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REVIEW

Calcium orthophosphate-based biocomposites and hybrid biomaterials

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Abstract In this review article, the state-of-the-art of calcium orthophosphate-based biocomposites and hybrid biomaterials suitable for biomedical applications is presented. This subject belongs to a rapidly expanding area of science and research, because these types of biomaterials offer many significant and exciting possibilities for hard tissue regeneration. Through the successful combinations of the desired properties of matrix materials with those of fillers (in such systems, calcium orthophosphates might play either role), innovative bone graft biomaterials can be designed. The review starts with an introduction to locate the reader. Further, general information on composites and hybrid materials including a brief description of their major constituents are presented. Various types of calcium orthophosphate-based bone-analogue biocomposites and hybrid biomaterials those are either already in use or being investigated for various biomedical applications are then extensively discussed. Many different formulations in terms of the material constituents, fabrication technologies, structural and bioactive properties, as well as both in vitro and in vivo characteristics have been already proposed. Among the others, the nano-structurally controlled biocomposites, those with nanosized calcium orthophosphates, biomimetically fabricated formulations with collagen, chitin and/or gelatin, as well as various functionally graded structures seem to be the most promising candidates for clinical applications. The specific advantages of using calcium orthophosphate-based biocomposites and hybrid biomaterials in the selected applications are highlighted. As the way from a laboratory to a hospital is a long one and the prospective biomedical candidates have to meet many different necessities, the review also examines the critical issues and scientific challenges that require further research and development.

Abbreviations

EVOH	Ethylene-vinyl alcohol copolymer
IBS	Injectable bone substitute
HDPE	High-density polyethylene
HPMC	Hydroxypropylmethylcellulose
PAA	Polyacrylic acid
PBT	Polybutyleneterephthalate
PCL	Poly(ε-caprolactone)
PDLLA	Poly-DL-lactic acid
PEEK	Polyetheretherketone
PEG	Polyethylene glycol
PGA	Polyglycolic acid
PHB	Polyhydroxybutyrate
PHBHV	Poly(hydroxybutyrate-*co*-hydroxyvalerate)
PHEMA	Polyhydroxyethyl methacrylate
PHV	Polyhydroxyvalerate
PLA	Polylactic acid
PLGA	Poly(lactic-*co*-glycolic) acid
PLLA	Poly(L-lactic acid)
PMMA	Polymethylmethacrylate
PPF	Poly(propylene-*co*-fumarate)
PS	Polysulfone
PSZ	Partially stabilized zirconia
PTFE	Polytetrafluoroethylene
PVA	Polyvinyl alcohol
PVAP	Polyvinyl alcohol phosphate
SEVA	Starch/ethylene vinyl alcohol copolymer

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Introduction

The fracture of bones due to various traumas or natural aging is a typical type of a tissue failure. An operative treatment frequently requires implantation of a temporary or a permanent prosthesis, which still is a challenge for orthopedic surgeons, especially in the cases of large bone defects. A fast aging of the population and serious drawbacks of natural bone grafts make the situation even worse; therefore, there is a high clinical demand for bone substitutes. Unfortunately, a medical application of xenografts (e.g., bovine bone) is generally associated with potential viral infections. In addition, xenografts have a low osteogenicity, an increased immunogenicity and, usually, resorb more rapidly than autogenous bone. Similar limitations are also valid for human allografts (i.e., tissue transplantation between individuals of the same species but of non-identical genetic composition), where the concerns about potential risks of transmitting tumor cells, a variety of bacterial and viral infections, as well as immunological and blood group incompatibility are even stronger [1–3]. Moreover, harvesting and conservation of allografts (exogenous bones) are additional limiting factors. Autografts (endogenous bones) are still the "golden standard" among any substitution materials because they are osteogenic, osteoinductive, osteoconductive, completely biocompatible, non-toxic, and do not cause any immunological problems (non-allergic). They contain viable osteogenic cells, bone matrix proteins, and support bone growth. Usually, autografts are well accepted by the body and rapidly integrated into the surrounding bone tissues. Due to these reasons, they are used routinely for a long period with good clinical results [3, 4]; however, it is fair to say on complication cases, those frequently happened in the past [5, 6]. Unfortunately, a limited number of donor sites restrict the quantity of autografts harvested from the iliac crest or other locations of the patient's own body. Also, their medical application is always associated with additional traumas and scars resulting from the extraction of a donor tissue during a superfluous surgical operation, which requires further healing at the donation site and can involve long-term postoperative pain [1, 6–9]. Thus, any types of a biologically derived transplant appear to be imperfect solutions, mainly due to a restricted quantity of donor tissues, donor site morbidity, as well as potential risks of an immunological incompatibility and disease transfer [7, 9, 10]. In this light, man-made materials (alloplastic or synthetic bone grafts) stand out as a reasonable option because they are easily available, might be processed and modified to suit the specific needs of a given application [11, 12]. What's more, there are no concerns about potential infections, immunological incompatibility, sterility, and donor site morbidity. Therefore, investigations on artificial materials for bone tissue repair appear to be one of the key subjects in the field of biomaterials research for clinical applications [13].

Currently, there are several classes of synthetic bone grafting biomaterials for in vivo applications [14–17]. The examples include natural coral, coral-derived materials, bovine porous demineralized bone, human demineralized bone matrix, bioactive glasses, glass–ceramics, and calcium orthophosphates [9]. All of these biomaterials are biocompatible and osteoconductive, guiding bone tissue from the edges toward the center of the defect, and aim to provide a scaffold of interconnected pores with pore dimensions ranging from 200 [18, 19] to 2 mm [20], to facilitate tissue and vessel ingrowths. Among them, porous bioceramics made of calcium orthophosphates appear to be very prominent due to both the excellent biocompatibility and bonding ability to living bone in the body. This is directly related to the fact that the inorganic material of mammalian calcified tissues, i.e., of bone and teeth, consists of calcium orthophosphates [21–23]. Due to this reason, other artificial materials are normally encapsulated by fibrous tissue, when implanted in body defects, while calcium orthophosphates are not [24]. Several types of calcium orthophosphate-based bioceramics with different chemical composition are already on the market [9, 25]. Unfortunately, as for any ceramic material, calcium orthophosphate bioceramics by itself lack the mechanical and elastic properties of the calcified tissues; namely, scaffolds made of calcium orthophosphates only suffer from a low elasticity, a high brittleness, a poor tensile strength, a low mechanical reliability, and fracture toughness, which leads to the concerns about their mechanical performance after implantation [26–28]. Besides, in many cases, it is difficult to form calcium orthophosphate bioceramics into the desired shapes.

The superior strength and partial elasticity of biological calcified tissues (e.g., bones) are due to the presence of bioorganic polymers (mainly, collagen type I fibers[1]) rather than to a natural ceramic (mainly, a poorly crystalline ion-substituted calcium-deficient hydroxyapatite, often referred to as "biological apatite") phase [30, 31]. The elastic collagen fibers are aligned in bone along the main stress directions. The biochemical composition of bone is given in Table 1 [32]. A decalcified bone becomes very flexible being easily twisted, whereas a bone without collagen is very brittle; thus, the inorganic nanocrystals of biological apatite provide with the hardness and stiffness, whereas the bioorganic fibers are responsible for the elasticity and

[1] One molecule of collagen type I is a triple helix with 338 repetitions of amino acid residues and is about 300 nm in length [29]. Additionally, bone contains small quantities of other bioorganic materials, such as proteins, polysaccharides, and lipids, as well as bone contains cells and blood vessels.

Table 1 The biochemical composition of bone [32]

Inorganic phases	wt%	Bioorganic phases	wt%
Calcium orthophosphates (biological apatite)	~60	Collagen type I	~20
Water	~9	Non-collagenous proteins: osteocalcin, osteonectin, osteopontin, thrombospondin, morphogenetic proteins, sialoprotein, serum proteins	~3
Carbonates	~4	Other traces: polysaccharides, lipids, cytokines	Balance
Citrates	~0.9	Primary bone cells: osteoblasts, osteocytes, osteoclasts	Balance
Sodium	~0.7		
Magnesium	~0.5		
Other traces: Cl^-, F^-, K^+ Sr^{2+}, Pb^{2+}, Zn^{2+}, Cu^{2+}, Fe^{2+}	Balance		

The composition is varied from species to species and from bone to bone

toughness [22, 33]. In bones, both types of materials integrate each other into a nanometric scale in such a way that the crystallite size, fibers orientation, short-range order between the components, etc. determine its nanostructure and therefore the function and mechanical properties of the entire composite [29, 34–38]. From the mechanical point of view, bone is a tough material at low strain rates but fractures more like a brittle material at high strain rates; generally, it is rather weak in tension and shear, particularly along the longitudinal plane. Besides, bone is an anisotropic material because its properties are directionally dependent [21, 22, 28].

It remains a great challenge to design the ideal bone graft that emulates nature's own structures or functions. Certainly, the successful design requires an appreciation of the structure of bone. According to expectations, the ideal bone graft should be benign, available in a variety of forms and sizes; all with sufficient mechanical properties for use in load-bearing sites form a chemical bond at the bone/implant interface, as well as be osteogenic, osteoinductive, osteoconductive, biocompatible, completely biodegradable at the expense of bone growth and moldable to fill and restore bone defects [26, 36, 39]. Further, it should resemble the chemical composition of bones (thus, the presence of calcium orthophosphates is mandatory), exhibit contiguous porosity to encourage invasion by the live host tissue, as well as possess both viscoelastic and semi-brittle behavior, as bones do [40–43]. Moreover, the degradation kinetics of the ideal implant should be adjusted to the healing rate of the human tissue with absence of any chemical or biological irritation and/or toxicity caused by substances, which are released due to corrosion or degradation. Ideally, the combined mechanical strength of the implant and the ingrowing bone should remain constant throughout the regenerative process. Furthermore, the substitution implant material should not disturb significantly the stress environment of the surrounding living tissue [44]. Finally, there is an opinion, that in the case of a serious trauma, bone should fracture rather than the implant [26]. A good sterilizability, storability, and processability, as well as a relatively low cost are also of a great importance to permit a clinical application. Unfortunately, no artificial biomaterial is yet available, which embodies all these requirements and unlikely it will appear in the nearest future. Until now, most of the available biomaterials appear to be either predominantly osteogenic or osteoinductive or else purely osteoconductive [2].

Careful consideration of the bone type and mechanical properties are needed to design bone substitutes. Indeed, in high load-bearing bones such as the femur, the stiffness of the implant needs to be adequate, not too stiff to result in strain shielding, but rigid enough to present stability. However, in relatively low load-bearing applications such as cranial bone repairs, it is more important to have stability and the correct three-dimensional shapes for esthetic reasons. One of the most promising alternatives is to apply materials with similar composition and nanostructure to that of bone tissue [36]. Mimicking the structure of calcified tissues and addressing the limitations of the individual materials, development of organic–inorganic hybrid biomaterials provides excellent possibilities for improving the conventional bone implants. In this sense, suitable biocomposites of tailored physical, biological, and mechanical properties with the predictable degradation behavior can be prepared by combining biologically relevant calcium orthophosphates with bioresorbable polymers [45, 46]. As a rule, the general behavior of these bioorganic/calcium orthophosphate composites is dependent on nature, structure, and relative contents of the constitutive components, although other parameters such as the preparation conditions also determine the properties of the final materials. Currently, biocomposites with calcium orthophosphates incorporated as either a filler or a coating (or both) either into or onto a biodegradable polymer matrix, in the form of particles or fibers, are increasingly considered for using as bone tissue engineering scaffolds due to their improved physical, biological, and mechanical properties [47–53]. In addition, such biocomposites could fulfill general

requirements to the next generation of biomaterials, those should combine the bioactive and bioresorbable properties to activate in vivo mechanisms of tissue regeneration, stimulating the body to heal itself and leading to the replacement of the implants by the regenerating tissue [46, 54, 55]. Thus, through the successful combinations of ductile polymer matrixes with hard and bioactive particulate bioceramic fillers, optimal materials can be designed and, ideally, this approach could lead to a superior construction to be used as either implants or posterior dental restorative material [56].

A lint-reinforced plaster was the first composite used in clinical orthopedics as an external immobilizer (bandage) in the treatment of bone fracture by Mathijsen in 1852 [57], followed by Dreesman in 1892 [58]. A great progress in the clinical application of various types of composite materials has been achieved since then. Based on the previous experience and newly gained knowledge, various composite materials with tailored mechanical and biological performance can be manufactured and used to meet various clinical requirements [59]. However, this review presents only a brief history and advances in the field of calcium orthophosphate-based biocomposites and hybrid biomaterials suitable for biomedical application. The majority of the reviewed literature is restricted to the recent publications; a limited number of papers published in the 20th century have been cited. Various aspects of the material constituents, fabrication technologies, structural and bioactive properties, and phase interaction have been considered and discussed in details. Finally, several critical issues and scientific challenges that are needed for further advancement are outlined.

General information on composites and biocomposites

According to Wikipedia, the free encyclopedia, "*composite materials* (or *composites* for short) are engineered materials made from two or more constituent materials with significantly different physical or chemical properties and which remain separate and distinct on a macroscopic level within the finished structure" [60]. Thus, composites are always heterogeneous. Following the point of view of some predecessors, we also consider that "for the purpose of this review, composites are defined as those having a distinct phase distributed through their bulk, as opposed to modular or coated components" [61, p. 1329]. For this reason, with a few important exceptions, the structures obtained by soaking of various materials in supersaturated solutions containing ions of calcium and orthophosphate (e.g., Refs. [62–67]), those obtained by coating of various materials by calcium orthophosphates (e.g., Refs. [68–73]), as well as calcium orthophosphates coated by other compounds [74] have not been considered; however, composite coatings have been considered. Occasionally, porous calcium orthophosphate scaffolds filled by cells inside the pores [75, 76], as well as calcium orthophosphates impregnated by biologically active substances [77] are also defined as composites; nevertheless, such structures have not been considered in this review either.

In any composite, there are two major categories of constituent materials: a matrix (or a continuous phase) and (a) dispersed phase(s). In order to create a composite, at least one portion of each type is required. General information on the major fabrication and processing techniques might be found elsewhere [61]. The continuous phase is responsible for filling the volume, as well as it surrounds, and supports the dispersed material(s) by maintaining their relative positions. The dispersed phase(s) is(are) usually responsible for enhancing one or more properties of the matrix. Most of the composites target an enhancement of mechanical properties of the matrix, such as stiffness and strength; however, other properties, such as erosion stability, transport properties (electrical or thermal), radiopacity, density, or biocompatibility, might also be of a great interest. This synergism produces the properties, which are unavailable from the individual constituent materials [78]. What's more, by controlling the volume fractions and local and global arrangement of the dispersed phase, the properties and design of composites can be varied and tailored to suit the necessary conditions. For example, in the case of ceramics, the dispersed phase serves to impede crack growth. In this case, it acts as reinforcement. A number of methods, including deflecting crack tips, forming bridges across crack faces, absorbing energy during pullout and causing a redistribution of stresses in regions adjacent to crack tips, can be used to accomplish this [79]. Other factors to be considered in composites are the volume fraction of (a) dispersed phase(s), its(their) orientation and homogeneity of the overall composite. For example, higher volume fractions of reinforcement phases tend to improve the mechanical properties of the composites, while continuous and aligned fibers best prevent crack propagation with the added property of anisotropic behavior. Furthermore, the uniform distribution of the dispersed phase is also desirable, as it imparts consistent properties to the composite [60, 78].

In general, composites might be simple, complex, graded, and hierarchical. The term "a simple composite" is referred to the composites those result from the homogeneous dispersion of one dispersed phase throughout a matrix. The term "a complex composite" is referred to the composites those result from the homogeneous dispersion of several dispersed phases throughout one matrix. The term "a graded composite" is referred to the composites those result from the intentionally structurally

inhomogeneous dispersion of one or several dispersed phases throughout one matrix. The term "a hierarchical composite" is referred to the cases, when fine entities of either a simple or a complex composite is somehow aggregated to form coarser ones (e.g., granules or particles) which afterwards are dispersed inside another matrix to produce the second hierarchical scale of the composite structure. Another classification type of the available composites is based on either the matrix materials (metals, ceramics and polymers) or the reinforcement dimensions/shapes (particulates, whiskers/short fibers, and continuous fibers) [59].

In most cases, three interdependent factors must be considered in designing of any composite: (i) selection of the suitable matrix and dispersed materials, (ii) choice of appropriate fabrication and processing methods, (iii) internal and external designs of the device itself [61]. Besides, any composite must be formed to shape. To do this, the matrix material can be added before or after the dispersed material has been placed into a mold cavity or onto the mold surface. The matrix material experiences a melding event, depending upon the nature of the matrix material, that can occur in various ways such as chemical polymerization, setting, curing, or solidification from a melted state. Due to a general inhomogeneity, the physical properties of many composite materials are not isotropic, but rather orthotropic (i.e., there are different properties or strengths in different orthogonal directions) [60, 78].

Biocomposites are defined as the composites able to interact well with the human body in vivo and, ideally, contain one or more component that stimulates the healing process and uptake of the implant. Thus, for biocomposites the biological compatibility appears to be more important than any other type of compatibility [59]. The most common properties from the bioorganic and inorganic domains to be combined in biocomposites have been summarized in Table 2 [36]. In 1990, Williams summarized the major types of biocomposites that were used in orthopedic applications that time [80]. In 2003, Wang published an excellent update [81]. For general advantages of the modern calcium orthophosphate-based biocomposites over calcium orthophosphate bioceramics and bioresorbable polymers individually, the interested readers are advised to get through "Composite materials strategy" chapter of Ref. [46].

Table 2 General respective properties from the bioorganic and inorganic domains, to be combined in various composites and hybrid materials [36]

Inorganic	Bioorganic
Hardness, brittleness	Elasticity, plasticity
High density	Low density
Thermal stability	Permeability
Hydrophilicity	Hydrophobicity
High refractive index	Selective complexation
Mixed valence slate (red-ox)	Chemical reactivity
Strength	Bioactivity

The major constituent materials of biocomposites for biomedical applications

Calcium orthophosphates

The main driving force behind the use of calcium orthophosphates as bone substitute materials is their chemical similarity to the mineral component of mammalian bones and teeth [21–23]. As a result, in addition to being nontoxic, they are biocompatible, not recognized as foreign materials in the body and, most importantly, both exhibit bioactive behavior and integrate into living tissue by the same processes active in remodeling healthy bone. This leads to an intimate physicochemical bond between the implants and bone, termed osteointegration [81]. More to the point, calcium orthophosphates are also known to support osteoblast adhesion and proliferation [82, 83]. Even so, the major limitations to use calcium orthophosphates as load-bearing biomaterials are their mechanical properties; namely, they are brittle with poor fatigue resistance [26–28]. The poor mechanical behavior is even more evident for highly porous ceramics and scaffolds because porosity >100 μm is considered as the requirement for proper vascularization and bone cell colonization [84–86], i.e., why, in biomedical applications calcium orthophosphates are used primarily as fillers and coatings [23].

The complete list of known calcium orthophosphates, including their standard abbreviations and the major properties, is given in Table 3, while the detailed information on calcium orthophosphates, their synthesis, structure, chemistry, other properties, and biomedical application have been comprehensively reviewed recently [23], where the interested readers are referred to. Even thorough more information might be found in various books and monographs [87–93].

Polymers

Polymers are a class of materials consisting of large molecules, often containing many thousands of small units, or monomers, joined together chemically to form one giant chain, thus creating very ductile materials. In this respect, polymers are comparable with major functional components of the biological environment: lipids, proteins, and polysaccharides. They differ from each other in chemical composition, molecular weight, polydispersity,

Table 3 Existing calcium orthophosphates and their major properties

Ca/P ionic ratio	Compound	Chemical formula	Solubility at 25 °C, $-\log(K_s)$	Solubility at 37 °C, $-\log(K_s)$	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	Data not found	0.0–2.0
0.5	Monocalcium phosphate anhydrous (MCPA)	$Ca(H_2PO_4)_2$	1.14	Data not found	[a]
1.0	Dicalcium phosphate dihydrate (DCPD), mineral brushite	$CaHPO_4 \cdot 2H_2O$	6.59	6.63	2.0–6.0
1.0	Dicalcium phosphate anhydrous (DCPA), mineral monetite	$CaHPO_4$	6.90	7.02	[a]
1.33	Octacalcium phosphate (OCP)	$Ca_8(HPO_4)_2(PO_4)_4 \cdot 5H_2O$	96.6	95.9	5.5–7.0
1.5	α-Tricalcium phosphate (α-TCP)	α-$Ca_3(PO_4)_2$	25.5	25.5	[b]
1.5	β-Tricalcium phosphate (β-TCP)	β-$Ca_3(PO_4)_2$	28.9	29.5	[b]
1.2–2.2	Amorphous calcium phosphate (ACP)	$Ca_xH_y(PO_4)_z \cdot nH_2O$, $n = 3$–4.5; 15–20% H_2O	[c]	[c]	~5–12[d]
1.5–1.67	Calcium-deficient hydroxyapatite (CDHA)[e]	$Ca_{10-x}(HPO_4)_x(PO_4)_{6-x}(OH)^f_{2-x}$ $(0 < x < 1)$	~85.1	~85.1	6.5–9.5
1.67	Hydroxyapatite (HA)	$Ca_{10}(PO_4)_6(OH)_2$	116.8	117.2	9.5–12
1.67	Fluorapatite (FA)	$Ca_{10}(PO_4)_6F_2$	120.0	119.2	7–12
2.0	Tetracalcium phosphate (TTCP), mineral hilgenstockite	$Ca_4(PO_4)_2O$	38–44	37–42	[b]

The solubility is given as the logarithm of the ion product of the given formulae (excluding hydrate water) with concentrations in mol/L [23]

[a] Stable at temperatures above 100 °C

[b] These compounds cannot be precipitated from aqueous solutions

[c] 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)

[d] Always metastable

[e] Occasionally, CDHA is named as precipitated HA

[f] In the case $x = 1$ (the boundary condition with Ca/P = 1.5), the chemical formula of CDHA looks as follows: $Ca_9(HPO_4)(PO_4)_5(OH)$

crystallinity, hydrophobicity, solubility, and thermal transitions. Besides, their properties can be fine-tuned over a wide range by varying the type of polymer, chain length, as well as by copolymerization or blending of two or more polymers [94, 95]. Opposite to ceramics, polymers exhibit substantial viscoelastic properties and can easily be fabricated into complex structures, such as sponge-like sheets, gels, or complex structures with intricate porous networks and channels [96]. X-ray transparent and non-magnetic polymeric materials are fully compatible with the modern diagnostic methods such as computed tomography and magnetic resonance imaging. Unfortunately, most of them are unable to meet the strict demands of the in vivo physiological environment. Namely, the main requirements to polymers suitable for biomedical applications are that they must be biocompatible, not eliciting an excessive or chronic inflammatory response upon implantation and, for those that degrade, that they breakdown into non-toxic products only. Unfortunately, polymers, for the most part, lack rigidity, ductility, and ultimate mechanical properties required in load-bearing applications. Moreover, the sterilization processes (autoclave, ethylene oxide, and ^{60}Co irradiation) may affect the polymer properties [97].

There is a variety of biocompatible polymers suitable for biomedical applications. For example, polyacrylates, poly(acrylonitrile-*co*-vinylchloride) and polylysine have been investigated for cell encapsulation and immunoisolation [98, 99]. Polyorthoesters and poly(ε-caprolactone) (PCL) have been investigated as drug-delivery devices, the latter for long-term sustained release because of their slow degradation rates [100]. PCL is a hydrolytic polyester having appropriate resorption period and releases non-toxic byproducts upon degradation [101]. Other polyesters and polytetrafluoroethylene (PTFE) are used for vascular tissue replacement. Polyurethanes are in use as coatings for pacemaker lead insulation and have been investigated for reconstruction of the meniscus [102, 103]. Polymers considered for orthopedic purposes include polyanhydrides, which have also been investigated as delivery devices (due to their rapid and well-defined surface erosion), for bone

augmentation or replacement since they can be photopolymerized in situ [100, 104, 105]. To overcome their poor mechanical properties, they have been copolymerized with imides or formulated to be crosslinkable in situ [105]. Other polymers, such as polyphosphazenes, can have their properties (e.g., degradation rate) easily modified by varying the nature of their side groups and have been shown to support osteoblast adhesion, which makes them candidate materials for skeletal tissue regeneration [105]. PPF has emerged as a good bone replacement material, exhibiting good mechanical properties (comparable to trabecular bone), possessing the capability to crosslink in vivo through the C=C bond and being hydrolytically degradable. It has also been examined as a material for drug-delivery devices [100, 104–107]. Polycarbonates have been suggested as suitable materials to make scaffolds for bone replacement and have been modified with tyrosine-derived amino acids to render them biodegradable [100]. Polydioxanone has been also tested for biomedical applications [108]. Polymethylmethacrylate (PMMA) is widely used in orthopedics, as a bone cement for implant fixation, as well as to repair certain fractures and bone defects, for example, osteoporotic vertebral bodies [109]. However, PMMA sets by a polymerization of toxic monomers, which also evolves significant amounts of heat that damages tissues. Moreover, it is neither degradable nor bioactive, it does not bond chemically to bones and might generate particulate debris leading to an inflammatory foreign body response [104, 110]. A number of other non-degradable polymers applied in orthopedic surgery include PE in its different modifications such as low density PE, high-density polyethylene (HDPE), and Ultrahigh molecular weight polyethylene (used as the articular surface of total hip replacement implants [111, 112]), polyethylene tereptha-late, polypropylene, and PTFE, which are applied to repair knee ligaments [113]. Polyactive™, a block copolymer of polyethylene glycol (PEG) and polybutyleneterephthalate (PBT), was also considered for biomedical application [114–118]. Cellulose [119] and its esters [120] are also popular. Finally yet importantly, polyethylene oxide, polyhydroxybutyrate (PHB), and blends thereof have also been tested for biomedical applications [46].

Nonetheless, the most popular synthetic polymers used in medicine are the linear aliphatic poly(α-hydroxyesters) such as PLA, polyglycolic acid (PGA) and their copolymers—poly(lactic-*co*-glycolic) acid (PLGA) (Table 4). These materials have been extensively studied; they appear to be the only synthetic and biodegradable polymers with an extensive FDA approval history [46, 105, 121–125]. They are biocompatible, mostly non-inflammatory, as well as degrade in vivo through hydrolysis and possible enzymatic action into products that are removed from the body by regular metabolic pathways [45, 100, 105, 125–130]. Besides, they might be used for drug-delivery purposes [131]. Poly(α-hydroxyesters) have been investigated as scaffolds for replacement and regeneration of a variety of tissues, cell carriers, controlled delivery devices for drugs or proteins (e.g., growth factors), membranes or films, screws, pins, and plates for orthopedic applications [100, 103, 105, 122, 125, 132–134]. Additionally, the degradation rate of PLGA can be adjusted by varying the amounts of the two component monomers (Table 4), which in orthopedic applications can be exploited to create materials that degrade in concert with bone ingrowth [129, 135]. Furthermore, PLGA is known to support osteoblast migration and proliferation [55, 105, 126, 136], which is a necessity for bone tissue regeneration. Unfortunately, such polymers on their own, though they reduce the effect of stress-shielding, are too weak to be used in load-bearing situations and are only recommended in certain clinical indications, such as ankle and elbow fractures [125, 130]. In addition, they exhibit bulk degradation, leading to both a loss in mechanical properties and lowering of the local solution pH that accelerates further degradation in an

Table 4 Major properties of several FDA approved biodegradable polymers [121]

Polymer	Thermal properties[a] (°C)	Tensile modulus (GPa)	Degradation time (months)
Polyglycolic acid (PGA)	t_g = 35–40, t_m = 225–230	7.06	6–12 (strength loss within 3 weeks)
L-polylactic acid (LPLA)	t_g = 60–65, t_m = 173–178	2.7	>24
D,L-polylactic acid (DLPLA)	t_g = 55–60 amorphous	1.9	12–16
85/15 D,L-polylactic-*co*-glycolic acid (85/15 DLPLGA)	t_g = 50–55 amorphous	2.0	5–6
75/25 D,L-polylactic-*co*-glycolic acid (75/25 DLPLGA)	t_g = 50–55 amorphous	2.0	4–5
65/35 D,L-polylactic-*co*-glycolic acid (65/35 DLPLGA)	t_g = 45–50 amorphous	2.0	3–4
50/50 D,L-polylactic-*co*-glycolic acid (50/50 DLPLGA)	t_g = 45–50 amorphous	2.0	1–2
PCL	t_g = (–60)–(–65), t_m = 58–63	0.4	>24

[a] t_g glass transition temperature, t_m melting point

autocatalytic manner. As the body is unable to cope with the vast amounts of implant degradation products, this might lead to an inflammatory foreign body response [105, 125, 132]. Finally, poly(α-hydroxyesters) do not possess the bioactive and osteoconductive properties of calcium orthophosphates [122, 137].

Several classifications of the biomedically relevant polymers are possible. For example, some authors distinguish between synthetic polymers like PLA and PGA or their copolymers with PCL, and polymers of biological origin like polysaccharides (starch, alginate, chitin/chitosan[2] [138–140], gelatin, cellulose, hyaluronic acid derivatives), proteins (soy, collagen, fibrin [9], silk), and a variety of biofibers, such as lignocellulosic natural fibers [8, 141, 142]. Other authors differentiate between resorbable or biodegradable (e.g., poly(α-hydroxyesters), polysaccharides and proteins) and non-resorbable (e.g., PE, PMMA, and cellulose) polymers [56, 142]. As synthetic polymers can be produced under the controlled conditions, they in general exhibit predictable and reproducible mechanical and physical properties such as tensile strength, elastic modulus, and degradation rate. Control of impurities is a further advantage of synthetic polymers. The list of synthetic biodegradable polymers used for biomedical application as scaffold materials is available as Table 1 in Ref. [142], while further details on polymers suitable for biomedical applications are available in the literatures [97, 134, 143–151] where the interested readers are referred. Good reviews on the synthesis of different biodegradable polymers [152], as well as on the experimental trends in polymer nanocomposites [153] are available elsewhere.

Inorganic materials and compounds (metals, ceramics, glass, oxides, carbon, etc.)

Titanium (Ti) is one of the best biocompatible metals and used most widely as implant [13, 154]. Besides, there are other metallic implants made of pure Zr, Hf, V, Nb, Ta, Re [154], Ni, Fe, Cu [155–157], Ag, stainless steels, and various alloys [157] suitable for biomedical application. Recent studies revealed even a greater biomedical potential of porous metals [158–160]. The metallic implants provide the necessary strength and toughness that are required in load-bearing parts of the body and, due to these advantages, metals will continue to play an important role as orthopedic biomaterials in the future, even though there are concerns with regard to the release of certain ions from and corrosion products of metallic implants. Of course, neither metals nor alloys are biomimetic[3] in terms of chemical composition because there are no elemental metals in the human body. In addition, even biocompatible metals are bioinert: while not rejected by the human body, any metallic implants cannot actively interact with the surrounding tissues. Nevertheless, in some cases (especially when they are coated by calcium orthophosphates; however, that is another story) the metallic implants can show a reasonable biocompatibility [162]. Only permanent implants are made of metals and alloys, in which degradation or corrosion is not desirable. However, during recent years a number of magnesium alloys have been proposed, which are aimed to degrade in the body in order to make room for the ingrowing bone [160, 163].

Special types of glasses and glass ceramics are also suitable materials for biomedical applications [164–166] and a special Na_2O–CaO–SiO_2–P_2O_5 glass named Bioglass® [11, 24, 27, 28, 167, 168] is the most popular among them. They are produced via standard glass production techniques and require pure raw materials. Bioglass® is a biocompatible and osteoconductive biomaterial. It bonds to bone without an intervening fibrous connective tissue interface and, due to these properties, it has been widely used for filling bone defects [169]. The primary shortcoming of Bioglass® is mechanical weakness and low fracture toughness due to an amorphous two-dimensional glass network. The bending strength of most Bioglass® compositions is in the range of 40 to 60 MPa, which is not suitable for major load-bearing applications. Making porosity in Bioglass®-based scaffolds is beneficial for even better resorption and bioactivity [170].

By heat treatment, a suitable glass can be converted into glass–crystal composites containing crystalline phase(s) of controlled sizes and contents. The resultant glass ceramics can have superior mechanical properties to the parent glass as well as to sintered crystalline ceramics. The bioactive apatite–wollastonite (A-W) glass ceramics is made from the parent glass in the pseudoternary system $3CaO \cdot P_2O_5$–$CaO \cdot SiO_2$–$MgO \cdot CaO \cdot 2SiO_2$, which is produced by a conventional melt-quenching method. The bioactivity of A-W glass ceramics is much higher than that of sintered HA. It possesses excellent mechanical properties and has therefore been used clinically for iliac and vertebrae prostheses and as intervertebral spacers [13, 171, 172].

Metal oxide ceramics, such as alumina (Al_2O_3, high purity, polycrystalline, fine grained), zirconia (ZrO_2), and some other oxides (e.g., TiO_2), have been widely studied due to their bioinertness, excellent tribological properties,

[2] Chitosan is a biodegradable and semicrystalline polysaccharide obtained from *N*-deacetylation of chitin, which is harvested from the exoskeleton of marine crustaceans.

[3] The term biomimetic can be defined as a processing technique that either mimics or inspires the biological mechanism, in part or whole [161].

high wear resistance, fracture toughness and strength, as well as a relatively low friction [13, 173]. Unfortunately, due to transformation from the tetragonal to the monoclinic phase, a volume change occurs when pure zirconia is cooled down, which causes cracking of the zirconia ceramics. Therefore, additives such as calcia (CaO), magnesia (MgO), and yttria (Y_2O_3) must be mixed with zirconia to stabilize the material in either the tetragonal or the cubic phase. Such material is called PSZ [174–176]. However, the brittle nature of any ceramics has limited their scope of clinical applications and hence more research needs to be conducted to improve their properties.

Calcium orthophosphate-based biocomposites and hybrid biomaterials

Generally, the use of calcium orthophosphate-based biocomposites and hybrid biomaterials for clinical applications has included several (partly overlapping) broad areas:

- biocomposites with polymers,
- cement-based biocomposites and concretes,
- nano-calcium orthophosphate-based biocomposites and nanocomposites,
- biocomposites with collagen,
- biocomposites with other bioorganic compounds and biological macromolecules,
- injectable bone substitutes (IBS),
- biocomposites with glasses, inorganic compounds, and metals,
- functionally graded biocomposites,
- biosensors.

The details of each subject are given below.

Biocomposites with polymers

Typically, the polymeric components of biocomposites and hybrid biomaterials comprise polymers that both have shown a good biocompatibility and are routinely used in surgical applications. In general, since polymers have a low modulus (2–7 GPa, as the maximum) as compared with that of bone (3–30 GPa), calcium orthophosphate bioceramics need to be loaded at a high-weight-percent ratio. Besides, general knowledge on composite mechanics suggests that any high-aspect-ratio particles, such as whiskers or fibers, significantly improve the modulus at a lower loading [147]. Thus, some attempts have been already performed to prepare biocomposites containing whisker-like [177–180] or needle-like [181–183] calcium orthophosphates, as well as calcium orthophosphate fibers [45, 184].

The history of implantable polymer–calcium orthophosphate biocomposites and hybrid biomaterials started in 1981[4] from the pioneering study by Prof. William Bonfield and colleagues performed on HA/PE composites [186, 187]. That initial study introduced a bone-analogue concept, when proposed biocomposites comprised a polymer ductile matrix of PE and a ceramic stiff phase of HA, and was substantially extended and developed in further investigations by that research group [94, 188–205]. More recent studies included investigations on the influence of surface topography of HA/PE composites on cell proliferation and attachment [206–212]. The material is composed of a particular combination of HA particles at a volume loading of ~40% uniformly dispensed in a HDPE matrix. The idea was to mimic bone by using a polymeric matrix that can develop a considerable anisotropic character through adequate orientation techniques reinforced with a bone-like ceramics that assures both a mechanical reinforcement and a bioactive character of the composite. Following FDA approval in 1994, in 1995 this material has become commercially available under the trade name HAPEX^{TM} (Smith and Nephew, Richards, USA), and until now remains the only clinically successful bioactive composite that appeared to be a major step in the implant field [28, 213]. The major production stages of HAPEX^{TM} include blending, compounding, and centrifugal milling. A bulk material or device is then created from this powder by compression and injection molding [59]. Besides, HA/HDPE biocomposites might be prepared by a hot rolling technique that facilitated uniform dispersion and blending of the reinforcements in the matrix [214].

A mechanical interlock between the two phases of HAPEX^{TM} is formed by shrinkage of HDPE onto the HA particles during cooling [94, 215]. Both HA particle size and their distribution in the HDPE matrix were recognized as important parameters affecting the mechanical behavior of HAPEX^{TM} [197]. Namely, smaller HA particles were found to lead to stiffer composites due to general increasing of interfaces between the polymer and the ceramics; furthermore, rigidity of HAPEX^{TM} was found to be proportional to HA volume fraction [189]. In this formulation, HA could be replaced by other calcium orthophosphates [216].

Initial clinical applications of HAPEX^{TM} came in orbital reconstruction [217] but since 1995, the main uses of this composite have been in the shafts of middle ear implants for the treatment of conductive hearing loss [218, 219]. In both applications, HAPEX^{TM} offers the advantage of in situ shaping, so a surgeon can make final alterations to optimize the fit of the prosthesis to the bone of a patient

[4] However, a more general topic "ceramic–plastic material as a bone substitute" is, at least, 18 years older [185].

and subsequent activity requires only limited mechanical loading with virtually no risk of failure from insufficient tensile strength [94, 167]. As compared with cortical bones, HA/PE composites have a superior fracture toughness for HA concentrations below 40% and similar fracture toughness in the 45–50% range. Their Young's modulus is in the range of 1 to 8 GPa, which is quite close to that of bone. The examination of the fracture surfaces revealed that only mechanical bond occurs between HA and PE. Unfortunately, the HA/PE composites are not biodegradable, the available surface area of HA is low and the presence of bioinert PE decreases the ability to bond to bones. Furthermore, HAPEX™ has been designed with a maximized density to increase its strength but the resulting lack of porosity limits the ingrowth of osteoblasts when the implant is placed into the body [26, 168]. Further details on HAPEX™ are available elsewhere [94]. Except of HAPEX™, other types of HA/PE biocomposites are also known [220–224].

Both linear and branched PE was used as a matrix and the biocomposites with the former were found to give a higher modulus [221]. The reinforcing mechanisms in calcium orthophosphate/polymer biocomposites have yet to be convincingly disclosed. Generally, if a poor filler choice is made, the polymeric matrix might be affected by the filler through reduction of molecular weight during composite processing, formation of an immobilized shell of polymer around the particles (transcrystallization, surface-induced crystallization, or epitaxial growth) and changes in conformation of the polymer due to particle surfaces and inter-particle spacing [94]. On the other hand, the reinforcing effect of calcium orthophosphate particles might depend on the molding technique employed: a higher orientation of the polymeric matrix was found to result in a higher mechanical performance of the composite [225, 226].

Many other blends of calcium orthophosphates with various polymers are possible, including rather unusual formulations with dendrimers [227]. The list of the appropriate calcium orthophosphates is shown in Table 3 (except of MCPM and MCPA—both are too acidic and, therefore, are not biocompatible [23]), while many biomedically suitable polymers have been listed above. The combination of calcium orthophosphates and polymers into biocomposites has a twofold purpose. The desirable mechanical properties of polymers compensate for a poor mechanical behavior of calcium orthophosphate bioceramics, while in turn the desirable bioactive properties of calcium orthophosphates improve those of polymers, expanding the possible uses of each material within the body [127–129, 228–231]. Namely, polymers have been added to calcium orthophosphates in order to improve their mechanical strength [127, 228] and calcium orthophosphate fillers have been blended with polymers to improve their compressive strength and modulus, in addition to increase their osteoconductive properties [48, 129, 137, 232–236]. Furthermore, biocompatibility of such biocomposites is enhanced because calcium orthophosphate fillers induce an increased initial flash spread of serum proteins compared with the more hydrophobic polymer surfaces [237]. What's more, experimental results of these biocomposites indicate favorable cell–material interactions with increased cell activities as compared with each polymer alone [230]. As a rule, with increasing of calcium orthophosphate content, both Young's modulus and bioactivity of the biocomposites increase, while the ductility decreases [26, 232]. Furthermore, such formulations can provide a sustained release of calcium and orthophosphate ions into the milieus, which is important for mineralized tissue regeneration [229]. Indeed, a combination of two different materials draws on the advantages of each one to create a superior biocomposite with respect to the materials on their own.

It is logical to assume that the proper biocomposite of a calcium orthophosphate (for instance, CDHA) with a bioorganic polymer (for instance, collagen) would yield the physical, chemical, and mechanical properties similar to those of human bones. Different ways have been already realized to bring these two components together into composites, like mechanical blending, ball milling, dispersion of ceramic fillers into a polymer–solvent solution, a melt extrusion of a ceramic/polymer powder mixture, coprecipitation, and electrochemical codeposition [32, 59, 238–240]. Besides, there is an in situ formation, which involves either synthesizing the reinforcement inside a preformed matrix material or synthesizing the matrix material around the reinforcement [59, 241]. For example, several papers have reported this method to produce various composites of apatites with carbon nanotubes [242–247]. Another example comprises using amino acid-capped gold nanoparticles as scaffolds to grow CDHA [248]. In certain cases, a mechano-chemical route [249], emulsions [250–253], freeze-drying [254] and freeze-thawing techniques [255], flame-sprayed technique [256], or gel-templated mineralization [257] might be applied to produce calcium othophosphates-based biocomposites. Various fabrication procedures are available elsewhere [32, 59, 238], where the interested readers are referred.

The interfacial bonding between a calcium orthophosphate and a polymer is an important issue of any biocomposite. If adhesion between the phases is poor, the mechanical properties of a biocomposite suffer. In order to solve the problem, various approaches have been already introduced. For example, a diisocyanate coupling agent was used to bind PEG/PBT (Polyactive™) block copolymers to HA filler particles. Using surface-modified HA

particles as a filler in a PEG/PBT matrix significantly improved the elastic modulus and strength of the polymer as compared with the polymers filled with ungrafted HA [234, 258]. Another group used processing conditions to achieve a better adhesion of the filler to the matrix. Ignjatovic et al. [127, 128, 259] prepared poly(L-lactic acid) (PLLA)/HA composites by pressing blends of varying PLLA and HA content at different temperatures and pressures. They found that maximum compressive strength was achieved at ~15 wt% of PLLA. Using blends with 20 wt% of PLLA, the authors also established that increasing the pressing temperature and pressure improved the mechanical properties. The former was explained by decrease in viscosity of the PLLA associated with a temperature increase, hence leading to improved wettability of HA particles. The latter was explained by increased compaction and penetration of pores at higher pressure, in conjunction with a greater fluidity of the polymer at higher temperatures. The combination of high pressures and temperatures was found to decrease porosity and guarantee a close apposition of a polymer to the particles, thereby improving the compressive strength [228] and fracture energy [260] of the biocomposites. The PLLA/HA biocomposites scaffolds were found to improve cell survival over plain PLLA scaffolds [261].

It is also possible to introduce porosity into calcium orthophosphate-based biocomposites, which is advantageous for most applications as bone substitution material. The porosity facilitates the migration of osteoblasts from surrounding bones to the implant site [129, 262, 263]. Various material processing strategies to prepare composite scaffolds with interconnected porosity comprise thermally induced phase separation, solvent casting, and particle leaching, solid freeform fabrication techniques, microsphere sintering, and coating [142, 264–266]. A supercritical gas foaming technique might be used as well [238, 267, 268].

Apatite-based biocomposites

A biological apatite is known to be the major inorganic phase of mammalian calcified tissues [21, 22]. Consequently, CDHA, HA, carbonateapatite (both with and without dopants) and, occasionally, FA have been applied to prepare biocomposites with other compounds, usually with the aim to improve the bioactivity. For example, PS composed with HA can be used as a starting material for long-term implants [269–271]. Retrieved in vivo, HA/PS biocomposite-coated samples from rabbit distal femurs demonstrated direct bone apposition to the coatings, as compared with the fibrous encapsulation that occurred when uncoated samples were used [269]. The resorption time of such biocomposites is a very important factor, which depends on polymer's microstructure and the presence of modifying phases [270].

Various apatite-containing biocomposites with PVA [255, 272–278], polyvinyl alcohol phosphate (PVAP) [280], and several other polymeric components [279, 281–292] have already been developed. Namely, PVA/CDHA biocomposite blocks were prepared by precipitation of CDHA in aqueous solutions of PVA [255]. An artificial cornea consisted of a porous nano-HA/PVA hydrogel skirt and a transparent center of PVA hydrogel has been prepared as well. The results displayed a good biocompatibility and interlocking between artificial cornea and host tissues [276, 277]. PVAP has been chosen as a polymer matrix, because its phosphate groups can act as a coupling/anchoring agent, which has a higher affinity toward the HA surface [280]. Greish and Brown [283–285] developed HA/Ca poly(vinyl phosphonate) biocomposites. A template-driven nucleation and mineral growth process for the high-affinity integration of CDHA with polyhydroxyethyl methacrylate (PHEMA) hydrogel scaffold have been developed as well [292].

Polyetheretherketone (PEEK) [177, 179, 293–299] and high-impact polystyrene [300] were applied to create biocomposites with HA having a potential for clinical use in load-bearing applications. The study on reinforcing PEEK with thermally sprayed HA particles revealed that the mechanical properties increased monotonically with the reinforcement concentration, with a maximum value in the study of 40% volume fraction of HA particles [295–297]. The reported ranges of stiffness within 2.8–16.0 GPa and strength within 45.5–69 MPa exceeded the lower values for human bone (7–30 GPa and 50–150 MPa, respectively) [296]. Modeling of the mechanical behavior of HA/PEEK biocomposites is available elsewhere [298].

Biodegradable poly(α-hydroxyesters) are well established in clinical medicine. Currently, they provide with a good choice when a suitable polymeric filler material is sought. For example, HA/PLGA composites were developed, which appeared to possess a cellular-compatibility suitable for bone tissue regeneration [301–308]. Zhang and Ma [48, 233] seeded highly porous PLLA foams with HA particles in order to improve the osteoconductivity of polymer scaffolds for bone tissue engineering. They pointed out that hydration of the foams prior to incubation in simulated body fluid increased the amount of carbonated CDHA material due to an increase in COOH and OH groups on the polymer surface, which apparently acted as nucleation sites for apatite. The following values of Young's modulus, compressive, bending, and tensile strengths for PLLA/HA composites have been achieved: 5–12 GPa, 78–137 MPa, 44–280 MPa, and 10–30 MPa, respectively [309]. However, these data do not appear to be in a good agreement with HA/PLLA biocomposite unit cell model predictions [310].

On their own, PGA and PLA are known to degrade to acidic products (glycolic and lactic acids, respectively) that both catalyze polymer degradation and cause inflammatory reactions of the surrounding tissues [311]. Thus, in biocomposites of poly(α-hydroxyesters) with calcium orthophosphates, the presence of slightly basic compounds (HA, TTCP) to some extent neutralizes the acid molecules, provides with a weak pH-buffering effect at the polymer surface and, therefore, more or less compensates these drawbacks [137, 312–314]. However, additives of even more basic chemicals (e.g., CaO, $CaCO_3$) might be necessary [142, 313, 315, 316]. Extensive cell culture experiments on pH-stabilized composites of PGA and carbonateapatite were reported, which afterwards were supported by extensive in vitro pH-studies [317]. A consequent development of this approach has led to designing of functionally graded composite skull implants consisting of polylactides, carbonateapatite, and $CaCO_3$ [318, 319]. Besides the pH-buffering effect, inclusion of calcium orthophosphates was found to modify both surface and bulk properties of the biodegradable poly(α-hydroxyesters) by increasing the hydrophilicity and water absorption of the polymer matrix, thus altering the scaffold degradation kinetics. For example, polymer biocomposites filled with HA particles was found to hydrolyze homogeneously due to water penetrating into interfacial regions [320].

Biocomposites of poly(α-hydroxyesters) with calcium orthophosphates are mainly prepared by incorporating the inorganic phase into a polymeric solution, followed by drying under vacuum. The resulting solid composites might be shaped using different processing techniques. One can also prepare these biocomposites by mixing HA particles with L-lactide prior the polymerization [312] or by a combination of slip-casting technique and hot-pressing [321]. A surfactant might be useful to keep the suspension homogeneity [322]. Besides, HA/PLA [251, 252] and HA/PLGA [253] microspheres might be prepared by a microemulsion technique. More complex carbonated-FA/PLA porous biocomposite scaffolds are also known [323]. An interesting list of references, assigned to the different ways of preparing HA/poly(α-hydroxyesters) biodegradable composites, might be found in publications by Durucan and Brown [49, 324, 325]. The authors prepared CDHA/PLA and CDHA/PLGA composites by solvent casting technique with a subsequent hydrolysis of α-TCP to CDHA in aqueous solutions. The presence of both polymers was found to inhibit α-TCP hydrolysis, if compared with that of single-phase α-TCP; what is more, the inhibiting effect of PLA exceeded that of PLGA [49, 324, 325]. The physical interactions between calcium orthophosphates and poly(α-hydroxyesters) might be easily seen in Fig. 1 [49]. Nevertheless, it should not be forgotten that typically non-melt-based routes lead to the development of composites with lower mechanical performance and many times require the use of toxic solvents and intensive hand labor [146].

The mechanical properties of poly(α-hydroxyesters) could be substantially improved by the addition of calcium orthophosphates [326, 327]. Shikinami and Okuno [137] developed CDHA/PLLA composites of very high mechanical properties; mini-screws and mini-plates made of these composites have been manufactured and tested [320]. They have shown easy handling and shaping according to the implant site geometry, total resorbability, good ability to bond directly to the bone tissue without

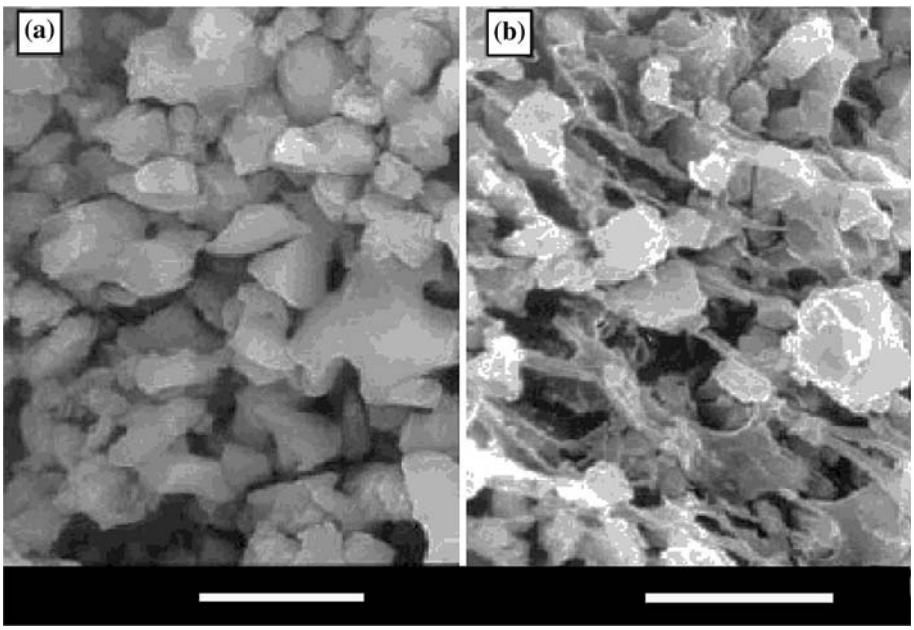

Fig. 1 SEM micrographs of **a** α-TCP compact; **b** α-TCP-PLGA biocomposite (bars = 5 μm). Reprinted from Ref. [49] with permission

interposed fibrous tissue, osteoconductivity, biocompatibility and high stiffness retainable for the period necessary to achieve bone union [320]. The initial bending strength of 280 MPa exceeded that of cortical bone (120–210 MPa), while the modulus was as high as 12 GPa [137]. The strength could be maintained above 200 MPa up to 25 weeks in phosphate-buffered saline solution. Such biocomposites were obtained from precipitation of a PLLA/dichloromethane solution, where small granules of uniformly distributed CDHA microparticles (average size of 3 μm) could be prepared [136]. Porous scaffolds of poly-DL-lactic acid (PDLLA) and HA have been manufactured as well [268, 328, 329]. Upon implantation into rabbit femora, a newly formed bone was observed and biodegradation was significantly enhanced if compared with single-phase HA bioceramics. This might be due to a local release of lactic acid, which in turn dissolves HA. In other studies, PLA and PGA fibers were combined with porous HA scaffolds. Such reinforcement did not hinder bone ingrowth into the implants, which supported further development of such biocomposites as bone graft substitutes [47, 48, 309, 330, 331].

Recently, blends (named as SEVA-C) of ethylene-vinyl alcohol copolymer (EVOH) with starch filled with 10–30 wt% HA have been fabricated to yield biocomposites with modulus up to ~7 GPa with a 30% HA loading [332–337]. The incorporation of bioactive fillers such as HA in SEVA-C aimed to assure the bioactive behavior of the composite and to provide the necessary stiffness within the typical range of human cortical bone properties. These biocomposites exhibited a strong in vitro bioactivity that was supported by the polymer's water-uptake capability [338]. However, the reinforcement of SEVA-C by HA particles was found to affect the rheological behavior of the blend. A degradation model of these biocomposites is available [339].

Higher homologues poly(3-hydroxybutyrate), 3-PHB, and poly(3-hydroxyvalerate), 3-PHV, show almost no biodegradation. Nevertheless, biocomposites of these polymers with calcium orthophosphates showed a good biocompatibility both in vitro and in vivo [94, 340–345]. Both bioactivity and mechanical properties of these biocomposites can be tailored by varying the volume percentage of calcium orthophosphates. Similarly, biocomposites of poly(hydroxybutyrate-*co*-hydroxyvalerate) (PHBHV) with both HA and amorphous carbonated apatite (almost ACP) appeared to have a promising potential for repair and replacement of damaged bones [346–349].

Along this line, PCL is used as a slowly biodegradable, a but well-biocompatible polymer. PCL/HA composites have been already discussed as suitable materials for substitution, regeneration, and repair of bone tissues [264, 350–357]. For example, biocomposites were obtained by infiltration of ε-caprolactone monomer into porous apatite blocks and in situ polymerization [353]. The composites were found to be biodegradable and might be applied as cancellous or trabecular bone replacement material or for cartilage regeneration. Both the mechanical performance and biocompatibility in osteoblast cell culture of PCL were shown to be strongly increased when HA was added [358]. Several preparation techniques of PCL/HA composites are known. For example, to make composite fibers of PCL/nano-HA, the desired amount of nano-HA powder was dispersed in a solvent using magnetic stirrer followed by ultrasonication for 30 min. Then, PCL was dissolved in this suspension, followed by the solvent evaporation [359]. The opposite preparation order is also possible: PCL was initially dissolved in chloroform at room temperature (7–10% weight/volume), then HA (~10 μm particle size) was suspended in the solution, sonicated for 60 s, followed by the solvent evaporation [129] or salt-leaching [360]. The mechanical properties obtained by this technique were about one-third that of trabecular bone. In a comparative study, PCL and biological apatite were mixed in the ratio 19:1 in an extruder [361]. At the end of the preparation, the mixture was cooled in an atmosphere of nitrogen. The authors observed that the presence of biological apatite improved the modulus while concurrently increasing the hydrophilicity of the polymeric substrate. Besides, an increase in apatite concentration was found to increase both the modulus and yield stress of the composite, which indicated to good interfacial interactions between the biological apatite and PCL. It was also observed that the presence of biological apatite stimulated osteoblasts attachment to the biomaterial and cell proliferation [361]. In another study, a PCL/HA biocomposite was prepared by blending in melt form at 120 °C until the torque reached equilibrium in the rheometer that was attached to the blender [362]. Then the sample was compression-molded and cut into specimens of appropriate size for testing. It was observed that the composite containing 20 wt% HA had the highest strength [362]. However, a direct grafting of PCL on the surface of HA particles seems to be the most interesting preparation technique [350]. HA porous scaffolds were coated by a PCL/HA composite coating [50]. In this system, PCL, as a coating component, was able to improve the brittleness and low strength of the HA scaffolds, whereas the particles in the coating were to improve the osteoconductivity and bioactivity of the coating layer. More complex PDLLA/PCL/HA biocomposites have been prepared as well [363]. Further details on both PCL/HA biocomposites and processing methodologies thereof might be found elsewhere [264].

The spread of attached human osteoblasts onto PLA and PCL films reinforced with CDHA and sintered HA was shown to be higher than for the polymers alone [152].

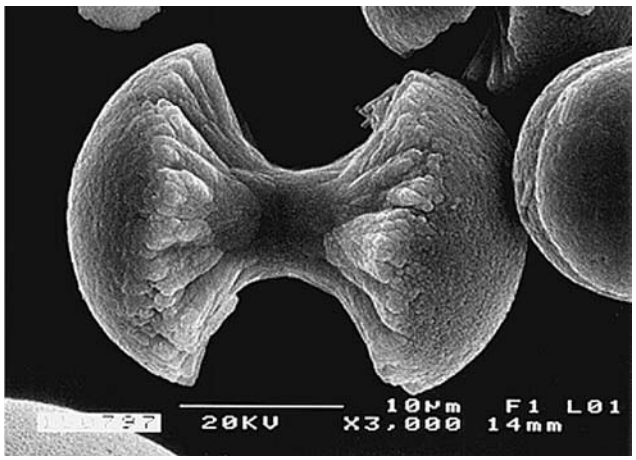

Fig. 2 A biomimetically grown aggregate of FA that was crystallized in a gelatin matrix. Its shape can be explained and simulated by a fractal growth mechanism. Scale bar: 10 μm. Reprinted from Ref. [366] with permission

Moreover, biochemical assays relating cell activity to DNA content allowed concluding that cell activity was more intense for the composite films [152]. Kim et al. [50] coated porous HA blocks with PCL from dichloromethane solution and performed drug-release studies. The antibiotic tetracycline hydrochloride was added into this layer, yielding a bioactive implant with drug release for longer than a week.

Yoon et al. [364] investigated the highest mechanical and chemical stability of FA by preparing FA/collagen biocomposites and studied their effect in osteoblast-like cell culture. The researchers found an increased cellular activity in FA composites compared with HA composites. This finding was confirmed in another study by means of variations in the fluoride content for FA-HA/PCL composites [365]. An interesting phenomenon of fractal growth of FA/gelatin composite crystals (Fig. 2) was achieved by diffusion of calcium- and orthophosphate + fluoride-solutions from the opposite sides into a tube filled with a gelatin gel [366–374]. The reasons of this phenomenon are not quite clear yet; besides, up to now nothing has yet been reported on a possible biomedical application of such very unusual structural composites.

TCP-based biocomposites

Both α-TCP and β-TCP have a higher solubility than HA (Table 3). Besides, they are faster resorbed in vivo.[5] Therefore, these calcium orthophosphates were used instead of HA to prepare completely biodegradable biocomposites [376–394]. For example, a biodegradable and osteoconductive biocomposite made of β-TCP particles and gelatin was proposed [385]. This material was tested in vivo with good results. It was found to be biocompatible, osteoconductive, and biodegradable with no need for a second surgical operation to remove the device after healing occurred. Herbal extracts might be added to this biocomposite [386]. Another research group prepared biocomposites of crosslinked gelatin with β-TCP; they found both a good biocompatibility and bone formation upon subcutaneous implantation in rats [387]. Yang et al. [392] extended this to porous (porosity about 75%) β-TCP/gelatin biocomposites those also contained BMP-4. Besides, cell-compatible and possessive some osteoinductive properties porous β-TCP/alginate-gelatin hybrid scaffolds were prepared and successfully tested in vitro [389]. More to the point, biocomposites of β-TCP with PLLA [382, 383] and copolyester lactide-*co*-glycolide-*co*-ε-caprolactone [384] were prepared. Although β-TCP was able to counter the acidic degradation of the polyester to some extent, it did not prevent a pH drop down to ~6. Nevertheless, implantation of this biocomposite in beagles' mandibular bones was successful [384].

Based on the self-reinforcement concept, biocomposites of TCP with polylactides were prepared and studied using conventional mechanical testing [395]. Bioresorbable scaffolds were fabricated from such biocomposites [396]. Chitosan was also used as the matrix for the incorporation of β-TCP by a solid/liquid phase separation of the polymer solution and subsequent sublimation of the solvent. Due to complexation of the functional groups of chitosan with calcium ions of β-TCP, these biocomposites had a better compressive modulus and strength [397]. PCL/β-TCP biocomposites were developed as well [398–401] and their in vitro degradation behavior was systematically monitored by immersion in simulated body fluid at 37 °C [400]. To extend this topic further, the PCL/β-TCP biocomposites might be loaded by drugs [401].

Cell culture tests on β-TCP/PLLA biocomposites were reported; the biocomposites showed no cytotoxicity and evidenced good cell attachment to its surface [376]. An in vitro study with primary rat calvarial osteoblasts showed an increased cellular activity in the BMP-loaded samples [392]. Other researchers investigated BMP-2-loaded porous β-TCP/gelatin biocomposites (porosity 95%, average pore size 180–200 μm) [402] and confirmed the precious study. Biocomposites of β-TCP and glutaraldehyde crosslinked gelatin were manufactured and tested in vitro to measure the material cytotoxicity [388]. The experimental results revealed that the amount of glutaraldehyde crosslinking agent should be less than 8% to decrease the toxicity on the osteoblasts and to avoid inhibition of cellular growth caused by the release of residual or uncrosslinked glutaraldehyde.

[5] However, there are some reports about a lack of TCP biodegradation after implantation in calvarial defects [375].

A long-term implantation study of PDLLA/α-TCP composites in a loaded sheep implant model showed good results after 12 months, but a strong osteolytic reaction after 24 months. This was ascribed to the almost complete dissolution of α-TCP to this time and an adverse reaction of the remaining PDLLA [403].

More complex calcium orthophosphate-based biocomposites are known as well. For example, there is a composite consisting of three interpenetrating networks: TCP, CDHA, and PLGA [404]. Firstly, a porous TCP network was produced by coating a polyurethane foam by hydrolysable α-TCP slurry. Then, a CDHA network was derived from a calcium orthophosphate cement filled in the porous TCP network. Finally, the remaining open pore network in the CDHA/α-TCP structures was infiltrated with PLGA. This biocomposite consists of three phases with different degradation behavior. It was postulated that bone would grow on the fastest degrading network of PLGA, while the remaining calcium orthophosphate phases would remain intact thus maintaining their geometry and load-bearing capability [404].

Other calcium orthophosphate-based biocomposites

The number of research papers devoted to biocomposites based on other calcium orthophosphates is substantially lesser than those devoted to apatites and TCP. Biphasic calcium phosphate (BCP)[6] appears to be the most popular among the remaining calcium orthophosphates. Collagen-coated BCP ceramics was studied and the biocompatibility toward osteoblasts was found to increase upon coating with collagen [405]. Another research group created porous PDLLA/BCP scaffolds and coated them with a hydrophilic PEG/vancomycin composite for both drug-delivery purposes and surface modification [406]. More to the point, PLGA/BCP composites were fabricated [407, 408] and their cytotoxicity and fibroblast properties were found to be acceptable for natural bone tissue reparation, filling, and augmentation [409, 410]. PCL/BCP biocomposites are known as well [411].

A choice of DCPD-based biocomposites of DCPD, albumin, and duplex DNA was prepared by water/oil/water interfacial reaction method [250]. Core-shell type DCPD/chitosan biocomposite fibers were prepared by a wet spinning method in another study [412]. The energy-dispersive X-ray spectroscopy analysis indicated that Ca and P atoms were mainly distributed on the outer layer of the composite fibers; however, a little amount of P atoms remained inside the fibers. This indicated that the composite fibers formed a unique core-shell structure with shell of calcium orthophosphate and core of chitosan [412]. Although, this is not to the point, it is interesting to mention that some DCPD/polymer composites could be used as proton conductors in battery devices [413, 414]. Nothing has been reported on their biocompatibility but, perhaps, sometime the improved formulations will be used to fabricate biocompatible batteries for implantable electronic devices.

Various ACP-based biocomposites for dental applications were developed [415–418]. Besides, several ACP-based formulations were investigated as potential biocomposites for bone grafting [349, 419–421]. Namely, ACP/PPF biocomposites were prepared by in situ precipitation [420], while PHB/carbonated ACP and PHBHV/carbonated ACP biocomposites appeared to be well suited as slowly biodegradable bone substitution material [349]. Another example comprises hybrid nano-capsules of ~50–70 nm in diameter which were fabricated by ACP mineralization of shell crosslinked polymer micelles and nanocages [421]. These nano-capsules consisted of a continuous ultrathin inorganic surface layer that infiltrated the outer crosslinked polymeric domains. They might be used as structurally robust, pH-responsive biocompatible hybrid nanostructures for drug delivery, bioimaging, and therapeutic applications [421].

Calcium orthophosphate cement-based biocomposites and concretes

Inorganic self-setting calcium orthophosphate cements, which harden in the body, were introduced by LeGeros et al. [422] and Brown and Chow [423, 424] in the early 1980s.[7] Since then, these cements have been broadly studied and many formulations have been proposed [427]. The cements set and harden due to various chemical interactions among calcium orthophosphates that finally lead to formation of a monolithic body consisting of either CHDA or DCPD with possible admixtures of other phases. Unfortunately, having the ceramic nature, calcium orthophosphate cements are brittle after hardening and the setting time is sometimes unsuitable for clinical procedures [427]. Therefore, various attempts have been performed to transform the cements into biocomposites, e.g., by adding hydroxylcarboxylic acids, to control the setting time [428], gelatin to improve both the mechanical properties and the setting time [391, 429–431] or osteocalcin/collagen to increase the bioactivity [432]. More to the point, various reinforcement additives of different shapes and nature are

[6] BCP is a solid composite of HA and β-TCP; however, similar composites of HA and α-TCP are possible as well [23].

[7] There is an opinion [425] that the self-setting calcium orthophosphate cements for orthopedic and dental restorative applications have first been described in the early 1970s by Driskell et al. [426] in US Patent No. 3913229.

widely used to improve the mechanical properties of calcium orthophosphate cements [427]. Even carbon nanotubes were used for this purpose [433]! Although the biomaterials community does not use this term, a substantial amount of the reinforced cement formulations might be defined as calcium orthophosphate-based concretes.[8] The idea behind the concretes is simple: if a strong filler is present in the matrix, it might stop crack propagation.

Various apatite-containing biocomposite formulations based on PMMA [435–445] and PEMA [94, 446, 447] have been already developed. Such biocomposites might be prepared by dispersion of apatite powder into a PMMA viscous fluid [448] and used for drug-delivery purposes [449]. When the mechanical properties of the biocomposite concretes composed of PMMA matrix and HA particles of various sizes were tested, the tensile results showed that strength was independent on particle sizes. In addition, up to 40 wt% HA could be added without impairing the mechanical properties [438, 439]. After immersion into Ringer's solution, the tensile strength was not altered, whereas the fatigue properties were significantly reduced. The biocompatibility of PMMA/HA biocomposites was tested in vivo and enhanced osteogenic properties of the implants compared with single-phase PMMA were observed [436, 440–443]. It was shown that not only the mechanical properties of PMMA were improved but the osteoblast response of PMMA was also enhanced with the addition of HA [440]. Thereby, by adding calcium orthophosphates, a non-biodegradable PMMA was made more bioactive and osteoconductive, yielding a well-processable biocomposite concrete. As a drawback, the PMMA/HA formulations possess a low flexural, compressive, and tensile strength.

A biocomposite made from HA granules and *bis*-phenol-α-glycidylmethacrylate-based resin appeared to possess comparable mechanical and biological properties to typical PMMA cement, leading to potential uses for implant fixation [450]. In order to improve the mechanical properties of calcium orthophosphate cements and stabilize them at the implant site, various researchers have resorted to formulations that set in situ, primarily through crosslinking reactions of the polymeric matrix. For example, TTCP was reacted with polyacrylic acid (PAA), forming a crosslinked CDHA/calcium polyacrylate biocomposite [451]. In aqueous solutions, TTCP hydrolyzes to CDHA [23] and the liberated calcium cations react with PAA, forming the crosslinked network [451]. Reed et al. [452] synthesized a dicarboxy polyphosphazene that can be crosslinked by calcium cations and cement-based (TTCP + DCPD) CDHA/polyphosphazene biocomposites with a compressive strength ~10 MPa and of ~65% porosity were prepared as a result. To mimic PMMA cements, PFF/β-TCP biocomposites were prepared with the addition of vinyl monomer to crosslink PPF. As a result, quick setting and degradable biocomposite cements with a low-heat output and compressive strengths in the range of 1 to 12 MPa were prepared by varying the molecular weight of PPF, as well as the contents of the monomer, β-TCP, initiator, and porogen (NaCl) [453, 454]. An acrylic cement with Sr-containing HA as a filler [110] and an injectable polydimethylsiloxane/HA cement [455] have been prepared as well.

In order to improve the mechanical properties of calcium orthophosphate cements, numerous researchers blended various polymers with the cements. For example, gelatin might be added to calcium orthophosphate cement formulations, primarily to stabilize the paste in aqueous solution before it develops adequate rigidity and, secondly, to improve the compressive strength [391, 429, 456]. Adding rod-like fillers to the cement formulations also caused an improvement in the mechanical properties [456]. For example, PAA and PVA were successfully used to improve the mechanical properties of a TTCP + DCPD cement but, unfortunately, with an inevitable and unacceptable reduction of both workability and setting time [457, 458]. Similar findings were reported in the presence of sodium alginate and sodium polyacrylate [459]. Other polymers, such as polyphosphazene, might be used as well [460–462]. Other examples of polymer/calcium orthophosphate cement formulations might be found elsewhere [463, 464].

Porous calcium orthophosphate scaffolds with interconnected macropores (~1 mm), micropores (~5 μm), and of high porosity (~80%) were prepared by coating polyurethane foams with a TTCP + DCPA cement, followed by firing at 1200 °C. In order to improve the mechanical properties of the scaffolds, the open micropores of the struts were then infiltrated by a PLGA solution to achieve an interpenetrating bioactive ceramic/biodegradable polymer composite structure. The PLGA-filled struts were further coated with a 58S bioactive glass/PLGA composite coating. The obtained complex porous biocomposites could be used as tissue engineering scaffolds for low-load-bearing applications [465]. A more complicated construction, in which the PLGA macroporous phase has been reinforced with a bioresorbable TTCP + DCPA cement, followed by surface coating of the entire construct by a non-stoichiomentic CDHA layer, has been designed as

[8] According to Wikipedia, the free encyclopedia: "*Concrete* is a construction material that consists of a cement (commonly Portland cement), aggregates (generally gravel and sand) and water. It solidifies and hardens after mixing and placement due to a chemical process known as hydration. The water reacts with the cement, which bonds the other components together, eventually creating a stone-like material" [434].

well [466]. The latter approach has culminated in a unique, three-phase biocomposite that is simple to fabricate, osteoconductive, and completely biodegradable.

A porosity level of 42 to 80% was introduced into calcium orthophosphate cement/chitosan biocomposites by the addition of the water-soluble mannitol [467]. Chitosan significantly improved the mechanical strength of the entire biocomposite [468]. A similar approach was used by other researchers who studied the effect of the addition of PLGA microparticles [469–472] (which can also be loaded with drugs or growth factors [473–475]) to calcium orthophosphate cements. These biocomposites were implanted into cranial defects of rats and a content of ~30 wt% of the microparticles was found to give the best results [469], while the addition of a growth factor to the biocomposites significantly increased bone contact at 2 weeks and enhanced new bone formation at 8 weeks [475]. The in vivo rabbit femur implant tests showed that PLGA/calcium orthophosphate cement formulations exhibited outstanding biocompatibility and bioactivity, as well as a better osteoconduction and degradability than pure calcium orthophosphate cements [470]. Further details on calcium orthophosphate cement-based biocomposites and concretes might be found in Ref. [427, chapter "Reinforced calcium orthophosphate cements"].

Nano-calcium orthophosphate-based biocomposites and nano-biocomposites

Nanophase materials are the materials that have grain sizes under ~100 nm. They have different mechanical and optical properties if compared with the large-grained materials of the same chemical composition. Namely, nanophase materials have the unique surface properties, such as an increased number of atoms, grain boundaries, and defects at the surface, huge surface area and altered electronic structure, if compared with the conventional micron-sized materials. For example, nano-HA (size ~67 nm) has a higher surface roughness of 17 nm if compared with 10 nm for the conventional submicron size HA (~180 nm), while the contact angles (a quantitative measure of the wetting of a solid by a liquid) are significantly lower for nano-HA (6.1) if compared with the conventional HA (11.51). Additionally, the diameter of individual pores in a nano-HA compact is five times smaller (pore diameter ~6.6 Å) than that in the conventional grain-sized HA compacts (pore diameter within 19.8–31.0 Å) [476–478]. Besides, nano-HA promotes osteoblast cells adhesion, differentiation, and proliferation, osteointegration and deposition of calcium containing minerals on its surface better than microcrystalline HA; thus enhancing formation of a new bone tissue within a short period [476–478]. More to the point, nano-HA was found to cause apoptosis of the leukemia P388 cells [479].

Composites of two or more materials, in which at least one of the materials is of a nanometer-scale, are defined as *nanocomposites* [32]. Natural bone mineral is a hierarchical nanocomposite of biological origin, because it consists of nano-sized blade-like crystals of biological apatite grown in intimate contact with an organic matrix rich in collagen fibers and organized in a complicated hierarchical structure [21, 22, 38]. Given the fact that the major organic phase of bone is collagen, i.e., a natural polymer (Table 1), it is obvious that a composite of a nanophase calcium orthophosphate with a biodegradable polymer should be advantageous as bone substitution material. The inorganic nanophase would be responsible for the mechanical strength (hardness) and bioactivity, while the polymer phase would provide the elasticity. In addition, the solubility of calcium orthophosphates depends on their crystallite size (smaller crystals have a higher solubility) and on their carbonate content (higher carbonate content increases the solubility) [480]. To the author's best knowledge, among calcium orthophosphates listed in Table 3, before very recently only apatites (CDHA, HA and, perhaps, FA) have been available in the nanocrystalline state. However, very recently, nano-DCPA [481–483] and nano-MCPM [484] have been synthesized and applied to prepare nano-biocomposites with strong ionic release to combat tooth caries.

A number of investigations have been conducted recently to determine the mineralization, biocompatibility, and mechanical properties of the nano-biocomposites based on various (bio)polymers and nano-HA.[9] These studies covered nano-HA/PLA [268, 485–492] and its copolymer with PGA [493–495], nano-HA/collagen [496–508], nano-HA/collagen/PLA [508–516], nano-HA/collagen/PVA [517], nano-HA/collagen/alginate [518, 519], nano-HA/gelatin [520–525], nano-HA/poly(hexamethylene adipamide) [526], nano-HA/PPF [527], nano-HA/polyamide [528–539], nano-HA/PVA [276, 277, 540–542], nano-HA/PVAP [280], nano-HA/poly(ethylene-*co*-acrylic) acid [543, 544], nano-HA/chitosan [545–548], nano-HA/konjac glucomannan/chitosan [549], nano-HA/PHEMA/PCL [550], nano-HA/PCL [322, 359, 551, 552], nano-HA/Ti [553, 554], PCL semi-interpenetrating nanocomposites [555], and many other biocompatible hybrid formulations [223, 257, 271, 347, 556–574]. Several nano-biocomposites were found to be applicable as carriers for growth factors delivery [34, 575, 576]. Besides, the data are available on the excellent biocompartibility of such nano-biocomposites [507]. The dispersion state of nanoparticles appears to be the critical parameter in controlling the mechanical properties of

[9] Unfortunately, in the majority of the already published papers it often remained unclear whether "nano-HA" represented the stoichiometric nano-HA or a non-stoichiometric nano-CDHA.

nano-biocomposites, as nanoparticles always tend to aggregate owing to their high surface energy [347].

Porous (porosity ~85%) biocomposites of nano-HA with collagen and PLA have been prepared by precipitation and freeze-drying; the nano-biocomposites did not show a pH drop upon in vitro degradation [509–511]. They were implanted in the radius of rabbits and showed a high biocompatibility and partial resorption after 12 weeks. Nano-HA/chitosan biocomposites with improved mechanical stability were prepared from HA/chitosan nanorods [577]. Nano-HA/PLLA biocomposites of high porosity (~90%) were prepared using thermally induced phase separation [578]. Besides, nano-HA was used to prepare biocomposites with PAA and the nanostructure of the resulting nanocrystals exhibited a core-shell configuration [579, 580].

Nano-HA crystals appeared to be suitable for intraosseous implantation and offered a potential to formulate enhanced biocomposites for clinical applications [581]. Thus, the biocompatibility of chitosan in osteoblast cell culture was significantly improved by addition of nano-HA [582]. Similar finding is valid for nano-HA/polyamide biocomposites [531]. Further details on nano-HA-based biocomposites might be found in an excellent review [32]. More to the point, a more general review on nanobiomaterial applications in orthopedics is also available [583], where the interested readers are referred.

Biocomposites with collagen

The main constituent of the bioorganic matrix of bones is type I collagen[10] (Table 1) with molecules about 300 nm in length. This protein is conducive to crystal formation in the associated inorganic matrix. It is easily degraded and resorbed by the body and allows good attachment to cells. Collagen alone is not effective as an osteoinductive material, but it becomes osteoconductive in combination with calcium orthophosphates [585]. Both collagen type I and HA were found to enhance osteoblast differentiation [586] but combined together, they were shown to accelerate osteogenesis. However, this tendency is not so straightforward: the data are available that implanted HA/collagen biocomposites enhanced regeneration of calvaria bone defects in young rats but postponed the regeneration of calvaria bone in aged rats [587]. Finally, the addition of calcium orthophosphates to collagen sheets was found to give a higher stability and an increased resistance to 3D swelling compared with the collagen reference [588]. Therefore, a bone-analogue based on these two constituents should possess the remarkable properties. Furthermore, the addition of bone marrow constituents gives osteogenic and osteoinductive properties to calcium orthophosphate/collagen biocomposites [1].

The unique characteristics of bones are the spatial orientation between the calcium orthophosphate nanophase and collagen macromolecules at the nanolevel [35], where nanocrystals (about 50-nm-length) of biological apatite are aligned parallel to the collagen fibrils [21, 22, 31, 38], which is believed to be the source of the mechanical strength of bones. The collagen molecules and the nanocrystals of biological apatite assembled into mineralized fibrils are approximately 6-nm-diameter and 300-nm-long [31, 35, 38, 510, 589]. Although the complete mechanisms involved in the bone building strategy are still unclear, the strengthening effect of apatite nanocrystals in calcified tissues might be explained by the fact that the collagen matrix is a load transfer medium and thus transfers the load to the intrinsically rigid inorganic nanocrystals. Furthermore, nanocrystals of biological apatite located in between tangled fibrils crosslink the fibers either through a mechanical interlocking or by forming calcium ion bridges, thus increasing deformation resistance of the collagenous fiber network [590].

When calcium orthophosphates are combined with collagen in a laboratory, the biocomposites appear to be substantially different from natural bone tissue due to a lack of real interaction between the two components, i.e., interactions that are able to modify the intrinsic characteristics of the singular components themselves. The main characteristics of the route, by which the mineralized hard tissues are formed in vivo, are that the organic matrix is laid down first and the inorganic reinforcing phase grows within this organic matrix [21, 22, 31, 38]. Although to date, neither the elegance of the biomineral assembly mechanisms nor the intricate composite nano-architectures have been duplicated by non-biological methods, the best way to mimic bone is to copy the way it is formed, namely by nucleation and growth of CDHA nanocrystals from a supersaturated solution both onto and within the collagen fibrils [591–593]. Such syntheses were denoted as "biologically inspired" which means they reproduce an ordered pattern and an environment very similar to natural ones [594–596]. The biologically inspired biocomposites of collagen and calcium orthophosphates (mainly, apatites) for bone substitute have a long history [29, 364, 499, 597–615] and started from the pioneering study by Mittelmeier and Nizard [616], who mixed calcium orthophosphate granules with a collagen web. Such combinations were found to be bioactive, osteoconductive, osteoinductive [29, 585, 617–619] and, in general, artificial grafts manufactured from this type of the biocomposites are likely to behave similarly to bones and be of more use in surgery

[10] The structural and biochemical properties of collagens have been widely investigated and over 25 collagen subtypes have been identified [584].

than those prepared from any other materials. Indeed, some data are available on the superiority of calcium orthophosphate/collagen biocomposite scaffolds over the artificial polymeric and calcium orthophosphate bioceramic scaffolds individually [620].

It has been found that calcium orthophosphates may be successfully precipitated onto a collagen substrate of whatever form or source [29, 36, 499, 621, 622]. However, adherence of calcium orthophosphate crystals to collagen did depend on how much the collagen had been denatured: the more fibrillar the collagen, the greater attachment. Clarke et al. [602] first reported the production of a biocomposite produced by precipitation of DCPD onto a collagen matrix with the aid of phosphorylated amino acids commonly associated with fracture sites. Apatite cements (DCPD + TTCP) have been mixed with a collagen suspension, hydrated, and allowed to set. CDHA crystals were found to nucleate on the collagen fibril network, giving a material with the mechanical properties weaker than those reported for bone. More to the point, these biocomposites were without the nanostructure similar to that of bone [599, 623]. The oriented growth of OCP crystals on collagen was achieved by an experimental device in which Ca^{2+} and PO_4^{3-} ions diffused into a collagen disk from the opposite directions [622, 624, 625]. Unfortunately, these experiments were designed to simulate the mechanism of in vivo precipitation of biological apatite only; due to this reason, the mechanical properties of the biocomposites were not tested [626].

Conventionally, collagen/calcium orthophosphate biocomposites can be prepared by blending or mixing of collagen and calcium orthophosphates, as well as by biomimetic methods [29, 32, 34, 37, 496, 499, 510, 576, 589, 594–596, 599, 621, 627–633]. Besides, collagen might be incorporated into calcium orthophosphate cements [599, 623, 634]. Typically, the type I collagen sponge is presoaked in PO_4^{3-}-containing a highly basic aqueous solution and then is immersed into a Ca^{2+}-containing solution to allow mineral deposition. Also, collagen I fibers might be dissolved in acetic acid and then this solution is added to phosphoric acid, followed by the neutralization synthesis (performed at 25 °C and solution pH within 9–10) between an aqueous suspension of $Ca(OH)_2$ and the H_3PO_4/collagen solution [594, 595]. In order to ensure the quality of the final product, it is necessary to control the Ca/P ionic ratio in the reaction solution. One way to do this is to dissolve a commercial calcium orthophosphate in an acid; another is to add Ca^{2+} and PO_4^{3-} ions in a certain ratio to the solution and after that induce the reaction [35]. Biomimetically, one can achieve an oriented growth of CDHA crystals onto dissolved collagen fibrils in aqueous solutions via a self-organization mechanism [628]. A number of authors produced calcium orthophosphate/collagen biocomposites by mixing preformed ceramic particles with a collagen suspension [635–637]. However, in all blended composites, the crystallite sizes of calcium orthophosphates were not uniform and the crystals were often aggregated and randomly distributed within a fibrous matrix of collagen. Therefore, no structural similarity to natural bone was obtained, and only a compositional similarity to that of natural bone was achieved. Crystallization of CDHA in aqueous solutions might be performed in the presence of a previously dispersed collagen [29, 499]. More to the point, collagen might be first dispersed in an acidic solution, followed by addition of calcium and orthophosphate ions and then coprecipitation of collagen and CDHA might be induced by either increasing the solution pH or adding mixing agents [37]. Although it resulted in biocomposites with poor mechanical properties, pressing of the HA/collagen mixtures at 40 °C under 200 MPa for several days is also known [638]. Attempts have been performed for a computer simulation of apatite/collagen composite formation process [639]. It is interesting to note, that collagen/HA biocomposites were found to possess some piezoelectric properties [640].

As the majority of the collagen/HA, biocomposites are conventionally processed by anchoring micro-HA particles into collagen matrix, it makes quite difficult to obtain a uniform and homogeneous composite graft. Besides, such biocomposites have inadequate mechanical properties; over and above, the proper pore sizes have not been achieved either. Further, microcrystalline HA, which is in contrast to nanocrystalline natural bone apatite, might take a longer time to be remodeled into a new bone tissue upon the implantation. In addition, some of the biocomposites exhibited very poor mechanical properties, probably due to a lack of strong interfacial bonding between the constituents. The aforementioned data clearly demonstrate that the chemical composition similar to bone is insufficient for manufacturing the proper bone grafts; both the mechanical properties and mimetic of the bone nanostructure are necessary to function as bone in recipient sites. There is a chance for improving osteointegration by reducing the grain size of HA crystals by activating ultrafine apatite growth into the matrix. This may lead to enhance the mechanical properties and osteointegration with improved biological and biochemical affinity to the host bone. Besides, the unidirectional porosity was found to have a positive influence on the ingrowth of the surrounding tissues into the pores of collagen/HA biocomposites [641].

Bovine collagen might be mixed with HA and such biocomposites are marketed commercially as bone-graft substitutes those further can be combined with bone marrow aspirated from the iliac crest of the site of the fracture. Application of these materials was compared with autografts for the management of acute fractures of long bones

with defects, which had been stabilized by internal or external fixation [642, 643]. These biocomposites are osteogenic, osteoinductive, and osteoconductive; however, they lack the structural strength and require harvest of the patient's bone marrow. Although no transmission of diseases has been recorded yet, the use of bovine collagen might be a source of concern [2].

Collagen sponges with an open porosity (30–100 μm) were prepared by a freeze-drying technique and then their surface was coated by a 10-μm layer of biomimetic apatite precipitated from simulated body fluid [644]. The researchers found a good in vitro performance with fibroblast cell culture. Collagen/HA microspheres or gel beads have been prepared in the intention of making injectable bone fillers [645, 646]. Liao et al. [647] succeeded in mimicking the bone structure by blending carbonateapatite with collagen. A similar material (mineralized collagen) was implanted into femur of rats and excellent clinical results were observed after 12 weeks [648]. Collagen/HA biocomposites were prepared and their mechanical performance was increased by crosslinking the collagen fibers with glutaraldehyde [500, 502, 503]. These biocomposites were tested in rabbits and showed a good biological performance, osteoconductivity, and biodegradation. A similar approach was selected to prepare HA/collagen microspheres (diameter ~5 μm) by a water–oil emulsion technique in which the surface was also crosslinked by glutaraldehyde [646]. That material showed a good in vitro performance with osteoblast cell culture. A porous bone-graft substitute was formed from a nano-HA/collagen biocomposite combined with PLA by a freeze-drying method; the resulting material was found to mimic natural bone at several hierarchical levels [510]. Subsequent in vitro experiments confirmed a good adhesion, proliferation, and migration of osteoblasts into this composite [509]. A further increase in biocompatibility might be achieved by the addition of silicon; thus, to enhance bone substitution, Si-substituted HA/collagen composites have been developed with silicon located preferentially in the collagen phase [501]. Porous (porosity level ~95% with interconnected pores of 50–100 μm) biocomposites of collagen (crosslinked with glutaraldehyde) and β-TCP have been prepared by a freeze-drying technique, followed by sublimation of the solvent; the biocomposites showed a good biocompatibility upon implantation in the rabbit jaw [649].

Biocomposites of calcium orthophosphates with collagen were found to be useful for drug-delivery purposes [519, 607, 650–652]. Namely, an HA/collagen–alginate (20 μL) with the rh-BMP2 (100 μg/mL, 15 μL) showed bone formation throughout the implant 5 weeks after implantation without obvious deformation of the material [519]. Gotterbarm et al. [651] developed a two-layered collagen/β-TCP implant augmented with chondral inductive growth factors for the repair of osteochondral defects in the trochlear groove of minipigs. This approach might be a new promising option for the treatment of deep osteochondral defects in joint surgery.

To conclude this part, one should note that biocomposites of apatites with collagen are a very hot topic of the research and up to now, just a few papers are devoted to biocomposites of other calcium orthophosphates with collagen [651, 653]. These biomaterials mimic natural bones to some extent, while their subsequent biological evaluation suggests that they are readily incorporated into the bone metabolism in a way similar to bone remodeling, instead of acting as permanent implant [510, 616]. Collagraft®, Bio-Oss®, and Healos® are the several examples of the commercially available calcium orthophosphate/collagen bone grafts for clinical use [32]. However, the performance of these biocomposites depends on the source of collagen from which it was processed. Several attempts have been made to simulate the collagen–HA interfacial behavior in real bone by means of crosslinking agents such as glutaraldehyde [500, 502, 503, 621, 646, 649] with the purpose to improve the mechanical properties of these biocomposites. Unfortunately, a further progress in this direction is restricted by a high cost, difficulty to control cross-infection, a poor definition of commercial sources of collagens, as well as by a lack of an appropriate technology to fabricate bone-resembling microstructures. Further details on calcium orthophosphate/collagen composites, including the list of the commercially available products, might be found elsewhere [32, 611].

Biocomposites with other bioorganic compounds and biological macromolecules

Besides collagen, both human and mammalian bodies contain dozens types of various bioorganic compounds, proteins, and biological macromolecules. The substantial amounts of them potentially might be used to prepare biocomposites with calcium orthophosphates. For example, a biologically strong adhesion (to prevent invasion of bacteria) between teeth and the surrounding epithelial tissues is attributed to a cell-adhesive protein, laminin [654]. In order to mimic the nature, a laminin/apatite biocomposite layer was successfully created on the surface of both titanium [655] and EVOH [656, 657] using the biomimetic approach.

Calcium orthophosphate/gelatin biocomposites are widely investigated as potential bone replacement biomaterials [254, 272–274, 366–374, 385–392, 402, 429–431, 456, 520–525, 658–669]. For example, gelatin foams were successfully mechanically reinforced by HA and then crosslinked by a carbodiimide derivative [254]. Such foams were shown to be a good carrier for antibiotic tetracycline

[662]. Several biocomposites of calcium orthophosphates with alginates[11] have been prepared [389, 518, 519, 523, 595, 670]. For example, porous HA/alginate composites based on hydrogels were prepared both biomimetically [595] and by using a freeze-drying technique [670]. Another research group succeeded in preparation of biphasic but monolithic scaffolds using a similar preparation route [671]. Their biocompatibility in cell culture experiments and in vitro biodegradability were high; however, a mechanical strength could be better.

Various biocomposites of calcium orthophosphates with chitosan [239, 397, 412, 419, 435, 467, 545–549, 566, 567, 577, 582, 663, 669, 672–683] and chitin [183, 394, 513, 684–688] are also very popular. For example, a solution-based method was developed to combine HA powders with chitin, in which the ceramic particles were uniformly dispersed [684, 685]. Unfortunately, it was difficult to obtain the uniform dispersions. The mechanical properties of the final biocomposites were not very good; due to a poor adhesion between the filler and the matrix both the tensile strength and modulus were found to decrease with the increase in the HA amount. Microscopic examination revealed that HA particles were intervened between the polymer chains, weakening their interactions, and decreasing the entire strength [684, 685].

Biocomposites of CDHA with water-soluble proteins, such as bovine serum albumin (BSA), might be prepared by a precipitation method [463, 689–692]. In such biocomposites, BSA is not strongly fixed to solid CDHA, which is useful for a sustained release. However, this is not the case if a water/oil/water interfacial reaction route has been used [250]. To extend this subject, inclusion of DNA into CDHA/BSA biocomposites was claimed [250, 693–695]. Besides, bionanocomposites of an unspecified calcium orthophosphate with DNA were prepared as well [696].

Akashi and co-workers [697] developed a procedure to prepare calcium orthophosphate-based biocomposites by soaking hydrogels in supersaturated by Ca^{2+} and PO_4^{3-} ions solutions in order to precipitate CDHA in the hydrogels (up to 70 wt% of CDHA could be added to these biocomposites). This procedure was applied to chitosan; the 3D shape of the resulting biocomposite was controlled by the shape of the starting chitosan hydrogel [698]. Another research group developed biocomposites based on in situ calcium orthophosphate mineralization of self-assembled supramolecular hydrogels [699].

Various biocomposites of CDHA with glutamic and aspartic amino acids, as well as poly-glutamic and poly-aspartic amino acids have been prepared and investigated by Bigi et al. [279, 281, 700–703]. These (poly)amino acids were quantitatively incorporated into CDHA crystals, provoking a reduction of the coherent length of the crystalline domains and decreasing the crystal sizes. The relative amounts of the (poly)amino acid content in the solid phase, determined through HPLC analysis, increased with their concentration in solution up to a maximum of about 7.8 wt% for CDHA/aspartic acid and 4.3 wt% for CDHA/glutamic acid biocomposites. The small crystal dimensions, which implied a great surface area, and the presence of (poly)amino acids were suggested to be relevant for possible application of these biocomposites for hard tissues replacement [279, 281, 700–703].

Recently, BCP (HA + β-TCP)/agarose macroporous scaffolds with controlled and complete interconnection, high porosity, thoroughly open pores, and tailored pore size were prepared for tissue engineering application [704, 705]. Agarose, a biodegradable polymer, was selected as the organic matrix, because it was a biocompatible hydrogel, which acted as gelling agent leading to strong gels and fast room temperature polymerization. Porous scaffolds with the designed architecture were manufactured by combining a low-temperature shaping method with stereo-lithography and two drying techniques. The biocompatibility of this BCP/agarose system was tested with mouse L929 fibroblast and human Saos-2 osteoblast during different colonization times [704].

Fibrin sealants are non-cytotoxic, fully resorbable, biological matrices that simulate the last stages of a natural coagulation cascade, forming a structured fibrin clot similar to a physiological clot [706]. Biocomposites of calcium orthophosphates with fibrin sealants might develop the clinical applications of bone substitutes. The 3D mesh of fibrin sealant interpenetrates the macro- and micro-porous structure of calcium orthophosphate ceramics [9]. The physical, chemical, and biological properties of calcium orthophosphate bioceramics and the fibrin glue might be cumulated in biocomposites, suitable for preparation of advanced bone grafts [707–718].

Furthermore, there are biocomposites of calcium orthophosphates with bisphosphonates [719], silk fibroin (that is a hard protein extracted from silk cocoon) [249, 562–564, 569, 570, 720–725], chitosan + silk fibroin [726], fibronectin [727], and casein phosphopeptides [728]. Besides, the reader's attention is pointed out to an interesting approach to crystallize CDHA inside poly(allylamine)/poly(styrene sulfonate) polyelectrolyte capsules resulting in empty biocomposite spheres of micron size [729]. Depending on the amount of precipitated CDHA, the thickness of the shell of biocomposite spheres can be varied between 25 and 150 nm. These biocomposite

[11] Alginates are a family of unbranched binary copolymers with a structure comprising 1–4 glycosidically linked β-D-mannuronic acid and its C-5 epimer α-Lguluronic acid [595].

capsules might find application as medical agents for bone repairing and catalytic microreactors [729].

Injectable bone substitutes

IBS represent ready-to-use suspensions of calcium orthophosphate powder(s) in a liquid carrier phase. They look like viscous pastes with the rheological properties, sufficient to inject them into bone defects by means of surgical syringes and needles. Usually, the necessary level of viscosity is created by the addition of water-soluble polymers [104, 730, 731]. Therefore the majority of calcium orthophosphate-based IBS formulations might be considered as a subgroup of calcium orthophosphate/polymer biocomposites. For example, an IBS was described that involved a silanized hydroxyethylcellulose carrier with BCP, consisting of HA and β-TCP [732]. The suspension is liquid at pH within 10–12, but gels quickly at pH < 9. Injectable composites can be formed with β-TCP to improve mechanical integrity [453]. Similarly, Bennett et al. [733] showed that a polydioxanone-*co*-glycolide-based biocomposite reinforced with HA or β-TCP can be used as an injectable or moldable putty. During the crosslinking reaction following injection, carbon dioxide is released allowing the formation of interconnected pores.

Daculsi et al. [84, 731, 734–740] developed viscous IBS biocomposites based on BCP (60% HA + 40% β-TCP) and 2% aqueous solution of hydroxypropylmethylcellulose (HPMC) that was said to be perfectly biocompatible, resorbable, and easily fitted bone defects (due to an initial plasticity). The best ratio BCP/HPMC aqueous solution was found to be at ~65/35 w/w. To extend this subject further, this type of IBS might be loaded by cells [741] or by microparticles [742].

The advanced characteristics of IBS come from their good mechanical properties and biocompatibility and the ease of tissue regeneration. Although the fabrication of IBS biocomposites in most cases improved the mechanical properties of the system and provided the material with resistance to fluids penetration, these achievements were limited by the amount of polymer that can be added to the paste. For instance, Mickiewicz et al. [463] reported that after a critical concentration (that depended on the type and molecular weight of the polymer, but was always around 10%), the polymer started forming a thick coating on the crystal clusters, preventing them from interlocking, originating plastic flow and, as a consequence, decreasing mechanical properties. More to the point, Fujishiro et al. [456] reported a decrease in mechanical properties with higher amounts of gel, which was attributed to the formation of pores due to leaching of gelatin in solution. Therefore, it seems that mechanical properties, although improved by the addition of polymers, are still a limitation for the application of calcium orthophosphate-based IBS formulations in load-bearing sites [146].

Biocomposites with glasses, inorganic materials, and metals

In order to overcome the problem of poor mechanical properties of calcium orthophosphate bioceramics, suitable biocomposites of calcium orthophosphates reinforced by various inorganic materials, glasses, and metals have been developed. Such biocomposites are mainly prepared by the common ceramic processing techniques such as thermal treatment after kneading [743–745], powder slurry coating [746], and metal–sol mixing [747]. For example, HA was combined with Bioglass® (Novabone Products, Alachua, FL) [748, 749] and with other glasses [750] to form glass–ceramics biocomposites. Other reinforcement materials for calcium orthophosphates are differentiated by either shape of the fillers, namely, particles [751, 752], platelets [753, 754], whiskers [484, 755, 756], fibers [757–759], or their chemical composition: zirconia and/or PSZ [250, 743–746, 755, 760–793], alumina [250, 751, 754, 793–802], titania [307, 747, 752, 803–817], other oxides [818–821], silica and/or glasses [822–829], wollastonite [171, 830–837], various metals and alloys [759, 794, 817, 838–851], calcium sulfate [852–854], silicon carbide [756], barium titanate [855], zeolite [856], and several other materials [271, 857–859]. All these materials have been added to calcium orthophosphate bioceramics to improve its reliability. Unfortunately, significant amounts of the reinforcing phases are needed to achieve the desired properties and, as these materials are either bioinert, significantly less bioactive than calcium orthophosphates or not bioresorbable, the ability of the biocomposites to form a stable interface with bone is poorer if compared with calcium orthophosphate bioceramics alone. Due to the presence of bioinert compounds, such formulations might be called bioinert/bioactive composites [822]. The ideal reinforcement material would impart mechanical integrity to a biocomposite at low loadings, without diminishing its bioactivity. As clearly seen from the amount of the references, apatite/zirconia biocomposites are most popular ones among the researchers.

There are several types of HA/glass biocomposites. The first one is also called bioactive glass–ceramics. A dense and homogeneous biocomposite was obtained after a heat treatment of the parent glass, which comprised ~38 wt% oxy-FAP ($Ca_{10}(PO_4)_6(O,F)_2$) and ~34 wt% β-wollastonite ($CaO \cdot SiO_2$) crystals, 50–100 nm in size in a MgO–CaO–SiO_2 glassy matrix [171, 830–837]. A-W glass–ceramics is an assembly of small apatite particles effectively reinforced by wollastonite. The bending strength, fracture toughness, and Young's modulus of A-W glass–ceramics are the

highest among bioactive glass and glass ceramics, enabling it to be used in some major compression load-bearing applications, such as vertebral prostheses and iliac crest replacement. It combines a high bioactivity with the suitable mechanical properties [860]. β-TCP/wollastonite biocomposites are also known [861–863]. More complicated biocomposites have been developed as well. For example, (A-W)/HDPE composite (AWPEX) biomaterials have been designed to match the mechanical strength of human cortical bone and to provide favorable bioactivity, with potential use in many orthopedic applications [864–867]. Other examples comprise wollastonite-reinforced HA/Ca polycarboxylate [868] and glass-reinforced HAP/polyacrylate [869] biocomposites.

HA/glass biocomposites can be prepared by simple sintering of appropriate HA/glass powder mixtures [870–873]. If sintering is carried out below 1000 °C, HA does not react with the bioactive glass [871, 872] or this reaction is limited [873]. Besides, reaction between HA and glasses depends on the glass composition. In another approach, small quantities of bioactive glass have been added to HA bioceramics in order to improve densification and/or mechanical properties [26]. In addition, biocomposites might be sintered from HA and silica [822]. In general, bioactive glass–ceramics maintain a high strength for a longer time than HA bioceramics under both the in vitro and in vivo conditions [829, 834].

Carbon nanotubes with their small dimensions, a high-aspect-ratio (length-to-diameter) as well as the exceptional mechanical properties, including extreme flexibility and strength, significant resistance to bending, high resilience and the ability to reverse any buckling of the tube, have the excellent potential to accomplish necessary mechanical properties [874]. Recent studies have even suggested that they may possess some bioactivity [875–878]. However, due to a huge difference in shapes, it is a challenge to prepare homogeneous mixtures of calcium orthophosphates and carbon nanotubes: "one can imagine something similar to achieving a homogeneous mixture of peas and spaghetti" [874, p. 7]. Additionally, non-functionalized carbon nanotubes tend to agglomerate and form bundles; besides, they are soluble in neither water nor organic solvents. Chemical functionalization allows carbon nanotubes to be dispersed more easily, which can improve interfacial bonding with calcium orthophosphates [247, 874].

Different strategies might be employed to prepare calcium orthophosphate/carbon nanotubes biocomposites. For example, apatites might be chemically synthesized using carboxyl-functionalized carbon nanotubes as a matrix [242–247]. Physico-chemical characterization of these biocomposites showed that nucleation of CDHA initiates through the carboxyl group [247]. Hot-pressing [879], plasma spraying [880], and laser surface alloying [881–883] techniques might be applied as well. The research on calcium orthophosphate (up to now, only apatites)/carbon nanotube biocomposites is in its early stages, with the first papers published in 2004 [246, 433]. Due to this reason, the mechanical property data for such biocomposites have been reported only in few papers; however, these results are encouraging. For example, Chen et al. [883] performed nanoindentation tests on biocomposite coatings to give hardness and Young's modulus values. They found that the higher the loading of nanotubes, the better the properties. Namely, at 20 wt% loading, hardness was increased by 43% and Young's modulus by 21% over a single-phase HA coating [883]. Scratching test results indicated that as alloyed HA biocomposite coatings exhibited improved wear resistance and lower friction coefficient with increasing the amount of carbon nanotubes in the precursor material powders [882]. Additionally, measurements of the elastic modulus and hardness of the biocomposite coatings indicated that the mechanical properties were also affected by the amount of carbon nanotubes [881]. Another research group performed compression tests on bulk HA/nanotubes biocomposites and found an increase in strength over single-phase HA [246]. However, the highest compressive strength they achieved for any material was only 102 MPa, which is similar to that of cortical bone but much lower than the typical values for dense HA [874]. More complex formulations, such as poly-L-lysine/HA/carbon nanotube hybrid nanocomposites, have also been developed [884]. Unfortunately, carbon nanotubes are very stable substances; they are neither bioresorbable nor biodegradable. Therefore, during the in vivo bioresorption, the nanotubes will get into the human body from the biocomposite matrix and might cause uncertain health problems. Except of carbon nanotubes, carbon fibers of microscopic dimensions are also used to reinforce HA bioceramics [885–887].

The main disadvantage of HA reinforced by PSZ is degradation of zirconia in wet environments [755, 760, 761, 783]. Transformation of the tetragonal ZrO_2 to the monoclinic phase on the surface results in formation of microcracks and consequently lowers the strength of the implant [888, 889].

An HA-based biocomposite reinforced with 20 vol.% of Ti particles was fabricated by hot-pressing [840]. Besides, calcium orthophosphates/Ti biocomposites might be prepared by powder metallurgy processing [842–844]. At high temperatures, the presence of Ti metal phase was found to promote dehydration and decomposition of HA into β-TCP and TTCP [840, 842] or partial formation of β-TCP and calcium titanate instead of HA [554, 843, 844]. Comparing with pure HA bioceramics manufactured under the same conditions, the HA/Ti biocomposites possessed a higher fracture toughness, bending strength, work of fracture, porosity, and lower elastic modulus, which is more suitable

for biomedical applications. However, the mechanical properties appeared to be not high enough to use HA/Ti biocomposites in load-bearing applications. Luckily, the histological evaluations revealed that HA/Ti biocomposites could be partially integrated with newborn bone tissues after 3 weeks and fully osteointegrated at 12 weeks in vivo [840]. Similar findings had been earlier made for HA bioceramics reinforced by addition of silver particulates (5–30 vol.%) and subsequent sintering of the HA/Ag powder compacts [838, 839]. Other studies on calcium orthophosphate/Ti biocomposites are available elsewhere [845–848].

To conclude this part, biocomposites consisting of calcium orthophosphates only should be briefly described. First of all, BCP itself, consisting of HA and α- or β-TCP, should be mentioned [23]. In the 1980s, BCP was called as "TCP ceramics complexed with HA" [890]. More to the point, 70% HA-powder + 30% HA-whisker biocomposites have been fabricated by pressureless sintering, hot-pressing, and hot-isostatic pressing. These biocomposites were found to exhibit an improved toughness, attaining the lower fracture-toughness limit of bone without a decrease of bioactivity and biocompatibility [891, 892]. Besides, a dual HA biocomposite that combined two HA materials with different porosities: HA with 75% porosity, for bone ingrowth and HA with 0% porosity, for load-bearing was manufactured. This dual HA biocomposite appeared to be suitable for use as an implant material for spinal interbody fusion as a substitute for iliac bone grafts, which could eliminate the disadvantages associated with autograft harvesting [893]. A biodegradable nanocomposite porous scaffold comprising a β-TCP matrix and HA nanofibres was developed and studied for load-bearing bone tissue engineering. HA nanofibres were prepared by a biomimetic precipitation method, the inclusion of which significantly enhanced the mechanical property of the scaffold, attaining a compressive strength of 9.87 MPa, comparable to the high-end value (2–10 MPa) of cancellous bone [894].

Functionally graded biocomposites

Although, in most cases, the homogeneous distribution of filler(s) inside a matrix is required [355], there are composites, where this is not the case. For example, functionally graded materials (commonly referred to as FGM) might be characterized by the intentional variations in composition and/or structure gradually over volume, resulting in corresponding changes in the properties of the composite. The main feature of such materials is the almost continuously graded composition that results in two different properties at the two ends of the structure. Such composites can be designed for specific function and applications. Various approaches based on the bulk (particulate processing), preform processing, layer processing, and melt processing are used to fabricate the functionally graded materials.

Bone is a biologically formed composite with variable density ranging from very dense and stiff (the cortical bone) to a soft and foamed structure (the trabecular bone). Normally the outer part of long bones consists of cortical bone with the density decreasing toward the core, where the trabecular bone is found. The trabecular bone is porous and the porosity is filled with osseous medulla [21, 22]. This brief description clearly indicates that bones are natural functionally graded composites.

The concept of FGM has been increasingly used for biomaterial design and currently it remains to be an important area of the research. For example, powder metallurgy methods have been used to fabricate HA/Ti functionally graded biocomposite dental implants offering the biocompatible HA on the tissue side and titanium on the outer side for mechanical strength [895–897]. The graded structure in the longitudinal direction contains more Ti in the upper section and more HA in the lower section. Actually, in the upper section the occlusal force is directly applied and Ti offers the required mechanical performance; in the lower part, which is implanted inside the bone, the HA confers the bioactive and osteoconductive properties to the material [895]. Since the optimum conditions of sintering for Ti and HA are very different, HA/Ti functionally graded biocomposites are difficult to fabricate and the sintering conditions for their mixtures are obliged to compromise. The expected properties of this implant are shown in Fig. 3 [896]. Functionally graded HA/Ti biocomposite coatings might be prepared by rf-plasma spraying [898]. A functionally graded HA/PMMA biocomposite was developed based on sedimentary HA distributions in a PMMA viscous fluid, using a centrifuge to avoid stress convergence on the interface. The stress–strain curves of this biocomposite showed sufficient strength for medical application along with the relaxation of brittleness and fragility [448]. A three-layered graded biocomposite membrane, with one face of 8% nano-carbonated CDHA/collagen/PLGA porous membrane, the opposite face of pure PLGA non-porous membrane, the middle layer of 4% nano-carbonated CDHA/collagen/PLGA as the transition, was prepared through the layer-by-layer casting method [512]. HA/glass FGM layers were coated on titanium alloy (Ti–6Al–4V) substrates. The design of these layers and the use of the glass were for achieving a strong bonding between the FGM-layered coatings and the substrates [899, 900]. More to the point, Ti alloy substrate has been combined with HA granules spread over the surface [901].

Functionally graded β-TCP/FA biocomposites combine the biostability of FA with bioresorbable properties of

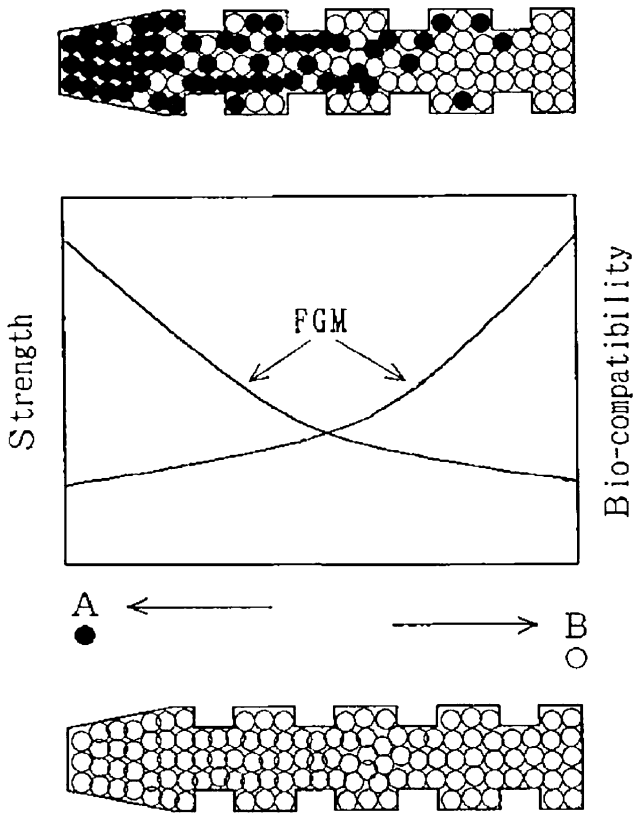

Fig. 3 Expected properties of functionally graded biocomposite dental implant. For comparison, the upper drawing shows a functionally graded implant and the lower one shows a conventional uniform implant. The properties are shown in the middle. The implant with the composition changed from a biocompatible metal (Ti) at one end (*left* in the figure), increasing the concentration of bioceramics (HA) toward 100% HA at the other end (*right* in the figure), could control both mechanical properties and biocompatibility without an abrupt change due to the formation of discrete boundary. This FGM biocomposite was designed to provide more titanium for the upper part where occlusal force is directly applied and more HA for the lower part, which is implanted inside the jawbone. Reprinted from Ref. [896] with permission

β-TCP [902]. An interesting multilayered (each layer of 1-mm-thick) structure consisting of β-TCP/FA biocomposites with different molar ratios has been prepared, giving rise to formation of an FGM (Fig. 4). After implantation, the preferential dissolution of β-TCP phase would result in functionally gradient porosity for bone ingrowth [903]. HA/zirconia-graded biocomposites were fabricated to enhance the mechanical properties of HA while retaining its bone bonding property [791]. TiO_2 and HA were found to be a good combination for FGM providing both a gradient of bioactivity and a good mechanical strength [903]. Besides, graded HA/$CaCO_3$ biocomposite structures for bone ingrowth have been developed as well [904]. Functionally graded composite skull implants consisting of polylactides, carbonateapatite, and $CaCO_3$ are

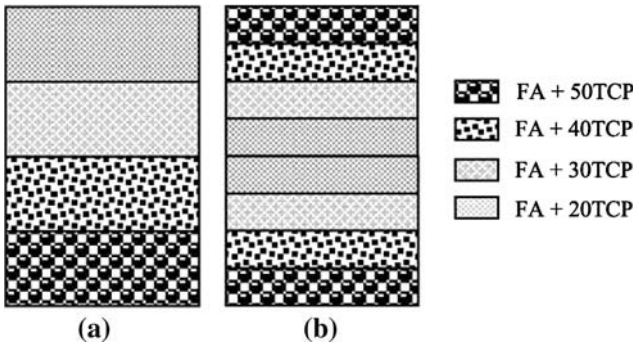

Fig. 4 A schematic diagram showing the arrangement of the FA/β-TCP composite layers: **a** non-symmetric FGM, **b** symmetric FGM. Reprinted from Ref. [902] with permission

known as well [318, 319]. The research in this field is quite promising but currently the mechanical properties of the available biocomposites are clearly in excess of the properties of bone [147].

Biosensors

A biosensor is a device for detection of an analyte that combines a biological component with a physicochemical detector component. Very briefly, it consists of three parts: a sensitive biological element; a transducer or a detector element that transforms the signal resulting from the interaction of the analyte with the biological element into another signal; and associated electronics that is primarily responsible for the display of the results in a user-friendly way [905].

The surface of biologically relevant calcium orthophosphates (CDHA, HA, α-TCP, β-TCP) has an excellent ability of adsorption for functional biomolecules such as proteins, albumins, DNA, and so on. Therefore, some calcium orthophosphate-based biocomposites and hybrid biomaterials were found to be applicable for biosensor manufacturing [288, 542, 851, 884]. For example, formation of poly-L-lysine/HA/carbon nanotube hybrid nanoparticles was described, and a general design strategy for an immunosensing platform was proposed based on adsorption of antibodies onto this nanocomposite [884]. In another article, a hybrid material formed by assembling of gold nanoparticles onto nano-HA was employed for the interface design of piezoelectric immunosensor, on which the antibodies were bound. The developed sensing interface appeared to possess some advantages, such as activation-free immobilization and high antigen-binding activities of antibodies, over using either nano-HA or gold nanoparticles alone [851]. Until now, just a few papers have been published on biosensor application of calcium orthophosphate-based biocomposites. Presumably, this subject will be

further developed in the future and, perhaps, sometime implantable biosensors will be designed to perform the continuous concentration monitoring of the important biological macromolecules. Possibly, those biocencors might be able to use an electric power, generated by DCPD/polymer composite-based battery devices [413, 414].

Interaction between the phases in calcium orthophosphate-based biocomposites

An important aspect that should be addressed in details is a mutual interaction between calcium orthophosphates and other phases in biocomposites and hybrid biomaterials. In general, an interaction between the phases in any composite can be either mechanical, when it results from radial compression forces exerted by the matrix on the filler particles (e.g., developed during cooling due to thermal contraction), or chemical, when the reactivity of the filler toward the matrix has an important role. In the latter case, it is important to distinguish a physical interaction from chemical bonding [225]. According to Wypych [906], physical interaction is more or less temporary, implicating hydrogen bonding or van der Waals forces, whereas chemical bonding is stronger and more permanent, involving covalent bond formation. Thus, a chemical interfacial bond between the phases is preferred to achieve a higher strength of a composite. The magnitude of the interfacial bond between the phases determines how well a weak matrix transmits stress to the strong fibers. However, while a bond between the matrix and reinforcement must exist for the purpose of stress transfer, it should not be so strong that it prevents toughening mechanisms, such as debonding and fiber pullout [874].

There is still doubt as to the exact bonding mechanism between bone minerals (biological apatite) and collagen, which undoubtedly plays a critical role in determining the mechanical properties of bones. Namely, bone minerals are not directly bonded to collagen, but through non-collagenous proteins that make up ~3% of bones (Table 1) and provide with active sites for biomineralization and for cellular attachment [32]. In bones, the interfacial bonding forces are mainly ionic bonds, hydrogen bonds, and hydrophobic interactions, which give the bones the unique composite behavior [49]. There is an opinion that, opposite to bones, there is no sign of chemical bonding between phases in conventional calcium orthophosphate/collagen biocomposites, probably due to a lack of suitable interfacial bonding during mixing [35]. However, this is not the case for phosphorylated collagens [633]. Anyway, Fourier-transformed infrared (FTIR) spectra of some calcium orthophosphate-based composites and collagen films were measured and transformed into absorption spectra using the Kramers-Kronig equation to demonstrate energy shifts of residues on the HA/collagen interface. After comparing FTIR spectra of biocomposites and collagen films in detail, red shifts of the absorption bands for C–O bonds were observed in the spectra of the biocomposites. These red shifts were described as a decrease in bonding energies of C–O bonds and assumed to be caused by an interaction to Ca^{2+} ions located on the surfaces of apatite nanocrystals, as shown in Fig. 5 [628]. Another proof of a chemical interaction between CDHA and collagen fibers was also evaluated in FTIR spectra of CDHA/collagen biocomposites, in which a shift of the band corresponding to $–COO^{-}$ stretching from 1340 to 1337 cm^{-1} was observed [594, 595]. More to the point, nucleation of CDHA crystals onto collagen through a chemical interaction with carboxylate

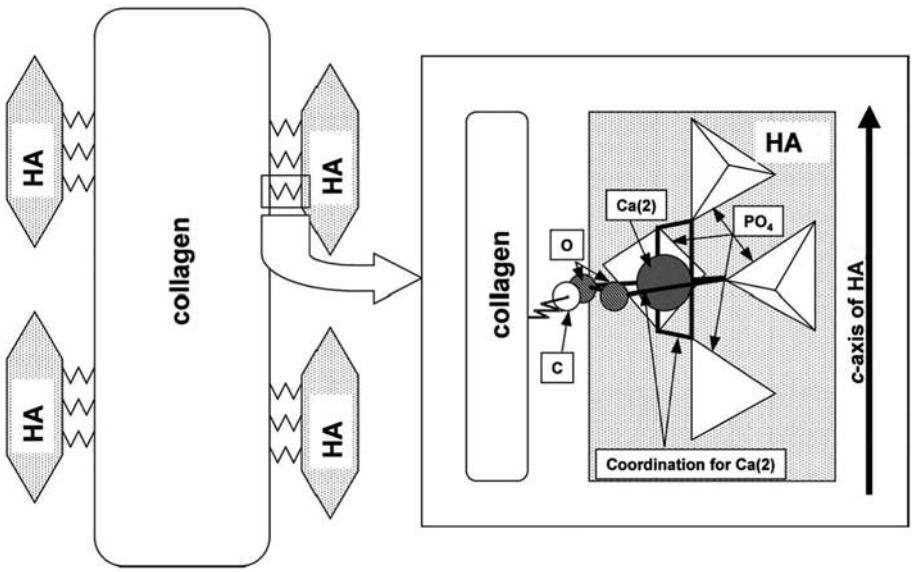

Fig. 5 A schematic diagram of the relation between self-organization (directional deposition of HA on collagen) and interfacial interaction in biocomposites. Direction of interaction between HA and collagen is restricted by covalent bond between COO and Ca(2) to maintain regular coordination number of 7. Reprinted from Ref. [628] with permission

groups of collagen macromolecules has been reported [907–909].

FTIR spectroscopy seems to be the major investigation tool of a possible chemical bonding among the phases in calcium orthophosphate-based biocomposites and hybrid biomaterials [220, 280, 287, 289, 382, 420, 502, 517, 526, 529, 536, 539, 541, 544, 549, 556, 565, 570, 595, 633, 666, 667, 726, 910, 911]. For example, the characteristic bands at 2918, 2850, and 1472 cm^{-1} for the hydrocarbon backbone of PE appeared to have zero shift in an HA/PE biocomposite. However, in the case of polyamide, some of the FTIR-bands indicated that the polar groups shifted apparently: the bands at 3304, 1273, and 692 cm^{-1} derived from stretching of N–H, stretching of C–N–H, and vibrating of N–H moved to 3306, 1275, and 690 cm^{-1} in an HA/polyamide biocomposite, respectively. Both stretching (3568 cm^{-1}) and vibrating (692 cm^{-1}) modes of hydroxyl in HA moved to 3570 and 690 cm^{-1} in the HA/polyamide buicomposite, respectively, indicating the formation of hydrogen bonds. Besides, the bands at 1094 and 1031 cm^{-1} of PO_4 modes also shifted to 1093 and 1033 cm^{-1} in the HA/polyamide biocomposite. The bands shift in a fingerprint area indicated that the hydroxyl and orthophosphate on the surface of HA might interact with plentiful carboxyl and amino groups of polyamide through nucleophilic addition [220]. Comparable conclusions were made for nano-HA/PVA [541], CDHA/alginate [595], ACP/PPF [420], HA/maleic anhydride [289], and β-TCP/PLLA [382] biocomposites, where a weak chemical bond was considered to form between Ca^{2+} ions located on the nano-HA, CDHA, ACP, HA, or β-TCP surface, respectively, and slightly polarized O atoms of C=O bonds in the surrounding bioorganic compounds. Schematically, this chemical interaction is shown in Fig. 6 [595].

Except of FTIR spectroscopy, other measurement techniques are also able to show some evidences of a chemical interaction between calcium orthophosphates and other compounds in biocomposites [280, 382, 536, 539, 541, 911–913]. For example, for CDHA/alendronate nanocrystals

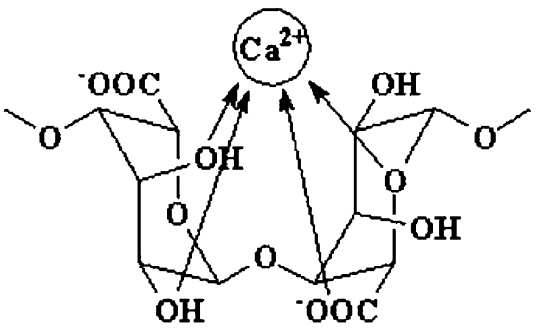

Fig. 6 A schematic diagram of Ca^{2+} ion binding with alginate chains. Reprinted from Ref. [595] with permission

such evidences were observed by thermogravimetric analysis: DTG plots of the nanocrystals appeared to be quite different from those obtained from mechanical mixtures of CDHA and calcium alendronate with similar compositions [912]. Analogous DTG results were obtained for nano-HA/PVA [541]. In the case of nano-HA/polyamide biocomposites, a hydrogen bonding between the phases was detected by differential scanning calorimetry technique [536]. Another example comprises application of the dynamic mechanical analysis to investigate softening mechanism of β-TCP/PLLA biocomposites [382]. In the case of nano-HA/PVAP composites, the indirect evidences of chemical bonding between the phases were found by X-ray diffraction and thermogravimetric analysis [280]. A strong structural correlation between the orientation of FA crystallites and the gelatin within the FA/gelatin composite spheres was discovered that indicated to a substantial reorganization of the macromolecular matrix within the area of a growing aggregate [366].

By means of the X-ray photo-electronic spectroscopy (XPS) technique, binding energies of Ca, P, and O atoms were found to have some differences between nano-HA (Ca, 350.5 and 345.5; O, 530.2; P, 132.5 eV) and nano-HA/konjac glucomannan/chitosan biocomposite (Ca, 352.1 and 347.4; O, 531.2; P, 133.4 eV), respectively [549]. Further measurements by FTIR and X-ray diffraction revealed that nano-HA was mainly linked with konjac glucomannan and chitosan by hydrogen bonding among OH^- and PO_4^{3-} of nano-HA and –C=O and –NH of konjac glucomannan and chitosan copolymer and there was a stable interface formed between the three phases in the biocomposite. Meanwhile, coordinate bonding might be formed between Ca^{2+} and –NH. Stable interfaces have been formed among the three phases in a biocomposite [549]. In HA/collagen biocomposites, a covalent bond formation between Ca^{2+} of HA and $RCOO^-$ of collagen molecules was found by XPS [503]. Similar XPS observations were also made for several other calcium orthophosphate-based biocomposites [529, 556, 565].

The interaction and adhesion between calcium orthophosphate fillers and respective matrixes have a significant effect on the properties of particulate-filled reinforced materials, being essential to transfer the load between the phases and thus improve the mechanical performance of the composites [287]. However, for the substantial amount of the biocomposites discussed in this review, the interaction between the phases is mechanical in nature. This is because the matrix often consists of compounds with no functional groups or unsaturated bonds, which can form ionic complexes with the constituents of calcium orthophosphates. Obviously, less coupling exists between nonpolar polymers and calcium orthophosphate ceramic particles. Therefore, polymers with functional groups pendant

to the polymer backbone, which can act as sites for bridging to calcium orthophosphates, are more promising in this respect [49]. Besides, the surface of calcium orthophosphates might be modified as well [116, 416, 417, 552, 914, 915]. In order to improve the situation, various supplementary reagents are applied. Namely, if the primary effect of a processing additive is to increase the interaction between the phases, such an additive can be regarded as a coupling agent [916]. Coupling agents establish chemical bridges between the matrix and the fillers, promoting the adhesion between the phases. In many cases, their effect is not unique, influencing also the rheology of composites [225].

Optimization of biocomposite properties with coupling agents is currently an important area of the research. The control and development of molecular-level associations of polymer with calcium orthophosphates is suggested to be significant for the resulting mechanical responses in the composites. It appears that a fundamental molecular understanding of interfacial behavior in biocomposite systems is an area not sufficiently addressed in the literature. Various experimental characterization techniques using electron microscopy, vibrational spectroscopy, X-ray diffraction, scanning probe microscopy, and others are used routinely to characterize these materials besides mechanical property characterization. In addition, atomic scale models for simulating the phase interaction and predicting responses in the novel material systems, where nanostructure and nanointerfaces are included, are important to understand and predict the load deformation behavior [147].

A hexamethylene diisocyanate coupling agent was used to bind PEG/PBT (Polyactive^{TM}) block copolymers [234] and other polymers [910] to HA filler particles. Thermogravimetric and infrared analysis demonstrated that the polymers were chemically bonded to the HA particles through the isocyanate groups, making it a suitable approach to improve the adhesion [910]. Other researchers used glutaraldehyde as a crosslinked reagent in various calcium orthophosphate-based biocomposites [388, 392, 500, 502, 503, 520, 525, 585, 621, 646, 649, 917]. The interfacial bonding between calcium orthophosphates and other components might be induced by using various coupling agents and surface modifiers, such as silanes [192, 234, 337, 540, 918–923], zirconates [225, 337, 339, 914, 924], titanates [225, 337, 924], phosphoric acid [543], alkaline pretreatment [722, 725], polyacids [115, 116, 234], and other chemicals. Besides, some polymers might be grafted onto the surface of calcium orthophosphates [552]. Structural modifications of the polymeric matrices, for instance, with the introduction of acrylic acid [195, 234, 919, 920], have also proved to be effective methods. For example, application of polyacids as a bonding agent for HA/Polyactive^{TM} composites caused the surface-modified HA particles to maintain better contact with the polymer at fracture and improved mechanical properties [115, 116, 234]. The use of titanate and zirconate coupling agents appeared to be very dependent on the molding technique employed [225]. Silane-coupled HA powders were tested before applying them as fillers in biodegradable composites [921–923]. This treatment allowed HA withstanding the attack of water without impairing overall bioactivity. Besides, chemically modified reinforcement phase–matrix interface was found to improve the mechanical properties of the biocomposites. Examples of such interface-modified biocomposites include chemically coupled HA/PE [919, 920], chemically formed HA/Ca poly(vinylphosphonate) [283], and PLA/HA fibers [184]. These biocomposites are able to consume a large amount of energy in the fracture.

The action of some coupling agents was found to combine two distinct mechanisms: (i) crosslinking of the polymeric matrix (valid for zirconate and titanate coupling agents) and (ii) improvement of the interfacial interactions between the major phases of the composites. This interfacial adhesion improvement appeared to be much dependent on the chemical nature (pH and type of metallic center) of the coupling agents [337]. Several studies claimed that silanes do interact with HA [192, 919–923]. It was shown that a silicon-containing inter-phase existed between HA and PE, which promoted the chemical adhesion between the HA particles and the polymer. A silane-coupling agent also facilitated penetration of PE into cavities of individual HA particles, which resulted in enhanced mechanical interlocking at the matrix-reinforcement interface [919, 920].

Addition of adhesion promoting agents might be an alternative to improve the interaction between the fillers and the matrix. For example, Morita et al. [925] used incorporation of 4-methacryloyloxyethyl trimellitate anhydride to promote adhesion of the polymer to HA. In another study, phosphoric ester was added to the liquid component of the formulation [926]. Both the strength and the affinity index of biocomposites were found to increase, probably due to the effects of copolymerization.

Possible interactions between BCP and HPMC have been investigated in IBS composites [736, 737, 927]. After mixing, there was a decrease in the mean diameter of BCP granules and this influenced the viscosity of the paste. Dissolution of grain boundaries of β-TCP crystals and precipitation of CDHA on HA crystal surface was found during the interaction between BCP and HPMC in aqueous solutions. Both phenomena were responsible for the observed granulometric changes [736, 737]; however, within the sensitivity of the employed measurement techniques, no chemical bonding between BCP and HPMC was detected [927].

A coprecipitation method was used to prepare CDHA/chitosan biocomposites [672]. Growth of CDHA crystals was inhibited by organic acids with more than two carboxyl groups, which strongly bind to CDHA surfaces via a COO–Ca bond. Transmission electron microscopy images revealed that CDHA-formed elliptic aggregates with chemical interactions (probably coordination bond) between Ca on its surface and amino groups of chitosan; the CDHA nanocrystals were found to align along the chitosan molecules, with the amino groups working as the nucleation sites [672]. Formation of calcium crosslinked polymer carboxylate salts was suggested during the setting of calcium orthophosphate cement (TTCP + DCPA)/polyphosphazane biocomposites; the chemical involvement of the polymer in the cement setting was concluded based on the results of pH monitoring [460–462].

A chemical bond between the phases was presumed in PCL/HA composites, prepared by the grafting technique [350]; unfortunately, no strong experimental evidences were provided. In another study, CDHA/poly(α-hydroxy-ester) composites were prepared by a low-temperature chemical route [324]. In that study, pre-composite structures were prepared by combining α-TCP with PLA, PLGA and copolymers thereof. The final biocomposite structure was achieved by in situ hydrolysis of α-TCP to CDHA performed at 56 °C either in solvent cast or pressed pre-composites. That transformation occurred without any chemical reaction between the polymer and calcium orthophosphates, as it was determined by FTIR spectroscopy [324].

In nearly every study on HA/carbon nanotubes biocomposites, the nanotubes have been functionalized before combining them with HA. Most researchers have done this by oxidation [242–246], although non-covalent functionalizing with sodium dodecylsulfate [246] and coating the nanotubes by a polymer [928] before combining them with HA have also been reported. Several studies by transmission electron microscopy have shown evidences that the functionalization has enhanced interaction between carbon nanotubes and HA [245, 246, 929].

If calcium orthophosphate-based biocomposites are able to sustain a high-temperature sintering (valid for the formulations consisting of inorganic components only), an inter-diffusion of chemical elements will take place between the phases. Such effect has been detected by energy-dispersive X-ray spectroscopy in HA/TiO_2 biocomposite particles with partial formation of calcium titanates; this process was found to be favorable to enhancing the cohesive strength of particles in the composite coating [817]. A similar high-temperature interaction between HA and zirconia [743, 768], as well as between HA and Ti [554, 840, 842–844], was also detected. Besides, partial decomposition of HA and formation of different calcium aluminates were detected in HA/Al_2O_3 biocomposites after sintering at 1200–1300 °C [795, 801, 802].

Bioactivity and biodegradation of calcium orthophosphate-based biocomposites

The continuous degradation of an implant causes a gradual load transfer to the healing tissue, preventing stress-shielding atrophy and stimulates the healing and remodeling of bones. Some requirements must be fulfilled by the ideal prosthetic biodegradable materials, such as biocompatibility, adequate initial strength and stiffness, retention of mechanical properties throughout sufficient time to assure its biofunctionality and non-toxicity of the degradation by-products [146]. Generally speaking, bioactivity (i.e., ability of bonding to bones) of biologically relevant calcium orthophosphates reinforced by other materials is usually lower than that of pure calcium orthophosphates [27, 28, 930].

In general, both bioactivity and biodegradability of any biocomposite are determined by the same properties of the constituents. Both processes are very multi-factorial because, after implantation, the surface of any graft is rapidly colonized by cells. Much more biology, than chemistry and material science altogether, is involved into these very complex processes and many specific details still remain unknown. In order to simplify the task, the biodegradability of the biologically relevant calcium orthophosphates might be described by a chemical dissolution in slightly acidic media (calcium orthophosphates are almost insoluble in alkaline solutions [87–93]), which, in the case of CDHA, might be described as a sequence of four successive chemical equations [427, 931, 932]:

$$Ca_{10-x}(HPO_4)_x(PO_4)_{6-x}(OH)_{2-x} + (2-x)H^+ \rightarrow Ca_{10-x}(HPO_4)_x(PO_4)_{6-x}(H_2O)_{2-x}{}^{(2-x)+} \quad (1)$$

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

$$Ca_3(PO_4)_2 + 2H^+ \rightarrow Ca^{2+} + 2CaHPO_4 \quad (3)$$

$$CaHPO_4 + H^+ \rightarrow Ca^{2+} + H_2PO_4{}^- \quad (4)$$

Strange enough, but the bioactivity mechanism of calcium orthophosphates is not well described in literature; therefore, biomaterials researchers [72] are forced to use a modified scheme for the bioactivity mechanism of bioactive glasses—the concept introduced by Prof. Hench [27, 28]. The mechanism of bonding of bioactive glasses to living tissue involves a sequence of 11 successive reaction steps. The initial five steps occurred on the surface of bioactive glasses are "chemistry" only,

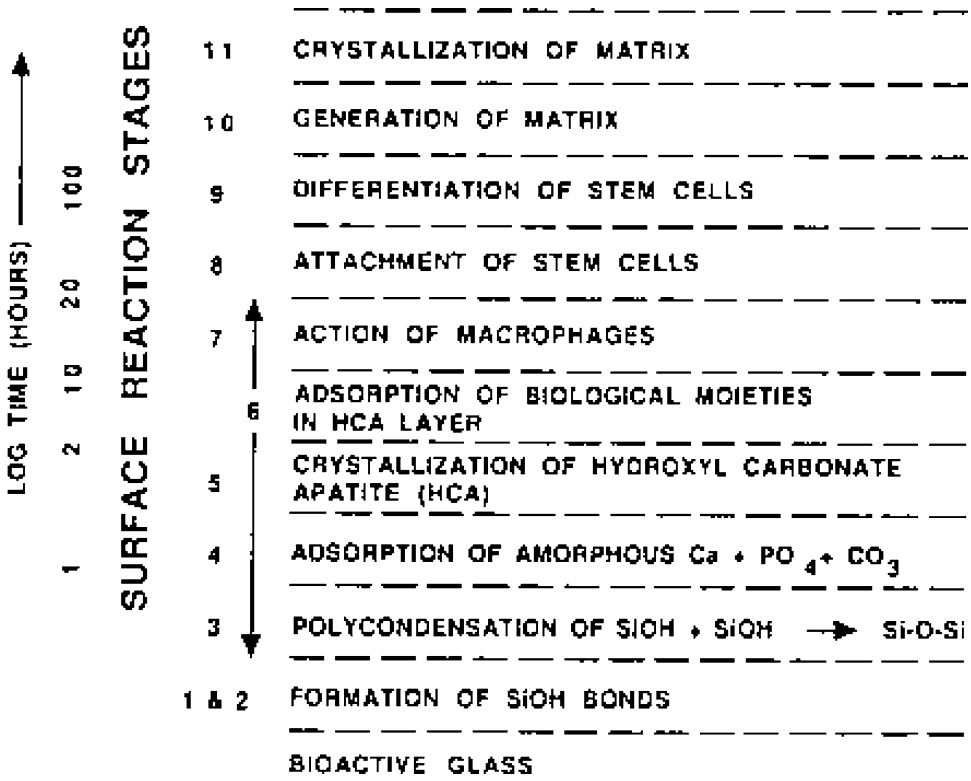

Fig. 7 The sequence of interfacial reactions involved in forming a bond between tissue and bioactive glasses. The border between "dead" and "alive" occurs approximately at stage 6. For want of anything better, the bioactivity mechanism of calcium orthophosphates should also be described by this scheme with omitting of several initial stages, as it was made for HA in Ref. [72], where three initial chemical stages of the Hench's mechanism were replaced by partial dissolution of HA. Reprinted from Ref. [28] with permission

whereas the remaining six steps belong to "biology" because the latter include colonization by osteoblasts, followed by proliferation and differentiation of the cells to form a new bone that had a mechanically strong bond to the implant surface (Fig. 7).

Biodegradability of polymers generally depends on the following factors: (1) chemical stability of the polymer backbone, (2) hydrophobicity of the monomer, (3) morphology of the polymer, (4) initial molecular weight, (5) fabrication processes, (6) geometry of the implant, (7) properties of the scaffold such as porosity and pore diameter [264]. A summary on degradation of PLA and PGA, as well as that of starch/ethylene vinyl alcohol copolymer (SEVA) is available in literature [146, p. 798 and p. 803, respectively], where the interested readers are referred to. Biodegradation of HA/PLLA and CDHA/PLLA composite rods in subcutis and medullary cavities of rabbits were investigated mechanically and histologically; the degradation was found to be faster for the case of using uncalcinated CDHA instead of calcinated HA [933]. In a more detailed study, new bone formation was detected at 2 weeks after implantation, especially for formulations with a high HA content [934]. More to the point, a direct contact between bones and these composites without intervening fibrous tissue was detected in this case [934, 935]. SEVA-C and SEVA-C/HA biocomposites were found to exhibit a non-cytotoxic behavior [936, 937], inducing a satisfactory tissue response when implanted as shown by in vivo studies [937]. Furthermore, SEVA-C/HA biocomposites induce a positive response on osteoblast-like cells to what concerns cell adhesion and proliferation [936].

Both in vitro (the samples were immersed into 1% trypsin/phosphate-buffered saline solution at 37 °C) and in vivo (implantation of samples into the posterolateral lumbar spine of rabbits) biodegradation have been investigated for nano-HA/collagen/PLA biocomposites [511]. The results demonstrated that weight loss increased continuously in vitro with a reduction in mass of 19.6% after 4 weeks. During the experimental period in vitro, the relative rate of reduction of the three components in this material was shown to differ greatly: collagen decreased the fastest, from 40% by weight to 20% in the composite; HA content increased from 45 to 60%, whereas PLA changed little. In vivo, the collagen/HA ratio appeared to be slightly higher near the transverse process than in the central part of the intertransverse process [511]. These data clearly demonstrate a biodegradation independence of various components of biocomposites.

Some challenges and critical issues

The scientific information summarized in this review represents the recent developments of calcium orthophosphate-based biocomposites and hybrid biomaterials

from a variety of approaches, starting from conventional ones to tissue engineering. Such formulations combined with osteoconductive, osteoinductive factors, and/or osteogenic cells have gained much interest as a new and versatile class of biomaterials, and are perceived to be beneficial in many aspects as bone grafts [32]. However, current applications of these biomaterials in medicine and surgery are still remarkably less than might be expected. In many biomedical applications, research and testing of such formulations have been introduced and highly developed but only in a very few cases an industrial production and commercial distribution of medical devices partially or entirely made of biocomposites have started. The medical application of biocomposites and hybrid biomaterials requires a better understanding of the objectives and limitations involved. Recently, the main critical issues have been summarized as follows [213]:

- There are not enough reliable experimental and clinical data supporting the long-term performance of biocomposites with respect to monolithic traditional materials.
- The design of biocomposites and hybrid biomaterials is far more complex than that of conventional monolithic materials because of the large number of additional design variables that must be considered.
- The available fabrication methods may limit the possible reinforcement configurations, may be time consuming, expensive, highly skilled and may require special cleaning and sterilization processes.
- There are no satisfactory standards yet for biocompatibility testing of the biocomposite implants because the ways in which the different components of any biocomposite interact to living tissues are not completely understood.
- There are no adequate standards for the assessment of biocomposite fatigue performance because the fatigue behavior of such materials is far more complex and difficult to predict than that of traditional materials [213].

On the other hand, in spite of an enormous progress in biocomposite processing, to achieve the desired characteristics researchers still need to develop more advanced technologies to fabricate a bone-resembling hierarchical organization over several length scales. Development of novel bone repair materials depends on the progress in research into the structure of natural bones. The key issues are not only to understand the fundamentals of biomineralization, but also to translate such knowledge into practical synthetic pathways to produce better bone grafts. Unfortunately, when it comes to the fabrication of composites mimicking natural bone from the nanometer to the micrometer dimensions, there are many key issues, including the control of morphology, incorporation of foreign ions, interaction with biomolecules, and assembly of the organic and inorganic phases, which are still not well understood. A processing gap between the lower-level building units and the higher-order architecture could severely limit the practical application of current calcium orthophosphate-based biocomposites and hybrid biomaterials. Therefore, further substantial research efforts have been outlined to address the following key challenges [32, 37]:

- Optimizing biocomposite processing conditions.
- Optimization of interfacial bonding and strength equivalent to natural bone.
- Optimization of the surface properties and pore size to maximize bone growth.
- Maintaining the adequate volume of the construct in vivo to allow bone formation to take place.
- Withstanding the load-bearing conditions.
- Matching the bioresorbability of the grafts and their biomechanical properties while forming new bone.
- Understanding the molecular mechanisms by which the cells and the biocomposite matrix interact with each other in vivo to promote bone regeneration.
- Supporting angiogenesis and vascularization for the growth of healthy bone cells and subsequent tissue formation and remodeling [32, 37].

The aforementioned critical issues have to be solved before a widespread commercial use of calcium orthophosphate-based biocomposites and hybrid biomaterials can be made in surgery and medicine.

Conclusions

All types of calcified tissues of humans and mammals appear to possess a complex hierarchical composite structure. Their mechanical properties are outstanding (considering weak constituents from which they are assembled) and far beyond those, that can be achieved using the same synthetic materials with present technologies. This is because biological organisms produce biocomposites that are organized in terms of both composition and structure, containing both brittle calcium orthophosphates and ductile bioorganic components in very complex structures, hierarchically organized at the nano-, micro-, and meso-levels. Additionally, the calcified tissues are always multifunctional, e.g., bone provides structural support for the body plus blood cell formation. The third defining characteristic of biological systems, in contrast with current synthetic systems, is their self-healing ability, which is nearly universal in nature. These complex structures, which have risen from millions of years of evolution,

inspire materials scientists in the design of novel biomaterials [938].

Until now, still no reasonable alternative exists to autogenous bone grafts in surgery. However, the studies summarized in this review have shown that the proper combination of a ductile matrix with a brittle, hard, and bioactive calcium orthophosphate filler offers many advantages for biomedical applications. Namely, the desirable properties of some components can compensate for a poor mechanical behavior of calcium orthophosphate bioceramics, while in turn the desirable bioactive properties of calcium orthophosphates improve those of other phases, thus expanding the possible application of each material within the body [94]. However, the reviewed literature clearly indicates that among possible types of calcium orthophosphate-based biocomposites and hybrid biomaterials only simple, complex, and graded ones (see classification of the composites in the section "General information on composites and biocomposites") have been investigated. Presumably, a future progress in this subject will require concentrating efforts on elaboration and development of hierarchical biocomposites. Furthermore, following the modern tendency of tissue engineering, a novel generation of calcium orthophosphate-based biocomposites and hybrid biomaterials should also contain a biological living part.

Much study remains to be done on a long way from a laboratory to clinics, and the success in this field depends on the effective cooperation of clinicians, chemists, biologists, bioengineers, and materials scientists.

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