following a metatarsal osteotomy in horses, Am. J. Vet. Res. 68 (2007) 370–378.

[249] K. Gellynck, E.A. Abou Neel, H. Li, N. Mardas, N. Donos, P. Buxton, A.M. Young, Cell attachment and response to photocured, degradable bone adhesives containing tricalcium phosphate and purmorphamine, Acta Biomaterialia 7 (2011) 2672–2677.

[250] A. Hanifi, M.H. Fathi, H. Mir Mohammad Sadeghi, J. Varshosaz, Mg^{2+} substituted calcium phosphate nano particles synthesis for non viral gene delivery application,, J. Mater. Sci. Mater. Med. 21 (2010) 2393–2401.

[251] A. Balamurugan, G. Balossier, J. Michel, S. Kannan, H. Benhayoune, A.H.S. Rebelo, J.M.F. Ferreira, Sol gel derived SiO_2-CaO-MgO-P_2O_5 bioglass system—Preparation and in vitro characterization, J. Biomed. Mater. Res. B 83B (2007) 546–553.

[252] W. Cao, L.L. Hench, Bioactive materials, Ceram. Int. 22 (1996) 493–507.

[253] C. Janning, E. Willbold, C. Vogt, J. Nellesen, A. Meyer-Lindenberg, H. Windhagen, F. Thorey, F. Witte, Magnesium hydroxide temporarily enhancing osteoblast activity and decreasing the osteoclast number in peri-implant bone remodelling, Acta Biomater. 6 (2010) 1861–1868.

[254] M. Brink, T. Turunen, R.-P. Happonen, A. Yli-Urpo, Compositional dependence of bioactivity of glasses in the system Na_2O-K_2O-MgO-CaO-B_2O_3-P_2O_5-SiO_2, J. Biomed. Mater. Res. 37 (1997) 114–121.

[255] A.J. Salinas, J. Román, M. Vallet-Regi, J.M. Oliveira, R.N. Correia, M.H. Fernandes, In vitro bioactivity of glass and glass-ceramics of the $3CaO{\cdot}P_2O_5$–$CaO{\cdot}SiO_2$–$CaO{\cdot}MgO{\cdot}2SiO_2$ system, Biomaterials 21 (2000) 251–257.

[256] J. Tamura, K. Kawanabe, M. Kobayashi, T. Nakamura, T. Kokubo, S. Yoshihara, T. Shibuya, Mechanical and biological properties of two types of bioactive bone cements containing MgO-CaO-SiO_2-P_2O_5-CaF_2 glass and glass—ceramic powder, J. Biomed. Mater. Res. 30 (1996) 85–94.

[257] J.M. Oliveira, R.N. Correia, M.H. Fernandes, Surface modifications of a glass and a glass-ceramic of the MgO-$3CaO{\cdot}P_2O_5$-SiO_2 system in a simulated body fluid, Biomaterials 16 (1995) 849–854.

[258] L.F. Boesel, M.H.V. Fernandes, R.L. Reis, The behavior of novel hydrophilic composite bone cements in simulated body fluids, J. Biomed. Mater. Res. B 70B (2004) 368–377.

[259] J.M. Gomez-Vega, E. Saiz, A.P. Tomsia, T. Oku, K. Suganuma, G.W. Marshall, S.J. Marshall, Novel bioactive functionally graded coatings on Ti6Al4V, Adv. Mater. 12 (2000) 894–898.

[260] Z. Chen, X. Mao, L. Tan, T. Friis, C. Wu, R. Crawford, Y. Xiao, Osteoimmunomodulatory properties of magnesium scaffolds coated with β-tricalcium phosphate, Biomaterials 35 (2014) 8553–8565.

[261] H. Zhou, M. Nedley, S. Bhaduri, The impacts of Mg^{2+} on strontium phosphate: a preliminary study, Mater. Lett. 113 (2013) 63–66.

[262] S. Meininger, C. Blum, M. Schamel, J.E. Barralet, A. Ignatius, U. Gbureck, Phytic acid as alternative setting retarder enhanced biological performance of dicalcium phosphate cement in vitro, Sci. Rep. 7 (2017).