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Mechanochemistry of Hydroxyapatite and Its Substituted Forms

N. V. BULINA, M. V. CHAIKINA

*Institute of Solid State Chemistry and Mechanochemistry, Siberian Branch of the Russian Academy of Sciences, Novosibirsk, Russia**E-mail: bulina@solid.nsc.ru*

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Abstract

The present review is concerned with advances in the area of hydroxyapatite mechanochemistry. The features of the mechanochemical method for obtaining this mineral, the reactions proceeding in the reaction chamber, the parameters affecting the process efficiency are considered, and the advantages of the method are listed. It has been shown that rapid mechanochemical synthesis of not only stoichiometric hydroxyapatite, but also various options of substitution in its structure within a wide range of concentrations can be carried out in a high-energy planetary mill at a high frequency of vial rotation.

Keywords: hydroxyapatite, substitution, synthesis methods, mechanochemistry, planetary mill

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HYDROXYAPATITE AND ITS SUBSTITUTED FORMS

Hydroxyapatite (HA) $\text{Ca}_5(\text{PO}_4)_3(\text{OH})$ is a mineral of natural origin (Fig. 1), which is a representative of a broad apatite group with the general chemical formula $\text{A}_5[\text{XO}_4]_3\text{Z}$ and the general hexagonal space group $P6_3/m$ [1].

As a rule, hydroxyapatite occurs in continental and marine phosphorus ores of geological or biogenic origin in the form of polycrystalline inclusions. The single crystals of HA (see Fig. 1, *a*) are found rather rarely [1–3]. Hydroxyapatite is the

basis of the mineral component of bone and dental tissues of humans and vertebrate animals [4]. Biogenic HA modified with various additives (substituent ions) accounts for 50–60 wt% of the human bone tissue. The HA nanocrystals inserted into a dense collagenous matrix in a special manner provide the strength of the bony skeleton. The bone tissue of humans is subjected to slow re-modelling during the whole lifetime (~5 % of the total skeleton mass is renewed every year). As a consequence of continuous resorption followed by the recovery of the formed cavities, the



Fig. 1. Natural HA crystal [3] (a), synthetic HA powder (b) and the unit cell of HA (c). Here and below in Fig. 2–9: HA – hydroxyapatite.

composition of bony mineral component (biogenic HA) changes during the lifetime due to the effect of internal (physiology, diseases) and external (life conditions, nutrition) factors. Hydroxyapatite is also detected as unfavourable calcificates, such as uroliths, dental calculi, deposits in menisci, vessels, and on artificial heart valves [4]. The studies into the possibility to suppress pathological calcification are actively performed in the area of molecular medicine.

The main area of synthetic HA application (see Fig. 1, b) is determined by its presence in human bone tissues due to which humans live an active life. Synthetic HA is characterised as non-toxic, biocompatible and osteoconductive material possessing the ability to stimulate the new formation of native bone tissue and thus finding wide application in bone material engineering, including bone cements, dense ceramic implants, and stable bioactive coatings on metal implants [5, 6]. At the same time, the ability of nanocrystalline HA to dissolve in the physiological environment allows using it not only as a stable biologically inert material but also as a bioresorbable one [7]. Implantation of the fine powder, porous granules or a porous 3D-product is accompanied by the slow bioresorption of the material, which gets gradually dissolved and at the same time is the source of the mineral component, necessary for building fully functional bone tissue at the site of a bone defect. In addition, synthetic HA can be used as a carrier for controllable targeted delivery of drugs and contrasting agents for malignant tumour hyperthermia [8, 9], for teeth sensitivity reduction and tooth enamel rebuilding [8]. Along with the medical applications of HA, its catalytic and sorption capacities are also used [10, 11], as well as fireproof and electrically insulating characteristics [12]. The high thermal stability of HA and its resistance to fire allow using this

material to make separators for electrochemical cells [12].

The chemical formula of HA is often presented in scientific publications as $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$, because the unit cell of HA (see Fig. 1, c) is composed of two formula units. A cell contains 10 calcium cations occupying two non-equivalent positions: 4 cations in Ca1 positions, each of them is surrounded by nine oxygen atoms of anionic (PO_4)-groups, and 6 cations in Ca2 positions, each of them surrounded by six oxygen atoms of the (PO_4)-group and one of the hydroxyl group [13]. The volumes of coordination polyhedrons of Ca1 and Ca2 cations are 31.84 and 21.54 Å³, respectively. The average Ca–O distance in the polyhedrons of Ca1 and Ca2 are 2.55 and 2.45 Å, respectively. The Ca2 cations form a hexagonal channel along the c axis, filled with OH[−] ions (see Fig. 1, c).

Unlike other calcium phosphates, HA structure allows a broad range of isovalent and heterovalent substitutions with interchanges of both cations and anionic groups. Either singular or multiple substitutions are possible, resulting in the formation of a series of solid solutions, where the limiting composition is a compound with full or partial substitution [14]. Unlike for metal systems, the density of atoms in HA lattice is substantially lower, so substitution is possible within the broad ranges of concentrations of the sizes of chemical elements substantially differing from each other in their electrochemical potential values. Different versions of substitutions in the structure of synthetic HA are under extensive investigation during the recent decades [15–19] because the introduction of substituting ions even in trace amounts can cause substantial changes in its physical, chemical, mechanical and biological characteristics (Fig. 2).

A substantial role in heterovalent substitution in HA is played by the hydroxyl group, which

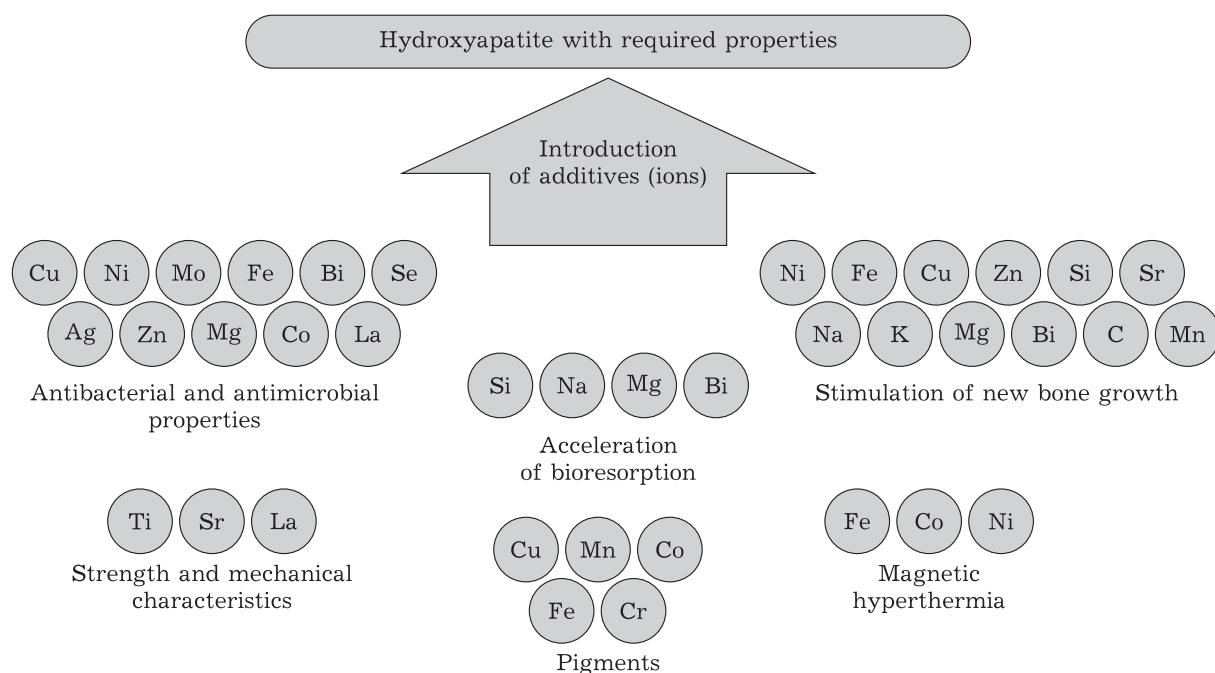


Fig. 2. Versions of possible substituting ions for HA structure with the indication of gained properties.

takes the necessity to compensate the charge. If the positive charge is lacking, a vacancy arises instead of the OH group, while if the positive charge is in excess, it is substituted by the O^{2-} anion. So, either excessive positive or negative charge can be compensated. However, the concentration of OH groups in the hydroxyl channel of HA is not high (there are only two groups per a unit cell of HA), so, as a rule, heterovalent substitution is limited by substitution degree ($x = 1$), which is even excessive for obtaining the required biological properties [16]. By means of the double heterovalent substitution of the cation and the anionic group simultaneously, the substituents can be chosen so that the excessive charges will compensate each other, and the limitation on the maximal substitution extent will be eliminated.

By present, the following possible substituents for cations and anionic groups of HA have been discovered [14, 16]:

1) for calcium cations: Li^+ , Na^+ , K^+ , Ag^+ , Mg^{2+} , Al^{3+} , Mn^{2+} , Fe^{2+} , Co^{2+} , Ni^{2+} , Cu^{2+} , Zn^{2+} , Sr^{2+} , Cd^{2+} , Ba^{2+} , Pb^{2+} , Bi^{2+} , Sn^{2+} , Eu^{2+} , Cr^{3+} , Fe^{3+} , Ne^{3+} , Gd^{3+} , La^{3+} , Ce^{3+} , Sm^{3+} , Eu^{3+} , Y^{3+} , Zr^{4+} , Ti^{4+} , Th^{4+} , U^{4+} , U^{6+} and $\square$, where $\square$ is a vacancy;

2) for the phosphate group: HPO_4^{2-} , CO_3^{2-} , SO_4^{2-} , CrO_4^{2-} , SeO_4^{2-} , BO_3^{3-} , AsO_4^{3-} , SiO_4^{3-} , VO_4^{3-} , CrO_4^{3-} , MnO_4^{3-} , ReO_5^{3-} , GeO_4^{4-} and BO_5^{5-} ;

3) for the hydroxyl group: F^- , Cl^- , Br^- , I^- , O^{2-} , O_2^{2-} , S^{2-} , BO_2^{2-} , CO_3^{2-} , NO_2^- , NO_3^- , O^{3-} and $\square$.

MECHANOCHEMICAL SYNTHESIS OF STOICHIOMETRIC HYDROXYAPATITE

Various solid-phase, liquid-phase, and combined methods are used to synthesise HA [20, 21]. The methods that are most frequently mentioned in publications are: precipitation from solutions, sol-gel, hydrothermal, ceramic, and mechanochemical. Under certain conditions, these synthesis methods allow obtaining a single-phase material in the amounts sufficient for subsequent application. The works involving HA synthesis by hydrolysis, pyrolysis, combustion, emulsion-based methods are known [20]. Either chemical reagents or natural materials, for example, cattle bones, can be used to synthesise HA [22].

A distinguishing feature of the solid-phase mechanochemical method is the synthesis through the mechanical destruction of the lattice of initial reagents [23, 24]. This is a rather simple single-stage process involving no solvents and requiring no additional treatment of the powder material obtained, or utilisation of the by-products. The method is based on the treatment of initial reagent mixture in a ball mill through continuous rotation together with the milling tools (balls) for a definite time interval. The solid-phase chemical reaction is initiated locally because of plastic deformation and point energy evolution as a result of ball impact and friction. Due to intense rotation, continuous mixing with a permanent renew-

al of reacting surfaces occurs, which promotes high conversion. If the interaction between solid reagents is impossible at room temperature, this chemical reaction can be initiated by the mechanochemical method. During mechanochemical treatment in certain planetary mills, temperature can rise up to 800 °C over a micron-sized area within a fraction of a second [24–26].

At the beginning of the reagent mixture treatment, intense grinding and mechanical activation proceed, accompanied by an increase in specific surface and the formation of various defects on the surface of particles, which enhances their reactivity [23, 27]. The average temperature of the reaction medium increases [25, 26], and the stage of chemical interaction of the components is thus launched, leading to the formation of a new structure with the required stoichiometry. The duration of reaction mixture treatment depends first of all on the kinetic energy of balls. This parameter is affected by mill type, its design and the frequency of vial rotation. The higher is accumulated kinetic energy of balls, the shorter time is necessary for the treatment of reaction mixture. For instance, to obtain HA powder in a shaker mill Spex 8000 (USA) with the oscillatory motion of balls at ~1000 cycles/min, it is necessary to treat the initial mixture for 20–30 h [28, 29]. The duration of HA synthesis in a planetary mill Fritsch Pulverisette 6 (Germany) at 370 r.p.m. can reach 60 h [30, 31], while 20 min is sufficient for the treatment in planetary mills AGO-2 and AGO-3 (Russia) at 1800 and 1200 r.p.m., respectively [32]. The material of milling balls, their size, number, the ratio of ball to powder mass, and the rate of mill cooling affect the duration of mechanochemical synthesis to a smaller extent [33, 34].

It should be stressed that if the kinetic energy of balls in the ball mill used for treatment is insufficient for the transition to the second stage, a significant increase in the time of initial mixture treatment would not lead to the desirable effect, namely the synthesis of the new compound, because permanently released energy dissipates in the form of heat, and the mill reaches its energy maximum with time. Structural and chemical transformations take place during mechanochemical synthesis only in the case if the applied strain exceeds the theoretical ultimate stress limit of the reagents [35].

The mechanochemical synthesis of HA has a limit, which is determined by the locally released energy. Each mill is characterised by its own limiting size of the formed HA crystallites, which

does not change with a further increase in the time of powder treatment under the same conditions [36, 37].

The works are known in which the mechanochemical synthesis of HA was carried out using the liquid phase. For instance, the authors of [38] compare the results of dry and wet mechanochemical processes in the planetary ball mill after the addition of different amounts of water to the initial powder mixture of $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$ and CaO. That investigation showed the advantage of the dry version, in which the synthesis proceeds faster, the wear of milling bodies is smaller, and there is no need to filtrate and dry the synthesised substance. In the case of mechanochemical synthesis in the liquid medium, the efficiency of chemical interaction between the components decreases substantially because of the absence of good contact between the particles [23].

Some authors [38–40] term the two-stage synthesis involving the treatment of initial reaction mixture in the ball mill and high-temperature annealing of the resulting powder as a mechanochemical method. This procedure cannot be called mechanochemical because the formation of HA structure proceeds during thermal treatment, while in the mill the powder is only homogenised and activated. In this case more suitable title is ceramic method, assisted by mechanical activation.

MECHANOCHMEICAL SYNTHESIS OF STOICHIOMETRIC HYDROXYAPATITE IN HIGH-ENERGY PLANETARY MILLS

The high rate of HA synthesis in planetary ball mills is provided by centrifugal forces arising during the rotation of each vial around its own axis and around their common planetary rotational axis. This centrifugal force is several ten times greater than the gravitational force and thus the energy in these mills is 2–3 orders of magnitude higher than in usual ball mills [23].

At the Institute of Solid State Chemistry and Mechanochemistry SB RAS own-produced high-energy planetary ball mills AGO-2 with the powder load weight of 20 g [41] and AGO-3 with 600 g powder load weight [42] are used for the mechanochemical synthesis of apatites at the vial rotation frequency of 1800 and 1200 r.p.m., respectively (centripetal acceleration ~40g).

The procedure developed for the mechanochemical synthesis of HA is based on the principle of acid salt neutralisation by a base (basic

TABLE 1

The reactions of mechanochemical synthesis of hydroxyapatite (HA) from different reagent mixtures with the indication of the standard Gibbs energy values ($\Delta_r G$) of these reactions

Reaction No.	Reactions of HA mechanochemical synthesis	$\Delta_r G$, kJ/mol
1	$3(\text{Ca}(\text{H}_2\text{PO}_4)_2 \cdot \text{H}_2\text{O}) + 7\text{CaO} \rightarrow \text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2 + 8\text{H}_2\text{O}$	-1164.59
2	$3(\text{Ca}(\text{H}_2\text{PO}_4)_2 \cdot \text{H}_2\text{O}) + 7\text{Ca}(\text{OH})_2 \rightarrow \text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2 + 15\text{H}_2\text{O}$	-765.96
3	$6(\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}) + 4\text{CaO} \rightarrow \text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2 + 14\text{H}_2\text{O}$	-690.28
4	$6(\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}) + 4\text{Ca}(\text{OH})_2 \rightarrow \text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2 + 18\text{H}_2\text{O}$	-462.60
5	$6\text{CaHPO}_4 + 4\text{CaO} \rightarrow \text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2 + 2\text{H}_2\text{O}$	-670.06
6	$6\text{CaHPO}_4 + 4\text{Ca}(\text{OH})_2 \rightarrow \text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2 + 6\text{H}_2\text{O}$	-442.38
7	$3\text{Ca}_3(\text{PO}_4)_2 + \text{CaO} + \text{H}_2\text{O} \rightarrow \text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$	-166.17
8	$3\text{Ca}_3(\text{PO}_4)_2 + \text{Ca}(\text{OH})_2 \rightarrow \text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$	-109.23
9	$3\text{Ca}_2\text{P}_2\text{O}_7 + 4\text{CaO} + \text{H}_2\text{O} \rightarrow \text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$	-631.24
10	$3\text{Ca}_2\text{P}_2\text{O}_7 + 4\text{Ca}(\text{OH})_2 \rightarrow \text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2 + 3\text{H}_2\text{O}$	-403.57

oxide) with the formation of the basic salt (HA) and some amount of water molecules (Table 1) during the joint treatment of reagents in the planetary ball mill. The reaction proceeds involving the solid phases similar to the case of acid-base interactions in liquid phases. This process has been called soft mechanochemistry [23, 32]. The initial reagents are mixtures that do not react during mixing in a mortar, but when the energy is supplied with the help of the mechanochemical route, HA structure is formed. The temperature of balls in the mills in the operation mode can reach 800 °C [23, 25, 26], therefore, temperature at the point of the direct contact of a ball with the surface of the vial or a neighbouring ball is substantially higher. Upon impact, pulsed local compression occurs at the ball contact point, followed by underpressure. The formation of water as reaction product and local heating with an increase in pressure during mechanochemical synthesis create the conditions similar to those of hydrothermal synthesis [23, 43].

It has been demonstrated in the studies of reactions involved in the mechanochemical synthesis of HA using different calcium oxides, hydroxides and phosphates (see Table 1) that the course of mechanochemical synthesis is affected both by thermodynamic and kinetic factors [32]. In this mode of mechanochemical treatment, the thermodynamic properties of a mixture of initial reagents manifest themselves at the initial stage of interaction. In the reactions that are most favourable from the viewpoint of energy, apatite nucleation starts more rapidly and actively (Fig. 3), however, reactions with hydroxides proceed with a higher efficiency, though they are less favour-

able than the reactions participated by oxides (see Table 1). An additional amount of water, released into the space between particles in the case when hydroxides are used, is likely to increase the molecular water layer on particle surface and enhance binding between the neighbouring particles due to hydrogen and donor-acceptor bonds of water molecules with the surface atoms and groups of the solid phase [23]. However, excessive amount of water molecules causes a negative effect. The release of a large amount of water (crystal water in reactions 1–4, see Table 1) at the intermediate stage of synthesis (mixture treatment for ~5 min) leads to substantial agglomeration and consolidation of powder, which is accompanied by its accretion to vial walls, and HA synthesis is hindered in spite of the active start. Due to the absence of any possibility for an efficient renewal of the zone of contact between unreacted components by mixing them, the complete conversion of initial reagents into the target product is observed at a time characteristic of less favourable reactions but with free-running mixtures (see Fig. 3).

It has been concluded in [32] that the synthesis of HA in the planetary ball mill with the centripetal acceleration ~40g proceeds best of all from the viewpoint of technology if a mixture of CaHPO_4 with CaO or $\text{Ca}(\text{OH})_2$ is employed (reactions 5 and 6, see Table 1). During the treatment of initial mixture for 20 min in AGO-3 planetary mill, single-phase free-flowing HA powder with a broad particle size range (Fig. 4), specific surface 40–50 m²/g, average crystallite size ~25 nm and lattice parameters $a = 9.43 \text{ \AA}$ and $c = 6.89 \text{ \AA}$ can be obtained.

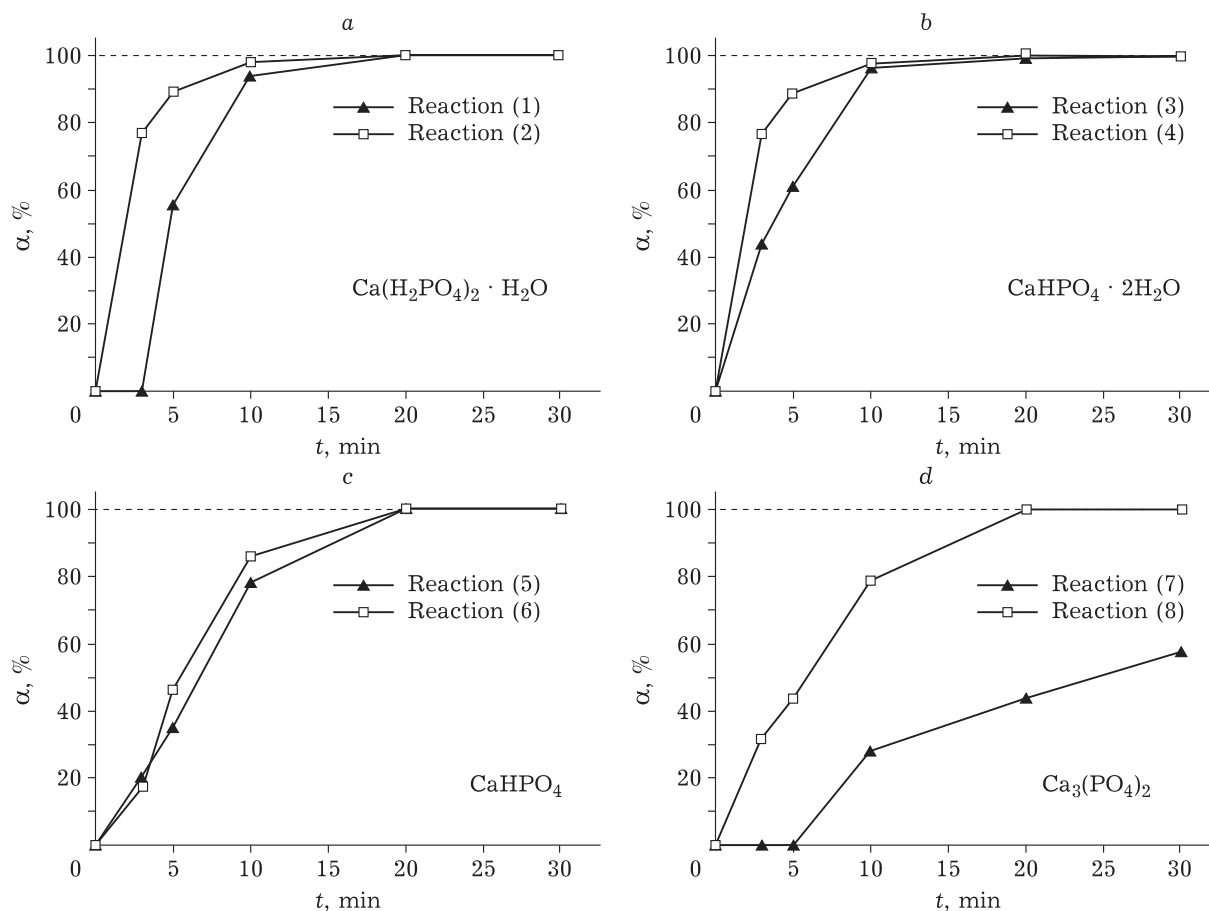


Fig. 3. HA transformation degree (α) for different time of synthesis from a mixture of CaO or $\text{Ca}(\text{OH})_2$ with $\text{Ca}(\text{H}_2\text{PO}_4)_2 \cdot \text{H}_2\text{O}$ (a), $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$ (b), CaHPO_4 (c) or $\text{Ca}_3(\text{PO}_4)_2$ (d).

The studies of HA structure formation in the planetary ball mill according to reaction 5 [36] have revealed the formation of calcium-deficient apatite with $\text{Ca}/\text{P} < 1.67$ within the first minutes of synthesis, which agrees with the conclusions made by the authors of [44]. Further mechanical treatment involves gradual insertion of lacking cations, which is depicted in the changes of HA lattice parameters. The synthesis of HA can be considered completed only after the stabilisation of lattice parameters. It should be noted that no clearly expressed stage of initial reagent amorphisation is observed during the mechanochemical synthesis of HA [36]. The synthesised HA is not transformed into the amorphous state even after a substantial increase in the duration of its treatment under the same conditions [36]. The reason is in subsequent mechanical activation of HA, which involves two competing processes: the formation of defects under the action of impact-and-shear load and their relaxation as a result of released energy.

It is noteworthy that the mechanochemical synthesis of HA in high-energy planetary ball

mills with centripetal acceleration of $\sim 40g$ is possible only when metal vials and metal milling bodies are used. Under these conditions, not only reaction mixture grinding but also metal attrition proceeds in the reaction zone, so even in the case if lining is employed, synthesis products inevitably contain admixtures of abraded milling equipment. Iron concentration in synthesis products is several thousandths wt% in the case if vials made of quenched stainless steel and balls made of constructional bearing-grade steel, lined with the initial reaction mixture, are used [32]. The presence of iron in such a low concentration is a positive feature if HA is intended for use in bone grafting because the low concentrations of iron cause increased proliferation of bone cells and promote the formation of new bone tissue [16].

One of the important advantages of the mechanochemical method of synthesis is retention of the required Ca/P molar ratio, which is essential for HA because the structure and properties of the product depend on this ratio. To synthesise stoichiometric HA, Ca/P ratio should be exactly 1.67. In the case of any deviation, a lack or excess

of calcium cations is observed, which results in the formation of so-called calcium-deficient or calcium-enriched HA [43], which has the same structure as stoichiometric HA but possesses substantially lower thermal stability (stoichiometric HA is stable up to 1300 °C [45]). Apatite of this kind is composed of a single phase directly after the synthesis (for any synthesis method), but contains impurity phases after annealing (Fig. 5). In this case, apatite is decomposed at a temperature of 400–700 °C (Fig. 6). Heating at a lower temperature is accompanied by the release of sorbed (up to 200 °C) and structural water (200–400 °C) and does not lead to any phase transformations. The Ca/P ratio in HA synthesised mechanochemically depends only on the corresponding ratios of components in the starting reaction mixture, which allows the synthesis of single-phase HA with any Ca/P ratio within the range of 1.5–1.9, with high reproducibility [43].

Mechanochemically synthesised HA is not toxic, biocompatible [46, 47], stable up to 1300 °C [45], so it can be immediately (without any additional procedures) used to make bioactive coatings on metal implants by micro-arc oxidation [37], to prepare dental cement [48], and as a biologically active additive into the enamel restoration products [49]. After separation of the 64–100 µm fraction, the powder can be used to make apatite coatings on metal implants by detonation sputtering [50]. After additional mechanical treatment of mechanochemically synthesised HA powder in a bead mill with the beads of a definite size [51], stable HA suspension with particle size ~1 µm can be prepared (Fig. 7) for the production of remineralising gels, toothpastes, and reconstructive bone surgery cements. The treatment of mechanochemically synthesised HA powder using a number of simple procedures, such as calcination and screening, allows obtaining free-flowing powder (Fig. 8) possessing increased fluidity [52]. This powder can be used as initial material to manufacture HA coatings and 3D items using the methods in which only friable powders within a specific size range can be employed (3D-printing, detonation sputtering, etc.).

MECHANOCHEMICAL SYNTHESIS OF SUBSTITUTED HYDROXYAPATITE

Mechanochemical synthesis allows obtaining different versions of single or multiple substitutions in HA structure (Table 2). One of the essen-

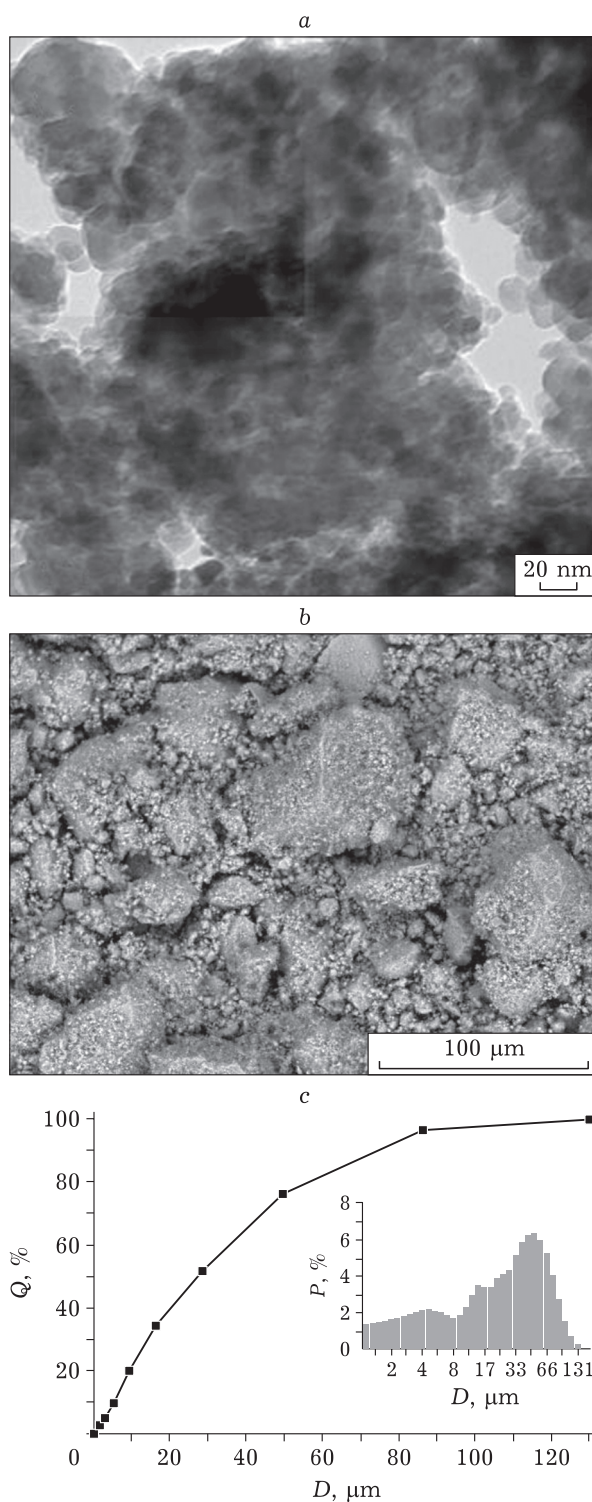


Fig. 4. HA powder obtained in the planetary ball mill AGO-3: (a) – TEM image; (b) – SEM image; (c) – particle size distribution, where Q is the cumulative contribution of particles. Insert: P is the fraction of the particles of a given size with respect to the total volume occupied by the particles, D is particle diameter.

tial advantages of this method is the possibility to assign the exact concentration of substituents, which is very important for medicine, because

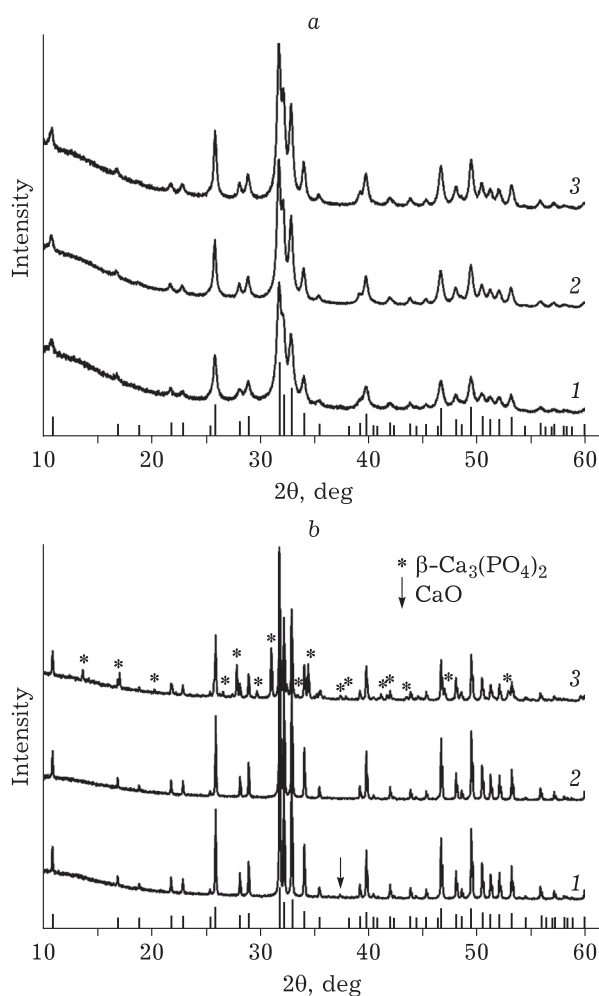


Fig. 5. Diffraction patterns of mechanochemically synthesised HA powders with Ca/P ratio equal to 1.7 (1), 1.667 (2), and 1.6 (3) immediately after mechanochemical synthesis (a) and after annealing at 1000 °C (b). The bar spectrum corresponds to the reflections of the HA phase according to Card No. 40-11-9308 of the powder database ICDD PDF.

many elements that impart useful properties to the material in low concentrations may turn out to be toxic in higher concentrations [16]. This method does not involve side products, so all reagents introduced into the reaction volume (vial) remain there till the synthesis is complete, thus the concentration of substituting ion remains unchanged.

The list of substituted HA synthesised up to date by the mechanochemical method in various mills through the treatment of initial reagents in the powdered form is shown in Table 2. One can see that the largest number of substitution versions was obtained in planetary mills with high rotation frequency. In this case, synthesis time was less than an hour, while in low-frequency mills it was several hours or even tens of hours. It

can be assumed that the synthesis of substituted apatites is hindered in low-energy mills. Substituent ions are point defects, bringing complications into lattice formation, so in the case of high concentrations of some substituents, a 2-fold increase in the duration of treatment process is necessary [36].

Oxides, hydroxides, and phosphates can be used as the carriers of substituent cations for the mechanochemical method [59, 64]. In the case of the substitution of anion groups, the components introduced into the reaction medium are corresponding oxides [79, 80], fluorides [70, 72–74], chlorides [75, 76] or carbonates [53, 77, 78]. It is necessary to take into account that the components of an initial mixture for synthesis should have comparable hardness, otherwise they would be ground (their reaction surfaces will be renewed) at different rates, so a harder reagent would not have enough time to react completely, and it will remain as impurity [59]. It is also to be taken into account that any by-products can be captured by the forming apatite lattice, so it is desirable to provide their absence. For instance, some researchers use nitrates [57] or ammonium-containing compounds [55, 60] for the mechanochemical synthesis of substituted HA, assuming the corresponding release of admixture phase, nitrogen dioxide or ammonium hydroxide, during the mechanochemical synthesis. In this case, it is necessary to take into account the fact that (NO₃)- and (NH₄)-groups can be partially captured by the HA lattice, so the resulting HA powder should be treated additionally to remove these admixtures.

Any substituent ions introduced into the structure cause changes in the structural characteristics of the material, so compulsory control is performed by means of powder diffraction studies and transmission IR spectroscopy. Phase composition, changes of the unit cell parameters and its volume are analysed. Structure refinement is carried out if possible, with the determination of substituent concentration. It is compulsory to analyse the existing chemical bonds and to determine the elemental composition of the synthesised substance. Essential additional information can be gained using such analysis methods as nuclear magnetic resonance, electron paramagnetic resonance, Mössbauer spectroscopy, transmission microscopy, simultaneous thermal analysis and *ex-situ* or *in-situ* thermal diffractometry.

It should be noted that IR spectroscopy in the reflection mode, unlike for transmission version,

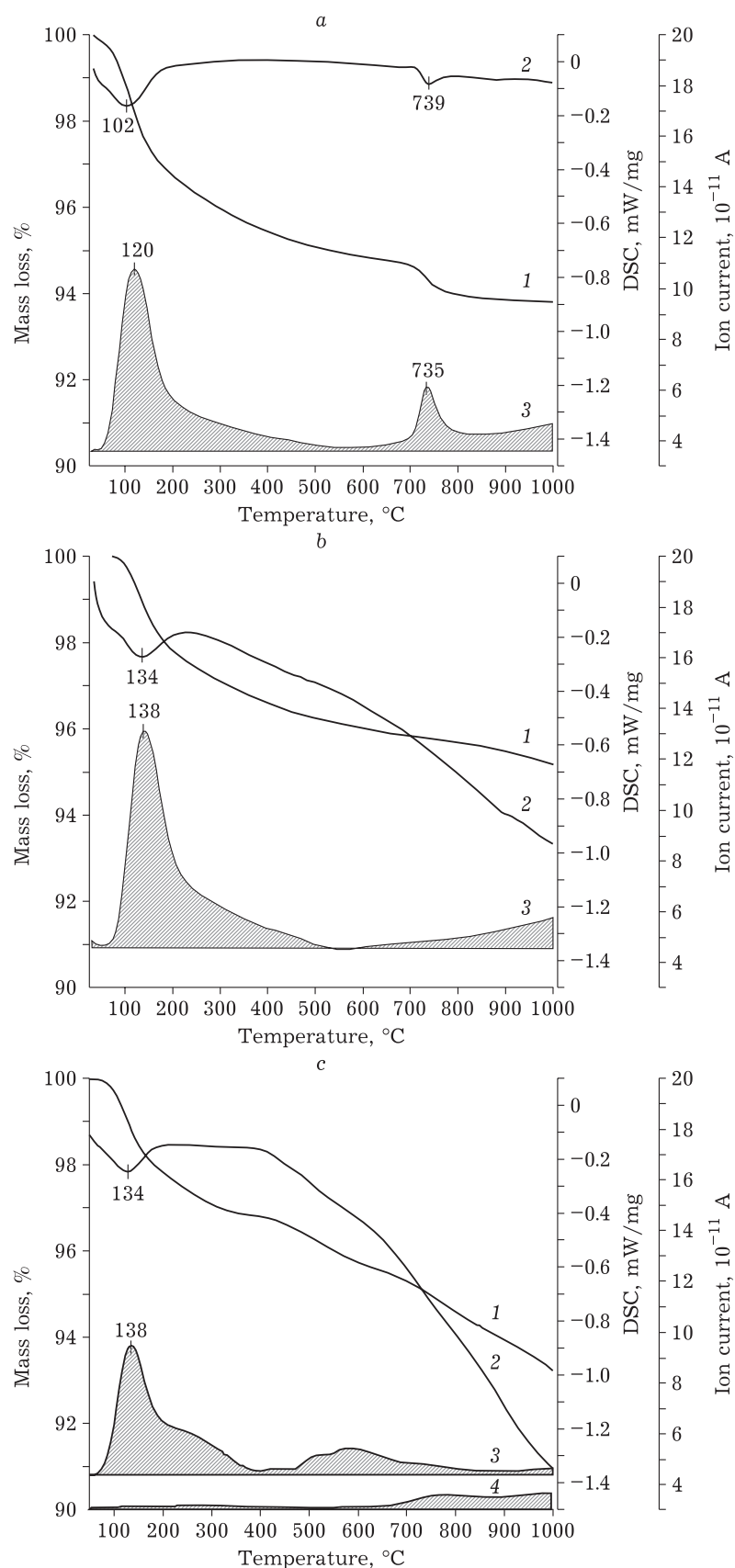


Fig. 6. Synchronous thermal analysis of HA samples with Ca/P ratio equal to 1.5 (a), 1.67 (b), and 1.9 (c): 1 – mass loss; 2 – DSC (the differential scanning calorimetry curve); 3 – H_2O evolution; 4 – CO_2 evolution.

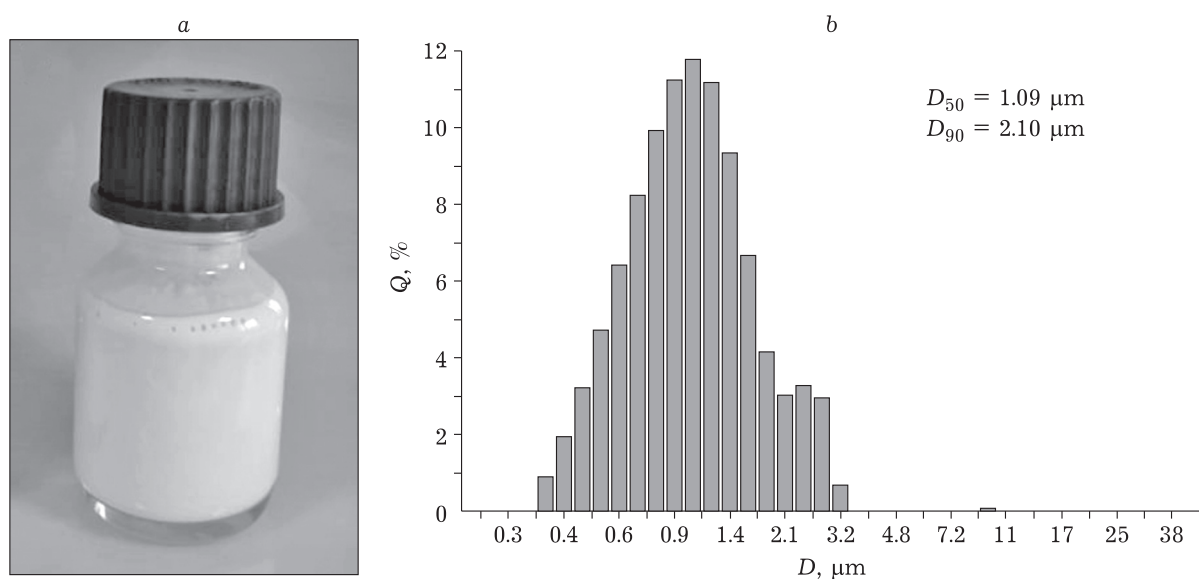


Fig. 7. Aqueous 30 % suspension of HA (a) and particle size distribution in it (b), where Q is the cumulative contribution of particles, D is particle size, D_{50} and D_{90} are particle size values for which Q is equal to 50 and 90 %, respectively.

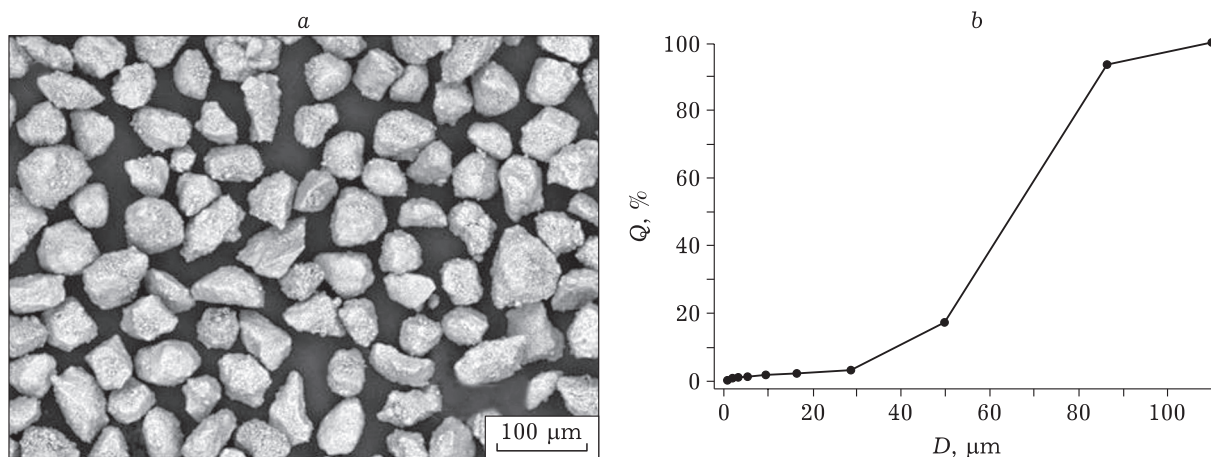


Fig. 8. SEM image of HA powder with the powder flow rate equal to 55 s/50 g (a), and particle size distribution in it (b), where Q is the cumulative contribution of particles, D is particle diameter.

is less sensitive in the high-frequency region, where the stretching vibrations of OH groups in HA manifest themselves (Fig. 9, inset). These OH groups render important information on their presence and concentration in HA structure. In the case of low OH group concentration, their bands may not appear in the reflection mode, thus producing a misleading impression of their absence. In both spectrum recording modes, OH group vibrations at 630 cm^{-1} appear, and this band can be used to follow the concentration of hydroxyl groups, but its intensity decreases substantially if the symmetry of the nearest surroundings is disturbed, which leads to the incorrect opinion on the decrease of the amount of OH groups in HA structure [58], so it is necessary to

measure the band at 3572 cm^{-1} . To analyse the structure of synthesised apatite, it is very important to have reliable information within the entire range ($500\text{--}4000\text{ cm}^{-1}$), because in addition to phosphate and hydroxyl groups characteristic of HA, the bands of other complex anions that can either be substituents in HA structure or belong to a side impurity also appear within this range.

Using transmission microscopy to analyse the structure of synthesised apatites, it is necessary to take into account the fact that in the high resolution mode, the apatites with low thermal stability start to decompose under the action of the mean in vacuum [56], defect-bearing nanocrystalline particles and amorphous phosphates start to crystallise (see a video record in Supplemen-

TABLE 2
Substituted hydroxyapatites synthesised mechanochemically without participation of liquids

Substituent	Formula	Substitution degree	Mill type	Mode	Synthesis time	References
H ⁺	Ca _{10-x} (HPO ₄) _x (PO ₄) _{6-x} (OH) _{2-x}	0.4 ≤ x ≤ 1	AGO-2	1800 r.p.m.	30 min	[43, 53]
K ⁺	Ca _{10-x} K _x (PO ₄) _{6+x} (OH) _{2-x}	x = 0.04	EL-2	850 r.p.m.	30 min	[54]
Na ⁺	Ca _{10-x} Na _x (PO ₄) _{6+x} (OH) _{2-x}	0.1 ≤ x ≤ 0.9	Fritsch	370 r.p.m.	15 h	[55]
Ag ⁺	Ca _{10-x} Ag _x (PO ₄) ₆ (OH) _{2-x}	0.2 ≤ x ≤ 1.5	AGO-2	1800 r.p.m.	30 min	[56]
		0.05 ≤ x ≤ 0.2	Fritsch Pulverisette	600 r.p.m.	3 h	[57]
Mg ²⁺	Ca _{10-x} Mg _x (PO ₄) ₆ (OH) ₂	x = 0.5	AGO-3	1200 r.p.m.	20 min	[58]
		0.2 ≤ x ≤ 2	AGO-2	1800 r.p.m.	30 min	[59]
		0.1 ≤ x ≤ 0.5	Retsch	370 r.p.m.	15 h	[60]
Ba ²⁺	Ca _{10-x} Ba _x (PO ₄) ₆ (OH) ₂	x = 1	EL-2	850 r.p.m.	30 min	[54]
Sr ²⁺	Ca _{10-x} Sr _x (PO ₄) ₆ (OH) ₂	0.2 ≤ x ≤ 10	AGO-2	1800 r.p.m.	30 min	[61]
		x = 1.5	AGO-3	1200 r.p.m.	20 min	[58]
Cu ²⁺	Ca _{10-x} Cu _x (PO ₄) ₆ (OH) ₂	0.2 ≤ x ≤ 2	AGO-2	1800 r.p.m.	30 min	[62]
Zn ²⁺	Ca _{10-x} Zn _x (PO ₄) ₆ (OH) ₂	0.2 ≤ x ≤ 2	AGO-2	1800 r.p.m.	30 min	[62]
Fe ²⁺	Ca _{10-x} Fe _x (PO ₄) ₆ (OH) _{2-x} O _x	0.5 ≤ x ≤ 1	AGO-2	1800 r.p.m.	30 min	[63]
Fe ³⁺	Ca _{10-x} Fe _x (PO ₄) ₆ (OH) _{2-x} O _x	0.5 ≤ x ≤ 1	AGO-2	1800 r.p.m.	30 min	[63]
Al ³⁺	Ca _{10-x} Al _x (PO ₄) ₆ (OH) _{2-x} O _x	0.2 ≤ x ≤ 1	Spex 8000M	1725 cycle/min	1 h	[64]
La ³⁺	Ca _{10-x} La _x (PO ₄) ₆ (OH) _{2-x}	0.2 ≤ x ≤ 2	AGO-2	1800 r.p.m.	30 min	[65]
Mg ²⁺ + Sr ²⁺	Ca _{10-x-y} Mg _x Sr _y (PO ₄) ₆ (OH) ₂	x = 1.5, y = 1.5	AGO-3	1200 r.p.m.	30 min	[58]
Sr ²⁺ + (SiO ₄) ⁴⁻	Ca _{10-x} Sr _x (PO ₄) _{6-y} (SiO ₄) _y (OH) _{2-y}	x = 0.5, y = 0.5	AGO-3	1200 r.p.m.	25 min	[66]
Zn ²⁺ + (SiO ₄) ⁴⁻	Ca _{10-x} Zn _x (PO ₄) _{6-y} (SiO ₄) _y (OH) _{2-y}	x = 0.1, y = 0.2	AGO-2	1800 r.p.m.	30 min	[46]
		0.2 ≤ x ≤ 1 0.2 ≤ y ≤ 1	AGO-2	1800 r.p.m.	30 min	[47]
		x = 0.5, y = 0.5	AGO-3	1200 r.p.m.	25 min	[67]

Substituent	Formula	Substitution degree	Mill type	Mode	Synthesis time	References
$\text{Fe}^{3+} + (\text{SiO}_4)^{4-}$	$\text{Ca}_{10-x}\text{Fe}_x(\text{PO}_4)_{6-y}(\text{SiO}_4)_y(\text{OH})_{2-x}\text{O}_{x/2}$	$0.2 \leq x \leq 1.5$	AGO-2	1800 r.p.m.	30 min	[68]
$\text{La}^{3+} + (\text{SiO}_4)^{4-}$	$\text{Ca}_{10-x}\text{La}_x(\text{PO}_4)_{6-x}(\text{SiO}_4)_x(\text{OH})_2$	$0.2 \leq x \leq 2$	AGO-2	1800 r.p.m.	30 min	[37]
		$x = 0.5$	AGO-3	1300 r.p.m.	25 min	[37]
	$\text{Ca}_{10-x}\text{La}_x(\text{PO}_4)_{6-x}(\text{SiO}_4)_x\text{O}_2$	$2 \leq x \leq 6$	AGO-2	1800 r.p.m.	30–100 min	[36]
$\text{Zn}^{2+} + \text{Ag}^+ + (\text{SiO}_4)^{4-}$	$\text{Ca}_{10-x-y}\text{Zn}_x\text{Ag}_y(\text{PO}_4)_{6-z}(\text{SiO}_4)_z(\text{OH})_{2-y-z}$	$x = 0.1,$ $y = 0.1,$ $z = 0.2$	AGO-2	1800 r.p.m.	30 min	[69]
F^-	$\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_{2-x}\text{F}_x$	$0.2 \leq x \leq 2$	AGO-2	1800 r.p.m.	30 min	[70]
		$0.1 \leq x \leq 2$	Fritsch Pulverisette 5	200 r.p.m.	40 h	[71]
		$0.5 \leq x \leq 2$	Fritsch Pulverisette 5	250 r.p.m.	10 h	[72]
			Fritsch Pulverisette 5	300 r.p.m.	6 h	[73]
$\text{F}^- + (\text{CO}_3)^{2-}$	$\text{Ca}_{10}(\text{PO}_4)_{6-y}(\text{CO}_3)_y\text{F}_x$	$x = 2$	Retsch	230 r.p.m.	9 h	[74]
Cl^-	$\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_{2-x}\text{Cl}_x$	$x = 2$	EI-2	850 r.p.m.	30 min	[75]
$\text{F}^- + \text{Cl}^-$	$\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_{2-2x-2y}\text{Cl}_x\text{F}_{2y}$	$0.125 \leq x \leq 0.375$ $0.375 \geq y \geq 0.125$	Spex 8000M	1060 cycle/min	1 h	[76]
$(\text{CO}_3)^{2-}$	$\text{Ca}_{10-x}(\text{PO}_4)_{6-x}(\text{CO}_3)_x(\text{OH})_{2-x}$	$x = 1$	AGO-2	1800 r.p.m.	30 min	[53]
	$\text{Ca}_{9+y}(\text{PO}_4)_5(\text{CO}_3)_x(\text{OH})_{1+2y}$	$x = 1$	Spex 8000D	~1000 cycle/min	6 h	[77]
			MTI SFM	450 r.p.m.	10 h	[78]
$(\text{SiO}_4)^{4-}$	$\text{Ca}_{10}(\text{PO}_4)_{6-x}(\text{SiO}_4)_x(\text{OH})_2$	$0.2 \leq x \leq 2$	AGO-2	1800 r.p.m.	30 min	[79]

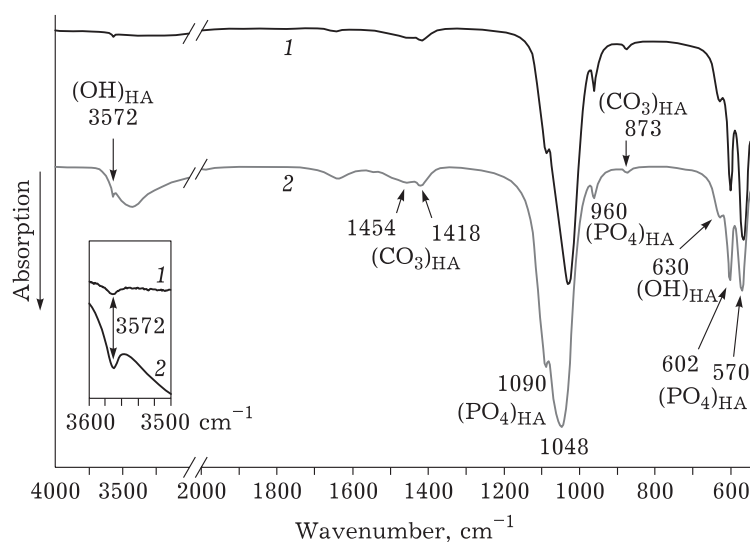


Fig. 9. IR spectra of the samples of mechanochemically synthesised HA, recorded in the reflection mode using the attachment for frustrated total internal reflection spectroscopy (1) and in the transmission mode in KBr tablets (2). The insert shows enlarged spectral region.

tary Materials for [43]), which does not allow one to obtain the information on synthesis product (the initial state of the substance before the impact of electron beam).

CONCLUSION

The importance of HA synthesis in large amounts can hardly be overestimated for the modern market. This material is a component of human bone tissues and is widely used in medicine to reconstruct bone defects resulting from traumas, definite diseases, or age-specific changes. The tendency of apatite to form various substitutions does not allow using the natural material because it contains impurity elements that alter the properties, and not always for the better.

Among diverse methods of HA synthesis, the procedure of mechanochemical synthesis deserves special attention. This method is simple to operate and allows obtaining the product directly in the powdered state without additional drying. The major advantage of this method is the dependence of atomic composition of the stoichiometric or substituted HA only on reagents ratio in the initial mixture. This ensures stable reproducibility of the target substance composition in the production of a large lot, and the simplicity of switching the synthesis procedure from one product composition to another.

Among the available mechanochemical equipment, the synthesis of HA and its modifications

proceeds with the highest efficiency in high-energy planetary ball mills AGO-2 and AGO-3, in which the material is obtained at the vial rotation frequency higher than 1000 r.p.m.. The average time of initial reagent mixture treatment in these mills is 30 min, and apatite can be obtained in the amount of 0.5 kg per cycle in AGO-3 mill, which opens the outlooks for commercial manufacture of the valuable material. A large number of the diverse versions of substitutions in the HA structure that can be prepared using these mills implies the ease of implementing this process within broad ranges of possible concentrations.

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