BINARY COMPOSITE MATERIALS WITH IMPROVED MORPHOLOGY AND SURFACE AREA AND THE PROCESSES FOR PREPARATION THEREOF

TECHNICAL FIELD

[0001] The present invention relates to inorganic composite materials with enhanced physico-chemical characteristics, including well-developed particle surface area and differentiated morphologies that involve layered structural elements, and the processes for preparation thereof. The said materials can find applications in biomedicine, foodstuff, animal feed and care, etc.

DESCRIPTION OF THE PRIOR ART

[0002] Composite biomaterials consisting of dual, or binary (i.e., core-shell), types of materials can enhance functions thereof due to a combination of different properties which are featured by their individual components. Furthermore, by combining the valuable properties of each of the components, the application field for such binary composite materials can be expanded widely. The recent sharp rise in environmental awareness has brought up the need for composites in which both components are biocompatible and/or environmentally friendly. From this standpoint, many previously popular and extensively used binary composites are now considered undesirable, because they contain (as a core component) either polymers or inorganics that are incompatible with biological objects or are non-biodegradable; examples include polyvinyl-based polymers, silica, metal oxides and so on.

[0003] Outer layer (shell) components of modern binary composites are much more biofriendly as they are intended to contact biological tissues. The most popular shell components for this purpose involve synthetic calcium phosphate derivatives, since they mimic their bioderived analogs, which are produced and employed by biological objects in their solid framework, i.e., shells, skeletons/bones, dentin/enamel, etc.

[0004] The challenge of recreating the bioderived composites via synthetic routes lies in the uniqueness of biosynthetic processes, which are often impossible to reproduce. Therefore, there is a continuous demand for novel types of composite materials possessing properties that are resembling their natural analogs as closely as possible. For a wide class of calcium phosphate derivatives, there is also a challenge in controlling the stepwise conversions of several closely related intermediates while halting these conversions on a specific step, providing a desirable intermediate.

[0005] Multiple sources report preparations of core-shell type composite materials with the outer layer(s) created from variously derived calcium phosphates. Meanwhile, their core components represent a range of substances, from polymers to inorganics of different origins.

[0006] For example, EP 1942508B1 [1] describes a method of preparation of magnetic core - ceramic shell (e.g., magnetite (Fe_3O_4) core - calcium phosphate ($Ca_3(PO_4)_2$) shell) nanocrystals for the use as a high-density magnetic recorder, sensor, or catalyst in chemical synthesis, and additionally, in the biomedical field. A disadvantage of this system is its poor environmental impact and high cost of reagents and intermediates, some of which represent toxic organic substances and/or solvents.

[0007] EP 3189832B1 [2] describes core-shell type particles and a method of their fabrication, whereas a core is made of a hydrophobic polymer and a shell contains calcium phosphate; such particles are claimed to be useful in medicines and cosmetics. The key ingredient of the core, polylactic acid (PLA), is strongly hydrophobic and thus the core preparation requires the use of toxic organic solvents, e.g., acetone, which upon synthesis needs to be evaporated for an extended time at low temperatures to avoid PLA hydrolysis in the aqueous suspension. The applicability of PLA as a core ingredient, in this case, is limited by the use of only hydrophobic cargo and by its low hydrolytic stability.

[0008] US 20130295186 A1 [3] describes a method of preparation of core-shell particles of nano/micro-size, which involves contacting the core, which is assembled from negatively charged polymers, with a solution containing calcium ions, removing the particles from the first solution, and contacting the particles with a second solution containing phosphate ions to obtain calcium phosphate-coated species. The method does not specify which type of calcium phosphate salt is formed as a shell; it does not define how the transition of polymeric calcium salt to the calcium phosphate salt occurs in the presence of a strong base used to facilitate the formation of calcium phosphate. The method also does use several toxic or harmful reagents and solvents and, therefore, is not suitable for use in biological objects.

[0009] Ma et al. [4] fabricated the nanostructured hydroxyapatite (HAP) hollow ellipsoidal capsules, using the ‘‘opposite ion core-shell’’ strategy. The size and shape of obtained HAP capsules are controllable by governing the size and morphology of the cores. Post-loading of the hollow HAP capsules with ibuprofen produced a drug-loaded carrier with sufficient loading capacity; however, the release of IBU was not efficient due to the interaction of IBU carboxy groups with hydroxy groups of HAP.

[0010] In recent years, considerable attention was given to the use of calcium carbonate as a potentially useful novel core material for binary composites involving calcium phosphates in the outer shell. calcium carbonate is continuously considered an attractive bone and dental repair material, biotemplate, etc. because it can be converted to HAP upon reaction with various sources of orthophosphates; moreover, calcium carbonate itself is safe and biocompatible to a high degree. Such reactions between calcium carbonate and orthophosphate anions residing in solution are directed by temperature, concentration, and especially by the pH level of reaction media. Several publications recently claimed a successful conversion of calcium carbonate to HAP upon reaction with an orthophosphate source.

[0011] For example, Xia *et al*. [5] used aqueous solutions of calcium carbonate and $(NH_4)_2HPO_4$ that were mixed under hydrothermal conditions to yield hollow HAP spheres.

[0012] Ruffini *et al*. [6] used wood-derived calcium carbonate in its calcite crystalline form to produce HAP under the hydrothermal reaction protocol.

[0013] Minh *et al*. [7] reacted calcium carbonate particles with H_3PO_4 in solutions of varying concentrations at 80 °C and found that the conversion reaction was slow and incomplete even after one week.

[0014] Engin and Girgin [8] used an H_3PO_4–H_2O–ethanol mixture for the conversion of calcium carbonate in the reaction with orthophosphate ions at 80 °C, receiving calcium phosphate products with a carbonate content of 8.5%, which is relatively high for carbonate-containing HAP species.

[0015] Verwilghen *et al*. [9] reacted calcium carbonate with $(NH_4)_2HPO_4$ in solution at pH 8.05 and 60 °C and observed CO_2 evolution upon formation of HAP.

[0016] Portela da Silva *et al*. [10] derived HAP from stoichiometric mixtures of calcium carbonate particles and $NH_4H_2PO_4$ solution of pH > 7 at 25 °C. They found that calcium monohydrogenphosphate dihydrate (a.k.a. dicalcium phosphate dihydrate, $CaHPO_4 \cdot 2H_2O$; DCPD) precipitates in the course of the reaction.

[0017] A number of prior art reports do deal with the source of calcium in the form of calcium carbonate solid particulates, or templates, which, like in the last case above, are used as a suspension in water or water-containing media.

[0018] Multiple disclosures were made within the last several years regarding so-called “surface-reacted calcium carbonate”, “surface-treated calcium carbonate”, “surface-modified calcium carbonate”, “functionalized calcium carbonate”, and so on, in which the initial solid calcium carbonate particles were treated with various chemical agents mostly of acidic nature, thus providing the altered surface structure of the particles. In these particles, the additional chemical elements were further embedded in the particle framework, and the crystalline structures of different porosity and surface area (that were different from the initial calcium carbonate) were formed as a result.

[0019] A "surface-reacted calcium carbonate", by definitions of several patents and patent applications by different claimants, is “a material comprising calcium carbonate and an insoluble, at least partially crystalline, **non-carbonate** calcium salt extending from the surface of at least part of the calcium carbonate. The calcium ions forming said at least partially crystalline non-carbonate calcium salt originate largely from the starting calcium carbonate material that also serves to form the surface-reacted calcium carbonate core”.

[0020] There was a multitude of publications and patent disclosures pertinent to the claimed use of such altered calcium carbonate species in various industrial applications, ranging from water treatment to paper additives to chemical catalysts to gas absorption mixtures to drug excipients to plastic fillers, and so on.

[0021] In some way, these surface-altered particles are similar to the binary structures, which are the subject of the current application. They retain the calcium carbonate core while assembling the shell from the building elements of the core together with the other chemical species provided both from the mentioned core and from phosphate anions reacting with the former elements, specifically, calcium ions.

[0022] The prior art contains several approaches to preparing such surface-altered structures.

[0023] US 6,666,953 B1 [11] describes the preparation of surface-reacted calcium carbonate from natural calcium carbonate, treated with one or more providers of H_3O^+ ions having a pKa of less than 2.5 (i.e., strong acids) and gaseous CO_2, used as fillers allowing an improvement in the quality of the paper.

[0024] WO 2005121257 A2 [12] discloses the production of surface-reacted calcium carbonate, used for manufacturing a dry mineral pigment. Such surface-reacted calcium carbonate is formed *in situ* by the multiple reactions of calcium carbonate particles in suspension with a medium-strong to strong acid and with gaseous CO_2 formed *in situ* and/or from an external supply, along with at least one compound of formula R-X, wherein one or more compounds of formula R-X are added that are selected from fatty acids, fatty amines or fatty alcohols.

[0025] WO 2004083316 A1 [13] refers to a surface-reacted calcium carbonate formed *in situ* by the double and/or multiple reactions between a calcium carbonate with one or more moderately strong to strong H_3O^+ ion donor(s) and gaseous CO_2 formed *in situ* and/or coming from an external supply, and a silicate salt of various nature and/or synthetic silica for the subsequent use in the papermaking industry.

[0026] EP 2443202 A1 [14] refers to the preparation of surface-reacted calcium carbonate in an aqueous environment, similarly to the previous art (*vide supra*) which aims at avoiding the mandatory implementation of medium-strong to strong acids and therefore uses milder acids for the partial dissolving of an initial calcium carbonate (used in the form of ground natural calcium carbonate). Per [14], such strong to medium-strong acids have pKa greater than 2.5 and pH that is equal to or lower than pH 7 and are selected from the group consisting of formic acid, acetic acid, propanoic acid and the mixtures thereof, with most preferred being acetic acid.

[0027] WO 2009074492 A1 [15] relates to the process of obtaining the surface-reacted calcium carbonate (*vide supra*), where the suspension of calcium carbonate in the precipitated form (instead of ground natural form, since the latter did not provide the same good results for the surface reaction) is treated with the source of medium-strong to strong H_3O^+ ions together with anion(s) that are capable of forming the insoluble calcium salts. Upon the contact of such mixture with precipitated calcium carbonate, a slurry of surface-reacted precipitated calcium carbonate is formed from the said anion(s) and solubilized calcium cations that are obtained during the reaction of H_3O^+ ions with the calcium carbonate in the initial suspension. The surface-reacted calcium carbonate thus formed can be used as a filler or a pigment in tissue paper, paints, plastics, water treatment, and so on.

[0028] WO 2019149628 A1 [16] refers to the use of functionalized calcium carbonate as an active ingredient for pharmaceutical use in the field of calcium fortification and the treatment of calcium deficiency. The functionalized calcium carbonate was prepared by treating the ground calcium carbonate with phosphoric acid at elevated temperatures with subsequent jet dryer isolation of said functionalized calcium carbonate.

[0029] US 20040020410 A1 [17] discloses the making of functionalized calcium carbonate from natural calcium carbonate (preferably a marble, calcite, chalk, or carbonate-containing dolomite), which is treated with a combination of one or more medium-strong to a strong provider(s) of H_3O^+ ions and an external CO_2 supply or from the recirculation of CO_2 or from the continuous addition of the same medium-strong to a strong provider of H_3O^+ ions. Such functionalized calcium carbonate is used as a filler or a pigment, allowing a reduction in the weight of paper for a constant surface area without loss of physical properties.

[0030] EP 2264108 A1 (WO 2010146530 A1) [18] and EP 2264109 A1 (WO 2010146531 A1) [19] refer to the employment of weak organic acids, such as citric acid, in combination with phosphoric acid in the preparation of surface-reacted calcium carbonate of high specific surface area. These disclosures are using the same internal source, i.e., natural calcium carbonate, for both calcium ions and gaseous CO_2 sources.

[0031] WO 2015173437 A1 [20] discloses the process for producing a calcium phosphate reactant in the form of a suspension in water for the use in treating liquid effluents or for treating substances contaminated by heavy metals. The said reactant is produced by a two-step process, in which in the first step a source of calcium ions is treated with a source of phosphate ions in water to obtain a suspension of calcium phosphate, and in the second step, a source of

hydroxide ions (i.e., strong base) (to set a pH > 8) and an extra source of calcium (to obtain a suspension of calcium phosphate reactant having a Ca/P molar ratio of more than 1.6) are added to the former suspension. While this method claims to produce hydroxyapatite during the first step, the actual suspension contains a range of other calcium phosphates and other calcium salts, including small amounts of calcium carbonate. The key ambiguity of the suggested method is that upon addition of the source of hydroxide ions and an extra source of calcium, which in the examples is reduced to the use of calcium hydroxide, is simply producing a physical mixture of calcium phosphate in the suspension form with said calcium hydroxide, without chemical binding/reaction. Also, the optimal particle size, for the treatment of liquid effluents per cited invention, has to be >50 um, which is a fairly large particle.

BACKGROUND OF THE INVENTION

[0032] The key points of all prior art related to the use of calcium carbonate in the solid state (as a core and as a calcium source simultaneously) and of orthophosphates as a phosphate source for the preparation of core-shell species are summarized as follows:

[0033] Such prior art is sharing two common features: one, the source of calcium ions for creating the “surface-treated”/”surface-modified”/”surface-functionalized” calcium carbonate particles with the morphologically and chemically different outer shell (calcium phosphate variations) is **directly derived** from the initial content of the solid calcium carbonate core, and two, the use of the acid(s) is imperative for recruiting calcium ions continuously dissolved from the core particles for binding with anions of the respective acid(s) (specifically for numerous examples *vide supra*, the phosphate anion of various types, such as hydrophosphate, dihydrophosphate, triphosphate, etc.).

[0034] Calcium carbonate is used in the form of suspension, i.e., it is not soluble in water and thus the actual reaction between orthophosphate ions and calcium ions occurs on the surface of the calcium carbonate particles, with a substantial initial prevalence of the orthophosphate anions, since calcium carbonate is practically insoluble in water. All these reaction systems must have a low acidity to initiate the calcium phosphate precipitation. This is achieved either by an orthophosphate ion source alone or by its combination with acid where the lowered acidity will initially dissolve calcium carbonate with the release of calcium cations into the solution. The latter, however, will instantly react with the orthophosphate anions to form insoluble calcium phosphate, which will immediately precipitate in the reaction zone, i.e., there will be no time-lagged circulation of solubilized calcium cations in the solution. The ratio between dissolved calcium carbonate and “survived” calcium carbonate (in the intact form of calcium carbonate) will heavily affect the integrity, morphology, and technical characteristics of the newly formed particles.

[0035] The “etching” process, i.e., the reaction of weak/medium-strong/strong acid with the surface of calcium carbonate, does create substantial irregularities of the initially well-shaped, e.g., spherical, calcium carbonate particles. Such irregularities are expressed in the distorted shape of the resulting shell-covered particles, creating an uneven thickness of the shell over the etched calcium carbonate core. While it is very much possible that there is incomplete coverage of calcium carbonate core with the newly created shell, it is also conceivable that the calcium carbonate core is completely dissolved and fully converted into the newly created shell, thus providing hollow particulate species, as it was described in several sources mentioned above.

These features would lead to qualitative disparity in the composite materials thus prepared, ranging from the morphological differences to the particle size distribution to the uneven Ca/P ratio, etc. As stated, the geometrical appearance of the core and the shell will be defined by the level of calcium carbonate core depletion, i.e., there will be a certain disfiguration in the thicknesses of the core and of the shell, based on the severity of calcium carbonate core dissolution and its further conversion into HAP shell (Fig.1). Actual shell and core thickness is hard to control using such "etching" methods, especially in the case when calcium carbonate core is profoundly depleted, and/or when it is made from the porous calcium carbonate derivatives, as the depth of the acid penetration into the pores is impossible to control.

[0036] Once the initial shell of calcium phosphate(s) is formed on the calcium carbonate core, the continuously growing thickness of the formed shell is defining the rate and the completion of the reaction. Reaction continuously forms a new solid phase, which grows on the **inner** surface of the shell, because it recruits Ca ions available on the surface of the internal calcium carbonate core. Therefore, the "older" layers of this continuously growing new solid phase are being moved outwards by the newer precipitates.

[0037] The acidic strength of the orthophosphate source defines to what extent the depletion of calcium carbonate proceeds, and in many cases, it leads to a complete disappearance of calcium carbonate core, yielding the hollow calcium phosphate particles, mostly of HAP type (therefore, oftentimes the names used for the final products, such as "surface-modified calcium carbonate", "surface-reacted calcium carbonate" etc. do not correctly reflect the actual particle condition). At the same time, the speed of transformation of the unstable or moderately stable calcium phosphate intermediates (amorphous calcium carbonate (ACP), monocalcium phosphate (MCP), dicalcium phosphate dihydrate (DCPD), dicalcium phosphate anhydrous (DCPA), tetracalcium phosphate (TCP), octacalcium phosphate (OCP), and so on) into HAP or HAP derivatives is determined by the temperature and the pH within the reaction zone (Fig. 2).

[0038] As long as the thickness of the shell increases, the reaction zone becomes progressively depleted with both hydroxide and orthophosphate anions that will take a progressively longer time to penetrate through the shell to reach the reaction zone. This, in turn, leads to incomplete conversion of the inner shell layers into HAP as the most stable form of calcium phosphates. As shown in [7], the conversion of calcium carbonate into HAP upon reaction with H_3PO_4 is not completed even after a week.

[0039] As the reaction progresses, more calcium is recruited into the formation of calcium phosphate, and the original counter-ion, carbonate, is released into the aqueous phase by permeating the shell of calcium phosphate outwards. While it is initially released in the reaction zone, it is trapped by phosphate precipitation, and eventually leads to the formation of HAP derivative called carbonated hydroxyapatite (CHA), which is enriched by CO_3^{2-} anions. Synthetic formation of CHA was reported by many prior art sources, for example [21, 22], and in addition represents a vital part of the biomineralization processes in bones, dentine, and enamel. The thicker the shell becomes, the more carbonate ions are trapped in the inner layers of the forming calcium phosphate, and thus the Ca/P ratio across the shell density changes, with outer layers being closer to a true HAP, while the inner layers are represented by CHA-like formations, where the amount of trapped carbonate ions is substantially higher than in the outer ones.

[0040] Such gradient of the carbonate concentration in the crystal structure of HAP, when the outer layers of the HPA shell do contain lesser amounts of carbonate, does affect the properties

of synthesized composites and does diminish the quality of the use of such composite materials in biomedical applications.

[0041] No prior sources related to “surface-reacted calcium carbonate”, “surface-treated calcium carbonate”, “surface-modified calcium carbonate”, “functionalized calcium carbonate” do mention an actual material balance of any of the chemical reactions that were used as examples in these publications; at best, some do list the amount of calcium in the shell or the amount of carbonate in it (in percentage to the total mass of the particles). This affects the reproducibility of the claimed methods and leads to discrepancies in the quality of the proposed composites.

[0042] Despite the various reports that are related to the core-shell materials in the prior art, there exists a definite demand for the new biocompatible and biodegradable binary composite materials of better stability and predictable properties, that closely resemble their natural analogs. These binary composites that include calcium carbonate core and calcium phosphate shell should provide a range of properties that are not delivered by the currently available binary composite materials.

[0043] Having this task at hand, the inventor unexpectedly found that if the calcium ion source is provided additionally, outside of the growing calcium phosphate shell on the calcium carbonate core, and this additional source is available in excess to the supplied (i.e., dosed continuously) phosphate ion source, then the calcium carbonate core remains intact and the growth of the shell is driven outward, by precipitating new layers of calcium phosphate atop of the previously formed ones (cf. Fig.3). This process is fundamentally different from the previously disclosed processes described *vide supra* (see it also presented on Fig.2.

SUMMARY OF THE INVENTION

[0044] The present invention provides a binary composite material of the core-shell type with improved morphology and surface area and the processes for preparation thereof.

[0045] The present invention departs from the known processes for the preparation of the core-shell composite materials based on the calcium carbonate core and calcium phosphate shell by forming the shell from a calcium ion source that is supplied **externally**, in addition to the calcium carbonate core; this external calcium ion source is reacted with phosphate ion source to form the calcium phosphate shell in a controlled, concentration-dependent manner. All previously known processes were employing the calcium ions for the shell formation that were derived from dissolving an **internal** source, i.e., the calcium carbonate core, which leads to malformations in the newly prepared core-shell composite material, since the core particles are partially (or sometimes even fully) dissolved, and thus the morphology, thickness, density, etc. of such newly formed particles are hard to reproduce, as is hard to reproduce their main properties, such as specific surface area, pore size, and the shape and the size of the morphological elements.

[0046] The present invention also departs from the known processes by better controlled formation of the shell, wherein the size, shape, porosity (if provided), and other properties of the core particles are not affected by the shell assembly process.

[0047] The present invention also departs from the known processes by better control of the reaction pH, which is achieved by continuous excess of the external calcium ion source as compared to the phosphate ion source, which is supplied by gradual, controlled addition of the

latter. Such regulation of reaction pH has an unexpected outcome in the shell formation, since the formed calcium phosphate (still in mostly hydroxyapatite (HAP) form but with multiple variations), provides morphological elements (i.e., crystalline formations) unexpectedly different from any of the previously described in the prior art.

[0048] An aspect of the present invention is to solve the shortcomings and drawbacks of known composite materials based on calcium carbonate core and calcium phosphate shell, as discussed earlier, by providing several advantages below.

[0049] One aspect of the present invention is to provide the process of preparation of binary core-shell composites, wherein the core comprises at least one component as calcium carbonate, and the shell comprises at least one component as calcium phosphate; both core and shell are biocompatible and biodegradable.

[0050] In another aspect, the process of preparation of such binary core-shell composites uses calcium carbonate in various forms and crystalline structures as a core, and calcium phosphate in various salt forms as a shell. The latter is formed as a result of the reaction of an externally supplied calcium ion source, which is not derived from the calcium carbonate core, and a phosphate ion source. Both externally supplied calcium ion source and phosphate ion source are provided in the form of aqueous or water/organic solvent solutions. Upon interaction of these solutions, the newly formed calcium phosphate salt precipitates on the surface of core particles of calcium carbonate, thus forming a required shell, wherein the overall integrity of the newly formed core-shell particles and their morphological, physico-chemical, and mechanical characteristics are much better controlled and, more importantly, are reproducible.

[0051] In yet another aspect of the present invention, the process of preparation of such binary core-shell composites does not use the acid(s) to react with the calcium carbonate core, and therefore the morphology and physico-chemical characteristics of the core material remain unaffected by the shell growth, and the morphology and physico-chemical characteristics of the formed shell are improved because of the better control and the fuller completion of the reaction since the reaction front is situated outside of the growing shell.

[0052] In yet another aspect of the present invention, the pH of the reaction media remains either neutral or above neutral for the most part of the shell formation process, which facilitates a more complete transition of the intermediate calcium phosphate precipitate into, e.g., hydroxyapatite and its variations, including but not limited to hydroxyapatite, calcium-deficient hydroxyapatite, carbonated hydroxyapatite, etc.

[0053] In yet another aspect of the present invention, the concentration of additionally supplied calcium ions is kept in continuous excess to the supplied phosphate ions, which is achieved by adding the phosphate ion source dropwise or portionwise to the suspension of calcium carbonate in aqueous or water/organic solvent solution containing **additional external** calcium ion source. This, in turn, provides a required pH level of at or above pH 7.5 for the most part of the shell formation.

[0054] In yet another aspect of the present invention, the process of formation of said core-shell composites is carried out at room temperature or upon heating, and the core-shell particles are isolated either immediately after reaction completion or after a certain time.

[0055] In yet another aspect of the present invention, the calcium carbonate core material is formed *in situ* with subsequent shell formation directly on the particles of the newly formed core.

[0056] Another aspect of the current invention provides binary shell-core composite materials that possess improved morphology and physico-chemical characteristics, such as morphological elements, specific surface area, and pore size. Said shell-core composite materials have an intact core (often porous), a defined particle size, unique morphological elements, and a Ca/P ratio that is higher than the typical calcium phosphate materials.

[0057] The exemplary embodiments for the current invention or other exemplary embodiments by the modification or addition of elements, that are possible to provide based on the scope of the current invention, are given below.

DETAILED DESCRIPTION OF THE INVENTION

[0058] The present invention relates in part or in whole to the following embodiments:

[0059] Item 1. A process for the preparation of binary composite material consisting of the core and the shell, according to which:

[0060] The use is made of a core material, which comprises at least one component being calcium carbonate, selected from but not limited to either naturally occurring calcium carbonate, such as limestone, chalk, dolomite, or marble, or combinations thereof, or synthesized calcium carbonate, both types being in the crystalline forms as calcite, aragonite, vaterite, or combinations thereof.

[0061] The use is made of the shell material, comprising at least one component being calcium phosphate, such as monocalcium phosphate monohydrate, dicalcium phosphate dihydrate, anhydrous dicalcium phosphate, tricalcium phosphate, tetracalcium phosphate, octacalcium phosphate, hydroxyapatite, calcium-deficient hydroxyapatite, or carbonated hydroxyapatite, or combinations thereof.

[0062] Item 2. The process according to item 1, wherein the core material is used directly, when it is a synthesized calcium carbonate, or used as naturally occurring calcium carbonate, treated using any conventional equipment such as a ball mill, a rod mill, a vibrating mill, a roll crusher, a centrifugal impact mill, a vertical bead mill, an attrition mill, a pin mill, a hammer mill, a pulverizer, a shredder and so on to diminish the core particles to the size optimal to be covered by the shell material using said process, wherein the core particle size is selected from the range of preferably 10 nM to 100 uM, more preferably 200 nM to 50 uM, most preferably 500 nM to 10 uM.

[0063] Item 3. The process according to any of the above items, wherein the shell is formed on the surface of the core particles while reacting a solution of a phosphate ion source with a solution of an additional external calcium ion source, wherein the said additional calcium ion source is not derived from the calcium carbonate that forms the core particles.

[0064] Item 4. The process according to any of the above items, wherein a solution of the phosphate ion source is added dropwise or portionwise to a suspension of the core particles in a solution of additional calcium ion source at such a speed that the pH of the reaction mixture is kept for the most part at or above pH 7.5 during the addition process.

[0065] Item 5. The process according to any of the above items, wherein the final binary core/shell composite material thus prepared has an atomic ratio of calcium to phosphorus (Ca/P) preferably above 1.6 but below 3.0, i.e., $1.6<Ca/P<3.0$, more preferably $1.8<Ca/P<2.5$, most preferably $2.0<Ca/P<2.3$.

[0066] Item 6. The process according to any of the above items, wherein an additional calcium ion source comprises calcium hydroxide or water-soluble calcium salt with various anions

derived from mono-, di-, tri, or polysubstituted acids or mixtures thereof, including but not limited to citrate, malonate, chloride, acetate, nitrate, lactate, gluconate, and so on.

[0067] Item 7. The process according to any of the above items, wherein a phosphorous ion source comprises orthophosphoric acid or water-soluble orthophosphate salt such as monohydrogenphosphate, dihydrogenphosphate, orthophosphate, with various cations of the metals in groups I and II of the periodic table or mixtures thereof, including but not limited to lithium, potassium, sodium, cesium, rubidium, ammonium, and so on.

[0068] Item 8. The process according to any of the above items, wherein the solvent for the process is water or water/organic solvent mixture.

[0069] Item 9. The process according to any of the above items, wherein the water/organic solvent mixture is made by diluting water with mono-, di-, tri-, or poly-functional alcohols, which include but are not limited to methanol, ethanol, propanol, isopropanol, ethylene glycol, diethylene glycol, triethylene glycol, polyethyleneglycol, propylene glycol, glycerin, mono- or di-substituted glycerin, and so on.

[0070] Item 10. The process according to any of the above items, wherein the concentration of organic solvent in the mixture does not lead to the precipitation of additional calcium ion source or phosphate ion source in the selected concentration ranges.

[0071] Item 11. The process according to any of the above items, wherein the concentration of the additional calcium ion source solution used for the shell preparation is selected from the range of preferably 0.05 to 3.00 M/L, more preferably 0.50 to 2.50 M/L, most preferably 1.00 to 2.00 M/L.

[0072] Item 12. The process according to any of the above items, wherein the concentration of the phosphate ion source solution used for the shell preparation is selected from the range of preferably 0.01 to 2.00 M/L, more preferably 0.50 to 1.75 M/L, most preferably 1.00 to 1.50 M/L.

[0073] Item 13. The process according to any of the above items, wherein the addition of the phosphate ion source is carried out at the temperature selected from the range of preferably 10 to 120 ^{o}C, more preferably 25 to 80 ^{o}C, most preferably 30 to 70 ^{o}C.

[0074] Item 14. The process according to any of the above items, wherein the stirring of the reaction mixture after addition of the phosphate ion source is carried out preferably for an additional 24 h, more preferably, for an additional 4 h, even more preferably for an additional 1 h. It is also feasible that the reaction product is isolated immediately after reaction completion, without additional stirring.

[0075] Item 15. The process according to any of the above items, wherein the additional stirring of the reaction mixture is carried out at the temperature selected from the range of preferably 10 to 120 ^{o}C, more preferably 25 to 80 ^{o}C, most preferably 30 to 70 ^{o}C.

[0076] Item 16. The process according to any of the above items, wherein the core material is synthesized *in situ* prior to the formation of the shell, using calcium ion source and carbonate ion source, in the solution in water or water/organic solvent mixture.

[0077] Item 17. The process according to item 16, wherein the water/organic solvent mixture is made by diluting water with mono-, di-, tri-, or poly-functional alcohols, which include but are not limited to methanol, ethanol, propanol, isopropanol, ethylene glycol, diethylene glycol, triethylene glycol, polyethyleneglycol, propyleneglycol, glycerin, mono- or di-substituted glycerin, and so on.

[0078] Item 18. The process according to item 16, wherein the calcium ion source comprises calcium hydroxide or water-soluble calcium salt with various anions derived from mono-, di-, tri, or polysubstituted acids or mixtures thereof, including but not limited to citrate, malonate, chloride, acetate, nitrate, lactate, gluconate, and so on.

[0079] Item 19. The process according to item 16, wherein the carbonate ion source comprises carbon dioxide or water-soluble carbonate or bicarbonate salt with various cations of the metals in groups I and II of the periodic table or mixtures thereof, including but not limited to lithium, potassium, sodium, cesium, rubidium, ammonium, and so on.

[0080] Item 20. The process according to item 16, wherein the concentration of the organic solvent in the water/organic solvent mixture is selected from the range of preferably 1 to 90%, more preferably 1 to 50%, most preferably 1 to 25%.

[0081] Item 21. The process according to item 16, wherein the concentrations of the carbonate ion source and the calcium ion source, used for *in* situ synthesis of the core material, are selected from the range of preferably 0.05 to 3.00 M/L, more preferably 0.50 to 1.75 M/L, most preferably 1.00 to 1.50 M/L.

[0082] Item 22. The process according to item 16, wherein the *in situ* synthesis of the core is carried out at the temperature selected from the range of preferably 10 to 120 ^{o}C, more preferably 25 to 80 ^{o}C, most preferably 30 to 70 ^{o}C.

[0083] Item 23. The process according to item 16, wherein both *in situ* synthesis of the core material and the following formation of the shell are both carried out at the same temperature selected per Item 22.

[0084] Item 24. The process according to item 16, wherein the *in situ* synthesis of the core material is carried out at room temperature and the following formation of the shell is carried out at the temperature selected from the range of preferably 10 to 120 ^{o}C, more preferably 25 to 80 ^{o}C, most preferably 30 to 70 ^{o}C.

[0085] Item 25. A binary composite material that is prepared according to all of the above items, and that consists of the core and the shell, wherein the core comprises at least one component as calcium carbonate, and the shell comprises at least one component as calcium phosphate. Both core and shell are biocompatible and biodegradable.

[0086] Item 26. The composite material according to item 25, wherein the core material comprises a derivative of calcium carbonate, selected from either naturally occurring calcium carbonate, such as limestone, chalk, dolomite, or marble, or from the synthesized calcium carbonate, all in the crystalline forms as calcite, aragonite, vaterite, or combinations thereof.

[0087] Item 27. The composite material according to item 25, wherein the shell material comprises a derivative of calcium phosphate such as monocalcium phosphate monohydrate, dicalcium phosphate dihydrate, anhydrous dicalcium phosphate, tricalcium phosphate, tetracalcium phosphate, octacalcium phosphate, hydroxyapatite, calcium-deficient hydroxyapatite, or carbonated hydroxyapatite, or the combinations thereof.

[0088] Item 28. The composite material according to item 25, wherein the material particles are tubular shaped, spheroid (oblate, prolate, or equant) shaped, rod shaped, cubic shaped, disc shaped, or even irregularly shaped.

[0089] Item 29. The composite material according to item 25, wherein the material particles have cluster-like morphology with cluster size preferably between 1 to 200 uM, more preferably between 2 to 100 uM, most preferably between 5 to 50 uM.

[0090] Item 30. The composite material according to item 25, wherein the material particles have an individual particle morphology with particle size preferably 10 nM to 120 uM, more preferably 200 nM to 50 uM, most preferably between 500 nM to 10 uM.

[0091] Item 31. The composite material according to item 25, wherein the material particles have the shell morphological elements occurring as plates, crossed plates, radiating plates, lamellae, needles, needle clusters, prisms, fans, rosettes, columns, hollow columns, flakes, florets, framboids, radiating dendrites, fern-like dendrites, stellar dendrites, arrowheads, or sheaths.

[0092] Item 32. The composite material according to item 25, wherein the material particles have the size of the shell morphological elements in the range of preferably 1 to 100 nM, more preferably 3 to 50 nM, most preferably 5 to 25 nM.

[0093] Item 33. The composite material according to item 25, wherein the material particles have the specific surface area (determined by BET method) in the range of preferably 20 to 160 m^2/g, more preferably 40 to 100 m^2/g, most preferably 50-75 m^2/g.

[0094] Item 34. The composite material according to item 25, wherein the material particles have a pore volume in the range of preferably 0.1 to 1.0 cm^3/g, more preferably 0.2 to 0.8 cm^3/g, most preferably 0.4 to 0.6 cm^3/g.

[0095] The disclosures and details of all publications, including the patents and patent applications cited herein are hereby incorporated for reference purposes. All of these do provide practical, exemplary, or other particulars that support the essentials that are set forth in the current application.

[0096] Many alterations of this invention can be made without leaving its scope and definitions, as can be figured by the individuals skilled in the art, and, therefore, while the detailed embodiments described herein are brought in for exemplary purposes, the current invention is not limited by the terms of the claims mentioned herein, along with the scope of equivalents to which such claims are entitled.

[0097] Should the disclosure of any of the patents, patent applications, and publications that are incorporated herein by reference conflict with the present invention while rendering an unclear term, the present invention shall take precedence.

[0098] Each and every claim is incorporated into the current invention specification as an embodiment and, therefore, each and every claim represents an addition to preferred embodiments of the current invention.

[0099] While preferred embodiments of this invention have been defined, their modifications can be made by any individual skilled in the art without deviating from the scope and disclosures of the current invention.

[0100] Each and every embodiment that is brought herein does serve exemplary purposes but is not limited by the actual content of a specific embodiment.

[0101] Multiple variations of the core-shell binary composites are available, as are the processes of their preparations, which may fall within the scope of the current invention, and therefore, the level of the current invention protection is not limited by the invention description and examples but is limited by the claims defined herewith, including all equivalents of the subject matter of the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0102] Figure 1. Schematic depiction of possible irregularities in the core-shell structures obtained during the “etching” of calcium carbonate core combined with precipitation of calcium phosphate shell.

[0103] Figure 2. Schematic representation of an active reaction zone during the interaction of solid CaCO3 with orthophosphate anions penetrating from the outer aqueous medium; reaction zone is congested between the core and the growing shell.

[0104] Figure 3. Schematic of the active reaction zone during the interaction of the solubilized calcium ion source with solubilized orthophosphate anions available in the aqueous medium.

[0105] Figure 4. SEM image of the particles prepared according to Example 1.

[0106] Figure 5. SEM image of the particles prepared according to Example 2.

[0107] Figure 6. SEM image of the particles prepared according to Example 3.

[0108] Figure 7. SEM image of the particles prepared according to Example 4.

[0109] Figure 8. a SEM image of DCPD and calcium carbonate particle blend prepared according to Example 5, prior heating of the reaction mixture.

[0110] Figure 9. SEM image of the particles prepared according to Example 5, after heating of the reaction mixture and maturation.

[0111] Figure 10. SEM image of the particles prepared according to Example 6.

[0112] Figure 11. SEM image of the particles prepared according to Example 7.

EXAMPLES

[0113] Since the current invention is described in general terms, the following examples are given as particular embodiments of the current invention that demonstrate the practice and advantages thereof. It is understood that the examples are given by way of illustration and are not intended to limit the specification or the claims to follow in any way.

[0114] Example 1 (batch 520)

[0115] This example illustrates a prior art, wherein calcium carbonate (in calcite form) reacts with phosphoric acid.

[0116] A suspension of calcium carbonate (3.00 g) in water (25 mL) was stirred and heated using a magnetic stirrer/hot plate (400 rpm, 70 °C). Orthophosphoric acid (30% aq., 4.60 mL) was carefully added to the suspension dropwise, within 12 min. Upon addition of the first few drops, the mixture began bubbling vigorously, indicating the emanation of gaseous CO_2. After the addition of all acid, the pH of the reaction mixture was measured (pH 7.0). The whole was stirred for an additional 1 h and then set aside for 24 h for maturation. The precipitate was filtered, washed with water, ethanol, and acetone; dried on air. Yield: 3.69 g, white microcrystals; SSA (BET) = 32 m^2/g, pore volume = 0.23 m^3/g.

[0117] Ca/P atomic ratio (EDX) = 1.56.

[0118] SEM image of the particles prepared according to Example 1 is depicted in Fig. 4.

[0119] Morphological analysis of prepared particles indicates the formation of HAP-like particles with pores substantially closed by HAP plates.

[0120] Example 2 (batch 305)

[0121] This example illustrates a prior art, wherein calcium carbonate (in calcite form) reacts with acetic acid, followed by a reaction with potassium dihydrogen phosphate.

[0122] A suspension of calcium carbonate (5.00 g) in water (25 mL) was stirred and heated using a magnetic stirrer/hot plate (400 rpm, 70 °C). Acetic acid (50% aq., 2.00 mL) was carefully added to the suspension dropwise, within 2 min. Upon addition of the first few drops, the mixture began bubbling vigorously, indicating the emanation of gaseous CO_2. After the addition of the acid, the mixture was stirred under the same conditions for 5 min, and a potassium dihydrogen phosphate solution (15% aq., 4.80 mL) was added to the mixture dropwise, within 7 min. The whole was stirred under the same conditions for another 1 h and then set aside for 24 h for maturation. The precipitate was filtered, washed with water, ethanol, and acetone; dried on air. Yield: 4.60 g, white microcrystals.

[0123] SEM image of the particles prepared according to Example 2 is depicted in Fig. 5. Morphological analysis of prepared particles indicates the partial formation of HAP crystals on malformed particles of calcium carbonate.

[0124] Example 3 (batch 308)

[0125] This example illustrates the attempted preparation of the current core-shell composite, wherein calcium carbonate and calcium phosphate were synthesized *in situ* simultaneously.

[0126] To a stirred (400 rpm) solution of calcium chloride (2M aq., 10.0 mL), water (50 mL) was added at room temperature, and the resulting solution was stirred for 3 min. A mixture of disodium hydrogen phosphate solution (0.3M aq., 20.0 mL) and sodium carbonate solution (2M aq., 7.0 mL) was added to calcium chloride solution in one portion at room temperature, and the whole was stirred for 1 h. The mixture was set aside for maturation for 24 h. The formed suspension was centrifuged (3,000 rpm, 3.00 min), subsequently washed/centrifuged using water, ethanol, and acetone, and dried on air. Yield: 2.20 g, white microcrystals.

[0127] SEM image of the particles prepared according to Example 3 is depicted in Fig. 6. Morphological analysis of prepared particles indicates the presence of irregularly shaped calcium carbonate particles sparsely covered with flakes of calcium phosphate (HAP).

[0128] Example 4 (batch 522)

[0129] This example illustrates the invention.

[0130] To a stirred (600 rpm) mixture of calcium chloride (2M aq., 5.00 mL) and water (25 mL) was added a solution of sodium carbonate (2M aq., 5.00 mL) in one portion at room temperature. The formed suspension of calcium carbonate was stirred for 3 min, and then slowly heated to 70 ^{o}C upon stirring. An additional portion of calcium chloride (2M aq., 5.00 mL) was supplied to the mixture, and the whole was stirred and heated under the same conditions for 5 min. Potassium dihydrogen phosphate solution (15% aq., 5.44 mL) was added to the suspension dropwise within 15 min. During additions, the pH of the reaction mixture was measured as basic (pH > 7.5). The whole was stirred for an additional 1 h and then set aside for 24 h for maturation. The formed precipitate was filtered, washed with water, ethanol, and acetone; dried on air. Yield: 1.37 g, white microcrystals; SSA (BET) = 91 m^2/g, pore volume = 0.54 m^3/g.

[0131] Ca/P atomic ratio (EDX) = 2.18.

[0132] SEM image of the particles prepared according to Example 4 is depicted in Fig. 7.

[0133] Morphological analysis of prepared particles indicates the presence of a highly developed surface of rosette-like plate crystals of calcium phosphate (HAP variation) with pores that are substantially more open than in the particles of Example 1.

[0134] Example 5 (batch 525)

[0135] This example illustrates the invention.

[0136] To a stirred (600 rpm) mixture of calcium chloride (2M aq., 5.00 mL) and water (25 mL) was added a solution of sodium carbonate (2M aq., 5.00 mL) in one portion at room temperature. The formed suspension of calcium carbonate was stirred for 3 min at room temperature, and then an additional portion of calcium chloride (2M aq., 5.00 mL) was supplied to the mixture, while it was stirred at room temperature for an extra 5 min. Potassium dihydrogen phosphate solution (15% aq., 5.44 mL) was added to the suspension dropwise within 15 min. During additions, the pH of the reaction mixture was measured as basic (pH > 7.5). The whole was stirred for an additional 10 min, after which an aliquot (5 mL) was taken from the mixture and kept separately. The whole was then heated up to 50 ^{o}C and stirred for 1 h. The mixture was then set aside for 24 h for maturation. The formed precipitate was filtered, washed with water, ethanol, and acetone; dried on air. Yield: 1.34 g, white microcrystals; SSA (BET) = 49 m^2/g, pore volume = 0.24 m^3/g.

[0137] Ca/P atomic ratio (EDX) = 2.10.

[0138] The precipitate from the aliquot was also filtered, washed with water, ethanol, and acetone; dried on air; a sample of this solid was subjected to SEM imaging.

[0139] SEM images of the particles prepared according to Example 5 are depicted in Fig.8 (sample from the aliquot, prior to heating) and Fig.9 (sample after heating and maturation).

[0140] Morphological analysis of particles obtained prior to heating indicates the presence of a mixture of calcium carbonate and dicalcium phosphate dihydrate (DCPD): first one in the form of spherical porous particles, second – in the form of large plates ("slabs") (Fig.8). However, upon heating of the mixture under basic (pH > 7.5) conditions, DCPD recrystallized into more stable HAP, forming the desired shell over the calcium carbonate core particles (Fig.9).

[0141] Example 6 (batch 424)

[0142] This example illustrates the invention.

[0143] The procedure is the same as used in Example 4, except that all stages of the reaction sequence, including the preparation of calcium carbonate, were carried out at 50 ^{o}C.

[0144] Yield: 1.38 g, white microcrystals; SSA (BET) = 107 m^2/g, pore volume = 0.61 m^3/g.

[0145] Ca/P atomic ratio (EDX) = 2.04.

[0146] SEM image of the particles prepared according to Example 6 is depicted in Fig. 10.

[0147] Morphological analysis of prepared particles indicates the presence of a highly developed surface of rosette-like plate crystals of calcium phosphate (HAP) with pores that are substantially more open than in the particles of Example 1.

[0148] Example 7 (batch 542)

[0149] This example illustrates the invention.

[0150] The procedure is the same as used in Example 4, except instead of synthesizing calcium carbonate *in situ*, the source of the calcium carbonate core was provided in the form of a suspension of pre-synthesized calcium carbonate (4.60 g) in water (100 mL), followed by supplying additional calcium chloride, and by dropwise addition of potassium dihydrogen phosphate per Example 4.

[0151] Yield: 4.83 g, white microcrystals; SSA (BET) = 61 m^2/g, pore volume = 0.28 m^3/g.

[0152] Ca/P atomic ratio (EDX) = 2.00.

[0153] SEM image of the particles prepared according to Example 7 is depicted in Fig. 11.

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Claims

1. A binary composite material that consists of the core and the shell, wherein:

The core comprises at least one component as calcium carbonate, and

The shell comprises at least one component as calcium phosphate, and

Both core and shell components are biocompatible, and

Both core and shell components are biodegradable.

2. The composite material according to claim 1, wherein the core material comprises a derivative of calcium carbonate, selected from either naturally occurring calcium carbonate, such as limestone, chalk, dolomite, or marble, or from the synthesized calcium carbonate, all in the crystalline forms as calcite, aragonite, vaterite, or combinations thereof.

3. The composite material according to claim 1, wherein the shell material comprises a derivative of calcium phosphate such as monocalcium phosphate monohydrate, dicalcium phosphate dihydrate, anhydrous dicalcium phosphate, tricalcium phosphate, tetracalcium phosphate, octacalcium phosphate, hydroxyapatite, calcium-deficient hydroxyapatite, or carbonated hydroxyapatite, or combinations thereof.

4. The composite material according to claim 1, wherein the material particles are tubular shaped, spheroid (oblate, prolate, or equant) shaped, rod shaped, cubic shaped, disc shaped, or irregularly shaped.

5. The composite material according to claim 1, wherein the material particles have cluster-like morphology with cluster size preferably from 1 to 200 uM, more preferably from 2 to 100 uM, most preferably from 5 to 50 uM.

6. The composite material according to claim 1, wherein the material particles have individual particle morphology with particle size preferably from 10 nM to 120 uM, more preferably from 100 nM to 50 uM, most preferably from 200 nM to 10 uM.

7. The composite material according to claim 1, wherein the material particles have the shell morphological elements occurring as plates, crossed plates, radiating plates, lamellae, needles, needle clusters, prisms, fans, rosettes, columns, hollow columns, flakes, florets, framboids, radiating dendrites, fern-like dendrites, stellar dendrites, arrowheads, or sheaths.

8. The composite material according to claim 1, wherein the material particles have the size of the shell morphological elements preferably from 1 to 100 nM, more preferably from 3 to 50 nM, most preferably from 5 to 25 nM.

9. The composite material according to claim 1, wherein the material particles have a specific surface area (SSA, BET method) preferably from 20 to 160 m^2/g, more preferably from 40 to 100 m^2/g, most preferably from 50 to 75 m^2/g.

10. The composite material according to claim 1, wherein the material particles have a pore volume preferably from 0.1 to 1.0 cm^3/g, more preferably 0.2 to 0.8 cm^3/g, most preferably 0.4 to 0.-6 cm^3/g.

11. The composite material according to claim 1, wherein the material particles have an atomic ratio of calcium to phosphorus (Ca/P) preferably above 1.6 but below 3.0, i.e., 1.6<Ca/P<3.0, more preferably 1.8<Ca/P<2.5, most preferably 2.0<Ca/P<2.3.

12. A process for the preparation of said binary composite material consisting of the core and the shell, according to which:

The use is made of a core material, which comprises at least one component being calcium carbonate, selected from but not limited to either naturally occurring calcium carbonate, such as limestone, chalk, dolomite, or marble, or combinations thereof, or synthesized calcium carbonate, all in the crystalline forms as calcite, aragonite, vaterite, or combinations thereof.

The use is made of a shell material, comprising at least one component being calcium phosphate, such as monocalcium phosphate monohydrate, dicalcium phosphate dihydrate, anhydrous dicalcium phosphate, tricalcium phosphate, tetracalcium phosphate, octacalcium phosphate, hydroxyapatite, calcium-deficient hydroxyapatite, or carbonated hydroxyapatite, or combinations thereof.

13. The process according to claim 12, wherein the core material is used directly when it is a synthesized calcium carbonate, or used as naturally occurring calcium carbonate, treated using any conventional equipment such as a ball mill, a rod mill, a vibrating mill, a roll crusher, a centrifugal impact mill, a vertical bead mill, an attrition mill, a pin mill, a hammer mill, a pulverizer, a shredder and so on to diminish the core particles to the size optimal to be covered by the shell material using said process, wherein the core particle size is selected from the range of preferably 10 nM to 100 uM, more preferably 200 nM to 50 uM, most preferably 500 nM to 10 uM.

14. The process according to claim 12, wherein the shell is formed on the surface of the core particles while reacting a solution of a phosphate ion source with a solution of an additional calcium ion source, wherein the said additional calcium ion source is supplied externally, i.e., is not derived from the calcium carbonate that forms the core particles.

15. The process according to claim 14, wherein a solution of the phosphate ion source is added dropwise or portionwise to a suspension of the core particles in a solution of additional calcium ion source at such a speed that the pH of the reaction mixture is kept for the most part at or above pH 7.5 during the addition process.

16. The process according to claim 14, wherein an additional calcium ion source comprises calcium hydroxide or water-soluble calcium salt with various anions derived from mono-, di-, tri, or polysubstituted acids or mixtures thereof, including but not limited to citrate, malonate, chloride, acetate, nitrate, lactate, gluconate, and so on.

17. The process according to claim 14, wherein a phosphorous ion source comprises orthophosphoric acid or water-soluble orthophosphate salt such as monohydrogenphosphate, dihydrogenphosphate, orthophosphate, with various cations of the metals in groups I and II of the periodic table or mixtures thereof, including but not limited to lithium, potassium, sodium, cesium, rubidium, ammonium, and so on.

18. The process according to claim 14, wherein the solvent for the process is water or water/organic solvent mixture.

19. The process according to claim 18, wherein the water/organic solvent mixture is made by diluting water with mono-, di-, tri-, or poly-functional alcohols, which include but are not limited to methanol, ethanol, propanol, isopropanol, ethylene glycol, diethylene glycol, triethylene glycol, polyethylene glycol, propylene glycol, glycerin, mono- or di-substituted glycerin, and so on.

20. The process according to claim 19, wherein the concentration of organic solvent in the mixture does not lead to the precipitation of additional calcium ion source or phosphate ion source in the selected concentration ranges.

21. The process according to claim 14, wherein the concentration of the additional calcium ion source solution used for the shell preparation is selected from the range of preferably 0.05 to 3.00 M/L, more preferably 0.50 to 2.50 M/L, most preferably 1.00 to 2.00 M/L.

22. The process according to claim 14, wherein the concentration of the phosphate ion source solution used for the shell preparation is selected from the range of preferably 0.01 to 2.00 M/L, more preferably 0.50 to 1.75 M/L, most preferably 1.00 to 1.50 M/L.

23. The process according to claim 14, wherein the addition of the phosphate ion source is carried out at the temperature selected from the range of preferably 10 to 120 ^{o}C, more preferably 25 to 80 ^{o}C, most preferably 30 to 70 ^{o}C.

24. The process according to claim 14, wherein the stirring of the reaction mixture after addition of the phosphate ion source is carried out preferably for an additional 24 h, more preferably for an additional 4 h, even more preferably for an additional 1 h.

25. The process according to claim 14, wherein the product of the reaction mixture after addition of the phosphate ion source is isolated immediately, without additional stirring.

26. The process according to claim 24, wherein the additional stirring of the reaction mixture is carried out at the temperature selected from the range of preferably 10 to 120 ^{o}C, more preferably 25 to 80 ^{o}C, most preferably 30 to 70 ^{o}C.

27. The process according to claim 14, wherein the core material is synthesized *in situ* prior to the formation of the shell, using calcium ion source and carbonate ion source, in the solution in water or water/organic solvent mixture.

28. The process according to claim 27, wherein the water/organic solvent mixture is made by diluting water with mono-, di-, tri-, or poly-functional alcohols, which include but are not limited to methanol, ethanol, propanol, isopropanol, ethylene glycol, diethylene glycol, triethylene glycol, polyethylene glycol, propylene glycol, glycerin, mono- or di-substituted glycerin, and so on.

29. The process according to claim 27, wherein the calcium ion source comprises calcium hydroxide or water-soluble calcium salt with various anions derived from mono-, di-, tri, or polysubstituted acids or mixtures thereof, including but not limited to citrate, malonate, chloride, acetate, nitrate, lactate, gluconate, and so on.

30. The process according to claim 27, wherein the carbonate ion source comprises carbon dioxide or water-soluble carbonate or bicarbonate salt with various cations of the metals in groups I and II of the

periodic table or mixtures thereof, including but not limited to lithium, potassium, sodium, cesium, rubidium, ammonium, and so on.

31. The process according to claim 27, wherein the concentration of the organic solvent in the water/organic solvent mixture is selected from the range of preferably 1 to 90%, more preferably 1 to 50%, most preferably 1 to 25%

32. The process according to claim 27, wherein the concentrations of the carbonate ion source and the calcium ion source, used for in situ synthesis of the core material, are selected from the range of preferably 0.05 to 3.00 M/L, more preferably 0.50 to 1.75 M/L, most preferably 1.00 to 1.50 M/L.

33. The process according to claim 27, wherein *in situ* synthesis of the core is carried out at the temperature selected from the range of preferably 10 to 120 ^{o}C, more preferably 25 to 80 ^{o}C, most preferably 30 to 70 ^{o}C.

34. The process according to claim 27, wherein both *in situ* synthesis of the core material and the following formation of the shell are both carried out at the same temperature selected per claim 33.

35. The process according to claim 27, wherein *in situ* synthesis of the core material is carried out at room temperature and the following formation of the shell is carried out at the temperature selected from the range of preferably 10 to 120 ^{o}C, more preferably 25 to 80 ^{o}C, most preferably 30 to 70 ^{o}C.