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Nanodimensional and Nanocrystalline Calcium Orthophosphates

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Abstract Nano-sized particles and crystals play an important role in the formation of calcified tissues of various animals. For example, nano-sized and nanocrystalline calcium orthophosphates in the form of apatites of biological origin represent the basic inorganic building blocks of bones and teeth of mammals. Namely, according the recent developments in biomineralization, tens to hundreds nanodimensional crystals of a biological apatite are self-assembled into these complex structures. This process occurs under a strict control by bioorganic matrixes. Furthermore, both a greater viability and a better proliferation of various types of cells have been detected on smaller crystals of calcium orthophosphates. Thus, the nano-sized and nanocrystalline forms of calcium orthophosphates have a great potential to revolutionize the hard tissue-engineering field, starting from bone repair and augmentation to controlled drug delivery systems. This review reports on current state of the art and recent developments on the subject, starting from synthesis and characterization to biomedical and clinical applications. Furthermore, the review also discusses possible directions for future research and development.

Keywords Calcium Orthophosphates, Hydroxyapatite, Nanodimensional, Nano-Sized, Nanocrystalline, Biomedical Applications, Bone Grafts, Tissue Engineering

1. Introduction

Living organisms can create the amazing ways to produce various high-performance materials and over 60 different inorganic minerals of biological origin have already been revealed[1]. Among them, calcium orthophosphates are of a special importance since they are the most important inorganic constituents of hard tissues in vertebrates[2, 3]. In the form of a poor crystalline, non-stoichiometric, ion-substituted CDHA (commonly referred to as “biological apatite”), calcium orthophosphates are present in bones, teeth, deer antlers and tendons of mammals to give these organs stability, hardness and function[2, 4, 5]. Through we still do not exactly know why the highly intelligent animals use conformable calcium orthophosphates as their crucial biomineral for survival[6], current biomedical questions of persistent pathological and physiological mineralization in the body force people to focus on the processes, including the occurrence, formation and degradation of calcium orthophosphates in living organisms[7, 8, 9].

Biological mineralization (or biomineralization) is a process of in vivo formation of inorganic minerals[1, 2]. In the biomineralization processes, organized assemblies oforganic macromolecules regulate nucleation, growth, morphology and assembly of inorganic crystals. Biologically formed calcium orthophosphates (biological apatite) are always nanodimensional and nanocrystalline, which have been formed in vivo under mild conditions. According to many reports, dimensions of biological apatite in the calcified tissues always possess a range of a few to hundreds of nanometers with the smallest building blocks on the nanometer size scale[2, 4, 5, 10, 11]. For example, tens to hundreds of nanometer-sized apatite crystals in a collagen matrix are combined into self-assembled structures during bone and teeth formation[2, 4, 5]. Recent advances suggest that this is a natural selection, since the nanostructured materials provide a better capability for the specific interactions with proteins[12].

Due to the aforementioned, nanodimensional and nanocrystalline forms of calcium orthophosphates are able to mimic both the composition and dimensions of constituent components of the calcified tissues. Thus, they can be utilized in biomineralization and as biomaterials due to the excellent biocompatibility[13, 14]. Further development of calcium orthophosphate-based biomaterials obviously will stand to benefit mostly from nanotechnology[15], which offers unique approaches to overcome shortcomings of many conventional materials. For example, nano-sized ceramics can exhibit significant ductility before failure contributed by the grain-boundary phase. Namely, already in 1987, Karch *et al.*, reported that, with nanodimensional grains, a brittle ceramic could permit a large plastic strain

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up to 100%[16]. In addition, nanostructured ceramics can be sintered at lower temperatures; thereby major problems associated with a high temperature sintering are also decreased. Thus, nanodimensional and nanocrystalline forms of bioceramics clearly represent a promising class of orthopedic and dental implant formulations with improved biological and biomechanical properties[17].

Many other advances have been made in biomaterial field due to a rapid growth of nanotechnology[18]. For example, a recent theory of "aggregation-based crystal growth"[19] and a new concept of "mesocrystals"[20, 21] highlighted the roles of nano-sized particles in biological crystal engineering. In this aspect, the study of calcium orthophosphates is a specific area in nanotechnology, because they might be applied readily to repair hard skeletal tissues of mammals[22-24].

Herein, an overview of nanodimensional and nanocrystalline apatites and other calcium orthophosphates in studies on biomineralization and biomaterials is given. The available calcium orthophosphates are listed in Table 1. To narrow the subject of this review, with a few important exceptions, undoped and un-substituted calcium orthophosphates are considered and discussed only. The readers interested in various nanodimensional and nanocrystalline ion-substituted calcium orthophosphates[25-63] are referred to the original publications. Furthermore, details on calcium orthophosphate-based nanodimensional biocomposites[64-85] or nanodimensional calcium orthophosphate-based biocomposites[86-104] are available in Refs.[105, 106].

This review is organized into several sections. After a brief introduction (current section), general information on "nano" is provided in the second section. The third section briefly compares the micron-sized and nanodimensional calcium orthophosphates. The forth section briefly discusses the presence of nano-sized and nanocrystalline calcium orthophosphates in normal calcified tissues of mammals. The structure of nano-sized and nanocrystalline apatites is described in the fifth section. Synthesis of nanodimensional and nanocrystalline calcium orthophosphates of various dimensions and shapes is reviewed in the sixth section, while the biomedical applications are examined in the seventh section. Finally, the summary and reasonable future perspectives in this active research area are given in the last section.

Table 1. Existing calcium orthophosphates and their major properties[204, 205].

Ca/P molar ratio	Compound	Formula	Solubility at 25 ºC, -log(K_s)	Solubility at 25 ºC, g/L	pH stability range in aqueous solutions at 25°C
0.5	Monocalcium phosphate monohydrate (MCPM)	$Ca(H_2PO_4)_2·H_2O$	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	$CaHPO_4·2H_2O$	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)	$Ca_8(HPO_4)_2(PO_4)_4·5H_2O$	96.6	~ 0.0081	5.5 – 7.0
1.5	α-Tricalcium phosphate (α-TCP)	$α\text{-}Ca_3(PO_4)_2$	25.5	~ 0.0025	[a]
1.5	β-Tricalcium phosphate (β-TCP)	$β\text{-}Ca_3(PO_4)_2$	28.9	~ 0.0005	[a]
1.2 – 2.2	Amorphous calcium phosphates (ACP)	$Ca_x(PO_4)_z·nH_2O$, 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)[269]. The comparative extent of dissolution in acidic buffer is: ACP >> α-TCP >> β-TCP > CDHA >> HA > FA[126].
[c] Stable at temperatures above 100°C.
[d] Always metastable.
[e] Occasionally, it is called "precipitated HA (PHA)".
[f] Existence of OA remains questionable.

2. General Information on "Nano"

The prefix "nano" specifically means a measure of 10^{-9} units. Although it is widely accepted that the prefix "nano" specifically refers to 10^{-9} units, in the context of nano-sized and nanocrystalline materials, the units should only be those of dimensions, rather than of any other unit of the scientific measurements. Besides, for practical purposes, it appears to be unrealistic to consider the prefix "nano" to solely and precisely refer to 10^{-9} m, just as it is not considered that "micro" specifically and solely concerns something with a dimension of precisely 10^{-6} m[107]. Currently, there is a general agreement that the subject of nanoscience and nanotechnology started after the famous talk: "There's plenty of room at the bottom" given by the Nobel Prize winner in physics Prof. Richard P. Feynman on December 26, 1959 at the annual meeting of the American Physical Society held at California Institute of Technology. This well-known talk has been widely published in various media (*e.g.*,[108]).

In a recent extensive discussion about a framework for definitions presented to the European Commission, the nano-scale has been defined as being of the order of 100 nm or less. Similarly, a nanomaterial has been defined as "any form of a material that is composed of discrete functional parts, many of which have one or more dimensions of the order of 100 nm or less"[109]. Other definitions logically follow this approach such as: a nanocrystalline material is "a material that is comprised of many crystals, the majority of which have one or more dimensions of the order of 100 nm or less" (normally, with presence of neither the micron-sized crystals nor an intergranular amorphous phase) and a nanocomposite is a "multi-phase material in which the majority of the dispersed phase components have one or more dimensions of the order of 100 nm or less"[107]. Similarly, nanostructured materials are defined as the materials containing structural elements (*e.g.*, clusters, crystallites or molecules) with dimensions in the 1 to 100 nm range[110], nanocoatings represent individual layers or multilayer surface coatings of 1 – 100 nm thick, nanopowders are extremely fine powders with an average particle size in the range of 1 – 100 nm and nanofibers are the fibers with a diameter within 1 – 100 nm[111, 112]. It also has been proposed to extend the lower size limit to 0.1 nm[113], which would include all existing organic molecules, allowing chemists to rightly claim they have been working on nanotechnology for very many years[114].

Strictly speaking, there are serious doubts that the term "nanomaterial" has a reasonable meaning. For example, let me cite Prof. David F. Williams, the Editor-in-Chief of *Biomaterials*: "… some words which have no rational basis whatsoever become part of everyday language so rapidly, even if so illogically, that it is impossible to reverse the process and their common use has to be accepted, or perhaps, accommodated. Nanomaterial is one such word, where I have argued that it should not exist, but accept that it does through common usage and have to recognise its existence[107]. The discussion about nanomaterial provides a hint of the analysis of a biomaterial that follows, since a prefix, which is an indicator of scale, cannot specify the integer that follows (in this case a material) unless that integer can be qualified by that scale. In other words, it is very clear what a nanometre is because nano – means 10^{-9} and a metre is a measure of length. In the case of nanomaterial, what is it about the material that is 10^{-9}. Is it the dimension of a crystal within the material, or of a grain boundary, a domain, or a molecule, or is it a parameter of a surface feature of the sample, or perhaps of the resistivity or thermal conductivity of the material. Clearly this is nonsense, but one has to accept that nanomaterials are here to stay, with even some journal titles containing the word."[115, p. 5898, left column]. Following this logic, such terms as "nanocomposite", "nanocoatings", "nanopowders", "nanofibers" and "nanocrystals" are senseless either and should be replaced, for example, by "composites with nano-sized (or nanodimensional) dispersed phase(s)", "coatings of nano-sized (or nanodimensional) thickness", "nano-sized (or nanodimensional) powders", "fibers of nano-sized (or nanodimensional) thickness" and "nano-sized (or nanodimensional) crystals", respectively. At least, this has been done in this review.

According to their geometry, all nanodimensional materials can be divided into three major categories: equiaxed, one dimensional (or fibrous) and two dimensional (or lamellar) forms. Selected examples and typical applications of each category of nanodimensional materials and their use in biomedical applications are available in literature[116]. It is important to note, that in literature on calcium orthophosphates there are cases, when the prefix "nano" has been applied for the structures, with the minimum dimensions exceeding 100 nm[44, 83, 117-133].

As a rule, nanodimensional materials can be manufactured from nearly any substance. Of crucial importance, there are two major characteristics conferring the special properties of any nanodimensional material. These are the quantum effects associated with the very small dimensions (currently, this is not applicable to the biomaterials field) and a large surface-to-volume ratio that is encountered at these dimensions. For instance, specific surface areas for submicron-sized particles are typically 60 – 80 m^2/g, while decreasing particle diameter to tens of nanometers increases the specific surface area up to 5 times more – an amazing amount of surface area per mass! Furthermore, all nanophase materials have the unique surface properties, such as an increased number of grain boundaries and defects on the surface, huge surface area and altered electronic structure, if compared to the micron-sized materials[107, 134]. While less than ~ 1 % of a micron-sized particle's atoms occupy the surface positions, over a tenth of the atoms in a 10-nm diameter particle reside on its surface and ~ 60 % in a 2-nm particle[135]. This very high surface-to-volume ratio of nanodimensional materials provides a tremendous driving

force for diffusion, especially at elevated temperatures, as well as causes a self-aggregation into larger particles. Besides, solubility of many substances increases with particle size decreasing[136, 137]. What's more, nanophase materials could have surface features (*e.g.*, a higher amount of nano-scale pores) to influence the type and amount of adsorption of selective proteins that could enhance specific osteoblast adhesion[138]. Finally and yet importantly, the nanodimensional and nanocrystalline materials have different mechanical, electrical, magnetic and optical properties if compared to the larger grained materials of the same chemical composition[139-142].

The nanostructured materials can take the form of powders, dispersions, coatings or bulk materials. In general, nanostructured materials contain a large volume fraction (greater than 50 %) of defects such as grain boundaries, interphase boundaries and dislocations, which strongly influences their chemical and physical properties. The great advantages of nanostructuring were first understood in electronic industry with the advent of thin film deposition processes. Other application areas have followed. For example, nanostructured bioceramics was found to improve friction and wear problems associated with joint replacement components because it was tougher and stronger than coarser-grained bioceramics[143]. Furthermore, nanostructuring has allowed chemical homogeneity and structural uniformity to an extent, which was once thought to impossible to achieve[110]. In calcium orthophosphate bioceramics, the major target of nanostructuring is to mimic the architecture of bones and teeth[144, 145].

3. Micron- and Submicron-Sized Calcium Orthophosphates versus The Nanodimensional Ones

The micron-sized calcium orthophosphate-based bioceramic powders suffer from poor sinterability, mainly due to a low surface area (typically 2 – 5 m2/g), while the specific surface area of nanodimensional calcium orthophosphates exceeds 100 m2/g[146]. In addition, the resorption process of synthetic micron-sized calcium orthophosphates was found to be quite different from that of bone mineral[147].

Although the nanodimensional and nanocrystalline features of natural calcium orthophosphates of bones and teeth had been known earlier[2, 148-153], the history of the systematic investigations of this field has started only in 1994. Namely, a careful search in scientific databases using various combinations of keywords "nano" + "calcium phosphate", "nano" + "apatite", "nano" + "hydroxyapatite", etc. in the article title revealed 5 papers published in 1994[154-158]. No papers published before 1994 with the aforementioned keywords in the title have been found.

Nanodimensional (size ~ 67 nm) HA was found to have a higher surface roughness of 17 nm if compared to 10 nm for the submicron-sized (~ 180 nm) HA, while the contact angles (a quantitative measure of the wetting of a solid by a liquid) were significantly lower for nano-sized HA (6.1) if compared to the submicron-sized HA (11.51). Additionally, the diameter of individual pores in nanodimensional HA compacts is several times smaller (pore diameter ~ 6.6 Å) than that in the submicron grain-sized HA compacts (pore diameter within 19.8 – 31.0 Å)[159]. A surface roughness is known to enhance the osteoblast functions while a porous structure improves the osteoinduction compared with smooth surfaces and nonporpous structure, respectively[138]. Furthermore, nanophase HA appeared to have ~ 11% more proteins of fetal bovine serum adsorbed per 1 cm2 than submicron-sized HA[160]. Interfacial interactions between calcined HA nano-sized crystals and various substrates were studied and a bonding strength appeared to be influenced not only by the nature of functional groups on the substrate but also by matching of surface roughness between the nano-sized crystals and the substrate[161]. More to the point, incorporating of nanodimensional particles of HA into polyacrylonitrile fibers were found to result in their crystallinity degree rising by about 5%[162]. In a comparative study on the influence of incorporated micron-sized and nano-sized HA particles into poly-L-lactide matrixes, addition of nano-sized HA was found to influence both thermal and dynamic mechanical properties in greater extents[163].

In general, nanostructured biomaterials[164] offer much improved performances than their larger particle sized counterparts due to their huge surface-to-volume ratio and unusual chemical synergistic effects. Such nanostructured systems constitute a bridge between single molecules and bulk material systems[165]. For instance, powders of nanocrystalline apatites[166-172] and β-TCP[173] were found to exhibit an improved sinterability and enhanced densification due to a greater surface area. This is explained by the fact that the distances of material transport during the sintering becomes shorter for ultrafine powders with a high specific surface area, resulting in a densification at a low temperature. Therefore, due to low grain growth rates, a low-temperature sintering appears to be effective to produce fine-grained apatite bioceramics[174]. Furthermore, the mechanical properties (namely, hardness and toughness) of HA bioceramics appeared to increase as the grain size decreased from sub-micrometers to nanometers[175].

More to the point, nano-sized HA is also expected to have a better bioactivity than coarser crystals[176-178]. Namely, Kim et al., found that osteoblasts (bone-forming cells) attached to the nano-sized HA/gelatin biocomposites to a significantly higher degree than to micrometer size analog did[179]. An increased osteoblast and decreased fibroblast (fibrous tissue-forming cells) adhesion on nanophase ceramics[180-184], as well as on nanocrystalline HA coatings on titanium, if compared to traditionally used plasma-sprayed HA coatings, was also discovered by other researchers[185-187]. Scientists also observed enhanced osteoclast (bone-resorbing cells) functions to show healthy remodeling of bone at the simulated implant surface[177]. Besides, the proliferation and osteogenic differentiation of periodontal ligament cells were found to be promoted when

a nanophase HA was used, if compared to dense HA bioceramics[188]. Thus, the underlying material property, responsible for this enhanced osteoblast function, is the surface roughness of the nanostructured surface[18]. Interestingly, but an increased osteoblast adhesion was discovered on nano-sized calcium orthophosphate powders with higher Ca/P ratios[189], which points out to some advantages of apatites over other calcium orthophosphates. Furthermore, a histological analysis revealed a superior biocompatibility and osteointegration of bone graft substitutes when nano-sized HA was employed in biocomposites[190-192]. However, data are available that nano-sized HA could inhibit growth of osteoblasts in a dose-dependent manner[193]. Furthermore, a cellular activity appeared to be affected by the shape and dimensions of nano-sized HA. Namely, the cellular activity of L929 mouse fibroblasts on nano-sized fibers with a diameter within 50 – 100 nm was significantly enhanced relative to that on a flat HA surface, while nanodimensional HA needles and sheets with a diameter/thickness of less than 30 nm inhibited cellular adhesion and/or subsequent activity because cells could not form focal adhesions of sufficient size[194].

Obviously, the volume fraction of grain boundaries in nanodimensional calcium orthophosphates is increased significantly leading to improved osteoblast adhesion, proliferation and mineralization. Therefore, a composition of these biomaterials at the nano-scale emulates the bone's hierarchic organization, to initiate the growth of an apatite layer and to allow for the cellular and tissue response of bone remodeling. These examples emphasize that nanophase materials deserve more attention in improving orthopedic implant failure rates. However, to reduce surface energy, all nano-sized materials tend to agglomerate and, to avoid self-aggregation of calcium orthophosphate nano-sized particles[195-198], special precautions might be necessary[54, 60, 120, 199-202].

Finally yet importantly, nano-sized crystals of CDHA obtained by precipitation methods in aqueous solutions were shown to exhibit physico-chemical characteristics rather similar to those of bone apatite[203]. In particular, their chemical composition departs from stoichiometry by calcium and hydroxide ions deficiency, leading to an increased solubility, and in turn bioresorption rate in vivo[148, 204-206]. The nano-sized crystals of CDHA have also a property to evolve in solution (maturation) like bone crystals. Namely, freshly precipitated CDHA has been shown to be analogous to embryonic bone mineral crystals whereas aged precipitates resemble bone crystals of old vertebrates[203].

4. Nanodimensional and Nanocrystalline Calcium Orthophosphates in Calcified Tissues of Mammals

4.1. Bones

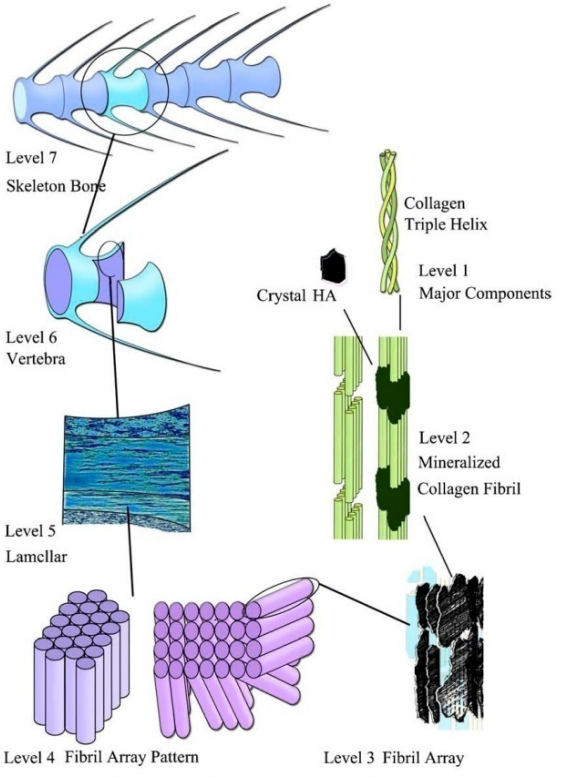

Figure 1. The seven hierarchical levels of organization of the zebrafish skeleton bone. Level 1: Isolated crystals and part of a collagen fibril with the triple helix structure. Level 2: Mineralized collagen fibrils. Level 3: The array of mineralized collagen fibrils with a cross-striation periodicity of nearly 60-70 nm. Level 4: Two fibril array patterns of organization as found in the zebrafish skeleton bone. Level 5: The lamellar structure in one vertebra. Level 6: A vertebra. Level 7: Skeleton bone. Reprinted from Ref.[208] with permission

Bone is the most typical calcified tissue of mammals and it comes in all sorts of shapes and sizes in order to achieve various functions of protection and mechanical support for the body. The major inorganic component of bone mineral is a biological apatite, which might be defined as a poorly crystalline, non-stoichiometric and ion substituted CDHA[2-5, 204-207]. From the material point of view, bone can be considered as an assembly of distinct levels of seven hierarchical structural units from macro- to micro- and to nano-scale (Fig. 1) to meet numerous functions[2, 5, 134, 208-210]. Furthermore, all these levels of bones permanently interact with cells and biological macromolecules. At the nanostructural level, tiny plate-like crystals of biological apatite in bone occur within the discrete spaces within the collagen fibrils and grow with specific crystalline orientation along the *c*-axes, which are roughly parallel to the long axes of the collagen fibrils[211]. Type I collagen molecules are self-assembled into fibrils with a periodicity of ~ 67 nm and ~ 40 nm gaps between the ends of their molecules, into which the apatite nano-sized crystals are placed. A biocomposite of these two constituents forms mineralized fibers. The fibers also may be cross-linked, which provides a highly dynamic system capable of modification through the selec-

tion of different amino acids to allow for different mechanical properties for different biomaterial applications[212]. This is why bone is usually termed a fiber-reinforced composite of a biological origin, in which nanometer-sized hard inclusions are embedded into a soft protein matrix[213]. Though dimensions of biological apatite crystals reported in the literature vary due to different treatment methods and analytical techniques, it is generally around the nanometric level with values in the ranges of 30 – 50 nm (length), 15 – 30 nm (width) and 2 – 10 nm (thickness)[214]. Some details on the stability reasons of nanodimensional apatites in bones are available in literature[215, 216].

Why does the nanometer scale appear to be so important to bones? It was recently demonstrated that natural biocomposites exhibit a generic mechanical structure in which the nanometer sizes of mineral particles are used to ensure the optimum strength and maximum tolerance of flaws[217, 218]. Furthermore, nanodimensional apatite has another crucial function for organisms. It is a huge reservoir of calcium and orthophosphate ions necessary for a wide variety of metabolic functions, which offer or consume calcium and orthophosphate ions through a so-called "remodeling" process because of a continuous resorption and formation of nanodimensional apatite by osteoclasts and osteoblasts, respectively, in a delicate equilibrium[2, 5]. Additional details on the structure, properties and composition of bones might be found in special literature[5, 207, 219].

4.2. Teeth

Teeth are another normal calcium orthophosphate-based calcified tissue of vertebrates. Unlike bone, teeth consist of at least two different biominerals: enamel (a crown, the part above the gum line) and dentin (root, the part below the gum line)[220]. Dental enamel contains up to 98% of biological apatite, ~ 1% of bioorganic compounds and up to 2% of water. Typical rods in enamel are composed of rod-like apatite crystals measuring 25 – 100 nm and an undetermined length of 100 nm to 100 μm or longer along the *c*-axis[221-223]. However, the apatite crystals in enamel were found to exhibit regular sub-domains or subunits with distinct chemical properties[224]. This subunit structure reflects an assembly mechanism for such biological crystals[225, 226]. Like that for bones (Fig. 1), seven levels of structural hierarchy have been also discovered in human enamel; moreover, the analysis of the enamel and bone hierarchical structures suggests similarities of the scale distribution at each level[227]. In enamel, nano-sized crystals of biological apatite at first form mineral nanodimensional fibrils; the latter always align lengthways, aggregating into fibrils and afterwards into thicker fibers; further, prism/interprism continua are formed from the fibers. At the micro-scale, prisms are assembled into prism bands, which present different arrangements across the thickness of the enamel layer. These compositional and structural characteristics endow enamel special properties such as anisotropic elastic modulus, effective viscoelastic properties, much higher fracture toughness and stress-strain relationships more similar to metals than ceramics[228].

Dentin contains ~ 50% of biological apatite, ~ 30% of bioorganic compounds and ~ 20% of water. In dentin, the nanodimensional building blocks (~ 25 nm width, ~ 4 nm thickness and ~ 35 nm length) of biological apatite are smaller than those of enamel. Dentin is analogous to bone in many aspects, for example, it has a similar composition and a hierarchical structure up to the level of the bone lamellae[204, 205]. Additional details on the structure, properties and composition of teeth might be found in special literature[229].

5. The structure of the Nanodimensional and Nanocrystalline Apatites

Due to the apatitic structure on natural calcified tissues, apatites appear to be the best investigated compounds among the available calcium orthophosphates (Table 1). Thus, nanodimensional and nanocrystalline apatites have been extensively studied by various physico-chemical techniques and chemical analysis methods[197, 230-242] with a special attention to the "nano" effect (*i.e.*, an enhanced contribution of the surface against the volume). Unfortunately, no publications on the structure of other nanodimensional and/or nanocrystalline calcium orthophosphates were found in the available literature.

Due to a nanocrystalline nature, various diffraction techniques have not yet given much information on the fine structural details related to apatite nano-sized crystals (assemblies of nano-sized particles give only broad diffraction patterns, similar to ones from an amorphous material)[230, 231]. Nevertheless, the diffraction studies with electron microprobes of 35 ± 10 nm in diameter clearly indicated a crystalline character of the nano-sized particles in these assemblies. Furthermore, high-resolution transmission electron microscopy results revealed that nano-sized particles of HA behaved a fine monocrystalline grain structure[197, 230].

Therefore, a recent progress on the structure of nanodimensional and nanocrystalline apatites has relied mainly on diverse spectroscopic methods, which are sensitive to disturbances of the closest environments of various ions. Namely, the structure analysis revealed an existence of structural disorder at the particle surface, which was explained by chemical interactions between the orthophosphate groups and either adsorbed water molecules or hydroxyl groups located at the surface of nano-sized apatites[232]. More to the point, infrared (FTIR) spectra of nanocrystalline apatites, in the ν_4 PO_4 domain, revealed the existence of additional bands of orthophosphate ions which could not be assigned to an apatitic environment and which were not present in well-crystallized apatites (Fig. 2). These bands were assigned to non-apatitic environments of PO_4^{3-} and HPO_4^{2-} ions of the nano-sized crystals. Thus, FTIR

spectra can be used to provide a sufficiently accurate evaluation of the amounts of such environments. Furthermore, the non-apatitic environments were found to correspond to hydrated domains of the nano-sized crystals, which were distinct from the apatite domains[234]. Hence, precipitated crystals of nano-sized apatite appeared to have a hydrated surface layer containing labile ionic species, which easily and rapidly could be exchanged by ions and/or macromolecules from the surrounding fluids[233, 232, 241]. For the as-precipitated apatites, such a layer appears to constitute mainly by water molecules coordinated to surface Ca^{2+} ions, approximately in the 1 : 1 ratio, while the OH groups account only for ~ 20% of the surface hydration species. The FTIR data indicated that water molecules, located on the surface of nanodimensional apatites, are coordinated to surface cations and experience hydrogen bonding significantly stronger than that in liquid water[240]. The surface hydrated layer is very delicate and becomes progressively transformed into a more stable apatitic lattice upon ageing in aqueous media. Furthermore, it irreversibly altered upon drying[234]. Outgassing at increasing temperatures up to ~ 300 °C resulted in a complete surface dehydration, accompanied by a decrease of the capability to re-adsorb water. Combination of these data with rehydration tests suggested that a significant part of the surface Ca^{2+} ions, once dehydrated, could undergo a relaxation inward the surface, more irreversibly as the outgassing temperature increased[239].

In another study, elongated nano-sized crystals of CDHA of ~ 10 nm thick and of ~ 30 – 50 nm length were synthesized followed by investigations with X-ray diffraction and nuclear magnetic resonance techniques. The nano-sized crystals of CDHA were shown to consist of a crystalline core with the composition close to the stoichiometric HA and a disordered (amorphous) surface layer of 1 – 2 nm thick[238, 239] with the composition close to DCPD[237]. Based on the total Ca/P ratio, on the one hand, and the crystal shape, on another hand, a thickness of the DCPD surface layer along the main crystal axis was estimated to be ~ 1 nm[237], which is close to dimensions of the unit-cells (Table 2). A similar structure of a crystalline core with the composition of the stoichiometric HA and a disordered (amorphous) surface layer was found by other researchers[243]; however, in yet another study devoted to nanodimensional carbonateapatites[244], the model of a crystalline core and an outer amorphous layer was not confirmed. Perhaps, this discrepancy could be explained by the presence of carbonates. A lack of hydroxide in nanodimensional apatites was detected; an extreme nanocrystallinity was found to place an upper bound on OH^- possible in apatites[245].

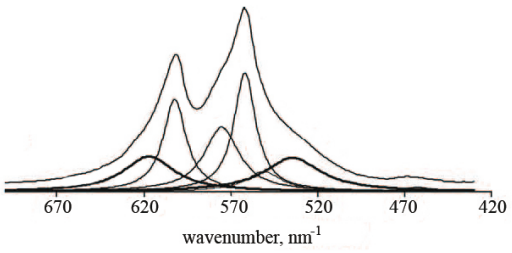

Figure 2. FTIR spectra of poorly crystalline apatites showing the non-apatitic environments of the orthophosphate ions (bold lines with peaks at 617 and 534 cm^{-1}) and the apatitic PO_4^{3-} (thin lines with peaks at 600, 575 and 560 cm^{-1}) and HPO_4^{2-} (thin line with peak at 550 cm^{-1}) in the ν_4 PO_4 domain. Reprinted from Ref.[234] with permission

Table 2. Crystallographic data of calcium orthophosphates[206].

Compound	Space group	Unit cell parameters	Z[a]	Density, g/cm^3
MCPM	triclinic $P\bar{1}$	a = 5.6261(5), b = 11.889(2), c = 6.4731(8) Å, α = 98.633(6)°, β = 118.262(6)°, γ = 83.344(6)°	2	2.23
MCPA	triclinic $P\bar{1}$	a = 7.5577(5), b = 8.2531(6), c = 5.5504(3) Å, α = 109.87(1)°, β = 93.68(1)°, γ = 109.15(1)°	2	2.58
DCPD	monoclinic Ia	a = 5.812(2), b = 15.180(3), c = 6.239(2) Å, β = 116.42(3)°	4	2.32
DCPA	triclinic $P\bar{1}$	a = 6.910(1), b = 6.627(2), c = 6.998(2) Å, α = 96.34(2)°, β = 103.82(2)°, γ = 88.33(2)°	4	2.89
OCP	triclinic $P\bar{1}$	a = 19.692(4), b = 9.523(2), c = 6.835(2) Å, α = 90.15(2)°, β = 92.54(2)°, γ = 108.65(1)°	1	2.61
α-TCP	monoclinic $P2_1/a$	a = 12.887(2), b = 27.280(4), c = 15.219(2) Å, β = 126.20(1)°	24	2.86
β-TCP	rhombohedral $R3cH$	$a = b$ = 10.4183(5), c = 37.3464(23) Å, γ = 120°	21[b]	3.08
HA	monoclinic $P2_1/b$ or hexagonal $P6_3/m$	a = 9.84214(8), b = 2a, c = 6.8814(7) Å, γ = 120° (monoclinic) $a = b$ = 9.4302(5), c = 6.8911(2) Å, γ = 120° (hexagonal)	4 2	3.16
FA	hexagonal $P6_3/m$	$a = b$ = 9.367, c = 6.884 Å, γ = 120°	2	3.20
OA	hexagonal $P\bar{6}$	$a = b$ = 9.432, c = 6.881 Å, α = 90.3°, β = 90.0°, γ = 119.9°	1	~ 3.2
TTCP	monoclinic $P2_1$	a = 7.023(1), b = 11.986(4), c = 9.473(2) Å, β = 90.90(1)°	4	3.05

[a] Number of formula units per unit cell.
[b] Per the hexagonal unit cell.

However, it is possible to address the structure of surface terminations of HA nano-sized particles to be amorphous or crystalline by properly selecting the preparation parameters and, in particular, the temperature; thus, nanodimensional HA without the amorphous layer on the surface has been prepared[246]. The two types of surfaces (amorphous or crystalline) of nanodimensional HA appeared to be quite similar in terms of their first hydration layer, as well as Lewis acid strength of exposed Ca^{2+} ions. Both features have a strong dependence on the local structure of surface sites (well probed by small molecules, such as H_2O and CO) that appeared essentially unaffected by the organization at a longer range. Interestingly, but once treated at 573 K, the crystalline surfaces of nanodimensional HA was found to adsorb multilayers of water in a larger extent than the amorphous ones[246].

Nevertheless, after summarizing the available data, the following statements on the structure of nano-sized crystals of apatites have been made:

(1) they involve non-apatitic anionic and cationic chemical environments (in another study, the researchers mentioned on "ordered and disordered HA"[238]),

(2) at least part of these environments are located on the surface of the nano-sized crystals and are in strong interaction with hydrated domains,

(3) immature samples show FTIR band fine substructure that is altered upon drying without leading to long-range order (LRO) modifications,

(4) this fine substructure shows striking similarities with the FTIR spectrum of OCP[235].

All these elements favor a model in which nano-sized crystals of apatites are covered with a rather fragile but structured surface hydrated layer containing relatively mobile ions (mainly, bivalent anions and cations: Ca^{2+}, HPO_4^{2-}, CO_3^{2-}) in "non-apatitic" sites (Fig. 3), which is supposed to be of either OCP or DCPD structure. Unfortunately, both the exact structure and the chemical composition of this hydrated layer are still uncertain (regrettably, as the hydrated layer cannot be isolated, it is not possible to standardize the methods for detailed studies)[235, 237-239]. Nevertheless, it is known that the surface layer might adsorb considerable amounts of foreign compounds (molecules and ions) in the percent mass range[247]. Strictly speaking, all the aforementioned apply to both biological apatite of calcified tissues[248] and micron-sized apatites as well[249]; nonetheless, in nano-sized crystals, the composition of the hydrated surface layer contributes to the global composition for a non-negligible proportion. The results of electron states spectroscopy of nanostructural HA bioceramics are available elsewhere[250, 251].

The hydrated surface layer confers unexpected properties to nano-sized apatite, is responsible for most of the properties of apatites, and, for example, can help to explain the regulation by biological apatites of the concentration in mineral ions in body fluids (homeostasis). These properties are important for living organisms; therefore, they need to be used in both material science and biotechnology[234]. The consideration of this type of surface state can help understanding and explaining the behavior of biological apatites in participating in homeostasis due to a very high specific surface area of bone crystals and in constituting an important ion reservoir with an availability that depends on the maturation state. The important consequences are that the surface of nanodimensional apatites has nothing in common with the bulk composition and that the chemistry of such materials (*e.g.*, binding of protein molecules) must be reconsidered[235, 237]. Interestingly, but, in response to an electrical potential, the surface of nano-sized HA bioceramics was found to exhibit dynamic changes in interfacial properties, such as wettability. The wettability modification enabled both a sharp switching from hydrophilic to hydrophobic states and a microscopic wettability patterning of the HA surface, which may be used for fabrication of spatially arrayed HA for biological cells immobilization or gene transfer[252].

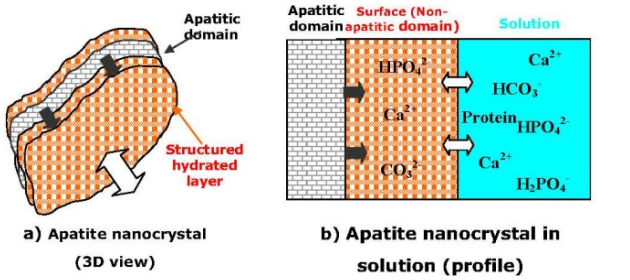

Figure 3. A schematic representation of the "surface hydrated layer model" for poorly crystalline apatite nanocrystals. Reprinted from Ref.[235] with permission

Furthermore, dry powders of nanodimensional HA were found to contain an X-ray amorphous portion with an unspecified location[253]. After mixing of an initial nano-sized HA powder with a physiological solution (aqueous isotonic 0.9 % NaCl solution for injections), this amorphous portion was fully converted into the crystalline phase of HA. The initial crystallite average size (~ 35 nm) was enlarged by a factor of about 4 within the first 100 min after mixing the powder with the physiological solution and no more structural changes were detected during the following period[253]. In the light of the aforementioned studies, presumably, the discovered X-ray amorphous component of the initial powder was located on the surface of nanodimensional HA.

6. Synthesis of the Nanodimensional and Nanocrystalline Calcium Orthophosphates

6.1. General Nanotechnological Approaches

The synthesis of nano-scale materials has received considerable attention and their novel properties can find numerous applications, for example, in the biomedical field. This has encouraged the invention of chemical, physical and biomimetic methods by which such nano-sized materials can

be obtained[134]. Generally, all approaches for preparation of nanodimensional and nanocrystalline materials can be categorized as "bottom-up" and "top-down" ones[142, 254]. The bottom-up approach refers to the build up of a material from the bottom, *i.e*., atom by atom, molecule by molecule or cluster by cluster and then assembles them into the final nanostructured material. An example is production of a nano-sized powder and its compaction into the final product (*e.g.*, hot-pressed or sintered nanostructured ceramics). The top-down approach starts from a bulk material and then, via different dimension decreasing techniques, such as milling, slicing or successive cutting, leads to the formation of nanodimensional materials[134]. Using this approach, a novel 2-dimensional carbon material graphene of just 1 atom thick has been prepared from bulk graphite. Furthermore, environmentally friendly methodologies of nanostructure synthesis have been summarized into a special review[255].

Concerning calcium orthophosphates, presumably, all of them (see Table 1) might be manufactured in a nanodimensional and/or a nanocrystalline state; however, not all of them (especially those with low Ca/P ionic ratios) have been prepared yet. The details on the available preparation techniques are given below.

6.2. Nanodimensional and Nanocrystalline Apatites

First of all, one should stress that the stoichiometric HA with well resolved X-ray diffraction patterns might be prepared mostly at temperatures exceeding ~ 700 ºC either by calcining of CDHA with the Ca/P molar ratio very close to 1.67 or by solid-state reactions of other calcium orthophosphates with various chemicals (e.g., DCPA + CaO). Thus, with the exception of a hydrothermal synthesis[256-258], in aqueous solutions only CDHA might be prepared[148, 204-206, 259-263]. As apatites (CDHA, HA and FA) belong to the sparingly soluble compounds (Table 1), simple mixing of calcium- and orthophosphate-containing aqueous solutions at pH > 9 results in formation of extremely supersaturated solutions and, therefore, a very fast precipitation of the tremendous amounts of very fine crystals[264], initially of ACP, those afterwards are re-crystallized into apatites[204-206, 265-268]. The dimensions of the precipitated nano-sized crystals might be slightly increased by the Ostwald ripening approach (maturation), that is, by boiling and/or ambient aging in the mother liquid (Fig. 4)[156, 169, 203, 235, 257, 267-272]. Heat treatment of ACP might be applied as well[273]. Therefore, preparation of nanodimensional and/or nanocrystalline apatites is not a problem at all and has been known for many years[156, 157, 274-276]; however, prefix "nano" had not been used before 1994. On the contrary, with the exception of a thermally stable FA (thus, big crystals of FA might be produced by a melt-growth process[277, 278]), manufacturing of big crystals of both CDHA and HA still is a challenge.

Many different methodologies have been proposed to prepare nanodimensional and/or nanocrystalline structures[279-286]. Prior to describing them, it is important to stress that in the vast majority of the available literature on apatites, the authors do not tell the difference between CDHA and HA. Therefore, getting through scientific papers, an attentive reader often finds statements, as: "Because natural bone is composed of both organic components (mainly type I collagen) and inorganic components (HA), …"[116, p. 357], "The HA nanorods are synthesized via a wet precipitation process …"[167, p. 2364], "… (TTCP) has been shown previously to be an essential component of self-setting calcium phosphate cements that form hydroxyapatite (HA) as the only end-product. …"[287, abstract], etc. The matter with distinguishing between CDHA and HA becomes even much more complicated, when researchers deal with nanodimensional and/or nanocrystalline apatites because the assemblies of nano-sized particles give only broad diffraction patterns, similar to ones from an amorphous material[230, 231]. While composing this review, I always tried to specify whether each cited study dealt with CDHA or HA; unfortunately, the necessary data were found in just a few papers. Therefore, in many cases, I was forced to mention just "apatites" without a further clarification. Thus, the readers are requested to be understandable on this uncertainty.

Figure 4. Variation of nanocrystalline apatite dimensions with maturation time. Reprinted from Ref.[235] with permission

The greater part of the published reports on synthesizing of nanodimensional and/or nanocrystalline apatites is focused on the bottom-up approach. Among the available preparation techniques, a wet chemical precipitation is the most popular one[74, 86, 88, 103, 119, 121, 167-169, 172, 178, 201, 203, 265, 274, 288-332]. Various authors discussed the effects of synthesis parameters, such as temperature[300-303, 322], time[301], calcium ion concentration[303], presents of surfactants[306-308], calcination[301] and the use of different reagents on the morphological properties of nanodimensional apatites. In general, the shape, stoichiometry, dimensions and specific surface area of nano-sized apatites appeared to be very sensitive to both the reaction temperature (Fig. 5) and the reactant addition rate[300, 315, 322]. Namely, particle sizes of nanodimensional apatites were observed to increase in a linear correlation with temperature[302, 322], which is a good indication that sizes of nanodimensional apatites can possibly be tailored. Furthermore, the initial pH values and reaction temperatures both play important roles in the morphology of the precipitated apatites, as well as on the phase formation and

degree of crystallinity[326]. For example, significant differences in the chemical composition, morphology and amorphous character of nano-sized CDHA produced through the reaction between aqueous solutions of Ca(NO3)2 and (NH4)2HPO4 can be induced, simply by changing the pH of the reactant hydrogen phosphate solution[327]. Thus, the solvent systems, dispersant species and drying methods appear to have effects on the particle size and dispersibility. However, some conflicting results have been obtained on how certain synthesis parameters can affect the morphological properties of these nano-sized particles. Nevertheless, it was commonly observed that nano-sized crystals of apatites synthesized through the chemical precipitation were often highly agglomerated; however, these agglomerates could be clusters of ultra-fine primary particles[304]. The prepared nanodimensional apatites might be consolidated to transparent bioceramics[330].

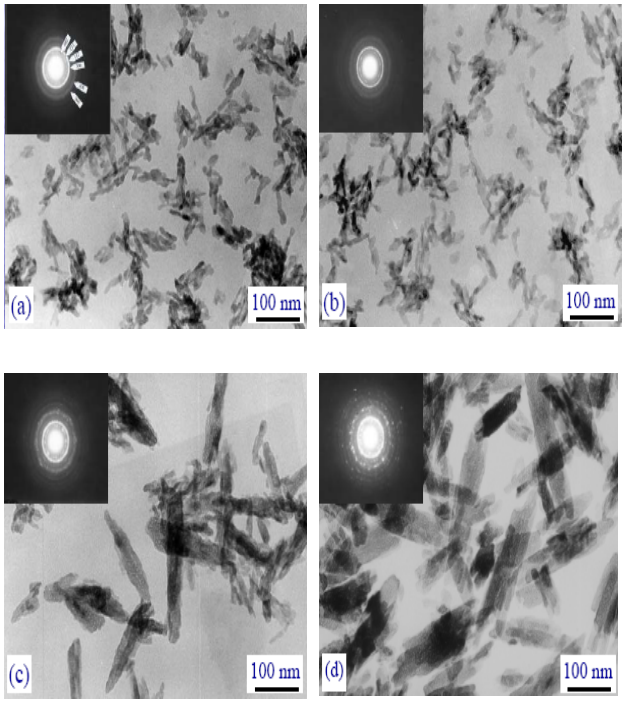

Figure 5. The influence of the reaction temperature on the crystal dimensions of precipitated CDHA: a – 25 ºC, b – 37 ºC, c – 55 ºC, d – 75 ºC

A hydrothermal synthesis[69, 72, 156, 157, 257, 258, 288, 322, 323, 333-357] seems to be the second most popular preparation technique of the nanodimensional and/or nanocrystalline apatites. The term "hydrothermal" refers to a chemical reaction of substances in a sealed heated solution above ambient temperature and pressure[358] and this process allows synthesis of highly pure fine-grained single crystals, with controlled morphology and narrow size distribution[333]. Extraneous additives, such as EDTA[351], surfactants[352, 359], anionic starburst dendrimer[353] etc., might be utilized to modify the morphology of nanodimensional and/or nanocrystalline apatites during the synthesis. Most of these techniques produced rod-like crystals or whiskers, while plate-like shapes were obtained in just a few studies[335, 345, 347].

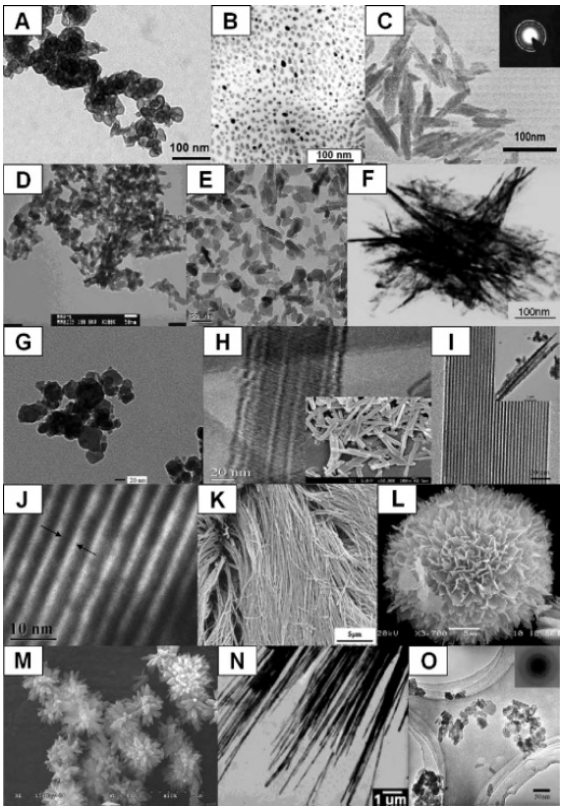

Figure 6. A variety of nano-scale calcium orthophosphates with different structures and morphologies synthesized by: (A and B) sol-gel processing, (C) co-precipitation, (D) emulsion technique, (E) hydrothermal process, (F) ultrasonic technique, (G) mechano-chemical method, (H – L) template method, (M) microwave processing, (N) emulsion-hydrothermal combination, (O) microwave-hydrothermal combination. Reprinted from Ref.[452] with permission

Other preparation methods of nanodimensional and/or nanocrystalline apatites of various states, shapes and sizes include sol-gel[30, 188, 231, 232, 270, 328, 360-376], co-precipitation[271, 333, 334, 377-380], mechanochemical approach[65, 250, 343, 348, 381-387], mechanical alloying[388, 389], ball milling[348, 383, 390-392], radio frequency induction plasma[393, 394], vibro-milling of bones[395], flame spray pyrolysis[396], liquid-solid-solution synthesis[397], electro-crystallization[158, 398, 399], electrochemical deposition[400], microwave processing[32, 69, 288, 333, 334, 342, 356, 401-415], hydrolysis of other calcium orthophosphates[416-418], double step stirring[419], emulsion-based[310, 349, 420-433], steam-assistant[434], sonochemical[435] and solvothermal[436] syntheses. However, still other preparation techniques are also known[31, 45, 147, 154, 275, 355, 437-457]. Continuous preparation procedures are also available[200, 458]. Application of both ultrasound[362, 459-461] and viscous systems[462] might be helpful. Furthermore, nanodimensional HA might be manufactured by a laser-induced fragmentation of HA targets in water[463-467] and in solvent-containing aqueous solutions[344, 371, 468], while dense nanocrystalline HA films might be produced by radio frequency magnetron sputtering[469, 470]. An interesting approach using sitting drop vapor diffusion technique should

be mentioned as well[471]. A comparison between the sol-gel synthesis and wet chemical precipitation technique was performed and both methods appeared to be suitable for synthesis of nanodimensional apatite[328]. By means of these methods, a variety of nanodimensional calcium orthophosphate building blocks with various structures and morphologies have been synthesized, including needle-like, spherical, fibrous and mesoporous nano-sized crystals, as well as nano-sized rods, hollow spheres, layered structures and flowers as shown in Fig. 6[452].

Table 3 presents some data on the chronological development of synthesis of nanodimensional apatites for the period of 1995 – 2004[147]. Among the methods described, the thinnest crystals of apatite (60 nm × 15 nm × 0.69 or 0.84 nm) have been prepared by Melikhov et al., they have been called "two dimensional crystalline HA"[296], while the smallest ones (size between 2.1 and 2.3 nm, i.e. around two times the HA unit cell parameters) have been found by Biggemann et al.,[197]. Liu et al.,[477, 478] and Han et al.,[476] synthesized nano-sized HA via a template mediated and a non-template mediated sol-gel techniques, respectively. Both triethylphosphate[477, 478] and other alkylphosphates[122] might be used to produce nanocrystalline apatites. Besides, nanodimensional ion-substituted CDHA might be precipitated from both a synthetic[378] and a simulated[479] body fluids. A relatively simple sol-gel process using ethanol and/or water as a solvent has also been reported to obtain the stoichiometric, nanocrystalline single phase HA[371].

Nanocrystalline HA powder was synthesized at a low calcination temperature of 750 ºC by the citric acid sol-gel combustion method[476]. The attractive features of this method were to synthesize materials with a high purity, a better homogeneity and a high surface area in a single step[476, 480]. An array of highly ordered HA nano-sized tubes of uniform length and diameter was synthesized by sol-gel auto-combustion method with porous anodic aluminum oxide template[370]. Varma et al., synthesized nano-sized HA by polymeric combustion method and self-propagating combustion synthesis by using novel body fluid solutions[481]. In another study, nanodimensional HA was synthesized by combustion in the aqueous system containing calcium nitrate + diammonium hydrogen orthophosphate with urea and glycine as fuels[482]. Furthermore, nano-sized particles of both FA and β-TCP might be synthesized by a simultaneous combustion of calcium carboxylate and tributylphosphate based precursors in a flame spray reactor[483]. Both a flame-based technique[484] and a spray drying approach[125, 485] might be applied as well. Furthermore, crystalline and phase pure nano-sized HA and CDHA were synthesized in a continuous hydrothermal flow system using supercritical water at t < 400 ºC and 24 MPa pressure[338].

Table 3. Synthesis of nanodimensional apatites – a chronological development[147].

Year	Process	Reference
1995	Synthesis of nanocrystalline HA (particle size ~ 20 nm) for the first time using calcium nitrate and diammonium hydrogen orthophosphate as precursors by solution spray dry method.	[472]
2000	Synthesis of biomimetic nanosized CDHA powders (~ 50 nm) at 37 °C and pH of 7.4 from calcium nitrate tetrahydrate and diammonium hydrogen orthophosphate salts in synthetic body fluid using a novel chemical precipitation technique.	[378]
2002	Preparation of nanosized HA particles and HA/chitosan nanocomposite.	[473]
2002	Direct precipitation from dilute calcium chloride and sodium orthophosphate solutions.	[474]
2003	Radio frequency plasma spray process employing fine spray dried HA powders (average size ~ 15 μm) as a feedstock.	[393]
2003	Sol-gel process using equimolar solutions of calcium nitrate and diammonium hydrogen orthophosphate dissolved in ethanol.	[371]
2003	Chemical precipitation through aqueous solutions of calcium chloride and ammonium hydrogen orthophosphate.	[301]
2003	Mechanochemical synthesis of nanosized HA and β-TCP powders using DCPD and CaO as starting materials.	[384]
2003	Synthesis of nano-powders via sucrose-templated sol-gel method using calcium nitrate and diammonium hydrogen orthophosphate as precursor chemicals.	[475]
2004	Hydrolysis method of DCPD and $CaCO_3$ by 2.5 M NaOH (aq).	[416]
2004	Citric acid sol-gel combustion process using calcium nitrate tetrahydrate, diammonium hydrogen orthophosphate and citric acid.	[476]

Nanodimensional powders of the stoichiometric HA of ~ 20 nm particle size were synthesized by hydrolysis of a mixture of DCPD and CaCO3 performed with 2.5 M aqueous solution of NaOH at 75 °C for 1 h. The only product synthesized was nanocrystalline HA and its crystallinity was improved with increasing annealing temperature[416]. Similar results were obtained in other studies[417, 418]. Furthermore, Xu et al., used radio frequency plasma spray process to synthesize nanodimensional HA powders with particle size in the range of 10 – 100 nm[393]. Kuriakose et al., synthesized nanocrystalline HA of size ~ 1.3 nm that was thermally stable until 1200 °C[371]. Nanocrystalline plate-shaped particles of HA were directly precipitated at ambient temperature and pH ~ 7.4 from dilute aqueous solutions of calcium chloride and sodium orthophosphate. The direct precipitation of nano-sized HA was achieved by submitting the aqueous suspension to microwave irradiation immediately after mixing[474]. A simple and easy approach for synthesizing thermally stable nanostructured stoichiometric HA powder under invariant pH conditions of 7.5, known as the NanoCaP process, was developed. Under these conditions, the synthesized HA not only remained in the nanostructured state but also did not exhibit any compositional fluctuations that were observed in conventional approaches for synthesizing HA[12]. Other preparation techniques of nano-sized apatite might be found elsewhere[275]. Bulk bioceramics made of nanocrystalline HA with a grain size of no more than 50 nm and a near-theoretical density might be prepared by application of a high (~ 3.5 GPa) pressure in uniaxial compaction of nanodimensional powders with subsequent sintering at 640 °C[168]. A similar approach was reported by another research group[406].

Mechanochemical processing is another compelling method to produce nanostructured apatites in the solid state[65, 238, 343, 381-386]. For example, Yeong et al., used the appropriate amounts of DCPA and calcium oxide. The initial stage of mechanical activation resulted in a significant refinement in crystallite and particle sizes, together with a degree of amorphization in the starting powder mixture. This was followed by steady formation and subsequent growth of HA crystallites with increasing degree of mechanical activation. Finally, a single-phase HA of an average particle size of ~ 25 nm, a specific surface area of ~ 76 m2/g and a high crystallinity was attained after 20 h of mechanical activation[382].

The use of macromolecules as templating agents to manipulate the growth of inorganic crystals has been realized in many biological systems. Namely, in the presence of biological macromolecules (such as collagen), nucleation and growth of nanocrystalline apatite to form highly organized bone minerals is one of the most fascinating processes in nature. These processes might be simulated. For example, layers of nanocrystalline apatite were formed in situ on the surface of various films at soaking them in aqueous solutions containing ions of calcium and orthophosphate. The in situ synthesized particles were found to be less agglomerated which was believed to be the result of nucleation of apatite crystallites on the regularly arranged side groups located on polymer chains[486, 487]. Another approach comprises precipitation of nanodimensional apatites from aqueous solutions in the presence of dissolved high molecular weight polyacrylic acid[488, 489] that acts as an inhibitor for the crystallization of apatite crystals[490, 491]. A similar inhibiting effect was found for dimethyl acetamide[492], polyvinyl alcohol[291] and several other (bio)polymers[493, 494]. This type of synthesis is expected to lead to formation of nanodimensional composites, which might be structurally more comparable to bones with closely related mechanical and biological properties. Furthermore, a control of particle size of aqueous colloids of apatite nano-sized particles was described involving a presence of amino acids[495, 496]. The amino acids ensured effective growth inhibition by a predominant adsorption onto the Ca-rich surfaces during the initial stages of crystallization. Thus, the nano-sized particles were formed by an oriented aggregation of primary crystallite domains along the c-axis direction. The size of the domains was shown to be governed by the interactions with the amino acid additives, which restricted a growth of the primary crystallites[495, 496]. Furthermore, nanodimensional apatites might be precipitated from aqueous solutions of gelatin[70, 497]. The development of nano-sized apatite in aqueous gelatin solutions was highly influenced by the concentration of gelatin: namely, a higher concentration of gelatin induced formation of tiny (4 nm × 9 nm) nano-sized crystals, while a lower concentration of gelatin contributed to the development of bigger (30 nm × 70 nm) nano-sized crystals. In this experiment, a higher concentration of gelatin supplied abundant reaction sites containing groups such as carboxyl, which could bind with calcium ions. This lead to formation of a very large number of nuclei and creation of a large number of tiny nano-sized crystals[70].

Although each of the reported approaches to produce nanodimensional apatites has both a scientific and a practical relevance, a little attention has been dedicated to the physicochemical details involved in the careful control of the particle size distribution and particle shape. Indeed, in the case of particle size distribution, most of the reported ways to synthesize nanodimensional apatites really produced a particle mixture with a wide size distribution from tens to hundreds of nanometers. Moreover, the control of particle shape is another problem for these methods, which commonly result in pin-like or irregular particles. It is well known that bone consists of homogeneous plate-like crystals of biological apatite of 15 – 30 nm wide and 30 – 50 nm long, while enamel consists of rod-like crystals of biological apatite of 25 – 100 nm thick and lengths of 100 nm to microns (Fig. 7)[2, 5, 207, 208, 210, 219, 227, 229]. The study of higher-level biomineralization and biomimetic assembly involves a search for advanced methods so that the synthesis of nano-sized apatite can be accurately controlled[498]. Namely, the size-controlled synthesis of materials can be achieved by using limited reaction spaces. For example, microemulsions have been shown to be one of the few

techniques, which is able to produce particle sizes in the range of nanometers and with minimum agglomeration[499]. Thus, microemulsions[349, 423-433], micelles[500] and reverse (inverse) micelles[339, 501-504] have been successfully applied to synthesize nanodimensional apatites with minimal agglomeration. It was found that experimental conditions, such as aqueous/organic phase volume ratio, pH, aging time, aging temperature and ion concentration in the aqueous phase can affect the crystalline phase, surface area, particle size and morphology of nanodimensional apatites.

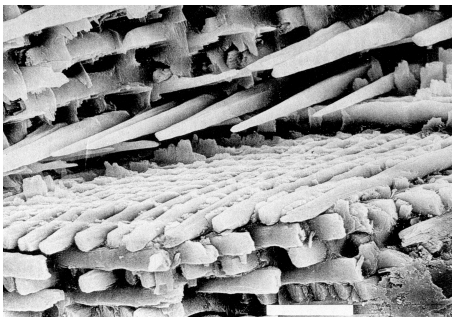

Figure 7. Scanning electron micrograph of the forming enamel of a continuously growing rat incisor showing ordered rods of calcium orthophosphates. Scale bar: 10 μm. Reprinted from Ref.[2] with permission

In some cases, special polymers can be used as spatial reaction vessels for fabrication of CDHA. For example, Shchukin et al., employed a poly(allylamine hydrochloride)/PO43- complex as a source of orthophosphate anions to capture calcium cations and make them react in the capsule volume[505]. Bose and Saha synthesized spherical-like nanocrystalline CDHA powder with particle diameters of ~ 30 and ~ 50 nm using the emulsion route[425]. Furthermore, nano-sized crystals of apatite might be aggregated into microspheres[438, 506]. Hexadecyl (cetyl)trimethylammonium bromide (CTAB) was selected as an efficient agent to modulate the formation of CDHA nano-sized particles[501, 502]. The particle size can be regulated feasibly by changing the concentration of CTAB in the supersaturated by calcium orthophosphates solutions. For example, three different types of spherical particles of nano-sized CDHA with average diameters of 20 ± 5, 40 ± 10 and 80 ± 12 nm were fabricated using a series of CTAB concentrations to control the particle size. The experimental results revealed that the dimensions of the prepared nano-sized CDHA were relatively uniform. In contrast, nano-sized CDHA grown in the absence of organic additives are typical, rod-like particles with lengths of hundreds of nanometers and width of tens of nanometers[507]. Colloidal formulations are known as well[54, 60, 202]. Interestingly, but nano-sized apatites might perform crystalline to amorphous phase transformation when powders were aged for 5 months in 30% relative humidity[508].

To conclude this part, the nano-sized particles of apatite might be functionalized and/or doped by various compounds (even by quantum dots[509, 510]) to provide new important properties[495, 511-518], e.g., fluorescence[27-29, 515, 516] and luminescence[54, 60, 510, 517, 518]. Both fluorescence and luminescence can be used as a tracking property for the nano-sized particles to give an observable indication of agent delivery, while the particles are served to protect the agent in vivo until it has reached the destination.

6.3. Nanodimensional and Nanocrystalline TCP

Many researchers have formulated synthesis of nanodimensional β-TCP. For example, Bow *et al.*, synthesized β-TCP powders of ~ 50 nm particle diameter at room temperature in anhydrous methanol as a solvent[519]. With increase in aging time, the phase transformation was found to take place from initial DCPA, to intermediate ACP phases, then to final β-TCP. The authors observed that incorporation of carbonates helped in suppressing formation of ACP phases with apatitic structure and its transformation into poorly crystalline (almost amorphous) CDHA and favored the formation of β-TCP phase[519]. Nano-sized particles of both FA and β-TCP were synthesized by a simultaneous combustion of calcium carboxylate and tributylphosphate based precursors in a flame spray reactor[483]. The same technique was used to synthesize nano-sized particles of amorphous TCP of 25 – 60 nm size[520-523], those after calcinations transformed into α-TCP or β-TCP. Nanodimensional β-TCP powders with an average grain size of ~ 100 nm[173, 524] and less[525] were prepared by wet precipitation methods, followed by calcining at elevated temperatures. Furthermore, a sol-gel technique[526], reverse micelle-mediated synthesis[527] and a polystyrene template method[528] are also applicable. In wet precipitation techniques, dialysis might be applied as a separation method[524]. When wet precipitation methods were used, initially nanodimensional CDHA with Ca/P ratio of ~ 1.50 was precipitated, that was transformed into nano-sized β-TCP at calcination.

To synthesize nano-sized TCP, other techniques, such as milling[529, 530], a high temperature flame spray pyrolysis[531] and pulsed laser ablation[532], might be employed as well. Afterwards, the nanodimensional β-TCP powders can be compacted into 3D specimens, followed by sintering to achieve the appropriate mechanical strength[173]. The maximal values of the bending strength, elastic modulus, Vickers hardness and compressive strength of the samples fabricated from nano-sized β-TCP powders were more than two-times higher as compared to those of bioceramics obtained from micron-sized β-TCP powders. However, the degradability of bioceramics sintered from nanodimensional powders was just about one fourth of that sintered from micron-sized powders. Thus, the degradability of β-TCP bioceramics could be additionally regulated by the particle dimensions[173].

Nano-sized whiskers of several calcium orthophosphates (HA, β-TCP and biphasic calcium phosphate BCP (HA + β-TCP)) were produced by using a novel microwave-assisted "combustion synthesis (auto ignition)/molten salt synthesis" hybrid route. Aqueous solutions containing $NaNO_3$, $Ca(NO_3)_2$ and KH_2PO_4 (with or without urea) were irradiated

in a household microwave oven for 5 min at 600 watts of power. The as-synthesized precursors were then simply stirred in water at room temperature for 1 h to obtain the nano-sized whiskers of the desired calcium orthophosphate[533]. Furthermore, nanostructured biphasic (HA + β-TCP) bioceramics was successfully prepared by microwave synthesis[534, 535] and a polymer matrix mediated process[536] in other studies. Good cellular activities of the biphasic bioceramics have been reported.

Layrolle and Lebugle developed a synthesis route of nano-sized FA and other calcium orthophosphates, using calcium diethoxide ($Ca(OEt)_2$) and H_3PO_4[154] (+ NH_4F to prepare FA[537]) as the initial reagents and anhydrous ethanol as a solvent. By a simple variance of the ratio of reagents, calcium orthophosphates of various chemical compositions were precipitated in ethanol. The precipitates were characterized and the results indicated that those calcium orthophosphates were amorphous and nanodimensional. Furthermore, they had large specific surface areas and possessed a high reactivity[154, 537].

6.4. Other Nanodimensional and Nanocrystalline Calcium Orthophosphates

Nano-sized particles of DCPD (with some amount of CDHA and ACP) of a relatively high monodispersity could be synthesized from aqueous solutions of calcium nitrate and H3PO4 in the presence of 2-carboxyethylphosphonic acid. They are produced in a discoid shape with a diameter of 30 – 80 nm and a height of less than ~ 5 nm. They form stable colloidal solutions displaying minimal agglomeration[538]. Nano-sized rods and nanodimensional fibers of DCPD with average diameters of 25 ± 5 nm (aspect ratio ~ 6) and 76 ± 20 nm (aspect ratio ~ 40), respectively, were synthesized by sucrose ester based reverse microemulsion technique[539]. A similar approach was used in another study[431]. Nanodimensional crystals of both DCPD and DCPA were prepared by EDTA-assisted hydrothermal method[351]. An interesting approach comprises precipitation of calcium orthophosphates inside nano-sized pores of another material. For example, nanodimensional clusters DCPD were immobilized into pores of an oxide network by immersion of this network into an acidic (pH = 2.7) calcium orthophosphate solution at 50 ºC[540]. The acid-base reaction between the calcium orthophosphate solution and the hydroxyl groups of the oxide network resulted in formation of nanodimensional clusters of DCPD immobilized inside the oxide pores. Interestingly, but the immobilized nanodimensional clusters of DCPD were further converted into those of ACP and CDHA by supplementary treatment of the oxide network in alkaline solutions[540]. Hollow nano-sized shells of undisclosed calcium orthophosphates (presumably, of ACP) with a size distribution of (120 – 185) ± 50 nm and predictable mean shell thickness from 10 to 40 nm were prepared by crystallization onto the surface of nanodimensional liposomes[541, 542]. Both the suspension stability and shell thickness control were achieved through the introduction of carboxyethylphosphoric acid. Variation of shell thickness and stoichiometry may be a way of manipulating the dissolution kinetics of ACP coating to control the release of encapsulated materials, necessary for drug delivery purposes[541, 542]. Other types of calcium orthophosphate shells with Ca/P ratios of 0.97 (DCPD or DCPD-like ACP) and 1.45 (CDHA or ACP) were prepared using liposome templates[543]. Roughly spherical DCPA particles of approx. 50 – 100 nm in sizes were synthesized via a spray-drying technique[125, 544-546], while ribbon-like fibers of nano-sized DCPA might be prepared upon hydrolysis in urea[417]. Furthermore, nanodimensional calcium orthophosphate powders with DCPD as the major phase have been synthesized by an inverse microemulsion system using kerosene as the oil phase, a cationic surfactant and a non-ionic surfactant[547]. Microskeletal constructions might be synthesized as well[548].

When it comes to ACP, it is nanodimensional in the vast majority cases. Approximately spherical nano-sized particles of ACP with a diameter of about 50 nm can be prepared by rapid precipitation from water[549] and subsequent colloidal stabilization by coating with polymers[550]. Nano-sized clusters of ACP[551] or those comprising a spherical core of 355 ± 20 DCPD units with density of 2.31 g/cm3 and radius of 2.30 ± 0.05 nm surrounded by 49 ± 4 peptide chains with a partial specific volume of 0.7 cm3/g, forming a tightly packed shell with an outer radius of 4.04 ± 0.15 nm were prepared by precipitation using 10 mg/ml of the 25-amino-acid N-terminal tryptic phosphopeptide of bovine β-casein as a stabilizing agent[552]. Nano-sized particles of ACP were prepared by mixing of solutions of Ca(NO3)2·4H2O (450 mmol/L) in acetone and (NH4)2HPO4 (30 mmol/L) in deionized water at pH within 10.0 – 11.0[553]. Furthermore, nanodimensional particles of ACP might be prepared by electrostatic spray pyrolysis[554, 555], pulsed laser ablation[532], spray drying[125], as well as by flame spray synthesis[457]. By means of the latter technique, one can produce nanodimensional ACPs with a broad Ca/P ratio within 0.5 – 1.5[457].

Self-assembled shell cross-linked poly(acrylic acid-b-isoprene) micelles and/or cross-linked poly(acrylic) acid nano-sized cages in aqueous solutions might be used as templates for preparation of polymer/calcium orthophosphate nanodimensional capsules of 50 – 70 nm in diameter, which consisted of spherical polymer nano-sized particles enclosed within a continuous 10 – 20 nm thick surface layer of ACP[556]. Synthesis of hollow spherical calcium orthophosphate nano-sized particles using polymeric templates has been also reported by other researchers[557]. Furthermore, bundles of surfactant-coated ACP nanodimensional filaments of ~ 2 nm in width and > 300 μm in length were synthesized in reverse micelles[558]. Bundles of the nanodimensional filaments were stable in the reverse micelle phase up to around 5 days, after which they transformed into 5 nm-wide surfactant-coated CDHA rods. Discrete filaments of 100 – 500 × 10 – 15 nm in size and a linear superstructure based on the side-on stacking of surfactant-coated ACP nano-sized rods were also prepared[490]. A double re-

verse-micelle strategy was realized to synthesize amine, carboxylate- and polyethylene glycol surface functionalized calcium orthophosphate nano-sized particles of an undisclosed nature[559]. Furthermore, the reverse micelle technique might be applied to prepare nanodimensional DCPA[501, 560].

Concerning OCP, an oriented growth of nanodimensional belts of OCP with a clean surface has been achieved by wet-chemical approach using cetyltrimethylammonium bromide[561]. Pulsed laser deposition technique was employed to obtain thin films of nanocrystalline OCP on pure Ti substrates[562]. The deposition was performed by a pulsed UV laser source in a flux of hot water vapors. High-resolution electron microscopy and X-ray diffraction at grazing incidence investigations indicated that the coatings were made of nanocrystalline OCP (unfortunately, the dimensions were not indicated). In vitro tests proved that both fibroblasts and osteoblasts adhered, reached a normal morphology, proliferated and remained viable when cultured on the nanocrystalline OCP coatings, supporting a good biocompatibility and absence of any toxicity[562].

Nanodimensional powders of BCP (both HA + β-TCP[563-565] and HA + α-TCP[566]) have been fabricated as well. To get the details, the interested readers are referred to the original publications.

Similar to that for apatites (see above), nano-sized particles of TCP, ACP and other calcium orthophosphates might be functionalized and/or doped by various compounds to provide new important properties[200, 559, 566-572], such as fluorescence[569, 570], luminescence[572] or a good disperseability in organic solvents[566]. Furthermore, nano-sized calcium orthophosphates might be used as templates to manufacture nanodimensional capsules[573].

6.5. Biomimetic construction using nanodimensional particles

Morphological control of bioinorganic materials is another interested issue in biomineralization, by which inorganic materials with complex morphologies can be produced. Complex forms or patterns with a hierarchical structure over several length scales are important features of biomineralization. Pattern formation in biomineralization is a process in which self-assembled organic templates are transformed by a material's replication into organized inorganic structures. Needless to mention, that researchers try to reproduce these processes in laboratories. For example, Chen et al., reported a way to create enamel-like structures by modifying synthetic nano-sized rods of apatite with a surfactant, bis(2-ethylhexyl)sulfosuccinate salt, that allowed the nano-sized rods to self-assemble into prism-like structures at the water/air interface[225]. A nanometer-scale rod array of apatite having preferred orientation to the c-axis was successfully prepared simply by soaking calcium-containing silicate glass substrates in Na2HPO4 aqueous solution at 80 °C for various periods[574]. A biomimetic bottom-up route to obtain the first hierarchical level of bone was reported[212]. A pH-induced self-assembly of peptide-amphiphile to make a nanostructured fibrous scaffold reminiscent of extracellular bone matrix was obtained. After the cross-linking of the scaffold, the fibers were able to direct mineralization of CDHA to form a biocomposite, in which the crystallographic c-axes of the nano-sized crystals of CDHA were aligned with the long axes of the fibers. This alignment was similar to that observed between collagen fibrils and crystals of biological apatite in bones[212]. Other attempts to fabricate artificial materials having bone-like both nanostructure and chemical composition were performed and several significant achievements were obtained[575, 576].

The classical model of biomineralization considers mineral formation as an amplification process in which individual atoms or molecules are added to existing nuclei or templates[1, 2, 577]. This process occurs in the presence of various bioorganic molecules, which deterministically modify nucleation, growth and facet stability. A model involving aggregation-based growth[578] recently challenged this conventional concept for the crystal growth. Inorganic nano-sized crystals were found to aggregate into ordered solid phases via oriented attachment to control the reactivity of nanophase materials in nature[19, 579]. A model of "bricks and mortar" was suggested to explain the biological aggregation of nano-sized apatite[580]. In this model, ACP acts as "mortar" to cement the crystallized "bricks" of nano-sized HA. Meanwhile, biological molecules control the construction process. By using nanodimensional spheres of HA as the building blocks, highly ordered enamel-like and bone-like apatites were hierarchically constructed in the presence of glycine and glutamate, respectively. It is interesting that, during the evolution of biological apatite, the amorphous "mortar" can be eventually turned into the "brick" by phase-to-phase transformation to ensure the integrity of biominerals[580].

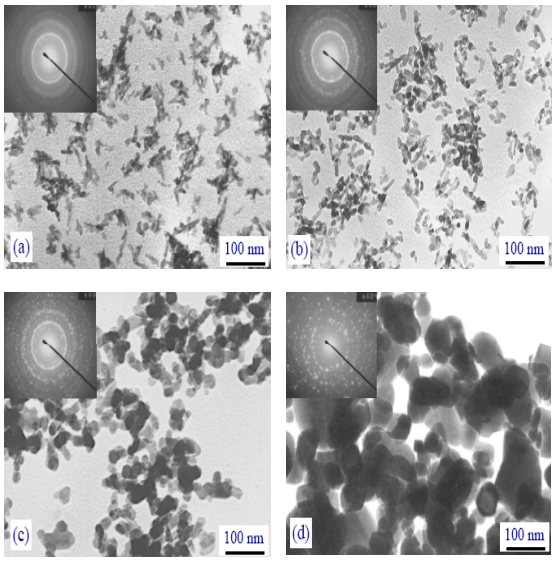

Figure 8. Particle sizes and crystallinity of HA powders after a heat treatment at various temperatures: a – 300 ºC, b – 500 ºC, c – 700 ºC, d – 900 ºC

7. Biomedical Applications of the Nanodimensional and Nanocrystalline Calcium Orthophosphates

7.1. Bone Repair

Due to advances in surgical practice and a fast aging of the population, there is a permanently increasing demand for bone grafts[581]. Modern grafts should not only replace the missing bones, but also should be intrinsically osteoinductive by acting as scaffolds for guided bone growth. Furthermore, an ability to form a biologically active apatite layer to bond to living bone it is an essential requirement to modern biomaterials[582]. In addition, a good graft should provide a framework to support new blood vessels and soft tissues in forming a bridge to existing bones[581].

Calcium orthophosphate bioceramics of micron dimensions have been used in dentistry, orthopedics and surgery for over 30 years because of their chemical similarity to calcified tissues of mammals and, therefore, excellent biocompatibility[148, 204-206, 259, 260]. Due to a rapid development of nanotechnology, the potential of nanodimensional and nanocrystalline forms of calcium orthophosphates has received a considerable attention[18] because they produce favorable results in repair of bone defects[583, 584]. For example, due to an improved sinterability, an enhanced densification and a better bioactivity than coarser crystals, they might be chosen as the major components of self-setting bone cements[14, 25, 520, 521, 585-589]. However, there is a study in which an increase of particle and crystallite sizes of TCP did not prolong but shortened the induction time until the cement setting reaction started[523], which was against the common physical rules (generally, smaller particles or crystallites should enhance reactivity). Nevertheless, two general directions of the biomedical application of nanodimensional and nanocrystalline calcium orthophosphates can be outlined: (i) using them in powder form as filling materials to impart bioactivity to various biocomposites and hybrid biomaterials[64-104, 179, 590]; (ii) manufacturing of either dense compacts or porous scaffolds, possessing the sufficient mechanical properties[74, 96, 294, 295, 575, 576, 591, 592]. As the nanodimensional and nanocrystalline calcium orthophosphates tend to agglomerate at heating (Fig. 8)[313, 593-595], normally a low-temperature[169, 371] and/or a rapid consolidation[169, 258, 323, 596-602] techniques must be employed. The low-temperature approach comprises gel hardening (at 4 ºC)[371] and uni-axial pressing at 150 – 200 ºC[169]. The rapid consolidation techniques comprise spark plasma sintering[169, 258, 323, 596-599], pressure sintering[597] and microwave sintering over the temperature range 1000 – 1300 ºC, using a rapid sintering schedule[600-602].

Furthermore, nanodimensional crystals of calcined HA might be fabricated by calcination at 800 ºC for 1 h with an anti-sintering agent surrounding the original nano-sized CDHA particles and the agent is subsequently removed by washing after the calcination[603-605]. These consolidation approaches provided a limited alteration of the initial nano-sized crystals, while the final bioceramics possessed the mechanical properties similar to those reached with sintered stoichiometric HA.

Already in 1990-s, implants prepared from nanodimensional apatites, as well as biocomposites of nanodimensional apatite with organic compounds were tested in vivo[606-608]. Cylinders made of both pure nanodimensional apatite and organoapatite containing a synthetic peptide were analyzed 28 days after implantation into spongy bones of Chinchilla rabbits. Both implant types were well incorporated and interface events were found to be similar to those observed on human bone surfaces with regard to resorption by osteoclast-like cells and bone formation by osteoblasts. That study revealed a suitability of such materials for both bone replacement and drug release purposes[606]. Similar results were obtained in other studies[607, 608].

Among the available commercial formulations, NanOss™ bone void filler from Angstrom Medica, Inc.[609] is considered as the first nanotechnological medical device received the clearance by the US Food and Drug Administration (FDA) in 2005. It is prepared by precipitation of nano-sized calcium orthophosphates from aqueous solutions and the resulting white powder is then compressed and heated to form a dense, transparent and nanocrystalline material. NanOss™ mimics the microstructure, composition and performance of human bone, as well as it is mechanically strong and osteoconductive. It is remodeled over time into human bone with applications in the sports medicine, trauma, spine and general orthopedics markets[609].

Ostim® (Osartis GmbH & Co. KG, Obernburg, Germany) is another popular commercial formulation. This ready-to-use injectable paste received CE (Conformite Europeenne) approval in 2002. Ostim® is a suspension of synthetic nanocrystalline HA (average crystal dimensions: 100 × 20 × 3 nm3 (a needle-like appearance); specific surface area ~ 100 m2/g) in water, prepared by a wet chemical reaction[610]. After completion, the HA content in the paste is ~ 35%. Ostim® does not harden when mixed with blood or spongiosa, so it is highly suitable for increasing the volume of autologous or homologous material. Simultaneously, its viscosity enables its applications to form-fit in close contact with the bone. Ostim® can be used in metaphyseal fractures and cysts, alveolar ridge augmentation, acetabulum reconstruction and periprosthetic fractures during hip prosthesis exchange operations, osteotomies, filling cages in spinal column surgery, etc.[609-622]. It might be incorporated into bones and a new bone formation is visible after only three months[623]. For a number of clinical applications, Ostim® might be combined with other types of calcium orthophosphate bioceramics, e.g., with a HA bioceramic core (Cerabone®)[610, 624] or with biphasic (β-TCP + HA) granules (BoneSaves®)[625]. Application of such combinations of a nanocrystalline Ostim® with the microcrystalline calcium orthophosphate bioceramics appeared to be an effective method for treatment of both tibia head compression fractures[610] and metaphyseal osseous volume defects in the

metaphyseal spongiosa[624]. Besides, such combinations might be used for acetabular bone impaction grafting procedures[625].

Cui et al., developed nano-sized HA/collagen biocomposites, which mimicked the nanostructure of bones[208, 626]. After implantation, such biocomposites can be incorporated into bone metabolism. Due to processing difficulties and poor mechanical properties of bulk calcium orthophosphates, their applications are currently confined to non-load-bearing implants and porous bodies/scaffolds. Porous 3D biocomposites of nanodimensional HA and collagen/polymer mimic bones in composition and microstructure and can be employed as a matrix for the tissue engineering of bone[89].

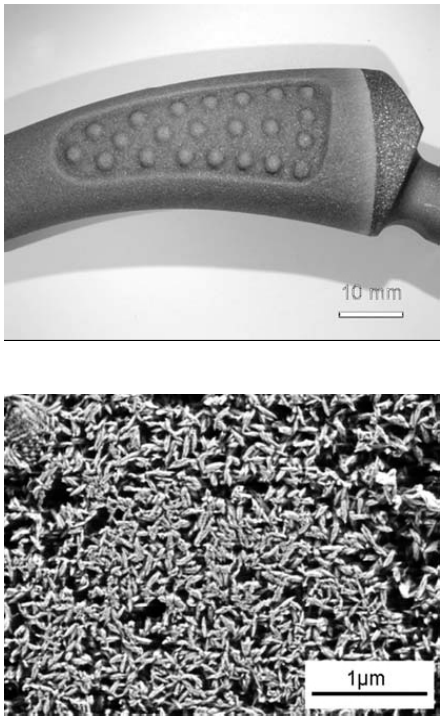

Figure 9. a – A photo of a titanium implant coated with electrochemically deposited HA at 37 ºC (Cenos® BoneMaster); b – A micrograph of a titanium implant surface coated with electrochemically deposited HA at 37 ºC. Reprinted from Ref.[650] with permission. Other micrographs of nano-CDHA coatings biomimetically deposited on NaOH-treated Ti6Al4V surfaces might be found in Ref.[651]

Owing to their low mechanical properties, the use of calcium orthophosphates in load-bearing applications is rather limited: calcium orthophosphates are too stiff and brittle for such use. Today's solutions for weight-bearing applications rely mostly on biologically friendly metals, like cobalt-chromium alloys, titanium and its alloys, as well as stainless steel 316L, but problems with stress-shielding and long-term service can cause failures. All these metals, although nontoxic, are always bioinert and cannot bond to bone directly. In order to improve the biological properties of the metallic implants, nanostructured calcium orthophosphates (mainly, apatites) are generally used as a coating material to accelerate bone growth and enhance bone fixation[186, 187, 316, 439, 562, 627-648]. The coating techniques include thermal spraying, sputter coating, pulsed laser deposition, dynamic mixing method, dip coating, sol-gel method, electrophoretic deposition, biomimetic process, hot isostatic pressing and some other methods[649]. In the majority cases, the coatings are composed of uniform nanocrystalline apatites (Fig. 9). They are capable in performing bone formation and promoting direct osseointegration with juxtaposed bone[652-655]. For example, an enhanced new bone formation can be clearly seen on nanophase HA-coated tantalum compared to micro-scale HA-coated tantalum and non-coated tantalum (see Fig. 2 in Ref.[116]). Furthermore, nanostructured calcium orthophosphates might be used as a coating material to impart surface bioactivity to other materials, e.g., glasses[656] and polymers[657, 658]. Finally but yet importantly, such coatings might be patterned, e.g., by laser direct writing[574] or electrohydrodynamic atomization spraying technique[659].

7.2. Nanodimensional and Nanocrystalline Calcium Orthophosphates and Bone-Related Cells

It is well accepted that bone-related cells (especially, osteoblasts and osteoclasts) play the key roles in the physiological formation of calcified tissues. Bone-related cells not only are speculated to take part in the formation of biominerals and macrostructure constructions of bones, but they also continuously modulate the density, regeneration and degradation of bones. Therefore, understanding the relationship between the bone-related cells and nano-sized calcium orthophosphates has been paid much attention in order to elucidate the formation mechanism of bones, to prevent and cure bone-related diseases and to design novel biomaterials. Better structural biomimicity and osteoconductivity can be achieved using nanodimensional and nanocrystalline calcium orthophosphates[178, 179, 185, 186, 660-663]. Biocompatibility of such biomaterials is the key question for their application possibility for clinical use. For example, adhesion, proliferation and differentiation of mesenchymal stem cells were studied on nano-sized HA/polyamide biocomposite scaffolds. The results indicated that such biocomposites exhibited a good biocompatibility and an extensive osteoconductivity with host bone in vitro and in vivo and proved that nano-sized HA/polyamide scaffolds had a potential to be used in orthopedic, reconstructive and maxillofacial surgery[664-666].

Most results demonstrate that nanostructured HA can improve cell attachment and mineralization in vivo, which suggests that nano-sized HA may be a better candidate for clinical use in terms of bioactivity[185, 186, 190, 667-669]. The size effects of nanodimensional HA on bone-related cells, as well as the influence of crystallinity of nano-sized HA were studied[507, 670]. Different nano-sized particles of HA, typically of 20 ± 5, 40 ± 10 and 80 ± 12 nm in diameter, were prepared and their effects on the proliferation of two types of bone-related cells, bone marrow mesenchymal stem cells (MSCs) and osteosarcoma cells (U2OS and MG63) were studied. The cell culture experiments showed an improved cytophilicity of the nanophase HA if compared to the

submicron-sized HA. A greater cell viability and proliferation of MSCs were measured for nano-sized HA, remarkably for 20 nm-sized particles. However, the opposite phenomenon occurred for bone tumour cells when nano-sized HA were co-cultured with cells. Nano-sized HA can inhibit proliferation of U2OS and MG63 cells and the inhibited strengths were inversely proportion to the particle size, i.e. smaller particles possessed a greater ability to prevent cell proliferation. This suggests that nano-sized HA can exhibit favorable cell proliferation to optimize biological functionality, in which the particle dimensions are believed to play a key role. These in vitro findings are of a great significance for the understanding of cytophilicity and biological activity of nano-sized particles during biomineralization[507]. Furthermore, an early osteogenic signal expression of rat bone marrow stromal cells appeared to be influenced by nanodimensional HA content[671]. On the other hand, there is a study on early bone healing, in which an importance of nanometer thick coatings of nanodimensional HA on titanium implants appeared to be insignificant if compared to the control[672].

Studies confirmed that nano-sized ACP had an improved bioactivity if compared to nano-sized HA since a better adhesion and proliferation of osteogenic cells had been observed on the ACP substrates[673]. However, in order to understand the influence of crystallinity of the nano-sized calcium orthophosphates on the osteogenic cells correctly, it was critical to use nano-sized ACP and HA of the same size distribution[670]. Thus, ACP and HA particles of ~ 20 nm size were synthesized and the effects of crystallinity were studied. The adhesion, proliferation and differentiation of MSC cells were measured on both ACP and HA films and compared at the same size scale. Surprisingly, more cells were adsorbed and proliferated on the films of the well crystallized nano-sized HA than those on the films of nano-sized ACP. Alkaline phosphatase activity assay and RT-PCR assay were also used to evaluate the differentiation of MSC cells. The results showed that the differentiation of MSC cells from osteoblasts was promoted significantly by nano-sized HA. These experimental phenomena clearly demonstrate that the crystallized phase of HA provides a better substrate for MSC cells than ACP, when the factor of size effect is removed. This new view on the relationship between the crystallinity of calcium orthophosphates and the responses of cells emphasized the importance of both size and phase control in the application of biomedical materials[670-673].

On the other hand, the chemical composition of the samples appears to be important. Interestingly, but in spite on the fact that the biological apatite of bones contains the substantial amount of carbonates, among investigated samples of nanocrystalline apatites, osteoclastic differentiation was found to be constrained on carbonate-rich samples, leading to smaller numbers of osteoclast-like cells and fewer resorption pits. Furthermore, the highest resorption rate was found for nanodimensional HA with a low carbonate content, which strongly stimulated the differentiation of osteoclast-like cells on its surface[674].

Cells are sufficiently sensitive and nano-scale alterations in topography might elicit diverse cell behavior[675-677]. How cells can recognize the particle size and other very small differences in the properties of nano-sized HA in these experiments remains unclear. Actually, determining the mechanisms whereby nano-sized particles of calcium orthophosphates and their sizes exert effects on bone-related cells will require further systematic studies.

7.3. Dental Applications

Dental caries is a ubiquitous and worldwide oral disease. At the initial stage of caries lesions, bacteria cause damage of dental enamel, which is the exterior coating of teeth and possesses remarkable hardness and resistance. As the most highly mineralized structure in vertebrate bodies, enamel is composed of numerous needle-like apatite crystals of nanodimensional sizes, which are bundled in parallel ordered prisms to ensure unique mechanical strength and biological protection. As a non-living tissue, the main constituent (~ 97 wt. %) of mature enamel is inorganic nanodimensional apatite so that enamel is scarcely self-repaired by living organisms after substantial mineral loss. Filling with artificial materials is a conventional treatment to repair damaged enamel. However, secondary caries frequently arise at the interfaces between the tooth and foreign materials[678].

Nanodimensional HA and CDHA are often considered as model compounds of dental enamel due to the chemical and phase similarities[148, 204, 205]. Therefore, enamel remineralization by using nanodimensional apatite or other calcium orthophosphates is suggested in dental research[679]. For example, toothpastes containing nanodimensional apatite could promote a partial remineralization of demineralized enamel[680-684], as well as possess some whitening effect[685]. Furthermore, nano-sized HA might be added to methacrylate-based root canal sealers[686], as well as to a fluoride-containing mouth rinse[687]. A remineralization potential of sports drink, containing nano-sized HA, was also investigated[688, 689]. A positive influence of addition of nanodimensional β-TCP against acid demineralization and promoted remineralization of enamel surface was detected as well[690]. Unfortunately, these chemically analogous compounds of enamel are not widely applied in clinical practices. The native structure of dental enamel is too complex to be remodeled and the synthesized apatite crystallites often have different dimensions, morphologies and orientations from the natural ones, which result in a poor adhesion and mechanical strength during dental restoration. Recent advances in biomineralization also indicate that features of smaller particles of nano-sized HA might approximate features of biological apatite more closely than features of the larger HA particles that are conventionally used[13]. For example, it has been demonstrated that nano-sized HA can be self-assembled to form enamel-like structures in the laboratory[225]. Therefore, a biomimetic technique is suggested as follows: the localized repair of the enamel surface can be improved by nano-sized HA (dimension of ~ 20 nm),

analogues to the basic building blocks of enamel rods. Furthermore, it is found that nano-sized HA can adsorb onto the enamel surface strongly and can even be integrated into the natural enamel structure[691].

It is surprising but nano-sized HA of ~ 20 nm can inhibit significantly a mineral loss from the enamel surface[228]. Without any treatment, the demineralization of the natural enamel surface was remarkable in acidic solution (pH ~ 4.5 ± 0.1, experimental period of 2 days) and damaged sites were observed. The mass loss rate was about 0.12 ± 0.04 mg/mm^2 per day. In contrast, a layer of nano-sized HA on the treated enamel surface was almost unchanged in acidic solution. The rate of mass loss of enamel coated by nano-sized HA approached zero (< 0.02 mg/mm^2 per day), which was beyond the sensitivity of the detection methods. Since the coating by nano-sized HA appeared to be insensitive to dissolution, the underlying enamel surface was well protected under slightly acidic conditions. Furthermore, the enamel surface coated by ~ 20 nm-sized HA had a hardness of 4.6 ± 0.4 GPa and an elastic modulus of 95.6 ± 8.4 GPa. These data appeared to be very similar to those of natural enamel samples, which are 4.2 ± 0.2 and 94.1 ± 5.4 GPa, respectively[228].

The similarity between ~ 20 nm-sized HA and building blocks of dental enamel results in a good fixation of artificial biomaterials to natural tissues. Moreover, the enamel structure appears to be reinforced by nano-sized HA since secondary caries formation is suppressed and hardness is retained[678, 692, 693]. This strategy may have prospective applications in dentistry as it offers an easy but effective method to reconstruct tooth enamel that is suffering from mineral losses. Generally, these studies also suggest that analogues of nanodimensional building blocks of biominerals should be highlighted in the entire subject of biomineralization.

In the case of nanodimensional DCPA, decreasing of DCPA particle dimensions were found to increase the Ca- and PO_4-ions releases from DCPA-based biocomposites. Therefore, biocomposites based on nano-sized DCPA, possessing both a high strength and good release of Ca- and PO_4-ions, may provide the needed and unique combination of stress-bearing and caries-inhibiting capabilities suitable for dental applications[546].

7.4. Other Applications

Several other applications of nanodimensional and nanostructured calcium orthophosphates are in progress, some of which are described here. For example, there is a report on a successful preparation of a multi-modal contrast agent based on nano-sized crystals of HA, which was engineered to show simultaneous contrast enhancement for three major molecular imaging techniques such as magnetic resonance imaging, X-ray imaging and near-infrared fluorescence imaging[694]. Furthermore, various compositions based on nanodimensional calcium orthophosphates have been already tested for cancer treatment[48, 60, 199, 354, 570, 695-697]. Besides, nanodimensional HA was found to be effective for proliferation inhibition of highly malignant melanoma cells[698] and human chronic myeloid leukemia K562 cells[699].

Surface modification of nanodimensional calcium orthophosphates was performed in order to modulate their colloid stability, prevent dissolution in the case of low pH, avoid inflammation, serve as an intermediate layer to allow strong bond formation between HA/polymer matrices and potentially enhance its bioactivity or improves its conjugation ability with special functional groups[12, 700-706]. Such surface modified nano-sized particles might be applied for oral insulin delivery[707].

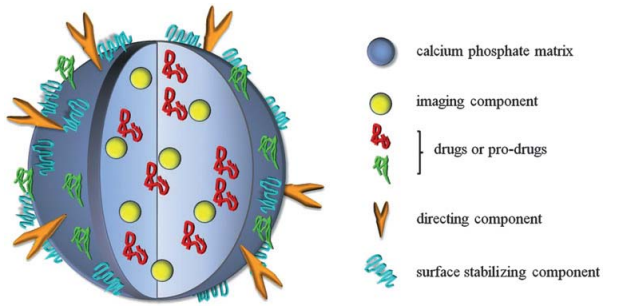

Figure 10. A generalized schematic setup of a nanodimensional particle of a calcium orthophosphate suitable for both imaging and drug delivery purposes. Reprinted from Ref.[756] with permission

In another aspect, many strategies have been employed to load various agents, *i.e.* therapeutic, bio imaging, *etc*., to nanodimensional calcium orthophosphates (mainly, apatites)[708]. In summary, these strategies can be broadly categorized into two main approaches. One approach is to load these agents during the synthesis – so called *in situ* loading. This is done by adding the desired agent(s) to the reaction mixture before the formation of a nanodimensional calcium orthophosphate is completed. The second approach is to load the agent(s) only after a nanodimensional calcium orthophosphate has been fully synthesized or, in other words, after the synthesis process – so called *ex situ* loading. This is mainly done through surface adsorption where the agents are adsorbed onto the surfaces of pre-synthesized nanodimensional particles[709]. Therefore, due to established biocompatibility, ease of handling and notorious adsorption affinity, nano-sized calcium orthophosphates have been applied as non-viral carriers for drug delivery and gene therapy[133, 203, 289, 318, 325, 511, 542, 559, 600d, 695, 710-721]. After loading with genes or drugs, nanodimensional calcium orthophosphates provide a protective environment that shields them from degradation while providing a convenient pathway for cell membrane penetration and controlled release of the genes or drugs[512]. The experimental results proved that nanodimensional calcium orthophosphates possessed a higher penetration rate into cell membranes and their transfection efficiency could be 25-fold higher than that of the micron-sized particles. Furthermore, due to the larger specific surface areas, nanodimensional calcium orthophosphates can hold larger load amounts of drugs than coarser particles. These results indicate the po-

tential of nano-sized calcium orthophosphates in gene delivery and as drug carriers[512, 722-725]. Since a charge of the particles influences their ability to pass through the cellular membrane and a positive charge is beneficial, positively charged nano-sized particles of calcium orthophosphate/polymer biocomposites were successfully applied for photodynamic therapy[726]. Furthermore, nanodimensional calcium orthophosphates can be stably loaded with radioisotopes[318, 727].

A transfer of functional foreign nucleic acids (DNA or RNA) into nuclei of living cells (transfection) with the aim of repairing missing cell function and to provide means to enhance or silence gene expression is currently used extensively in the laboratory and is fast becoming a therapeutic reality. As nucleic acids alone are unable to penetrate the cell wall, efficient carriers are required[728, 729]. Nanodimensional calcium orthophosphates can be represented as a unique class of the non-viral vectors, which can serve as efficient and alternative DNA carriers for targeted delivery of genes[289, 696, 697, 708, 714, 730-742] and cells[567, 743-749]. The standard transfection method using calcium orthophosphates, first introduced by Graham and van der Eb in 1973[748], is still used in biochemistry. It involves a straightforward *in situ* precipitation of calcium orthophosphate/DNA aggregates. A similar experimental approach is used to load calcium orthophosphates by drugs[719]. Interestingly, but the transfection efficiency of nanodimensional calcium orthophosphates were found to depend on Ca/P ionic ratio: namely, calcium orthophosphates with Ca/P = 1.30 ratio exhibited a fourfold increase in the transfection efficiency over the ones with Ca/P = 1.65 ratio composition[289]. This data emphasizes the importance of understanding the interaction between calcium orthophosphates and DNA to optimize the DNA uptake and its channeling to the nucleus of the cell. Besides, it has been demonstrated that surface modified particles of nano-sized calcium orthophosphates can be used *in vivo* to target genes specifically to a liver[750]. Attachment of galactose moiety onto the particle surface has increased the targetability of the nano-sized particles. Furthermore, this surface modification makes it possible for site-specific gene delivery[750, 751]. Assemblies of block-copolymer/nano-sized calcium orthophosphate were prepared and used for cell transfection; a high biocompatibility of this system was emphasized[752]. Structures that are even more complex are known as well[753-755]. A schematic drawing of a functionalized nano-sized particle suitable for both imaging and drug delivery purposes is shown in Fig. 10[756]. Furthermore, vaccination to protect against human infectious diseases may be enhanced by using adjuvants that can selectively stimulate immuno-regulatory responses and nano-sized particles of calcium orthophosphates were found to be suitable for such purposes[757, 758].

In all these new applications of nano-sized calcium orthophosphates, knowledge of the exact internalization pathway into the cells represents the first necessary step towards the detailed investigation and optimization of the functional mechanism. The main groups of pathways into the cell are diffusion, passive and active transport, as well as a number of endocytic mechanisms[695]. Bigger particles of far above 10 nm are internalized by eukaryotic cells through the endocytic pathways including phagocytosis, macropinocytosis, clathrin-mediated endocytosis and non-clathrin-mediated endocytosis such as internalization via caveolae. To date, the exact internalization pathway of nano-sized calcium orthophosphates into cells has not been determined and there are many questions that remain to be answered, particularly, concerning possible interactions of calcium orthophosphates with nucleic acids. Furthermore, the mechanisms of cellular uptake and transport to the cell nucleus of calcium orthophosphate/DNA nanodimensional complexes remain unclear either. Therefore, there is a need to conduct a focused study on the synthesis of various forms of nano-sized calcium orthophosphates that could elucidate the mechanisms of binding, transport and release of attached plasmid DNA for understanding the gene delivery method. Research is also warranted to understand the tracking of DNA intracellularly[745] to understand the release and transport of DNA into cellular nuclei.

Concerning the healing abilities of nano-sized calcium orthophosphates, an *in vitro* inhibiting effect and even apoptotic action of un-functionalized nano-sized HA of about 50 nm diameter on a hepatoma cell line in the concentration range of 50 – 200 mg/1 was reported[759]. A similar inhibiting effect was discovered for discrete nano-sized particles of HA, which appeared to cause apoptosis of leukemia P388 cells[119] and rat macrophages[760]. This effect might be due to a harmful increase in the intracellular calcium concentration. However, the correlation between the particle dimensions and the apoptotic action of nano-sized calcium orthophosphates appears not to be straightforward. Namely, the apoptosis efficacy of nanodimensional particles of HA of various sizes was found to decrease in the order of 45 nm > 26 nm > 78 nm > 175 nm[761].

Hollow nano-sized spheres are extremely attractive constructions because they can greatly enhance the load quantity. Though these novel biomaterials can improve the total intake of drugs, they also bring new problems, *e.g.*, uncontrolled release kinetics and unreasonable metabolism pathway of the carriers[762]. In order to solve these problems, calcium orthophosphates were selected as suitable biomaterials to construct nanodimensional spheres hollow inside[198, 541, 542, 717, 763, 764]. Such spheres with dimensions ranged from 110 to 180 nm were synthesized by an ultrasonic-assisted wet chemical reaction in the presence of a modifier[765]. In addition, they might be prepared through emulsions[766]. Transmission electron microscopy investigations revealed that the uniform nanodimensional spheres were formed and they were well dispersed in the solutions. Thickness of the shells was about 45 nm; thus, they always had ~ 60 nm-sized internal cavities, which could be used to load drugs. The hollow spheres appeared to be stable in both air and aqueous solutions without ultrasonic application.

However, when an ultrasonic treatment (40 kHz, 150 W) was applied, the hollow structures deconstructed to form pin-like nano-sized crystals of calcium orthophosphates[765]. During this transformation, the encapsulated drugs and chemicals are released[559, 765]. Different from a free and slow diffusion of encapsulated drugs from the cavity through the shells[199], the release kinetics in this system was triggered and controlled by ultrasound. Furthermore, the power density of ultrasound can conveniently regulate the release dynamics. Besides, the formed pin-like nano-sized crystals of calcium orthophosphates had similar behavior to the biological apatite of bones. Thus, a combination of the hollow calcium orthophosphate nanospheres and ultrasonic treatment might provide a good system for drug delivery and release[765].

8. Non-Biomedical Applications of the Nanodimensional and Nanocrystalline Calcium Orthophosphates

Just a few publications are available on non-biomedical applications of the nanodimensional and nanocrystalline calcium orthophosphates. For example, nano-sized particles of calcium orthophosphates with a mean size of 150 ± 20 nm filled with a solution containing luminol, haematin and fluorescein were found to improve the ease and accuracy of H_2O_2 sensing[767]. Besides, nanodimensional HA particles were tested as a component of a green slow-release fertilizer composition[768]. Also, addition of nanodimensional HA remarkably inhibits desorption of heavy metals from soils, which increases their geochemical stability in metal contaminated soils[769]. Furthermore, nanodimensional HA was found to hold a great potential to remove cationic heavy metal species from industrial wastewater[770-774]. Finally yet importantly, nanodimensional and nanocrystalline calcium orthophosphates occasionally might possess a catalytic activity[775, 776].

9. Summary and Perspectives

As the basic building blocks of calcified tissues of mammals, nano-sized calcium orthophosphates of the apatitic structure play an important role in the construction of these biominerals. Therefore, they appear to be almost the ideal biomaterials due to their good biocompatibility and bioresorbability. Even more enhanced applications are expected in drug delivery systems[777]. However, there is still an unanswered question concerning their structure: whether the majority of nanodimensional calcium orthophosphates appear to be almost amorphous (according to numerous results of X-ray diffraction studies) due to their nanoscopic dimensions of well-crystallized structures or due to a really amorphous (*i.e.*, retaining only a short-range order at the scale of few atomic neighbors) matter? A good attempt to discuss this topic is available in literature[778], where the interested readers are referred to.

In future, an ability to functionalize surfaces with different molecules of varying nature and dimensions by means of their attachment to cells will enable them to act selectively on biological species such as proteins and peptides. The capability of synthesizing and processing of nanodimensional and nanocrystalline calcium orthophosphates with the controlled structures and topographies, in attempts to simulate the basic units of bones and teeth, will provide a possibility of designing novel proactive bioceramics necessary for enhanced repair efficacy. The various primary positive results on the biocompatibility and biomimicity of novel nanostructured bioceramics merit further confirmations. Namely, much work remains to be undertaken to address the following key challenges and critical issues of nanodimensional and nanocrystalline calcium orthophosphates[779]:

- Consistency of the processing technologies;
- Optimization the structure and properties mimicking bones;
- Matching the strength of nanodimensional and nanocrystalline constructs with those of bones in order to provide a uniform distribution of stresses (load sharing);
- Optimizing bioresorption without comprising the mechanical properties;
- Assessing the inflammatory response to validate their biosafety.

Furthermore, substantial research efforts are required in the analysis of cells and their different behaviors with regard to their interactions with nanodimensional and nanocrystalline calcium orthophosphates[779]. An important but still unsolved question is how the cells can recognize the particle dimensions and crystallinity of nano-sized calcium orthophosphates. What is the signal for nanodimensional biomaterials to promote cell proliferation and differentiation and how can the pathways be found out? According to the experiments results on transfection, nano-sized particles can enter into cells readily but many details of this process remain unclear. Namely, the pathways for the nano-sized particles to enter the cells through the membranes should be revealed[780]. A greater influence of the hydrated surface layer with labile ionic species of smaller particles and crystals (see section *5. The structure of the nanodimensional and nanocrystalline apatites* for the details) might be another possible option, to be confirmed experimentally. Then, it is important to examine the metabolism process of nano-sized calcium orthophosphates inside cells, so the existing forms of these particles during the biological processes could be understood. Further, a critical step will be the investigation of possible changes of gene or protein expression in the absence and presence of various nano-sized calcium orthophosphates, which may directly be related to cell proliferation and differentiation[13].

Understanding of the interactions between nano-sized particles and living cells is still a great challenge[779].

Namely, elucidating mechanisms, by which cells internalize and process nanodimensional particles, is of great importance for understanding their potential toxicity and for improving the targeted delivery of nanodimensional particles for biomedical applications. Already, some data are available that clathrin-mediated endocytosis might be responsible for the uptake of nano-sized HA[695]. In another study, nanodimensional particles of HA were sequestered within a specialized membrane-bound surface-connected compartment, directly connected to the extracellular space[781]. Future studies will focus on (1) the detailed interfacial structure of nanodimensional calcium orthophosphates and the specific adsorption of proteins or other matrices; (2) an uptake processes of the nano-sized particles by cells; (3) metabolism of nano-sized calcium orthophosphates inside the cells and its possible interference with physiological reactions. Another important topic is a biological security of nano-sized particles in general[144, 145, 782, 783] and those of calcium orthophosphates particularly[178, 376, 784]. For example, toxicity of nano-sized HA was found to vary considerably, which was related to their physico-chemical properties. Furthermore, cell death correlate strongly with the load of nano-sized particles. Namely, the biological effects of rod-shaped apatite, 50 – 80 nm in length, were investigated on human monocyte-derived macrophages[178]. High concentrations of apatite (200 nano-sized particles per cell) were incubated for 24 hours with the macrophages in both serum and serum-free conditions. This induced high levels of lactate dehydrogenase release, which is an indicator of cellular damage. However, lower concentrations (20 and 2 nano-sized particles per cell) of the rod-shaped apatite did not affect the cell viability similarly to the control group that did not contain nano-sized apatite[178]. Similarly, intracellular dissolution of nano-sized HA as a function of time suggests that increased cytoplasmic calcium load is likely to be the cause of cell death[784]. Furthermore, nano-sized calcium orthophosphates were found to interfere with cell cycle of cultured human ovarian granulosa cells thus increasing cell apoptosis[785]. That pilot study suggested that effects of nano-sized particles on ovarian function should be extensively investigated. Additional examples of cytotoxicity experiments of nanodimensional calcium orthophosphates are well described in a recent review[709].

To finalize this topic, one should stress that, *in vivo* evaluation of nano-sized particles includes the particle's activity, biodistribution and pharmacokinetic properties[786]. Ultimately, all these properties are determined by dimensions, surface charge, morphology and surface chemistry. Furthermore, nano-sized particles penetrate and leave biological organisms more readily using a number of pathways. Namely, very small (< 10 nm) particles are generally eliminated from the body via renal clearance, *i.e.* being filtered through the kidneys and eliminated through urine, while nano-sized particles of larger dimensions are phagocytized by tissue macrophages of the reticuloendothelial system in the liver and spleen[713]. For example, intravenously administered nanodimensional (~ 40 nm and ~ 200 nm) rod-shaped crystals of apatite showed clearance from the bloodstream within two hours, with ~ 90 % of them being cleared in the first 10 minutes post injection; those nanodimensional crystals of apatite were observed primarily in the liver with a minority seen in the spleen[318]. These results indicate that bloodstream clearance occurs rapidly for a wide range of nanodimensional sizes. The accumulation of nanodimensional (50 – 100 nm in size) apatite in the liver was also noted in another study[510].

Thus, understanding the biological influence of nano-sized and nanocrystalline calcium orthophosphates is essential for a future development of bionanotechnology[787]. This interdisciplinary approach is very complicated and the effective collaboration of scientists from different disciplines is the key[13].

10. Conclusions

With a high surface area, un-agglomerated nanodimensional and nanocrystalline bioceramic particles are of interest for many applications including injectable or controlled setting bone cements, high strength porous or non-porous synthetic bone grafts and the reinforcing phase in biocomposites that attempt to mimic both the complex structure and superior mechanical properties of bone. Therefore, nano-sized and nanocrystalline calcium orthophosphates have already gained much regard in the biomedical field due to their superior biocompatibility and biomechanical properties. This is easily seen from a permanent increasing of the amount of publications. At present, apatites (HA and CDHA) and β-TCP are the major calcium orthophosphates used in clinics. Currently, nanodimensional apatites are used primarily as bioactive coatings on bioinert materials like titanium and its alloys, in bone tissue repairs and implants, as well as for drug delivery purposes. The nano-sized β-TCP exhibits a significant biological affinity and activity and responds very well to the physiological environment. A lot of research is expected for much enhanced applications of the nanodimensional and nanocrystalline calcium orthophosphates for both drug delivery systems and as resorbable scaffolds that can be replaced by the endogenous hard tissues with the passage of time[147, 787].

Although the nanostructured biomaterials may have many potential advantages in the context of promoting bone cell responses[534-536, 677], it is important to remember that studies on nanophase materials have only just begun; there are still many other issues regarding human health that must be answered. Since particles of very low size have higher reactivity and effectiveness, a rapid technical development of nanometer-scaled particles in the biomedical field leads to concerns regarding the unknown risks of such materials[782, 783]. These nano-sized particles might induce inflammatory reactions, cytotoxicity, oxidative stresses or thrombogenesis when injected for drug delivery purposes. Namely, nano-sized particles may enter the human body through

pores and may accumulate in the cells of the respiratory or other organ systems (when becoming dislodged through wear debris) and the health effects are yet to be largely known. This could happen during commercial-scale processing of the nano-sized particles as well as using these materials as implants[790]. Besides, nano-sized particles might be the objects whose existence has not been assumed by living body defense system[18, 144, 145]. Up to now, only a small number of short-term and small-scale health effects of single nanodimensional materials have been examined in toxicological studies, usually of the lungs[783]. Therefore, prior to clinical applications, any toxicity concerns of the nanophase materials[791-796] need to be overcome.

In summary, despite the challenges that lie ahead, significant evidences now exist elucidating that nanophase biomaterials represent an important growing area of research that may improve bonding between the implants and the surrounding tissues. It has proven to be a versatile approach that can increase bone cell functions on a wide range of orthopedic implant chemistries. Even if the nanodimensional and nanocrystalline calcium orthophosphates do not provide the ultimate answer for increasing bone cell responses (due to some potential problems as mentioned above), researchers have learned a tremendous amount of information concerning bone cell recognition with nanostructured surfaces that will most certainly aid in improving orthopedic implant efficacy[144, 145].

11. Post-Conclusion Remarks

According to Prof. D. F. Williams[115], the term "nanomaterial" should not exist because it is senseless (see section *2. General information on "nano"*). Following this logic, the term "nanoapatite" is senseless as well. However, it is presented in the titles of several publications, namely Refs.[606, 629, 653, 667]. In a slightly modified form, the term "nano-apatite" is presented in the titles of several other publications, namely Refs.[89, 100, 226, 511, 631, 735, 789]. Furthermore, similar terms "nano-HA"[103, 575, 608, 659, 681, 692], "nano-hydroxyapatite"[42, 87, 91, 92, 96, 97, 102, 119, 190, 191, 294, 295, 314, 338, 451, 459, 486, 492, 578, 583, 606, 627, 628, 641, 664, 666, 677, 682, 685, 687, 693, 698, 701, 703, 705, 770, 773], nano-fluorapatite[104, 684] and "nanohydroxyapatite"[86, 93, 99, 162, 201, 239, 240, 242, 246, 253, 274, 320, 329, 362, 462, 576, 656, 664, 764] are presented in the titles of still other publications. Presumably, it is wiser not to use these terms anymore.

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