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Preparation, Structural Characterization, and Biomedical Applications of Gypsum-Based Nanocomposite Bone Cements

Hesham F. El-Maghraby and Yaser E. Greish

Abstract

Hard tissues are natural nanocomposites comprising collagen nanofibers that are interlocked with hydroxyapatite (HAp) nanocrystallites. This mechanical interlocking at the nanoscale provides the unique properties of hard tissues (bone and teeth). Upon fracture, cements are usually used for treatment of simple fractures or as an adhesive for the treatment of complicated fractures that require the use of metallic implants. Most of the commercially available bone cements are polymer-based, and lack the required bioactivity for a successful cementation. Besides calcium phosphate cements, gypsum is one of the early recognized and used biomaterials as a basis for a self-setting cementation. It is based on the controlled hydration of plaster of Paris at room temperature and its subsequent conversion to a self-setting solid gypsum product. In our work, we have taken this process further towards the development of a set of nanocomposites that have enhanced bioactivity and mechanical properties. This chapter will outline the formation, characterization, and properties of gypsum-based nanocomposites for bone cement applications. These modified cements can be formulated at room temperature and have been shown to possess a high degree of bioactivity, and are considered potential candidates for bone fracture and defect treatment.

Keywords: gypsum, bone cement, nanocomposite, biomimetic, apatite-forming ability

1. Introduction

Hard tissues, such as bone and teeth, are natural composites consisting of two types of material. The first material is an organic extracellular matrix that contains collagen, accounts for approximately 30–35% of the dry weight of bone, and is responsible for providing flexibility and resilience to the bone. The second material consists primarily of calcium and phosphorous salts, especially hydroxyapatite [$\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$; HAp], accounts for approximately 65–70% of the dry weight of bone, and contributes to the hardness and rigidity of the bone [1]. Hard tissues, in general, are responsible for providing support for the whole body, for the attachment to ligaments and tendons, and protect vital organs. Based on the composition of hard tissues, they are also considered as a reservoir for the minerals in addition to iron that maintains the process of hemostasis.

Bone can be classified macroscopically as cortical tissue and cancellous (trabecular) tissue [1]. Both types are morphologically lamellar bone. Cortical tissue relies on osteons for cell communication. Because trabecular width is small, the canaliculi can communicate directly with blood vessels in the medullary canal. The basic differences between cortical tissue and cancellous tissue relate to porosity and apparent density. The porosity of cortical tissue typically ranges from 5–30%, and that of cancellous tissue ranges from 30–90%. The apparent density of cortical tissue is approximately 1.8 g/cm^3 , and that of cancellous tissue typically ranges from 0.1 to 1.0 g/cm^3 . The distinction between cortical tissue and cancellous tissue is arbitrary. However, in biomechanical terms, the two tissues are often considered one material with a specific range of porosity and density.. The organization of cortical and cancellous tissue in bone allows adaptation to function. Cortical tissue always surrounds cancellous tissue, but the relative quantity of each type of tissue varies with the bone's functional requirements. In long bones, the diaphysis's cortical tissue is arranged as a hollow cylinder to best resist bending. The metaphyseal region of the long bones flares to increase the bone volume and surface area in a manner that minimizes the stress of joint contact. The cancellous tissue in this region provides an intricate network that distributes weight-bearing forces and joint reaction forces into the bulk of the bone tissue [2–4]. **Figure 1** shows a schematic diagram of a typical human bone, showing its detailed composition as well as the various types of bone.

If fractured or damaged, hard tissues are either left to self-heal, depending on the extent of the fracture or replaced partially or totally by an implant. **Figure 2** shows the mechanism of self-healing of fractured bone. However, surgical intervening is mostly required to ensure proper fixation of the fractured bone and avoid future health consequences. In this regard, natural or synthetic materials, also known as biomaterials, are often used to partially or totally fix the fractured bone. The term “biomaterials” is used to indicate materials that constitute parts of medical implants, extracorporeal devices, and disposables utilized in medicine, surgery, dentistry, veterinary medicine, and in every aspect of patient health care [5, 6].

Biomaterials can be generally divided into three main categories that are regulated by tissue reaction. In basic context, inert materials (more narrowly, almost inert) preclude no or minimal tissue reaction. Active materials enhance bonding to surround tissue by promoting, for example, new bone formation. In the underlying tissue, degradable or resorbable materials are introduced or can even dissolve completely over a period. Commonly, metals are inert, ceramics may be inert, active or resorbable, and polymers may be resorbable or inert. The main property required of a biomaterial is that it does not elicit an adverse reaction when placed into service. In addition to biomaterials used for partial or total fixation of the fractured bone, an additional class of materials known as “bone cements” is also used for stand-alone

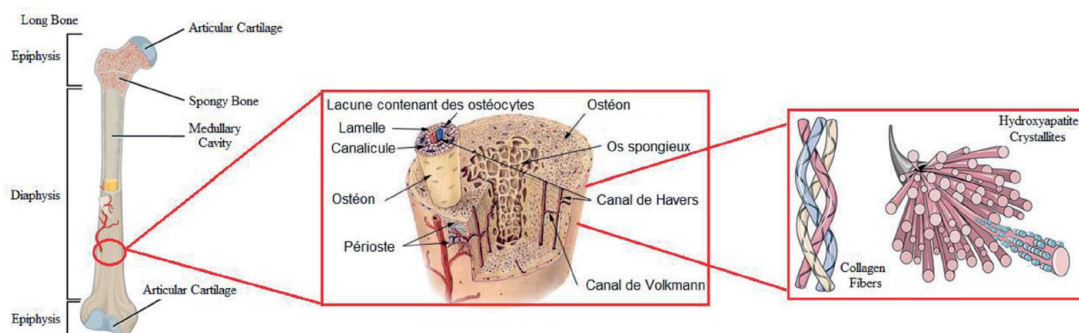


Figure 1.
Detailed structure of a typical human bone.

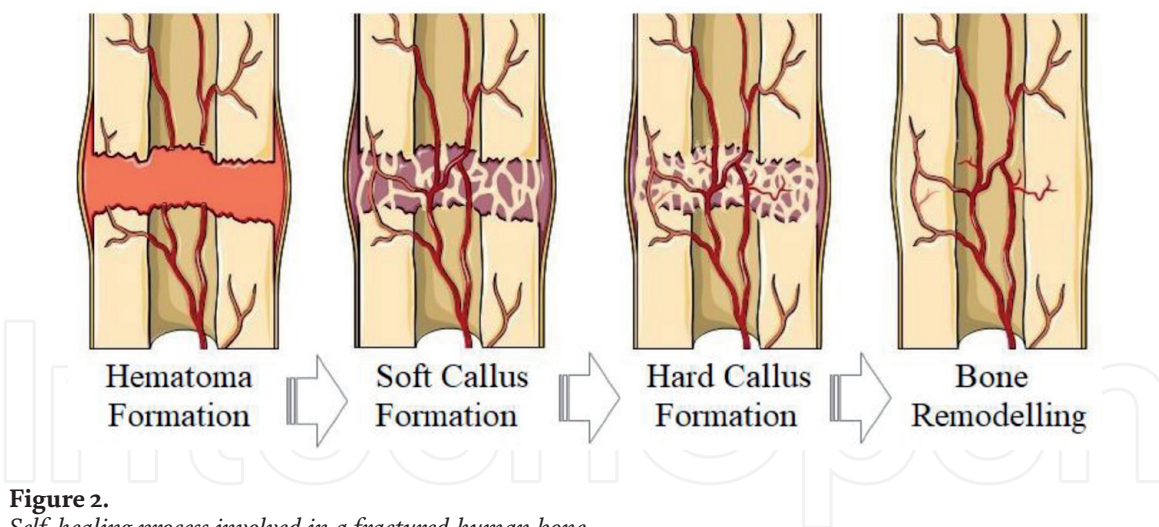


Figure 2.
Self-healing process involved in a fractured human bone.

fixation of the fractures bone or as an auxiliary material with other biomaterials to help in the fixation process. More details about bone cements will be discussed in the following sections.

2. Bone cements

By definition, bone cements are biomaterials that are obtained by mixing a powder phase with a liquid phase, forming a paste that can solidify into a final set product upon implantation within the body [7]. Bone cements are highly characterized by the ability to be injected in the body, extending their application to minimally invasive surgical applications [7]. The first known bone cement is poly(methyl methacrylate) (PMMA), which was used in 1940s as a bone filler to close fractures and defects in the skull [8]. PMMA was also used to fix total hip arthroplasty replacement components, similar to a total hip replacement [9]. This process takes place through the in-situ polymerization of the PMMA; hence a set product is formed.

Biocompatible polymeric bone cements are further classified as bioinert, bioactive, or biodegradable depending on their composition. However, none of them possesses a similar chemical composition to that of natural hard tissues. Accordingly, non-polymeric bone cements were investigated. These include calcium phosphate cements, as well as gypsum-based cements [10]. These cements are based on formulations that are composed of the mineral powder and an aqueous liquid. Their blending results in the hydration of the powder and the instant chemical transformation to the final set product [10].

2.1 Gypsum bone cements

Gypsum is one of the first used biomaterials. It is a common non-metallic mineral consisting of hydrated calcium sulfate ($\text{CaSO}_4 \cdot 2\text{H}_2\text{O}$). It crystallizes in the monoclinic system in white or colorless crystals; Gypsum is formed through the hydration of its hemihydrate precursor (Plaster of Paris; POP) according to Eq. (1):



This reaction can take place at room temperature. A two-phase suspension of hemihydrate particles in a saturated aqueous solution is formed as the hemihydrate dissolves. Crystals nucleate in the suspension as the solution becomes super-saturated with dihydrate and form a precipitate. Until the solution is no longer

saturated, nucleation and crystal formation proceed, leading to the further dissolution of the hemihydrate. Alternative dissolution and precipitation keep, with the growth of existing crystals or nucleation of new crystals [11].

The transformation of POP to gypsum is often followed by simple characterization techniques, such as x-ray diffraction (XRD), infrared spectroscopy (IR), and scanning electron microscopy (SEM). **Figure 3** shows a comparison between the XRD patterns (3a), IR spectra (3b), and SEM micrographs of POP and gypsum phases. POP is characterized by its XRD peaks at 2θ values of 14.79, 25.48, 29.34, 29.77, 31.84, 33.03, 38.46, 39.77, 41.34, 42.31, 45.36, 47.64, 48.66, and 49.32° ; as shown in **Figure 3a**. Gypsum, on the other hand, is characterized by its XRD peaks at 2θ values of 11.64, 20.76, 23.43, 25.48, 28.19, 29.17, 31.13, 32.16, 33.35, 34.61, 36.02, 36.611, 37.38, 40.69, 42.20, 43.40, 44.27, 45.57, 46.49, 47.06, and 48.51° ; as shown in **Figure 3a**. These peaks were in accordance with their standard XRD cards 01–0999, and 33–0311 for gypsum and POP phases, respectively.

Figure 3b shows the IR spectra of POP and gypsum solid powders. Both POP and gypsum have water of crystallization, $\frac{1}{2}\text{H}_2\text{O}$ in POP, and $2\text{H}_2\text{O}$ in gypsum. This was shown in the IR spectra as relatively broad bands with medium-strong intensities. Both appeared as a doublet at 3549.7 and 3607 cm^{-1} [12]. In the IR spectrum of gypsum, more broadness of this assembly was observed, extending its absorption to have a broad shoulder at 3416 cm^{-1} [12]. These differences are attributed to the difference in the proportion of water of crystallization in the two phases. Sulfate ions are shown in these phases' patterns at four places; a sharp strong intensity doublet at 604 and 656 cm^{-1} , a relatively broad but very strong band with a peak at 1143.9 cm^{-1} , and a medium intensity sharp band at 1630.9 cm^{-1} [12]. All four bands appeared with almost the same intensity in the two IR spectra of POP and gypsum.

The microstructure of POP and gypsum powders is shown in **Figure 3c,d**. POP phase is known to exist in the form of irregular shaped crystals with a polydisperse particle size distribution, as shown in **Figure 3c**. Upon reaction with water and formation of gypsum, the dissolution-precipitation mechanism by which reaction proceeds results in the formation of smaller crystallites with a more uniform size distribution, as shown in **Figure 3d**.

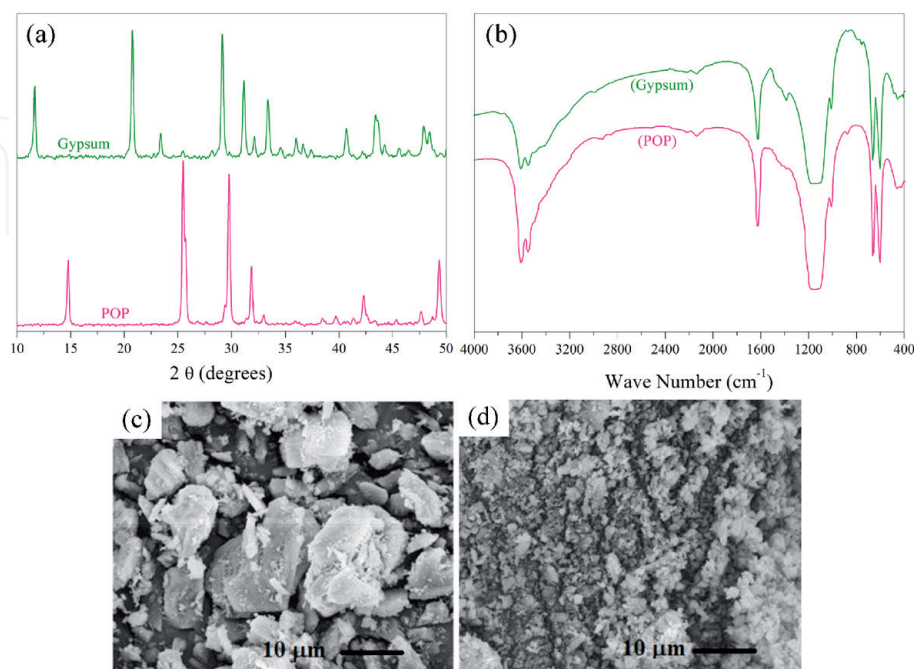


Figure 3. Physico-chemical characterization of gypsum and POP: (a) X-ray diffraction analysis, (b): Fourier-transformed infrared spectroscopy, Scanning electron micrographs of (c) POP and (d) gypsum powders.

There are two varieties of the gypsum hemihydrate form, α - and β -, which differ in crystal size, surface area, and lattice imperfections. While these materials are chemically similar, their physical properties vary considerably. The dental stone from which diagnostic casts is the α -hemihydrate type. When compared to the β -hemihydrate, it is very difficult and relatively insoluble. The β -hemihydrate is distinguished by an aggregate of interstitial capillary pores of abnormal crystals, while the α -hemihydrate comprises cleavage fragments and rod and prism-shaped crystals [13]. The α -form needs much less water than the β -form (0.3 versus 0.6 g/g of hemihydrate, respectively) due to their various particle characteristics. As a result, the α -form results in a super thick, heavier and less soluble dihydrate than the β -form [11]. The formed gypsum exhibits a layered structure with the water molecules alternating with calcium sulfate layers explaining this mineral's easy cleavage [14], as shown in **Figure 4**. The hemihydrate has the water molecules arranged in channels between chains of calcium sulfate. It explains the ease with which this compound can lose most of its coordinated water without disrupting the structure.

Gypsum as one of the oldest known construction materials today is manufactured in a huge amounts for renders, plasters, indoor finishing, retardants for cement, ceramics, and medical supplements or implants [15–20]. The wide applications of gypsum plaster are primarily based on its unique properties, e.g., setting time, suitable workability, and volume stability. However, some disadvantages appear when neat gypsum plaster is used, where a relatively high amount of water is required for mixing. The setting time may accordingly be too long, and as a result, it adversely affects the set product's mechanical properties. These properties are merely developed by introducing other ingredients to form what is known as gypsum composites as an attempt to improve the plaster properties.

Gypsum is a highly biocompatible material that is one of the simplest synthetic bone graft materials with the longest clinical history, spanning more than 100 years [21]. It is classified as a bioresorbable material. It has been used effectively for the treatment of periodontal disorders, endodontic lesions, alveolar bone loss and augmentation of the maxillary sinus [21]. It has also been used to promote healing and stop failure of the grafting material as a binder. In addition, it is tissue compliant and does not interfere with the process of healing [22]. At rates as high as 1 mm per week, Ricci et al. [23] observed a rapid rate of dissolution of both in vitro and in vivo gypsum from the outer surface inwards. Despite this dissolution, they reported

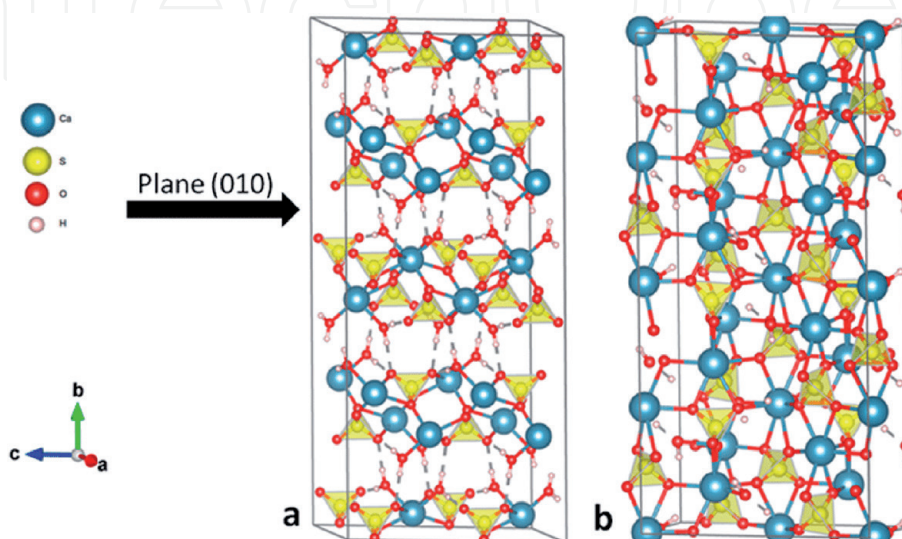


Figure 4.
 Crystal structure of (a) gypsum, and (b) POP phases [14].

that while bone was not observed to come into direct contact with gypsum, gypsum stimulated new bone formation. The formed bone took the shape of concentric rings in surrounding tissue, and histologically, these deposits stain like bone mineral and often showed attachment of osteoid and new bone [23].

2.2 Biomedical applications of gypsum bone cements

Gypsum and its precursor; POP, have been used as bone void fillers for more than a century [24]. Kelly et al. in 2001 used Osteosets (surgical grade calcium sulfate, Wright Medical Technology, Arlington TN) to fill bone defects caused by benign bone tumors, trauma, cyst, etc. [25]. They concluded that surgical grade calcium sulfate is reliable, convenient, safe, and readily available bone graft substitute that yields consistent results [25]. Osteosets, Borrelli et al. [26] successfully treated non-union osseous defects caused by trauma with a combination of autogenous iliac bone and Osteoset using the same surgical-grade gypsum. In 2005, Chen et al. concluded that, as an artificial bone expander with a fair fusion rate, surgeons may use calcium sulfate combined with locally harvested morselized bone [27].

Lazary et al. showed that MC3T3-E1 osteoblastic mouse cells placed on a gypsum disc expressed genes that are relevant in the formation of new bones in a way that is different and better than poly(methyl methacrylate) (PMMA), which is a typical bone void filler [28]. They also concluded that a more effective bone repair environment was created by gypsum. Because of its unique crystal structure and high calcium content, it is also chosen to have the potential for osteoinductivity [27, 28]. In addition to the above-mentioned characteristics, Rohmiller et al. suggested gypsum as a cement for lumbar pedicle screw fixation [29]. They found it more promising than PMMA, in particular because, unlike the exothermic hardening of PMMA [29], no heat forms during its framework. In a parallel study, it was found that cells plated on gypsum disc express genes important in new bone formation with different expression ratios compared to PMMA, generally used as a bone void filler, suggesting that gypsum provides a more efficient environment for bone repair. These findings indicate that gypsum possess a potential Osteoinductivity, as a result of its special crystal structure and high calcium content [30].

Properties and applications of gypsum-based bone cements were also enhanced through the inclusion of various types of additives; natural or synthetic and inorganic or organic. One of these additives' main objectives is to improve the bioactive and mechanical properties of gypsum as a bone cement so that its biomedical applications are further extended. One of the first reports about the use of additives to gypsum was shown by Sanad et al. in 1982, where a combination of calcium oxide (CaO) and gum Arabic was found to enhance the mechanical properties of gypsum [31]. This was related to lime (CaO) precipitation in the hydration and setting processes of POP, while the gum Arabic acted as a gluing matrix [31].

One of the effective approaches to modulating the mechanical properties of gypsum [32–35] has been considered to be the blending of gypsum with polymers. The presence of such functional groups, such as hydroxyl and carboxyl groups, on these polymers is often preferred. These were found to connect with the gypsum products set together with the calcium sites. In general, polymers that do not have these groups are passive during the gypsum setting reaction. However, the mechanical interlocking of these polymers with the gypsum crystals collected improves the overall mechanical performance of the composites made. For biomedical applications, polymers used with gypsum should be biocompatible to avoid rejection by the human immune system. Different polymers could be used in this regard, ranging from bioactive to bioinert, depending on the application type and site. El-Maghraby et al. evaluated gypsum composites with poly(vinyl alcohol) and

its copolymers with vinyl acetate and itaconic acid [36]. They concluded that the presence of carboxylic acid-groups along the polymeric ingredients enhanced the mineralization ability of the produced composites. In another study, a novel injectable, photo-cross-linkable PCL/calcium sulfate system has been developed to overcome calcium sulfate brittleness and fast resorption rate enhancing its performance in bone regeneration techniques [37]. Moreover, the addition of viscous polymers, such as Carboxymethylcellulose (CMC), and hyaluronan, improved the handling characteristics and mechanical properties of the CS [38, 39]. Gelatin was also used as a natural additive to a mixture of gypsum and POP, which result in the formation of a porous scaffold upon setting [40]. This novel composite system showed high potential in tissue engineering applications [40]. Mineralization of a gypsum-PLLA composite bone cement indicated that the material may be osteoconductive. Both gypsum and PLLA are classified as bioresorbable biomaterials. Therefore, their composite bone cement can be designed in such a way that its overall degradation can be controlled [41, 42].

2.3 Resorption of gypsum bone cement

Gypsum is classified as a resorbable biomaterial. This characteristic does not interfere with its wide application as a bone cement, where the resorption of gypsum cement after implantation could be controlled to match the fixation of the fractured bone and the subsequent bone formation. The resorption of gypsum has been studied by various authors. Randolph et al. patented the ideas of having it in the form of pellets that will release certain ingredients upon dissolution [43–45]. Besides, Hanker et al. patented the gypsum resorption concept for the repair of damaged bone [46]. Doadrio et al. developed a gypsum-based cement and used it to deliver an antibiotic; cephalexin [47]. The inclusion of this drug was shown not to affect the structural composition or the physicochemical properties of gypsum [47].

Despite the benefit of gypsum bioresorption, which makes it an appealing candidate for particular applications, its relatively low mechanical properties have limited its scope of use as a bone replacement implant or even as bone cement. To boost its mechanical properties, various materials were mixed with gypsum; what is referred to as biphasic composites [48]. POP has often been mixed with various ceramic and polymeric ingredients to form gypsum composites there from.

On the other hand, the expedited sorption rate of gypsum can be reduced significantly through the use of various additives, particle/bead size, and sintering techniques of the ready-made gypsum made biomaterials. It was shown that the degradation rate of sintered CS specimens can be adjusted through the introduction of pores. Through various techniques, the introduction of spherical pores with amounts ranging from 6.7 to 68% into sintered CS specimens was reflected on a corresponding variable degradation rate in Hank's solution in the range of 1.9–7.7%/day [49]. Upon using different-sized calcium sulfate beads, their ability to elute multiple antibiotics in vitro was observed, as a possible method to improve the therapeutic delivery in patients [50].

2.4 Intrinsic bioactivity of gypsum bone cements

Preliminary evaluation of biomaterials, implants, and cements is intended to be in a closer contact with hard tissues, occurs through the study of the bone-like apatite formation and growth ability of the potential biomaterials. This process is also termed “biomimetic”, where bone-like apatite formation and growth resembles the natural mineralization of collagen in nature, which takes place during the continued bone formation process with time. This process was discussed in details in a

previous work by Hafiz Uddin et al. [51] and was first recognized and established by Kokubo et al. in 1981 and reported in 1990 [52].

The hypothesis behind this approach is to mimic the biomineralization process where Ca^{2+} and PO_4^{3-} ions deposit in the form of apatite nanocrystallites onto certain nucleation sites along the collagen nanofibers. These nucleation sites are the functional groups along with the various amino acids within the collagen fibrils, such as -OH, -COOH, and -NH₂ groups. Accordingly, biomaterials that possess any of these groups upon the immersion of a simulated body fluid (SBF), will undergo a similar mechanism resulting in the deposition of bone-like apatite spherulites, which were shown to contain apatite nanocrystallites. Protein-free SBF media contain ions with concentrations similar to those in the human blood plasma, and are supersaturated with respect to stoichiometric HAp (Ca/P 1.67). **Table 1** shows a detailed composition of a typical SBF solution.

The mechanism of biomimetic deposition of bone-like apatite takes place at a physiologic pH and temperature through the instant gravitation and binding of the Ca^{2+} ions from the solution onto the surface functional groups, followed by the attachment of the PO_4^{3-} ions, hence nuclei of bone-like HAp are formed. Upon continued immersion in SBF, these nuclei further grow and adopt a typical bone-like apatite morphology. **Figure 5** shows a schematic representation of the apatite formation's biomimetic process onto OH-carrying biomaterial surfaces, such as silicate-containing implants.. Similarly, biomaterial surfaces that provide these functional groups were widely explored for the biomimetic formation of nanostructured bone-like apatite.

Gypsum, as a final set product, was also investigated in our laboratories for its affinity towards the biomimetic deposition of bone-like HAp [36, 53]. In a typical experiment, gypsum samples were immersed in a freshly prepared SBF medium and maintained at a physiologic temperature of 37.4°C for up to 2 weeks. Aliquots were collected at various time intervals to study the variation of the most relevant ions; Ca^{2+} , PO_4^{3-} , and SO_4^{2-} , in the medium as a function of time. Dry samples at the end of the 15-days experiment were collected and studied by scanning electron microscopy for the variation of its surface morphology. **Figure 6** shows typical SEM micrographs of a SBF-treated gypsum sample (**b**), compared to a pristine gypsum sample (**a**). Upon further treatment of the SBF-treated gypsum sample in a more concentrated SBF solution (1.5X), further growth of the deposited apatite nanostructured spherulites were shown with a more detailed bone-like morphology as shown in **Figure 6c**. Elemental analysis of the nanostructured spherulites indicated the presence of Ca and P peaks that confirmed the identity of the deposited apatite [36, 53].

In a typical SBF experiment, both Ca^{2+} and PO_4^{3-} ions are leached out from solution as a result of initially being supersaturated with respect to these ions. This process results in the precipitation of the corresponding nanostructured bone-like apatite spherulites. Chemical analysis of these ions with time usually confirms these findings. However, the immersion of pure gypsum in SBF for up to 15 days

Type of solution	Concentration (mM)							
	Na ⁺	K ⁺	Ca ²⁺	Mg ²⁺	HCO ₃ ⁻	Cl ⁻	HPO ₄ ²⁻	SO ₄ ²⁻
SBF	142.0	5.0	2.5	1.5	4.2	148.0	1.0	0.5
Blood plasma	142.0	5.0	2.5	1.5	27.0	103.0	1.0	0.5

Table 1.
 A detailed composition of a typical SBF solution, compared with a blood plasma [52].

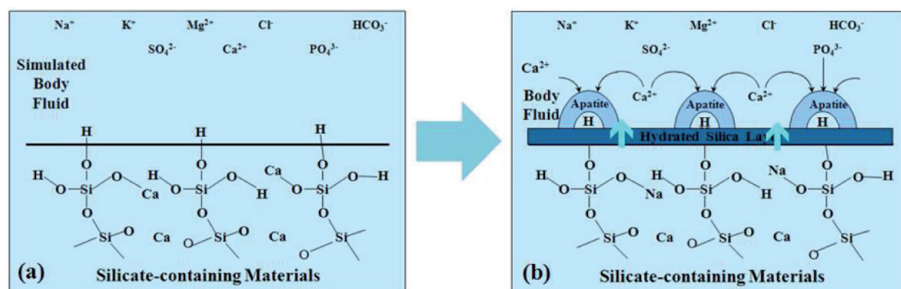


Figure 5.
A schematic representation of the mechanism of biomimetic deposition of bone-like apatite spherulites on a typical silicate-based biomaterial; before (a), and after (b) immersion in a simulated body fluid.

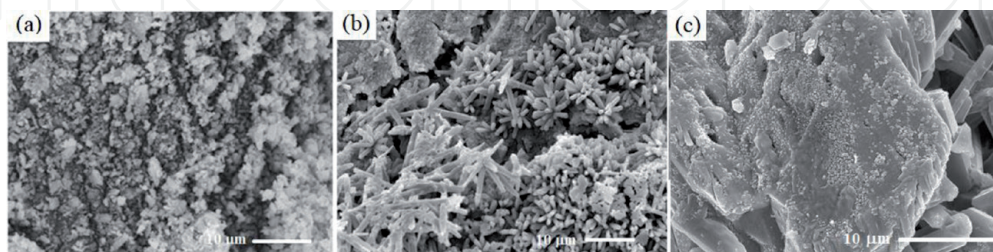


Figure 6.
Scanning electron micrographs of (a) set gypsum surface and nanotextured, bone-like apatite formation onto the surfaces of a set gypsum cement sample after immersion in (b) SBF and (c) 1.5 SBF media at 37°C.

showed the decrease of the concentration of the PO_4^{3-} ions with time, with an unexpected increase in the concentration of the Ca^{2+} ions, as shown in **Figure 7** [53]. To explain this behavior, the concentration of SO_4^{2-} ions were also analyzed and was also proven to show a continued increase with time. The combined increase in the concentrations of Ca^{2+} and SO_4^{2-} ions with time was attributed to gypsum's bioresorbable nature. It is believed that the process of biomimetic mineralization of gypsum takes place through a combined mechanism of dissolution (via resorption) of gypsum crystal surfaces and the subsequent release of Ca^{2+} and SO_4^{2-} ions into solution. This is followed by an abrupt increase in the supersaturation of the SBF medium with respect to Ca^{2+} and PO_4^{3-} ions and their eventual precipitation in the form of the nanostructured bone-like apatite spherulites. Gypsum bone cement with biomimetically grown nano-textured apatite was successfully used as a drug delivery vehicle in addition to its cementation effect. This is attributed to the add-value of the nanotextured apatite spherulites that can be used as drug carriers, where the sorption of gypsum cement results in the slow release of the drugs. An example was shown in the sustained release cephalexin and gentamicin from both pure calcium sulfate and nanocomposite cements into SBF, which was demonstrated in the work of Hesarakı et al. [54].

2.5 Nano-textured gypsum bone cements with enhanced bioactivity

In addition to the intrinsic bioactivity of pristine gypsum bone cements and its ability to form bone-like nano-textured apatite on its surfaces, these bioactivity indicators were further enhanced through the inclusion of bioactive fillers. These include calcium phosphates, which are known for their structural similarity to bone apatite, and calcium silicates, which were the first candidates to show an enhanced affinity to grow bone-like nanotextured apatite spherulites in SBF media [55–62]. In addition, POP-based biomaterials have also exhibited promise as grafts in a pre-clinical repair model of intrabony periodontal defects, as well as in clinical reports for sinus augmentation and treatments of femoral shaft non-unions [60–62].

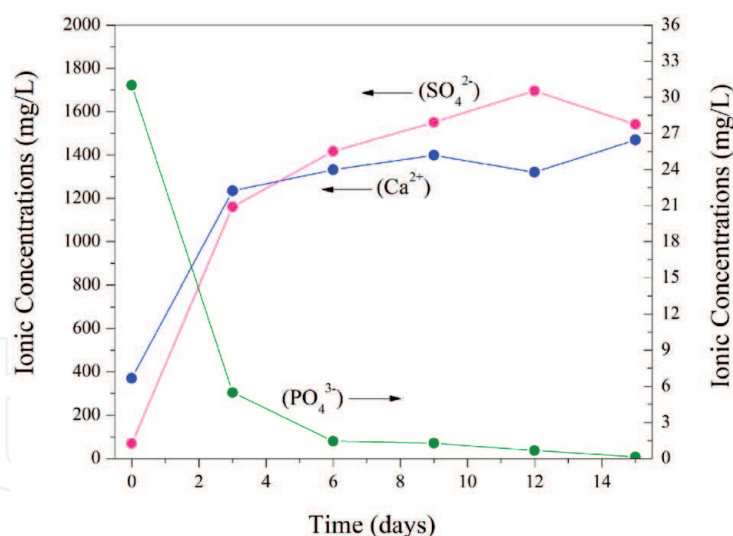


Figure 7.

Variation of the ionic concentrations of Ca^{2+} , PO_4^{3-} , and SO_4^{2-} ions in SBF media with time as a result of immersion of gypsum samples for up to 15 days at 37°C.

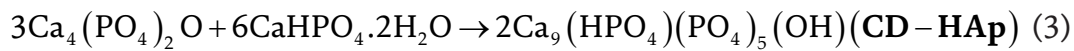
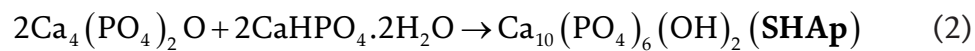
2.6 Calcium phosphate-doped gypsum bone cements

POP was applied to enhance the setting reactions of a biodegradable calcium phosphate cement that was composed of β -tricalcium phosphate (β - $Ca_3(PO_4)_2$; β -TCP) and monocalcium phosphate monohydrate ($Ca(H_2PO_4)_2 \cdot H_2O$; MCPM) [56] due to its relatively faster setting process. These composites of cement have been shown to be osteo-conductive [56]. The setting time, workability, and porosity of a cement composed of an aqueous slurry of β -TCP [57] were also modulated using POP. When combined with β -TCP, Nilsson et al. [58] realized the essential function of gypsum, helping to create pores in the implanted material, thereby ensuring the growth of new bone tissue. The use of β -TCP in a CS matrix produced significantly more vital new bone fill and preserved bone dimensions than β -TCP alone [59]. Composite bone cement was also made of gypsum and granules of β -TCP, and dicalcium phosphate dihydrate, and were shown to have a greater bone filling ability than did pure gypsum cement [60]. Moreover, the physical properties of the bone regenerated with the CS/CP composite were similar to or greater than native bone [60].

Combinations of ready-made HAp particles with gypsum were also evaluated. Sato et al. indicated the promising characteristics of gypsum after mixing it with HAp particles, based on the relatively fast absorption of gypsum without interfering with bone healing [48]. Cabanas et al. concluded that for a paste of calcium sulfate-calcium phosphate cements to be injected percutaneously using a syringe or implanted operatively, it was essential to control parameters such as working time, setting time, or thermodynamic behavior [61]. It was also shown by Guo et al. that a calcium phosphate-doped gypsum bone cement has a controlled setting time within the range of 5–20 min., and the material can easily be molded before setting [62]. A novel HAp-gypsum-POP cement system was successfully used as a reservoir for the delivery of growth factor-beta 1 (TGF-1) and vascular endothelial growth factor (VEGF) [63].

Two novel dual-setting apatite-gypsum bone cements were studied, in which the setting reaction of POP and its transformation to gypsum was combined with the setting reaction of apatitic calcium phosphate precursors [64, 65]. These precursors normally react with water at room temperature through an acid–base reaction

leading to the formation of calcium phosphate bone cements with various degrees of stoichiometry, as shown in Eqs. (2) and (3):



As observed in both cases, the findings showed a remarkable delay in the growth kinetics of gypsum, with different extensions depending on the starting Ca/P molar ratios of the apatite and its proportion in the composites. The synthetic version of Ca-def apatite's bioresorbability also revealed its retardation effect on the formation of gypsum. An overall near-physiological pH regimen was obtained by mixing POP in their solutions with each of the Ca-def apatites [64]. However, variations in the pH of the studied solutions showed the effect of POP on decreasing the alkalinity of the media containing SHAp precursors [65].

Fabrication of osteoconductive scaffold with osteoinductive capability and appropriate resorption rate was also achieved through the introduction of Strontium in the crystal structure of gypsum as well as the combined effect of HAp. Together, Sr-gypsum/HAp was shown to promote bone formation by recruiting and stimulating osteogenic differentiation of BMSCs [66].

2.7 Calcium silicate-doped gypsum bone cements

Silicate-based materials have been proven to possess an excellent affinity towards the biomimetic deposition of nano-textured bone-like apatite spherulites in SBF media. Accordingly, they were considered bioactive, and their inclusion in the formation of composite biomaterials is highly believed to lead to enhancement of the bioactivity of the biomaterials produced thereof. Accordingly, silicates were considered potential candidates to be added to gypsum bone cements to further enhance their bioactivity. Silicate-based materials; either crystalline or amorphous, could be used in this regard as they share the mechanism of biomimetic deposition of apatite when exposed to SBF media. In the work of Greish et al. [53], highly crystalline wollastonite fibers were added to gypsum bone cements in order to study their effect on the mechanical properties and bioactivity of the produced composite cement systems. Due to the silicate composition of the wollastonite fibers and the gypsum matrix's intrinsic bioactivity, both phases were shown to develop nano-structured apatite coatings onto their surfaces; **Figure 8a**. Furthermore, alkali-treated wollastonite fibers were shown to have an extensive formation of these apatitic coatings on its surfaces, as shown in **Figure 8b**. These novel cements provide a dual mechanism of biomimetic deposition of the bone-like spherulites, hence show an enhanced bioactivity as compared with pure gypsum cements [53]. Tricalcium silicate was also added to gypsum in the work of Huan et al. [67] to improve its handling and physical properties, in addition to improved mechanical properties. Furthermore, the composite made thereafter was also shown to have enhanced bioactivity and favorable resorption characteristics as compared with pure gypsum cement [67]. A ternary organic-inorganic composite bone cements of tricalcium silicate/sodium alginate/POP (C₃S/SA/POP) were successfully shown to exhibit good proliferation, excellent attachment, enhanced alkaline phosphatase activity, increased calcium deposition, and osteogenic-related gene expressions with growing calcium sulfate component [68].

In the course of 3D printing, POP was also supplemented with silicate materials. In order to boost the scaffold efficiency, a combined cement was integrated functionally

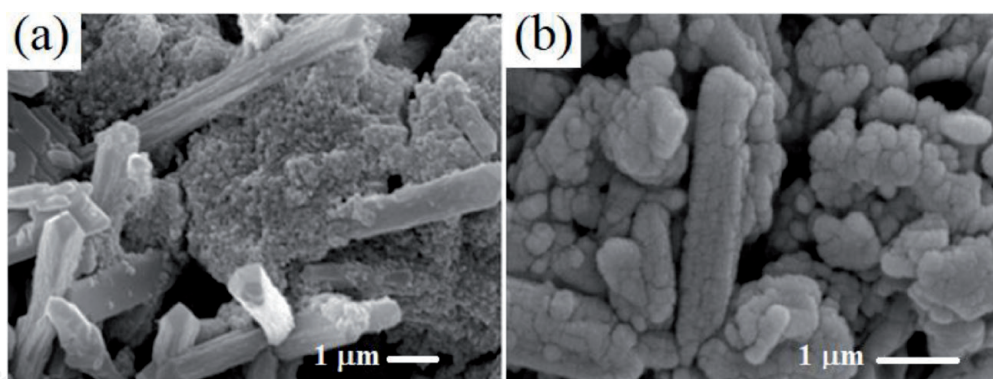


Figure 8. Scanning electron micrographs of gypsum cements containing a) pristine, and b) alkali-treated wollastonite fibers, after immersion in SBF media for 15 days at 37°C.

into mesoporous calcium silicate (MCS) via a 3D printing technique. Compared to printed MCS scaffolds, the characteristics showed that 20 percent CSH integration over 4 weeks of hydration increased their compressive strength by 2 times. Moreover, MCS component in the composite scaffolds exhibited sustained release behavior of dexamethasone drugs to assist bone regeneration [69]. Similarly, scaffolds made of POP and mesoporous bioactive glass (MBG) scaffolds successfully fabricated using a 3D printing technique, which had a regular and uniform square macroporous structure, high porosity and excellent apatite mineralization ability. Thus 3D printed POP/MBG scaffolds would be promising candidates for promoting bone regeneration [70].

3. Conclusions

Bone cements are widely used for the treatment of bone defects and fractures. Gypsum-based bone cements are characterized by their ease of preparation and affordability. Gypsum has been classified as a bioresorbable material. Moreover, our ongoing research has clearly shown a string evidence of its bioactivity where gypsum is mineralized in SBF media in a manner similar to that was initially proposed for the biomimetic growth of bone-like apatite on the surfaces of bioactive materials. Moreover, the inclusion of other biocompatible fillers further enhance its bioactivity. The biomimetically-grown bone-like apatite adopts the morphology of nanostructured spherulites which are made of apatite nanocrystallites. The overall assembly of nanostructured gypsum-based bone cements, therefore, represents a potential modality for the treatment of fractured bone with an enhanced bioactivity. Moreover, an added value of the improvement in the mechanical properties of these composite cements is highly believed to extend the applications of these cements to be used as bone implants for non-load bearing applications.

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Conflict of interest

The authors hereby declare the absence of any conflict of interest with other researchers and research entities.

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