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EP 0540819 A
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(54) Silicon-substituted hydroxyapatite

(57) A synthetic silicon-substituted hydroxyapatite comprising from 0.1% to 1.6% by weight of silicon may be used as a synthetic bone material for use in bone substitution, coatings for metallic implants, and for making hydroxyapatite-polymer composites. The silicon-substituted hydroxyapatite is prepared by reacting a calcium salt or calcium hydroxide with orthophosphoric acid or a salt of orthophosphoric acid in the presence of a silicon-containing compound, under conditions such the silicon-containing compound yields Si ions and a precipitate of a silicon-substituted hydroxyapatite is formed which may be dried and sintered.

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SILICON-SUBSTITUTED HYDROXYAPATITE AND PROCESS FOR THE PREPARATION THEREOF

The present invention relates to a silicon-substituted hydroxyapatite and to a process for the preparation thereof.

The apatite group of minerals are based on calcium phosphate, with naturally occurring apatite having a molar ratio of Ca/P of 0.7. Hydroxyapatite, which has the chemical formula $Ca_{10}(PO_4)_6(OH)_2$, and hydroxyapatite - glass composites have been used in the recent past as skeletal reconstitution materials and it has been observed that bonding of these bioactive materials to living tissues is achieved through a bone-like apatite layer formed on their surfaces in a body environment. Formation of a bone-like apatite layer on implant material thus plays a vital role in osseointegration of the implant.

K. Hata et al., J. Am. Ceram. Soc., 78, 1049-1053 (1995) have shown that a bone-like apatite layer is formed on the surfaces of CaO and SiO_2 glass-ceramics in simulated body fluid. It is suggested by the authors that the mechanism of formation of the apatite layer comprises the dissolution of calcium and silicate ions from the glass surface which helps the formation of an apatite layer with silicate ions providing nucleation sites. Another mechanism proposed by Hench et al., J. Biomed. Mater. Res., 2, 117, 1971 is that the pH of the surface of the implant becomes alkaline due to dissolution of ions which in turn causes supersaturation resulting in the precipitation of a bone-like apatite layer. Other mechanisms have also been suggested, including the proposal by Li et al., J. Mater. Sci. Mater. Med., 3, 452, 1992, that dissolution of amorphous calcium phosphate from the glass creates a negatively charged surface which attracts calcium ions to the implant surface and finally forms an apatite layer.

Silicate sulphate apatite has been synthesised by a solid state method, K.S. Leshkivich et al., J.Mater. Sci. Mater. Med., 4, 86-94, 1993, and found excellent biocompatability in *in vivo* tests and this material has been suggested for use as a low-load bearing bone graft material.

Silicon has been shown, in small quantities, to have a significant effect on the development and growth of the hard tissue of living bodies.

We have now developed a silicon-substituted hydroxyapatite material which has a much higher bioactivity than that of pure hydroxyapatite and this can be used as a synthetic bone material.

Accordingly, the present invention provides a synthetic silicon-substituted hydroxyapatite which comprises from 0.1% to 1.6% by weight of silicon.

Preferably, the synthetic silicon-substituted hydroxyapatite comprises from 0.5 to 1.0% by weight of silicon.

The silicon-substituted hydroxyapatite material can be used as a synthetic bone material, for example for use in bone substitution, coatings for metallic implants and for making hydroxyapatite-polymer composites.

In another aspect the present invention provides a process for the preparation of a silicon-substituted hydroxyapatite, which process comprises reacting a calcium salt or calcium hydroxide with orthophosphoric acid or a salt of orthophosphoric acid in the presence of a silicon containing compound under conditions such that the silicon containing compound yields Si ions and a precipitate of a silicon-substituted hydroxyapatite is formed.

The process of the present invention may be carried out by reacting an aqueous solution of a calcium salt or calcium hydroxide and a silicon compound at a pH in the range of from 9 to 13 with an aqueous solution comprising a salt of orthophosphic acid at a pH in the range of from 9 to 13. The calcium salt is preferably calcium nitrate and, in particular, calcium nitrate 4-hydrate. The salt of orthophosphoric is preferably diammonium orthophosphate or triammonium orthophosphate. The pH of the aqueous solution of the calcium salt and/or the pH of the aqueous solution of the salt of orthophosphoric acid is preferably adjusted using ammonia, for example concentrated aqueous ammonia. The preferred pH of each solution is about pH 11.

An alternative way of carrying out the process of the present invention comprises reacting an aqueous solution of calcium hydroxide and a silicon compound with an aqueous solution of orthophosphoric acid. The pH of the aqueous solution of calcium hydroxide is preferably in the range of from 10 to 14, more preferably about 12.3. The pH of the aqueous solution of orthophosphoric acid is preferably in the range of from 1 to 3, more preferably from 1 to 1.5.

In each of the embodiments of the process of the invention the silicon compound is preferably silicon acetate and, in particular, silicon acetate 4-hydrate.

The precipitated silicon-substituted hydroxyapatite is separated from the reaction mixture, for example by filtration, washed and dried to preferably result in a phase pure silicon-substituted hydroxyapatite material. The dried filter cake material may then be powdered using conventional techniques.

The dried silicon-substituted hydroxyapatite material may then be sintered using conventional techniques, for example at a temperature of about

1200°C. Upon sintering, some of the silicon-substituted hydroxyapatite material decomposes to tricalcium phosphate (TCP). Preferably, substantially all of the TCP is α TCP.

The present invention will be further described with reference to the following Examples.

EXAMPLE 1

141.69g of calcium nitrate 4-hydrate was dissolved in 600ml of double distilled water. The pH of solution was adjusted to 11.0 using a concentrated ammonia solution. 1200ml of double distilled water was then added to the solution. The solution was filtered. 8.46g of silicon acetate 4-hydrate was added to the constantly stirred calcium nitrate solution. The solution was heated at 65°C for one hour, with stirring. Most of the silicon acetate 4-hydrate dissolved in the solution and only a very little remained suspended in the solution. The solution was constantly stirred and cooled down to the pre-determined temperature of the experiment. The solution was named as **Solution A**.

47.54g of diammonium hydrogen orthophosphate was dissolved in 360ml of double distilled water. The pH of the solution was adjusted to 11 using a concentrated ammonia solution. 480ml of double distilled water was then added to the constantly stirred solution. The solution was filtered. The solution was named as **Solution B**.

Solution B was added dropwise to constantly stirred **Solution A** at the predetermined temperatures of 3°, 25°, 60° and 90°C over a period of 2 hours. The precipitates so formed (A,B,C and D, respectively) were each agitated at room temperature for one hour and left overnight. Each precipitate was filtered using a Buchner funnel and washed several times using double distilled water. The filter cakes were dried for 20 hours in a drier at 85°C in filtered air. The dried materials were powdered using a pestle and mortar.

The microstructures of the precipitates were studied using a JEOL 100 CX transmission electron microscope (TEM). Carbon coated 200 mesh copper grids were dipped in a dilute suspension of the precipitate and examined in the bright field mode at a magnification of 50000x using an accelerating voltage of 100 kV. The TEM micrographs indicated that the precipitate had a spheroidal shape when precipitated at 3°C and an increasingly acicular shape when precipitated at 60° and 90°C.

X-ray diffraction studies of powdered samples were performed using Siemens D5000 diffractometer. Cu $_{K\alpha}$ radiation ($K\alpha$ = 1.5418 Å) was used with a linear position sensitive detector and a nickel diffracted beam monochromator.

Fourier transform infrared Nicolet 800 spectrometer (FTIR) with a Mtech photoacoustic (PAS) cell was used to analyse the powered samples. Spectra were obtained at 4 cm^{-1} resolution averaging 128 scans. The FTIR spectra of the samples precipitated at 3° and 25°C showed phosphate bands at 1085, 1030, 961,600 and 563 cm^{-1}, carbonate bands at 1455, 1418, 1327 and 883 cm^{-1} and a hydroxyl band at 3567 cm^{-1} with a broad peak.

A GBC Integra XM sequential inductively coupled plasma spectrometer (ICPS) was used to analyse for calcium, phosphorous, silicon and other trace elements in the prepared hydroxyapatites. The carbonate content in the dry powder of silicon substituted hydroxyapatite was determined as carbon using a Control Equipment Corporation Model 240 XA CHN element analyser. The results are given in Table 1 below:

TABLE 1

Sample	Ca mg/kg	P mg/kg	Si mg/kg	Mg mg/kg	Na mg/kg	Al mg/kg	Fe mg/kg	Cu mg/kg	Ba mg/kg	Sr mg/kg	Carbonate mg/kg
A	450800	185200	10146	15.4	4.98	27.8	25.8	1.1	<0.2	65.5	12500
B	408800	181300	10748	67.5	24.0	21.3	22.2	<1.0	2.2	61.1	8000
C	417700	176200	8820	4.4	10.6	15.4	23.5	2.6	<0.2	66.3	7000
D	463100	182100	10330	3.4	18.7	22.5	26.7	2.1	<0.2	68.1	9000
HA at 3°C	35400	181000	34.0	18.2	106	13.6	<1.0	3.2	1.6	66.2	10000
HA at 90°C	344000	179000	81.5	17.8	54.9	155.0	<1.0	4.8	1.4	56.0	7000

HA = hydroxyapatite

EXAMPLE 2

The procedure of Example 1 was repeated, using an amount of 4.23g of silicon acetate 4-hydrate. Precipitation was again carried out at temperatures of 30, 25°, 60° and 90°C to form precipitates A, B, C and D.

The precipitates were subjected to ICPS analysis, and the results are given in Table 2 below:

TABLE 2

Sample	Ca mg/kg	P mg/kg	Si mg/kg	Mg mg/kg	Na mg/kg	Al mg/kg	Fe mg/kg	Cu mg/kg	Ba mg/kg	Sr mg/kg	Carbonate mg/kg
A	458200	191400	4526	7.8	191	23.6	20.0	<1.0	0.3	60.8	9000
B	469700	194200	4188	<1.0	30.4	20.2	33.3	1.2	<0.2	64.5	6000
C	433400	186600	4429	3.1	30.3	22.0	44.9	2.0	<0.2	64.6	6000
D	454700	185500	4820	1.8	44.9	28.6	25.9	<1.0	<0.2	65.3	7000

EXAMPLE 3

The procedure of Example 1 was repeated, using amounts of 1.06g and 12.69g of silicon acetate 4-hydrate, respectively. The precipitations were carried out at 3°C to give precipitates A and B, respectively.

The precipitates were subjected to ICPS analysis and the results are given in Table 3 below:

TABLE 3

Sample	Ca mg/kg	P mg/kg	Si mg/kg	Mg mg/kg	Na mg/kg	Al mg/kg	Fe mg/kg	Cu mg/kg	Ba mg/kg	Sr mg/kg	Carbonate mg/kg
A	424000	252000	1883	0.9	55.3	37.6	12.1	1.0	<0.1	63.6	11500
B	393000	268000	16101	10.3	64.9	10.5	24.6	0.8	3.6	67.9	16500

EXAMPLE 4

44.46g of calcium hydroxide was dissolved in 600ml of double distilled water. 0.564g of silicon acetate 4-hydrate was dissolved in the calcium hydroxide solution. The solution was named as **Solution A.**

38.02g of orthophosphoric acid was dissolved in 360ml of double distilled water. The solution was named as **Solution B.**

Solution B was added dropwise to **Solution A** over a period of 2 hours at a temperature of 3°C. The precipitate so formed, designated precipitate A, was stirred for 1 hour and left overnight. Precipitate A was filtered using a Buchner funnel and washed several times using double distilled water. The filtered cake was dried for 20 hours in a drier at 85°C in filtered air. The dried material was powdered using a pestle and mortar.

This procedure was repeated, using amounts of 2.82, 5.64 and 8.46g of silicon acetate 4-hydrate. The precipitations were again carried out at 3°C. to give precipitates B, C and D, respectively.

The precipitates A, B, C and D were subjected to ICPS analysis and the results are given in Table 4 below:

TABLE 4

Sample	Ca mg/kg	P mg/kg	Si mg/kg	Mg mg/kg	Na mg/kg	Al mg/kg	Fe mg/kg	Cu mg/kg	Ba mg/kg	Sr mg/kg	Carbonate mg/kg
A	424000	244000	814	41.0	48.4	17.5	24.6	0.5	2.6	2.9	50000
B	433000	240000	2957	31.4	115.3	18.8	27.1	<0.5	<0.1	2.1	45000
C	395000	250000	5337	27.5	54.7	22.3	28.4	0.8	<0.1	4.5	60000
D	390000	271000	5634	23.7	27.1	10.8	31.6	<0.5	<0.1	2.0	110500

EXAMPLE 5

The silicon substituted hydroxyapatite material of Example 2A was pressed and sintered at 1200°C at a heating rate of 2.5°C/minute and a dwell time of 4 hours at the final temperature. The sintered sample was polished with diamond paper and a mirror-like surface was obtained. Hydroxyapatite was also pressed and sintered under the same conditions.

The samples were soaked in a simulated body fluid. After 1 day, the sintered silicon substituted hydroxyapatite material of Example 2A had formed a bone-like apatite layer, whereas the sintered hydroxyapatite formed a similar layer only after immersion in the fluid for 14 days.

CLAIMS:

1. A synthetic silicon-substituted hydroxyapatite which comprises from 0.1% to 1.6% by weight of silicon.

2. A synthetic silicon-substituted hydroxyapatite as claimed in claim 1 which comprises from 0.5% to 1.0% by weight of silicon.

3. A synthetic bone material which comprises a synthetic silicon-substituted hydroxyapatite as claimed in claim 1 or claim 2.

4. A process for the preparation of a silicon-substituted hydroxyapatite, which process comprises reacting a calcium salt or calcium hydroxide with orthophosphoric acid or a salt of orthophosphoric acid in the presence of a silicon containing compound under conditions such that the silicon containing compound yields Si ions and a precipitate of a silicon-substituted hydroxyapatite is formed.

5. A process as claimed in claim 4 wherein an aqueous solution of a calcium salt and a silicon compound at a pH in the range of from 9 to 13 is reacted with an aqueous solution comprising a salt of orthophosphoric acid at a pH in the range of from 9 to 13.

6. A process as claimed in claim 5 wherein the calcium salt is calcium nitrate.

7. A process as claimed in claim 5 wherein the salt of orthophosphoric acid is diammonium orthophosphate.

8. A process as claimed in any one of claims 5 to 7 wherein the pH of the aqueous solution of the calcium salt and/or the pH of the aqueous solution of the salt of orthophosphoric acid is adjusted using ammonia.

9. A process as claimed in claim 8 wherein the pH of each solution is adjusted to about 11.

10. A process as claimed in claim 4 wherein an aqueous solution of calcium hydroxide and a silicon compound is reacted with an aqueous solution of orthophosphoric acid.

11. A process as claimed in any one of claims 4 to 10 wherein the silicon compound is silicon acetate.

12. A process as claimed in any one of claims 4 to 11 wherein the precipitated silicon-substituted hydroxyapatite is separated from the solution and dried.

13. A process as claimed in claim 12 wherein the dried silicon-substituted hydroxyapatite is sintered.

16

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Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.O): C1A (AVG2)

Int Cl (Ed.6): C01B 25/32

Other: ONLINE: WPI

Documents considered to be relevant:

Category	Identity of document and relevant passage	Relevant to claims
X	EP 0540819 A SANGI see table 1 on p4	1-3
X	Derwent Abstract 95261158/34 & JP070165518A NIPPON CHEM IND	1
X	Derwent Abstract 95-084415/12 & JP070008550A KONDO	1
X	Derwent Abstract 85-071156/12 & JP600024848A MIRAI	1

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
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