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(54) **SURFACE-MODIFIED NANOPARTICLES**

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(57) **ABSTRACT**

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A composition comprises surface-modified nanoparticles of
at least one metal phosphate. The nanoparticles bear, on at
least a portion of their surfaces, a surface modification com-
prising at least one organosilane surface modifier comprising
at least one organic moiety comprising at least about six
carbon atoms.

SURFACE-MODIFIED NANOPARTICLES

STATEMENT OF PRIORITY

[0001] This application claims the priorities of U.S. Provisional Applications Nos. 61/051,468 and 61/051,477, both filed May 8, 2008, the contents of which are hereby incorporated by reference.

FIELD

[0002] This invention relates to compositions comprising surface-modified metal phosphate nanoparticles and, in another aspect, to articles comprising the compositions.

BACKGROUND

[0003] Metal phosphates (for example, alkaline earth phosphates such as magnesium phosphate and calcium phosphate) have numerous applications. Alkaline earth phosphates are used in anti-rust coatings, in flame retardants, in antacids, and in producing fluorescent particles. Iron phosphates find application in cathode material for lithium ion batteries.

[0004] Aluminum, manganese, cobalt, tin, and nickel phosphates are used in heterogeneous catalysis. Zinc phosphate is commonly used as a pigment in anti-corrosion protection. Zirconium phosphates are used as solid acid catalysts. Various lanthanide phosphates are useful as fluorescent and laser materials.

[0005] Calcium phosphates are particularly useful, however, due to their classification as biocompatible materials. Under physiological conditions calcium phosphates can dissolve, and the resulting dissolution products can be readily assimilated by the human body. Biocompatible calcium phosphates include hydroxyapatite (HAP; $[\text{Ca}_5(\text{PO}_4)_3\text{OH}]$), dicalcium phosphate (DCP; $[\text{Ca}(\text{HPO}_4)\cdot 2\text{H}_2\text{O}]$), tricalcium phosphate (TCP; $[\text{Ca}_3(\text{PO}_4)_2]$), tetracalcium phosphate (TTCP; $[\text{Ca}_4\text{O}(\text{PO}_4)_2]$), and amorphous calcium phosphate.

[0006] Of the biocompatible calcium phosphates, hydroxyapatite can be more stable under physiological conditions. Thus, hydroxyapatite has been used for bone repair after major trauma or surgery (for example, in coatings for titanium and titanium alloys). Hydroxyapatite has also been used in the separation and purification of proteins and in drug delivery systems. Other calcium phosphates have been used as dietary supplements in breakfast cereals, as tableting agents in some pharmaceutical preparations, in feed for poultry, as anti-caking agents in powdered spices, as raw materials for the production of phosphoric acid and fertilizers, in porcelain and dental powders, as antacids, and as calcium supplements.

[0007] For some of these applications (for example, adjuvants for vaccines, cores or carriers for biologically active molecules, controlled release matrices, coating implant materials, protein purification, and dental applications), non-agglomerated nanoparticles of calcium phosphate can be desired. The preferred sizes, morphologies, and/or degrees of crystallinity of the nanoparticles vary according to the nature of each specific application.

[0008] Numerous methods have been used for the synthesis of hydroxyapatite nanoparticles including chemical precipitation, hydrothermal reactions, freeze drying, solgel formation, phase transformation, mechanochemical synthesis, spray drying, microwave sintering, plasma synthesis, and the like. Hydroxyapatite nanoparticles have often been synthesized by the reaction of aqueous solutions of calcium ion-

containing and phosphate ion-containing salts (the so-called "wet process"), followed by thermal treatment. Nanoparticles obtained by this method generally have had a needle-like (acicular) morphology with varying degrees of crystallinity, depending upon the nature of the thermal treatment. Such acicular nanoparticles can be used as coating implant materials but have limited or no use in some of the other applications mentioned above.

[0009] Various additives have been used to control hydroxyapatite particle growth and/or to alter hydroxyapatite particle morphology but with only limited success. For example, polymers and solvent combinations have been used in the above-described wet process to suppress crystal growth along one axis, but only a few approaches have provided particles with decreased aspect ratios or particles of spherical morphology but relatively large particle size.

[0010] Solid-state reaction of precursors, plasma spraying, pulsed laser deposition, and flame spray pyrolysis methods have resulted in hydroxyapatite nanoparticles of different morphologies (for example, spherical or oblong), but these have often been in the form of micron-sized agglomerates of nanoparticles that have been of limited use in certain applications. Numerous researchers have carried out post-synthesis surface modification of hydroxyapatite to de-agglomerate the particles.

[0011] Generally the synthesis of spherical hydroxyapatite nanoparticles has involved the use of either surfactants or polymers to control the morphology and the size of the resulting particles. The capability of such methods to provide nanoparticles in the form of redispersible dry powder (for example, dry powder that can be redispersed in an appropriate solvent to provide a non-agglomerated nanoparticle dispersion), however, has generally not been evident.

SUMMARY

[0012] Thus, we recognize that there is a need for metal phosphate nanoparticles (particularly, calcium phosphate nanoparticles) of desired primary particle sizes and/or particle morphologies that are surface-modified so as to be compatible with (and therefore dispersible in) a variety of media (for example, solvents, polymers, paints, coatings, cosmetic formulations, pharmaceutical formulations, and the like). In particular, we recognize that there is a need for very small nanoparticles (for example, having average primary particle diameters of less than about 20 nm) that are biocompatible and preferably of spherical morphology, which can be effectively used in, for example, inhalable aerosol drug delivery systems. In order to facilitate industrial use, such nanoparticles preferably can be provided in the form of a redispersible powder.

[0013] Briefly, in one aspect, this invention provides such a composition, which comprises surface-modified nanoparticles of at least one metal phosphate (most preferably, calcium phosphate). The nanoparticles bear, on at least a portion of their surfaces, a surface modification comprising at least one organosilane surface modifier comprising at least one organic moiety comprising at least about six carbon atoms. Preferably, the organic moiety has from about 6 to about 24 carbon atoms.

[0014] It has been discovered that use of the above-described relatively long-chain organosilane surface modifiers can enable the preparation of substantially non-agglomerated metal phosphate nanoparticles. The nanoparticles of the invention can be relatively simply prepared from relatively

inexpensive metal phosphate precursors (for example, a metal cation source such as a metal salt, and a phosphate anion source such as phosphoric acid) and can be grown to preferred average primary particle sizes (for example, average primary particle diameters of about 1 nm to about 50 nm). By varying the nature of the organosilane surface modifier (for example, the carbon chain length of its organic moiety and/or the presence or absence of various functional groups) and/or its amount, the surface characteristics of the nanoparticles can be controllably tailored and their compatibility with a particular medium can be enhanced.

[0015] Surprisingly, the use of relatively long-chain organosilane surface modifier(s) can provide nanoparticles that are also redispersible and preferably of substantially spherical morphology. This can be especially advantageous for the production of calcium phosphate nanoparticles having average primary particle diameters in the range of about 1 nm to about 20 nm. Such nanoparticles can be well-suited for use in various pharmaceutical, medical, and dental applications, particularly those (for example, inhalable aerosol drug delivery systems) requiring or desiring relatively small, redispersible, biocompatible nanoparticles of spherical morphology.

[0016] Thus, in at least preferred embodiments, the composition of the invention can meet the above-mentioned need in the art for redispersible metal phosphate nanoparticles (particularly, calcium phosphate nanoparticles) of desired primary particle sizes and/or morphologies that are surface-modified so as to be compatible with (and therefore dispersible in) a variety of media, and/or that can be easily tailored to fit the characteristics of a particular medium. The composition can therefore further comprise, for example, at least one carrier material or medium (for example, a material or mixture of materials in the form of a gas, a liquid, a bulk solid, a powder, an oil, a gel, a dispersion, and the like).

[0017] In another aspect, this invention also provides an article comprising the composition of the invention.

DETAILED DESCRIPTION

[0018] In the following detailed description, various sets of numerical ranges (for example, of the number of carbon atoms in a particular moiety, of the amount of a particular component, and the like) are described, and, within each set, any lower limit of a range can be paired with any upper limit of a range.

Definitions

[0019] As used in this patent application:

[0020] “agglomeration” means an association of primary particles, which can range from relatively weak (based upon, for example, charge or polarity) to relatively strong (based upon, for example, chemical bonding);

[0021] “nanoparticles” means particles having a diameter of less than 100 nm;

[0022] “primary particle size or diameter” means the size or diameter of a non-associated single nanoparticle;

[0023] “redispersible” (in regard to nanoparticles) means nanoparticles that can be “dried” or precipitated from an original dispersion of the nanoparticles in aqueous or organic solvent or a combination thereof (for example, by removal of the solvent and/or by a change in solvent polarity) to form a powder or a wet precipitate or gel that can be dispersed again in the original dispersion solvent (or a solvent of essentially the same polarity as that of the original dispersion solvent) to

provide a nanoparticle dispersion (preferably, without substantial change in primary particle size (and/or average particle size as measured by dynamic light scattering) relative to the original dispersion and/or without substantial sedimentation of the nanoparticles over a period of at least four hours (for example, with size change and/or sedimentation of less than 25 percent (preferably, less than 20 percent; more preferably, less than 15 percent; most preferably, less than 10 percent), where the sedimentation percentage is by weight, based upon the total weight of nanoparticles in the dispersion));

[0024] “sol” means a dispersion or suspension of colloidal particles in a liquid phase; and “substantially spherical” (in regard to nanoparticles) means at least a major portion of the nanoparticles have an aspect ratio less than or equal to 2.0 (preferably, less than or equal to 1.5; more preferably, less than or equal to 1.25; most preferably, 1.0).

Preparation of Surface-Modified Nanoparticles

[0025] The surface-modified metal phosphate nanoparticles of the composition of the invention can be prepared by any of a variety of known or hereafter developed particle surface modification methods. Preferred preparative methods include those that can provide the desired surface modification while maintaining or producing substantially non-agglomerated nanoparticles. Preferred preparative methods include in situ surface modification during nanoparticle synthesis, post-synthesis surface modification, and combinations thereof (more preferably, in situ methods).

[0026] For example, in post-synthesis surface modification, starting metal phosphate nanoparticles can be prepared by essentially any method that can provide nanosized particles (for a range of applications, preferably, having average primary particle diameters of 1 nanometer (nm) (more preferably, about 2 nm; most preferably, about 3 nm) to about 50 nm (more preferably, about 30 nm; most preferably, about 20 nm), where any lower limit can be paired with any upper limit of the size range) that are capable of then being surface modified with organosilane. Useful methods for producing such starting metal phosphate nanoparticles include those described, for example, in U.S. Patent Application Publication Nos. 2004/0170699 (Chane-ching et al), 2006/0257306 (Yamamoto et al.), and 2007/0196509 (Riman et al); by Stouwdam et al. in “Improvement in the Luminescence Properties and Processability of LaF₃/Ln and LaPO₄/Ln Nanoparticles by Surface Modification,” *Langmuir* 20, 11763 (2004); and by Mai et al in “Orderly Aligned and Highly Luminescent Monodisperse Rare-Earth Orthophosphate Nanocrystals Synthesized by a Limited Anion-Exchange Reaction,” *Chemistry of Materials* 19, 4514 (2007); the descriptions of which are incorporated herein by reference.

[0027] The starting metal phosphate nanoparticles can then be dispersed in a liquid medium (for example, alcohol, ether, or a polar aprotic solvent) and optionally any water residues removed. The organosilane surface modification agent can then be added to the resulting dispersion (preferably, by mixing in an organic solvent and/or water; optionally, a catalyst can be present to facilitate hydrolysis of the organosilane) and the resulting mixture heated under reflux to a temperature between room temperature and the boiling point of the liquid medium (at atmospheric pressure). Optionally, any resulting water can be removed. The resulting surface-modified nano-

particles can be separated (for example, by filtration or by precipitation followed by centrifugation), washed, and, optionally, dried.

[0028] A preferred in situ process comprises (a) combining (preferably, in at least one solvent) (1) at least one metal cation source, (2) at least one phosphate anion source, (3) at least one organic base comprising at least one organic moiety comprising at least about five carbon atoms, and (4) at least one organosilane comprising at least one organic moiety comprising at least about six carbon atoms; and (b) allowing the metal cation source and the phosphate anion source to react in the presence of the organic base and the organosilane (for example, to form surface-modified metal phosphate nanoparticles).

[0029] Preferably, the metal cation source is a metal salt comprising at least one metal cation and at least one anion that is capable of being displaced by phosphate anion, and/or the phosphate anion source is selected from phosphorus-containing compounds (for example, phosphoric acid or an organoammonium phosphate salt) that are capable of providing phosphate anion either directly or upon dissolution or dispersion (for example, in aqueous or non-aqueous solvent), oxidation, or hydrolysis, and combinations thereof.

[0030] Use of the above-described metal phosphate precursors including an organic base and a relatively long-chain organosilane can enable the preparation of substantially non-agglomerated metal phosphate nanoparticles that are redispersible and preferably of substantially spherical morphology. The nanoparticles can be grown to preferred average primary particle sizes (for example, average primary particle diameters of about 1 nm to about 50 nm). Preferred embodiments of the process can enable control of average primary particle size and/or particle morphology by varying, for example, the reaction temperature, time, pH, choice and/or amounts of reactants, and/or the order and/or manner of combination of reactants.

[0031] Metal cation sources suitable for use in the preferred in situ process include metal salts comprising at least one metal cation and at least one anion that can be displaced by phosphate anion. Such salts can be prepared in situ, if desired (for example, by the reaction of a metal hydroxide, a metal carbonate, or a metal oxide with a mineral acid). Useful metal cations include those of transition metals (including the lanthanides and the actinides thorium and uranium), alkaline earth metals, alkali metals, post-transition metals, and the like, and combinations thereof.

[0032] Preferred transition metals include titanium, vanadium, chromium, manganese, iron, cobalt, nickel, copper, zinc, yttrium, zirconium, niobium, molybdenum, ruthenium, cadmium, hafnium, tantalum, tungsten, lanthanum, cerium, neodymium, samarium, europium, gadolinium, terbium, dysprosium, erbium, ytterbium, thorium, and combinations thereof (more preferably, titanium, manganese, iron, cobalt, zinc, yttrium, zirconium, niobium, tantalum, lanthanum, cerium, europium, gadolinium, terbium, dysprosium, erbium, and combinations thereof; most preferably, manganese, iron, zinc, yttrium, zirconium, niobium, tantalum, lanthanum, cerium, europium, gadolinium, terbium, and combinations thereof). Preferred post-transition metals include aluminum, gallium, indium, tin, lead, antimony, bismuth, and combinations thereof (more preferably, aluminum, gallium, tin, antimony, bismuth, and combinations thereof; most preferably, aluminum).

[0033] Preferred alkaline earth metals include beryllium, calcium, strontium, magnesium, barium, and combinations thereof (more preferably, calcium, strontium, magnesium, barium, and combinations thereof; even more preferably, calcium, magnesium, strontium, and combinations thereof; most preferably, calcium). Preferred alkali metals include lithium, sodium, potassium, rubidium, cesium, and combinations thereof (more preferably, lithium, sodium, potassium, and combinations thereof; most preferably, sodium, potassium, and combinations thereof).

[0034] Preferably, the metal cation is a divalent metal cation (more preferably, a divalent alkaline earth metal cation; even more preferably, divalent calcium or magnesium; most preferably, divalent calcium). Alkaline earth metals and combinations thereof are preferred.

[0035] Useful anions include halide, nitrate, acetate, carbonate, alkanoate (for example, formate, propionate, hexanoate, neodecanoate, and the like), alkoxide, lactate, oleate, acetylacetonate, sulfate, thiosulfate, sulfonate, bromate, perchlorate, tribromoacetate, trichloroacetate, trifluoroacetate, sulfide, hydroxide, oxide, and the like, and combinations thereof. Preferred anions include halide, nitrate, sulfate, carbonate, acetate, hydroxide, oxide, and combinations thereof (more preferably, halide, nitrate, acetate, and combinations thereof; most preferably, halide and combinations thereof).

[0036] Mixed metal salts, mixed anion salts, and/or mixtures of salts can be utilized, if desired. The salts can comprise other metal cations (for example, at levels up to about 10 mole percent, based upon the total number of moles of metal cation), but preferably all metals in the salts are selected from those described above. Similarly, the salts can comprise other anions (for example, at levels up to about 10 mole percent, based upon the total number of moles of anion), but preferably all anions in the salts are selected from those described above.

[0037] Representative examples of useful metal salts include calcium chloride hexahydrate, calcium chloride dihydrate, calcium chloride (anhydrous), calcium bromide hexahydrate, calcium nitrate tetrahydrate, calcium acetate monohydrate, calcium propionate, calcium lactate pentahydrate, calcium 2-ethylhexanoate, calcium methoxyethoxide, calcium carbonate, magnesium chloride hexahydrate, magnesium bromide hexahydrate, magnesium ethoxide, magnesium hydroxide, magnesium nitrate hexahydrate, magnesium acetate tetrahydrate, magnesium oleate, magnesium sulfate heptahydrate, zinc chloride (anhydrous), zinc acetate dihydrate, zinc carbonate hydroxide, zinc bromide dihydrate, zinc nitrate hexahydrate, zinc neodecanoate, zinc oxide, zinc sulfate heptahydrate, cobalt chloride hexahydrate, manganese (II) chloride tetrahydrate, manganese (II) bromide tetrahydrate, manganese (II) nitrate tetrahydrate, manganese (II) acetate tetrahydrate, manganese (III) acetylacetonate, europium (III) chloride hexahydrate, europium (III) nitrate hexahydrate, europium (II) chloride, europium (III) oxide, terbium (III) chloride hexahydrate, terbium (III) nitrate hexahydrate, terbium (III,IV) oxide, and the like, and combinations thereof. More preferred metal salts include those having anions selected from halide, nitrate, acetate, and combinations thereof. The halides are most preferred. Hydrated metal salts can be preferred (for example, to facilitate hydrolysis of the organosilane).

[0038] Such metal salts can be prepared by known methods. Many of such salts are commercially available.

[0039] Phosphate anion sources suitable for use in the preferred in situ process include phosphorus-containing compounds that provide phosphate anion either directly or upon dissolution or dispersion (for example, in aqueous or non-aqueous solvent), oxidation, or hydrolysis, and combinations thereof. Such compounds include phosphoric acid (H_3PO_4); phosphorous acid (H_3PO_3); hypophosphorous acid (H_3PO_2); thiophosphoric acid; phosphoric acid esters; thiophosphoric acid esters (for example, diethylchlorothiophosphate, diethyldithiophosphate, ethyldichlorothiophosphate, trimethylthiophosphate, and the like); phosphite esters (for example, dimethylphosphite, trimethylphosphite, diisopropylphosphite, diethylhydrogenphosphite, diisobutylphosphite, diolelylhydrogenphosphite, diphenylhydrogenphosphite, triphenylphosphite, ethylenechlorophosphite, tris(trimethylsilyl) phosphite, and the like); thiophosphite esters (for example, triauryltrithiophosphite, triethyltrithiophosphite, and the like); phosphate salts of alkali metal cations, ammonium cation, or organoammonium cations; thiophosphate salts of alkali metal cations, ammonium cation, or organoammonium cations (for example, ammonium diethyldithiophosphate, potassium diethyldithiophosphate, sodium dithiophosphatetrihydrate, and the like); phosphite salts of alkali metal cations, ammonium cation, or organoammonium cations (for example, disodium hydrogenphosphite pentahydrate and the like); hypophosphite salts of alkali metal cations, ammonium cation, or organoammonium cations (for example, sodium hypophosphite hydrate, potassium hypophosphite, ammonium hypophosphite, ethylpiperidiniumhypophosphite, tetrabutylammonium hypophosphite, and the like); phosphorus oxides (for example, P_2O_5 and the like); phosphorus halides and/or oxyhalides (for example, POCl_3 , PCl_5 , PCl_3 , POBr_3 , PBr_5 , PBr_3 , difluorophosphoric acid, fluorophosphoric acid, and the like); phosphorus sulfides (for example, P_2S_5 , P_2S_3 , P_4S_3 , and the like); phosphorus halosulfides (for example, PSCl_3 , PSBr_3 , and the like); polyphosphoric acid; polyphosphoric acid esters; polyphosphate salts of alkali metal cations, ammonium cation, or organoammonium cations; and the like; and combinations thereof.

[0040] Preferred phosphate anion sources include phosphoric acid, phosphoric acid esters, organoammonium phosphate salts, and combinations thereof (more preferably, phosphoric acid, organoammonium phosphate salts, and combinations thereof; most preferably, phosphoric acid).

[0041] Useful phosphoric acid esters include alkylphosphates, and the like, and combinations thereof. Representative examples of useful alkylphosphates include mono-, di-, and trialkylphosphates comprising alkyl moieties having from one to about 12 carbon atoms such as methylphosphate, ethylphosphate, propylphosphate, butylphosphate, pentylphosphate, hexylphosphate, dimethylphosphate, diethylphosphate, dipropylphosphate, dibutylphosphate, dipentylphosphate, dihexylphosphate, di-2-ethylhexylphosphate, methylethylphosphate, ethylbutylphosphate, ethylpropylphosphate, trimethylphosphate, triethylphosphate, tripropylphosphate, tributylphosphate, tripentylphosphate, trihexylphosphate, tri-2-ethylhexylphosphate, ethyl dimethylphosphate, ethyl dibutylphosphate, and the like, and combinations thereof. Also useful are arylphosphates such as triphenylphosphate; alkylphosphate salts such as ammonium dilaurylphosphate; aminoethanoldihydrogenphosphate; and the like; and combinations thereof.

[0042] Preferred phosphoric acid esters include mono-, di-, and trialkylphosphates comprising alkyl moieties having

from one to about four carbon atoms (for example, methylphosphate, ethylphosphate, propylphosphate, butylphosphate, dimethylphosphate, diethylphosphate, dipropylphosphate, dibutylphosphate, methylethylphosphate, ethylbutylphosphate, ethylpropylphosphate, trimethylphosphate, triethylphosphate, tripropylphosphate, tributylphosphate, ethyl dimethylphosphate, ethyl dibutylphosphate, and combinations thereof). More preferred phosphoric acid esters include mono- and dialkylphosphates comprising alkyl moieties having one to about four carbon atoms (for example, methylphosphate, ethylphosphate, propyl phosphate, butylphosphate, dimethylphosphate, diethylphosphate, dipropylphosphate, dibutylphosphate, methylethylphosphate, ethylbutylphosphate, ethylpropylphosphate, and combinations thereof). Most preferred phosphoric acid esters include monoalkylphosphates having from one to about four carbon atoms (for example, methylphosphate, ethylphosphate, propylphosphate, butylphosphate, and combinations thereof).

[0043] Useful polyphosphoric acid esters include esters of di-, tri-, tetra-, and pentaphosphoric acid and a monohydric alcohol and/or polyhydric alcohol, and the like, and combinations thereof. Representative examples of polyphosphoric acid esters include polyphosphoric acid methyl ester, polyphosphoric acid ethyl ester, polyphosphoric acid propyl ester, polyphosphoric acid butyl ester, polyphosphoric acid pentyl ester, polyphosphoric acid dimethyl ester, polyphosphoric acid diethyl ester, polyphosphoric acid dipropyl ester, polyphosphoric acid dibutyl ester, diphosphoric acid methylethyl ester, diphosphoric acid ethylbutyl ester, diphosphoric acid ethylpropyl ester, diphosphoric acid ethylhexyl ester, trialkyl esters of di-, tri-, tetra-, and penta-phosphoric acids, tetraalkyl esters of di-, tri-, tetra-, and penta-phosphoric acids, pentaalkyl esters of di-, tri-, tetra-, and penta-phosphoric acids, hexaalkyl esters of di-, tri-, tetra-, and penta-phosphoric acids, and the like, and combinations thereof. Preferred polyphosphoric acid esters include those having an ester group containing one to about four carbon atoms (for example, polyphosphoric acid methyl ester, polyphosphoric acid ethyl ester, polyphosphoric acid propyl ester, and polyphosphoric acid butyl ester), and combinations thereof.

[0044] Useful salts include alkali metal (for example, sodium or potassium) phosphates and polyphosphates, ammonium phosphates and polyphosphates, organoammonium (for example, mono-, di-, tri-, and tetraalkylammonium) phosphates and polyphosphates, and the like (including hydroxylamine phosphate), and combinations thereof. Representative examples of useful alkali metal phosphates include sodium dihydrogen phosphate (monobasic), sodium hydrogen phosphate (dibasic), trisodium phosphate (tribasic), potassium dihydrogen phosphate, lithium dihydrogenphosphate, sodium tripolyphosphate, sodium hexametaphosphate, potassium pyrophosphate, and the like, and combinations thereof.

[0045] Representative examples of useful organoammonium phosphates and polyphosphates include ethylammonium phosphate, diethylammonium phosphate, trimethylammonium phosphate, triethylammonium phosphate, tributylammonium pyrophosphate, methyltriethylammonium dibutylphosphate, pentytriethylammonium phosphate, hexyltriethylammonium phosphate, octyltriethylammonium phosphate, dodecyltrimethylammonium phosphate, hexadecyltrimethylammonium dihydrogen phosphate, tetramethylammonium dihydrogen phosphate, tetraethylammonium

dihydrogenphosphate, tetrabutylammonium phosphate, tetrahexylammonium dihydrogen phosphate, di-2-ethylhexylammonium hexafluorophosphate, tetramethylammonium hexafluorophosphate, tetraethylammonium hexafluorophosphate, tetrapropylammonium hexafluorophosphate, tetrabutylammonium hexafluorophosphate, tetrahexylammonium hexafluorophosphate, phenyltrimethylammonium hexafluorophosphate, benzyltrimethylammonium hexafluorophosphate, and the like, and combinations thereof.

[0046] Preferred organoammonium phosphate salts include pentyltriethylammonium phosphate, hexyltriethylammonium phosphate, octyltriethylammonium phosphate, dodecyltrimethylammonium phosphate, hexadecyltrimethylammonium dihydrogen phosphate, tetrahexylammonium dihydrogen phosphate, di-2-ethylhexylammonium hexafluorophosphate, tetrahexylammonium hexafluorophosphate, phenyltrimethylammonium hexafluorophosphate, benzyltrimethylammonium hexafluorophosphate, and combinations thereof (more preferably, hexyltriethylammonium phosphate, octyltriethylammonium phosphate, dodecyltrimethylammonium phosphate, tetrahexylammonium dihydrogen phosphate, di-2-ethylhexylammonium hexafluorophosphate, tetrahexylammonium hexafluorophosphate, and combinations thereof most preferably, octyltriethylammonium phosphate, di-2-ethylhexylammonium hexafluorophosphate, and combinations thereof).

[0047] Preferred phosphate salts include organoammonium phosphates, and combinations thereof (more preferably, mono-, di-, tri-, and tetraalkylammonium phosphates, and combinations thereof most preferably, tetraalkylammonium phosphates, and combinations thereof). Most preferably, the preferred salts comprise at least one organic moiety comprising at least about five carbon atoms.

[0048] Such phosphate anion sources can be prepared by known methods. Many of such sources (for example, phosphoric acid, alkylphosphates, and polyphosphoric acid esters) are commercially available.

[0049] Organic bases suitable for use in the preferred in situ process include those organic amines and organoammonium hydroxides that comprise at least one organic moiety comprising at least about five carbon atoms (preferably, at least about six carbon atoms; more preferably, at least about eight carbon atoms), and combinations thereof (preferably, an organic amine). The organic moiety can be linear, branched, alicyclic, aromatic, or a combination thereof (preferably, linear or branched), with the proviso that carbon atoms in a cyclic moiety count only as half their number toward the requisite minimum of five (for example, a phenyl ring counts as three carbon atoms rather than six and must be supplemented by, for example, an attached ethyl moiety). Preferably, the organic moiety comprises from about 6 to about 24 carbon atoms (more preferably, from about 6 to about 18 carbon atoms; most preferably, from about 8 to about 12 carbon atoms). Representative examples of suitable organic amines include monoalkylamines such as hexylamine, heptylamine, octylamine, nonylamine, decylamine, dodecylamine, hexadecylamine, and octadecylamine; dialkylamines such as dihexylamine, di-n-heptylamine, di-n-octylamine, bis(2-ethylhexyl)amine, di-sec-octylamine, di-n-nonylamine, di-n-decylamine, di-n-undecylamine, di-n-tridecylamine, and dicyclooctylamine; trialkylamines such as trihexylamine, triheptylamine, triisooctylamine, trioctylamine, tridodecylamine, tris(4-methylcyclohexyl)amine, tri-n-heptylamine, trionylamine, N, N-didecylmethylamine, N,

N-dimethylcyclohexylamine, N, N-dimethyldodecylamine, N, N-dimethyloctylamine, and tris(2-ethylhexyl)amine; arylamines such as diphenylstearylamine; polyethylene glycol mono- and diamines; and the like; and combinations thereof.

[0050] Preferred organic amines include hexylamine, octylamine, decylamine, dodecylamine, hexadecylamine, dihexylamine, di-n-octylamine, bis(2-ethylhexyl)amine, di-sec-octylamine, di-n-decylamine, trihexylamine, trioctylamine, triisooctylamine, trionylamine, tridodecylamine, tris(4-methylcyclohexyl)amine, tri-n-heptylamine, N, N-didecylmethylamine, N, N-dimethylcyclohexylamine, N, N-dimethyldodecylamine, N, N-dimethyloctylamine, tris(2-ethylhexyl)amine, and combinations thereof (more preferably, hexylamine, octylamine, decylamine, dodecylamine, dihexylamine, di-n-octylamine, bis(2-ethylhexyl)amine, di-sec-octylamine, trihexylamine, trioctylamine, triisooctylamine, tridodecylamine, tri-n-heptylamine, N, N-dimethyloctylamine, tris(2-ethylhexyl)amine, and combinations thereof; most preferably, dihexylamine, di-n-octylamine, bis(2-ethylhexyl)amine, di-sec-octylamine, trihexylamine, trioctylamine, triisooctylamine, tris(2-ethylhexyl)amine, and combinations thereof).

[0051] Representative examples of suitable organoammonium hydroxides include benzyltriethylammonium hydroxide, benzyltrimethylammonium hydroxide, hexane-1,6-bis(tributylammonium)dihydroxide, 3-(trifluoromethyl)phenyltrimethylammonium hydroxide, dodecyltrimethylethylammonium hydroxide, phenyltrimethylammonium hydroxide, cetyltrimethylammonium hydroxide, triethylphenylammonium hydroxide, tetradecylammonium hydroxide, tetrabutylammonium hydroxide, tetramethylammonium hydroxide, tetrapropylammonium hydroxide, tetrahexylammonium hydroxide, tetraoctylammonium hydroxide, tetrapentylammonium hydroxide, methyltriethylammonium hydroxide, tetraoctadecylammonium hydroxide, dimethyldiethylammonium hydroxide, methyltripropylammonium hydroxide, tetradecyltriethylammonium hydroxide, ethyltrimethylammonium hydroxide, tris(2-hydroxyethyl)methylammonium hydroxide, and the like, and combinations thereof.

[0052] Preferred organoammonium hydroxides include benzyltriethylammonium hydroxide, benzyltrimethylammonium hydroxide, dodecyltrimethylethylammonium hydroxide, cetyltrimethylammonium hydroxide, triethylphenylammonium hydroxide, tetradecylammonium hydroxide, tetrahexylammonium hydroxide, tetraoctylammonium hydroxide, tetrapentylammonium hydroxide, tetraoctadecylammonium hydroxide, tetradecyltriethylammonium hydroxide, and combinations thereof (more preferably, dodecyltrimethylethylammonium hydroxide, cetyltrimethylammonium hydroxide, tetradecylammonium hydroxide, tetrahexylammonium hydroxide, tetraoctylammonium hydroxide, tetraoctadecylammonium hydroxide, tetradecyltriethylammonium hydroxide, and combinations thereof; most preferably, dodecyltrimethylethylammonium hydroxide, cetyltrimethylammonium hydroxide, and combinations thereof).

[0053] Such organic bases can be prepared by known methods. Many of such bases (for example, dodecyltrimethylethylammonium hydroxide, cetyltrimethylammonium hydroxide, tetradecylammonium hydroxide, tetrahexylammonium hydroxide, and tetraoctylammonium hydroxide) are commercially available.

[0054] The organic bases (as well as the phosphate anion sources) can be used in neat solid or liquid form or can be used in the form of a solution in organic solvent (for example, an alkanol such as methanol). A wide range of concentrations can be useful (for example, from about 5 to about 90 weight percent in alkanol, based upon the total weight of the solution).

[0055] In a preferred embodiment of the preferred in situ process, the organic base can be combined with the phosphate anion source (for example, phosphoric acid), dissolved in a polar organic solvent or in at least a portion of the organosilane, and used in the form of the resulting solution. Polar organic solvents useful for dissolving the organic base include acetone, diethylether, alkanols (for example, methanol, ethanol, and isopropanol), dimethylsulfoxide (DMSO), dimethylformamide (DMF), tetrahydrofuran (THF), ethyl acetate, and the like, and mixtures thereof, with alkanols being preferred and methanol more preferred.

[0056] When the phosphate anion source is an organoammonium phosphate or polyphosphate comprising at least one organic moiety that comprises at least about five carbon atoms, the organoammonium phosphate or polyphosphate can serve as both the phosphate anion source and the organic base, without the need for addition of a separate organic base. Such dual functionality is not limited to these components, however, as other materials can simultaneously serve as more than one of the four reaction mixture components.

[0057] Organosilanes suitable for use in the preferred in situ process include those organosilanes that comprise at least one organic moiety comprising at least about six carbon atoms (preferably, at least about seven carbon atoms; more preferably, at least about eight carbon atoms), and combinations thereof. The organic moiety can be linear, branched, alicyclic, aromatic, or a combination thereof (preferably, linear or branched), with the proviso that carbon atoms in a cyclic moiety count only as half their number toward the requisite minimum of six (for example, a phenyl ring counts as three carbon atoms rather than six and must be supplemented by, for example, an attached propyl moiety). Preferably, the organic moiety comprises from about 6 to about 24 carbon atoms (more preferably, from about 7 to about 18 carbon atoms; even more preferably, from about 8 to about 12 carbon atoms). Most preferably, the organic moiety has about 8 carbon atoms (and is preferably branched). Preferably, the organosilane is selected from alkoxysilanes, halosilanes, acyloxysilanes, and aminosilanes (including primary, secondary, and tertiary amines), and combinations thereof.

[0058] A class of useful organosilanes can be represented by the following general Formula I:



wherein y is an integer of 1 to 3 (preferably, 2 or 3; more preferably, 3); each R is independently selected from hydrogen and organic moieties that are linear, branched, alicyclic, aromatic, or a combination thereof (preferably, linear or branched) and that have from about 6 to about 24 carbon atoms (more preferably, from about 7 to about 18 carbon atoms; even more preferably, from about 8 to about 12 carbon atoms; most preferably, about 8 carbon atoms), with the proviso that carbon atoms in a cyclic moiety count only as half their number toward the requisite minimum of 6 carbon atoms (for example, a phenyl ring counts as three carbon atoms rather than six and must be supplemented by, for example, an attached propyl moiety), and that optionally further comprise

at least one functional group selected from heterocyclic, acryloxy, methacryloxy, cyano, isocyano, cyanato, isocyanato, phosphino, amino, amido, vinyl, epoxy, glycidoxo, alkyl, carbon-carbon triple bond-containing, mercapto, siloxy, halo-carbon (for example, fluorocarbon), carbon-nitrogen double bond-containing, and carbon-carbon double bond-containing groups, and combinations thereof; with the proviso that at least one R group is an organic moiety; and each X is independently selected from hydrocarbyloxy, fluoroalkane-sulfonate, and alkoxy groups having from 1 to about 8 carbon atoms (preferably, 1 to about 4 carbon atoms; more preferably, 1 to about 2 carbon atoms; most preferably, 1 carbon atom), chlorine, bromine, iodine, acyloxy, amino moieties —NR'R', wherein each R' is independently selected from hydrogen and organic moieties having from 1 to about 10 carbon atoms, and combinations thereof. Preferably, at least one X is independently selected from alkoxy, acyloxy, chlorine, bromine, amino, and combinations thereof (more preferably, alkoxy, acyloxy, chlorine, amino, and combinations thereof; even more preferably, alkoxy, chlorine, amino, and combinations thereof; most preferably, alkoxy and combinations thereof). Preferably, at least one X is a hydrolyzable moiety.

[0059] When a functional group-containing organosilane is utilized, the particular functional group can be selected so as to be compatible with a material to which the resulting metal phosphate nanoparticles are to be added. Representative examples of heterocyclic functional groups include substituted and unsubstituted pyrroles, pyrazoles, imidazoles, pyrrolidines, pyridines, pyrimidines, oxazoles, thiazoles, furans, thiophenes, dithianes, isocyanurates, and the like, and combinations thereof. Representative examples of acryloxy functional groups include acryloxy, alkylacryloxy groups such as methacryloxy, and the like, and combinations thereof. Representative examples of carbon-carbon double bond-containing functional groups include alkenyl, cyclopentadienyl, styryl, phenyl, and the like, and combinations thereof.

[0060] Representative examples of useful organosilanes include phenyltrimethoxysilane; phenyltriethoxysilane; phenylethyltrimethoxysilane; diphenyldimethoxysilane; diphenyldiethoxysilane; N-[3-(triethoxysilyl)propyl]-4,5-dihydroimidazole; beta-trimethoxysilyl-2-pyridine; N-phenylaminopropyltrimethoxysilane; (N, N-diethyl-3-aminopropyl)trimethoxysilane; N, N-didecyl-N-methyl-N-(3-trimethoxysilylpropyl)ammonium chloride; 3-(N-styrylmethyl-2-aminoethylamino)propyltrimethoxysilane; methacryloxy-propenyltrimethoxysilane; 3-methacryloxypropyltrimethoxysilane; 3-methacryloxypropyltris(methoxyethoxy)silane; 3-cyclopentadienylpropyltriethoxysilane; 7-oct-1-enyltrimethoxysilane; 3-glycidoxypropyl-trimethoxysilane; gamma-glycidoxypropylmethyldimethoxysilane; gamma-glycidoxypropylmethyldiethoxysilane; gamma-glycidoxypropyldimethylethoxysilane; n-octyltriethoxysilane; n-octyltrimethoxysilane; isooctyltrimethoxysilane; hexyltriethoxysilane; 3-triethoxysilyl-N-(1,3-dimethyl-butyliden)propylamine; 3-acryloxypropyltrimethoxysilane; methacryloxypropylmethyldiethoxysilane; methacryloxypropylmethyldimethoxysilane; glycidoxypropylmethyldiethoxysilane; 2-(3,4-epoxycyclohexyl)-ethyltrimethoxysilane; aminophenyltrimethoxysilane; p-chloromethylphenyltri-n-propoxysilane; diphenylsilanediol; epoxyhexyltriethoxysilane; dococetyltrimethoxysilane; 1,4-bis(trimethoxysilyl)benzene; trimethoxysilyl-1,3-

dithiane; n-trimethoxysilylpropylcarbamoylcaprolactam; 2-(diphenylphosphine)ethyltriethoxysilane; N, N-dioctyl-n'-triethoxysilylpropylurea; N-cyclohexylaminopropyltrimethoxysilane; 11-bromoundecyltrimethoxysilane; 1, 2-bis(trimethoxysilyl)decane; bis[(3-methyldimethoxysilyl)propyl]polypropylene oxide; [(bicycloheptenyl)ethyl]trimethoxysilane; N-(6-aminohexyl)aminopropyltrimethoxysilane; [2-(3-cyclohexenyl)ethyl]trimethoxysilane; (3-cyclopentadienylpropyl)triethoxysilane; 3-(1,3-dimethylbutylidene)aminopropyltriethoxysilane; polyethyleneglycoltrialkoxysilane; n-octadecyltrichlorosilane; isooctyltrichlorosilane; 4-phenylbutyltrichlorosilane; 4-phenylbutylmethyldichlorosilane; n-dodecyltrichlorosilane; di-n-octyldichlorosilane; n-decyltrichlorosilane; n-decyldimethylchlorosilane; (cyclohexylmethyl)trichlorosilane; tridodecylbromosilane; diphenylmethylbromosilane; tert-butylmethoxyphenylbromosilane; trioctylbromosilane; 1,3-di-n-octyltetramethyldisilazane; phenylmethylbis(dimethylamino)silane; 1,3-bis(4-biphenyl)tetramethyldisilazane; 1,3-dioctadecyltetramethyldisilazane; 1,3-divinyl-1,3-diphenyl-1,3-dimethyldisilazane; and the like; and combinations thereof.

[0061] Preferred organosilanes include (N, N-diethyl-3-aminopropyl)trimethoxysilane; N, N-didecyl-N-methyl-N-(3-trimethoxysilylpropyl)ammonium chloride; 3-(N-styrylmethyl-2-aminoethylamino)propyltrimethoxysilane; methacryloxy-propenyltrimethoxysilane; 3-methacryloxypropyltrimethoxysilane; 3-cyclopentadienylpropyltriethoxysilane; 7-oct-1-enyltrimethoxysilane; 3-glycidoxypropyl-trimethoxysilane; gamma-glycidoxypropylmethyldiethoxysilane; n-octyltriethoxysilane; n-octyltrimethoxysilane; isooctyltrimethoxysilane; hexyltriethoxysilane; 3-acryloxypropyltrimethoxysilane; methacryloxypropylmethyldimethoxysilane; 2-(3,4 epoxycyclohexyl)-ethyltrimethoxysilane; p-chloromethylphenyltri-n-propoxysilane; epoxyhexyltriethoxysilane; dococentyltrimethoxysilane; N-cyclohexylaminopropyltrimethoxysilane; polyethyleneglycoltrimethoxysilane; n-octadecyltrichlorosilane; isooctyltrichlorosilane; 4-n-dodecyltrichlorosilane; di-n-octyldichlorosilane; n-decyltrichlorosilane; n-decyldimethylchlorosilane; (cyclohexylmethyl)trichlorosilane; trioctylbromosilane; tridodecylbromosilane; 1, 3-di-n-octyltetramethyldisilazane; dioctadecyltetramethyldisilazane; and combinations thereof.

[0062] More preferred organosilanes include (N, N-didecyl-N-methyl-N-(3-trimethoxysilylpropyl)ammonium chloride; 3-methacryloxypropyltrimethoxysilane; 3-glycidoxypropyltrimethoxysilane; gamma-glycidoxypropylmethyldiethoxysilane; n-octyltriethoxysilane; n-octyltrimethoxysilane; isooctyltrimethoxysilane; hexyltriethoxysilane; 3-acryloxypropyltrimethoxysilane; 2-(3, 4-epoxycyclohexyl)-ethyltrimethoxysilane; epoxyhexyltriethoxysilane; N-cyclohexylaminopropyltrimethoxysilane; polyethyleneglycoltrimethoxysilane; isooctyltrichlorosilane; n-decyltrichlorosilane; (cyclohexylmethyl)trichlorosilane; trioctylbromosilane; 1, 3-di-n-octyltetramethyldisilazane; and combinations thereof.

[0063] Most preferred organosilanes include n-octyltrimethoxysilane; isooctyltrimethoxysilane; hexyltriethoxysilane; polyethyleneglycoltrimethoxysilane; and combinations thereof.

[0064] Such organosilanes can be prepared by known methods (for example, from organosilane precursor compounds such as corresponding halosilanes or hydrosilanes).

[0065] Many of such organosilanes (for example, 3-methacryloxypropyltrimethoxysilane; 3-glycidoxypropyltrimethoxysilane; n-octyltrimethoxysilane; isooctyltrimethoxysilane; hexyltriethoxysilane; 3-acryloxypropyltrimethoxysilane; 2-(3, 4-epoxycyclohexyl)-ethyltrimethoxysilane; N-cyclohexylaminopropyltrimethoxysilane; polyethyleneglycoltrimethoxysilane; isooctyltrichlorosilane; and 1, 3-di-n-octyltetramethyldisilazane) are commercially available.

[0066] Solvents can be used in carrying out the preferred in situ process, if desired. Suitable solvents include those in which the various metal phosphate precursors or reaction mixture components can be substantially soluble or dispersible. Most preferably, the solvent will be capable of dissolving the reactants and products of the process, while keeping the desired metal phosphate nanoparticles well-dispersed.

[0067] Useful solvents for dissolving or dispersing more polar components such as the organic base and/or the phosphate anion source include polar organic solvents (for example, dimethylsulfoxide (DMSO), dimethylformamide (DMF), formamide, acetonitrile, acetone, methylethylketone (MEK), alkanols (for example, methanol, ethanol, isopropanol, 2-methoxyethanol, 1-methoxy-2-propanol, 1-methoxy-2-methyl-2-propanol, ethylene glycol, and the like, and combinations thereof), N-methyl pyrrolidinone (NMP), and the like, and combinations thereof. Preferred polar organic solvents can include acetonitrile, acetone, MEK, alkanols, and combinations thereof, due to their relatively high polarities and relatively low boiling points. More preferred polar organic solvents can include alkanols (most preferably, methanol, ethanol, and combinations thereof), however, due to the generally good solubility of reaction byproducts in these solvents and the ease of solvent removal (along with the byproducts) during purification.

[0068] Useful solvents for dissolving or dispersing less polar components such as the long-chain organosilanes include non-polar organic solvents such as alkanes (for example, hexane, heptane, octane, and the like, and combinations thereof) and aromatic hydrocarbons (for example, toluene, benzene, xylene, and the like, and combinations thereof), as well as more polar solvents such as esters (for example, ethyl acetate and the like, and combinations thereof), ethers (for example, tetrahydrofuran (THF), diethylether, and the like, and combinations thereof), and halocarbons (for example, carbon tetrachloride and the like, and combinations thereof), and the like, and combinations thereof. Preferred non-polar organic solvents include hexane, heptane, octane, toluene, and combinations thereof, due to their boiling points.

[0069] Mixtures of the polar and non-polar solvents can advantageously be utilized to facilitate separation of the resulting metal phosphate nanoparticles from reaction byproducts. Water in relatively small amounts can speed the kinetics of growth of the metal phosphate nanoparticles and/or facilitate hydrolysis of the organosilane surface modifier, but the presence of water in relatively larger amounts (for example, a water to metal ratio of greater than about 25) can cause nanoparticle agglomeration and/or loss of substantially spherical morphology.

[0070] The preferred in situ process can be carried out by combining at least one metal cation source, at least one phos-

phate anion source, at least one organic base comprising at least one organic moiety comprising at least about five carbon atoms, and at least one organosilane comprising at least one organic moiety comprising at least about six carbon atoms (preferably, in at least one solvent). Generally, any order and manner of combination of the four reaction mixture components can be utilized, although it can sometimes be preferable to dissolve or disperse one or more components (for example, the phosphate anion source and the organic base) separately in solvent prior to combination with the other components.

[0071] Depending upon the specific chemical natures of the selected components and the amount of water present, certain orders and manners of combination can assist in minimizing agglomeration and enabling the formation of nanoparticles. For example, it can be preferable (for example, when using relatively more reactive phosphate anion sources such as phosphoric acid) to separately form a mixture of the phosphate anion source and the organic base and a mixture of the metal cation source and the organosilane. These two mixtures can then be combined.

[0072] The metal cation source and the phosphate anion source can be combined in generally stoichiometric amounts, based upon the moles of metal cation and the moles of phosphate anion. For example, these components can be combined in amounts such that the metal to phosphorus molar ratio ranges from about $0.8/n$ to about $6.0/n$, where n is the valency of the metal. Preferably, the molar ratio ranges from about $1.0/n$ to about $4.0/n$ (more preferably, from about $1.4/n$ to about $3.4/n$).

[0073] The metal cation source (for example, a metal salt comprising a metal cation and counteranion(s)) and the organic base can be combined in generally stoichiometric amounts, based upon the moles of basic groups and the moles of counteranion. For example, these components can be combined in amounts such that the organic base to metal molar ratio ranges from about $0.5\ n/b$ to about $3.0\ n/b$, where n is the valency of the metal and b is the number of basic groups per mole of organic base. Preferably, the molar ratio ranges from about $0.6\ n/b$ to about $2.0\ n/b$ (more preferably, from about $0.7\ n/b$ to about $1.5\ n/b$).

[0074] The metal cation source and the organosilane can be combined in amounts such that the molar ratio of metal to silicon ranges from about 0.1 to about 20 (preferably, from about 0.2 to about 15; more preferably, from about 0.3 to about 10). If desired, however, the organosilane can be used in larger amounts, so as to function as a reaction solvent.

[0075] Generally less than 100 percent of the combined organosilane attaches (for example, physically or chemically) to the metal phosphate nanoparticles to provide surface modification.

[0076] Mechanical agitation or stirring can be used, if desired, to facilitate mixing. Optionally, heating can be used to facilitate dissolution, reaction, and/or primary particle size growth. The reaction mixture components can be combined in a pressure vessel, if desired (for example, this can be useful for reactions carried out at temperatures above the boiling point of a selected solvent). An inert atmosphere (for example, nitrogen) can optionally be utilized (for example, to minimize the presence of moisture or air).

[0077] To influence, for example, the morphology, magnetic properties, conductivity, light absorption or emission characteristics, and/or the crystallinity of the resulting nanoparticles, various compounds (foreign ions) can be added before, during, or after nanoparticle precipitation. Preferred

additive compounds include 2nd-5th main group and transition metal compounds (more preferably, magnesium, strontium, barium, aluminum, indium, tin, lead, antimony, bismuth, titanium, vanadium, chromium, manganese, iron, cobalt, nickel, zinc, yttrium, zirconium, niobium, molybdenum, cadmium, hafnium, tantalum, and tungsten compounds, and combinations thereof; most preferably, magnesium, strontium, aluminum, tin, antimony, titanium, manganese, iron, zinc, yttrium, zirconium, niobium, and tantalum compounds, and combinations thereof) including lanthanide compounds (more preferably, europium, terbium, dysprosium, samarium, erbium, praseodymium, and cerium compounds, and combinations thereof; most preferably, cerium, europium, terbium, and dysprosium compounds, and combinations thereof). Such additive compounds preferably can be added to the reaction mixture in dissolved form and/or preferably can be used in an amount from about 0.01 to about 20 mole percent, based on the total number of moles of metal (present, for example, in the form of metal phosphate).

[0078] Other common additives (for example, dyes, pigments, catalysts, and the like) can also be utilized. Monomer(s), oligomer(s), and/or polymer(s) of various types can be present in the reaction mixture (for example, in order to form a polymeric composite comprising the resulting metal phosphate nanoparticles).

[0079] The resulting nanoparticles can be isolated (for example, from a resulting sol) and/or purified by using standard techniques such as decantation (for example, following centrifugation or settling optionally induced by cosolvent addition), filtration, rotary evaporation for solvent removal, dialysis, diafiltration, and the like, and combinations thereof. The characteristics of the resulting product can be evaluated by ultraviolet-visible spectroscopy (absorption characteristics), X-ray diffraction (crystalline particle size, crystalline phase, and particle size distribution), transmission electron microscopy (particle sizes, crystalline phase, and particle size distributions), and dynamic light scattering (degree of agglomeration).

[0080] Upon solvent removal (for example, by rotary evaporation, air or oven drying, centrifugation and decantation, a change in solvent polarity followed by gravitational settling and decantation, or the like), the resulting nanoparticles can be in the form of a powder or gel that can be re-dispersed in solvent (for example, a polar or a non-polar solvent, depending upon the specific chemical nature of the organosilane). The resulting nanoparticles can range in average primary particle diameter from about 1 nm to about 50 nm or more (preferably, from about 1 nm to about 30 nm; more preferably, from about 1 nm to about 20 nm; even more preferably, from about 1 nm to about 15 nm; most preferably, from about 2 nm to about 10 nm), where any lower limit can be paired with any upper limit of the size ranges as explained above.

[0081] The nanoparticles can be used in various different applications (for example, calcium phosphate nanoparticles can be used in various pharmaceutical, medical, and dental applications). Preferred embodiments of the preferred in situ process can provide substantially spherical nanoparticles (for example, substantially spherical calcium phosphate nanoparticles useful in inhalable aerosol drug delivery systems).

Composition and Articles Comprising the Surface-Modified Nanoparticles

[0082] The above-described preparative methods can produce metal phosphate (most preferably, calcium phosphate)

nanoparticles bearing, on at least a portion of their surfaces, a surface modification comprising at least one organosilane surface modifier comprising at least one organic moiety comprising at least about six carbon atoms. Preferably, the organic moiety has from about 6 to about 24 carbon atoms (more preferably, from about 7 to about 18 carbon atoms; even more preferably, from about 8 to about 12 carbon atoms; most preferably, about 8 carbon atoms (and is preferably branched)).

[0083] The organosilane surface modifier can be derived from a precursor organosilane compound and, when so derived, can comprise the precursor organosilane compound or a residue thereof (that is, a portion of the compound that remains after chemical reaction). The surface modifier can be attached or bonded to the surface of the nanoparticle by a relatively strong physical bond or by a chemical bond (for example, a covalent or ionic bond). For example, organosilane surface modifiers can be derived from alkoxysilanes through hydrolysis of the alkoxysilane and formation of a silicon-oxygen-metal or silicon-oxygen-phosphorus covalent attachment to the metal phosphate nanoparticle. Preferably, the organosilane surface modifier is derived from a precursor organosilane compound selected from alkoxysilanes, halosilanes, acyloxysilanes, aminosilanes (including primary, secondary, and tertiary amines), and combinations thereof.

[0084] For use in at least some preferred applications, the surface-modified nanoparticles preferably have average primary particle diameters of 1 nm (more preferably, about 2 nm; most preferably, about 3 nm) to about 20 nanometers (more preferably, about 15 nm; most preferably, about 10 nm) and/or preferably comprise from about 1 weight percent (more preferably, about 2 weight percent; most preferably, about 10 weight percent) to about 90 weight percent surface modifier (more preferably, about 70 weight percent; most preferably, about 50 weight percent), based upon the total weight of the surface-modified nanoparticles (where any lower limit of a range can be paired with any upper limit of the range).

[0085] The composition of the invention can consist or consist essentially of the surface-modified nanoparticles or can further comprise a carrier material or medium (for example, a material or mixture of materials in the form of a gas, a liquid, a bulk solid, a powder, an oil, a gel, a dispersion, and the like). When the composition is in the form of, for example, a dispersion of the surface-modified nanoparticles in a liquid carrier, unreacted and/or polymerized organosilane can also be present (and can be removed, if desired, by various methods such as solvent washing and/or dialysis).

[0086] The nature (and amount) of the carrier material can vary widely, depending upon the particular application, as is known in the art. The surface-modified nanoparticles can be used, for example, in biomedical applications (including as adjuvants or excipients for drugs and vaccines, as carriers for various proteins and other growth factors, as components of dental hygiene agents such as mouthwashes and toothpastes, as artificial prosthetic fillers, as drug delivery and gene therapy vectors, and the like), as adsorption materials for chromatography columns, as catalysts, in fluorescent materials, in flame retardants, and in anti-corrosion coatings. Preferred embodiments can be useful, for example, in making dental hygiene products and cements, as carriers and/or aerosolization aids for drugs, in dietary formulations, and in fluorescent materials.

[0087] Due to the biocompatibility of the surface modifier, however, preferred uses for the surface-modified nanoparticles (particularly, calcium phosphate) include use in dietary, cosmetic, and pharmaceutical formulations. The nanoparticles can be used in oral or dental care compositions and nutritional supplements. In such cases, useful carrier materials can include water, water-based liquids, oils, gels, emulsions, microemulsions, dispersions, and the like, and mixtures thereof. The compositions can further comprise, for example, additives commonly used in cosmetics and/or dietary formulations such as fragrances, emulsifiers, thickeners, flavorings, solubilizers, dyes, antibiotics, moisturizers, and the like, and mixtures thereof. The formulation can be borne on a paper or fabric carrier (for example, a woven or non-woven material) to provide a means of delivery other than by application of a powder or dispersion (for example, in the form of a wipe, an adhesive tape, or a flame-retardant web).

[0088] A particularly preferred use is in pharmaceutical formulations comprising any of a variety of medicaments. For example, the surface-modified nanoparticles can be used to enhance the mixing and/or delivery of medicaments including antiallergics, analgesics, glucocorticoids, bronchodilators, antihistamines, therapeutic proteins and peptides, anti-tussives, anginal preparations, antibiotics, anti-inflammatory preparations, diuretics, hormones, and combinations of any two or more of these. Noted categories include beta-agonists, bronchodilators, anticholinergics, anti-leukotrienes, mediator release inhibitors, 5-lipoxygenase inhibitors, and phosphodiesterase inhibitors.

[0089] The pharmaceutical formulations can further comprise one or more excipients. Suitable excipients include those listed in the Handbook of Pharmaceutical Excipients (Rowe, et al., APhA Publications, 2003), which include microcrystalline cellulose, dicalcium phosphate, lactose monohydrate (a preferred sugar), mannose, sorbitol, calcium carbonate, starches, and magnesium or zinc stearates. The surface-modified nanoparticles can aid in the preparation of excipient/medicament blends (for example, by reducing mixing times, reducing attrition during processing, and improving the homogeneity of the blends).

[0090] The surface-modified nanoparticles can be particularly useful in pharmaceutical inhalation powder formulations (for example, comprising a medicament and optional excipient(s) such as sugar(s) for use in nasal or oral inhalation drug delivery) to enhance the flow characteristics of the powder. The nanoparticles can be present in the formulations in an amount that is at least sufficient to improve the flowability or floodability of the powder relative to corresponding powder that is substantially free of the nanoparticles (for example, the nanoparticles can be used in an amount less than or equal to about 10 weight percent, less than or equal to about 5 weight percent, less than or equal to about 1 weight percent, less than or equal to about 0.1 weight percent, or even less than or equal to about 0.01 weight percent (such as 0.001 weight percent), based upon the total weight of the formulation). Such formulations can generally be prepared by mixing one or more powders (for example, having an average particle size, generally measured as an effective diameter, of less than or equal to about 1,000 microns, more typically less than or equal to about 100 microns) with the surface-modified nanoparticles using any suitable, conventional mixing or blending process.

[0091] For example, the surface-modified nanoparticles can be added to an organic solvent so as to form a dispersion,

and the powder(s) can be added to the dispersion and the resulting combination stirred or agitated for a period of time to facilitate mixing. The solvent can then be removed by evaporation, with or without the aid of vacuum. Useful solvents include toluene, isopropanol, heptane, hexane, octane, and the like, and mixtures thereof. Preferably, the nanoparticles are calcium phosphate nanoparticles, and the solvent is heptane. In an alternative method, the surface-modified nanoparticles and the powder(s) can be dry blended, if desired.

[0092] The surface-modified nanoparticles can be selected to provide the pharmaceutical inhalation powder formulations with a degree of flowability. The hydrophobic or hydrophilic character of the organosilane surface modifier can be varied (for example, by varying the length of the carbon chain of the organic moiety and/or by varying the chemical nature of other moieties present). If desired, the organosilane surface modifiers can also be used in combination with other hydrophobic or hydrophilic surface modifiers, so that, depending upon the character of the processing solvent or the powder(s), the resulting formulation can exhibit substantially free-flowing properties.

[0093] The surface modifiers can be described as comprising a headgroup (a part that interacts primarily with the nanoparticle surface) and a tailgroup (a part that interacts with the solvent). Useful headgroups include those that comprise alkoxy, hydroxyl, halo, thiol, silanol, amino, ammonium, phosphate, phosphonate, phosphonic acid, phosphinate, phosphinic acid, phosphine oxide, sulfate, sulfonate, sulfonic acid, sulfinate, carboxylate, carboxylic acid, carbonate, boronate, stannate, hydroxamic acid, and/or like moieties. Multiple headgroups can extend from the same tailgroup, as in the case of 2-dodecylsuccinic acid and (1-aminooctyl)phosphonic acid. Useful hydrophobic and/or hydrophilic tailgroups include those that comprise single or multiple alkyl, aryl, cycloalkyl, cycloalkenyl, haloalkyl, oligo-ethylene glycol, oligo-ethyleneimine, dialkyl ether, dialkyl thioether, aminoalkyl, and/or like moieties. Multiple tailgroups can extend from the same headgroup, as in the case of trioctylphosphine oxide.

[0094] Suitable surface modifiers can thus be selected based upon the nature of the processing solvents and powder(s) used and the properties desired in the resulting formulation. When a processing solvent is hydrophobic, for example, one skilled in the art can select from among various hydrophobic surface modifiers to achieve a surface-modified nanoparticle that is compatible with the hydrophobic solvent; when the processing solvent is hydrophilic, one skilled in the art can select from various hydrophilic surface modifiers; and, when the solvent is a hydrofluorocarbon, one skilled in the art can select from among various compatible surface modifiers; and so forth. The nature of the powder(s) and the desired final properties can also affect the selection of the surface modifiers. The nanoparticle can have a plurality of different surface modifiers (for example, a combination of hydrophilic and hydrophobic modifiers) that combine to provide nanoparticles having a desired set of characteristics. The surface modifiers can generally be selected to provide a statistically averaged, randomly surface-modified nanoparticle.

[0095] The surface modifiers can be present on the surface of the nanoparticles in an amount sufficient to provide surface-modified nanoparticles with the properties necessary for compatibility with the powder(s). For example, the surface modifiers can be present in an amount sufficient to form a

discontinuous or continuous monolayer on the surface of at least a portion (preferably, a substantial portion) of the nanoparticle.

[0096] The resulting pharmaceutical inhalation powder formulations can be stored in a storage article or device (preferably, a dry powder inhaler comprising a mouthpiece and a powder containment system) prior to dosing. This storage article or device can comprise, for example, a reservoir, capsule, blister, or dimpled tape and can be a multi-dose or single-dose device.

EXAMPLES

[0097] Objects and advantages of this invention are further illustrated by the following examples, but the particular materials and amounts thereof recited in these examples, as well as other conditions and details, should not be construed to unduly limit this invention.

[0098] These examples are merely for illustrative purposes only and are not meant to be limiting on the scope of the appended claims.

[0099] All parts, percentages, ratios, etc. in the examples and the rest of the specification are by weight, unless noted otherwise. Solvents and other reagents used were obtained from Sigma-Aldrich Chemical Company, St. Louis, Mo., unless otherwise noted. All chemicals and reagents were used without further purification unless noted otherwise.

Materials

[0100] Calcium chloride hexahydrate (98 percent (%) purity), manganese (II) chloride tetrahydrate (99.99% purity), crystalline phosphoric acid (99% purity; Fluka), and methyltrimethoxysilane (98% purity) were obtained from Sigma-Aldrich Chemical Company, St. Louis, Mo.

[0101] Zinc chloride (anhydrous; 99.99% purity), europium (III) chloride hexahydrate (99.9% purity), terbium (III) chloride hexahydrate (99.9% purity), isobutyltrimethoxysilane (97% purity), n-octyltrimethoxysilane (97% purity), and tri-n-octylamine (98% purity) were purchased from Alfa Aesar, Ward Hill, Mass.

[0102] Isooctyltrimethoxysilane (greater than 95% purity) was purchased from Gelest Inc., Morrisville, Pa.

[0103] n-Octadecyltrimethoxysilane (95% purity) was purchased from TCI America, Portland, Oreg.

[0104] Magnesium chloride hexahydrate (99% purity) was purchased from EM Science, Gibbstown, N.J.

[0105] Cobalt chloride hexahydrate (99.9% purity) was purchased from Fisher Scientific, Fairlawn, N.J.

[0106] Methanol (ACS grade; BDH) and ethanol (200 proof; absolute) were obtained from VWR, West Chester, Pa. and AAPER, Shelbyville, Kent., respectively.

[0107] Heptane, xylenes, hexanes, and toluene were purchased from EMD Chemicals, Gibbstown, N.J.

[0108] α -Lactose monohydrate (100% total lactose, 4% present as β -lactose) was purchased from Sigma-Aldrich, St. Louis, Mo., and was then micronized to a final particle size (d50) of approximately 1.5-2.0 micrometers at Micron Technologies in Exton, Pa.

[0109] Budesonide was purchased from OnBio, Richmond Hill, Ontario, Canada.

TEST METHODS

X-ray Diffraction (XRD)

[0110] Reflection geometry X-ray diffraction data were collected using a Bruker™ D8 Advance diffractometer

(Bruker-AXS, Madison, Wisc., USA), copper K_{α} radiation, and Vantec™ detector registry of the scattered radiation. The diffractometer was fitted with variable incident beam slits and fixed diffracted beam slits. The survey scan was conducted in coupled continuous mode from 5 to 80 degrees (2 θ) using a 0.015 degree step size and 2 second dwell time. X-ray generator settings of 40 kV and 40 mA were employed. Tested samples were first milled to produce a fine powder and applied as dry powders to specimen holders containing glass inserts.

Particle Size Determination in Dispersion

[0111] Particle size distribution was measured by Dynamic Light Scattering (DLS) using a Malvern Instruments Zetasizer-NanoZS™, Model No. ZEN3600 particle size analyzer (available from Malvern Instruments, Malvern, U.K.). 10 weight percent (% w/w) dispersions of sample compositions were prepared in hexane for DLS measurements. A small (50 mg) aliquot was taken from the dispersion and diluted with 2.5 g of hexane.

[0112] The resulting diluted sample was mixed well and then transferred to a glass cuvette. Light scattering data was recorded with the sample temperature set at 25° C. For all measurements, the solvent (hexane) and the dispersions were filtered using 0.2 micrometer (p) polytetrafluoroethylene (PTFE) filter. For transforming autocorrelation function into particle size, standard values for the viscosity (0.294×10^{-3} Pa.s; 0.294 cp) and refractive index (1.375) of hexane and the viscosity (0.39×10^{-3} Pa.s; 0.39 cp) and refractive index (1.39) of heptane at 25° C. were used. Refractive index values of 1.63 for calcium phosphate, 1.51 for magnesium phosphate, 1.59 for zinc phosphate, and 1.61 for cobalt phosphate were used. The reported Z-average diameter (average agglomerated particle diameter, d , in nm) was based upon an intensity weighted distribution. Particle size distribution was also measured as a function of time in order to study the stability of the dispersion and the agglomeration of the particles by collecting the DLS data over a period of 18 hours with a time delay of 2 hours between measurements. All results are reported in terms of particle size, d (nm), and polydispersity index (Pdl).

Transmission Electron Microscopy (TEM)

[0113] Samples were prepared by placing a drop of a 2 weight percent heptane or hexane colloidal suspension onto the carbon side of a carbon grid sample holder (type 01801, from Ted Pella Inc., Redding Calif., USA). Excess solvent was wicked from the sample holder, and the remaining slurry was air dried for 5 minutes before use. The samples were examined in a JEOL™ JSM 200CX transmission electron microscope (TEM) (JEOL, Tokyo, Japan) at 200 KV. Pictures of the particulate material were imaged at 50 and 100 Kx and Selected Area Diffraction (SAD) was used to determine crystal type and size. Some dark field imaging was conducted to illuminate the crystal phases and again determine crystal size. The images and SAD patterns were captured and digitized for image analysis.

Pharmaceutical Performance

[0114] A small amount (nominally 2 mg) of powder was weighed into a size three Shionogi Quali-V™ hydroxypropyl methylcellulose capsule (Shionogi Qualicaps, Madrid, Spain) and loaded into an Aerolizer™ device ("DPI" device, commercially available as a Foradil™ Aerolizer™ product,

available from Schering Plough Co., Kenilworth, N.J.), which was tested for pharmaceutical performance using a Next Generation Pharmaceutical Impactor ("NGI") (MSP Corporation, Shoreview, Minn.). Samples of micronized lactose and micronized budesonide powder were tested in addition to testing samples of nanoparticle-modified lactose and nanoparticle-modified budesonide powders. The NGI was coupled with a USP throat (United States Pharmacopeia, USP 24 <601>Aerosols, Metered Dose Inhalers, and Dry Powder Inhalers) and operated at a volumetric flow rate of 60 liters per minute (lpm) for a collection time of four seconds. A suitable coupler was affixed to the USP throat to provide an air-tight seal between the DPI device and the throat. For all testing, the stage cups of the NGI were coated with a surfactant to prevent particle bounce and re-entrainment.

[0115] The amount of lactose or budesonide collected on each component of the NGI testing apparatus was determined by rinsing the component with a measured volume of an appropriate solvent and subjecting the rinsed material to high pressure liquid chromatography (HPLC) analysis with charged aerosol detection to determine lactose or budesonide concentration. Data that was returned from HPLC analysis was analyzed to determine the average amount of drug collected on the DPI and capsule, the USP throat, and on each component of the NGI per delivered dose.

[0116] Using the individual component values, the respirable fraction and delivery efficiency were calculated for each powder sample. Respirable mass is defined as the percentage of the total delivered dose that is measured to be smaller than the respirable limit of 4.5 micrometers in aerodynamic diameter. Respirable fraction is defined as the percentage of a delivered dose that reaches the entry of the throat and is smaller than the respirable limit. Delivery efficiency is defined as the respirable mass divided by the total delivered dose. When using the NGI, respirable mass is collected in cups 3, 4, 5, 6, and 7, and on the filter. Mass collected in the throat and cups 1 and 2 are considered non-respirable.

Examples 1-16 and Comparative Examples C1-C3

Surface-Modified Nanoparticles

[0117] In a 3-neck round bottom reaction flask connected to a condenser via a Dean-Stark receiver, Component Mixture 1 was mixed with Component Mixture 2 as specified in Table 1 below, and the resulting reaction mixture was stirred at Reaction Condition A of Table 1 in a stream of nitrogen until one cloudy and one clear layer were observed in the reaction flask. At this temperature, Component Mixture 3 was added as specified in Table 1. The reaction mixture was then maintained under Reaction Condition 2 as indicated in Table 1. To the warm reaction mixture was added a four-fold excess of methanol (by volume) leading to the precipitation of white solid. Centrifugation of the mixture, followed by subsequent washes of the solid with ethanol, provided clean powder of metal phosphate. The powder was dried in an oven (200° C.) for 15 minutes to give dried metal phosphate powder. The redispersibility characteristics of the dried powder were determined, as shown in Table 1. The dried powder was further characterized by XRD, DLS, and TEM as appropriate, and the results are reported in Table 1.

[0118] Generally, the dried powder was easily redispersed in solvents such as toluene, xylene, hexane, and heptane at ambient temperature to yield optically clear and stable dispersions. In many cases, the dried powder was stored in a vial

for several months and then redispersed in the above solvents to yield optically clear and stable dispersions.

[0119] In Example 1, the redispersibility characteristics were somewhat different. To the warm reaction mixture of Example 1 was added 160 g of methanol, and the mixture was centrifuged at 3500 rpm (revolutions per minute) for 10 minutes. The resulting supernatant was discarded, another 160 g of methanol was added to the resulting gel-like precipitate, and the resulting mixture was centrifuged again. 35 g of hexane was added to precipitate that was isolated by removing the resulting supernatant, and the resulting mixture was centrifuged to remove any residues which settled at the bottom. The resulting supernatant was washed with 320 g methanol and 160 g ethanol. The solvent was removed using a rotary

evaporator to provide a sticky gel, which on drying yielded a glassy solid. This glassy solid could not be redispersed to give a stable dispersion in heptane, hexane, or xylene, but the sticky gel was redispersed in heptane, hexane, and xylene to give optically clear and stable dispersions.

[0120] For Examples 14 and 15, the resulting dried powders were stored for 8 weeks, dispersions of each were prepared, and the particle size distributions of each were then measured by DLS as a function of time. The resulting data (reported in Table 2) showed essentially no change in Z-average particle diameter with progression of time and, when averaged, showed the mean average particle sizes reported in Table 3. This data indicated that there had been essentially no loss of redispersibility upon storage.

TABLE 1

Example No.	Component Mixture 1	Component Mixture 2	Reaction Condition A	Component Mixture 3
C1	Calcium Chloride Hexahydrate (4.4 g)	Tri-n-octylamine (7.6 g)	130° C. for 20 minutes	Phosphoric acid (2 g) & Tri-n-octylamine (7 g) in methyl alcohol (2 g)
C2	Calcium Chloride Hexahydrate (4 g)	Methyltrimethoxysilane (7.45 g)	130° C. until one cloudy and one clear layer observed	Phosphoric acid (1.8 g) & Tri-n-octylamine (12.9 g) in methyl alcohol (6 g)
C3	Calcium Chloride Hexahydrate (4.4 g)	Isobutyltrimethoxysilane (12.5 g)	130° C. until one cloudy and one clear layer observed	Phosphoric acid (2 g) & Tri-n-octylamine (14.2 g) in methyl alcohol (g)
1	Calcium Chloride Hexahydrate (4 g)	n-Octyltrimethoxysilane (12.8 g)	130° C. until one cloudy and one clear layer observed	Phosphoric acid 1.8 g) & Tri-n-octylamine (12.9 g) in methyl alcohol (6 g)
2	Calcium Chloride Hexahydrate (19.7 g)	Isooctyltrimethoxysilane (50 g)	130° C. until one cloudy and one clear layer observed	Phosphoric acid (8.8 g) & Tri-n-octylamine (63.6 g) in Isooctyltrimethoxysilane (50 g)
3	Calcium Chloride Hexahydrate (13.8 g)	Isooctyltrimethoxysilane (35 g)	130° C. until one cloudy and one clear layer observed	Phosphoric acid (6.2 g) & Tri-n-octylamine (44.6 g) in Isooctyltrimethoxysilane (35 g)
4	Calcium Chloride Hexahydrate (4 g)	Isooctyltrimethoxysilane (10.2 g)	130° C. until one cloudy and one clear layer observed	Phosphoric acid (1.8 g) & Tri-n-octylamine (12.9 g) in Isooctyltrimethoxysilane (10.2 g)
5	Calcium Chloride Hexahydrate (4 g)	Isooctyltrimethoxysilane (10.1 g)	130° C. until one cloudy and one clear layer observed	Phosphoric acid (1.2 g) & Tri-n-octylamine (12.9 g) in Isooctyltrimethoxysilane (10.1 g)
6	Calcium Chloride Hexahydrate (4 g)	Isooctyltrimethoxysilane (10.2 g)	130° C. until one cloudy and one clear layer observed	Phosphoric acid (1.8 g) & Tri-n-octylamine (12.9 g) in methyl alcohol (2 g)
7	Calcium Chloride Hexahydrate (4.4 g)	Isooctyltrimethoxysilane (14 g)	130° C. until one cloudy	Phosphoric acid (2 g), Tri-n-butyl amine (2 g) & Tri-n-octylamine (10.4 g) in

TABLE 1-continued

						and one clear layer observed	methyl alcohol (5 g)
8	Isooctyltrimethoxysilane (12.8 g)	Phosphoric acid (1.8 g) & Tri-n-octylamine (12.9 g)	110° C. for 10 minutes			Calcium Chloride Hexahydrate (4 g)	
9	Calcium Chloride Hexahydrate (2.5 g)	Octadecyltrimethoxysilane (8.2 g)	130° C. until one cloudy and one clear layer observed			Phosphoric acid (0.9 g), Tri-n-octylamine (6.5 g) & n-Octadecyltrimethoxysilane (8.2 g)	
10	Magnesium Chloride Hexahydrate (3.7 g)	Isooctyltrimethoxysilane (10.1 g)	130° C. until one cloudy and one clear layer observed			Phosphoric acid (1.8 g) & Tri-n-octylamine (12.9 g) in Isooctyltrimethoxysilane (10.1 g).	
11	Calcium Chloride Hexahydrate (3.8 g) and EuCl ₃ •6H ₂ O (0.33 g)	Isooctyltrimethoxysilane (10.8 g)	130° C. until one cloudy and one clear layer observed			Phosphoric acid (1.8 g) & Tri-n-octylamine (12.9 g) in Isooctyltrimethoxysilane (10.8 g)	
12	Calcium Chloride Hexahydrate (3.8 g) and TbCl ₃ •6H ₂ O (0.34 g)	Isooctyltrimethoxysilane (10.2 g)	130° C. until one cloudy and one clear layer observed			Phosphoric acid (1.8 g) & Tri-n-octylamine (12.9 g) in Isooctyltrimethoxysilane (10.2 g).	
13	Zinc Chloride (2.7 g) in water (2.2 g)	Isooctyltrimethoxysilane (14 g)	130° C. until one cloudy and one clear layer observed			Phosphoric acid (1.9 g) & Tri-n-octylamine (14.1 g) in methyl alcohol (2 g)	
14	Cobalt (II) Chloride (4.7 g)	Isooctyltrimethoxysilane (14 g)	130° C. until one cloudy and one clear layer observed			Phosphoric acid (1.9 g) & Tri-n-octylamine (14.1 g) in methyl alcohol (2 g)	
15	Zinc Chloride (4.9 g) and Manganese (II) Chloride (0.79 g) in water (4 g)	Isooctyltrimethoxysilane (28.1 g)	130° C. until one cloudy and one clear layer observed			Phosphoric acid (3.9 g) & Tri-n-octylamine (28.2 g) in methyl alcohol (5 g)	
16	Calcium Chloride Hexahydrate (20 g)	Isooctyltrimethoxysilane (64.2 g)	120° C. until one cloudy and one clear layer observed			Phosphoric acid (9.0 g) & Tri-n-octylamine (64.6 g) in methyl alcohol (16 g)	
Example No.	Reaction Condition B	d (nm)	PdI	XRD	TEM	Redispersibility	
C1	Added heptane (35 g); 110° C. for 2 hours					No redispersion	
C2	Added heptane (35 g); 100° C. for 0.5 hour					No redispersion	
C3	Added heptane (30 g); 110° C. for 15 minutes			Broad peaks; nanosized material		Redispersible but unstable	
1	Added heptane	40.84	0.259			Redisperible from gel only (2	

TABLE 1-continued

	(35 g); 110° C. for 2.5 hours					months) prior to complete drying
2	110° C. for 3 hours	21.93	0.218	Broad peaks; nanosized material		Redispersible even after storage as powder for 5 months
3	110° C. for 3 hours	27.43	0.25	Broad peaks; nanosized material	Unagglomerated; primary particle size 2-10 nm	Redispersible even after storage as powder for 5 months
4	110° C. for 3 hours	38.69	0.085	Broad peaks; nanosized material	Unagglomerated; primary particle size 2-8 nm (average = 4.7 nm based on 89 particles)	Redispersible even after storage as powder for 3 months
5	110° C. for 2 hours	61.31	0.104			Redispersible even after storage as powder for 3 months
6	Added heptane (33 g); 110° C. for 15 hours	47.66	0.453		—	Redispersible even after storage as powder for 3 months
7	Added heptane (20 g); 110° C. for 2 hours	23.79	0.448	Broad peaks; nanosized material		Redispersible even after storage as powder for 2 weeks
8	Added n- octane (50 g); 110° C. for 15 hours	—	—	Broad peaks; nanosized material		Redispersible even after storage as powder for 3 weeks
9	Added heptane (26.6 g); 110° C. for 2 hours	—	—			Redispersible even after storage as powder for 3 months
10	110° C. for 2 hours	92.59	0.15	Broad peaks; nanosized material	Unagglomerated; primary particle size 2-15 nm	Redispersible even after storage as powder for 3 months
11	110° C. for 2 hours	31.9	0.328	Broad peaks; nanosized material		Redispersible even after storage as powder for 3 months
12	110° C. for 2 hours	69.29	0.176	Broad peaks; nanosized material	—	Redispersible even after storage as powder for 3 months
13	Added heptane (75 g); 110° C. for 2 hours	57.82	0.403	Broad peaks; nanosized material	Unagglomerated; primary particle size 2-10 nm	Redispersible even after storage as powder for 2 months
14	Added heptane (75 g); 110° C. for 2 hours	36.55	0.398	Broad peaks; nanosized material	Unagglomerated; primary particle size 2-10 nm	Redispersible even after storage for 2 months as powder
15	Added heptane (75 g); 110° C. for 2 hours	75.87	0.186	Broad peaks; nanosized material		Redispersible even after storage for 2 months as powder
16	Added heptane	—	—	Broad peaks;		Redispersible even after

TABLE 1-continued

(140 g); 110° C. for 1.5 hours	nanosized material	storage for 2 months as powder
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TABLE 2

Time (hours)	Example 14 d (nm)	Example 14 PdI	Example 15 d (nm)	Example 15 PdI
0	34.45	0.309	62.62	0.214
2	34.35	0.297	58.51	0.175
4	33.96	0.297	59.23	0.171
6	34.31	0.304	59.08	0.199
8	34.49	0.303	59.85	0.213
10	34.35	0.302	59.56	0.207
12	34.53	0.290	60.62	0.211
14	34.42	0.299	59.37	0.198
16	34.31	0.300	58.66	0.187
18	34.64	0.303	59.85	0.199

TABLE 3

Example No.	Mean d (nm)	Standard Deviation	Mean PdI	Standard Deviation
14	34.38	0.1817	0.301	0.005
15	59.74	1.187	0.197	0.015

Examples 17-19 and Comparative Examples C4 and C5

Pharmaceutical Compositions Comprising Surface-Modified Nanoparticles

Example 17 and Comparative Example C4

[0121] A stock dispersion of the surface-modified calcium phosphate nanoparticles of Example 2 above (5 nm nominal size, isooctyltrimethoxysilane surface-modified) with a concentration of 0.002 g/mL was prepared by adding the surface-modified nanoparticles (1.0 g) to a 500 mL volumetric flask and filling the remainder of the volume with heptane. A stir bar was placed in the flask, and the mixture was stirred on a stir plate until the nanoparticles became fully dispersed based on visual appearance.

[0122] Micronized lactose powder (10.0 g) and the stock nanoparticle dispersion (approximately 220 mL) were added to a round bottom flask (1.0 L). The flask was sealed with a rubber stopper, and the mixture was deagglomerated by sonication and hand swirling for approximately 3 to 5 minutes and until no agglomerated material could be seen sticking on the sides of the flask. The flask was then placed on a rotary evaporator to remove the solvent. The rotary evaporator was set to a nominal temperature of 50° C. and operated under vacuum. After removal of essentially all of the solvent, the remaining powder was caked on the flask sides. The flask was then placed in a vacuum oven (508-635 torr) at 45° C. for approximately 1 hour to further remove any residual solvent. A stiff bristle brush was used to remove the caked powder from the walls of the flask, and the powder was subsequently forced through a 400 mesh sieve to break up the caked material. The sieved material was then collected and placed in a

container for later use. The resulting nanoparticle-modified lactose powder composition had a nominal concentration of surface-modified nanoparticles of 4 weight percent. The respirable fractions and delivery efficiencies of the lactose powder (Comparative Example C4) and the nanoparticle-modified lactose powder (Example 17) were measured by the above procedure, and the results are set forth in Table 5 below.

Example 18 and Comparative Example C4

[0123] Another blend of lactose with 4 weight percent isooctyltrimethoxysilane surface-modified calcium phosphate nanoparticles was prepared essentially as described above, except that the surface-modified nanoparticles of Example 3 above were utilized. The respirable fractions and delivery efficiencies of the lactose powder (Comparative Example C4) and the nanoparticle-modified lactose powder (Example 18) were measured by the above procedure, and the results are set forth in Table 5 below.

Example 19 and Comparative Example C5

[0124] A series of budesonide powders with varying surface-modified nanoparticle content, ranging from nominal concentrations of 0.5 to 2.0 weight percent, were prepared. A stock dispersion of surface-modified nanoparticles (5 nm nominal size, isooctyltrimethoxysilane surface-modified) was prepared by adding the surface-modified calcium phosphate nanoparticles of Example 16 above to a volumetric flask and filling the remainder of the volume with heptane. The powder blending parameters are summarized in Table 4 below.

[0125] Micronized budesonide powder, heptane, and the stock nanoparticle dispersion were added to a round bottom flask (0.25 L). A small amount of heptane was used to rinse the graduated cylinder used to measure the stock nanoparticle dispersion and to provide a quantitative transfer of nanoparticles to the round bottom flask. The flask was sealed with a glass stopper, and the mixture was deagglomerated by sonication and hand swirling for approximately 3 to 5 minutes and until no agglomerated material could be seen sticking on the sides of the flask. The flask was then placed on a rotary evaporator to remove the solvent. The rotary evaporator was set to a nominal temperature of 60° C. and operated under vacuum. After removal of essentially all of the solvent, the remaining powder was caked on the flask sides. The flask was then placed in a drying oven for approximately one hour to further remove any residual solvent. After cooling to room temperature, the flask containing the dry powder was sonicated to break up the caked material. The powder was subsequently forced through a 60 mesh sieve to further break up the caked material. The sieved material was then collected and placed in a container for later use. The respirable fractions and delivery efficiencies of the budesonide powder (Comparative Example C5) and the nanoparticle-modified budesonide powder (Example 19) were measured by the above procedure, and the results are set forth in Table 5 below.

TABLE 4

Blending Parameter	Example 19A: Budesonide/0.5% Calcium Phosphate Blend	Example 19B: Budesonide/1.0% Calcium Phosphate Blend	Example 19C: Budesonide/2.0% Calcium Phosphate Blend
Mass of budesonide powder (g)	3.98	3.96	2.94
Volume of heptane (mL)	120	120	50
Concentration of stock nanoparticle dispersion (g/mL)	0.005 (1 gram powder in 200 mL heptane)	0.005 (1 gram powder in 200 mL heptane)	0.001 (0.10 gram in 100 mL heptane)
Volume of stock nanoparticle dispersion added to budesonide powder (mL)	4	8	60
Total volume of heptane [from stock nanoparticle dispersion + additional heptane] (mL)	124	128	110
Oven temperature (° F.)	120	120	85

TABLE 5

Example No.	% Respirable Fraction	% Delivery Efficiency
C4	63	34
17	71	62
18	78	70
C5	55	34
19A	84	68
19B	86	68
19C	82	70

[0126] The referenced descriptions contained in the patents, patent documents, and publications cited herein are incorporated by reference in their entirety as if each were individually incorporated. Various unforeseeable modifications and alterations to this invention will become apparent to those skilled in the art without departing from the scope and spirit of this invention. It should be understood that this invention is not intended to be unduly limited by the illustrative embodiments and examples set forth herein and that such examples and embodiments are presented by way of example only, with the scope of the invention intended to be limited only by the claims set forth herein as follows:

1. A composition comprising surface-modified nanoparticles of at least one metal phosphate, said nanoparticles bearing, on at least a portion of their surfaces, a surface modification comprising at least one organosilane surface modifier comprising at least one organic moiety comprising at least six carbon atoms.

2. The composition of claim 1, wherein the metal of said metal phosphate is selected from transition metals, alkaline earth metals, alkali metals, post-transition metals, and combinations thereof

3. The composition of claim 1, wherein the metal of said metal phosphate is divalent.

4. The composition of claim 1, wherein the metal of said metal phosphate is selected from alkaline earth metals and combinations thereof

5. The composition of claim 1, wherein the metal of said metal phosphate is calcium.

6. The composition of claim 1, wherein said organosilane surface modifier is derived from a precursor organosilane compound selected from alkoxysilanes, halosilanes, acyloxysilanes, aminosilanes, and combinations thereof

7. The composition of claim 1, wherein said organosilane surface modifier comprises at least one organic moiety having from 6 to 24 carbon atoms.

8. The composition of claim 1, wherein said organosilane surface modifier is derived from a precursor organosilane compound selected from those represented by the following general Formula I:



wherein y is an integer of 1 to 3; each R is independently selected from hydrogen and organic moieties that are linear, branched, alicyclic, aromatic, or a combination thereof and that have from 6 to 24 carbon atoms, with the proviso that carbon atoms in a cyclic moiety count only as half their number toward the requisite minimum of 6 carbon atoms, and that optionally further comprise at least one functional group selected from heterocyclic, acryloxy, methacryloxy, cyano, isocyanato, cyanato, isocyanato, phosphino, amino, amido, vinyl, epoxy, glycidoxo, alkyl, carbon-carbon triple bond-containing, mercapto, siloxy, halocarbon, carbon-nitrogen double bond-containing, and carbon-carbon double bond-containing groups, and combinations thereof; with the proviso that at least one said R group is a said organic moiety; and each X is independently selected from hydrocarbyloxy, fluoroalkanesulfonate, and alkoxy groups having from 1 to 8 carbon atoms, chlorine, bromine, iodine, acyloxy, amino moieties —NR'R', wherein each R' is independently selected from hydrogen and organic moieties having from 1 to 10 carbon atoms, and combinations thereof.

9. The composition of claim 8, wherein said y is 2 or 3; wherein said organic moiety of said R is linear, branched, or a combination thereof wherein said organic moiety of said R has from 7 to 18 carbon atoms; and/or wherein at least one

said X is independently selected from alkoxy, acyloxy, chlorine, bromine, amino, and combinations thereof

10. (canceled)

11. (canceled)

12. (canceled)

13. The composition of claim 1, wherein said organosilane surface modifier is derived from a trialkoxysilane.

14. The composition of claim 1, wherein said surface-modified nanoparticles have average primary particle diameters of 1 nm to 50 nm.

15. The composition of claim 1, wherein said surface-modified nanoparticles comprise from 1 weight percent to 90 weight percent of said surface modifier, based upon the total weight of said surface-modified nanoparticles.

16. The composition of claim 1, wherein said surface-modified nanoparticles are redispersible; and/or wherein said surface-modified nanoparticles are substantially spherical.

17. (canceled)

18. A composition comprising surface-modified nanoparticles of calcium phosphate, said nanoparticles bearing, on at least a portion of their surfaces, a surface modification com-

prising at least one alkoxy silane surface modifier comprising at least one linear or branched organic moiety comprising at least seven carbon atoms.

19. The composition of claim 18, wherein said surface-modified nanoparticles are redispersible, substantially spherical, have average primary particle diameters of 1 nm to 20 nm, and comprise from 1 weight percent to 90 weight percent of said surface modification, based upon the total weight of said surface-modified nanoparticles.

20. The composition of claim 1, wherein said composition further comprises at least one carrier material.

21. (canceled)

22. (canceled)

23. The composition of claim 20, wherein said composition is a pharmaceutical formulation comprising a medicament.

24. The composition of claim 23, wherein said medicament is a powder.

25. An article comprising the composition of claim 23.

26. An article comprising the composition of claim 24, wherein said article is a dry powder inhaler.

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