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Calcium Orthophosphate ($CaPO_4$) Scaffolds for Bone Tissue Engineering Applications

Sergey V. Dorozhkin [1,*]

[1] Independent Researher

Abstract

The chemical and structural similarities of calcium orthophosphates (abbreviated as $CaPO_4$) to the mineral composition of natural bones and teeth have made them a good candidate for bone tissue engineering applications. Nowadays, a variety of natural or synthetic $CaPO_4$-based biomaterials is produced and has been extensively used for dental and orthopedic applications. Despite their inherent brittleness, $CaPO_4$ materials possess several appealing characteristics as scaffold materials. Namely, their biocompatibility and variable stoichiometry, thus surface charge density, functionality and dissolution properties, make them suitable for both drug and growth factor delivery. Therefore, $CaPO_4$, especially hydroxyapatite (HA) and tricalcium phosphates (TCPs), have attracted a significant interest in simultaneous use as bone grafts and drug delivery vehicles. Namely, $CaPO_4$-based three-dimensional (3D) scaffolds and/or carriers have been designed to induce bone formation and vascularization. These scaffolds are usually porous and harbor various types of drugs, biologically active molecules and/or cells. Over the past few decades, their application as bone grafts in combination with stem cells has gained much importance. This review discusses the source, manufacturing methods and advantages of using $CaPO_4$ scaffolds for bone tissue engineering applications. Perspective future applications comprise drug delivery and tissue engineering purposes.

Corresponding Author: Sergey V. Dorozhkin, Kudrinskaja sq. 1-155, Moscow 123242, Russia. E-mail: sedorozhkin@yandex.ru

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Introduction

Bones are organs and the living support structures that give the body form and shape. In the musculoskeletal system, bones act as the levers and pivots that control for direction and range of movement. Bones also function to protect our vital organs and act as a reservoir for critical vitamins and nutrients such as calcium. Bone tissues have an innate ability to remodel and regenerate themselves; however, when defects appear to be too large or when the normal repair process has been interrupted or disregulated, bones become unable to completely heal without external intervention [1].

In general, utilization of fixation devices and implants, such as fixation plates, intramedullary nails etc., often in combination with autografts/allografts and artificial bone substitutes appears to be the standard intervention strategy for complicated fractures. The benefits of using autografts are obvious. Briefly, they provide a matrix to support cell attachment and migration to generate new bone (osteoconductivity), contain growth factors and proteins that stimulate osteogenic differentiation (osteoinductivity), as well as contain live cells that act as a source for new bone formation (osteogenesis). A constraint of autografts is the limited availability of tissue, the frequent requirement of a second surgical site (e.g., iliac crest) and the subsequent risk of donor site morbidity. An alternative to autografts are allografts, which can be derived from donor patients or other species (that is xenografts, such as bovine bone chips). Allografts are more readily available and range from small bone chips to whole bone segments. As a result, allografts are osteoconductive, can be osteoinductive (if growths factors are preserved during the treatment process), but are not osteogenic due to lack of living cells. The complication rate and requirement for surgical revision have been reported to be significantly higher in bone allografts compared to autografts due to poor remodeling capability. In addition, there is a risk of disease transmission and immune reaction, associated with allografts [2].

Therefore, clinicians are looking to emerging fields, such as tissue engineering and clinical regenerative medicine, to overcome the limitations with current intervention strategies associated with complicated bone defects. Tissue engineering involves the use of scaffolds, biochemical factors or cells to restore the structure and function of tissues that have been damaged by disease or trauma. Within this field, bone tissue engineering is one of the most developed and deployed research areas [3].

The purpose of this review is to evaluate the role and impact of one particular subset of biomaterials in tissue engineering applications, namely: calcium orthophosphate ($CaPO_4$) scaffolds for hard tissue regeneration. The focus is on the recent developments of new formulations and their formation into scaffolds with the requisite anatomical shape and architecture. Methods that can be used to manipulate the materials structure and the variables that affect the materials performance in these applications are analyzed.

General Knowledge and Definitions

According to the available literature, the term "tissue engineering" first appeared in 1984 in a paper by Wolter and Meyer [4] to overcome the major limitations of tissue grafting. Further, it was officially coined in 1988 at a meeting of the U.S. National Science Foundation as "the application of the principles and methods of engineering and life sciences towards the fundamental understanding of structure/function relationships in normal and pathological mammalian tissues and the development of biological substitutes to restore, maintain or improve functions" [5]. Thus, this field of science started more than two decades ago [6, 7] and the famous publication by Langer and Vacanti [8] has greatly contributed to the promotion of tissue engineering research worldwide. Since then, the better definitions for tissue engineering have been sought and the following ones were proposed by Prof. David Williams (that time he was the Editor-in-Chief of Biomaterials journal) in 1999 and 2008, respectively: "The persuasion of the body to heal itself, through the delivery to the appropriate sites of molecular signals, cells and/or supporting structures" (1999) and "Tissue engineering is the creation of new tissue for the therapeutic reconstruction of the human body, by the deliberate and controlled stimulation of selected target cells through a systematic combination of molecular and mechanical signals" (2008) [9].

Tissue engineering may be achieved through several different routes but there is a basic paradigm of ex vivo tissue regeneration, which may serve as a template, in which there is a progression from cell sourcing through cell manipulation and signaling to tissue expression and construct formation, followed by implantation into the host and its full incorporation into that host. In the centre of this paradigm is the seeding of the required cells into a biomaterial scaffold or matrix, wherein they produce the new tissue. Usually, although not necessarily, the biomaterial is required to degrade or dissolve as the new tissue forms [9].

Nevertheless, tissue/organ repair has been the ultimate goal of surgery from ancient times to nowadays [10, 11]. The repair has traditionally taken two major forms: tissue grafting followed by organ transplantation and alloplastic or synthetic material replacement. Both approaches, however, have limitations. Grafting requires second surgical sites with associated morbidity and is restricted by limited amounts of material, especially for organ replacement. Synthetic materials often integrate poorly with host tissue and fail over time due to wear and fatigue or adverse body response [12]. In addition, all modern orthopedic implants lack three of the most critical abilities of living tissues: (i) self-repairing; (ii) maintaining of blood supply; (iii) self-modifying their structure and properties in response to external aspects such as a mechanical load [13]. Needless to mention, that bones not only possess all of these properties but, in addition, they are self-generating, hierarchical, multifunctional, nonlinear, composite and biodegradable; therefore, the ideal artificial bone grafts must possess similar properties [14].

Bone substitute materials can be defined as "a synthetic, inorganic or biologically organic combination – biomaterial – which can be inserted for the treatment of a bone defect instead of autogenous or allogenous bone" [15]. This is a broad definition and a variety of materials have been used over time to substitute or generate bone tissue. In order to be ultimately applicable in the human body, one of the key requirements is that the bone substitute materials must be non-carcinogenic, non-toxic, non-teratogenic and possess a high cell and tissue biocompatibility (ability of a material to perform with an adequate response in a specific application). Since the inorganic part of bones and teeth of mammals consist of $CaPO_4$ of biological origin, synthetically manufactured $CaPO_4$ (a list of the known $CaPO_4$, including their standard abbreviations and major properties, is summarized in Table 1 [16, 17]), appear to fulfill all these requirements.

In 2007, a "diamond concept" of bone tissue engineering was proposed as a "standard tissue engineering approach to provide solutions for impaired fracture healing, bone restoration and regeneration" [18, 19], which has become widely accepted and acknowledged in the field of bone tissue engineering. According to this concept, the ideal bone tissue engineering approaches should utilize an osteoconductive (i.e., guiding bone ingrowth) three-dimensional (3D) structure (e.g., scaffold, matrices), contain osteogenic (i.e., bone forming) cells and osteoinductive (i.e., inducing bone formation) factors, but must also have sufficient mechanical properties and promote vascularization. Since cells and osteoinductive factors do not contain $CaPO_4$, let me discuss scaffolds only.

According to Wikipedia, the free encyclopedia, a term "scaffold" has several definitions depending on the specific application. For example, in construction, it is "a temporary structure that supports workers and equipment above the ground or floor". In chemistry, it is "a structure that is used to hold up or support another material, such as a drug, crystal or protein". In tissue engineering, it is "an artificial structure capable of supporting three-dimensional tissue formation" [20]. In spite of the differences, all these definitions contain the meaning on "a structure that supports", which is the key. Since bone substitute materials are always implanted, the bone grafting scaffolds must be manufactured from the materials, which are well tolerated by the human bodies, among which $CaPO_4$ appear to be most promising candidates.

Scaffolds and their Major Properties

Since the shortage of donor tissues or organs appears to be the biggest issue for organ transplantation, it would be very convenient to both patients and physicians if devastated tissues or organs

Table 1. Existing calcium orthophosphates and their major properties [16, 17].

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

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

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

[c] Stable at temperatures above 100°C.

[d] Always metastable.

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

[f] Existence of OA remains questionable.

of patients can be regenerated by simple cell injections to the target sites. Unfortunately, such cases are rare. The majority of large-sized tissues and organs with distinct 3D form require a support for their formation from cells. The support is called scaffold, template and/ or artificial extracellular matrix [21-28]. The major function of scaffolds is to balance temporary mechanical functions with mass transport to aid biological delivery and tissue regeneration [12]. Thus, scaffolds play a role of temporary extracellular matrixes and assist proliferation, differentiation and biosynthesis of cells on the surface of their own. In addition, scaffolds placed at the regeneration sites prevent disturbing cells from invasion into the sites of action [29, 30]. However, for the future of tissue engineering, the term 'template' might become more suitable because, according to David F. Williams, the term scaffold "conveys an old fashioned meaning of an inert external structure that is temporarily used to assist in the construction or repair of inanimate objects such as buildings, taking no part in the characteristics of the finished product." [31, p. 1129].

Therefore, the idea behind tissue engineering is to create or engineer autografts by either expanding autologous cells in vitro guided by a scaffold or implanting an acellular template in vivo and allowing the patient's cells to repair the tissue guided by the scaffold. The first phase is the in vitro formation of a tissue construct by placing the chosen cells and scaffolds in a metabolically and mechanically supportive environment with growth media (in a bioreactor), in which the cells proliferate and elaborate extracellular matrix. It is expected that cells infiltrate into the porous matrix and consequently proliferate and differentiate therein [32, 33]. In the second phase, the construct is implanted in the appropriate anatomic location, where remodeling in vivo is intended to recapitulate the normal functional architecture of an organ or a tissue [34, 35]. The key processes occurring during both in vitro and in vivo phases of the tissue formation and maturation are: (1) cell proliferation, sorting and differentiation, (2) extracellular matrix production and organization, (3) biodegradation of the scaffold, (4) remodeling and potentially growth of the tissue [36].

To achieve the goal of tissue reconstruction, the scaffolds (templates) must meet a number of the specific requirements [21, 27, 31]. First, for an appropriate use in the human body, all scaffolds need to be made from highly biocompatible materials that do not elicit any adverse permanent immune responses in the host tissue after local implantation. The potential group of biomaterials comprise bioceramics, biodegradable polymers and their biocomposites [37]. Further, a reasonable surface roughness is necessary to facilitate cell seeding and fixation [38-43]. In addition, artificial scaffolds must bond to the host tissues without formation of any type of scar tissues, creating a stable interface. A high porosity and an adequate pore dimensions (Table 2) are very important to allow cell migration, vascularization, as well as a diffusion of nutrients [44, 45]. A sufficient mechanical strength and stiffness are mandatory to oppose contraction forces and later for the remodeling of damaged tissues [46, 47]. A French architect Robert le Ricolais (1894 – 1977) stated: "The art of structure is where to put the holes". Therefore, to enable proper tissue ingrowth, vascularization and nutrient delivery, scaffolds should have a highly interconnected porous network, formed by a combination of macro- and micropores, in which more than ~ 60 % of the pores should have a size ranging from ~ 150 μm to ~ 400 μm and at least ~ 20 % should be smaller than ~ 20 μm [44, 45, 48-56]. What's more, the entire geometry of porous scaffolds appears to significantly influence the cellular response and the rate of bone tissue regeneration. Namely, rates of tissue generation were found to increase with curvature and appeared to be much larger on concave surfaces as compared to convex and planar ones [57]. In addition, scaffolds must be manufactured from the materials with controlled biodegradability and/or bioresorbability, such as $CaPO_4$, so that a new bone will eventually replace the scaffold [23, 50, 58]. Furthermore, the degradation by-products of scaffolds must be non-cytotoxic. More to the point, the resorption rate has to coincide as much as possible with the rate of bone formation (i.e., between a few months and about 2 years) [59]. This means that while cells are fabricating their own natural matrix structure around themselves, the scaffold is able to provide a structural integrity within the body and eventually it will break down leaving the newly formed tissue that will take over the

Table 2. A hierarchical pore size distribution that an ideal scaffold should exhibit [45].

Pore sizes of a 3D scaffold	**A biochemical effect or function**
< 1 µm	Interaction with proteins
	Responsible for bioactivity
1 – 20 µm	Type of cells attracted
	Cellular development
	Orientation and directionality of cellular ingrowth
100 – 1000 µm	Cellular growth
	Bone ingrowth
	Predominant function in the mechanical strength
> 1000 µm	Implant functionality
	Implant shape
	Implant esthetics

mechanical load. However, one should bear in mind that the scaffold's architecture changes with the degradation process and the degradation by-products affect the biological response. Besides, scaffolds should be easily fabricated into a variety of shapes and sizes [60], be malleable to fit irregularly shaped defects, while the fabrication processes should be effortlessly scalable for mass production. In many cases, ease of processability, as well as easiness of conformation and injectability, such as self-setting $CaPO_4$ formulations possess [61], can determine the choice of a certain biomaterial. Finally, sterilization with no loss of properties is a crucial step in scaffold production at both a laboratory and an industrial level [23-25]. Thus, each scaffold (template) should fulfill many functions before, during and after implantation.

In order to achieve the desired properties at the minimum expenses, the production process should be optimized [62]. The main goal is to develop a high potential synthetic bone substitute (so called "smart scaffold") which will not only promote osteoconduction but also osteopromotion, i.e. the ability to enhance of osteoinduction [63]. In the case of $CaPO_4$, a smart scaffold represents a biphasic (HA/β-TCP ratio of 20/80) formulation with a total porosity of ~ 73 %, constituted of macropores (> 100 μm), mesopores (10 – 100 μm) and a high content (~ 40 %) of micropores (< 10 μm) with the crystal dimensions within < 0.5 to 1 μm and the specific surface area ~ $6m^2/g$ [64]. With the advent of $CaPO_4$ in tissue engineering, the search is on for the ultimate option consisting of a synthetic smart scaffold impregnated with cells and growth factors. Fig. 1 schematically depicts a possible fabrication process of such item that, afterwards, will be implanted into a living organism to induce bone regeneration [65].

To finalize this topic, one should mention on fundamental unfeasibility to create so-called "ideal scaffold" for bone grafting. Since bones of human skeleton have very different dimensions, shapes and structures depending on their functions and locations, synthetic bone grafts of various sizes, shapes, porosity, mechanical strength, composition and resorbability appear to be necessary. Therefore, bioceramic scaffolds of 0 to 15 % porosity are used as both ilium and intervertebral spacers, where a high strength is required, those of 30 to 40 % porosity are useful as spinous process spacer for laminoplasty, where both bone formation and middle strength are necessary, while ones of 40 to 60 % porosity appear to be useful for the calvarias plate, where a fast bone formation is needed (Fig. 2) [66]. Furthermore, defining the optimum parameters for artificial scaffolds is in fact an attempt to find a reasonable compromise between various conflicting functional requirements. Namely, an increased mechanical strength of bone substitutes requires solid and dense structures, while colonization of their surfaces by cells requires interconnected porosity. Additional details and arguments on this subject are well described elsewhere [67], in which the authors concluded: "there is enough evidence to postulate that ideal scaffold architecture does not exist." (p. 478).

$CaPO_4$ Bioceramics

Currently, $CaPO_4$ bioceramics can be prepared from various sources [68-74]. Nevertheless, up to now, all attempts to synthesize bone replacement materials for clinical applications featuring the physiological tolerance, biocompatibility and a long-term stability have had only a relative success; this clearly demonstrates both the superiority and a complexity of the natural structures [14].

In general, a characterization of $CaPO_4$ bioceramics should be performed from various viewpoints such as the chemical composition (including stoichiometry and purity), homogeneity, phase distribution, morphology, grain sizes and shape, grain boundaries, crystallite size, crystallinity, pores, cracks, surface roughness, etc. Among the known types of $CaPO_4$ (Table 1), the vast majority of $CaPO_4$ bioceramics is based on HA [75-80], both types of TCP [75, 81-91] and various multiphasic formulations thereof [92]. Biphasic formulations (commonly abbreviated as BCP – biphasic calcium phosphate) are the simplest among the latter ones. They include β-TCP + HA [93-101], α-TCP + HA [102-104] and biphasic TCP (commonly abbreviated as BTCP) consisting of α-TCP and β-TCP [105-110]. In addition, triphasic formulations (HA + α-TCP + β-TCP) have been prepared as well [111-114]. Further details on this topic might be found in a special review [92]. Leaving aside a big subject of DCPD-forming self-setting formulations [61, 115], one should note that just a few

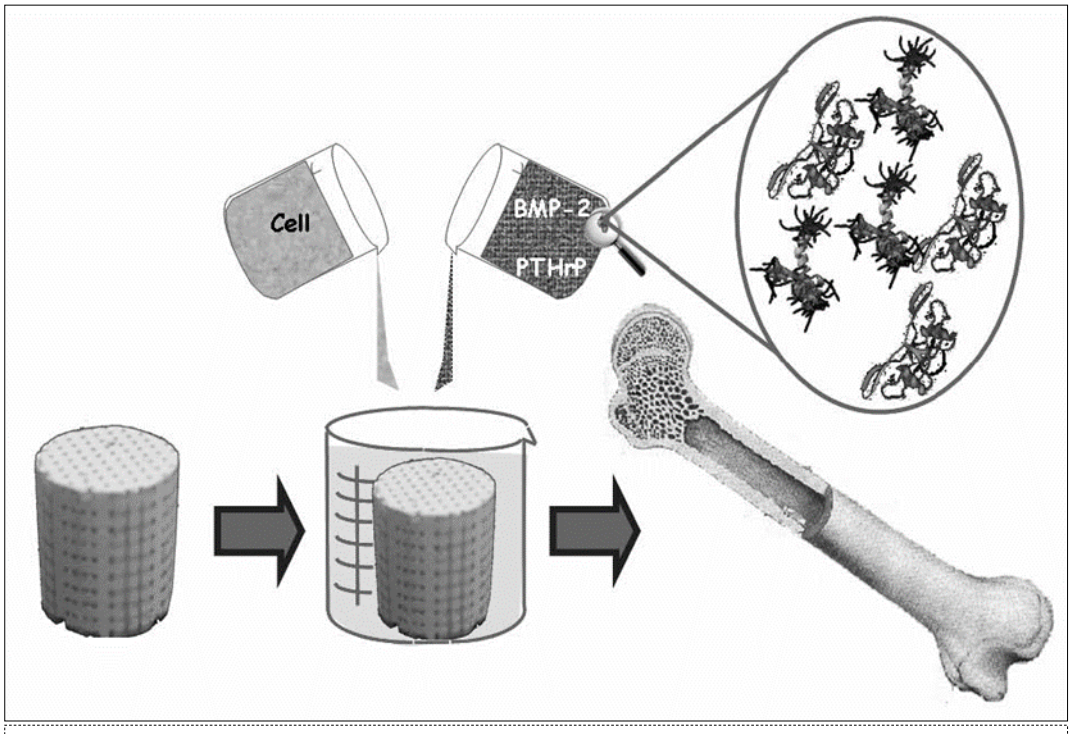


Fig. 1. A schematic view of a third generation biomaterial, in which porous $CaPO_4$ bioceramics acts as a scaffold or a template for cells, growth factors, *etc*. Reprinted from Ref. [65] with permission.

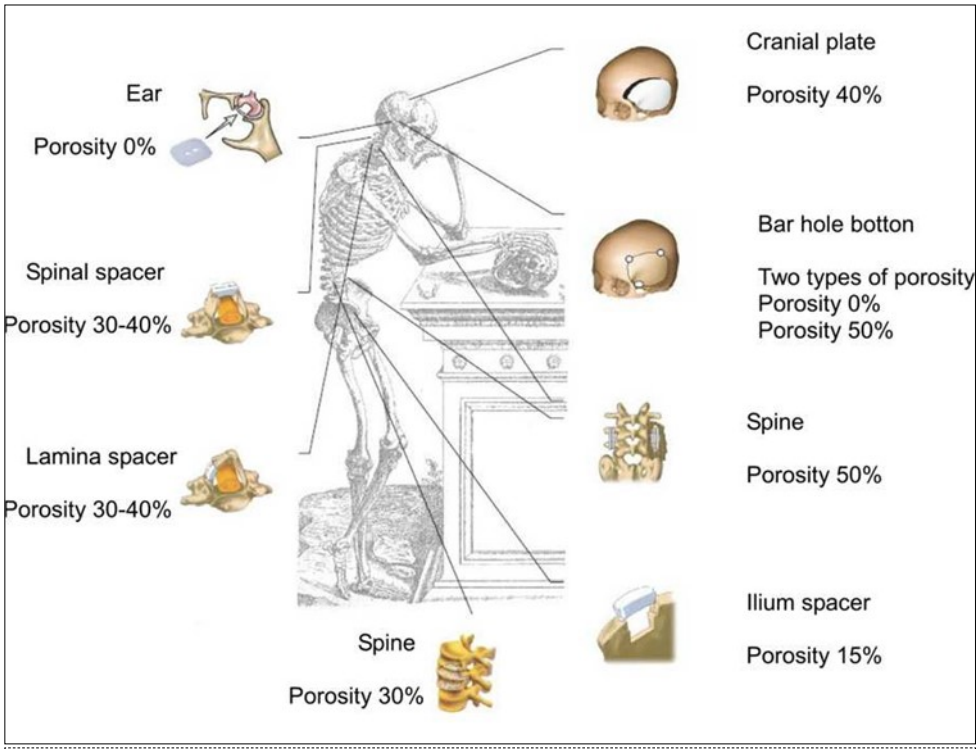


Fig. 2. A schematic drawing presenting the potential usage of bioceramic scaffolds with various degrees of porosity. Reprinted from Ref. [66] with permission.

publications on bioceramics, prepared from other types of $CaPO_4$, are available [116-124].

The preparation techniques of various $CaPO_4$ have been extensively reviewed in literature [125-129] where the interested readers are referred to. Briefly, when compared to both α- and β-TCP, HA is a more stable phase under the physiological conditions, as it has a lower solubility (Table 1) and, thus, slower resorption kinetics [130-132]. Therefore, the BCP concept is determined by the optimum balance of a more stable phase of HA and a more soluble TCP. Due to a higher biodegradability of the α- or β-TCP component, the reactivity of BCP increases with the TCP/HA ratio increasing. Thus, in vivo bioresorbability of BCP can be controlled through the phase composition [94]. Similar conclusions are also valid for the biphasic TCP (in which α-TCP is a more soluble phase), as well as for both triphasic (HA, α-TCP and β-TCP) and yet more complex formulations [92].

As implants made of sintered HA are found in bone defects for many years after implantation (Fig. 3, bottom), bioceramics made of more soluble types of $CaPO_4$ [75, 81-124, 133, 134] are preferable for the biomedical purposes (Fig. 3, top). Furthermore, the experimental results showed that BCP had a higher ability to adsorb fibrinogen, insulin or type I collagen than HA [135]. Thus, according to both observed and measured bone formation parameters, $CaPO_4$ bioceramics have been ranked as follows: low sintering temperature BCP (rough and smooth) ≈ medium sintering temperature BCP ≈ TCP > calcined low sintering temperature HA > non-calcined low sintering temperature HA > high sintering temperature BCP (rough and smooth) > high sintering temperature HA [136]. This sequence has been developed in year 2000 and, thus, neither multiphase formulations, nor other $CaPO_4$ have been included.

Scaffolds from $CaPO_4$

Forming and Shaping

In order to fabricate scaffolds in progressively complex shapes, scientists are investigating the use of both old and new manufacturing techniques. These techniques range from an adaptation of the age-old pottery techniques to the newest manufacturing methods for high-temperature ceramic parts for airplane engines. Namely, reverse engineering [137, 138] and rapid prototyping [139-141] technologies have revolutionized a generation of physical models, allowing the engineers to efficiently and accurately produce physical models and customized implants with high levels of geometric intricacy. Combined with the computer-aided design and manufacturing (CAD/CAM), complex physical objects of the anatomical structure can be fabricated in a variety of shapes and sizes. In a typical application, an image of a bone defect in a patient can be taken and used to develop a 3D CAD computer model [142-146]. Then a computer can reduce the model to slices or layers. Afterwards, 3D objects and coatings are constructed layer-by-layer using rapid prototyping techniques. The examples comprise fused deposition modeling [147, 148], selective laser sintering [149-155], laser cladding [156-159], 3D printing and/or plotting [86, 160-174], solid freeform fabrication [175-183] and stereolithography [184-187]. 3D printing and/or plotting of the $CaPO_4$-based self-setting formulations could be performed as well [172, 173]. In the specific case of ceramic scaffolds, a sintering step is usually applied after printing the green bodies. Furthermore, a thermal printing process of melted $CaPO_4$ has been proposed [188], while, in some cases, laser processing might be applied as well [189, 190]. A schematic of 3D printing technique, as well as some 3D printed items are shown in Fig. 4 [10]. A custom-made implant of actual dimensions would reduce the time it takes to perform the medical implantation procedure and subsequently lower the risk to the patient. Another advantage of a pre-fabricated, exact-fitting implant is that it can be used more effectively and applied directly to the damaged site rather than a replacement, which is formulated during surgery from a paste or granular material [176, 190-192].

In addition to the aforementioned modern techniques, classical forming and shaping approaches are still widely used. The selection of the desired technique depends greatly on the ultimate application of scaffolds, e.g., whether they are for a hard-tissue replacement or an integration of the device within the

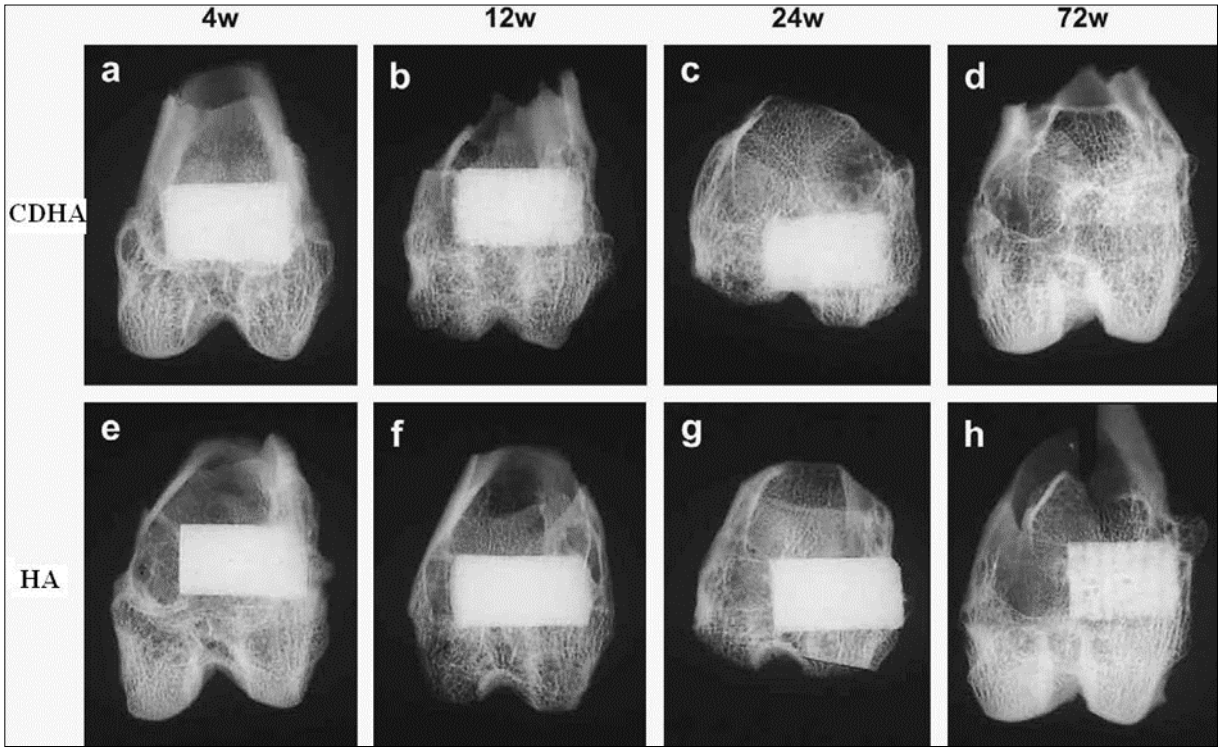


Fig. 3. Soft X-ray photographs of the operated portion of the rabbit femur. Four weeks (a), 12 weeks (b), 24 weeks (c) and 72 weeks (d) after implantation of CDHA; 4 weeks (e), 12 weeks (f), 24 weeks (g) and 72 weeks (h) after implantation of sintered HA. Reprinted from Ref. [133] with permission.

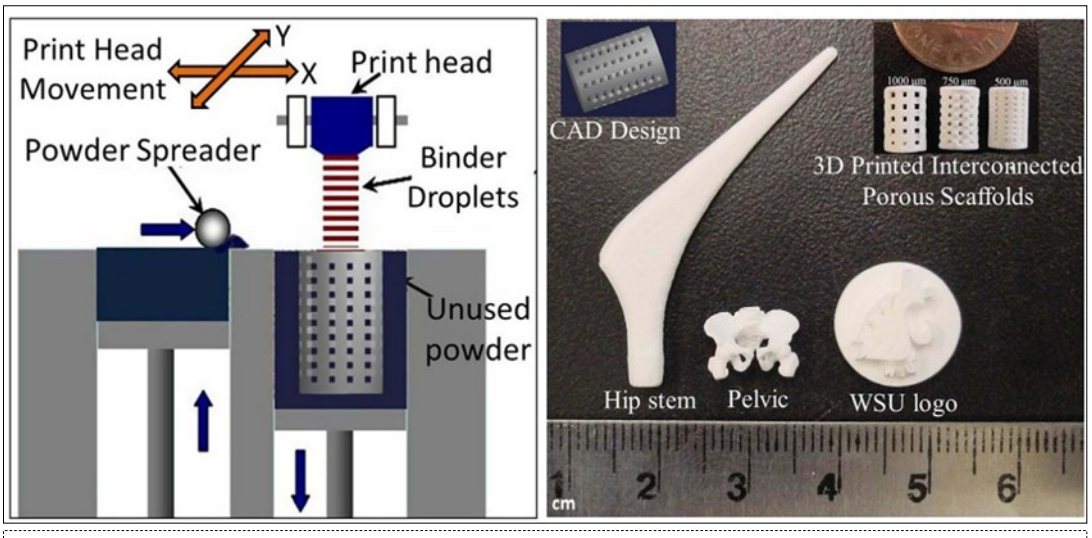


Fig. 4. A schematic of 3D printing and some 3D printed parts (fabricated at Washington State University) showing the versatility of 3D printing technology for ceramic scaffolds fabrication with complex architectural features. Reprinted from Ref. [10] with permission.

surrounding tissues. In general, three types of the processing technologies might be used: (1) employment of a lubricant and a liquid binder with ceramic powders for shaping and subsequent firing; (2) application of self -setting and self-hardening properties of water-wet molded powders; (3) materials are melted to form a liquid and are shaped during cooling and solidification [193-196]. Since $CaPO_4$ are either thermally unstable (MCPM, MCPA, DCPA, DCPD, OCP, ACP, CDHA) or have a melting point at temperatures exceeding ~ 1400 °C with a partial decomposition (α-TCP, β-TCP, HA, FA, TTCP), only the first and the second consolidation approaches are used to prepare bulk b ioceramics and scaffolds. The methods include uniaxial compaction [197-199], isostatic pressing (cold or hot) [100, 200-207], granulation [208-214], loose packing [215], slip casting [88, 216-221], gel casting [184, 222-230], pressure mold forming [231, 232], injection molding [233-235], polymer replication [236-243], ultrasonic machining [244], extrusion [245-251], slurry dipping and spraying [252]. Depending on the fabrication technique used, various parameters such as solid loading of the ceramic slurry, type and amount of additives (binders, surfactants, dispersants, etc.), temperature, etc. should be optimized to maximize the mechanical strength of the scaffolds. In addition, to form ceramic sheets from slurries, tape casting [225, 253-257], doctor blade [258] and colander methods can be employed [193-196]. Furthermore, flexible, ultrathin (of 1 to several microns thick), freestanding HA sheets were produced by a pulsed laser deposition technique, followed by thin film isolation technology [259]. Various combinations of several techniques are also possible [90, 225, 260-262]. More to the point, some of these processes might be performed under the electromagnetic field, which helps crystal aligning [217, 220, 263-266]. Finally, the prepared $CaPO_4$ bioceramics might be subjected by additional treatments (e.g., chemical, thermal and/or hydrothermal ones) to convert one type of $CaPO_4$ into another one [243].

To prepare bulk bioceramics, powders are usually pressed damp in metal dies or dry in lubricated dies at pressures high enough to form sufficiently strong structures to hold together until they are sintered [267]. An organic binder, such as polyvinyl alcohol, helps to bind the powder particles altogether. Afterwards, the binder is removed by heating in air to oxidize the organic phases to carbon dioxide and water. Since many binders contain water, drying at ~ 100 °C is a critical step in preparing damp-formed pieces for firing. Too much or too little water in the compacts can lead to blowing apart the ware on heating or crumbling, respectively [193-196, 201]. Furthermore, removal of water during drying often results in subsequent shrinkage of the product. In addition, due to local variations in water content, warping and even cracks may be developed during drying. Dry pressing and hydrostatic molding can minimize these problems [196]. Finally, the manufactured green samples are sintered.

It is important to note that forming and shaping of any ceramic products require a proper selection of the raw materials in terms of particle sizes and size distribution. Namely, tough and strong scaffolds consist of pure, fine and homogeneous microstructures. To attain this, pure powders with small average size and high surface area must be used as the starting sources. However, for maximum packing and least shrinkage after firing, mixing of ~ 70 % coarse and ~ 30 % fine powders have been suggested [196]. Mixing is usually carried out in a ball mill for uniformity of properties and reaction during subsequent firing. Mechanical die forming or sometimes extrusion through a die orifice can be used to produce a fixed cross-section.

Finally, to produce the accurate shaping, necessary for the fine design of scaffolds, machine finishing might be essential [144, 193, 268, 269]. Unfortunately, cutting tools developed for metals are usually useless for bioceramics due to their fragility; therefore, grinding and polishing appear to be the convenient finishing techniques [144, 193]. In addition, the surface of scaffolds might be modified by various supplementary treatments [270].

Sintering and Firing

A sintering (or firing) procedure appears to be of a great importance to manufacture bioceramic scaffolds with the required mechanical properties. Usually, this stage is carried out according to controlled temperature programs of electric furnaces in adjusted ambience of air with necessary additional gasses;

however, always at temperatures below the melting points of the materials. The firing step can include temporary holds at intermediate temperatures to burn out organic binders [193-196]. The heating rate, sintering temperature and holding time depend on the starting materials. For example, in the case of HA, these values are in the ranges of 0.5 – 3 °C/min, 1000 – 1250 °C and 2 – 5 h, respectively [271]. In the majority cases, sintering allows a structure to retain its shape. However, this process might be accompanied by a considerable degree of shrinkage [272-274], which must be accommodated in the fabrication process. For instance, in the case of FA sintering, a linear shrinkage was found to occur at ~ 715 °C and the material reached its final density at ~ 890 °C. Above this value, grain growth became important and induced an intra-granular porosity, which was responsible for density decrease. At ~ 1180 °C, a liquid phase was formed due to formation of a binary eutectic between FA and fluorite contained in the powder as impurity. This liquid phase further promoted the coarsening process and induced formation of large pores at high temperatures [275].

In general, sintering occurs only when the driving force is sufficiently high, while the latter relates to the decrease in surface and interfacial energies of the system by matter (molecules, atoms or ions) transport, which can proceed by solid, liquid or gaseous phase diffusion. Namely, when solids are heated to high temperatures, their constituents are driven to move to fill up pores and open channels between the grains of powders, as well as to compensate for the surface energy differences among their convex and concave surfaces (matter moves from convex to concave). At the initial stages, bottlenecks are formed and grow among the particles. Existing vacancies tend to flow away from the surfaces of sharply curved necks; this is an equivalent of a material flow towards the necks, which grow as the voids shrink. Small contact areas among the particles expand and, at the same time, a density of the compact increases and the total void volume decreases. As the pores and open channels are closed during a heat treatment, the particles become tightly bonded together and density, strength and fatigue resistance of the sintered object improve greatly. Grain-boundary diffusion was identified as the dominant mechanism for densification [276]. Furthermore, strong chemical bonds are formed among the particles and loosely compacted green bodies are hardened to denser materials [193-196]. Further knowledge on the ceramic sintering process might be found elsewhere [277].

In the case of $CaPO_4$, the earliest paper on their sintering was published in 1971 [278]. Since then, numerous papers on this subject were published and several specific processes were found to occur during $CaPO_4$ sintering. Firstly, moisture, carbonates and all other volatile chemicals remaining from the synthesis stage, such as ammonia, nitrates and any organic compounds, are removed as gaseous products. Secondly, unless powders are sintered, the removal of these gases facilitates production of denser ceramics with subsequent shrinkage of the samples. Thirdly, all chemical changes are accompanied by a concurrent increase in crystal size and a decrease in the specific surface area. Fourthly, a chemical decomposition of all acidic orthophosphates and their transformation into other phosphates (e.g., $2HPO_4^{2-} \rightarrow P_2O_7^{4-} + H_2O\uparrow$) takes place. Besides, sintering causes toughening [79], densification [80, 279], partial dehydroxylation (in the case of HA) [80], grain growth [276, 280], as well as it increases the mechanical strength [281-283]. The latter events are due to presence of air and other gases filling gaps among the particles of un-sintered powders. At sintering, the gases move towards the outside of powders and green bodies shrink owing to decrease of distances among the particles. For example, sintering of a biologically formed apatites was investigated [284, 285] and the obtained products were characterized [286, 287]. In all cases, the numerical value of Ca/P ratio in sintered apatites of biological origin was higher than that of the stoichiometric HA. One should mention that in the vast majority cases, $CaPO_4$ with Ca/P ratio < 1.5 (Table 1) are not sintered, since these compounds are thermally unstable, while sintering of non-stoichiometric $CaPO_4$ (CDHA and ACP) always leads to their transformation into various types of biphasic, triphasic and multiphase formulations [92].

An extensive study on the effects of sintering temperature and time on the properties of HA bioceramics revealed a correlation between these parameters and density, porosity, grain size, chemical composition and strength of the scaffolds [288].

Namely, sintering below ~ 1000 °C was found to result in initial particle coalescence, with little or no densification and a significant loss of the surface area and porosity. The degree of densification appeared to depend on the sintering temperature whereas the degree of ionic diffusion was governed by the period of sintering [288]. To enhance sinterability of $CaPO_4$, a variety of sintering additives might be added [289-292].

Solid-state pressureless sintering is the simplest procedure. For example, HA scaffolds can be pressurelessly sintered up to the theoretical density at 1000 – 1200 °C. Processing at even higher temperatures usually lead to exaggerated grain growth and decomposition because HA becomes unstable at temperatures exceeding ~ 1300 °C [125-129, 293-296]. The decomposition temperature of HA is a function of the partial pressure of water vapor. Moreover, processing under vacuum leads to an earlier decomposition of HA, while processing under high partial pressure of water prevents from the decomposition. On the other hand, a presence of water in the sintering atmosphere was reported to inhibit densification of HA and accelerated grain growth [297]. Unexpectedly, an application of a magnetic field during sintering was found to influence the growth of HA grains [280]. A definite correlation between hardness, density and a grain size in sintered HA bioceramics was found: despite exhibiting high bulk density, hardness started to decrease at a certain critical grain size limit [298-300].

Since grain growth occurs mainly during the final stage of sintering, to avoid this, a new method called "two-step sintering" (TSS) was proposed [301]. The method consists of suppressing grain boundary migration responsible for grain growth, while keeping grain boundary diffusion that promotes densification. The TSS approach was successfully applied to $CaPO_4$ bioceramics [91, 99, 302-306]. For example, HA compacts prepared from nanodimensional powders were two-step sintered. The average grain size of near full dense (> 98 %) HA bioceramics made via conventional sintering was found to be ~ 1.7 μm, while that for TSS HA bioceramics was ~ 190 nm (i.e., ~ 9 times less) with simultaneous increasing the fracture toughness of samples from 0.98 ± 0.12 to 1.92 ± 0.20 MPa $m^{1/2}$. In addition, due to the lower second step sintering temperature, no HA phase decomposition was detected in TSS method [302].

Hot pressing [300, 307-313], hot isostatic pressing [100, 200, 205, 207] or hot pressing with post-sintering [314, 315] processes make it possible to decrease a temperature of the densification process, diminish the grain size, as well as achieve higher densities. This leads to finer microstructures, higher thermal stability and subsequently better mechanical properties of $CaPO_4$ scaffolds. Both microwave [316-325] and spark plasma [82, 116, 326-335] sintering techniques are alternative methods to the conventional sintering, hot pressing and hot isostatic pressing. Both alternative methods were found to be time and energy efficient densification techniques. Further developments are still possible. For example, a hydrothermal hot pressing method has been developed to fabricate OCP [117], CDHA [336], HA/β-TCP [310] and HA [311-314, 337] bioceramics with neither thermal dehydration nor thermal decomposition. Further details on the sintering and firing processes of $CaPO_4$ bioceramics are available in literature [127, 338, 339].

To conclude this section, one should mention that the sintering stage is not always necessary. For example, $CaPO_4$-based scaffolds with the reasonable mechanical properties might be prepared by means of self-setting (self-hardening) formulations [61]. Furthermore, the reader's attention is paid on an excellent review on various ceramic manufacturing techniques [340].

The Major Properties

Mechanical Properties

The modern generation of biomedical materials should stimulate the body's own self-repairing abilities [341]. Therefore, during healing, a mature bone should replace the modern grafts and this process must occur without transient loss of the mechanical support. Unluckily for material scientists, a human body provides one of the most inhospitable environments for the implanted biomaterials. It is warm, wet and both chemically and biologically active. For example, a diversity of body fluids in various tissues might have a solution pH varying from 1 to 9. In addition, a body is capable of generating quite massive force concentrations and the variance in such characteristics among

individuals might be enormous. Typically, bones are subjected to ~ 4 MPa loads, whereas tendons and ligaments experience peak stresses in the range of 40 – 80 MPa. The hip joints are subjected to an average load up to three times body weight (3,000 N) and peak loads experienced during jumping can be as high as 10 times body weight. These stresses are repetitive and fluctuating depending on the nature of the activities, which can include standing, sitting, jogging, stretching and climbing. Therefore, all types of implants must sustain attacks of a great variety of aggressive conditions [342]. Regrettably, there is presently no artificial material fulfilling all these requirements.

Now it is important to mention, that the mechanical behavior of any ceramics is rather specific. Namely, ceramics is brittle, which is attributed to high strength ionic bonds. Thus, it is not possible for plastic deformation to happen prior to failure, as a slip cannot occur. Therefore, ceramics fail in a dramatic manner. Namely, if a crack is initiated, its progress will not be hindered by the deformation of material ahead of the crack, as would be the case in a ductile material (e.g., a metal). In ceramics, the crack will continue to propagate, rapidly resulting in a catastrophic breakdown. In addition, the mechanical data typically have a considerable amount of scatter [194]. Alas, all of these are applicable to $CaPO_4$ bioceramics.

For dense bioceramics, the strength is a function of the grain sizes. Namely, finer grain size bioceramics have smaller flaws at the grain boundaries and thus are stronger than one with larger grain sizes. Thus, in general, the strength for ceramics is proportional to the inverse square root of the grain sizes [343]. In addition, the mechanical properties decrease significantly with increasing content of an amorphous phase, microporosity and grain sizes, while a high crystallinity, a low porosity and small grain sizes tend to give a higher stiffness, a higher compressive and tensile strength and a greater fracture toughness. Furthermore, ceramics strength appears to be very sensitive to a slow crack growth [344]. Accordingly, from the mechanical point of view, $CaPO_4$ scaffolds appear to be brittle polycrystalline materials for which the mechanical properties are governed by crystallinity, grain size, grain boundaries, porosity and composition [345]. Thus, it possesses poor mechanical properties (for instance, a low impact and fracture resistances) that do not allow $CaPO_4$ scaffolds to be used in load-bearing areas, such as artificial teeth or bones. For example, fracture toughness (this is a property, which describes the ability of a material containing a crack to resist fracture and is one of the most important properties of any material for virtually all design applications) of HA bioceramics does not exceed the value of ~ 1.2 $MPa \cdot m^{1/2}$ [346] (human bone: 2 – 12 $MPa \cdot m^{1/2}$). It decreases exponentially with the porosity increasing [347]. Generally, fracture toughness increases with grain size decreasing. However, in some materials, especially non-cubic ceramics, fracture toughness reaches the maximum and rapidly drops with decreasing grain size. For example, a fracture toughness of pure hot pressed HA with grain sizes between 0.2 – 1.2 μm was investigated. The authors found two distinct trends, where fracture toughness decreased with increasing grain size above ~ 0.4 μm and subsequently decreased with decreasing grain size. The maximum fracture toughness measured was 1.20 ± 0.05 $MPa \cdot m^{1/2}$ at ~ 0.4 μm [307]. Fracture energy of HA bioceramics is in the range of 2.3 – 20 J/m^2, while the Weibull modulus (it is a measure of the spread or scatter in fracture strength) is low (~ 5 – 12) in wet environments, which means that HA behaves as a typical brittle ceramics and indicates to a low reliability of HA implants [348]. Porosity has a great influence on the Weibull modulus [349, 350]. In addition, that the reliability of HA scaffolds was found to depend on deformation mode (bending or compression), along with pore size and pore size distribution: a reliability was higher for smaller average pore sizes in bending but lower for smaller pore sizes in compression [351]. Interestingly that 3 peaks of internal friction were found at temperatures about –40, 80 and 130 °C for HA but no internal friction peaks were obtained for FA in the measured temperature range; this effect was attributed to the differences of F^- and OH^- positions in FA and HA, respectively [352]. The differences in internal friction values were also found between HA and TCP [353].

Bending, compressive and tensile strengths of dense HA bioceramics are in the ranges of 38 – 250 MPa, 120 – 900 MPa and 38 – 300 MPa, respectively. Similar values for porous HA scaffolds are substantially lower: 2 – 11 MPa, 2 – 100 MPa and ~ 3 MPa, respectively [348]. These wide variations in the properties are due to both structural variations (e.g., an

influence of remaining microporosity, grain sizes, presence of impurities, etc.) and manufacturing processes, as well as they are caused by a statistical nature of the strength distribution. Strength was found to increase with Ca/P ratio increasing, reaching the maximum value around Ca/P ~ 1.67 (stoichiometric HA) and decreases suddenly when Ca/P > 1.67 [348]. Furthermore, strength decreases almost exponentially with porosity increasing [354, 355]. However, by changing the pore geometry, it is possible to influence the strength of porous bioceramics. It is also worth mentioning that porous $CaPO_4$ scaffolds are considerably less fatigue resistant than dense bioceramics (in materials science, fatigue is the progressive and localized structural damage that occurs when a material is subjected to cyclic loading). Both grain sizes and porosity are reported to influence the fracture path, which itself has a little effect on the fracture toughness of $CaPO_4$ bioceramics [345, 356]. However, no obvious decrease in mechanical properties was found after $CaPO_4$ bioceramics had been aged in the various solutions during the different periods of time [357].

Young's (or elastic) modulus of dense HA bioceramics is in the range of 35 – 120 GPa [358, 359], which is more or less similar to those of the most resistant components of the natural calcified tissues (dental enamel: ~ 74 GPa, dentine: ~ 21 GPa, compact bone: ~ 18 – 22 GPa). This value depends on porosity [360]. Nevertheless, dense bulk compacts of HA have mechanical resistances of the order of 100 MPa versus ~ 300 MPa of human bones, diminishing drastically their resistances in the case of porous bulk compacts [361]. Young's modulus measured in bending is between 44 and 88 GPa. To investigate the subject in more details, various types of modeling and calculations are increasingly used [362-366]. For example, the elastic properties of HA appeared to be significantly affected by the presence of vacancies, which softened HA via reducing its elastic modules [366]. In addition, a considerable anisotropy in the stress-strain behavior of the perfect HA crystals was found by ab initio calculations [363]. The crystals appeared to be brittle for tension along the z-axis with the maximum stress of ~ 9.6 GPa at 10 % strain. Furthermore, the structural analysis of the HA crystal under various stages of tensile strain revealed that the deformation behavior manifested itself mainly in the rotation of PO_4 tetrahedrons with concomitant movements of both the columnar and axial Ca ions [363]. Data for single crystals are also available [367]. Vickers hardness (that is a measure of the resistance to permanent indentation) of dense HA bioceramics is within 3 – 7 GPa, while the Poisson's ratio (that is the ratio of the contraction or transverse strain to the extension or axial strain) for HA is about 0.27, which is close to that of bones (~ 0.3). At temperatures within 1000 – 1100 °C, dense HA bioceramics was found to exhibit superplasticity with a deformation mechanism based on grain boundary sliding [332, 368, 369]. Furthermore, both wear resistance and friction coefficient of dense HA bioceramics are comparable to those of dental enamel [348].

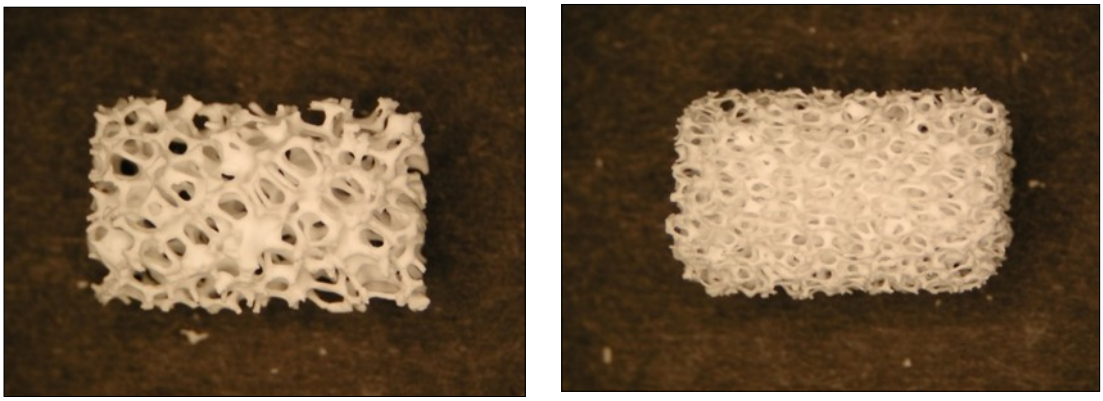
Due to a high brittleness (associated to a low crack resistance), the biomedical applications of $CaPO_4$ bioceramics are focused on production of non-load-bearing implants, such as pieces for middle ear surgery, filling of bone defects in oral or orthopedic surgery, as well as coating of dental implants and metallic prosthesis (see below) [370, 371]. Therefore, ways are continuously sought to improve the reliability of $CaPO_4$ bioceramics. Namely, the mechanical properties of sintered bioceramics might be improved by changing the morphology of the initial $CaPO_4$ [372]. In addition, diverse reinforcements (ceramics, metals or polymers) have been applied to manufacture various biocomposites and hybrid biomaterials [373], but that is another story. However, successful hybrid formulations consisted of $CaPO_4$ only [374-381] are within the scope of this review. Namely, bulk HA bioceramics might be reinforced by HA whiskers [375-379]. Furthermore, various biphasic apatite/TCP formulations were tested [374, 380, 381] and, for example, a superior superplasticity of HA/β-TCP biocomposites to HA bioceramics was detected [380].

Another approach to improve the mechanical properties of $CaPO_4$ bioceramics is to cover the items by polymeric coatings [382-384] or infiltrate porous structures by polymers [385-387]; however, this is still other story. Further details on the mechanical properties of $CaPO_4$ bioceramics are available elsewhere [347, 348, 388], where the interested readers are referred to.

Porosity

Porosity is defined as a percentage of voids in solids and this morphological property is independent of the material. The surface area of porous bodies is much higher, which guarantees a good mechanical fixation in addition to providing sites on the surface that allow chemical bonding between the bioceramic scaffolds and bones [389]. Furthermore, a porous material may have both closed (isolated) pores and open (interconnected) pores. The latter look like tunnels, which are accessible by gases, liquids and particulate suspensions [390]. The open-cell nature of porous materials (also known as reticulated materials) is a unique characteristic essential in many applications. In addition, pore dimensions are also important. Namely, the dimensions of open pores are directly related to bone formation, since such pores grant both the surface and space for cell adhesion and bone ingrowth [391-393]. On the other hand, pore interconnection provides the ways for cell distribution and migration, as well as it allows an efficient in vivo blood vessel formation suitable for sustaining bone tissue neo-formation and possibly remodeling [135, 394-399]. Explicitly, porous $CaPO_4$ scaffolds are colonized easily by cells and bone tissues [394, 398, 400-407]. Therefore, interconnecting macroporosity (pore size > 100 μm) [97, 389, 394, 408, 409] is intentionally introduced into solid scaffolds (Fig. 5). Calcining of natural bones appears to be the simplest way to prepare porous $CaPO_4$ scaffolds [68-74]. In addition, macroporosity might be formed artificially due to a release of various easily removable compounds and, for that reason, incorporation of pore-creating additives (porogens) is the most popular technique to create macroporosity. The porogens are crystals, particles or fibers of either volatile (they evolve gases at elevated temperatures) or soluble substances. The popular examples comprise paraffin [410-412], naphthalene [345, 413-415], sucrose [416, 417], $NaHCO_3$ [418-420], NaCl [421, 422], polymethylmethacrylate [87, 423-425], hydrogen peroxide [426-431], cellulose derivatives [77]. Several other compounds [338, 355, 432-443] might be used as porogens either. The ideal porogen should be nontoxic and be removed at ambient temperature, thereby allowing the bioceramic/porogen mixture to be injected directly into a defect site and allowing the scaffold to fit the defect [444]. Sintering particles, preferably spheres of equal size, is a similar way to generate porous 3D scaffolds of $CaPO_4$. However, pores resulting from this method are often irregular in size and shape and not fully interconnected with one another. Schematic drawings of various types of the ceramic porosity are shown in Fig. 6 [445].

Many other techniques, such as replication of polymer foams by impregnation [236-238, 241, 446-450] (Fig. 5), various types of casting [218, 219, 225, 227, 431, 451-459], suspension foaming [114], surfactant washing [460], microemulsions [461, 462], ice templating [463-466], as well as many other approaches [12, 81, 84, 87, 88, 154, 467-501] have been applied to fabricate porous $CaPO_4$ scaffolds. Some of them have been summarized in Table 3 [444]. In addition, both natural $CaCO_3$ porous materials, such as coral skeletons [502, 503] or shells [503, 504], and artificially prepared ones [505] can be converted into porous $CaPO_4$ under the hydrothermal conditions (250 °C, 24 – 48 h) with the microstructure undamaged. Porous HA scaffolds can also be obtained by hydrothermal hot pressing. This technique allows solidification of the HA powder at 100 – 300 °C (30 MPa, 2 h) [337]. In another approach, bi-continuous water-filled microemulsions have been used as pre-organized systems for the fabrication of needle-like frameworks of crystalline HA (2 °C, 3 weeks) [461, 462]. Besides, porous $CaPO_4$ might be prepared by a combination of gel casting and foam burn out methods [260, 262], as well as by hardening of the self-setting formulations [411, 412, 419, 420, 422, 432, 433, 490]. Lithography was used to print a polymeric material, followed by packing with HA and sintering [471]. Hot pressing was applied as well [308, 309]. More to the point, a HA suspension can be cast into a porous $CaCO_3$ skeleton, which is then dissolved, leaving a porous network [467]. 3D periodic macroporous frame of HA has been fabricated via a template-assisted colloidal processing technique [472, 473]. In addition, porous HA scaffolds might be prepared by using different starting HA powders and sintering at various temperatures by a pressureless sintering [469]. Porous scaffolds with an improved strength might be fabricated from $CaPO_4$ fibers or whiskers. In general, fibrous porous materials are known to exhibit an improved strength due to fiber



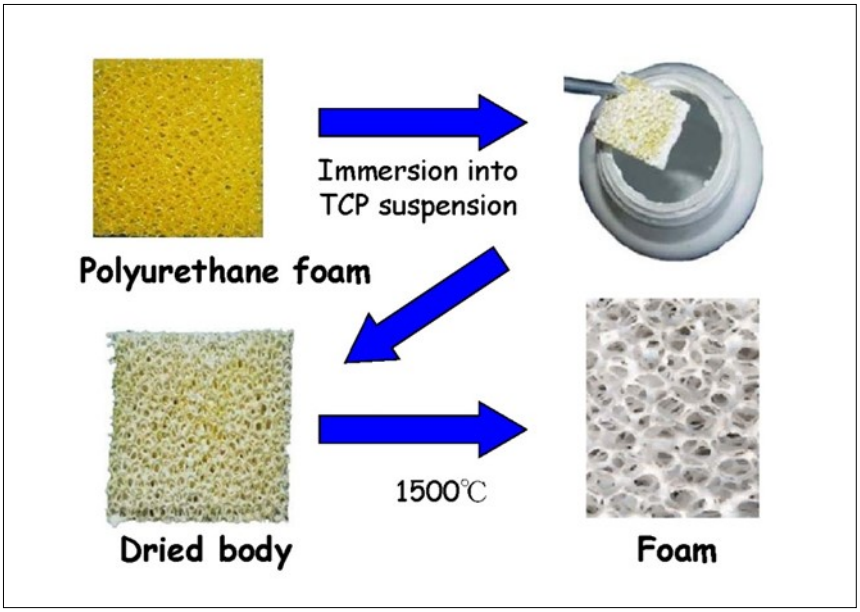


Fig. 5. Photographs of a commercially available porous $CaPO_4$ scaffolds with different porosity (top) and a method of their production (bottom). For photos, the horizontal field width is 20 mm.

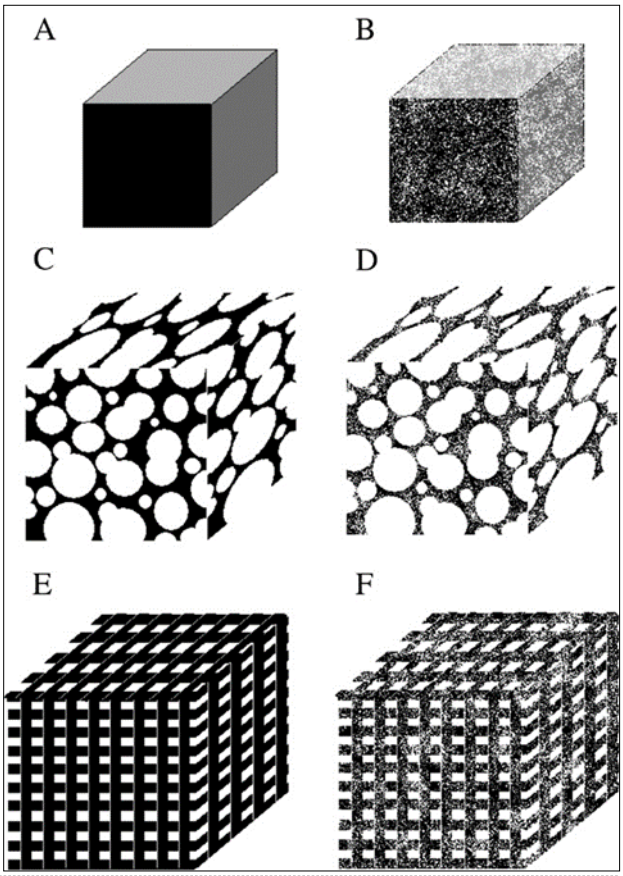


Fig. 6. Schematic drawings of various types of the ceramic porosity: A – non-porous, B – microporous, C – macroporous (spherical), D – macroporous (spherical) + micropores, E – macroporous (3D-printing), F – macroporous (3D-printing) + micropores. Reprinted from Ref. [445] with permission.

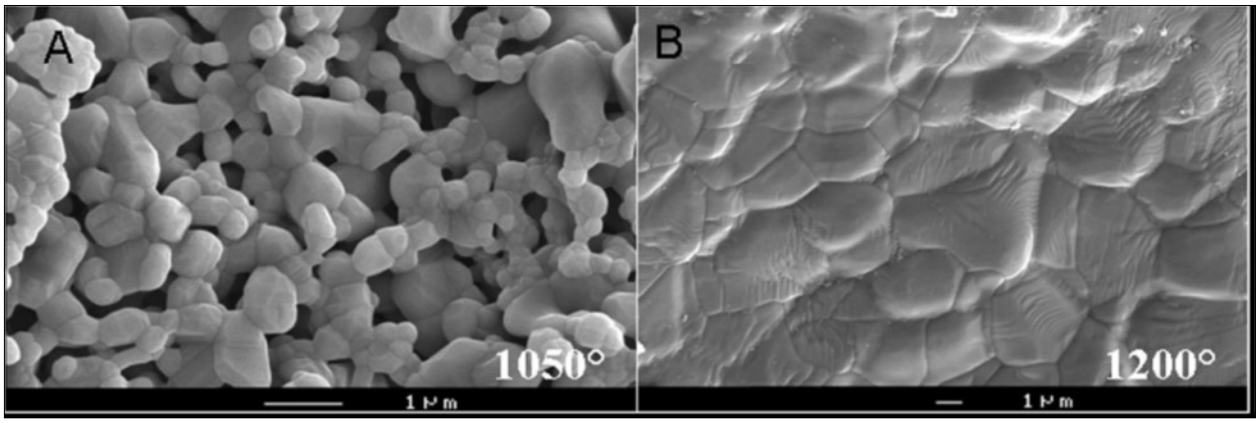


Fig. 7. SEM pictures of HA bioceramics sintered at (A) 1050 °C and (B) 1200 °C. Note the presence of microporosity in A and not in B. Reprinted from Ref. [516] with permission.

Table 3. The procedures used to manufacture porous $CaPO_4$ scaffolds for tissue engineering [444].

Year	Location	Process	Apatite from:	Sintering	Compressive strength	Pore size	Porosity	Method of porosity control
2006	Deville *et al.* Berkeley, CA	HA + ammonium methacrylate in polytetrafluoroethylene mold, freeze dried and sintered	HA #30	Yes:1300 ºC	16 MPa 65 MPa 145 MPa	open unidirectional 50 – 150 µm	> 60 % 56 % 47 %	Porosity control: slurry conc. Structure controlled by physics of ice front formation.
2006	Saiz *et al.* Berkeley, CA	Polymer foams coated, compressed after infiltration, then calcined.	HA powder	Yes: 700 – 1300 ºC	–	100 – 200 µm	–	Porosity control: extent of compression, HA loading
2006	Murugan *et al.* Singapore + USA	Bovine bone cleaned, calcined	bovine bone	Yes: 500 ºC	–	retention of nano-sized pores	–	Porosity control: native porosity of bovine bone
2006	Xu *et al.* Gaithersburg, MD	Directly injectable $CaPO_4$ cement, self hardens, mannitol as porogen	nano-crystalline HA	No	2.2 – 4.2 MPa (flexural)	0 – 50% macroporous	65 – 82 %	Porosity control: mannitol mass fraction in mixture
2004	Landi *et al.* Italy + Indonesia	Sponge impregnation, isotactic pressing, sintering of HA in simulated body fluid	CaO + H_3PO_4	Yes: 1250 ºC for 1 hr	23 ± 3.8 MPa	closed 6% open 60%	66 %	Porosity control: possibly by controlling HA particle size. Not suggested by authors
2003	Charriere *et al.* EPFL, Switzerland	Thermoplastic negative porosity by Ink jet printing, slip casting process for HA	DCPA + calcite	No: 90 ºC for 1 day	12.5 ± 4.6 MPa	–	44 %	Porosity control: negative printing
2003	Almirall *et al.* Barcelona, Spain	α-TCP foamed with hydrogen peroxide at different conc., liq. ratios, poured in polytetrafluoroethylene molds	α-TCP + (10% and 20% H_2O_2)	No: 60 ºC for 2 hr	1.41 ± 0.27 MPa 2.69 ± 0.91 MPa	35.7% macro 29.7% micro 26.8% macro 33.8% micro	65.5 % 60.7 %	Porosity control: different concentration, α-TCP particle sizes
2003	Ramay *et al.* Seattle, WA	Slurries of HA prepared: gel-casting + polymer sponge technique, sintered.	HA powder	Yes: 600 ºC for1 hr 1350 ºC for 2 hr	0.5 – 5 MPa	200 – 400 µm	70 – 77 %	Porosity control: replicate of polymer sponge template
2003	Miao *et al.* Singapore	TTCP to $CaPO_4$ cement. Slurry cast on polymer foam, sintered.	TTCP	Yes: 1200 ºC for 2 hr	–	1 mm macro 5 µm micro	~ 70%	Porosity control: Recoating time, polyurethane foam
2003	Uemura *et al.* China + Japan	Slurry of HA with polyoxyethylene lauryl ether (cross-linked) and sintered	HA powders	Yes: 1200 ºC for 3 hr	2.25 MPa (0 wk) 4.92MPa(12wks) 11.2 MPa (24	500 µm 200 µm interconnects	~ 77 %	Porosity control: polymer interconnects cross-linking
2003	Ma *et al.* Singapore + USA	Electrophoretic deposition of HA, sintering.	HA powders	Yes: 1200 ºC for 2 hr	860 MPa	0.5 µm 130 µm	~ 20 %	Porosity control: electrophoresis field
2002	Barralet *et al.* Birmingham, London, UK	$CaPO_4$ cement + sodium phosphate ice, evaporated	$CaCO_3$ + DCPD	1st step: 1400 ºC for 1 day	0.6 ± 0.27 MPa	2 µm	62 ± 9 %	Porosity control: porogen shape.

interlocking, crack deflection and/or pullout [27]. Namely, porous scaffolds with well-controlled open pores was processed by sintering of fibrous HA particles [468]. In another approach, porosity was achieved by firing apatite-fiber compacts mixed with carbon beads and agar. By varying the compaction pressure, firing temperature and carbon/HA ratio, the total porosity was controlled in the ranges from ~ 40 % to ~ 85 % [77]. Finally, a superporous (~ 85 % porosity) HA scaffolds was developed as well [60, 487, 488]. Additional information on the processing routes to produce porous ceramics might be found in literature [506, 507].

Scaffold microporosity (pore size < 10 μm), which is defined by its capacity to be impregnated by biological fluids [508], results from the sintering process, while the pore dimensions mainly depend on the material composition, thermal cycle and sintering time. The microporosity provides both a greater surface area for protein adsorption and increased ionic solubility. For example, embedded osteocytes distributed throughout microporous rods might form a mechanosensory network, which would not be possible in scaffolds without microporosity [509, 510]. $CaPO_4$ scaffolds with nanodimensional (< 100 nm) pores might be fabricated as well [195, 511-515]. It is important to stress, that differences in porogens usually influence the scaffolds' macroporosity, while differences in sintering temperatures and conditions affect the percentage of microporosity. Usually, the higher the sintering temperature, the lower both the microporosity content and the specific surface area of the scaffolds. Namely, HA bioceramics sintered at ~ 1200 °C shows significantly less microporosity and a dramatic change in crystal sizes, if compared with that sintered at ~ 1050 °C (Fig. 7) [516]. Furthermore, the average shape of pores was found to transform from strongly oblate to round at higher sintering temperatures [517]. The total porosity (macroporosity + microporosity) of $CaPO_4$ scaffolds was reported to be ~ 70 % [518] or even ~ 85 % [60, 487, 488] of the entire volume. In the case of coralline HA or bovine-derived apatites, the porosity of the original biologic material (coral or bovine bone) is usually preserved during processing [519]. To finalize the production topic, creation of the desired porosity in $CaPO_4$ scaffolds is a rather complicated engineering task and the interested readers are referred to the additional publications on the subject [355, 393, 489, 520-528].

Regarding the biomedical importance of porosity, studies revealed that increasing of both the specific surface area and pore volume of scaffolds might greatly accelerate the in vivo process of apatite deposition and, therefore, enhance the bone-forming bioactivity. More importantly, a precise control over the porosity, pore dimensions and internal pore architecture of the scaffolds on different length scales is essential for understanding of the structure-bioactivity relationship and the rational design of better bone-forming biomaterials [526, 529, 530]. Namely, in antibiotic charging experiments, $CaPO_4$ scaffolds with nanodimensional (< 100 nm) pores showed a much higher charging capacity (1621 μg/g) than that of commercially available $CaPO_4$ (100 μg/g), which did not contain nanodimensional porosity [522]. In other experiments, porous blocks of HA were found to be viable carriers with sustained release profiles for drugs [531] and antibiotics over 12 days [532] and 12 weeks [533], respectively. Unfortunately, porosity significantly decreases the strength of implants [348, 356, 388]. Thus, porous $CaPO_4$ implants cannot be loaded and are used to fill only small bone defects. However, their strength increases gradually when bones ingrow into the porous network of $CaPO_4$ implants [131, 534-537]. For example, bending strengths of 40 – 60 MPa for porous HA implants filled with 50 – 60 % of cortical bone were reported [534], while in another study an ingrown bone increased strength of porous HA scaffolds by a factor of 3 to 4 [536].

Unfortunately, the biomedical effects of scaffolds' porosity are not straightforward. For example, the in vivo response of $CaPO_4$ of different porosity was investigated and a hardly any effect of macropore dimensions (~ 150, ~ 260, ~ 510 and ~ 1220 μm) was observed [538]. In another study, a greater differentiation of mesenchymal stem cells was observed when cultured on ~ 200 μm pore size HA scaffolds when compared to those on ~ 500 μm pore size HA [539]. The latter finding was attributed to the fact that a higher pore volume in ~ 500 μm macropore scaffolds might contribute to a lack of cell confluency leading to the cells proliferating before beginning differentiation. Besides,

the authors hypothesized that scaffolds with a less than the optimal pore dimensions induced quiescence in differentiated osteoblasts due to reduced cell confluences [539]. In still another study, the use of BCP (HA/TCP = 65/35 wt. %) scaffolds with cubic pores of ~ 500 μm resulted in the highest bone formation compared with the scaffold with lower (~ 100 μm) or higher (~ 1000 μm) pore sizes [540]. Furthermore, $CaPO_4$ scaffolds with greater strut porosity appeared to be more osteoinductive [541]. Already in 1979, Holmes suggested that the optimal pore range was 200 – 400 μm with the average human osteon size of ~ 223 μm [542]. In 1997, Tsurga and coworkers implied that the optimal pore size of scaffolds that supported ectopic bone formation was 300 – 400 μm [543]. Thus, there is no need to create $CaPO_4$ scaffolds with very big pores; however, the pores must be interconnected [42, 408, 409, 544]. Interconnectivity governs a depth of cells or tissue penetration into the porous scaffolds, as well as it allows development of blood vessels required for new bone nourishing and wastes removal [508, 545]. Nevertheless, the total porosity of implanted scaffolds appears to be important. For example, 60 % porous β-TCP granules achieved a higher bone fusion rate than 75 % porous β-TCP granules in lumbar posterolateral fusion [509].

Loading by Bioactive Compounds, Drugs and Cells

After being prepared, porous $CaPO_4$ scaffolds are frequently loaded by various types of biomolecules, bioactive compounds, drugs and other therapeutic agents, as well as by genes and/or cells. All of them are added to the scaffolds in hopes that they will match a functionality of the native tissues, provide remodeling to the construct to aid in host integration, and/or be able to spur the host tissue to perform desired actions [546].

Various techniques to incorporate the bioactive compounds and/or cells into pores of the scaffolds, as well as onto the scaffolds' surface have been reported. The examples comprise blending, surface modification, adsorption, impregnation, centrifugation and vacuum based-techniques [547, 548]. Among them, adsorption and impregnation allow these moieties to be incorporated onto the surface of the scaffolds, while centrifugation and vacuum based-techniques enable them to enter into the pores [548]. Generally, bioactive compounds, such as growth factors, are incorporated by simple impregnation followed by drying, and the type of bonding with the substrate and the release rate are often undetermined [549]. Such associations do not allow chemical bonding between growth factors $CaPO_4$ scaffolds. In such cases, the release rates are difficult to control. For example, precipitation and clustering of the bioactive molecules may occur and the release is only determined by local dissolution and diffusion rules.

An uncontrolled release of bioactive compounds has been related to an accelerated resorption of bone tissue and of the implant. Since bioactive compounds can stimulate the degradation as well as the formation of bone (depending on their local concentrations), they could impair the surface osteoconductivity [550]. Namely, bisphosphonates, well established molecules as successful antiresorptive agents for the prevention and treatment of post-menopausal osteoporosis [551], by affecting bone remodeling, could also block the bone repair process: the drug at too high concentration could have detrimental effects on the fixation of the implant over longer periods of time. On the contrary, adsorption leads to stable association and control of the amount of bioactive molecules contained in the solid implant and, thus, of the dose released. Generally, the release is rather low because most of the bioactive molecules adsorbed are irreversibly bound and they are not spontaneously released in a cell culture media [552].

Functionally Graded $CaPO_4$ Scaffolds

Generally, functionally gradient materials (FGMs) are defined as materials, having either compositional or structural gradient from their surface to the interior. The idea of FGMs allows one device to possess two different properties. One of the most important combinations for the biomedical field is that of a mechanical strength and biocompatibility. Namely, only surface properties govern a biocompatibility of the entire device. In contrast, the strongest material determines the mechanical strength of the entire device.

Within the scope of this review, functionally graded $CaPO_4$ scaffolds are considered and discussed only. Such formulations have been developed [87, 455, 458, 524, 553-565]. For example, dense sintered bodies with gradual compositional changes from α-TCP to HA were prepared by sintering a diamond-coated HA

compacts at 1280 °C under a reduced pressure, followed by heating under the atmospheric conditions [553]. The content of α-TCP gradually decreased, while the content of HA increased with increasing depth from the surface. These functionally gradient scaffolds consisting of HA core and α-TCP surface showed a potential value as bone-substituting biomaterials [553]. Two types of functionally gradient FA/β-TCP biocomposites were prepared in another study [554]. As shown in Fig. 8, one of the graded biocomposites was in the shape of a disk and contained four different layers of about 1 mm thick. The other graded biocomposite was also in the shape of a disk but contained two sets of the four layers, each layer being 0.5 mm thick controlled by using a certain amount of the mixed powders. The final FA/β-TCP graded structures were formed at 100 MPa and sintered at 1300 °C for 2 h [554]. The same approach was used in still another study, but HA was used instead of FA and CDHA was used instead of β-TCP [565]. $CaPO_4$ coatings with graded crystallinity were prepared as well [560].

Besides, it is well known that a bone cross-section from cancellous to cortical bone is non-uniform in porosity and pore dimensions. Thus, in various attempts to mimic the porous structure of bones, $CaPO_4$ bioceramics with graded porosity have been fabricated [87, 390, 455, 458, 524, 553-558]. For example, graded porous $CaPO_4$ scaffolds can be produced by means of tape casting and lamination (Fig. 9, top). Other manufacturing techniques, such as a compression molding process (Fig. 9, bottom) followed by impregnation and firing, are known as well [390]. In the first method, a HA slurry was mixed with a pore former. The mixed slurry was then cast into a tape. Using the same method, different tapes with different pore former sizes were prepared individually. The different tape layers were then laminated together. Firing was then done to remove the pore formers and sinter the HA particle compacts, resulting in scaffolds with graded porosity [557]. This method was also used to prepare graded porous HA with a dense part (core or layer) in order to improve the mechanical strength, as dense ceramics are much stronger than porous ceramics. However, as in the pressure infiltration of mixed particles, this multiple tape casting also has the problem of poor connectivity of pores, although the pore size and the porosity are relatively easy to control. Furthermore, the lamination step also introduces additional discontinuity of the porosity on the interfaces between the stacked layers.

Since diverse biomedical applications require different configurations and shapes, the graded (or gradient) porous scaffolds can be grouped according to both the overall shape and the structural configuration [390]. The basic shapes include rectangular blocks and cylinders (or disks). For the cylindrical shape, there are configurations of dense core – porous layer, less porous core – more porous layer, dense layer – porous core and less porous layer – more porous core. For the rectangular shape, in the gradient direction i.e., the direction with varying porosity, pore size or composition, there are configurations of porous top – dense bottom (same as porous bottom – dense top), porous top – dense center – porous bottom, dense top – porous center – dense bottom, etc. Concerning biomedical applications, a dense core – porous layer structure is suitable for implants of a high mechanical strength and with bone ingrowth for stabilization, whereas a less porous layer – more porous core configuration can be used for drug delivery systems. Furthermore, a porous top – dense bottom structure can be shaped into implants of articulate surfaces for wear resistance and with porous ends for bone ingrowth fixation; while a dense top – porous center – dense bottom arrangement mimics the structure of head skull. Further details on scaffolds with graded porosity might be found in literature [390].

Biological Properties and the in Vivo Behavior

The most important differences between bioactive scaffolds and all other implanted materials comprise inclusion in the metabolic processes of the organism, adaptation of either surface or the entire material to the biomedium, integration of a bioactive implant with bone tissues at the molecular level or the complete replacement of a resorbable bioceramics by healthy bone tissues. All of the enumerated processes are related to the effect of an organism on the implant. Nevertheless, another aspect of implantation is also important – the effect of the implant on the organism. For example, using of bone implants from corpses or animals, even after they have been treated in various ways, provokes a substantially negative immune reactions in the organism, which substantially limits the

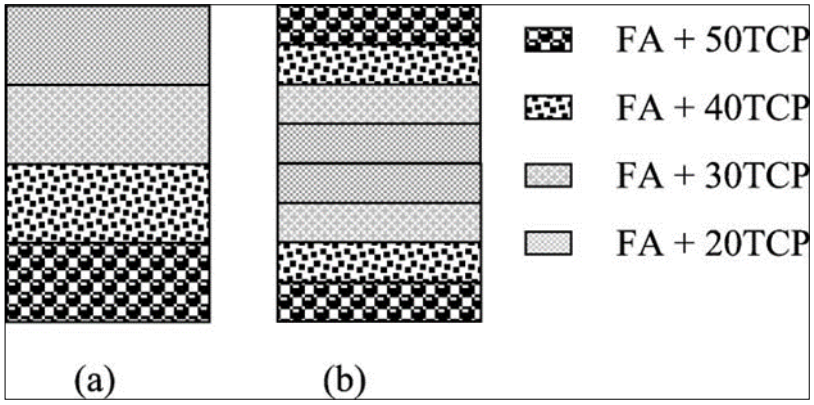


Fig. 8. A schematic diagram showing the arrangement of the FA/β-TCP biocomposite layers. (a) A non-symmetric functionally gradient material (FGM); (b) symmetric FGM. Reprinted from Ref. [554] with permission.

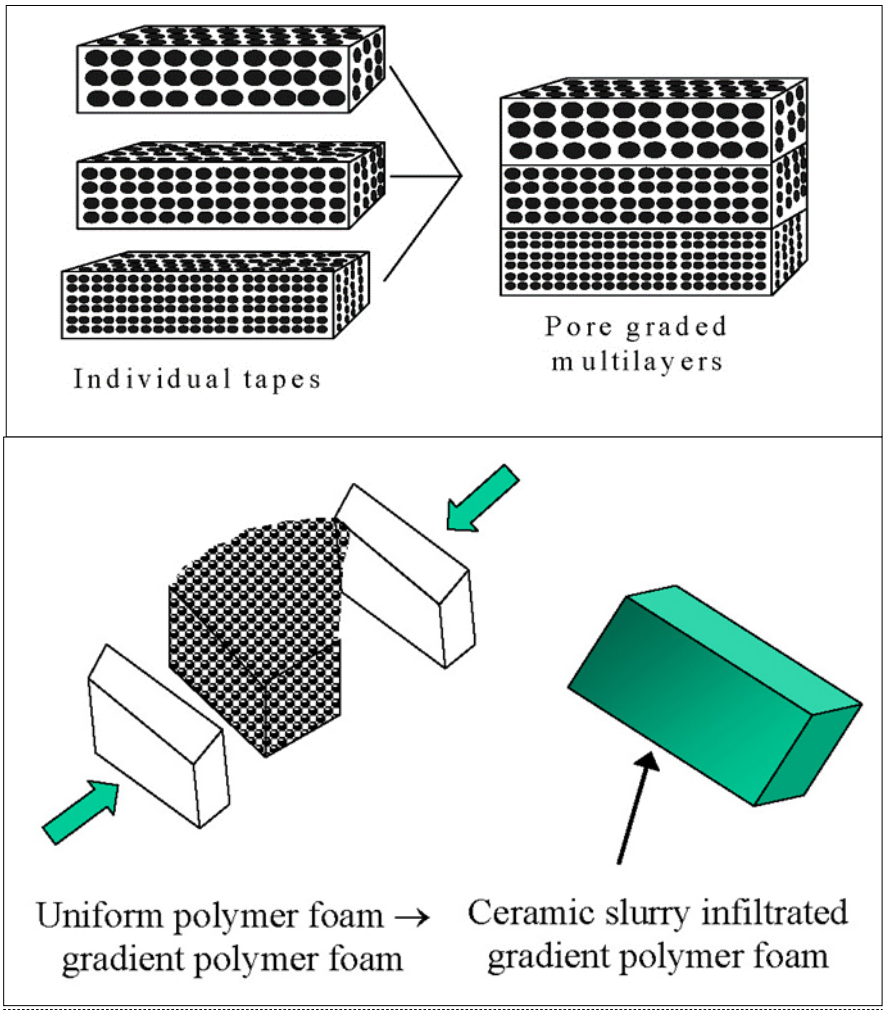


Fig. 9. Schematic illustrations of fabrication of pore-graded bioceramics: top – lamination of individual tapes, manufactured by tape casting; bottom – a compression molding process. Reprinted from Ref. [390] with permission

application of such implants. In this connection, it is useful to dwell on the biological properties of bioceramic scaffolds, particularly those of $CaPO_4$, which in the course of time may be resorbed completely [566].

Interactions with the Surrounding Tissues and the Host Responses

All interactions between implants and the surrounding tissues are dynamic processes. Water, dissolved ions, various biomolecules and cells surround the implant surface within initial few seconds after the implantation. It has been accepted that no foreign material placed inside a living body is completely compatible. The only substances that conform completely are those manufactured by the body itself (autogenous), while any other substance, which is recognized as foreign, initiates some types of reactions (a host-tissue response). The reactions occurring at the biomaterial/tissue interfaces lead to time-dependent changes in the surface characteristics of both the implanted biomaterials and the surrounding tissues [567].

In order to develop new scaffolds, it is necessary to understand the in vivo host responses. Like any other species, biomaterials and bioceramics react chemically with their environment and, ideally, they should neither induce any changes nor provoke undesired reactions in the neighboring or distant tissues. In general, living organisms can treat artificial implants as biotoxic (or bioincompatible [568]), bioinert (or biostable [59]), biotolerant (or biocompatible [568]), bioactive and bioresorbable materials [566-569]. Biotoxic (e.g., alloys containing cadmium, vanadium, lead and other toxic elements) materials release to the body substances in toxic concentrations and/or trigger the formation of antigens that may cause immune reactions ranging from simple allergies to inflammation to septic rejection with the associated severe health consequences. They cause atrophy, pathological change or rejection of living tissue near the material as a result of chemical, galvanic or other processes. Bioinert (this term should be used with care, since it is clear that any material introduced into the physiological environment will induce a response. However, for the purposes of biomedical implants, the term can be defined as a minimal level of response from the host tissue), such as zirconia, alumina, carbon and titanium, as well as biotolerant (e.g., polymethylmethacrylate, titanium and Co-Cr alloy) materials do not release any toxic constituents but also do not show positive interaction with living tissue. They evoke a physiological response to form a fibrous capsule, thus, isolating the material from the body. In such cases, thickness of the layer of fibrous tissue separating the material from other tissues of an organism can serve as a measure of bioinertness. Generally, both bioactivity and bioresorbability phenomena are fine examples of chemical reactivity and $CaPO_4$ (both non-substituted and ion-substituted ones) fall into these two categories of bioceramics [566-569]. A bioactive material will dissolve slightly but promote formation of a surface layer of biological apatite before interfacing directly with the tissue at the atomic level, that result in formation of a direct chemical bonds to bones. Such implants provide a good stabilization for materials that are subject to mechanical loading. A bioresorbable material will dissolve over time (regardless of the mechanism leading to the material removal) and allow a newly formed tissue to grow into any surface irregularities but may not necessarily interface directly with the material. Consequently, the functions of bioresorbable materials are to participate in dynamic processes of formation and re-absorption occurring in bone tissues; thus, bioresorbable materials are used as scaffolds or filling spacers allowing to the tissues their infiltration and substitution [193, 338, 570-572].

It is important to stress, that a distinction between the bioactive and bioresorbable bioceramics might be associated with structural factors only. Namely, bioceramics made from non-porous, dense and highly crystalline HA behaves as a bioinert (but a bioactive) material and is retained in an organism for at least 5 – 7 years without noticeable changes (Fig. 3 bottom), while a highly porous bioceramics of the same composition can be resorbed approximately within a year. Furthermore, submicron-sized HA powders are biodegraded even faster than the highly porous HA scaffolds. Other examples of bioresorbable materials comprise porous bioceramic scaffolds made of biphasic, triphasic or multiphasic $CaPO_4$ formulations [92] or bone grafts (dense or porous) made of CDHA [133], TCP [87, 573, 574] and/or ACP [434, 575]. One must stress that at the beginning of 2000-s the concepts of bioactive and bioresorbable materials have been converged and

bioactive materials are made bioresorbable, while bioresorbable ones are made bioactive [576].

Although in certain in vivo experiments inflammatory reactions were observed after implantation or injection of $CaPO_4$ [577-586], the general conclusion on using $CaPO_4$ with Ca/P ionic ratio within 1.0 – 1.7 is that all types of implants (scaffolds of various porosities and structures, as well as, powders or granules) are not only nontoxic but also induce neither inflammatory nor foreign-body reactions [120, 587, 588]. The biological response to implanted $CaPO_4$ scaffolds follows a similar cascade observed in fracture healing. This cascade includes a hematoma formation, inflammation, neovascularization, osteoclastic resorption and a new bone formation. An intermediate layer of fibrous tissue between the implants and bones has been never detected. Furthermore, $CaPO_4$ implants display the ability to directly bond to bones [566-569]. For further details, the interested readers are referred to a good review on cellular perspectives of bioceramic scaffolds for bone tissue engineering [444].

One should note that the aforementioned rare cases of the inflammatory reactions to $CaPO_4$ scaffolds were often caused by "other" reasons. For example, a high rate of wound inflammation occurred when highly porous HA scaffolds were used. In that particular case, the inflammation was explained by sharp implant edges, which irritated surrounding soft tissues [578]. To avoid this, only rounded material should be used for implantation (Fig. 10) [589]. Another reason for inflammation produced by HA scaffolds could be due to micro movements of the implants, leading to simultaneous disruption of a large number of micro-vessels, which grow into the pores of scaffolds. This would immediately produce an inflammatory reaction. Additionally, problems could arise in clinical tests connected with migration of granules used for alveolar ridge augmentation, because it might be difficult to achieve a mechanical stability of implants at the implantation sites [578]. Besides, presence of calcium pyrophosphate impurity might be the reason of inflammation [581]. Additional details on inflammatory cell responses to $CaPO_4$ might be found in a special review on this topic [582].

Osteoinduction

Before recently, it was generally considered, that alone, any type of synthetic scaffolds possessed neither osteogenic (osteogenesis is the process of laying down new bone material by osteoblasts [590]) nor osteoinductive (is the property of the material to induce bone formation de novo or ectopically (i.e., in non-bone forming sites) [590]) properties and demonstrated a minimal immediate structural support. However, a number of reports have already shown the osteoinductive properties of certain types of $CaPO_4$ bioceramics [164, 516, 541, 591-610] and the amount of such publications rapidly increases. For example, bone formation was found to occur in dog muscle inside porous $CaPO_4$ scaffolds with surface microporosity, while bone was not observed on the surface of dense bioceramics [595]. Furthermore, implantation of porous β-TCP scaffolds appeared to induce bone formation in soft tissues of dogs, while no bone formation was detected in any α-TCP ones [592]. More to the point, titanium implants coated by a microporous layer of OCP were found to induce ectopic bone formation in goat muscles, while a smooth layer of carbonated apatite on the same implants was not able to induce bone formation there [593, 594]. In another study, β-TCP powder, biphasic (HA + β-TCP) powder and intact biphasic (HA + β-TCP) rods were implanted into leg muscles of mice and dorsal muscles of rabbits [601]. One month and three months after implantation, samples were harvested for biological and histological analysis. New bone tissues were observed in 10 of 10 samples for β-TCP powder, 3 of 10 samples biphasic powder and 9 of 10 samples for intact biphasic rods at 3rd month in mice, but not in rabbits. The authors concluded that the chemical composition was the prerequisite in osteoinduction, while porosity contributed to more bone formation [601]. Therefore, researchers have already discovered the ways to prepare osteoinductive $CaPO_4$ scaffolds.

Unfortunately, the underlying mechanism(s) leading to bone induction by synthetic materials remains largely unknown. Nevertheless, besides the specific genetic factors [599] and chosen animals [601], the dissolution/precipitation behavior of $CaPO_4$ [611], their particle size [609], microporosity [597, 601, 612, 613], physicochemical properties [595, 597], composition [601], the specific surface area [613],

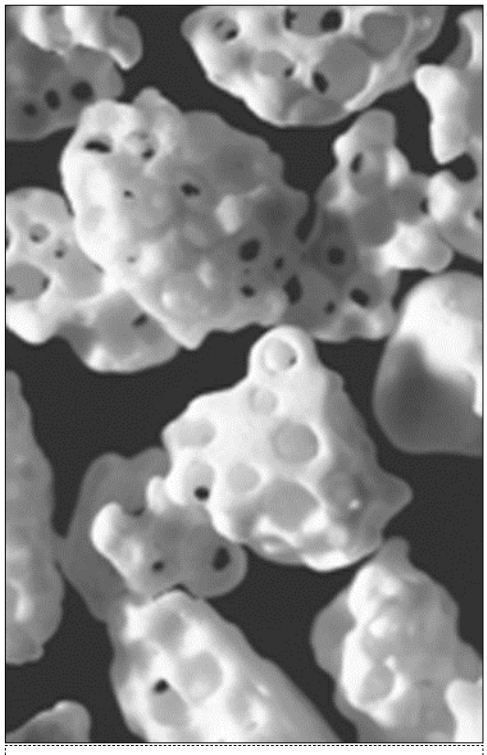


Fig. 10. Rounded β-TCP granules of 2.6 – 4.8 mm in size, providing no sharp edges for combination with bone cement. Reprinted from Ref. [589] with permission.

nanostructure [600], as well as the surface topography and geometry [596, 614-618] have been pointed out as the relevant parameters. A positive effect of increased microporosity on the ectopic bone formation could be both direct and indirect. Firstly, an increased microporosity is directly related to the changes in surface topography, i.e. increases a surface roughness, which affects the cellular differentiation [618]. Secondly, an increased microporosity indirectly means a larger surface that is exposed to the body fluids leading to elevated dissolution/precipitation phenomena as compared to non-microporous surfaces. In addition, other hypotheses are also available. Namely, Reddi explained the apparent osteoinductive properties as an ability of particular bioceramics to concentrate bone growth factors, which are circulating in biological fluids, and those growth factors induce bone formation [614]. Other researchers proposed a similar hypothesis that the intrinsic osteoinduction by $CaPO_4$ scaffolds was a result of adsorption of osteoinductive substances on their surface [596]. Moreover, Ripamonti [615] and Kuboki et al., [616] independently postulated that the geometry of $CaPO_4$ bioceramics is a critical parameter in bone induction. Specifically, bone induction by $CaPO_4$ was never observed on flat surfaces. All osteoinductive cases were observed on either porous scaffolds or structures contained well-defined concavities. What's more, bone formation was never observed on the peripheries of porous scaffolds and was always found inside the pores or concavities, aligning the surface [193]. Some researchers speculated that a low oxygen tension in the central region of implants might provoke a dedifferentiation of pericytes from blood micro-vessels into osteoblasts [619]. Finally but yet importantly, both nano-structured rough surfaces and a surface charge on implants were found to cause an asymmetrical division of the stem cells into osteoblasts, which is important for osteoinduction [612].

Nevertheless, to finalize this topic, it is worth citing a conclusion made by Boyan and Schwartz [620]: "Synthetic materials are presently used routinely as osteoconductive bone graft substitutes, but before purely synthetic materials can be used to treat bone defects in humans where an osteoinductive agent is

required, a more complete appreciation of the biology of bone regeneration is needed. An understanding is needed of how synthetic materials modulate the migration, attachment, proliferation and differentiation of mesenchymal stem cells, how cells on the surface of a material affect other progenitor cells in the peri-implant tissue, how vascular progenitors can be recruited and a neovasculature maintained, and how remodeling of newly formed bone can be controlled." (p. 9).

Biodegradation

Shortly after implantation, a healing process is initiated by compositional changes of the surrounding bio-fluids and adsorption of biomolecules. Following this, various types of cells reach the surface of $CaPO_4$ scaffolds and the adsorbed layer dictates the ways the cells respond. Further, a biodegradation (which can be envisioned as an in vivo process by which an implanted material breaks down into either simpler components or components of the smaller dimensions) of the implanted $CaPO_4$ scaffolds begin. This process can occur by three possible ways: 1) physical: due to abrasion, fracture and/or disintegration, 2) chemical: due to physicochemical dissolution of the implanted phases of $CaPO_4$ with a possibility of phase transformations into other phases of $CaPO_4$, as well as their precipitation and 3) biological: due to cellular activity (so called, bioresorption). In biological systems, all these processes take place simultaneously and/or in competition with each other. Since the existing $CaPO_4$ are differentiated by Ca/P ratio, basicity/acidity and solubility (Table 1), in the first instance, their degradation kinetics and mechanisms depend on the chosen type of $CaPO_4$ [621, 622]. Since dissolution is a physical chemistry process, it is controlled by some factors, such as $CaPO_4$ solubility, surface area to volume ratio, local acidity, fluid convection and temperature. For HA and FA, the dissolution mechanism in acids has been described by a sequence of four successive chemical equations, in which several other $CaPO_4$, such as TCP, DCPD/DCPA and MCPM/MCPA, appear as virtual intermediate phases [623, 624].

With a few exceptions, dissolution rates of $CaPO_4$ are inversely proportional to the Ca/P ratio (except of TTCP), phase purity and crystalline size, as well as it is directly related to both the porosity and the surface area. In addition, phase transformations might occur with DCPA, DCPD, OCP, α-TCP, β-TCP and ACP because they are unstable in aqueous environment under the physiological conditions [625]. Bioresorption is a biological process mediated by cells (mainly, osteoclasts and, in a lesser extent, macrophages) [626, 627]. It depends on the response of cells to their environment. Osteoclasts attach firmly to the implant and dissolve $CaPO_4$ by secreting an enzyme carbonic anhydrase or any other acid, leading to a local pH drop to ~ 4 – 5 [628]. Formation of multiple spine-like crystals at the exposed areas of β-TCP was discovered [629]. Furthermore, nanodimensional particles of $CaPO_4$ can also be phagocytosed by cells, i.e. they are incorporated into cytoplasm and thereafter dissolved by acid attack and/or enzymatic processes [630]. A study is available [631], in which a comparison was made between the solubility and osteoclastic resorbability of 3 types of $CaPO_4$ (DCPA, ACP and HA) + β-calcium pyrophosphate (β-CPP) powders having the monodisperse particle size distributions. The authors discovered that with the exception of β-CPP, the difference in solubility among different calcium phosphates became neither mitigated nor reversed but augmented in the resorptive osteoclastic milieu. Namely, DCPA (the phase with the highest solubility) was resorbed more intensely than any other calcium phosphate, whereas HA (the phase with the lowest solubility) was resorbed the least. β-CPP became retained inside the cells for the longest period of time, indicating hindered digestion of only this particular type of calcium phosphate. Genesis of osteoclasts was found to be mildly hindered in the presence of HA, ACP and DCPA, but not in the presence of β-CPP. HA appeared to be the most viable compound with respect to the mitochondrial succinic dehydrogenase activity. The authors concluded that chemistry did have a direct effect on biology, while biology neither overrode nor reversed the chemical propensities of calcium phosphates with which it interacted, but rather augmented and took a direct advantage of them [631]. Similar conclusions on both the resorbability and dissolution behavior of OCP, β-TCP and HA were made in another study [625]. In addition, in vivo biodegradation of MCPA was found to be faster than that of bovine HA [632]. Thus, one can conclude that in

vivo biodegradation kinetics of $CaPO_4$ seems to correlate well with their solubility. Nevertheless, one must keep in mind that this is a very complicated combination of various non-equilibrium processes, occurring simultaneously and/or in competition with each other [633].

Strictly speaking, the processes happen in vitro do not necessarily represent the ones occurring in vivo and vice versa; nevertheless, in vitro experiments are widely performed. Usually, an in vitro biodegradation of $CaPO_4$ scaffolds is simulated by suspending them in a slightly acidic (pH ~ 4) buffer and monitoring the release of major ions with time [622, 634-637]. An acidic buffer, to some extent, mimics the acidic environment during osteoclastic activity. In one study, an in vivo behavior of porous β-TCP scaffolds prepared from rod-shaped particles and that prepared from non-rod-shaped particles in the rabbit femur was compared. Although the porosities of both types of β-TCP scaffolds were almost the same, a more active osteogenesis was preserved in the region where rod-shaped ones were implanted [638]. Furthermore, the dimensions of both the particles [609] and the surface microstructure [604] were found to influence the osteoinductive potential. These results implied that the microstructure affected the activity of bone cells and subsequent bone replacement.

Cellular Response

Fixation of any implants in the body is a complex dynamic process that remodels the interface between the implants and living tissues at all dimensional levels, from the molecular up to the cell and tissue morphology level, and at all time scales, from the first second up to several years after implantation. Immediately following the implantation, a space filled with biological fluids appears next to the implant surface. With time, cells are adsorbed at the implant surface that will give rise to their proliferation and differentiation towards bone cells, followed by revascularisation and eventual gap closing. Ideally, a strong bond is formed between the implants and surrounding tissues [568]. An interesting study on the interfacial interactions between calcined HA and substrates has been performed [639], where the interested readers are referred for further details.

The aforementioned paragraph clearly demonstrates an importance of studies on cellular responses to $CaPO_4$ scaffolds. Therefore, such investigations have been performed extensively for several decades [582, 640-655]. For example, bioceramic discs made of 7 different types of $CaPO_4$ (TTCP, HA, carbonate apatite, β-TCP, α-TCP, OCP and DCPD) were incubated in osteoclastic cell cultures for 2 days. In all cases, similar cell morphologies and good cell viability were observed; hoverer, different levels of resorbability of various types of $CaPO_4$ were detected [643]. Similar results were found for fluoridated HA coatings [645]. Experiments performed with human osteoblasts revealed that nanostructured bioceramics prepared from nano-sized HA showed significant enhancement in mineralization compared to microstructured HA bioceramics [644]. In addition, the influence of lengths and surface areas of rod-shaped HA on cellular response were studied. Again, similar cell morphologies and good cell viability were observed; however, it was concluded that high surface area could increase cell-particle interaction [648]. Nevertheless, another study with cellular response to rod-shaped HA bioceramics, revealed that some types of crystals might trigger a severe inflammatory response [651]. In addition, $CaPO_4$-based sealers appeared to show less cytotoxicity and inflammatory mediators compared with other sealers [646]. More examples are available in literature.

Cellular biodegradation of $CaPO_4$ scaffolds is known to depend on its phases. For example, a higher solubility of β-TCP was shown to prevent L-929 fibroblast cell adhesion, thereby leading to damage and rupture of the cells [656]. A mouse ectopic model study indicated the maximal bone growth for the 80 : 20 β-TCP : HA biphasic formulations preloaded with human mesenchymal stem cells when compared to other $CaPO_4$ [657]. The effects of substrate microstructure and crystallinity have been corroborated with an in vivo rabbit femur model, where rod-like crystalline β-TCP was reported to enhance osteogenesis when compared to non-rod like crystalline β-TCP [638]. Additionally, using a dog mandibular defect model, a higher bone formation on a scaffold surface coated by nanodimensional HA was observed when compared to that coated by a

micro-dimensional HA [658]. Furthermore, studies revealed a stronger stress signaling response by osteoblast precursor cells in 3D scaffolds when compared to 2D surfaces [659].

Mesenchymal stem cells are one of the most attractive cellular lines for application as bone grafts [660, 661]. Early investigations by Okumura, et al. indicated an adhesion, proliferation and differentiation, which ultimately became new bone and integrated with HA scaffolds [641]. Later, a sustained co-culture of endothelial cells and osteoblasts on HA scaffolds for up to 6 weeks was demonstrated [662]. Furthermore, a release of factors by endothelial and osteoblast cells in co-culture supported proliferation and differentiation was suggested to ultimately result in microcapillary-like vessel formation and supported a neo-tissue growth within the scaffold [444]. More to the point, investigation of rat calvaria osteoblasts cultured on transparent HA bioceramics, as well as the analysis of osteogenic-induced human bone marrow stromal cells at different time points of culturing indicated to a good cytocompatibility of HA bioceramics and revealed favorable cell proliferation. The positive results for other types of cells have been obtained in other studies [202, 403-405, 663-665].

Interestingly that HA scaffolds with marrow stromal cells in a perfused environment were reported to result in ~ 85 % increase in mean core strength, a ~ 130 % increase in failure energy and a ~ 355 % increase in post-failure strength. The increase in mineral quantity and promotion of the uniform mineral distribution in that study was suggested to attribute to the perfusion effect [535]. Additionally, other investigators indicated to mechanical properties increasing for other $CaPO_4$ scaffolds after induced osteogenesis [534, 537].

To finalize this section, one should mention on the recent developments to influence the cellular response. First, to facilitate interactions with cells, the surface of $CaPO_4$ scaffolds can be functionalized [666-670]. Second, it appears that crystals of biological apatite of calcified tissues exhibit different orientations depending on the tissue. Namely, in vertebrate bones and tooth enamel surfaces, the respective *a*, *b*-planes and *c*-planes of the apatite crystals are preferentially exposed. Therefore, ideally, this should be taken into account in artificial bone grafts. Recently, a novel process to fabricate dense HA bioceramics with highly preferred orientation to the a,b-plane was developed.

The results revealed that increasing the *a*,*b*-plane orientation degree shifted the surface charge from negative to positive and decreased the surface wettability with simultaneous decreasing of cell attachment efficiency [671-673]. The latter finding resulted in further developments on preparation of oriented $CaPO_4$ compounds [674-676].

Future Developments

Philosophically, the increase in life expectancy requires biological solutions to all biomedical problems, including orthopedic ones, which previously were managed with mechanical solutions. Therefore, since the end of 1990's, the biomaterials research focuses on tissue regeneration instead of tissue replacement [677].

The alternatives include use hierarchical bioactive scaffolds to engineer in vitro living cellular constructs for transplantation or use bioresorbable bioactive particulates or porous networks to activate in vivo the mechanisms of tissue regeneration [678, 679]. Thus, the aim of $CaPO_4$ is to prepare artificial porous scaffolds able to provide the physical and chemical cues to guide cell seeding, differentiation and assembly into 3D tissues of a newly formed bone. Particle sizes, shape and surface roughness of the scaffolds are known to affect cellular adhesion, proliferation and phenotype [33-39]. Additionally, the surface energy might play a role in attracting particular proteins to the $CaPO_4$ surface and, in turn, this will affect the cells affinity to the material. More to the point, cells are exceedingly sensitive to the chemical composition and their bone-forming functions can be dependent on grain morphology of the scaffolds. For example, osteoblast functions were found to increase on nanodimensional fibers if compared to nanodimensional spheres because the former more closely approximated the shape of biological apatite in bones [680]. Besides, a significantly higher osteoblast proliferation on HA bioceramics sintered at 1200 °C as compared to that on HA bioceramics sintered at 800 °C and 1000 °C was reported [681]. Furthermore, since ions of calcium and

orthophosphate are known to regulate bone metabolism, $CaPO_4$ appear to be among the few bone graft substitute materials, which can be considered as a drug. A schematic drawing of the key scaffold properties affecting a cascade of biological processes occurring after $CaPO_4$ implantation is shown in Fig. 11 [682].

Thus, to meet the tissue engineering requirements, much attention is devoted to further improvements of $CaPO_4$ scaffolds [683-685]. From the chemical point of view, the developments include synthesis of novel ion-substituted $CaPO_4$ [686-690]. From the material point of view, the major research topics include nanodimensional and nanocrystalline structures [691-694], amorphous compounds [695, 696], (bio)organic/$CaPO_4$ biocomposites and hybrid formulations [373, 697, 698], biphasic, triphasic and multiphasic formulations [92], as well as various types of structures, forms and shapes. The latter comprise fibers, whiskers and filaments [699-712], macro-, micro- and nano-sized spheres, beads and granules [711-731], micro- and nano-sized tubes [732-736], porous 3D scaffolds made of ACP [737], TCP [81, 84, 738-741], HA [56, 742-746] and biphasic formulations [716, 728, 741, 747-752], structures with graded porosity [87, 390, 455, 458, 524, 553-558] and hierarchically organized ones [753, 754]. Furthermore, an addition of defects through an intensive milling [755, 756] or their removal by a thermal treatment [757] can be used to modify a chemical reactivity of $CaPO_4$. Besides, more attention should be paid to a crystallographically aligned $CaPO_4$ bioceramics [758].

Clinical Applications

To date, there are just a few publications on clinical application of cell-seeded $CaPO_4$ scaffolds for bone tissue engineering of humans. Namely, Quarto et al., [759] were the first to report a treatment of large (4 – 7 cm) bone defects of the tibia, ulna and humerus in three patients from 16 to 41 years old, where the conventional surgical therapies had failed. The authors implanted a custom-made unresorbable porous HA scaffolds seeded with in vitro expanded autologous bone marrow stromal cells. In all three patients, radiographs and computed tomographic scans revealed abundant callus formation along the implants and good integration at the interfaces with the host bones by the second month after surgery [759]. In the same year, Vacanti et al., [760] reported the case of a man who had a traumatic avulsion of the distal phalanx of a thumb. The phalanx was replaced with a specially treated natural coral (porous HA; 500-pore ProOsteon) implant that was previously seeded with in vitro expanded autologous periosteal cells. The procedure resulted in the functional restoration of a stable and biomechanically sound thumb of normal length, without the pain and complications that are usually associated with harvesting a bone graft.

Morishita et al., [761] treated a defect resulting from surgery of benign bone tumors in three patients using HA scaffolds seeded with in vitro expanded autologous bone marrow stromal cells after osteogenic differentiation of the cells. Two bone defects in a tibia and one defect in a femur were treated. Although ectopic implants in nude mice were mentioned to show the osteogenicity of the cells, details such as the percentage of the implants containing bone and at what quantities were not reported. Furthermore, cell-seeded $CaPO_4$ scaffolds were found to be superior to autograft, allograft or cell-seeded allograft in terms of bone formation at ectopic implantation sites [762].

An innovative appliance named the stem cell screen-enrich-combine(-biomaterials) circulating system (SECCS) was designed in another study [763]. In that study, 42 patients who required bone graft underwent SECCS-based treatment. Their bone marrow samples and β-TCP granules were processed in the SECCS for 10-15 minutes, to produce MSC/β-TCP composites. These composites were grafted back into bone defect sites. The results showed 85.53% ± 7.95% autologous mesenchymal stem cells were successfully screened, enriched, and seeded on the β-TCP scaffolds synchronously. Clinically, all patients obtained satisfactory bone healing [763].

Besides, it has been hypothesized that dental follicle cells combined with β-TCP scaffolds might become a novel therapeutic strategy to restore periodontal defects [764]. In still another study, the behavior of human periodontal ligament stem cells on a HA-coated genipin-chitosan scaffold in vitro was studied followed by evaluation on bone repair in vivo [765]. The study demonstrated the potential of this formulation for bone regeneration.

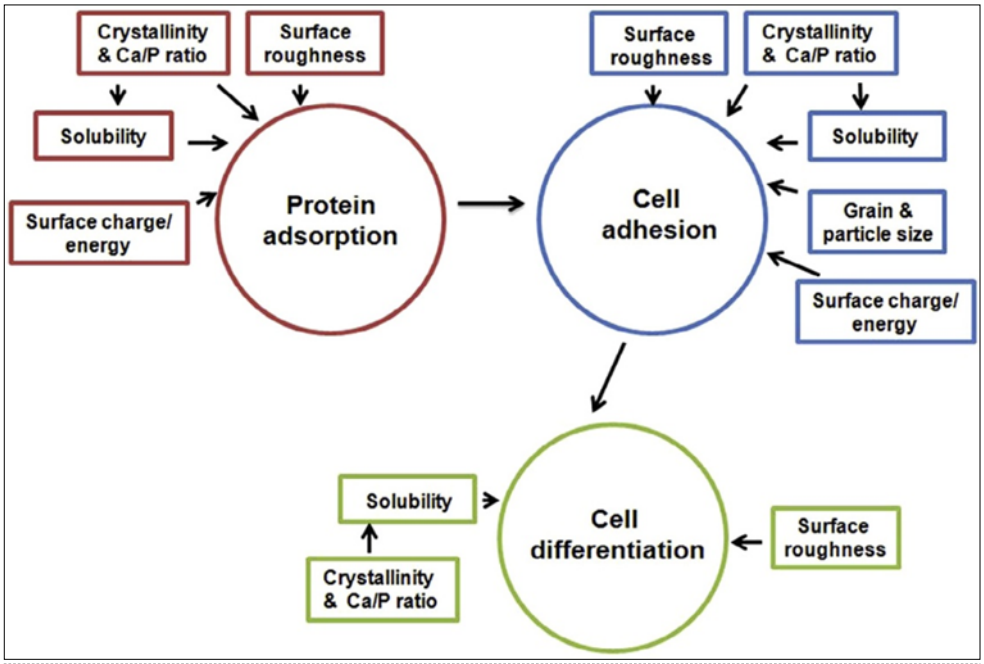


Fig. 11. A schematic drawing of the key scaffold properties affecting a cascade of biological processes occurring after $CaPO_4$ implantation. Reprinted from Ref. [682] with permission.

To finalize this section, one must mention that $CaPO_4$ scaffolds are also used in veterinary orthopedics for favoring animal bone healing in areas, in which bony defects exist [766, 767].

Conclusions

The field of bone tissue engineering has experienced exponential growth over the last 30 years, however the disconnect between research and the clinic, with a pull towards complexity in academia and a push back towards simplicity and in the clinical setting, looms to hinder further progress in the field. From a clinical point of view, bone defects and fractures vary in its specific cause e.g., fracture (single- vs. multi-fragmentary), non-unions, tumor, etc. and each patient has an naturally personalized endogenous healing pattern based on their physical status, age, relevant comorbidities, compliance and loading patterns, and life style choices such as smoking, diet, etc. Therefore, a "one concept fits all" solution is unlikely to be successful in any therapy concept rooted in regenerative medicine. In addition, researchers also need to take into account the end user of the products, namely the surgeons. Over complicated engineering designs can hinder the overall adoption rate of new technologies and treatment options, emphasis should be placed on product usability and technical feasibility. Moreover, due to the innate regenerative potential of bones, researchers should place less emphasis on precisely mimicking the physical properties of the tissue to be regenerated and more on facilitating and leverage the guidance of the endogenous regenerative capabilities of the host tissues [768].

To conclude, one should mention that despite the remarkable scientific progress over the last decades, we are still far away from "pulling a newly engineered organ out of the Petri dish". Therefore, a variety of scaffolds have been already developed for bone tissue engineering to be used as spacemakers, biodegradable substitutes for transplanting to the new bones, matrices for drug delivery system, as well as supporting structures enhancing adhesion, proliferation and production of seeded cells according to the circumstances of the bone defects. Nevertheless, scaffolds to be clinically completely satisfied have not been developed yet. Therefore, development of more functional scaffolds is required [768].

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