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Biocomposites and hybrid biomaterials based on calcium orthophosphates

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Abbreviations: A-W, apatite-wollastonite; BMP, bone morphogenetic protein; BSA, bovine serum albumin; EVOH, a copolymer of ethylene and vinyl alcohol; HDPE, high-density polyethylene; HIPS, high impact polystyrene; HPMC, hydroxypropylmethylcellulose; IBS, injectable bone substitute; PAA, polyacrylic acid; PBT, polybutyleneterephthalate; PCL, poly(ε-caprolactone); PDLLA, poly(D,L-lactic acid); PE, polyethylene; 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; PLGC, *co*-polyester lactide-*co*-glycolide-*co*-ε-caprolactone; PLLA, poly(L-lactic acid); PMMA, polymethylmethacrylate; PP, polypropylene; PPF, poly(propylene-*co*-fumarate); PS, polysulfone; PSZ, partially stabilized zirconia; PTFE, polytetrafluoroethylene; PVA, polyvinyl alcohol; PVAP, polyvinyl alcohol phosphate; SEVA-C, a blend of EVOH with starch; UHMWPE, ultrahigh molecular weight polyethylene

The state-of-the-art of biocomposites and hybrid biomaterials based on calcium orthophosphates that are suitable for biomedical applications is presented in this review. Since these types of biomaterials offer many significant and exciting possibilities for hard tissue regeneration, this subject belongs to a rapidly expanding area of biomedical research. Through 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. Various types of biocomposites and hybrid biomaterials based on calcium orthophosphates, either those already in use or being investigated for biomedical applications, are 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 already been proposed. Among the others, the nanostructurally controlled biocomposites, those containing nanodimensional compounds, 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 biocomposites and hybrid biomaterials based on calcium orthophosphates in the selected applications are highlighted. As the way from the laboratory to the hospital is a long one, and the prospective biomedical candidates have to meet many different necessities, this review also examines the critical issues and scientific challenges that require further research and development.

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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 is still a challenge for orthopedic surgeons, especially in the case of large bone defects. A rapidly aging population and serious drawbacks to using natural bone grafts make the situation even worse; therefore, there is a high clinical demand for bone substitutes. Unfortunately, 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 nonidentical 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-allergenic). They contain viable osteogenic cells, bone matrix proteins and support bone growth. Usually, autografts are well accepted by the body and rapidly integrate into the surrounding bone tissues. For these reasons, they are routinely used for a long period with good clinical results,[3-6] and it is fair to say that complications mostly arose in the past.[7,8] 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. In addition, their medical

Table 1. The biochemical composition* of bones[36]

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.

application always involves 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.[1,8-11] Thus, any types of biologically derived transplants 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.[9,11,12] In this light, man-made materials (alloplastic or synthetic bone grafts) stand out as a reasonable option, because they are easily available and might be processed and modified to suit the specific needs of a given application.[13-15] What's more, there are no concerns about potential infections, immunological incompatibility, sterility or 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.[16]

Currently, there are several classes of synthetic bone grafting biomaterials for in vivo applications.[17-21] Examples include natural coral, coral-derived materials, bovine porous demineralized bone, human demineralized bone matrix, bioactive glasses, glass-ceramics and calcium orthophosphates.[11] 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 μm[22,23] to 2 mm,[24] to facilitate tissue and vessel ingrowths. Among them, porous bioceramics made of calcium orthophosphates appear very promising due to both excellent biocompatibility and their ability to bond to living bone in the body. This is directly related to the fact that the inorganic material of mammalian calcified tissues, i.e., of bones and teeth, consists of calcium orthophosphates.[25-27] For this reason, other artificial materials are normally encapsulated by fibrous tissue when implanted in body defects, while calcium orthophosphates are not.[28] Many types of calcium orthophosphate-based bioceramics with different chemical composition are already on the market. Unfortunately, as with any ceramic material, calcium orthophosphate bioceramics alone lack the mechanical and elastic properties of calcified tissues. Namely, scaffolds made of calcium orthophosphates suffer from a low elasticity, a high brittleness, a poor tensile strength, a low mechanical reliability and fracture toughness, which leads to various concerns about their mechanical performance after implantation.[29-31] In addition, 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[32]) rather than to a natural ceramic (mainly, a poorly crystalline, ion-substituted CDHA, often referred to as "biological apatite") phase.[34,35] The elastic collagen fibers are aligned along the main stress directions in bone. The biochemical composition of bones is given in **Table 1**.[36] A decalcified bone becomes very flexible and is easily twisted, whereas a bone without collagen is very brittle; thus, the inorganic, nano-sized crystals of biological apatite provide hardness and stiffness, while the bioorganic fibers are responsible for the elasticity and toughness.[26,37] In bones, both types of materials integrate with each other on a nanometric scale in such a way that the crystallite size, fiber orientation, short-range order between the components, etc. determine its nanostructure and, therefore, the function and mechanical properties of the entire composite.[33,38-42] 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.[25,26,31]

It remains a great challenge to design the ideal bone graft, one 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.[29,40,43] 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.[44-47] 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 that 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 significantly disturb the stress environment of the surrounding living tissue.[48] Finally, there is the opinion that, in the case of a serious trauma, the bone should fracture rather than the implant.[29] A good sterilizability, storability and processability as well as a relatively low cost are also of a great importance to permit clinical application. Unfortunately, no artificial biomaterial is yet available that embodies all these requirements, and it is unlikely that one will appear in the near future. To date, 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 aesthetic reasons. One of the most promising alternatives is to apply materials with similar composition and nanostructure to that of bone tissue.[40] Mimicking the structure of calcified tissues and addressing the limitations of the individual materials in the development of organic-inorganic hybrid biomaterials provides excellent possibilities for improving conventional bone implants. In this sense, suitable biocomposites tailored to physical, biological and mechanical properties and predictable degradation behavior can be prepared by combining biologically relevant calcium orthophosphates with bioresorbable polymers.[49,50] As a rule, the general behavior of these bioorganic/calcium orthophosphate biocomposites 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) and either into or onto a biodegradable polymer matrix in the form of particles or fibers are increasingly considered for use as bone tissue engineering scaffolds due to their improved physical, biological and mechanical properties.[51-57] In addition, such biocomposites could set out general requirements for the next generation of biomaterials; they should combine bioactive and bioresorbable properties to activate in vivo mechanisms of tissue regeneration, stimulating the body to heal itself and leading to replacement of the implants by the regenerating tissue.[50,58,59] 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.[60]

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,[61] followed by Dreesman in 1892.[62] A great progress in the clinical application of various types of composite materials has been achieved since then. Based on past experience and newly gained knowledge, various composite materials with tailored mechanical and biological performance can now be manufactured and used to meet various clinical requirements.[63] This review presents only a brief history as well as 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 as well as phase interactions have been considered and discussed in detail. 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, which remain separate and distinct on a macroscopic level within the finished structure."[64] Thus, composites are always heterogeneous. Furthermore, the phases of any composite retain their identities and properties and are bonded, which is why an interface is maintained between them. This provides improved specific or synergistic characteristics that cannot be obtained by any of the original phases alone.[65] 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".[66] For this reason, with a few important exceptions, the structures obtained by soaking various materials in supersaturated solutions containing ions of calcium and orthophosphate (reviewed in ref. 67–73), those obtained by coating of various materials by calcium orthophosphates (reviewed in ref. 74–82) as well as calcium orthophosphates coated by other compounds[83-87] have not been considered; however, composite coatings have been considered. Occasionally, porous calcium orthophosphate scaffolds filled by cells inside the pores[88-91] as well as calcium orthophosphates impregnated by biologically active substances[92,93] are also defined as composites and/or hybrids; 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). To create a composite, at least one portion of each type is required. General information on the major fabrication and processing techniques may be found elsewhere.[66,94] The continuous phase is responsible for filling the volume as well as surrounding and supporting 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

Table 2. General respective properties from the bioorganic and inorganic domains, to be combined in various composites and hybrid materials[40]

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

of a great interest. This synergism produces properties that are unavailable from the individual constituent materials.[94,95] 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.[96] Other factors to be considered in composites include 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.[64,94,95]

In general, composites might be simple, complex, graded or hierarchical. The term "a simple composite" refers to composites that result from the homogeneous dispersion of one dispersed phase throughout a matrix. The term "a complex composite" refers to composites that result from the homogeneous dispersion of several dispersed phases throughout one matrix. The term "a graded composite" refers to composites that result from the intentionally structurally inhomogeneous dispersion of one or several dispersed phases throughout one matrix. The term "a hierarchical composite" refers to those cases in which fine entities of either a simple or a complex composite are 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. There is another set of four types of composites: (1) fibrous composites, where the fibers are in a matrix; (2) laminar composites, in which the phases are in layers; (3) particulate composites, where the particles or flakes are in a matrix and (4) hybrid composites, which are combinations of any of the above. Yet another classification system of the available composites is based on the matrix materials (metals, ceramics and polymers).[63]

In most cases, three interdependent factors must be considered in designing of any composite: (1) the selection of a suitable matrix and dispersed materials, (2) the choice of appropriate fabrication and processing methods and (3) both internal and external design of the device itself.[66] Furthermore, 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 that, depending upon the nature of the matrix material, 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).[64,94,95]

In order to prepare any type of a composite, at least two different materials must be mixed. Thus, a phase miscibility phenomenon appears to be of paramount importance.[97,98] Furthermore, the interfacial strength among the phases is a very important factor, because a lack of adhesion among the phases will result in an early failure at the interface and thus in a decrease in the mechanical properties, especially the tensile strength. From a chemical point of view, we can distinguish several types of interactions among the composite components: materials with strong (covalent, coordination, ionic) interactions; those with weak interactions (van der Waals forces, hydrogen bonds, hydrophilic-hydrophobic balance) and those without chemical interactions among the components.[99] Wetting is also important in bonding or adherence of the materials. It depends on the hydrophilicity or polarity of the filler(s) and the available polar groups of the matrix.

Biocomposites are defined as non-toxic composites that are able to interact well with the human body in vivo and, ideally, contain one or more component(s) that stimulate(s) the healing process and uptake of the implant.[100] Thus, for biocomposites, biological compatibility appears to be more important than any other type of compatibility.[63,101,102] Interestingly, according to the databases, the first paper with the term "biocomposite" in the title was published in 1987,[103] and the first one containing a combination of the terms "biocomposite" and HA in the title was published in 1991.[104] Thus, this subject appears to be quite new. The most common properties from the bioorganic and inorganic domains to be combined in biocomposites have been summarized in **Table 2**.[40] For general advantages of the modern calcium orthophosphate-based biocomposites over calcium orthophosphate bioceramics and bioresorbable polymers individually, interested readers are advised to see the "Composite Materials Strategy" section of reference 50.

The Major Constituents of Biocomposites and Hybrid Biomaterials for Bone Grafting

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.[25-27] As a result, in addition to being nontoxic, they are biocompatible, not recognized as foreign materials in the body and, most importantly, exhibit both bioactive behavior and the ability to integrate into living tissue by the same

Table 3. Existing calcium orthophosphates and their major properties[27]

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

[a]These compounds cannot be precipitated from aqueous solutions. [b]Cannot be measured precisely. However, the following values were found: 25.7 ± 0.1 (pH = 7.40), 29.9 ± 0.1 (pH = 6.00), 32.7 ± 0.1 (pH = 5.28). The comparative extent of dissolution in acidic buffer is: ACP >> α-TCP >> β-TCP > CDHA >> HA > FA. [c]Stable at temperatures above 100°C. [d]Always metastable. [e]Occasionally, it is called "precipitated HA (PHA)". [f]Existence of OA remains questionable.

processes active in remodeling healthy bone. This leads to an intimate physicochemical bond between the implants and bone, termed osteointegration.[105] More to the point, calcium orthophosphates are also known to support osteoblast adhesion and proliferation.[106,107] Even so, the major limitations to the use of calcium orthophosphates as load-bearing biomaterials are their mechanical properties; namely, they are brittle with poor fatigue resistance.[29-31] Their poor mechanical behavior is even more evident for highly porous ceramics and scaffolds. Because porosity greater than 100 μm is the requirement for proper vascularization and bone cell colonization,[108-110] in biomedical applications, calcium orthophosphates are used primarily as fillers and coatings.[27]

The complete list of known calcium orthophosphates, including their standard abbreviations and major properties, is given in **Table 3**, while the detailed information on calcium orthophosphates, their synthesis, structure, chemistry, other properties and biomedical application has been comprehensively reviewed recently in reference 27. Even more thorough information on calcium orthophosphates might be found in special books and monographs.[111-117]

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, crystallinity, hydrophobicity, solubility and thermal transitions. Their properties can be fine-tuned over a wide range by varying the type of polymer or chain length as well as by copolymerization or blending of two or more polymers.[118-120] Unlike ceramics, polymers exhibit substantial viscoelastic properties and easily can be fabricated into complex structures, such as sponge-like sheets, gels or complex structures with intricate porous networks and channels.[121] Being X-ray transparent and non-magnetic, polymeric materials are fully compatible with modern diagnostic methods, such as CT 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 for polymers suitable for biomedical applications are that they must be biocompatible, not elicit an excessive or chronic inflammatory response upon implantation and, for those that degrade, they must breakdown into non-toxic products only. Unfortunately, polymers, for the most part, lack rigidity, ductility and, ultimately, the mechanical properties required in load-bearing applications. Thus, despite their good biocompatibility, many of the polymeric materials are mainly used for soft tissue replacements (such as skin, blood vessel, cartilage, ligament replacement, etc.). Moreover, the sterilization processes (autoclave, ethylene oxide and 60 Co irradiation) may affect the polymer properties.[122]

There are a variety of biocompatible polymers suitable for biomedical applications.[123,124] For example, polyacrylates,

Table 4. Major properties of several FDA approved biodegradable polymers[152]

Polymer	Thermal properties*, °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
poly(ε-caprolactone) (PCL)	t_g = (-60)–(-65) t_m = 58–63	0.4	>24

*t_g, glass transition temperature; t_m, melting point.

poly(acrylonitrile-*co*-vinylchloride) and polylysine have been investigated for cell encapsulation and immunoisolation.[125,126] Polyorthoesters and PCL have been investigated as drug delivery devices, the latter for long-term sustained release because of its slow degradation rates.[127] PCL is a hydrolytic polyester with an appropriate resorption period that releases non-toxic byproducts upon degradation.[128] Other polyesters and PTFE are used for vascular tissue replacement. Polyurethanes are in use as coatings for pacemakers' lead insulation and have been investigated for reconstruction of the meniscus.[129,130] Polymers considered for orthopedic purposes include polyanhydrides, which have also been investigated as delivery devices (due to their rapid and well-defined surface erosion) and for bone augmentation or replacement, since they can be photopolymerized in situ.[127,131,132] To overcome their poor mechanical properties, they have been copolymerized with imides or formulated to be cross-linkable in situ.[132] 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.[132] PPF has emerged as a good bone replacement material, exhibiting good mechanical properties (comparable to trabecular bone), possessing the capability to cross-link in vivo through the C=C bond and being hydrolytically degradable. It has also been examined as a material for drug delivery devices.[127,131-134] 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.[127] Polydioxanone has been also tested for biomedical applications.[135] 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.[136,137] However, PMMA sets via a polymerization of toxic monomers, which also produces a significant amount of heat that damages tissues. Moreover, it is neither degradable nor bioactive, does not bond chemically to bones and might generate particulate debris, leading to an inflammatory foreign body response.[131,138] A number of other nondegradable polymers applied in orthopedic surgery include PE in its different modifications, such as low density PE, HDPE and UHMWPE (used as the articular surface of total hip replacement implants[139,140]), polyethylene terepthalate, PP and PTFE, which are applied to repair knee ligaments.[141] Polyactive™, a block copolymer of PEG and PBT, has also been considered for biomedical application.[142-147] Cellulose[148,149] and its esters[150,151] are also popular. Finally, and importantly, polyethylene oxide, PHB and blends thereof have also been tested for biomedical applications.[50]

Nonetheless, the most popular synthetic polymers used in medicine are the linear aliphatic poly(α-hydroxyesters), such as PLA, PGA and their copolymers, 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.[50,132,152-156] They are biocompatible, mostly non-inflammatory and can degrade in vivo through hydrolysis and, possibly, enzymatic action into products that are removed from the body by regular metabolic pathways.[49,127,132,156-161] They might also be used for drug delivery purposes.[162] 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.[127,132,153,154,156,163-165] 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.[160,166] Furthermore, PLGA is known to support osteoblast migration and proliferation,[59,132,157,167] 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.[156,161] In addition, they exhibit bulk degradation, leading to both a loss in mechanical properties and lowering of the local solution pH, which further accelerates degradation in an 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.[132,156,163] Finally, poly(α-hydroxyesters) do not possess the bioactive and osteoconductive properties of calcium orthophosphates.[153,168]

Several classifications of the biomedically relevant polymers are possible. For example, some authors distinguish between synthetic polymers, like PLA, PGA or their copolymers, and PCL and polymers of biological origin like polysaccharides (starch, alginate, chitin/chitosan,[169-171] gelatin, cellulose, hyaluronic acid derivatives), proteins (soy, collagen, fibrin,[11] silk) and a variety of biofibers, such as lignocellulosic natural fibers.[10,172,173] Natural polymers often posses highly organized structures and may contain an extracellular substance, called ligand, which is necessary to bind with cell receptors. However, they always contain various impurities that should be gotten rid of prior to use. As synthetic polymers can be produced under controlled conditions, in general, they 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. Other authors differentiate between resorbable or biodegradable [e.g., poly(α-hydroxyesters), polysaccharides and proteins] and non-resorbable (e.g., PE, PP, PMMA and cellulose) polymers.[60,173] Furthermore, polymeric materials can be broadly classified as thermoplastics and thermosets. HDPE and PEEK are examples of thermoplastics, while polydimethylsiloxane and PMMA are the examples of thermosets.[122] The list of synthetic biodegradable polymers used for biomedical application as scaffold materials is available as Table 1 in reference 173, while further details on polymers suitable for biomedical applications are available in the literature (refs. 122,165,174-183), where interested readers are referred. Good reviews on the synthesis of different biodegradable polymers[184] as well as on the experimental trends in polymer composites[185] are available elsewhere.

Inorganic materials and compounds. *Metals.* Titanium (Ti) is one of the best biocompatible metals and is used most widely as an implant.[16,186,187] Besides Ti, there are other metallic implants made of pure Zr, Hf, V, Nb, Ta, Re,[186] Ni, Fe, Cu,[188-190] Ag, stainless steels and various alloys[190] suitable for biomedical application. Recent studies revealed an even greater biomedical potential for porous metals.[191-194] Metallic implants provide the necessary strength and toughness 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 (the term biomimetic can be defined as a processing technique that either mimics or inspires the biological mechanism, in part or whole[195]) in terms of chemical composition, because there are no elemental metals in the human body. In addition, even biocompatible metals are bioinert; although they are not rejected by the human body, 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 show a reasonable biocompatibility.[196] Only permanent implants are made of metals and alloys, in which degradation or corrosion is not desirable. However, in recent years, a number of magnesium implants have been proposed which are aimed to degrade in the body in order to make room for ingrowing bones.[193,197,198]

Glasses and glass-ceramics. Special types of glasses and glass-ceramics are also suitable materials for biomedical applications,[199-201] and a special Na_2O-CaO-SiO_2-P_2O_5 glass, named Bioglass®,[13,28,30,31,202,203] 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.[204] 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 40–60 MPa, which is not suitable for major load-bearing applications. Making porosity in Bioglass®-based scaffolds is beneficial, even for better resorption and bioactivity.[205]

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 A-W glass-ceramics are 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. They possess excellent mechanical properties and have, therefore, been used clinically for iliac and vertebrae prostheses and as intervertebral spacers.[16,206-208]

Ceramics. 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, SiO_2) have been widely studied due to their bioinertness, excellent tribological properties, high wear resistance, fracture toughness and strength as well as relatively low friction.[16,209] 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.[210-212] However, the brittle nature of ceramics has limited their scope of clinical applications, and hence, more research needs to be conducted to improve their properties.

Carbon. Due to its bioinertness, excellent tribological properties, fracture toughness and strength as well as low friction, elemental carbon has been used as a biomaterial at least since 1972.[213] Applications include orthopedic prostheses, vitreous carbon roots for replacement teeth, structural skeletal extensions,

bone bridges and hip prostheses. Biomedical properties of amorphous carbon were studied as well.[214] However, current trends primarily represent investigations on biomedical applications of carbon nanotubes.[215,216]

Carbon nanotubes, with their small dimensions, high aspect (length to diameter) ratio as well as 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 excellent potential for accomplishing the necessary mechanical properties.[217] Recent studies have even suggested that they may possess some bioactivity.[218-221] However, non-functionalized carbon nanotubes tend to agglomerate and form bundles. Besides, they are soluble in neither water nor organic solvents. Luckily, chemical functionalization[82,222] allows carbon nanotubes to be dispersed more easily, which can improve interfacial bonding with other components of the composites. Furthermore, functionalization of carbon nanotubes with carboxylic groups was found to confer a capacity to induce calcification similar to woven bones.[223] Interestingly, carbon nanotubes might be functionalized by in situ deposition of CDHA on their surface.[224]

Biocomposites and Hybrid Biomaterials Based on Calcium Orthophosphates

Generally, the available biocomposites and hybrid biomaterials based on calcium orthophosphates might be divided into several (partly overlapping) broad areas:

- biocomposites with polymers,
- self-setting formulations and concretes,
- formulations based on nanodimensional calcium orthophosphates and nanodimensional biocomposites,
- biocomposites with collagen,
- formulations with other bioorganic compounds and/or biological macromolecules,
- injectable bone substitutes (IBS),
- biocomposites with glasses, inorganic compounds, carbon and metals,
- functionally graded formulations and
- biosensors

The details on each subject are discussed below.

Biocomposites with polymers. Typically, the polymeric components of biocomposites and hybrid biomaterials comprise polymers that have shown both 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 % 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.[179] Thus, some attempts have already been made to prepare biocomposites containing whisker-like[225-229] or needle-like[230-232] calcium orthophosphates as well as calcium orthophosphate fibers.[49,233]

The history of implantable polymer-calcium orthophosphate biocomposites and hybrid biomaterials started in 1981[234] with the pioneering study by Prof. William Bonfield and colleagues performed on HA/PE formulations.[236,237] That initial study introduced a bone analog concept, in which proposed biocomposites comprised a polymer ductile matrix of PE and a ceramic stiff phase of HA that was substantially extended and developed in further investigations by that research group.[102,238-254] More recent studies have included investigations on the influence of surface topography of HA/PE composites on cell proliferation and attachment.[255-261] The material is composed of a particular combination of HA particles at a volume loading of ~40% uniformly dispensed in a HDPE matrix. Alternatively, PP might be used instead of PE.[262-264] The idea was to mimic bones by using a polymeric matrix that can develop a considerable anisotropic character through adequate orientation techniques, reinforced with a bone-like bioceramic material that assures both a mechanical reinforcement and a bioactive character of the composite. Following FDA approval in 1994, in 1995 this material became commercially available under the trade name HAPEX™ (Smith and Nephew, Richards), and, to date, it has been implanted in over 300,000 patients with successful results. It remains the only clinically successful bioactive composite and appeared to be a major step in the implant field.[31,265] The major production stages of HAPEX™ include blending, compounding and centrifugal milling. A bulk material or device is then created from this powder by compression and injection molding.[63] Alternatively, HA/HDPE biocomposites might be prepared by a hot rolling technique that facilitates uniform dispersion and blending of the reinforcements in the matrix.[266]

A mechanical interlock between the two phases of HAPEX™ is formed by the shrinkage of HDPE onto the HA particles during cooling.[102,267] Both HA particle size and their distribution in the HDPE matrix are recognized as important parameters affecting the mechanical behavior of HAPEX™.[247] Smaller HA particles, for example, were found to lead to stiffer composites due to the increase in interfaces between the polymer and the ceramics. In addition, rigidity of HAPEX™ was found to be proportional to HA volume fraction.[239] Coupling agents, e.g., 3-trimethoxysiyl propylmethacrylate for HA and acrylic acid for HDPE, might be used to improve bonding (by both chemical adhesion and mechanical coupling) between HA and HDPE.[268,269] Obviously, other calcium orthophosphates might be used instead of HA in biocomposites with PE.[270] Indeed, attempts were made to improve the mechanical properties of HAPEX™ by incorporating other ceramic phases into the polymer matrix, such as PSZ[271] and alumina.[272] A partial replacement of HA filler particles by PSZ particles was found to lead to an increase in the strength and fracture toughness of HA/HDPE biocomposites. The compressive stress, set up by the volume expansion associated with the tetragonal-to-monoclinic phase transformation of PSZ, inhibits or retards the crack propagation within the composite. This results in an enhanced fracture toughness of the HA/ZrO_2/HDPE biocomposite.[271]

Various studies revealed that HAPEX™ attached directly to bones by chemical bonding (a bioactive fixation) rather than by forming fibrous encapsulation (a morphological fixation). Initial clinical applications of HAPEX™ came in orbital

reconstruction,[273] 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.[274,275] In both applications, HAPEX™ 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, and subsequent activity requires only limited mechanical loading with virtually no risk of failure from insufficient tensile strength.[102,202] 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 1–8 GPa, which is quite close to that of bone. The examination of the fracture surfaces revealed that only a 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.[29,203] Further details on HAPEX™ are available elsewhere.[102] In addition to HAPEX™, other types of HA/PE biocomposites are also known.[276-282]

Both linear and branched PE were used as a matrix, and the biocomposites with the former were found to give a higher modulus.[277] 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 interparticle spacing.[102] 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.[282,283]

Many other blends of calcium orthophosphates with various polymers are possible, including rather unusual formulations with dendrimers.[284] Even light-curable polymer/calcium orthophosphate formulations are known.[285] The list of the appropriate calcium orthophosphates is shown in **Table 3** (except MCPM and MCPA, as both are too acidic and, therefore, are not biocompatible;[27] however, to overcome this drawback, they might be mixed with basic compounds, such as HA, TTCP, $CaCO_3$, CaO, etc.). Many biomedically suitable polymers have been listed above. The combination of calcium orthophosphates and polymers into biocomposites has a two-fold 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.[158-160,286-290] Namely, polymers have been added to calcium orthophosphates in order to improve their mechanical strength,[158,286] and calcium orthophosphate fillers have been blended with polymers to improve their compressive strength and modulus in addition to increasing their osteoconductive properties.[52,160,168,291-295] 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.[296] What's more, experimental results of these biocomposites indicate favorable cell-material interactions with increased cell activities as compared with each polymer alone.[288] As a rule, with increasing of calcium orthophosphate content, both Young's modulus and bioactivity of the biocomposites increase, while the ductility decreases.[29,291] Furthermore, such formulations can provide a sustained release of calcium and orthophosphate ions into the milieus, which is important for mineralized tissue regeneration.[287] 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 physical, chemical and mechanical properties similar to those of human bones. Different methods for bringing these two components together into biocomposites have already been realized, including mechanical blending, compounding, ball milling, dispersion of ceramic fillers into a polymer-solvent solution, a melt extrusion of a ceramic/polymer powder mixture, coprecipitation and electrochemical co-deposition.[36,63,297-299] Three methods for preparing a homogeneous blend of HA with PLLA were compared.[297] First, a dry process, consisting of mixing ceramic powder and polymer pellets before a compression molding step, was used. The second technique was based on the dispersion of ceramic fillers into a polymer-solvent solution. The third method was a melt extrusion of a ceramic/polymer powder mixture. Mixing dry powders led to a ceramic particle network around the polymer pellets, whereas the solvent and melt methods produced a homogeneous dispersion of HA in the matrix. The main drawback of the solvent casting method is the risk of potentially toxic organic solvent residues. The melt extrusion method was shown to be a good way to prepare homogeneous ceramic/polymer blends.[297]

There is also in situ formation, which involves either synthesizing the reinforcement inside a preformed matrix material or synthesizing the matrix material around the reinforcement.[63,300,301] This is one of the most attractive routes, since it avoids extensive particle agglomeration. Several papers have reported that the in situ formation technique has produced various composites of apatites with carbon nanotubes.[302-308] Other appoaches include using amino acid-capped nano-sized gold particles as scaffolds to grow CDHA[309] and in preparation of nano-sized HA/polyamide biocomposites.[310,311] In certain cases, a mechanochemical route,[312] emulsions,[313-316] freeze-drying[317] and freeze-thawing techniques,[318] flame-sprayed technique[319] or gel-templated mineralization[320] might be applied to produce calcium othophosphates-based biocomposites. Various fabrication procedures are well described elsewhere in references 36, 63 and 297, where the interested readers are referred.

The interfacial bonding between a calcium orthophosphate and a polymer is an important issue for any biocomposite. Four

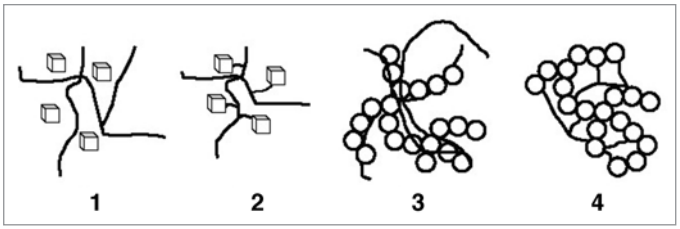

Figure 1. Four types of mutual arrangements of nano-sized particles to a polymer chain: (1) inorganic particles embedded in an inorganic polymer, (2) incorporation of particles by bonding to the polymer backbone, (3) interpenetrating network with chemical bonds, (4) inorganic-organic hybrid polymer. Reprinted from reference 321 with permission.

types of mutual arrangements of nanodimensional particles to polymer chains have been classified by Kickelbick (**Fig. 1**): (1) inorganic particles embedded in inorganic polymer, (2) incorporation of particles by bonding to the polymer backbone, (3) an interpenetrating network with chemical bonds and (4) an inorganic-organic hybrid polymer.[321] If adhesion among the phases is poor, the mechanical properties of a biocomposite suffer. 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.[293,322] Another group used processing conditions to achieve a better adhesion of the filler to the matrix. Ignjatovic et al. prepared PLLA/HA composites by pressing blends of varying PLLA and HA content at different temperatures and pressures.[158,159,323] They found that maximum compressive strength was achieved at ~15 wt% of PLLA. By 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 a 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[286] and fracture energy[324] of the biocomposites. The PLLA/HA biocomposites' scaffolds were found to improve cell survival over plain PLLA scaffolds.[325]

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 migration of osteoblasts from surrounding bones to the implant site.[160,326,327] 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.[173,328-330] A supercritical gas foaming technique might be used as well.[297,331,332]

Apatite-based formulations. A biological apatite is known to be the major inorganic phase of mammalian calcified tissues.[25,26] 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 of improving the bioactivity. For example, PS composed with HA can be used as a starting material for long-term implants.[333-335] 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.[333] The resorption time of such biocomposites is a very important factor, which depends on polymer's microstructure and the presence of modifying phases.[334]

Various apatite-containing biocomposites with PVA,[318,336-344] PVAP[345] and several other polymeric components[346-358] have already been developed. Namely, PVA/CDHA biocomposite blocks were prepared by precipitation of CDHA in aqueous solutions of PVA.[318] An artificial cornea consisting of a porous nanosized HA/PVA hydrogel skirt and a transparent center of PVA hydrogel has been prepared as well. The results displayed good biocompatibility and interlocking between artificial cornea and host tissues.[340,341] PVAP has been chosen as a polymer matrix, because its phosphate groups can act as a coupling/anchoring agent with a higher affinity toward the HA surface.[345] Greish and Brown developed HA/Ca poly(vinyl phosphonate) biocomposites.[349-351] A template-driven nucleation and mineral growth process for the high-affinity integration of CDHA with PHEMA hydrogel scaffold has been developed as well.[358]

PEEK[225,227,359-365,367] and HIPS[366] were applied to create biocomposites with HA because of their 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.[361-363] 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).[362] Modeling of the mechanical behavior of HA/PEEK biocomposites is available elsewhere.[364]

Biodegradable poly(α-hydroxyesters) are well established in clinical medicine. Currently, they provide a good choice when a suitable polymeric filler material is sought. For example, HA/PLGA composites have been developed that appear to possess a cellular compatibility suitable for bone tissue regeneration.[368-376] Zhang and Ma seeded highly porous PLLA foams with HA particles in order to improve the osteoconductivity of polymer scaffolds for bone tissue engineering.[52,292] 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 of 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.[377] However, these data do not appear

to be in a good agreement with HA/PLLA biocomposite unit cell model predictions.[378]

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.[379] However, in biocomposites of poly(α-hydroxyesters) with calcium orthophosphates, the presence of slightly basic compounds (HA, TTCP) neutralizes the acid molecules to some extent and provides a weak pH-buffering effect at the polymer surface, therefore more or less compensating for their drawbacks.[168,380-382] However, additives of even more basic chemicals (e.g., CaO, $CaCO_3$) might be necessary.[173,381,383,384] Extensive cell culture experiments on pH-stabilized composites of PGA and carbonateapatite were reported, which afterwards were supported by extensive in vitro pH studies.[385] A consequent development of this approach has led to the designing of functionally graded composite skull implants consisting of polylactides, carbonateapatite and $CaCO_3$.[386,387] 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 were found to hydrolyze homogeneously due to water penetrating into interfacial regions.[388]

Biocomposites of poly(α-hydroxyesters) with calcium orthophosphates are prepared mainly by incorporating the inorganic phase into a polymeric solution followed by drying under vacuum. The resulting solid biocomposites might be shaped using different processing techniques. One can also prepare these biocomposites by mixing HA particles with L-lactide prior to the polymerization[380] or by a combination of a slip-casting technique and hot pressing.[389] Addition of a surfactant (surface active agent) might be useful to keep the suspension homogenous.[390] Furthermore, HA/PLA[314,315] and HA/PLGA[316] microspheres might be prepared by a microemulsion technique. More complex carbonated FA/PLA[391] and PLGA/carbon nanotubes/HA[392] porous biocomposite scaffolds are also known. 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.[53,393,394] The authors prepared CDHA/PLA and CDHA/PLGA biocomposites using a 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 compared with that of single-phase α-TCP alone; what's more, the inhibiting effect of PLA exceeded that of PLGA.[53,393,394] The physical interactions between calcium orthophosphates and poly(α-hydroxyesters) might be easily seen in **Figure 2**.[53] Another set of good pictures might be found in reference 87. Nevertheless, it should not be forgotten that, typically, non-melt-based routes lead to the development of composites with lower mechanical performance and often times require the use of toxic solvents and intensive hand labor.[178]

The mechanical properties of poly(α-hydroxyesters) could be substantially improved by the addition of calcium orthophosphates.[395,396] Shikinami and Okuno developed CDHA/PLLA composites with very high mechanical properties;[168] mini-screws and mini-plates made of these composites have been manufactured and tested.[388] 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 interposed fibrous tissue, osteoconductivity, biocompatibility and high stiffness that can be retained for the period necessary to achieve bone union.[388] The initial bending strength of ~280 MPa exceeded that of cortical bone (120–210 MPa), while the modulus was as high as 12 GPa.[168] 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.[167] Porous scaffolds of PDLLA and HA have been manufactured as well.[332,397,398] Upon implantation into rabbit femora, a newly formed bone was observed, and biodegradation was significantly enhanced 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.[50,51,377,399,400]

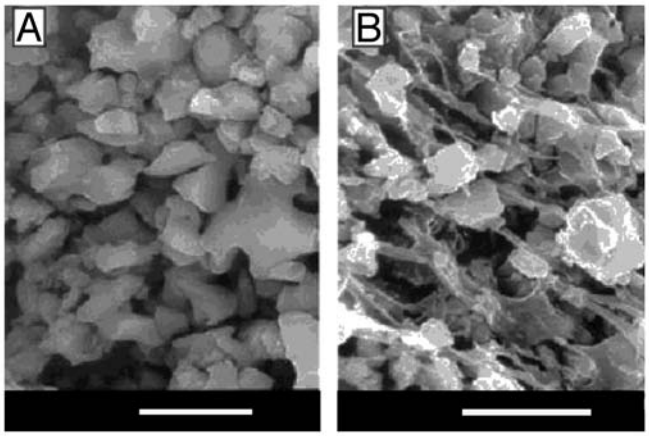

Figure 2. SEM micrographs of (A) α-TCP compact; (B) α-TCP/PLGA biocomposite (bars = 5 μm). Reprinted from reference 53 with permission.

Blends (named SEVA-C) of EVOH with starch filled with 10–30 wt% HA have been fabricated to yield biocomposites with moduli up to ~7 GPa and a 30% HA loading.[401-406] The incorporation of bioactive fillers, such as HA into SEVA-C, aimed to insure 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, which was supported by the polymer's water-uptake capability.[407] 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 has been developed.[408]

Higher homologs poly(3-hydroxybutyrate), 3-PHB and poly(3-hydroxyvalerate), 3-PHV, show almost no biodegradation.

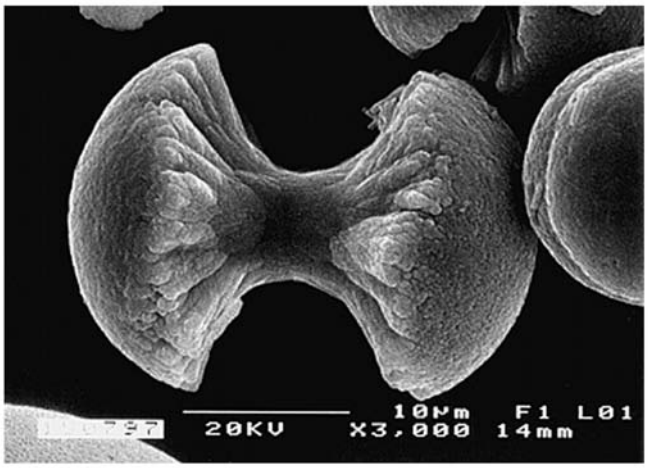

Figure 3. A biomimetically grown aggregate of FA that was crystallized in a gelatin matrix. Its shape can be explained and simulated by a fractal growth mechanism. Scale bar: 10 μm. Reprinted from reference 444 with permission.

Nevertheless, biocomposites of these polymers with calcium orthophosphates show a good biocompatibility both in vitro and in vivo.[102,409-415] Both bioactivity and mechanical properties of these biocomposites can be tailored by varying the volume percentage of calcium orthophosphates. Similarly, biocomposites of PHBHV with both HA and amorphous carbonated apatite (almost ACP) appeared to have promising potential for repair and replacement of damaged bones.[416-419]

Along these lines, PCL is used as a slowly biodegradable but good biocompatible polymer. PCL/HA and PCL/CDHA biocomposites have already been discussed as suitable materials for substitution, regeneration and repair of bone tissues.[328,420-433] For example, biocomposites were obtained by infiltration of ε-caprolactone monomer into porous apatite blocks and by in situ polymerization.[423] 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.[434] Several preparation techniques of PCL/HA biocomposites are known. For example, to make biocomposite fibers of PCL with nanodimensional HA, the desired amount of nanodimensional 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 solvent evaporation.[435] The opposite preparation order has also been used: 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 1 min, followed by solvent evaporation[160] or salt-leaching.[436] 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 a 19:1 ratio in an extruder.[437] 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. In addition, an increase in apatite concentration was found to increase both the modulus and yield stress of the composite, which indicated 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.[437] 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.[438] 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.[438] However, a direct grafting of PCL onto the surface of HA particles seems to be the most interesting preparation technique.[420] In another study, HA porous scaffolds were coated by a PCL/HA composite coating.[54] In this system, PCL as a coating component was able to improve the brittleness and low strength of the HA scaffolds, while the particles in the coating improved the osteoconductivity and bioactivity of the coating layer. More complex formulations, such as PDLLA/PCL/HA,[439] PLLA/PCL/HA[440] and supramolecular PCL/functionalized HA[441] biocomposites, have been prepared as well. Further details on both the PCL/HA biocomposites and the processing methodologies thereof might be found in reference 328.

A spread of human osteoblasts attached to PLA and PCL films reinforced with CDHA and sintered HA was shown to have higher stength than the polymers alone.[184] Moreover, biochemical assays relating cell activity to DNA content allowed for the conclusion that cell activity was more intense for the composite films.[184] Kim et al. 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.[54]

Yoon et al. investigated the highest mechanical and chemical stability of FA by preparing FA/collagen biocomposites and studying their effect on osteoblast-like cell culture.[442] 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.[443] An interesting phenomenon of fractal growth of FA/gelatin composite crystals (**Fig. 3**) was achieved by diffusion of calcium^{-} and orthophosphate^{+} fluoride solutions from opposite sides into a tube filled with a gelatin gel.[444-453] The reasons for this phenomenon are not quite clear yet; besides, up to now, nothing has yet been reported on a possible biomedical application for such very unusual structural composites.

TCP-based formulations. Both α-TCP and β-TCP have a higher solubility than HA (**Table 3**), and they are resorbed more quickly in vivo.[454] Therefore, these calcium orthophosphates were widely used instead of apatites to prepare completely biodegradable biocomposites.[456-479] For example, a biodegradable and osteoconductive biocomposite made of β-TCP particles and gelatin was proposed.[466] 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. Both herbal extracts[467] and K_2HPO_4[468] might be added to this formulation. Another research group prepared biocomposites of cross-linked gelatin with β-TCP, and both a good biocompatibility and bone formation upon subcutaneous implantation in rats were found.[469] Yang et al.[474] extended this to porous (porosity ~75%) β-TCP/gelatin biocomposites that also contained BMP-4. Porous β-TCP/alginate-gelatin hybrid scaffolds that were cell-compatible and possessing some osteoinductive properties were aso prepared and successfully tested in vitro.[471] Biocomposites of β-TCP with PLLA[462-464] and PLGC[465] were prepared as well. 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.[465] α-TCP/gelatin formulations are known as well.[477]

Based on a self-reinforcement concept, biocomposites of TCP with polylactides were prepared and studied using conventional mechanical testing.[480] Resorbable scaffolds were fabricated from such biocomposites.[481] Chitosan was 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 high compressive modulus and strength.[482] PCL/β-TCP biocomposites were developed in other studies,[483-486] and their in vitro degradation behavior was systematically monitored by immersion in simulated body fluid at 37°C.[485] To extend this topic further, PCL/β-TCP biocomposites might be loaded by drugs.[486]

Cell culture tests on β-TCP/PLLA biocomposites were reported; the biocomposites showed no cytotoxicity and evidenced good cell attachment to its surface.[456] An in vitro study with primary rat calvarial osteoblasts showed an increased cellular activity in the BMP-loaded samples.[474] Other researchers investigated BMP-2-loaded porous β-TCP/gelatin biocomposites (porosity ~95%, average pore size 180–200 μm)[487] and confirmed the results of the previous study. Biocomposites of β-TCP and glutaraldehyde cross-linked gelatin were manufactured and tested in vitro to measure the material cytotoxicity.[470] The experimental results revealed that the amount of glutaraldehyde cross-linking agent should be less than 8% to decrease toxicity on the osteoblasts and to avoid inhibition of cellular growth caused by the release of residual or un-cross-linked glutaraldehyde. 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 at this time and an adverse reaction of the remaining PDLLA.[488]

More complex calcium orthophosphate-based formulations are known as well. For example, there is a biocomposite consisting of three interpenetrating networks: TCP, CDHA and PLGA.[489] First, a porous TCP network was produced by coating a polyurethane foam with a hydrolysable α-TCP slurry. Then, a CDHA network was derived from a calcium orthophosphate cement and used to fill 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 behaviors. 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.[489]

Formulations based on other calcium orthophosphates. The number of research publications devoted to formulations based on other calcium orthophosphates is substantially less than those devoted to apatites and TCP. Biphasic calcium phosphate (BCP), which is a solid composite of HA and β-TCP (however, similar formulations of HA and α-TCP, as well as of α-TCP and β-TCP, are possible as well) appears to be most popular among the remaining calcium orthophosphates. For example, collagen-coated BCP ceramics were studied, and their biocompatibility toward osteoblasts was found to increase upon coating with collagen.[490] 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.[491] More relevantly, both PLGA/BCP[492,493] and PLLA/BCP[494] biocomposites were fabricated, and their cytotoxicity and fibroblast properties were found to be acceptable for natural bone tissue reparation, filling and augmentation.[495,496] PCL/BCP[497] and gelatin/BCP[498,499] biocomposites are known as well.

A choice of DCPD-based biocomposites of DCPD, albumin and duplex DNA was prepared by a water/oil/water interfacial reaction method.[313] Core-shell-type DCPD/chitosan biocomposite fibers were prepared by a wet spinning method in another study.[500] 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 small number of P atoms remained inside the fibers. This indicated that the composite fibers formed a unique core-shell structure with a shell of calcium orthophosphate and core of chitosan.[500] A similar formulation was prepared for further applications in bone cement biocomposites.[501] DCPA/BSA biocomposites were synthesized through the coprecipitation of BSA on the nanodimensional particles of DCPA performed in ethanol.[502] Nanodimensional DCPA was synthesized and incorporated into dental resins to form dental biocomposites.[503-505] As an aside, it is interesting to mention that some DCPD/polymer composites could be used as proton conductors in battery devices.[506,507] Nothing has been reported on their biocompatibility yet, but perhaps sometime, improved formulations will be used to fabricate biocompatible batteries for implantable electronic devices.

Various ACP-based biocomposites and hybrid formulations for dental applications have been developed,[508-511] and several ACP-based formulations have been investigated as potential biocomposites for bone grafting[419,512-514] and drug delivery.[515] ACP/PPF biocomposites were prepared by in situ precipitation,[513] while PHB/carbonated ACP and PHBHV/carbonated ACP biocomposites appeared to be well-suited as slowly biodegradable bone substitution materials.[419] Another example is hybrid nanodimensional capsules, ~50–70 nm in diameter, which were fabricated by ACP mineralization of shell cross-linked polymer micelles and nano-sized cages.[514] These nano-sized capsules consisted of

a continuous ultrathin inorganic surface layer that infiltrated the outer cross-linked polymeric domains. They might be used as structurally robust, pH-responsive biocompatible hybrid nanostructures for drug delivery, bioimaging and therapeutic applications.[514]

Self-setting formulations and concretes. Inorganic self-setting calcium orthophosphate cements, which harden in the body, were introduced by LeGeros et al.[516] and Brown and Chow[517,518] in the early 1980s.[519] Since then, these cements have been broadly studied, and many formulations have been proposed. The cements set and harden due to various chemical interactions among calcium orthophosphates, which finally lead to formation of a monolithic body consisting of either CHDA or DCPD, with possible admixtures of other phases. Unfortunately, because of their ceramic natures, calcium orthophosphate cements are brittle after hardening, and the setting time is sometimes unsuitable for clinical procedures.[519] Therefore, various attempts have been made to transform the cements into biocomposites, e.g., by adding hydroxylcarboxylic acids to control the setting time,[520] gelatin to improve both the mechanical properties and the setting time[473,521-523] or osteocalcin/collagen to increase the bioactivity.[524] More to the point, various reinforcement additives of different shapes and nature are widely used to improve the mechanical properties of calcium orthophosphate cements. Even carbon nanotubes were used for this purpose![525] 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.[526] 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[527-540] and PEMA[102,541,542] have been already developed. Such biocomposites might be prepared by dispersion of apatite powder into a PMMA viscous fluid[543] and could be used for drug delivery purposes.[544] When the mechanical properties of the concretes composed of PMMA matrix and HA particles of various sizes were tested, the tensile results showed that strength was independent of particle size. In addition, up to 40% more weight in HA could be added without impairing the mechanical properties.[530,531] 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 was observed.[528,532-535] 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.[532] Thereby, by adding of calcium orthophosphates, a non-biodegradable PMMA was made more bioactive and osteoconductive, yielding a well-processible 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.[545] 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 cross-linking reactions of the polymeric matrix. For example, TTCP reacting with PAA formed a cross-linked CDHA/calcium polyacrylate biocomposite.[546] In aqueous solutions, TTCP hydrolyzes to CDHA,[27] and the liberated calcium cations react with PAA, forming the cross-linked network.[546] Reed et al. synthesized a dicarboxy polyphosphazene that can be cross-linked 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.[547] To mimic PMMA cements, PFF/β-TCP biocomposites were prepared with the addition of vinyl monomer to cross-link PPF. As a result, quick-setting and degradable biocomposite cements with a low heat output and compressive strengths in the range of 1–12 MPa could be prepared by varying the molecular weight of PPF as well as the contents of the monomer, β-TCP initiator and NaCl as a porogen.[548,549] An acrylic cement with Sr-containing HA as a filler,[138] an injectable polydimethylsiloxane/HA cement,[550] biocomposites consisting of PLGA microspheres and a calcium orthophosphate cement[551,552] as well as a hybrid cement formulation of chitosan oligosaccharide/gelatin/calcium orthophosphate[553] were prepared as well.

In order to improve the mechanical properties of self-setting formulations, 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, second, to improve the compressive strength.[473,521,554] Adding rod-like fillers to the self-setting formulations also caused an improvement in the mechanical properties.[554] 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.[555,556] Similar findings were reported in the presence of sodium alginate and sodium polyacrylate.[557] Other polymers, such as polyphosphazene, might be used instead.[558-560] Other examples of polymer/calcium orthophosphate cement formulations might be found elsewhere.[561,562]

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 1,200°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 complex porous biocomposites obtained could be used as tissue engineering scaffolds for low load-bearing applications.[563] 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 well.[564] The latter approach has culminated in a unique, three-phase

biocomposite that is simple to fabricate, osteoconductive and completely biodegradable.

A porosity level of 42–80% was introduced into calcium orthophosphate cement/chitosan biocomposites by the addition of the water-soluble mannitol.[565] Chitosan significantly improved the mechanical strength of the entire biocomposite.[566] A similar approach was used by other researchers who studied the effect of the addition of PLGA microparticles[567-570] (which can also be loaded with drugs or growth factors[571-573]) 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,[567] 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.[573] 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.[568]

Formulations based on nanodimensional calcium orthophosphates and nanodimensional biocomposites. Nanodimensional and nanophasic materials are materials that have particles or grain sizes less than 100 nm, respectively. Thus, one should clearly differentiate between nanodimensional composites and composites based on nanodimensional compounds. The former might be any type of composite that has been disintegrated to particles with dimensions < 100 nm, while the latter are made up of two or more materials, in which at least one of the materials is of a nanometer scale.

Nanodimensional and nanophasic materials have different mechanical and optical properties than large grained materials of the same chemical composition. In particular, they possess unique surface properties, such as an increased number of atoms, grain boundaries and defects at the surface, huge surface area and altered electronic structure compared with conventional micron-sized materials. For example, nanodimensional HA (size ~67 nm) has a higher surface roughness of 17 nm compared to 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 nanodimensional HA (6.1) if compared with the conventional HA (11.51). Additionally, the diameter of individual pores in nanodimensional HA compacts 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).[574-576] Besides, nanodimensional HA promotes osteoblast cell 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.[574-576] More to the point, nanodimensional HA was found to cause apoptosis of the leukemia P388 cells.[577]

Natural bones and teeth are hierarchical biocomposites of biological origin based on nanodimensional compounds, because they consist of nano-sized blade-like crystals of biological apatite grown in intimate contact with the organic matrix, which is rich in bioorganic fibers and organized in complicated hierarchical structures. Given the fact that the major bioorganic phase of bones is collagen, i.e., a natural polymer (**Table 1**), it is obvious that a composite of a nanodimensional calcium orthophosphate with a biodegradable polymer should be advantageous as bone substitution material. The inorganic nanodimensional phase would be responsible for the mechanical strength (hardness) and bioactivity, while the polymeric 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).[578] To the author's best knowledge, among the calcium orthophosphates listed in **Table 3**, only apatites (CDHA, HA and, perhaps, FA) were available in a nanodimensional state until very recently. However, recently, nano-sized DCPA[503-505] and nano-sized MCPM[579] have been synthesized and applied to prepare biocomposites with strong ionic release to combat tooth caries. Presumably, all the calcium orthophosphates in **Table 3** might be manufactured in a nanodimensional and/or nanocrystalline state; however, not all of them have been prepared yet.

A number of investigations have been conducted recently to determine the mineralization, biocompatibility and mechanical properties of biocomposites based on various (bio)polymers and nanodimensional HA. Unfortunately, in the majority of the papers that have been published, it is unclear whether "nanodimensional HA," in fact, represented the nanodimensional stoichiometric HA or a nanodimensional non-stoichiometric CDHA. These studies covered biocomposites with PLA[332,580-589] and its copolymer with PGA,[590-593] collagen,[594-607] collagen + PLA,[607-615] collagen + PVA,[616] collagen + alginate,[617,618] gelatin,[619-624] PPF,[625-627] polyamide,[310,311,628-639] PVA,[340,341,640-642] PVAP,[345] poly(ethylene-*co*-acrylic) acid,[643,644] chitosan[645-651] and its derivatives,[652] konjac glucomannan + chitosan,[653] PHEMA + PCL,[654] PCL,[390,435,655,656] cellulose,[70,71,657-659] Ti,[660-662] PCL semi-interpenetrating biocomposites[663] and many other biocompatible hybrid formulations.[279,320,335,417,664-683] Furthermore, each of the aforementioned formulations might be covered by a layer of nanodimensional calcium orthophosphate, as was done by Zandi et al., who coated a biocomposite of nano-sized rods HA with gelatin by nano-sized HA. Several nanodimensional biocomposites were found to be applicable as carriers for delivery of drugs and growth factors[38,685-687] and were promising as vectors with ultra high gene loading and transfection efficiency.[688] Data are available on the excellent biocompatibility of such biocomposites.[605] The dispersion state of nano-sized particles appears to be the critical parameter in controlling the mechanical properties of nanodimensional biocomposites, as nano-sized particles always tend to aggregate owing to their high surface energy.[417] A comparison was made of the mechanical properties of biocomposites with nano-sized and micron-sized HA with a polyamide. The results showed that the bending and tensile strengths of the biocomposite increased with increasing content of nanodimensional HA but decreased with increasing micron-sized HA content.[310] A SEM image of the mineralized collagen fibrils demonstrating homogeneity of the nanodimensional biocomposite and the close interaction between the mineral phase and the reconstituted collagen fibrils is shown in **Figure 4**.[689]

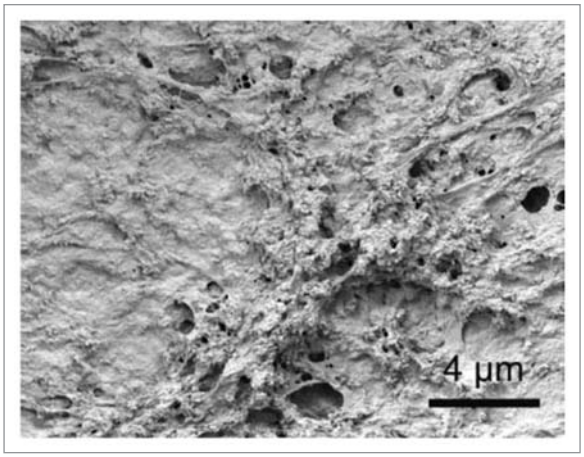

Figure 4. Scanning electron microscopy image of reconstituted mineralized collagen I fibrils. An example of an organic-inorganic nanostructural composite, mimicking the extracellular matrix of bone tissue on the nanometer scale. Reprinted from reference 689 with permission.

Porous (porosity ~85%) biocomposites of nano-sized HA with collagen and PLA have been prepared by precipitation and freeze-drying; these biocomposites did not show a pH drop upon in vitro degradation.[608-610] They were implanted in the radius of rabbits and showed a high biocompatibility and partial resorption after 12 weeks. Nano-sized HA/chitosan biocomposites with improved mechanical stability were prepared from HA/chitosan nano-sized rods.[690] Nano-sized HA/PLLA biocomposites of high porosity (~90%) were prepared using thermally induced phase separation.[691] Nanodimensional HA was also used to prepare biocomposites with PAA, and the nanostructure of the resulting nano-sized crystals exhibited a core-shell configuration.[692,693]

Nanodimensional crystals of HA appear to be suitable for intraosseous implantation and offer the potential to formulate enhanced biocomposites for clinical applications.[694] For example, the biocompatibility of chitosan in osteoblast cell culture was significantly improved by the addition of nano-sized HA.[695] Similar findings are valid for nanodimensional HA/polyamide biocomposites.[630] Further details on nanodimensional biocomposites might be found in an excellent review in reference 36. More to the point, a more general review on applications of nanodimensional biomaterials in orthopedics is also available,[696] where interested readers are referred.

Biocomposites with collagen. The main constituent of the bioorganic matrix of bones is type I collagen (**Table 1**) with molecules about 300 nm in length. The structural and biochemical properties of collagens have been widely investigated, and over 25 collagen subtypes have been identified.[697,698] 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.[699] Both collagen type I and HA were found to enhance osteoblast differentiation,[700] but together, they were shown to accelerate osteogenesis. However, this tendency is not so straightforward: in the available data, implanted HA/collagen biocomposites enhanced regeneration of calvaria bone defects in young rats but postponed the regeneration of calvaria bone in aged rats.[701] 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 collagen.[702] Therefore, a bone analog based on these two constituents should possess remarkable properties. Furthermore, addition of bone marrow constituents gives osteogenic and osteoinductive properties to calcium orthophosphate/collagen biocomposites.[1]

The unique characteristics of bones originate from the spatial orientation between the nanodimentional crystals of biological apatite and collagen macromolecules at the nano scale,[39] where the crystals (about 50 nm length) are aligned parallel to the collagen fibrils,[25,26,35,42] which is believed to be the source of the mechanical strength of bones. The collagen molecules and the crystals of biological apatite assembled into mineralized fibrils are approximately 6 nm in diameter and 300 nm long.[35,39,42,609,703] Although the complete mechanisms involved in the bone building strategy are still unclear, the strengthening effect of nanodimentional crystals of biological apatite 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 crystals. Furthermore, the crystals of biological apatite located in between tangled fibrils cross-link the fibers, either through mechanical interlocking or by forming calcium ion bridges, thus increasing deformation resistance of the collagenous fiber network.[704]

When calcium orthophosphates are combined with collagen in a laboratory, the prepared biocomposites appear to be substantially different from natural bone tissue due to a lack of real interaction between the two components, i.e., the interactions that are able to modify the intrinsic characteristics of the singular components themselves. The main characteristic of the route by which the mineralized hard tissues are formed in vivo is that the organic matrix is laid down first, and the inorganic reinforcing phase grows within this organic matrix.[25,26,35,42] Although, to date, neither the elegance of the biomineral assembly mechanisms nor the intricate composite nano-sized architectures have been duplicated by nonbiological methods, the best way to mimic bone is to copy the way it is formed, namely by nucleation and growth of CDHA nano-sized crystals from a supersaturated solution both onto and within the collagen fibrils.[705-707] Such syntheses were denoted as "biologically inspired" which means they reproduce an ordered pattern and an environment very similar to natural ones.[708-710] The biologically inspired biocomposites of collagen and calcium orthophosphates (mainly, apatites) for bone substitute have a long history,[33,442,597,711-730] which began with the pioneering study by Mittelmeier and Nizard,[731] who mixed calcium orthophosphate granules with a collagen web. Such combinations were found to be bioactive, osteoconductive, osteoinductive,[33,699,732-734] and, in general, artificial grafts manufactured from this type of biocomposites are likely to behave similarly to bones and be of more use in surgery than those prepared from any other materials. Indeed, data are available on the superiority of calcium orthophosphate/collagen biocomposite scaffolds over the artificial polymeric and calcium orthophosphate bioceramic scaffolds individually.[735]

It has been found that calcium orthophosphates may be successfully precipitated onto a collagen substrate of whatever form or source.[33,40,597,736,737] However, adherence of calcium orthophosphate crystals to collagen does depend on how much the collagen had been denatured: the more fibrillar the collagen, the greater attachment. Clarke et al. 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.[716] 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, producing a material with weaker mechanical properties than those reported for bone. Even more significantly, the prepared biocomposites were without a nanostructure similar to that of bone.[713,738] 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 disc from the opposite directions.[737,739,740] Unfortunately, these experiments were designed to simulate the mechanism of in vivo precipitation of biological apatite only; for this reason, the mechanical properties of the biocomposites were not tested.[741]

Conventionally, collagen/calcium orthophosphate biocomposites have been prepared by blending or mixing of collagen and calcium orthophosphates, as well as by biomimetic methods.[33,36,38,41,594,597,609,686,703,708-710,713,736,745-757] For example, Tampieri et al.[710] produced and compared artificial bone like tissue apatite/collagen biocomposites prepared using two different methodologies: (1) dispersion of apatite in a collagen aqueous suspension followed by freeze-drying and (2) direct nucleation of an apatitic phase on assembling collagen fibrils. Biocomposites obtained using first method were similar to uncalcified natural collagen. The crystallite sizes were not uniform and were often aggregated and randomly distributed into the matrix, proving that there was no real interaction between apatite and collagen fibers. However, the second method allowed the direct nucleation of nano-sized crystals of apatite on self-assembled collagen fibers. In this case, the two components (CDHA and collagen) exhibited strong interactions, highlighted by several analysis techniques, which showed a complete analogy of the composite with calcified natural tissue.[710] Other production techniques are also possible. For example, using a polymer-induced, liquid-precursor process, collagen/apatite biocomposites mimicking the nanostructure of bones, wherein nano-sized crystals of apatite were embedded within the collagen fibrils, were prepared.[757] More complicated formulations, such as magnetite-enriched HA/collagen[758] and HA/collagen/PVA[759] biocomposites, have been developed as well.

Furthermore, collagen might be incorporated into various calcium orthophosphate cements.[713,738,760-764] Typically, a type I collagen sponge is presoaked in a PO_4^{3-}-containing, highly basic aqueous solution and then immersed into a Ca^{2+}-containing solution to allow mineral deposition. Alternatively, collagen I fibers might be dissolved in acetic acid, then this solution added to phosphoric acid, followed by a 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.[708,709] 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.[39] Biomimetically, one can achieve an oriented growth of CDHA crystals onto dissolved collagen fibrils in aqueous solutions via a self-organization mechanism.[747] A number of authors produced calcium orthophosphate/collagen biocomposites by mixing preformed ceramic particles with a collagen suspension.[765-767] 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. Instead, CDHA crystallization from aqueous solutions might be performed in the presence of a previously dispersed collagen,[33,597] or, more to the point, collagen might be first dispersed in an acidic solution, followed by addition of calcium and orthophosphate ions; then, coprecipitation of collagen and CDHA might be induced by either increasing the solution pH or adding mixing agents.[41] Although it resulted in biocomposites with poor mechanical properties, pressing of the apatite/collagen mixtures at 40°C under 200 MPa for several days is also possible.[768] Attempts have been made to create a computer simulation of the apatite/collagen composite formation process.[769] It is interesting to note that such biocomposites were found to possess some piezoelectric properties.[770]

As the majority of the collagen/HA biocomposites are conventionally processed by anchoring micron-sized HA particles into a collagen matrix, it is 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, in contrast to nanocrystalline bone apatite, might take a longer time to be remodeled into a new bone tissue upon implantation. In addition, some of the biocomposites exhibit very poor mechanical properties, probably due to a lack of strong interfacial bonding between the constituents. The aforementioned data clearly demonstrate that a chemical composition similar to bone is insufficient for manufacturing the proper grafts; both the mechanical properties and mimetic bone nanostructure are necessary for a graft 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 the enhancement of mechanical properties and osteointegration, with improved biological and biochemical affinity to the host bone. Besides, porosity was found to have a positive influence on the ingrowth of the surrounding tissues into the pores of collagen/HA biocomposites.[771,772]

Another approach is to mix bovine collagen with calcium orthophosphates. These biocomposites are marketed commercially as bone graft substitutes and can further be combined with bone marrow aspirated from the iliac crest of the site of the fracture. Collagraft®, BioOss® and Healos® are several examples of the commercially available grafts for clinical use.[36] Application of these materials was compared with autografts for the

management of acute fractures of long bones with defects that had been stabilized by internal or external fixation.[773,774] These biocomposites are osteogenic, osteoinductive and osteoconductive; however, they lack structural strength and require a 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.[775] The researchers found a good in vitro performance with fibroblast cell culture. Other preparation techniques are also possible.[776] Collagen/HA microspheres or gel beads have been prepared with the intention of making injectable bone fillers.[777,778] Liao et al. succeeded in mimicking the bone structure by blending carbonateapatite with collagen.[779] A similar material (mineralized collagen) was implanted into femur of rats, and excellent clinical results were observed after 12 weeks.[780] Collagen/HA biocomposites were prepared, and their mechanical performance was increased by cross-linking the collagen fibers with glutaraldehyde.[598,600,601] 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 cross-linked by glutaraldehyde.[778] That material showed a good in vitro performance with osteoblast cell culture. A porous bone graft substitute was formed from a nano-sized HA/collagen biocomposite combined with PLA by a freeze-drying method; the resulting material was found to mimic natural bones at several hierarchical levels.[609] Subsequent in vitro experiments confirmed a good adhesion, proliferation and migration of osteoblasts into this composite.[608] A further increase in biocompatibility might be achieved by the addition of various dopants. For example, to enhance bone substitution, Si-substituted HA/collagen composites have been developed, with silicon located preferentially in the collagen phase.[599] Porous (porosity level ~95% with interconnected pores of 50–100 μm) biocomposites of collagen (cross-linked 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.[781]

Biocomposites of calcium orthophosphates with collagen were found to be useful for drug delivery purposes.[618,721,764,782-784] Namely, an HA/collagen-alginate (20 μl) with rh-BMP2 (100 μg/ml, 15 μl) showed bone formation throughout the implant 5 weeks after implantation without obvious deformation of the material.[618] Gotterbarm et al. developed a two-layered collagen/β-TCP implant augmented with chondral inductive growth factors for repair of osteochondral defects in the trochlear groove of minipigs. This approach might be a promising new option for the treatment of deep osteochondral defects in joint surgery.[783]

To conclude this part, one should note that biocomposites of apatites with collagen are a very hot topic in research, and, up to now, just a few papers are devoted to biocomposites of other calcium orthophosphates with collagen.[742-744,783,785-788] 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.[609,731] However, the performance of these biocomposites depends on the source of the collagen from which it was processed. Several attempts have been made to simulate the collagen-HA interfacial behavior in real bone by means of cross-linking agents, such as glutaraldehyde,[598,600,601,736,778,781] with the intention of improving the mechanical properties of these biocomposites. Unfortunately, further progress in this direction is restricted by high cost, the difficulty of controlling cross-infection, a poor definition of commercial sources of collagens as well as by a lack of appropriate technology for fabricating bone-resembling microstructures. Further details on calcium orthophosphate/collagen biocomposites might be found elsewhere.[36,725]

Formulations with other bioorganic compounds and/or biological macromolecules. The biggest practical problems with collagen type I are its cost and the poor definition of commercial sources of this material, which makes it difficult to follow up on well-controlled processing. Therefore, collagen type I can be replaced by other compounds. One should notice that, besides collagen, both human and mammalian bodies contain dozens types of various bioorganic compounds, proteins and biological macromolecules. The substantial amount 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.[789] In order to mimic nature, a laminin/apatite biocomposite layer was successfully created on the surface of both titanium[790] and EVOH[791,792] using the biomimetic approach. A more complicated laminin/DNA/apatite biocomposite layer was found to be an efficient gene transfer system.[793]

Calcium orthophosphate/gelatin biocomposites have been widely investigated as potential bone replacement biomaterials.[317,336-338,444-452,466-474,487,521-523,554,619-624,794-807] For example, gelatin foams were successfully mechanically reinforced by HA and then cross-linked by a carbodiimide derivative.[317] Such foams were shown to be good carriers for antibiotic tetracycline.[798] Several biocomposites of calcium orthophosphates with alginates have been prepared.[471,617,618,622,709,808,809] For example, porous HA/alginate composites based on hydrogels were prepared both biomimetically[709] and using a freeze-drying technique.[808] Another research group succeeded in preparing biphasic but monolithic scaffolds using a similar preparation route.[810] Their biocompatibility in cell culture experiments and in vitro biodegradability were high; however, their mechanical strength could be better.

Various biocomposites of calcium orthophosphates with chitosan[298,482,500,512,527,565,645-653,674,675,690,695,799,807,811-828] and chitin[232,476,612,829-833] 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.[829,830] Unfortunately, it was difficult to obtain 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 increase of the amount of HA. Microscopic examination revealed that HA particles were intervened between the polymer chains, weakening their interactions and decreasing the overall strength.[829,830] Other manufacturing techniques might be found in the aforementioned references; I just would like to mention an interesting approach in which a HA/chitosan biocomposite was produced by a hydrothermal process from the natural $CaCO_3$/chitosan biocomposite of crab shells.[827] Biocomposites of natural HA with chitosan were found to possess both a good hard tissue biocompatibility and an excellent osteoconductivity, which is suitable for artificial bone implants and frame materials for tissue engineering.[823] Data are available that show the addition of HA into chitosan improved cell attachment and provided a higher cell proliferation and well-spread morphology when compared with chitosan alone.[650] More complex formulations, such as silk fibers, reinforced HA/chitosan[834] and HA/collagen/chitosan[835] biocomposites, have been studied as well. Interestingly, hybrid biocomposites of nano-sized HA with chitin/chitosan might be used for removal of Fe(III) [836] and fluorides[837,838] from aqueous solutions. Further details on the biocomposites and hybrid biomaterials of calcium orthophosphates with chitosan are available in the literature.[836]

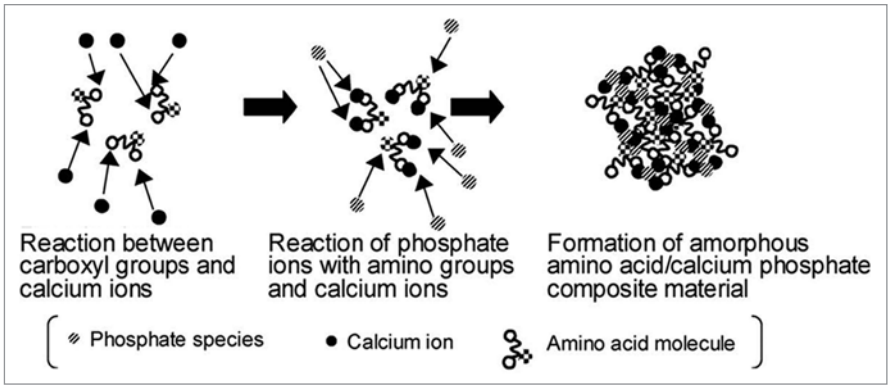

Figure 5. A proposed mechanism for the formation of ACP/amino acid biocomposites in aqueous solutions. Reprinted from reference 856 with permission.

Biocomposites of CDHA with water-soluble proteins, such as BSA, might be prepared by a precipitation method.[561,839-842] 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.[313] To extend this subject, inclusion of DNA into CDHA/BSA biocomposites was claimed.[313,843-845] Furthermore, nanodimentional biocomposites of an unspecified calcium orthophosphate with DNA[846] as well as biocomposites of nano-sized crystals of biomimetic apatite with C_{60} and Au-DNA nano-sized particles[847] were also prepared.

Akashi and coworkers developed a procedure for preparing calcium orthophosphate-based biocomposites by soaking hydrogels in solutions supersaturated by Ca^{2+} and PO_4^{3-} ions in order to precipitate CDHA in the hydrogels (up to 70% more weight in CDHA could be added to these biocomposites).[848] This procedure was applied to chitosan; the 3D shape of the resulting biocomposite was controlled by the shape of the starting chitosan hydrogel.[849] Another research group developed biocomposites based on in situ calcium orthophosphate mineralization of self-assembled supramolecular hydrogels.[850] Other experimental approaches are also possible.[851]

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.[346,347,852-855] 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.[346,347,852-855] A schematic description of a biocomposite formation from amino acids and ACP is shown in **Figure 5**.[856]

Furthermore, 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 applications.[857,858] Agarose, a biodegradable polymer, was selected as the organic matrix, because it is a biocompatible hydrogel that acts 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 fibroblasts and human SAOS-2 osteoblasts during different colonization times.[859]

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.[860] Biocomposites of calcium orthophosphates with fibrin sealants might help develop the clinical applications of bone substitutes. The 3D mesh of fibrin sealant interpenetrates the macro- and microporous structure of calcium orthophosphate ceramics.[11] The physical, chemical and biological properties of calcium orthophosphate bioceramics and the fibrin glue might cumulate in biocomposites suitable for preparation of advanced bone grafts.[861-873]

Furthermore, there are biocomposites of calcium orthophosphates with bisphosphonates,[874] silk fibroin (that is a hard protein extracted from silk cocoon),[312,670-672,677,678,875-881] chitosan + silk fibroin,[882] fibronectin,[883] chondroitin sulfate,[299,733,884] casein phosphopeptides[885] and vitamins.[886] The reader's attention is also drawn to an interesting approach to crystallizing CDHA

inside poly(allylamine)/poly(styrene sulfonate) polyelectrolyte capsules, resulting in empty biocomposite spheres of micron size.[887] 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 capsules might find application as medical agents for bone repairing and catalytic microreactors.[887]

Injectable bone substitutes (IBS). With the development of minimally invasive surgical methods, for example, percutaneous surgery, directly injectable biomaterials are needed. The challenge is to place a biomaterial at the site of surgery by the least invasive method. In this regard, IBS appear to be a convenient alternative to solid bone-filling materials. They represent ready-to-use suspensions of calcium orthophosphate microspheres,[888,889] nano-sized rods[890] or powder(s) in a liquid carrier phase. However, addition of other phases, such as calcium sulfate,[891] is also possible. They look like opaque viscous pastes with rheological properties sufficient to inject them into bone defects by means of surgical syringes and needles. Besides, IBS could be easily produced in a sterile stage. Their stable composition and mechanical properties are suitable for reproducibility of the biological response.[892] All types of IBS are divided into two major groups: self-setting formulations and those that do not set. Cements and concretes belong to the former (see the "Self-setting formulations and concretes" section above), while those that fall into the latter are described here.

IBS requires suitable rheological properties to ensure bonding of the mineral phase in situ with good cell permeability. Usually, the necessary level of viscosity is created by addition of water-soluble polymers.[131,893,894] Therefore, the majority of calcium orthophosphate-based IBS formulations might be considered a subgroup of calcium orthophosphate/polymer biocomposites. For example, an IBS was described that involved a silanized hydroxyethylcellulose carrier with BCP (HA + β-TCP).[895] The suspension is liquid at a pH within 10–12, but it gels quickly at a pH < 9. Injectable composites can be formed with β-TCP to improve mechanical integrity.[548] Similarly, Bennett et al. showed that a polydioxanone-*co*-glycolide-based biocomposite reinforced with HA or β-TCP can be used as an injectable or moldable putty.[896] During the cross-linking reaction following injection, carbon dioxide is released, allowing the formation of interconnected pores. Furthermore, HA/poly(L-lactide-*co*-ε-caprolactone) biocomposite microparticles were fabricated as an injectable scaffold via the Pickering emulsion route in the absence of any molecular surfactants. A stable injectable oil-in-water emulsion was obtained using water-dispersed HA nano-sized crystals as the particulate emulsifier and a dichloromethane solution of poly(L-lactide-*co*-ε-caprolactone) as an oil phase.[897]

Daculsi et al. developed viscous IBS biocomposites based on BCP (60% HA + 40% β-TCP) and a 2% aqueous solution of HPMC that was said to be perfectly biocompatible, resorbable and easily fitted to bone defects (due to an initial plasticity).[108,894,898-905] The best ratio BCP/HPMC aqueous solution was found to be at ~65/35 w/w. To extend this subject further, IBS might be loaded by cells,[906,907] radiopaque elements[908] or microparticles[909] as well as be functionalized by nucleic acids.[890] Self-hardening formulations based on Si-HPMC hydrogel are known as well.[906] The list of the commercially available calcium orthophosphate-based IBS formulations is presented in **Table 5**.[910]

The advanced characteristics of IBS come from their good rheological 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. reported that after a critical concentration (which 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 their mechanical properties.[561] More to the point, Fujishiro et al. reported a decrease in mechanical properties when using higher amounts of gel, which was attributed to formation of pores due to leaching of gelatin in solution.[554] 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.[178] Further details on IBS might be found in a recent review in reference 892.

Biocomposites with glasses, inorganic materials, carbon and metals. 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 common ceramic processing techniques, such as thermal treatment after kneading,[911-913] powder slurry coating[914] and metal-sol mixing.[915] For example, HA was combined with Bioglass® (Novabone Products, Alachua, FL)[916,917] and with other glasses[918] to form glass-ceramic biocomposites. Other reinforcement materials for calcium orthophosphates are differentiated either by shape of the fillers, namely, particles,[919,920] platelets,[921,922] whiskers,[579,923-925] fibers[926-930] or by their chemical composition, zirconia and/or PSZ,[313,911-914,923,931-966] alumina,[313,919,922,965,967-996] other oxides,[925,997-1004] silica and/or glasses,[1005-1014] wollastonite,[206,1015-1025] mullite,[1026,1027] various metals and alloys,[540,928,967,997,1028-1045] calcium sulfate,[1046-1049] calcium carbonate,[1050,1051] silicon carbide,[683,924] barium titanate,[1052] zeolite,[1053] boron nitride[1054] and several other materials.[335,1055-1057] More complicated formulations, such as HA/aluminum oxide/carbon nanotubes,[1058] have been developed as well. All these materials have been added to calcium orthophosphate bioceramics to improve their 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 poor compared with calcium orthophosphate bioceramics alone. Due to the presence of bioinert compounds, such formulations might be called bioinert/bioactive composites.[1005] The ideal reinforcement material would impart mechanical integrity to a biocomposite at low loadings without diminishing its bioactivity.

Table 5. A list of some commercial non-setting calcium orthophosphate IBS and pastes with indication of producer, product name, composition (when available) and form[910]

Producer	Product name	Composition	Form
ApaTech (UK)	Actifuse™	HA, polymer and aqueous solution	Pre-mixed
	Actifuse™ Shape Actifuse™ ABX	Si-substituted calcium orthophosphate and a polymer	Pre-mixed
Baxter (US)	TricOs T, TricOs	BCP (60% HA, 40% β-TCP) granules and Tissucol (fibrin glue)	To be mixed
Berkeley Advanced Biomaterials	Bi-Ostetic Putty	not disclosed	Not disclosed
BioForm (US)	Calcium hydroxylapatite implant	HA powder embedded in a mixture of glycerine, water and carboxymethylcellulose	Pre-mixed
Biomatlante (FR)	MBCP Gel®	BCP granules (60% HA, 40% β-TCP; 0.08–0.2 mm) and 2% HPMC	Pre-mixed
	Hydr'Os	BCP granules (60% HA, 40% β-TCP; micro- and nano-sized particles) and saline solution	Pre-mixed
Degradable solutions (CH)	Easy graft™	β-TCP or BCP granules (0.45–1.0 mm) coated with 10 μm PLGA, N-methyl-2-pyrrolydone	To be mixed
Dentsply (US)	Pepgen P-15® flow	HA (0.25–0.42 mm), P-15 peptide and aqueous Na hyaluronate solution	To be mixed
DePuy Spine (US)	Healos® Fx	HA (20–30%) and collagen	To be mixed
Fluidinova (P)	nanoXIM TCP	β-TCP (5 or 15%) and water	Pre-mixed
	nanoXIM HA	HA (5, 15, 30 or 40%) and water	Pre-mixed
Integra LifeSciences (US)	Mozaik Osteoconductive Scaffold	β-TCP (80%) and type 1 collagen (20%)	To be mixed
Mathys Ltd., (CH)	Ceros® Putty/cyclOS® Putty	β-TCP granules (0.125–0.71 mm; 94%) and recombinant Na hyaluronate powder (6%)	To be mixed
Medtronic (US)	Mastergraft®	BCP (85% HA, 15% β-TCP) and bovine collagen	To be mixed
Osartis/AAP (GER)	Ostim®	Nanocrystalline HA (35%) and water (65%)	Pre-mixed
Smith & Nephew (US)	JAXTCP	β-TCP granules and an aqueous solution of 1.75% carboxymethylcellulose and 10% glycerol	To be mixed
Stryker (US)	Calstrux™	β-TCP granules and carboxymethylcellulose	To be mixed
Teknimed (FR)	Nanogel	HA (100–200 nm) (30%) and water (70%)	Pre-mixed
Therics (US)	Therigraft™ Putty	β-TCP granules and polymer	Pre-mixed
Zimmer (US)	Collagraft	BCP granules (65% HA, 35% β-TCP; 0.5–1.0 mm), bovine collagen and bone marrow aspirate	To be mixed

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.[206,1015-1025] A-W glass-ceramics are 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 them to be used in some major compression load-bearing applications, such as vertebral prostheses and iliac crest replacement. They combine a high bioactivity with suitable mechanical properties.[1059] β-TCP/wollastonite biocomposites are also known.[1060-1062] More complicated formulations 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.[1063-1066] Other examples include wollastonite-reinforced HA/Ca polycarboxylate,[1067] glass-reinforced HA/polyacrylate[1068] as well as collagen[1069] and gelatin[1070] calcium phosphate silicate/wollastonite biocomposites.

HA/glass biocomposites can be prepared by simple sintering of appropriate HA/glass powder mixtures.[1071-1074] If sintering is performed below 1,000°C, HA does not react with the bioactive glass[1072,1073] or the reaction is limited.[1074] Besides, reactions between HA and glasses depend 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.[29] Biocomposites might also be sintered from HA and silica.[1005] In general, bioactive glass-ceramics maintain a high strength for a longer time than HA bioceramics under both in vitro and in vivo conditions.[1012,1019]

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."[217] Nevertheless, different strategies might be employed to prepare calcium orthophosphate/carbon nanotube biocomposites. For example, apatites might be chemically synthesized by using carboxyl functionalized

carbon nanotubes as a matrix.[302-308] Physicochemical characterization of these biocomposites showed that nucleation of CDHA is initiated through the carboxyl group.[302] Hot pressing,[1075] plasma spraying,[1076] laser surface alloying,[1077-1079] spark plasma sintering[1080] and precipitation[1081] techniques might be applied as well. Due to carbon oxidation at elevated temperature, sintering of calcium orthophosphate/carbon nanotube biocomposites must be performed in a deoxidizing atmosphere.[1082] 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.[307,525] For this reason, the mechanical property data for such biocomposites have been reported only in a few papers; however, these results are encouraging. For example, Chen et al. performed nano-indentation tests on biocomposite coatings to give hardness and Young's modulus values.[1079] They found that the higher the loading of the nanotubes, the better the mechanical properties. Namely, at 20 wt% loading, hardness was increased by ~43% and Young's modulus by ~21% over a single-phase HA coating.[1079] Scratching test results indicated that alloyed HA biocomposite coatings exhibited improved wear resistance and a lower friction coefficient when the amount of carbon nanotubes in the precursor material powders was increased.[1078] 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.[1077] Another research group performed compression tests on bulk HA/carbon nanotubes biocomposites and found an increase in strength over single-phase HA.[307] 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.[217] More complex formulations, such as poly-l-lysine/HA/carbon nanotube hybrid biocomposites, have also been developed.[1083] Furthermore, calcium orthophosphate/carbon nanotube biocomposites might be immobilized by hemoglobin.[1084] Unfortunately, carbon nanotubes are very stable substances; they are neither bioresorbable nor biodegradable. Therefore, during in vivo bioresorption, the nanotubes will get into the human body from the biocomposite matrix and might cause uncertain health problems. Certainly, this problem must be solved. To conclude the carbon subject, one should mention the application of carbon fibers of microscopic dimensions,[1085-1087] nanodimensional diamonds[1088] and C_{60}[847] to reinforce HA bioceramics.

As clearly seen from the amount of references, apatite/zirconia biocomposites are the most popular among researchers. The main disadvantage of HA reinforced by PSZ is degradation of zirconia in wet environments.[923,932,933,955] Transformation of the tetragonal ZrO_2 to the monoclinic phase on the surface results in the formation of microcracks and, consequently, lowers the strength of the implant.[1089,1090] Interestingly, though, Fe_3O_4/HA composites possess photocatalytic properties.[1003,1004]

Various biocomposites of calcium orthophosphates with metals and alloys have been fabricated as well.[540,928,967,997,1028-1045] For example, an HA-based biocomposite reinforced with 20 vol.% of Ti particles was fabricated by hot pressing.[1030] Calcium orthophosphate/Ti biocomposites might be prepared by powder metallurgy processing.[1032-1034] At high temperatures, the presence of Ti metal phase was found to promote dehydration and decomposition of HA into β-TCP and TTCP[1030,1032] or partial formation of β-TCP and calcium titanate instead of HA.[661,1033,1034] Compared 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 makes them more suitable for biomedical applications. However, the mechanical properties appear not to be 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.[1030] Similar findings had earlier been made for HA bioceramics reinforced by the addition of silver particulates (5–30 vol. %) and subsequent sintering of the HA/Ag powder compacts.[1028,1029] The addition of silver also imparts an antimicrobial activity.[1042] Other studies on calcium orthophosphate/Ti biocomposites are available elsewhere in reference 1035–1038.

To conclude this section, biocomposites consisting only of calcium orthophosphates should be briefly described. First, all multiphasic and polyphasic calcium orthophosphates should be mentioned. For example, circa 1980, BCP was described as "TCP ceramics complexed with HA,"[1091] Even nowadays BCP is occasionally called a "nanocomposite,"[1092] Furthermore, fluoridated HA [described by a chemical formula $Ca_{10}(PO_4)_6(OH)_{2-x}F_x$, where $0 < x < 2$] might be mentioned as a composite;[1093] however, the applicability of the term "composite" for such systems is doubtful. One should better consider 70% HA-powder + 30% HA-whisker biocomposites, which were 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.[1094,1095] 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 also 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.[1096] A biodegradable biocomposite porous scaffold comprised of a β-TCP matrix and nano-sized fibers of HA was developed and studied for load-bearing bone tissue engineering. The nano-sized fibers of HA 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.[1097] Finally, it is interesting to mention a successful reinforcement of carbonateapatite porous blocks by newly prepared carbonateapatite crystals (i.e., by the same compound; thus, a biocomposite of two different carbonateapatites was obtained).[1098] First, a calcium salt was introduced to micropores of carbonateapatite blocks. Then, the calcium salt was carbonated to form calcite inside the micropores of the carbonateapatite blocks by exposing the blocks to carbon dioxide. For the third step, the blocks were immersed in a Na_2HPO_4

aqueous solution. In this process, calcite inside the micropores of the carbonateapatite blocks was transformed to carbonateapatite and the newly formed crystals of carbonateapatite entangled on those of the existing carbonateapatite blocks. Due to bonding between the newly formed carbonateapatite crystals and the existing ones in the carbonateapatite blocks, the mechanical strength of the blocks became ~1.5 times higher compared with that before the treatment.[1098]

Functionally graded formulations. Although, in most cases, the homogeneous distribution of filler(s) inside a matrix is required,[426] 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 structured 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, which results in two different properties at the two ends of the structure. Such composites can be designed for specific functions and applications. Various approaches based on 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 (cortical bone) to a soft and foamed structure (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 pores are filled with osseous medulla.[25,26] 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 an important area of research. For example, many studies have been performed to fabricate porosity-graded calcium orthophosphate bioceramics in attempts to mimic the porous structure of bones.[1099-1102] This is a structural approach to fabricating FGM. Besides that, there is a compositional approach. 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.[1103-1105] 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 bioactive and osteoconductive properties to the material.[1103] 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 **Figure 6**.[1104] Such biocomposites might be both symmetrical[1106] and asymmetrical.[1107] Furthermore, functionally graded HA/Ti biocomposite coatings might be prepared by RF plasma spraying.[1108] More to the point, a Ti alloy substrate has been combined with HA granules that could be spread over the surface.[1109]

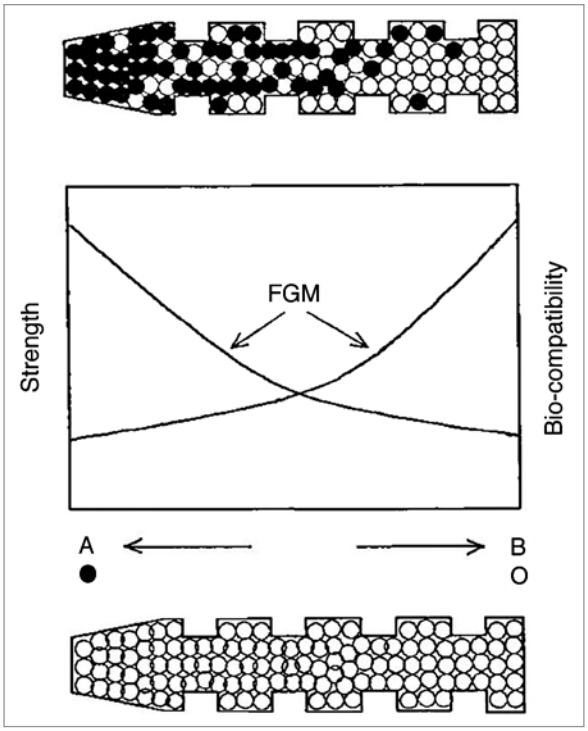

Figure 6. Expected properties of functionally graded biocomposite dental implant. For comparison, the upper drawing shows a functionally graded implant and the lower one shows a conventional uniform implant. The properties are shown in the middle. The implant with the composition changed from a biocompatible 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 reference 1104 with permission.

A series of functionally graded HA coatings incorporated with various percentages of silver were deposited on titanium substrates using ion beam-assisted deposition. The analysis of the coating's cross-section revealed a decreased crystallinity as well as a distribution of nano-sized (10–50 nm) silver particles from the coating/substrate interface to top surface.[1110] 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 biomedical applications along with the relaxation of brittleness and fragility.[543] A compositionally graded collagen/nanodimensional HA biocomposite scaffold might be prepared by an in situ diffusion method.[1111] Chemical and microstructural analysis revealed a gradient of the Ca-to-P ratio across the width of the scaffold template, resulting in the formation of a Ca-rich side and a Ca-depleted side of the scaffold. The Ca-rich side featured low porosity and agglomerates of the nanodimensional HA crystallites, while the Ca-depleted side featured higher porosity and nanodimensional HA crystallites integrated with collagen

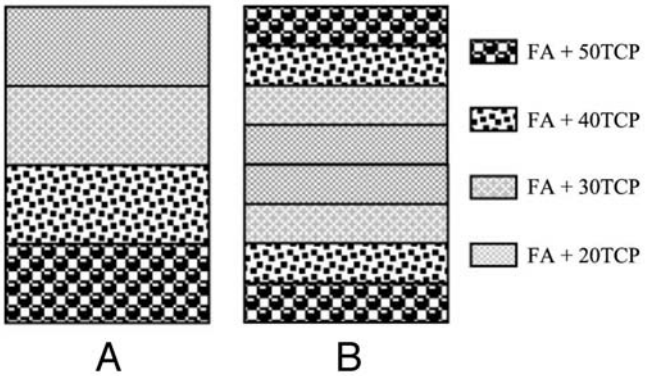

Figure 7. A schematic diagram showing the arrangement of the FA/β-TCP biocomposite layers. (A) A non-symmetric functionally gradient material (FGM); (B) symmetric FGM. Reprinted from reference 1116 with permission.

fibrils to form a porous network structure.[1111] A three-layered, graded biocomposite membrane with one face of 8% nanodimensional carbonateapatite/collagen/PLGA porous membrane, the opposite face of pure PLGA non-porous membrane and the middle layer of 4% nanodimensional carbonateapatite/collagen/PLGA as the transition was prepared using the layer-by-layer casting method.[611] Functionally graded non-woven meshes of PCL incorporated by nano-sized particles of β-TCP were prepared using a hybrid twin-screw extrusion/electrospinning process.[1112] A functionally graded HA/silk fibroin biocomposite was prepared by pulse electric current sintering.[1113] 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 meant to achieve a strong bond between the FGM layered coatings and the substrates.[1114,1115]

Functionally graded β-TCP/FA biocomposites combine the biostability of FA with the bioresorbable properties of β-TCP.[1116] An interesting multilayered (each layer 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.** 7). After implantation, the preferential dissolution of the β-TCP phase would result in functionally gradient porosity for bone ingrowth.[1116] Functionally graded fluoridated HA with a gradient of fluoride[1117] and carbonated HA with a gradient of carbonate[1118] were synthesized as well. HA/zirconia graded biocomposites were fabricated to enhance the mechanical properties of HA while retaining its bone bonding property.[963] TiO_2 and HA were found to be a good combination for FGM, providing both a gradient of bioactivity and good mechanical strength.[1119] In addition, graded HA/$CaCO_3$ biocomposite structures for bone ingrowth were also developed.[1120] Functionally graded composite skull implants consisting of polylactides, carbonateapatite and $CaCO_3$ are known as well.[386,387] Thus, the research in this field is quite promising, but currently, the mechanical properties of the available biocomposites do not match the corresponding properties of bones.[179]

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, which transforms the signal resulting from the interaction of the analyte and the biological element into another signal, and the associated electronics, which are primarily responsible for the display of the results in a user-friendly way.[1121]

The surface of biologically relevant calcium orthophosphates (CDHA, HA, α-TCP, β-TCP, DCPD, DCPA) has an excellent capacity for adsorption of functional biomolecules, such as proteins, albumins, DNA as well as some other types of chemicals. Therefore, several calcium orthophosphate-based biocomposites and hybrid biomaterials were found to be applicable for biosensor manufacturing.[354,642,1041,1083,1122-1127] For example, formation of poly-l-lysine/HA/carbon nanotube hybrid nanodimensional particles was described, and a general design strategy for an immunosensing platform was proposed based on adsorption of antibodies onto this biocomposite.[1083] In another paper, a hybrid material formed by assembling nanodimensional particles of gold onto nano-sized HA was employed for the interface design of a piezoelectric immunosensor on which the antibodies were bound. The sensing interface that was developed appeared to possess some advantages, such as activation-free immobilization and high antigen-binding activities of antibodies, over using nano-sized either HA or gold alone.[1041] A novel tyrosinase biosensor based on nano-sized HA/chitosan composites has been developed for the detection of phenolic compounds.[1125] Further details on the subject are available in the aforementioned references.

To date, not many papers have been published on the biosensor application of calcium orthophosphate-based biocomposites and hybrid biomaterials. Presumably, this subject will be further developed in future, and, perhaps sometime, implantable biosensors will be designed to perform the continuous concentration monitoring of the important biological macromolecules in vivo. Possibly, those implantable biocencors will be able to use electric power generated by DCPD/polymer composite-based battery devices.[506,507]

Interaction Among the Phases in Calcium Orthophosphate-Based Formulations

An important aspect that should be addressed in detail is a mutual interaction among calcium orthophosphates and other phases in biocomposites and hybrid biomaterials. In general, an interaction among the phases in any composite can be either mechanical, when it results from radial compression forces exerted by the matrix on the filler particles (for example, 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.[282] According to Wypych,[1128] 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 among the phases is preferred to achieve higher strength in a composite. The magnitude of the interfacial bond among the phases determines how well a weak matrix transmits stress to the strong fibers. However,

while a bond among the matrix and reinforcements 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.[217]

There is still doubt as to the exact bonding mechanism among bone minerals (biological apatite) and bioorganics (collagen), which undoubtedly plays a critical role in determining the mechanical properties of bones. Namely, bone minerals are not bonded directly 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.[36] In bones, the interfacial bonding forces are mainly ionic bonds, hydrogen bonds and hydrophobic interactions, which give the bones their unique composite behavior.[53] There is an opinion that, in contrast to bones, there is no sign of chemical bonding among the phases in conventional calcium orthophosphate/collagen biocomposites, probably due to a lack of suitable interfacial bonding during mixing.[39] However, this is not the case for phosphorylated collagens.[753] Interested readers are directed to a density functional theory study of the interaction of collagen peptides with hydroxyapatite surfaces.[1129]

Anyway, the 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 apatite/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 of bonding energies of C-O bonds and assumed to be caused by an interaction with Ca^{2+} ions located on the surfaces of apatite nano-sized crystals as shown in **Figure 8**.[747] Another proof of a chemical interaction between apatite and collagen was also evaluated in FTIR spectra of CDHA/collagen biocomposites, in which a shift of the band corresponding to -COO^- stretching from 1,340 to 1,337 cm^{-1} was observed.[708,709] More to the point, nucleation of apatite crystals onto collagen through a chemical interaction with carboxylate groups of collagen macromolecules has been reported in references 1130–1132.

FTIR spectroscopy seems to be the major tool for studying a possible chemical bonding among the phases in calcium orthophosphate-based biocomposites and hybrid biomaterials.[276,310,345,353,355,462,513,600,616,629,635,638,641,644,653,664,673,678,709,753,802,803,847,882,1133-1136] For example, the characteristic bands at 2,918, 2,850 and 1,472 cm^{-1} for the hydrocarbon backbone of PE appeared to have zero shift in an HA/PE biocomposite. However, in the case of polyamide, several FTIR bands indicated that the polar groups shifted significantly: the bands at 3,304, 1,273 and 692 cm^{-1} derived from stretching of N-H, stretching of C-N-H and vibrating of N-H moved to 3,306, 1,275 and 690 cm^{-1}, respectively, in the HA/polyamide biocomposites. Furthermore, both stretching (3,568 cm^{-1}) and vibrating (692 cm^{-1}) modes of hydroxide in HA moved to 3,570 and 690 cm^{-1} in the HA/polyamide biocomposites, respectively, indicating the formation of hydrogen bonds. In addition, bands at 1,094 and 1,031 cm^{-1} of PO_4 modes also shifted to 1,093 and 1,033 cm^{-1} in the HA/polyamide biocomposite. That the bands shifted in a fingerprint area indicated that the hydroxide and orthophosphate on the surface of HA might interact with plentiful carboxyl and amino groups of polyamide through nucleophilic addition.[276] Comparable conclusions were made for HA/PVA,[641] CDHA/alginate,[709] ACP/PPF,[513] HA/maleic anhydride[355] and β-TCP/PLLA[462] biocomposites, in which weak chemical bonds were considered to form between Ca^{2+} ions located on the HA, CDHA, ACP or β-TCP surface, respectively, and slightly polarized O atoms of C=O bonds in the surrounding bioorganic compounds. The data obtained suggest that crystallization of calcium orthophosphates in chitosan-containing solutions is substantially modulated by a chemical interaction of the components; apparently, a part of calcium is captured by chitosan and does not participate in the formation of the main mineral phase.[1136] This type of the chemical interaction is shown schematically in **Figure 9**.[709]

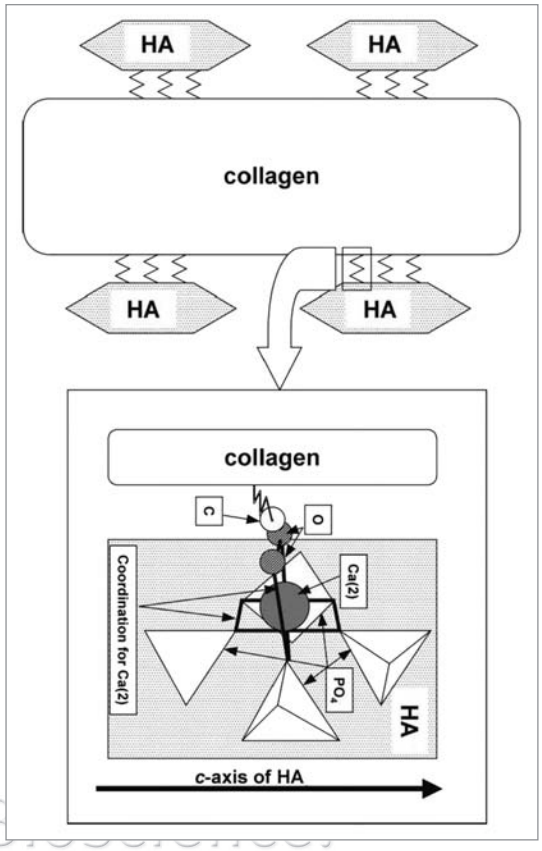

Figure 8. A schematic drawing of the relation between self-organization (directional deposition of HA on collagen) and interfacial interaction in biocomposites. Direction of interaction between HA and collagen is restricted by covalent bonding between COO and Ca(2) to maintain regular coordination number of 7. Reprinted from reference 747 with permission.

Besides FTIR spectroscopy, other measurement techniques are also able to show some evidence of a chemical interaction among the phases in calcium orthophosphate-based biocomposites and hybrid biomaterials.[345,462,635,638,641,1134-1138] For example, for nano-sized crystals of CDHA/alendronate such evidence was obtained by thermogravimetric analysis: DTG plots of the

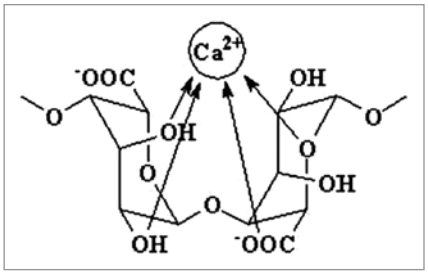

Figure 9. A schematic diagram of Ca^{2+} ion binding with alginate chains. Reprinted from reference 709 with permission.

crystals appeared to be quite different from those obtained from mechanical mixtures of CDHA and calcium alendronate with similar compositions.[1137] Analogous DTG results were obtained for nano-sized HA/PVA biocomposites.[641] In the case of biocomposites of nano-sized HA with polyamide, a hydrogen bonding among the phases was detected by a differential scanning calorimetry technique.[635] Another example comprises application of dynamic mechanical analysis to investigate the softening mechanism of β-TCP/PLLA biocomposites.[462] As to biocomposites of nano-sized HA with PVAP, some indirect evidence of chemical bonding among the phases was found by X-ray diffraction and thermogravimetric analysis.[345] A strong structural correlation between the orientation of FA crystallites and gelatin within the FA/gelatin composite spheres was discovered, indicating a substantial reorganization of the macromolecular matrix within the area of a growing aggregate.[444] Recently, chemical interactions between HA and organic molecules have been elucidated using ab initio calculation methods.[1139]

By means of the X-ray photoelectronic spectroscopy (XPS) technique, binding energies of Ca, P and O atoms were found to vary between nano-sized HA (Ca: 350.5 and 345.5; O: 530.2; P: 132.5 eV) and nano-sized HA/konjac glucomannan/chitosan biocomposite (Ca: 352.1 and 347.4; O: 531.2; P: 133.4 eV).[653] Further measurements by FTIR and X-ray diffraction revealed that nano-sized HA was mainly linked to konjac glucomannan and chitosan by hydrogen bonding among OH^- and PO_4^{3-} ions of HA and -C=O and -NH groups of konjac glucomannan and chitosan copolymer, and there was a stable interface formed among 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.[653] In HA/collagen biocomposites, a covalent bond formation between Ca^{2+} ions of HA and $RCOO^-$ groups of collagen molecules was found by XPS.[601] Similar XPS observations were also made for several other calcium orthophosphate-based biocomposites and hybrid biomaterials.[629,664,673]

The interaction and adhesion between calcium orthophosphate fillers and their respective matrices have significant effects on the properties of particulate-filled, reinforced materials, as these forces are essential to load transfer among the phases and thus to improving the mechanical performance of the biocomposites.[353] However, for a substantial amount of the aforementioned formulations, the interaction among the phases is mechanical in nature. This is because the matrix often consists of compounds with no functional groups or unsaturated bonds that 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.[53]

In order to improve the situation, various supplementary reagents are applied. If the primary effect of a processing additive is to increase the interaction between the phases, such additives can be regarded as coupling agents.[1140] These agents establish chemical bridges between the matrix and the fillers, promoting adhesion among the phases. In many cases, their effect is not unique; they might, for example, also influence rheology of the composites.[282] In the case of calcium orthophosphates, a hexamethylene diisocyanate coupling agent was used to bind PEG/PBT (Polyactive™) block copolymers[293] and other polymers[1133] 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 adhesion.[1133] Other researchers used glutaraldehyde as a cross-linked reagent.[470,474,598,600,601,619,624,699,736,778,781,1141] Alternatively, the interfacial bonding among calcium orthophosphates and other components might be induced by silanes,[242,268,269,293,406,640,1142-1145] zirconates,[282,406,408,1146,1147] titanates,[282,406,1146] phosphoric acid,[643] alkaline pretreatment,[877,880] polyacids[143,144,293] and some other chemicals. Furthermore, some polymers might be grafted onto the surface of calcium orthophosphate particles.[656] Structural modifications of the polymeric matrices, for instance, with introduction of acrylic acid,[245,268,269,293] have also proved to be effective. For example, application of polyacids as a bonding agent for HA/Polyactive™ composites caused the surface modified HA particles to maintain better contact with polymers at the fracture and improved mechanical properties.[143,144,293] The use of titanate and zirconate coupling agents appeared to be very dependent on the molding technique employed.[282] Silane-coupled HA powders were tested before applying them as fillers in biodegradable composites.[1143-1145] This treatment allowed HA to withstand the attack of water without impairing overall bioactivity. Besides that, a chemically modified reinforcement phase-matrix interface was found to improve the mechanical properties of the biocomposites. The examples include chemically coupled HA/PE,[268,269] chemically formed HA/Ca poly(vinylphosphonate)[349] and PLA/HA fibers.[233] These biocomposites are able to consume a large amount of energy at the fracture.

The action of some coupling agents was found to combine two distinct mechanisms: (1) cross-linking of the polymeric matrix (valid for zirconate and titanate coupling agents) and (2) improvement of the interfacial interactions among the major phases of the biocomposites. This interfacial adhesion improvement appeared to be much dependent on the chemical nature (pH and type of metallic center) of the coupling agents.[406] Several works claimed that silanes do interact with HA.[242,268,269,1143-1145] It was shown that a silicon-containing interphase existed between

HA and PE that promoted 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.[268,269]

Thus, the optimization of biocomposite properties by coupling agents is currently an important area of the research. The control and development of molecular-level associations of polymers with calcium orthophosphates is suggested to be significant for the resulting mechanical responses in biocomposites. It appears that a fundamental molecular understanding of the interfacial behavior in biocomposites 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 beyond mechanical property characterization. In addition, atomic scale models for simulating phase interaction and predicting responses in the novel material systems, where nanostructures and nano-interfaces are included, are important to understand and predict load deformation behavior.[179]

In addition to the aforementioned, the surface of calcium orthophosphates might be modified as well.[144,509,510,656,1147-1154] An interesting approach for HA surface modification was described by Lee et al.[1154] First, in situ synthesis of surface thiol-functionalized HA (HA-SH) was realized by adding 3-mercaptopropionic acid during hydrothermal synthesis of HA (**Fig. 10A**). This was followed by grafting polymerization of ethylene glycol methacrylate phosphate by radical chain transfer, generating the sulfur-centered radicals on the HA surfaces (**Fig. 10B**), which initiated the surface grafting polymerization of ethylene glycol methacrylate phosphate (**Fig. 10C**).[1154] Other examples might be found in the literature.[144,509,510,656,1147-1153] In general, the purpose of surface modifying is not only to guarantee the even distribution of calcium orthophosphate particles at a high loading level in the matrix, but also to prevent or delay the debonding process of calcium orthophosphate particles from the matrix. Obviously, all surface modifiers must satisfy several biomedical requirements, such as no toxicity, good biocompatibility and no changes in the biological or physicochemical properties of the fillers.

Addition of adhesion-promoting agents might be an alternative to improve the interaction between the fillers and the matrix. For example, Morita et al. incorporated 4-methacryloyloxyethyl trimellitate anhydride to promote adhesion of the polymer to HA.[1155] In another study, phosphoric ester was added to the liquid component of the formulation.[1156] Both the strength and the affinity index of biocomposites were found to increase, probably due to the effects of co-polymerization.

Possible interactions between BCP and HPMC have been investigated in IBS composites.[900,901,1157] 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 the HA crystal surface were found during the interaction. Both phenomena were responsible for the observed granulometric changes;[900,901] however, within the sensitivity of the employed measurement techniques, no chemical bonding between BCP and HPMC was detected.[1157]

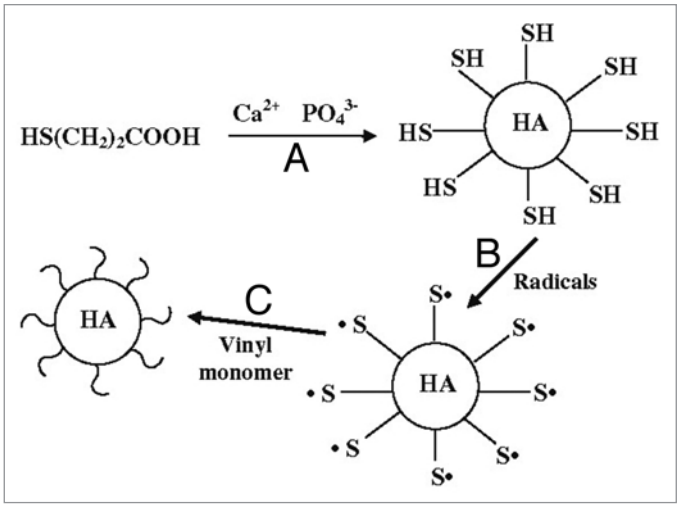

Figure 10. Surface modification of HA particles by grafting polymerization according to Lee et al.[1154] (A) surface thiol functionalized HA, (B) sulfur-centered radical on HA surface, (C) surface grafting polymerization of ethylene glycol methacrylate phosphate. Reprinted from reference 99 with permission.

A coprecipitation technique was used to prepare CDHA/chitosan biocomposites.[811] Growth of CDHA crystals was inhibited by organic acids with more than two carboxyl groups, which strongly bind to CDHA surfaces via COO-Ca bonds. 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 nano-sized crystals of CDHA were found to align along the chitosan molecules, with the amino groups working as the nucleation sites.[811] Formation of calcium cross-linked polymer carboxylate salts was suggested during setting of calcium orthophosphate cement (TTCP + DCPA)/polyphosphazane biocomposites; a chemical involvement of the polymer in the cement setting was determined based on the results of pH monitoring.[558-560]

A chemical bond between the phases was presumed in PCL/HA composites prepared by the grafting technique;[420] unfortunately, no strong experimental evidences were provided. In another study, CDHA/poly(α-hydroxyester) composites were prepared by a low temperature chemical route.[393] In that study, pre-composite structures were prepared by combining α-TCP with PLA, PLGA and copolymers thereof. The final biocomposite 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 determined by FTIR spectroscopy.[393]

In nearly every study on HA/carbon nanotubes biocomposites, the nanotubes were functionalized before combining them with HA. Most researchers did this by oxidation,[303-307] although noncovalent functionalizing with sodium dodecylsulfate[307] and coating the nanotubes by a polymer[1158] before combining

them with HA were also reported. Several studies by transmission electron microscopy revealed evidence that the functionalization enhanced interaction between carbon nanotubes and HA.[306,307,1159]

For calcium orthophosphate-based biocomposites able to sustain high-temperature sintering (valid for the formulations consisting of inorganic components only), an interdiffusion of chemical elements might take place among the phases. Such an effect was 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.[997] A similar high-temperature interaction between HA and zirconia[911,940] as well as between HA and Ti[661,1030,1032-1034] was also detected. Namely, lower Ti content composites sintered at 1,200°C showed main crystalline phases as $CaTiO_3$, CaO and Ti_xP_y, while an increase in Ti content to 50 vol.% revealed Ti_2O and residual α-Ti as additional phases. Thus, the chemical reactions between HA and Ti were expressed by the following unbalanced illustrative equation:[1032]

(1) $$Ti + Ca_{10}(PO_4)_6(OH)_2 \rightarrow CaTiO_3 + CaO + Ti_xP_y + (Ti_2O) + (Ca_4P_2O_9) + H_2O$$

Besides, partial decomposition of HA and formation of different calcium aluminates were detected in HA/Al_2O_3 biocomposites after sintering at 1,200–1,300°C. This has been attributed to the diffusion of Ca^{2+} from HA into the alumina matrix, and the depletion of Ca^{2+} from HA leads to the decomposition of HA into β-TCP.[968,974-976] Presumably, all these processes influence the mechanical strength of the biocomposites.

Bioactivity and Biodegradation of Calcium Orthophosphate-Based Formulations

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 long enough to assure its biofunctionality and the non-toxicity of the degradation by-products.[178] 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.[30,31,1160]

In general, both bioactivity and biodegradability of any biocomposite and/or hybrid biomaterial are determined by the same properties of the constituents. Both processes are very multifactorial, because during implantation, the surface of any graft comes into contact with biological fluids and, shortly afterwards, is colonized by cells. Much more biology than chemistry and material science together is involved in these very complex processes, and many specific details still remain unknown. 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[111-117]), which, in the case of CDHA, might be described as a sequence of four successive chemical equations (2–5):[519,1161,1162]

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

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

(4) $$Ca_3(PO_4)_2 + 2H^+ = Ca^{2+} + 2CaHPO_4$$

(5) $$CaHPO_4 + H^+ = Ca^{2+} + H_2PO_4^-$$

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 and (7) properties of the scaffold, such as porosity and pore diameter.[328] A summary on degradation of PLA and PGA as well as that of SEVA-C is available in the literature (reviewed in ref. 178, p. 798 and p. 803, respectively), where the interested readers are referred. Biodegradation of HA/PLLA and CDHA/PLLA biocomposite rods in subcutis and medullary cavities of rabbits were investigated mechanically and histologically; the degradation was found to be faster when using uncalcinated CDHA instead of calcinated HA.[1163] In a more detailed study, new bone formation was detected at 2 weeks after implantation, especially for formulations with a high HA content.[1164] More to the point, direct contact between bones and these composites without intervening fibrous tissue was detected in this case.[1164,1165] Both SEVA-C and SEVA-C/HA biocomposites were found to exhibit non-cytotoxic behavior,[1166,1167] inducing a satisfactory tissue response when implanted as shown by in vivo studies.[1167] Furthermore, SEVA-C/HA biocomposites induce a positive response in osteoblast-like cells for what concerns cell adhesion and proliferation.[1166] An in vivo study on biodegradation of microspheres [PLGA, gelatin and poly(trimethylene carbonate) were used]/calcium orthophosphate cement biocomposites revealed that they exhibited microsphere degradation after 12 weeks of subcutaneous implantation, which was accompanied by a decrease in compression strength.[1168] Interestingly, though, the amount of calcium orthophosphates in biocomposites was found to have a greater effect on the early stages of osteoblast behavior (cell attachment and proliferation) rather than the immediate and late stages (proliferation and differentiation).[1169]

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-sized HA/collagen/PLA biocomposites.[610] The results demonstrated that weight loss increased continuously in vitro, with a reduction in mass of ~20% after 4 weeks. During the experimental period in vitro, a relative rate of reduction of the three components in this material was shown to differ greatly: collagen decreased the

fastest, from 40% weight to ~20% in the composite; HA content increased from 45 to ~60%; 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.[610] Hasegawa et al.[1170] performed an in vivo study, spanning a period of 5–7 y, on high-strength HA/PLLA biocomposite rods for the internal fixation of bone fractures. In that work, both uncalcined CDHA and calcined HA were used as reinforcing phases in a PLLA matrix. Those composites were implanted in the femur of 25 rabbits. It was found that the implanted materials were resorbed after 6 y of implantation. The presence of remodeled bone and trabecular bone bonding was the significant outcome. These data clearly demonstrate the 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 or 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.[36,1171] 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 have industrial production and commercial distribution of medical devices partially or entirely made of biocomposites been 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:[265]

• 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 and may require special cleaning and sterilization processes as well as highly skilled personnel.

• 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 with 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.[265]

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 grafting materials depends on the progress of 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 biocomposites mimicing natural bones, from the nanometer to the micrometer dimensions, there are many key issues, including 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:[36,41]

• Optimization of 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.[36,41]

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 biocomposite structure. Their mechanical properties are outstanding (considering the 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. For example, 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.[1172]

Obviously, no single-phase biomaterial is able to provide all the essential features of bones and/or other calcified tissues, and therefore, there is a great need to engineer multi-phase biomaterials (biocomposites) with a structure and composition mimicking those of natural bones. 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.[102] However, the reviewed literature clearly indicates that, among possible types of calcium orthophosphate-based biocomposites and hybrid biomaterials, only simple, complex and graded ones, as well as fibrous, laminar and particulate ones (see classification types of the composites in the "General Information on Composites and Biocomposites" section) have been investigated. Presumably, future progress in this subject will require concentrating efforts on elaboration and development of both hierarchical and hybrid biocomposites. Furthermore, following the modern tendency of tissue engineering, a novel generation of calcium orthophosphate-based biocomposites and hybrid biomaterials should also contain a living biological part.

To conclude, the future of the calcium orthophosphate-based biocomposites and hybrid biomaterials is now directly dependent on the formation of multidisciplinary teams composed of experts but, primarily, experts ready to work in close collaboration with others and thus be able to deal efficiently with the complexity of the human organism. The physical chemistries of solids, solid surfaces, polymer dispersion and solutions as well as material-cell interactions are among the phenomena to be tackled. Furthermore, much work remains to be done on the long way from laboratory to clinic, and success depends on the effective cooperation of clinicians, chemists, biologists, bioengineers and materials scientists.

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