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Hydroxyapatite and Hydroxyapatite-Based Ceramics

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Abstract—Data are summarized on the synthesis of hydroxyapatite (HA) by wet-chemical processes, solid-state reactions, and hydrothermal treatment. The conditions for HA preparation via precipitation from solutions of calcium chloride, dibasic ammonium phosphate, and aqueous ammonia are discussed at length. Detailed analysis of the fabrication and properties of calcium-phosphate-based ceramics is presented. The techniques for producing dense and porous HA ceramics are considered. The fabrication and medical applications of HA granules are discussed. Data are presented on HA-based composites.

INTRODUCTION

The development of advanced materials for biomedical applications is among the most important problems facing modern materials engineering [1–9]. The greatest potential for bone substitution is shown by materials based on hydroxyapatite (HA), $Ca_{10}(PO_4)_6(OH)_2$, which can develop tight bonding with bone tissue, exhibits osteoconductive behavior, is stable toward bioresorption, and has no adverse effects on the human organism [1–5, 10]. The biological behavior of HA ceramics depends on many factors, in particular, on their chemical and phase composition, microstructure, pore size, and pore volume.

In surgery, use is made of both dense and porous ceramics, depending on the requirements for the bearing strength of implants. Porous ceramics have low strength and are, therefore, suitable for implantation into tissues which experience no substantial stresses (operations for the middle ear and some maxillofacial applications) and for local drug delivery [11–16]. Pores in implants are necessary for osteointegration, a process which depends on the pore size, volume, and interconnectivity. It is believed that the minimum pore size for bone ingrowth into implants is 100–135 μm. With increasing porosity and pore interconnectivity, the bone ingrowth and fixation processes become more effective. The division of osteogenic cells is preceded by protein adsorption. Consequently, the presence of small, submicron pores, comparable in size to blood-plasma proteins must also favor biointegration [11, 17, 18]. Thus, the pore-size distribution in bioceramics should be bimodal.

Of particular interest are HA granules, which find application in maxillofacial surgery and implantable drug delivery systems. There are various techniques for producing granules: crushing followed by pelletizing, spray drying, quenching in liquids, and hydrothermal synthesis. The last technique may yield irregularly shaped or nearly spherical granules. Spherical geometry is preferable for avoiding inflammatory processes and for achieving osteointegration [13, 19].

Ceramics can serve as a basis for producing composites. Considerable research effort is focused on HA-matrix composites reinforced with fine particles, microlamellae, or fibers with the aim of raising their strength to a level necessary for hard tissue replacement implants.

In this review article, we summarize the available information about the synthesis, structure, and properties of HA and the fabrication and mechanical properties of HA-based ceramics and composites.

STRUCTURE AND PROPERTIES OF BONE

Precise knowledge of the physical, chemical, and mechanical properties of bone is critical for the development of new bone substitute materials.

Human bone is a complex, actively functioning, constantly varying system. The structural–functional unit of bone is an osteon, a microscopic system of osseous tubes (cylinders) inserted in one another. In the center of the system, there is a nutrient canal 10 to 100 μm in diameter, containing a blood capillary. The number of osseous tubes constituting an osteon may vary from 4 to 20. Osteons form *substantia compacta*, with spongy bone as a porous matrix. Bone is covered with a thin layer of connective tissue (periosteum), containing vessels and nerves, which reach the bone bulk

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Table 1. Bone composition (%) of adults

Calcium	34.8
Phosphorus	15.2
Sodium	0.9
Magnesium	0.72
Potassium	0.03
Carbonates	7.4
Fluorine	0.03
Chlorine	0.13
Pyrophosphates	0.07
Other elements	0.04

Table 2. Mechanical properties of hard tissues

Tissue	Compressive strength, MPa	Tensile strength, MPa	Modulus of normal elasticity, GPa
Cortical tissue of bone	88–164	89–114	3.9–11.7
Dentin	295	52	18.2
Enamel	384	10	82.4

through so-called nutrient foramens. The inner layer of periosteum contains a large amount of osteoblasts, which are responsible for bone growth [10, 20, 21].

Bone is a ceramic–organic composite consisting mainly of collagen (20%), calcium phosphate (69%), and water (9%). Other organic substances, such as proteins, polysaccharides, and lipoids, are present in small amounts [22]. Collagen is located in bone tissue and has the form of fibrils 100 to 2000 nm in diameter. Calcium phosphate in the form of crystallized HA ensures bone rigidity. The HA crystals have the shape of needles 40–60 nm in length, 20 nm in width, and 1.5–5 nm in thickness [10]. The mineral component of bone is similar to HA but contains fluoride, magnesium, sodium, and other ions as impurities (Table 1) [1].

Bone is rather nonuniform in microstructure and mechanical properties. The latter depend on porosity (5 to 95%), the degree of mineralization, and orientation of collagen fibers [21]. For example, cortical bone is a nanostructured composite made up of an HA-based matrix and collagen fibers. The matrix has a layered microstructure, which, in turn, provides a basis for oriented cylindrical formations on a macroscopic scale [23]. This complex structure is responsible for the high strength and fracture toughness of bone tissue, in line with the known concepts embodied in the fracture mechanics of brittle-matrix composites [24–26]. Hard dental tissue contains lesser amounts of organic substances, but the mineral component of dentin consists of cylindrical HA crystals [1].

Table 2 summarizes data on the mechanical strength and modulus of normal elasticity of cortical bone, dentin, and enamel. The mechanical properties of these tissues differ owing to the difference in composition and microstructure. The compressive strength of the spongy substance in the proximal region of the tibia is as low as 3.5 MPa, that of the spongy substance in the head of the hip joint is 1–15 MPa, and that of the cortical bone in the superior articular surface of the tibia is 3–23 MPa [1, 10]. According to some estimates [1], the strength of cortical bone may attain 150 MPa.

SYNTHESIS AND PROPERTIES OF HA

HA powder can be prepared wet chemically, by solid-state reactions, and by hydrothermal treatment [3, 7, 27].

The preparation technique has a significant effect on the powder morphology, specific surface, stoichiometry, and crystallinity.

Wet-chemical procedures involve HA precipitation via mixing aqueous solutions of compounds containing Ca^{2+} and PO_4^{3-} ions at pH > 7, followed by holding the precipitate under appropriate conditions. The most commonly used Ca^{2+} sources are $CaCl_2$, $Ca(NO_3)_2$, $Ca(OH)_2$, $CaCO_3$, $CaSO_4 \cdot 2H_2O$, and $(CH_3COO)_2Ca$; typical phosphorus sources are H_3PO_4, $NH_4H_2PO_4$, $(NH_4)_2HPO_4$, Na_3PO_4, and K_3PO_4. The pH of the solution is adjusted with ammonia gas, NH_4OH, or NaOH. Characteristically, in the initial stage of the process the precipitate differs in composition from HA. Storage of the calcium phosphate precipitate under appropriate conditions increases the Ca : P ratio and leads to HA crystallization. The rate of this process depends on many factors, including the concentrations of the starting salts, mixing sequence and rate, solution pH, reaction temperature, and holding time. In view of this, control over all synthesis conditions is critical for obtaining reproducible results.

Among the many wet-chemical techniques, there are several classical procedures which have been described, with some modifications, in most foreign reports and patents. One such procedure uses $Ca(NO_3)_2$ as the calcium source and is based on the reaction [28–30]

$$10Ca(NO_3)_2 + 6(NH_4)_2HPO_4 + 8NH_4OH = Ca_{10}(PO_4)_6(OH)_2 + 20NH_4NO_3. \quad (1)$$

Klyuchnikov [31] recommended the reaction

$$10Ca(NO_3)_2 + 6KH_2PO_4 + 14NaOH = Ca_{10}(PO_4)_6(OH)_2 + 6KNO_3 + 14NaNO_3 + 12H_2O. \quad (2)$$

After gradual crystal growth from solution, the HA precipitate is collected on a filter, washed with water and ethanol, and dried at 40–50°C.

Kibal'chits and Komarov [32] described high-speed HA synthesis using potassium compounds instead of sodium and ammonium compounds. They obtained HA by rapidly mixing $Ca(NO_3)_2$ and Ca_3PO_4 solutions. The Ca : P atomic ratio was initially 1.58 and increased to 1.67 h over a period of 6 h.

Another group of classical wet-chemical processes are based on the reaction [33]

$$10Ca(OH)_2 + 6H_3PO_4 = Ca_{10}(PO_4)_6(OH)_2 + 18H_2O. \quad (3)$$

This reaction is also described in foreign (mainly Japanese) patents. In some patents, $Ca(OH)_2$ and H_3PO_4 are partially or fully replaced by other reagents. For example, Aizawa *et al.* [34] prepared high-quality HA by reacting a stoichiometric mixture of $Ca(OH)_2$, $Ca_3(PO_4)_2$, $(NH_4)_3PO_4$, and H_3PO_4, followed by ultrasonic treatment at 10–30 kHz. Kokubo [35] described HA formation on the addition of $Ca(OH)_2$ to an aqueous $Ca_3(PO_4)_2$ suspension with stirring in the temperature range 5 to 100°C in an inert atmosphere. The mixture is adjusted to pH 10 by adding $Ca(OH)_2$ until the Ca : P ratio is 1.6. Next, the reaction is run until the Ca : P ratio attains 1.67, adjusting pH to 7–11.

Orlovskii *et al.* [36] investigated HA formation from $CaCl_2$, $(NH_4)_2HPO_4$, and aqueous ammonia. The system was studied by the solubility method in Tananaev's residual-concentration approach. According to their results, $Ca_3(PO_4)_2$ and/or HA can be formed, depending on precipitation conditions (initial composition, solution pH, etc.).

In the last group of classical wet-chemical techniques for the preparation of HA, use is made of the reaction between $CaCO_3$ and aqueous H_3PO_4. A noteworthy procedure for HA synthesis is $CaCO_3$ calcination between 800 and 1300°C for 0.5–10 h, followed by cooling the resultant CaO to below 500°C in an inert atmosphere and slaking in a turbulent flow in an aqueous solution [3].

The alkoxide route is known to have great potential for the synthesis of mixed oxides and to offer strong possibilities for improving the purity and reducing the particle size of materials [37]. Turova and Yanovskaya [38] reported HA synthesis through the formation of a solution of calcium ethoxide, $Ca(EtO)_2$, followed by reaction with phosphoric acid and annealing of the product in air:

$$Ca \xrightarrow{EtOH} Ca(EtO)_2 \quad (4)$$
$$\xrightarrow{H_3PO_4} Ca_x(PO_4)_y(EtO)_z \cdot n\text{EtOH} \xrightarrow{H_2O,\ t} Ca_5(PO_4)_3OH.$$

Before annealing, the reaction product is amorphous as determined by x-ray diffraction.

The above examples demonstrate that the wet-chemical techniques of HA synthesis involve many process variables, which has an adverse effect on the reproducibility of the process and makes it difficult to maintain the stoichiometric Ca : P ratio during synthesis and to obtain HA powder with controlled chemical and physical properties. The main process parameters are the pH of the solution and the reaction temperature and duration.

Dry processes of HA preparation involve solid-state diffusion during calcination of mixtures containing appropriate amounts of Ca^{2+} and PO_4^{3-} ions in the temperature range 1000–1300°C. Water vapor is used as a source of OH groups. For example, HA can be synthesized from alkaline-earth (Ca, Sr, or Ba) salts and H_3PO_4 [3].

HA can also be prepared by calcining mixtures of $Ca_3(PO_4)_2$ and $CaCO_3$, CaP_2O_7 and $CaCO_3$, or $CaHPO_4 \cdot 2H_2O$ and CaO between 900 and 1300°C in the presence of water vapor [39].

Dry processes ensure the formation of stoichiometric HA (Ca : P = 1.67) but require much power (high temperatures) and time. Moreover, the products of such processes typically lack homogeneity.

In many works, HA was synthesized by hydrothermal processes, which involve reactions at high temperatures and pressures and require expensive equipment [3, 40–42]. Typical starting reagents are $CaCO_3$ and ammonium phosphate or $Ca(NO_3)_2$ and $(NH_4)_2HPO_4$ in aqueous ammonia. Feenstra and de Groot [43] and Jarcho *et al.* [44] used calcium pyrophosphate, $Ca_2P_2O_7$. In the latter work, $Ca_2P_2O_7$ was reacted with H_3PO_4. According to Yubao *et al.* [45], stoichiometric HA can be prepared under hydrothermal conditions by the reaction

$$3Ca_2P_2O_7 + 4CaO + H_2O = Ca_{10}(PO_4)_6(OH)_2. \quad (5)$$

Yubao *et al.* [46] analyzed the effect of NH_4OH on the growth rate of HA crystals. In the absence of NH_4OH, the growth of prismatic crystals took 96 h even at 500°C and 80 MPa. The introduction of NH_4OH was found to substantially raise the reaction rate. Hydrothermal synthesis is commonly carried out in gold capsules. The starting reagents and H_2O must occupy 50–60% of the autoclave volume, depending on the synthesis temperature.

In addition to the three groups of techniques described above, there are a number of processes which are used less frequently. For example, HA can be obtained by hydrolyzing a 2 : 1 mixture of $K_4P_2O_7$ and $CaCl_2$ for two weeks [40].

There is also considerable interest in HA synthesis via freeze-drying a mixture of calcium acetate and triethyl phosphate [3]. The method offers the possibility of preparing fine-particle, high-porosity materials.

Thus, there are three main approaches to preparing HA powder, each encompassing a variety of processes, among which the wet-chemical processes are the simplest.

HA belongs to the apatite group and has the composition $Ca_{10}(PO_4)_6(OH)_2$. The structure of fluorapatite, a

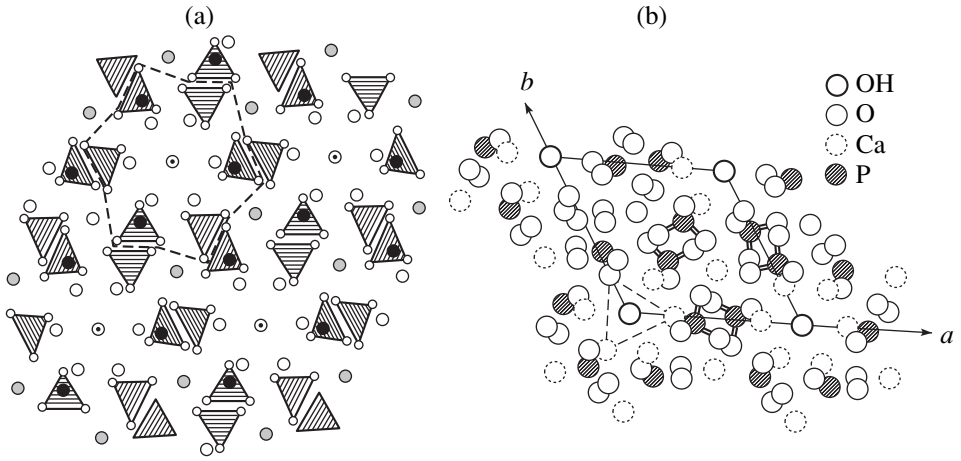

Fig. 1. (a) Atomic structure of HA and (b) its projection along the *c* axis.

structural analog of HA, was first determined by Náray-Szabó. His works laid the foundation for subsequent x-ray diffraction studies of HA, fluorapatite, and chlorapatite, and his conclusions about the structure of fluorapatite were confirmed by later refinements. HA has a hexagonal structure (sp. gr. $P6_3/m$, two formula units per unit cell) with lattice parameters $a = 0.942$ nm and $c = 0.687$ nm. The ideal formula of HA is $Ca_{10}(PO_4)_6(OH)_2$. The atomic structure of HA and its projection along the *c* axis are shown in Fig. 1. The Ca atoms reside in two positions: six atoms per unit cell are in position Ca(II) and four atoms are in position Ca(I). Ca(I) is located on the threefold axis and is coordinated by nine oxygens of phosphate groups. The Ca(II) atoms form equilateral triangles. Within each triangle, a fluorine atom lies centered on the hexagonal axis; the OH groups reside in an off-center position [3].

A fundamental problem in the chemistry of apatites, including HA, is that of isomorphous substitutions. Comparison studies of HA, fluorapatite, and chlorapatite are of considerable interest in gaining greater insight into the growth of new tissue. As shown earlier [47], fluoride ions substitute readily for hydroxyl groups in the structure of $Ca_{10}(PO_4)_6(OH)_2$ because fluorapatite is thermodynamically more stable than HA. The structural–thermochemical model proposed in [48] was used to examine the energetics of the interaction between fluoride, chloride, and hydroxide ions in the Ca channels of HA and the interaction between the Ca channels and PO_4^{3-} groups. The HA structure can be divided into two subsystems: Ca channels containing F^-, Cl^-, or OH^- ions and the calcium phosphate framework. The incorporation of fluoride and chloride ions into the framework is unlikely, while CO_3^{2-} ions may substitute for PO_4^{3-} groups. The two subsystems (Ca channels and framework) are interdependent, and isomorphous substitutions in the Ca channels depend on the energy (strength) of the P–O bonds in the framework.

It follows from the above that various substitutions are possible in HA. Certain substituents may occupy, fully or partially, different positions in the HA structure [3, 10].

HA-BASED CERAMICS

A question of major importance in the development of implant materials is their mechanical strength. Bioceramics must be close in strength to bone tissue; exhibit a high fatigue resistance under both static and dynamic loads, especially in the corrosive medium of the human organism; and possess a good fracture toughness. Of particular importance is the problem of biomechanical compatibility. For example, the modulus of normal elasticity of spongy bone varies from 0.005 to 0.5 GPa, depending on its location and age [10, 21, 49]. At the same time, the elastic modulus of corundum ceramics for medical applications is about 380 GPa. The difference by a factor of 7600 (a factor of 55 with respect to the cortical part of bone tissue) leads to the shielding of bone tissue from mechanical load by the implant. This has an adverse effect on bone tissue, which must experience mechanical stresses in order to remain viable. Moreover, the resultant stress gradient may cause fracture along the bone–implant interface [49]. A great hardness of implanted materials may accelerate the rate of bone wear.

Dense HA ceramics. Calcium-phosphate-based ceramics can be fabricated by various techniques, depending on the desired microstructure and properties of the material [6, 10]. To produce implants capable of withstanding mechanical loads, it is reasonable to use densely sintered ceramics, which surpass porous ceramics in strength. Ceramics should consist of fine

grains because, according to the well-known Hall–Petch formula [50]

$$\sigma = \sigma_0 + bd^{-1/2}, \quad (6)$$

where σ_0 and b are constants and d is the grain size, mechanical strength increases with decreasing grain size. Dense ceramics can be produced by pressing or slip casting followed by pressureless sintering or hot uniaxial or isostatic pressing [10, 51–55]. The density of the ceramics thus fabricated approaches theoretical density (3.16 g/cm^3 [3]).

HA sintering is complicated by the loss of OH^- radicals and high-temperature HA decomposition [56–58]. The former process can be represented by the reaction scheme

$$\begin{aligned} &Ca_{10}(PO_4)_6(OH)_2 \\ &= Ca_{10}(PO_4)_6(OH)_{2-2x}O_x\square_x + xH_2O, \end{aligned} \quad (7)$$

where $\square_x$ designates a vacancy and $x < 1$.

Oxyhydroxyapatite, $Ca_{10}(PO_4)_6(OH)_{2-2x}O_x\square_x$, forms at 900°C in air and at 850°C in an atmosphere free of water vapor.

At high temperatures, HA may decompose into $Ca_3(PO_4)_2$ and $Ca_4P_2O_9$ by the reaction

$$\begin{aligned} Ca_{10}(PO_4)_6(OH)_2 &= 2\alpha\text{-}Ca_3(PO_4)_2 \\ &+ Ca_4P_2O_9 + H_2O. \end{aligned} \quad (8)$$

It is believed that HA can be sintered without decomposition at temperatures of up to ≃1300°C. The highest possible sintering temperature depends on the sintering atmosphere (partial pressure of water vapor) [10]: increasing the ambient humidity stabilizes HA to higher temperatures. At the same time, there is experimental evidence that HA with Ca : P = 1.68 does not decompose at temperatures of up to 1450°C over a period of 3 h [6, 37]. Increasing the temperature to 1500°C leads to rapid HA decomposition. Sintering of fine-particle HA powder at 1300°C for 3 h ensures a nearly theoretical density. Sintering at higher temperatures is accompanied by secondary recrystallization: as the sintering temperature is raised from 1300 to 1450°C, the grain size increases from 4 to 14 μm. The grain size as a function of heat-treatment temperature exhibits Arrhenius behavior with an apparent activation energy of 196 kJ/mol [6].

Clearly, the optimal sintering temperature and duration depend on the prior history and particle size of the powder, which influence its sintering behavior and the phase composition of the resulting material. Increasing the particle size of the HA powder from 1 to 4.2 μm markedly raises the shrinkage onset temperature. In spite of the higher green density of coarse-particle compacts, the sintered density increases with decreasing particle size.

Powder consolidation can be activated via liquid-assisted sintering. To this end, Fateeva *et al.* [59] proposed to introduce up to 5% Na_3PO_4, which was shown to reduce the sintering temperature necessary for the preparation of dense HA ceramics by about 50°C. Liquid-phase sintering can also be ensured by phosphate or silicate glass additions. The use of Bioglass® (2.6 mol % P_2O_5, 26.9 mol % CaO, 24.0 mol % Na_2O, 46.1 mol % SiO_2) as a sintering aid made it possible to improve not only the mechanical properties of HA ceramics but also their behavior in biological environments [7, 60].

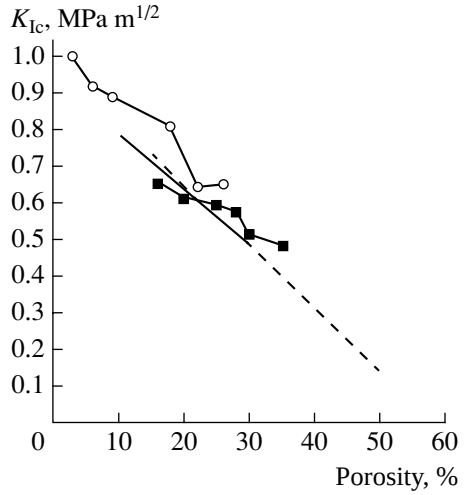

Fig. 2. Fracture toughness as a function of porosity for dense HA ceramics [10].

The key characteristics of dense ceramics are bending strength, tensile strength, and fracture toughness. The bending, compressive, and tensile strength values of HA ceramics lie in the ranges 38–250, 120–150, and 38–300 MPa, respectively [1–5, 10, 61]. The large scatter is due to the random strength distribution and the effects of residual microporosity, grain size, impurities, etc. With increasing Ca : P ratio, the strength increases, reaches a peak at Ca : P ≃ 1.67, and sharply decreases for Ca : P > 1.67 [10].

Weibull's modulus of dense HA ceramics lies in the range 5–18, characteristic of brittle materials. The decelerated crack propagation coefficient ranges from 26 to 80 in a dry atmosphere (against 30 for alumina ceramics) and from 12 to 49 in a humid atmosphere, indicating a high sensitivity to decelerated crack propagation [1, 10, 24].

Young's modulus of dense HA ceramics varies from 35 to 120 GPa [10, 23], depending on the residual porosity and impurities. Young's modulus in bending is 44–88 GPa. The Vickers hardness of dense ceramics is 3–7 GPa. Dense HA ceramics exhibit superplasticity at temperatures between 1000 and 1100°C due to grain-boundary slip. The wear resistance and friction coefficient of dense HA ceramics are comparable to those of enamel. Fracture toughness K_{Ic} is 0.8–1.2 MPa m$^{1/2}$ and decreases almost linearly with increasing porosity (Fig. 2). The unit rupture work is 2.3 to 20.0 J/m^2.

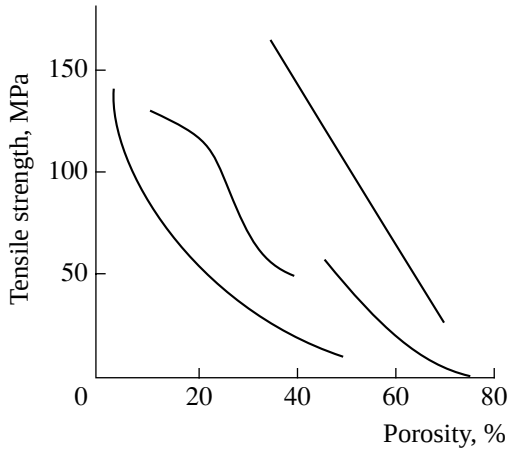

Fig. 3. Tensile strength as a function of porosity for HA ceramics [10].

The low K_{Ic} and Weibull modulus, coupled with the high sensitivity to decelerated crack propagation, point to a low reliability of articles of dense HA ceramics. Roots of teeth fabricated of dense HA ceramics were studied in vivo and clinically. The bonding between the gum and HA implant was comparable to that ensured by the natural binder. Moreover, good bonding was achieved between the implant and bone. These results are of great importance because inadequate bonding leads to an increased mobility and, eventually, loss of teeth. Unfortunately, most of the loaded dental implants were destroyed within a year after implantation because of the low strength of the ceramic [10, 21, 61].

Among the most important applications of dense HA ceramics are hypodermic devices for long-term ambulant intestinal dialysis, monitoring of blood pressure and sugar, and optical examination of internal tissues [1, 52]. Dense HA ceramics exhibit excellent biocompatibility with skin, far exceeding that of silicone rubber, which is widely used for these purposes.

Porous HA ceramics. For a number of applications, porous ceramics containing interconnected channel pores are more attractive. Such ceramics can be used as bone graft substitutes, e.g., for the superior articular surface of the tibia [6], or in drug delivery systems [11–16, 62–66]. To ensure blood supply to contact surfaces [11] and bone ingrowth and fixation [11, 17, 18], the diameter of interconnected pores must be at least 100–135 μm. Also necessary are smaller pores, which favor protein adsorption and adhesion of osteogenic cells. Thus, the pore-size distribution in porous ceramics should be bimodal.

Porous ceramics are commonly produced by burning out organic pore formers (polyurethane sponges) or via foaming with the use of hydrogen peroxide [6, 66–72]. The porosity of ceramics attains 50–60% when use is made of sodium dodecylbenzenesulfonate and about 80% with glycine or agar [3]. By adding 37 wt % flour with a particle size from 40 to 200 μm, Slosarzyk *et al.* [67] obtained HA ceramics with a porosity of up to 46%, in which the pore size attained 100 μm and the pore size distribution was uni- or bimodal, depending on the sintering temperature. Komlev *et al.* [73] devised a procedure for preparing HA ceramics with a porosity of up to 70%, containing small and large interconnected pores.

To modify the biological behavior of porous ceramics, the pore surface can be coated with tricalcium phosphate (TCP). To this end, ceramic bodies are impregnated with a dibasic ammonium phosphate solution and then heat-treated at 900°C [74].

Pore morphology is critical to the osteointegration process. Suchanek and Yoshimura [10], burning out pore formers, could produce cylindrical channel pores up to 500 μm in diameter and more than 5 mm in length.

Porous ceramics can be produced at physiological temperature without sintering [75]. The strength of such materials is very low. The preparation process models in vivo HA formation. Durucan and Brown [75] investigated Ca-deficient HA and carbonate hydroxyapatite (CHA) prepared by the reactions

$$6CaHPO_4 + 3Ca_4(PO_4)_2O = 2Ca_9HPO_4(PO_4)_5OH + H_2O, \quad (9)$$

$$0.625NaHCO_3 + 2CaHPO_4 + 2Ca_4(PO_4)_2O = 1.067Ca_{9.375}Na_{0.586}(PO_4)_{5.375}(CO_3)_{0.586}(OH)_{1.961} + 0.3125H_2O. \quad (10)$$

The synthesized powders were pressed at 70 MPa and exposed to a humid atmosphere at 38°C. The porosity of the resultant materials was 27–39%. The tensile strength was 12–18 MPa for Ca-deficient HA and 9–14 MPa for CHA; the compressive strength was 83–172 and 57–80 MPa, respectively. The mechanical properties of the materials were interpreted in terms of their microstructure near physiological temperature. The strength level was rather high, in spite of the large amount of pores, whose morphology and percentage have a significant effect on mechanical properties [76, 77].

Whereas the compressive strength of porous ceramics is sufficiently high, 2–100 MPa, their bending strength (2–11 MPa) is lower than the necessary level by a factor of 2–3. With increasing porosity, the strength of ceramics decreases sharply (Fig. 3). The effect of porosity Π on the compressive strength σ and Young's modulus E of HA and TCP ceramics produced by sintering at 1100°C was studied in [78–80]. Both σ and E were found to drop with increasing porosity: $\ln\sigma = 6.4 - 3.9\Pi$ for HA, $\ln\sigma = 6.6 - 6.2\Pi$ for TCP, and $\ln E = 4.6 - 4.0\Pi$ for HA. Extrapolation to zero porosity yielded σ = 70 MPa and E = 9.2 GPa for HA and σ = 135 MPa and E = 21 GPa for TCP. The strength of HA was substantially lower than that reported earlier [1, 10].

The strength of implants gradually increases in the process of bone ingrowth into the pore network. According to Martin [21], the bending strength of porous implants filled with 50–60% bone tissue is 40–60 MPa.

The fracture toughness of HA ceramics varies nonmonotonically with grain size and reaches a peak at a grain size of about 0.4 μm [81, 82]. The maximum strength and fracture toughness are 135 MPa and 1.25 MPa $m^{1/2}$, respectively. Sodium phosphate additions lead to grain growth and reduce K_{Ic} to 0.95 MPa $m^{1/2}$.

The strength of porous ceramics can be enhanced by using fibers. Fibrous porous materials are known to possess improved strength owing to the bonding between the fibers, changes in crack trajectories, and fiber stretching. Moreover, the fibrous HA scaffold can be reinforced with HA–polymer biodegrading bone substance. The fabrication of fibrous porous calcium phosphate ceramics has been the subject of many studies. Fibrous porous textures can be produced by several techniques [10, 83, 84]:

(1) sintering of β-$Ca_3(PO_4)_2$ fibers followed by processing in molten salts, yielding a porous HA scaffold;

(2) sintering of HA fibers or hydrothermal treatment of α-TCP;

(3) dynamic densification of calcium orthophosphate and β-calcium metaphosphate fibers.

Unfortunately, the mechanical properties of the materials prepared by these procedures are below the necessary level.

Porous HA ceramics in the form of blocks and granules find many medical applications [1–5].

Porous HA ceramic granules. Granulation involves a number of physicochemical and mechanical processes leading to the formation of particles with controlled dimensions, shape, structure, and physical properties.

Various techniques and facilities are used to granulate powders, in particular HA. The known processes can be classified as follows [85]:

(1) spraying of a liquid phase, followed by crystallization upon drying or cooling;

(2) pressing of a solid phase, followed by grinding into granules of desired size;

(3) powder agglomeration in the presence of a liquid phase, followed by pelletizing and consolidation of the agglomerates upon the removal of the liquid phase;

(4) vapor deposition with the formation of solid granules;

(5) chemical reaction in a vapor–liquid mixture;

(6) chemical reaction in a vapor–liquid–solid mixture.

The granulation efficiency depends on the mechanism of the process, which is, in turn, determined by the granulation technique and the facilities used.

The greatest interest has developed in the first process, which allows one to produce spherical granules and to vary their diameter over a wide range. A liquid, e.g., an anhydrous melt, is sprayed to produce approximately monosized drops, which then crystallize on cooling in an inert medium such as water, oil, or liquid nitrogen. In particular, Paul and Sharma [13] used mixtures of liquid paraffin and an HA suspension in a binder (chitosan) solution. The suspension was sprayed into liquid paraffin and stirred at 500 rpm with a paddle stirrer, which led to the formation of spherical granules. This process, however, has the drawback of utilizing molten paraffin. Komlev *et al.* [86, 87] devised a simpler procedure for producing porous HA granules: spheroidizing in immiscible liquids. HA granules were prepared by spraying a liquid phase, followed by heat treatment. As a binder, they used gelatin, which ensured good bonding between the powder particles. An HA suspension in an aqueous gelatin solution was dispersed in an inert liquid (vegetable oil), which does not mix with aqueous gelatin. Owing to surface tension, the resulting granules had a spherical shape. The granule size could be varied from 50 to more than 2000 μm. Figure 4 shows a SEM micrograph of an HA granule and its microstructure after heat treatment at 1200°C for 1 h.

In a number of countries, HA granules are produced on a commercial scale, e.g., Interpore® 200 (425–1000 μm), Pro Osteon® (1–9 mm), and Osteogen® (300–1000 μm) granules [13].

Ceramic granules find application in restorative surgery and drug delivery systems [1, 13, 66, 88–97].

In restorative surgery, granules are used in treating parodontopathy (local and generalized, moderate and acute parodontitis and idiopathic parodontopathy accompanying insulin-independent diabetes mellitus); periodontal, follicular, and residual maxillary cysts; etc. For instance, in the Maxillofacial Surgery and Dentistry Clinic of the War Medicine Academy, HA granules are mainly used to fill the cavities left after maxillary cystectomy [91].

A very important application field for HA granules and porous ceramics is drug delivery. The use of ceramics for solving this problem is a relatively new approach: although the first studies were carried out as early as 1930, ceramic drug delivery systems were devised only in the 1980s, and the first clinical results were reported in 1998 [92].

A major problem with drug delivery systems is to maintain a constant drug concentration in blood over a preset time (slow pharmacokinetics), because periodic peroral or parenteral introduction of drugs may result in drug accumulation to above the permissible concentration and, hence, intoxication (Fig. 5) [93].

The use of HA ceramics for drug delivery ensures controlled, local drug release over a period of up to one year [94].

In vivo tests on Vistar rats showed slow release of a drug-modeling preparation from porous spherical HA

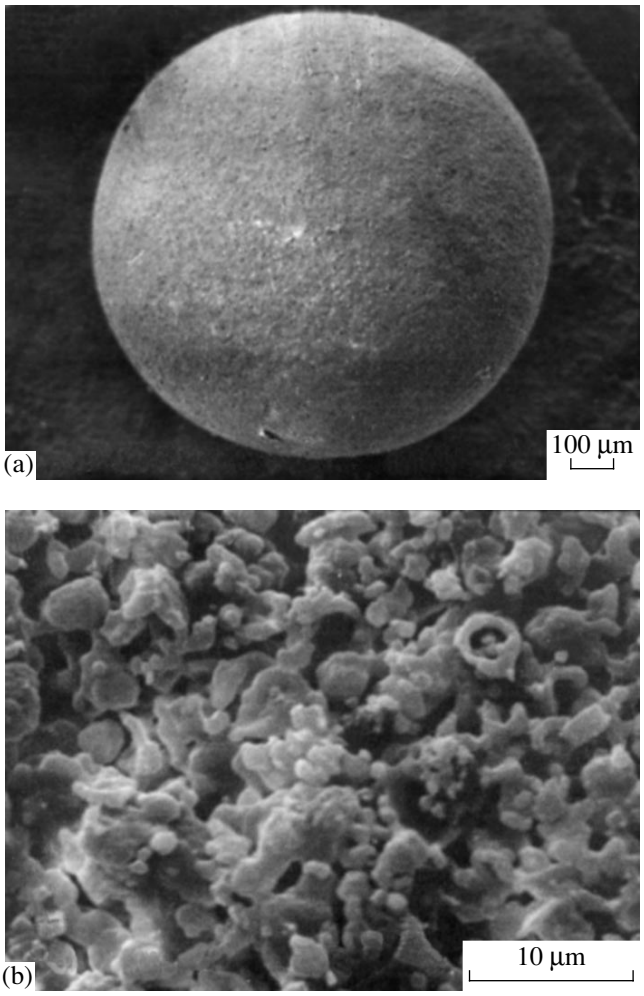

Fig. 4. (a) HA granule and (b) its microstructure after heat treatment at 1200°C for 1 h.

granules. The drug concentration in their blood attained 0.98 mg/ml after 2–3 h, stabilized at this level for 40 h, and then gradually decreased over a period of 100 h. This result can be interpreted as due to the presence of a large amount of small, interconnected pores and the small diffusion coefficient of the preparation in the porous matrix owing to the action of capillary forces [98].

HA-BASED COMPOSITES

The insufficiently high mechanical strength of HA ceramics restricts their application in surgery. Better mechanical properties are offered by composites. Appropriate additives may improve the mechanical characteristics of ceramics. Their biological properties, primarily biocompatibility with living tissue, must remain unchanged.

There are two main groups of HA-containing composites [7]:

(1) ceramics reinforced with small particles or discrete and continuous fibers [99–103];

(2) biocompatible polymers reinforced with small ceramic particles [104–112].

The strength of oxide ceramics can be raised by introducing small particles of yttria partially stabilized zirconia, $ZrO_2\langle Y_2O_3\rangle$, which undergoes a tetragonal-to-monoclinic phase transformation under mechanical stress. The interaction of HA with ZrO_2 and the bending strength and fracture toughness as functions of the HA : $ZrO_2\langle Y_2O_3\rangle$ ratio were studied in [100, 102]. It was found that both the bending strength and fracture toughness increase with ZrO_2 content. The bending strength of materials containing 50% ZrO_2 and fired at 1400°C was higher than that of pure HA by a factor of 2–3. However, zirconia is of limited use in strengthening HA ceramics because calcium from HA stabilizes zirconia at the sintering temperature [100]. The possibility of reinforcing HA matrices with inorganic fibers, e.g., Al_2O_3 or SiC, is restricted by the thermal expansion mismatch between the matrix and fibers, which gives rise to tensile stresses in the matrix, thereby reducing its strength. Suchanek and Yoshimura [10] showed that the strength and fracture toughness of hot-pressed HA ceramics can be enhanced by a factor of 2 and 6, respectively, by reinforcement with short metallic (stainless steel or Hastelloy) fibers (≤20 vol %). The com-

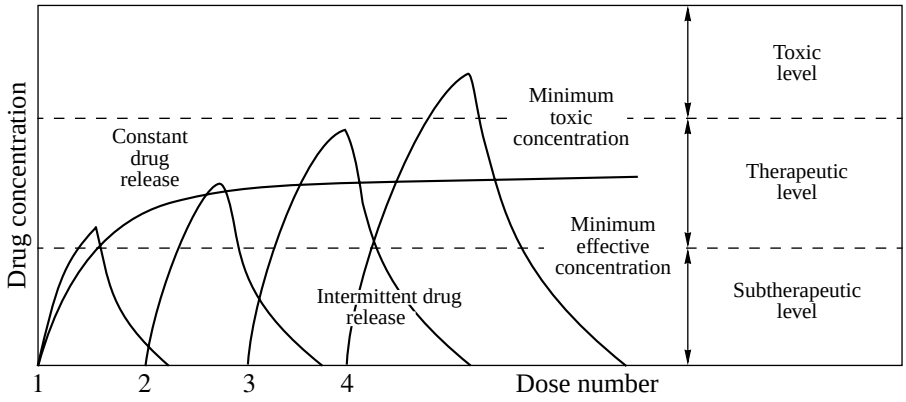

Fig. 5. Kinetics of drug release.

posites thus produced have a strength of up to 224 MPa, fracture toughness in the range 6.0–7.4 MPa $m^{1/2}$, and modulus of normal elasticity of up to 142 GPa. However, ceramic–metal implants are susceptible to corrosion and react with tissue.

One of the most interesting approaches to enhancing the strength and reducing the brittleness of HA ceramics is the fabrication of HA–polymer composites.

Polyethylene-based composites were designed in [105, 109, 110]. It was shown that, as the HA content increases to 40%, Young's modulus of the composite rises and attains 1–8 GPa, which is close to that of living bone. However, polyethylene is a bioinert material, which weakens the bonding between the implant and bone tissue.

Several works were centered on HA–collagen composites [104, 108], which are similar in composition to living bone. Such composites can be produced by mixing HA powder and collagen solution, followed by curing the mixture under UV radiation or pressing at 40°C under a pressure of 200 MPa. The strength of the materials thus prepared is however rather low: tensile strength of 6.5 GPa and Young's modulus of 2 GPa.

An alternative approach is to introduce a polymer into a ceramic matrix to obtain composites with a continuous ceramic skeleton, in contrast to those reported in [104–111]. The biological and mechanical properties of such ceramic–polymer composites must differ markedly from those of polymer–ceramic materials.

In recent years, there has been considerable research effort devoted to new ceramic-matrix composites reinforced with particles, fibers, and metals. There are however many inherent difficulties to be overcome, e.g., corrosion and adverse reactions with tissue in the case of HA–metal composites. The introduction of foreign materials into HA ceramics may reduce their biocompatibility and promote HA decomposition with the formation of TCP. The presence of TCP in HA promotes biodegradation and favors slow crack growth. Yet another undesirable effect of reinforcement is the increase in the modulus of elasticity.

Note that the above difficulties restrict the application field of HA-based composites. Nevertheless, HA–polymer composites (HA–polyethylene [105, 109, 110], HA–collagen [104, 108], HA–polylactide [107, 112], HA–polymethylmethacrylate [106, 111], and others) continue to be a field of intense research.

REFERENCES

1. Aoki, H., *Science and Medical Applications of Hydroxyapatite*, Tokyo: JAAS, 1991.
2. Williams, D.F., Science and Applications of Biomaterials, *Adv. Mater. Technol. Monitor.*, 1994, no. 2, pp. 1–38.
3. Orlovskii, V.P., Sukhanova, G.E., Ezhova, Zh.A., and Rodicheva, G.V., Hydroxyapatite Bioceramics, *Zh. Vses. Khim. O–va. im. D.I. Mendeleeva*, 1991, vol. 36, no. 6, pp. 683–688.
4. Hench, L.L., Bioceramics and the Future, *Ceramics and Society*, Vincenzini, P., Ed., Faenza: Techna, 1995, pp. 101–120.
5. Tret'yakov, Yu.D. and Brylev, O.A., New Generation of Inorganic Functional Materials, *Ross. Khim. Zh.*, 2000, vol. 7, no. 4, pp. 10–16.
6. Doremus, R.H., Review Bioceramics, *J. Mater. Sci.*, 1992, vol. 27, no. 3, pp. 285–296.
7. Cao, W. and Hench, L.L., Bioactive Materials, *J. Ceram. Int.*, 1996, vol. 22, no. 6, pp. 493–507.
8. Sarkisov, P.D., Mikhailenko, N.Yu., Batrak, I.K., *et al.*, Calcium Phosphate Glass-Ceramic Coatings for Titanium Implants, in *Problemy implantologii v otorinolaringologii* (Implants in Otorhinolaryngology), Moscow: Press-Solo, 2000, p. 18.
9. Sarkisov, P.D., Michailenko, N.Yu., Stroganova, E.E., *et al.*, Glass-Based Bioactive Calcium Phosphate Materials, *Proc. XIX Int. Congress on Glass*, Edinburg, 2001, p. 23.
10. Suchanek, W. and Yoshimura, M., Processing and Properties of HA-Based Biomaterials for Use as Hard Tissue Replacement Implants, *J. Mater. Res. Soc.*, 1998, vol. 13, no. 1, pp. 94–103.
11. Hing, K.A., Best, S.M., Tanner, K.A., *et al.*, Quantification of Bone Ingrowth within Bone Derived Porous Hydroxyapatite Implants of Varying Density, *J. Mater. Sci.: Mater. Med.*, 1999, vol. 10, no. 10/11, pp. 633–670.
12. Krajewski, A., Ravaglioli, A., Roncari, E., *et al.*, Porous Ceramic Bodies for Drug, *J. Mater. Sci.: Mater. Med.*, 2000, vol. 11, no. 12, pp. 763–772.
13. Paul, W. and Sharma, C.P., Development of Porous Spherical Hydroxyapatite Granules: Application towards Protein Delivery, *J. Mater. Sci.: Mater. Med.*, 1999, vol. 10, no. 7, pp. 383–388.
14. Vaz, L., Lopes, A.B., and Almeida, M., Porosity Control of Hydroxyapatite Implants, *J. Mater. Sci.: Mater. Med.*, 1999, vol. 10, no. 10/11, pp. 239–242.
15. Lio, D., Fabrication of Hydroxyapatite Ceramic with Controlled Porosity, *J. Mater. Sci.: Mater. Med.*, 1997, vol. 8, no. 8, pp. 227–232.
16. Itokazu, M., Esaki, M., Yamamoto, K., *et al.*, Local Drug Delivery System Using Ceramics: Vacuum Method for Impregnating a Chemotherapeutic Agent into a Porous Hydroxyapatite Block, *J. Mater. Sci.: Mater. Med.*, 1999, vol. 10, no. 4, pp. 249–252.
17. Lu, J.X., Flautre, B., and Anselme, K., Role of Interconnections in Porous Bioceramics on Bone Recolonization *In Vitro* and *In Vivo*, *J. Mater. Sci.: Mater. Med.*, 1999, vol. 10, no. 2, pp. 111–120.
18. Yamamoto, M., Tabata, Y., Kawasaki, H., and Ikada, Y., Promotion of Fibrovascular Tissue Ingrowth into Porous Sponges by Basic Fibroblast Growth Factor, *J. Mater. Sci.: Mater. Med.*, 2000, vol. 11, no. 14, pp. 213–218.
19. Weinlander, M., Plenk, H., Jr., Adar, F., and Holmes, R., *Bioceramics and the Human Body*, Ravaglioli, A. and Krajewski, A., Eds., London: Elsevier, 1992, p. 317.
20. Samusev, R.P. and Selin, Yu.M., *Anatomiya cheloveka* (Human Anatomy), Moscow: Meditsina, 1990.
21. Martin, R.B., Bone as a Ceramic Composite Material, *Mater. Sci. Forum*, 1999, vol. 7, no. 1, pp. 5–16.

22. Gunderson, S.L. and Schiavone, R.C., *International Encyclopedia of Composites*, Lee, S.M., Ed., New York: VCH, 1991, vol. 5.
23. Katz, J.L., *The Mechanical Properties of Biological Materials*, Cambridge: Cambridge Univ. Press, 1980.
24. Barinov, S.M. and Shevchenko, V.Ya., *Prochnost' tekhnicheskoi keramiki* (Strength of Technical Ceramics), Moscow: Nauka, 1997.
25. Shevchenko, V.Ya. and Barinov, S.M., *Tekhnicheskaya keramika* (Technical Ceramics), Moscow: Nauka, 1993.
26. Buravov, A.D., Barinov, S.M., Grigorjev, O.N., *et al.*, *Carbon- and Ceramic-Matrix Composites*, London: Chapman and Hall, 1995, p. 380.
27. Monma, H.J., Processing of Synthetic Hydroxyapatite, *J. Ceram. Soc. Jpn., Dent. Res.*, 1980, vol. 8, no. 40, pp. 97–102.
28. Slosarczyk, A., Stobierska, E., Paszkiewicz, Z., and Gawlicki, M., Calcium Phosphate Materials Prepared from Precipitates with Various Calcium : Phosphorus Molar Ratios, *J. Am. Ceram. Soc.*, 1996, vol. 79, no. 10, pp. 2539–2544.
29. Mortier, A., Lemaitre, J., Rondrique, L., *et al.*, Synthesis and Thermal Behavior of Well Crystallized Calcium-Deficient Phosphate Apatite, *J. Solid State Chem.*, 1989, vol. 26, no. 2, pp. 215–219.
30. Barinov, S.M. and Komlev, V.S., Hydroxyapatite-Base Granules for Targeted and Time-Controlled Drug Delivery, *Book of Lectures Presented at the 3rd Course on Biomaterials*, Rustichelli, F. and Davidson, C., Eds., Ancona, 2001, pp. 1–7.
31. Klyuchnikov, N.G., *Rukovodstvo po neorganicheskomu sintezu* (A Guide to Inorganic Synthesis), Moscow: Khimiya, 1965.
32. Kibal'chits, V. and Komarov, V.F., High-Speed Synthesis of Hydroxyapatite Crystals, *Zh. Neorg. Khim.*, 1980, vol. 25, no. 2, pp. 565–567.
33. Orlovskii, V.P. and Barinov, S.M., Hydroxyapatite and Hydroxyapatite-Matrix Ceramics: A Survey, *Russ. J. Inorg. Chem.*, 2001, vol. 46, no. 2, pp. 129–149.
34. Aizawa, M., Hanazawa, T., Itatani, K., *et al.*, Characterization of Hydroxyapatite Powders Prepared by Ultrasonic Spray-Pyrolysis Technique, *J. Mater. Sci.*, 1999, vol. 34, no. 12, p. 2865.
35. Kokubo, T., Potential of Ceramics as Biomaterials, *Ceramics and Society*, Brook, R.J., Ed., Faenza: Techna, 1995.
36. Orlovskii, V.P., Ezhova, Zh.A., Rodicheva, G.V., *et al.*, Hydroxyapatite Phase Relations in the System $CaCl_2$–$(NH_4)_2HPO_4$–NH_4OH–H_2O (25°C), *Zh. Neorg. Khim.*, 1992, vol. 37, no. 4, pp. 881–883.
37. Orlovskii, V.P., Ezhova, Zh.A., Rodicheva, G.V., *et al.*, Structural Transformations of Hydroxyapatite in the Range 100–1600°C, *Zh. Neorg. Khim.*, 1990, vol. 34, no. 5, p. 1337.
38. Turova, N.Ya. and Yanovskaya, M.I., Synthesis of Hydroxyapatite Crystals, *Izv. Akad. Nauk SSSR, Neorg. Mater.*, 1983, vol. 19, no. 5, p. 693.
39. Hench, L.L., Bioceramics and the Future, *Ceramics and Society*, Brook, R.J., Ed., Faenza: Techna, 1995.
40. Zhang, S. and Gonsalves, K.E., Preparation and Characterization of Thermally Stable Nanohydroxyapatite, *J. Mater. Sci.: Mater. Med.*, 1997, vol. 8, no. 8, pp. 25–28.
41. Elliort, J.C., *Structure and Chemistry of the Apatites and Other Calcium Orthophosphates*, Amsterdam: Elsevier, 1994.
42. Dubok, V.A. and Ul'yanin, N.V., Synthesis, Properties, and Applications of Osteotropic Substitute Materials Based on Hydroxyapatite Ceramics, *Ortop., Travmatol. Protez.*, 1998, vol. 6, no. 3, pp. 26–30.
43. Feenstra, L. and de Groot, K., *Bioceramics of Calcium Phosphate*, Boca Raton: CRC, 1983.
44. Jarcho, M., Bolen, C.H., Thomas, M.B., *et al.*, Synthesis and Characterization in Dense Polycrystalline Form, *J. Mater. Sci.*, 1976, vol. 11, no. 10, p. 2027.
45. Yubao, L., de Groot, K., de Wijn, J., *et al.*, Morphology and Composition of Nanograde Calcium Phosphate Needle-like Crystals Formed by Simple Hydrothermal Treatment, *J. Mater. Sci.: Mater. Med.*, 1994, vol. 5, pp. 326–331.
46. Yubao, L., Klein, C.P., de Wijn, J., *et al.*, Shape Change and Phase Transition of Needle-like Non-Stoichiometric Apatite Crystals, *J. Mater. Sci.: Mater. Med.*, 1991, vol. 2, no. 1, pp. 51–55.
47. Orlovskii, V.P., Ionov, S.P., and Rusakova, R.A., Hydroxyapatite Phase Relations in the System $CaCl_2$–$(NH_4)_2HPO_4$–NH_4OH–H_2O, *Dokl. Akad. Nauk*, 1992, vol. 325, no. 5, p. 522.
48. Orlovskii, V.P. and Ionov, S.P., Synthesis of Hydroxyapatite in the System $CaCl_2$–$(NH_4)_2HPO_4$–NH_4OH–H_2O, *Zh. Neorg. Khim.*, 1995, vol. 40, no. 12, p. 1961.
49. Vincent, J., *Structural Biomaterials*, Princeton: Princeton Univ. Press, 1990.
50. Kelly, A., *Strong Solids*, London: Oxford Univ. Press, 1971. Translated under the title *Vysokoprochnye materialy*, Moscow: Mir, 1976.
51. Hosoi, K., Hashida, T., Takahashi, H., *et al.*, New Processing Technique for Hydroxyapatite Ceramics by the Hydrothermal Hot-Pressing Method, *J. Am. Ceram. Soc.*, 1996, vol. 80, no. 10, pp. 2771–2774.
52. Hench, L.L., Bioceramics: From Concept to Clinic, *J. Am. Ceram. Soc.*, 1991, vol. 75, no. 7, pp. 1487–1510.
53. LeGeros, R.Z., Biodegradation and Bioresorption of Calcium Phosphate Ceramics, *J. Clin. Mater.*, 1993, vol. 35, no. 14, p. 65.
54. De With, G., Van Dijk, H.J.A., Hattu, N., and Prijs, K., Preparation, Microstructure, and Mechanical Properties of Dense Polycrystalline Hydroxyapatite, *J. Mater. Sci.*, 1981, vol. 16, no. 7, pp. 1592–1598.
55. Hech, L.L., Bioceramics, *J. Am. Ceram. Soc.*, 1998, vol. 82, no. 7, pp. 1705–1733.
56. Ruys, A.J., Wei, M., Sorrell, C.C., *et al.*, Sintering Effects on Strength of Hydroxyapatite, *Biomaterials*, 1995, vol. 16, no. 5, pp. 409–415.
57. Wang, P.E. and Chaki, T.K., Sintering Behavior and Mechanical Properties of Hydroxyapatite and Dicalcium Phosphate, *J. Mater. Sci.: Mater. Med.*, 1993, vol. 4, no. 3, pp. 150–158.
58. Cuneyt Tas, A., Korkusuz, E., Timucin, M., and Akkas, N., An Investigation of the Chemical Synthesis and High Temperature Sintering Behavior of Calcium

HA and Tricalcium Phosphate Bioceramics, *J. Mater. Sci.: Mater. Med.*, 1997, vol. 8, no. 2, pp. 91–96.

59. Fateeva, L.V., Golovkov, Yu.M., Barinov, S.M., *et al.*, Effect of Sodium Phosphate on the Sintering Behavior of Hydroxyapatite Ceramics, *Ogneupory Tekh. Keram.*, 2001, no. 1, p. 6.
60. Santos, J.D., Reis, R.L., Monteiro, F.J., *et al.*, Liquid Phase Sintering of Hydroxyapatite by Phosphate and Silicate Glass Additions: Structure and Properties of the Composites, *J. Mater. Sci.: Mater. Med.*, 1995, vol. 6, no. 4, p. 348.
61. Ratner, B.D., New Ideas in Biomaterials Sciences—Path to Engineering Biomaterials, *J. Biomed. Mater. Res.*, 1993, vol. 27, no. 6, pp. 837–850.
62. Solov'ev, M.M., Ivasenko, I.N., Alekhova, T.M., *et al.*, Effect of Hydroxyapatite on Cavity Healing in Carious Teeth, *Stomatologiya*, 1992, nos. 3–6, pp. 8–10.
63. Hupp, J.R. and Me Kenna, S.J., Use of Porous Hydroxylapatite Blocks for Augmentation of Atrophic Mandibles, *J. Oral Maxillofac. Surg.*, 1998, no. 7, pp. 538–545.
64. Stahe, S.S. and Frourn, S.J., Histologic and Clinical Responses to Porous Hydroxylapatite Implants in Human Periodontal Defects: Three to Twelve Months Postimplantation, *J. Periodontol.*, 1987, no. 10, pp. 689–695.
65. Uchida, A., Nade, S., Eric, M., and Ching, W., Bone Ingrowth into Three Different Porous Ceramics Implanted into the Tibia of Rats and Rabbits, *J. Orthop. Res.*, 1985, no. 3, pp. 65–77.
66. Uchida, A., Shinto, Y., Araki, N., and Ono, K., Slow Release of Anticancer Drugs from Porous Calcium Hydroxyapatite Ceramic, *J. Orthop. Res.*, 1992, no. 10, pp. 440–445.
67. Slosarzyk, A., Stobierska, E., and Paszkiewicz, Z., Porous Hydroxyapatite Ceramics, *J. Mater. Sci. Lett.*, 1999, vol. 19, no. 18, p. 1163.
68. Yamasaki, N., Kai, T., Nishioka, M., *et al.*, Porous Hydroxyapatite Ceramics Prepared by Hydrothermal Hot-Pressing, *J. Mater. Sci. Lett.*, 1990, vol. 10, no. 10, p. 1150.
69. Tanner, K.E., Downes, R.N., and Bonfield, W., Clinical Application of Hydroxyapatite Reinforced Polyethylene, *Br. Ceram. Trans. J.*, 1994, no. 3, pp. 104–107.
70. Liu, D., Preparation and Characterization of Porous HA Bioceramic via a Slip-Casting Route, *J. Ceram. Int.*, 1997, vol. 24, no. 4, pp. 441–446.
71. Engin, N.O. and Tas, A.C., Preparation of Porous $Ca_{10}(PO_4)_6(OH)_2$ and *bgr*-$Ca_3(PO_4)_2$ Bioceramics, *J. Am. Ceram. Soc.*, 2000, vol. 84, no. 7, pp. 1581–1584.
72. Sepulveda, P., Ortega, F.S., and Murilo, D.M., Properties of Highly Porous Hydroxyapatite Obtained by the Gel Casting of Foams, *J. Am. Ceram. Soc.*, 2000, vol. 3, no. 12, pp. 3021–3024.
73. Komlev, V.S., Barinov, S.M., Orlovskii, V.P., and Kurdyumov, S.G., Porous Hydroxyapatite Ceramics with a Bimodal Pore Size Distribution, *Ogneupory Tekh. Keram.*, 2001, no. 6, pp. 23–25.
74. Donath, K., Relation of Tissue to Calcium Phosphate Ceramics, *Osseous*, 1991, vol. 1, p. 100.
75. Durucan, C. and Brown, P.W., α-Tricalcium Phosphate Hydrolysis to Hydroxyapatite at and near Physiological Temperature, *J. Mater. Sci.: Mater. Med.*, 2000, vol. 11, no. 6, p. 365.
76. Krasulin, Yu.L., Barinov, S.M., and Ivanov, V.S., *Struktura i razrushenie materialov iz poroshkov tugoplavkikh soedinenii* (Structure and Fracture of Materials Prepared from Powders of Refractory Compounds), Moscow: Nauka, 1985.
77. Andrievskii, R.A., Strength of Sintered Bodies, *Poroshk. Metall.* (Kiev), 1982, no. 1, p. 37.
78. Metsger, D.S., Rieger, M.R., and Foreman, D.W., Mechanical Properties of Sintered Hydroxyapatite and Tricalcium Phosphate Ceramic, *J. Mater. Sci.: Mater. Med.*, 1999, vol. 10, no. 1, p. 9.
79. Hing, K.A., Best, S.M., and Bonfield, W., Characterization of Porous Hydroxyapatite, *J. Mater. Sci.: Mater. Med.*, 1999, vol. 10, no. 3, pp. 135–145.
80. Tas, A.C. and Ozgur Engin, N., Manufacture of Macroporous Calcium Hydroxyapatite Bioceramics, *J. Eur. Ceram. Soc.*, 1999, vol. 19, no. 13/14, p. 2569.
81. Nakajima, T., Ichiro Ono, M.D., and Tohru Tateshita, M.D., Porous Hydroxyapatite Ceramics and Their Ability to Be Fixed by Commercially Available Screws, *Biomaterials*, 1999, vol. 20, no. 17, p. 1595.
82. Roncari, E., Galassi, C., and Pinasco, P., Tape Casting of Porous Hydroxyapatite Ceramics, *J. Mater. Sci. Lett.*, vol. 20, no. 1, pp. 33–35.
83. Powers, J.M., Yaszemski, M.J., Thomson, R.C., and Mikos, A.G., Hydroxyapatite Fiber Reinforced Poly(*a*-hydroxy ester) Foams for Bone Regeneration, *Biomaterials*, 1998, vol. 19, no. 21, pp. 1935–1943.
84. Yoshio Ota, Y., Iwashita, T., Kasuga, T., *et al.*, Novel Preparation Method of Hydroxyapatite Fibers, *J. Am. Ceram. Soc.*, 1998, vol. 81, no. 6, pp. 1665–1733.
85. Klassen, P.V. and Grishaev, I.G., *Osnovy tekhniki granulirovaniya* (Fundamentals of Granulation), Moscow: Khimiya, 1982.
86. Komlev, V.S., Barinov, S.M., and Fadeeva, I.V., Porous Hydroxyapatite Ceramic Granules for Drug Delivery Systems, *Novye Tekhnol.–21 Vek*, 2001, no. 5, pp. 18–19.
87. Komlev, V.S., Barinov, S.M., Orlovskii, V.P., and Kurdyumov, S.G., Porous Hydroxyapatite Ceramic Granules, *Ogneupory Tekh. Keram.*, 2001, no. 5, pp. 18–20.
88. Gautier, H., Merle, C., Auget, J.L., and Daculsi, G., Isostatic Compression, a New Process for Incorporating Vancomycin into Biphasic Calcium Phosphate: Comparison with a Classical Method, *Biomaterials*, 2000, vol. 21, no. 2, pp. 243–249.
89. Kovalevskii, A.M., Surgical Treatment of Generalized Parodontitis Using Biopolymers and Bioceramics: A Clinical–Experimental Investigation, *Cand. Sci. (Med.) Dissertation*, St. Petersburg, 1998.
90. Fedosenko, T.D., Application of Hydroxyapatite Preparations in Combined Therapy of Parodontopathy, *Extended Abstract of Cand. Sci. (Med.) Dissertation*, St. Petersburg, 1994.
91. Chernysh, V.F., Shutov, Yu.N., and Kovalevskii, A.M., New Methods in Parodontium Surgery, *Parodontologiya*, 1997, no. 4, pp. 19–23.

92. Dash, A.K. and Cudworth, G.C., Therapeutic Applications of Implantable Drug Delivery Systems, *J. Pharmacol. Toxicol. Methods*, 1998, no. 1, pp. 1–12.

93. Chien, Y.W., *Novel Drug Delivery Systems*, New York: Marcel Dekker, 1992, 2nd ed.

94. Lasserre, A. and Bajpai, P.K., Ceramic Drug-Delivery Devices, *Crit. Rev. Therap. Drug Carrier Syst.*, 1998, no. 11, pp. 1–56.

95. Tyle, P., *Drug Delivery Devices: Fundamentals and Applications*, New York: Marcel Dekker, 1988.

96. Morrell, R., *Handbook of Properties of Technical and Engineering Ceramics. Part 1: An Introduction for the Engineer and Designer*, London: Her Majesty's Stationary Office, 1989.

97. Leont'ev, V.K., Volozhin, A.I., Kurdyumov, S.G., *et al.*, Clinical Application of the New Preparations Gidroksiapol and Kolapol: First Results, *Stomatologiya*, 1995, no. 5, p. 69.

98. Komlev, V.S., Porous Hydroxyapatite Ceramics and Related Composites, *Extended Abstract of Cand. Sci. (Eng.) Dissertation*, Moscow: Inst. of Physicochemical Problems in Ceramic Science, Russ. Acad. Sci., 2001.

99. Dewith, G. and Gorbijn, A.T., Metal Fibre Reinforced Hydroxyapatite Ceramics, *J. Mater. Sci.*, 1989, vol. 24, no. 14, pp. 3411–3415.

100. Tamari, N., Kondo, N., Mouki, M., *et al.*, Effect of Calcium Fluoride Addition on Densification and Mechanical Properties of Hydroxyapatite–Zirconia Composite Ceramics, *J. Ceram. Soc. Jpn.*, 1987, vol. 95, no. 8, p. 806.

101. Li, J., Forbreg, S., and Hermansson, L., Evaluation of the Mechanical Properties of Hot Isostatically Pressed Titania and Titania–Calcium Phosphate Composites, *Biomaterials*, 1991, vol. 12, no. 5, pp. 438–440.

102. Young-Min Kong, Y.M., Sona Kim, S., and Lee, S., Reinforcement of Hydroxyapatite Bioceramic by Addition of ZrO_2 Coated with Al_2O_3, *J. Am. Ceram. Soc.*, 1999, vol. 83, no. 11, p. 2963.

103. Towler, M.R. and Gibson, I.R., The Effect of Low Levels of Zirconia Addition of the Mechanical Properties of Hydroxyapatite, *J. Mater. Sci. Lett.*, 2001, vol. 20, no. 18, p. 1719.

104. Bakos, D., Soldan, M., and Hernandez-Fuentes, I., Hydroxyapatite–Collagen–Hyaluronic Acid Composite, *Biomaterials*, 1999, vol. 20, no. 2, pp. 191–195.

105. Bonfield, W., Grynpas, M.D., Tully, A.E., *et al.*, Hydroxyapatite Reinforced Polyethylene—a Mechanically Compatible Implant, *Biomaterials*, 1981, vol. 2, no. 1, pp. 137–156.

106. Dalby, M.J., Di Silvio, L., Harper, E.J., and Bonfield, W., *In Vitro* Evaluation of New Polymethylmethacrylate Cement Reinforced with Hydroxyapatite, *J. Mater. Sci.: Mater. Med.*, 1999, vol. 10, no. 12, p. 793.

107. Ignjatovic, N. and Delijic, K., The Designing of Properties of Hydroxyapatite/Poly-*L*-lactide Composite Biomaterials by Hot Pressing, *J. Zeit. Metal.*, 2001, vol. 92, no. 2, pp. 145–149.

108. Knepper, M., Moricca, S., and Milthorpe, B.K., Stability of Hydroxyapatite While Processing Short-Fibre Reinforced Hydroxyapatite Ceramics, *Biomaterials*, 1997, vol. 18, no. 23, p. 1523.

109. Di Silvio, L., Dalby, M., and Bonfield, W., *In Vitro* Response of Osteoblasts to Hydroxyapatite-Reinforced Polyethylene Composites, *J. Mater. Sci.: Mater. Med.*, 1998, vol. 9, no. 12, pp. 845–848.

110. Wang, M., Bonfield, W., and Joseph, R., Hydroxyapatite–Polyethylene Composites for Bone Substitution: Effects of Ceramic Particle Size, *Biomaterials*, 1998, vol. 18, no. 24, pp. 2357–2366.

111. Watson, K.E., Tenhuisen, K.S., and Brown, P.W., The Formation of Hydroxyapatite–Calcium Polyacrylate Composites, *J. Mater. Sci.: Mater. Med.*, 1999, vol. 10, no. 4, pp. 205–213.

112. Okuno, M. and Shikinami, Y., Bioresorbable Devices Made of Forged Composites of Hydroxyapatite (HA) Particles and Poly-*L*-lactide (PLLA): Part I: Basic Characteristics, *Biomaterials*, 1999, vol. 19, no. 9, p. 859.