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(54) Title: INJECTABLE RESORBABLE CERAMIC COMPOSITIONS

(57) **Abstract:** The present invention relates to a ceramic precursor composition for resorbable or partly resorbable high-strength bioelements, wherein the precursor composition comprises 40-70 wt-% of one or more silicate with Ca as the main cation, 40-20 wt-% of a Ca-sulphate, and greater than 0 wt-% to less than 10 wt-% of an acidic soluble Ca-salt, the remainder, if any, comprises additives. The invention also relates to a slurry, a cured material, a medical implant, and a carrier material for drug delivery made from said precursor composition, as well as a method of manufacturing said a cured chemically bonded ceramic material.



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INJECTABLE RESORBABLE CERAMIC COMPOSITIONS

Field of the invention

The present invention relates to ceramic precursor compositions and chemically bonded ceramic (CBC) materials, especially Ca-based, and a composite biomaterial suitable for orthopaedic applications. The CBC-system includes a binding phase (chemical cement) and additional phases with specified chemistry imparting to the biomaterial the ability of initial strength followed by interaction with the body tissue including body liquid, to form a resorbable or partly resorbable biomaterial. The invention also relates to a slurry and a cured ceramic material, a method of manufacturing said cured material, and medical implants and carrier materials made from said cured or non-cured precursor composition.

Background

For materials to be used as bone void fillers, which have to interact with human tissue it is advantageous to make the biomaterials as biocompatible and bioactive as possible. This can be achieved principally by at least two routes – developing stable biocompatible materials or resorbable materials allowing new bone tissue to substitute the biomaterial. The first route to make more stable materials, e.g. PMMA-based materials or Ca-aluminate-based materials, is especially suitable for osteoporotic clinical situations. For active or young patients a resorbable material, e.g. soluble glasses and phosphate-based materials, may be the most attractive route, where interaction with living tissue is more pronounced. It is well known that the calcium aluminates can have a considerably higher compressive strength than those of the present resorbable materials.

The traditional resorbable phases contain oxides of Ca and P (or S). Ca-phosphates and or Ca-sulphates and glass containing CaO, P₂O₅, SiO₂ and Na₂O are typical representatives for this low-mechanical strength category of bioelements.

In EP 1 123 081 B1 and EP 0 555 807 Ca-silicate is mentioned as an additional phase for drug uses (less than 10%) and for bone substitute products as an additional divalent compound. Regarding biocompatibility of Ca-silicate materials

work have been done on the endodontic treatment material, Proroot or MTA, and on the Wollastonite materials. See J. Saidon, et al, "Cells and tissue reactions to mineral trioxide aggregate and Portland cement", Oral surgery medicine pathology, April (2003) 483-489. Wollastonite is an established biomaterial in the form of sintered ceramic pieces. A survey of bone cements is found in S. M. Kenny and M. Buggy, "Bone cements and fillers: A Review", Journal of Materials Science: Materials in Medicine, 14 (2003) 923-938.

In view of the prior art materials for use, particularly in bone void filling, there is a need for a biocompatible material exhibiting resorption and sufficiently high strength, and thus load-bearing capacity with controlled setting time and pH, shortly after application, as well as later on.

Brief description of the invention

To fulfil said needs, the present invention provides ceramic precursor compositions and cured products exhibiting the above-mentioned features.

The object of the present invention is to provide ceramic precursor compositions based on chemically bonded ceramics as main phases, which when cured, provides a sufficiently high-strength (compressive strength more than 50 MPa) ceramic product. Said strength is achieved shortly after application of a slurry, paste or semi-hardened mixture of the ceramic precursor composition in a defective site. The initial high strength makes load-bearing possible for the defective site during the resorption stage, where new bone tissue takes over the load-bearing capacity.

During curing, the binding phases according to the present invention consumes or takes up a great deal of water, whereby the cured ceramic product exhibits a low residual porosity, which contributes to the high strength.

According to a first aspect, there is provided a ceramic precursor composition comprising one or more particulate Ca-silicate, a Ca-sulphate as essential features, and an acidic soluble Ca-salt. Said compounds will form the main binding phases in the cured material. The remainder, if any, comprises additives.

The ceramic precursor composition is defined in claim 1.

These components are necessary in order to achieve a pH of less than 11, a setting time of less than 20 minutes (according to the Gillmore needle method) and a compressive strength of more than 50 MPa. A high pH lead to a negative cellular response from the surrounding tissue. A pH of higher than 11 (measured in immersion testing in water, without changing the liquid) has been found to result in a negative tissue reaction. A short setting time is preferred since the patient cannot be moved from the operation room before an injectable material has set. In clinical circles, a setting time of less than 20 minutes is considered acceptable. An injectable material needs to form a strong solid body. It has been proven that a strength above 50 MPa is sufficient for orthopaedic use. Up to now, no other available resorbable material has fulfilled all of these criteria.

The constituents of the ceramic precursor composition are particulate matter, unless stated otherwise. The percentages given represent wt-%, unless stated otherwise, based on the total weight of the precursor composition.

According to a second aspect, there is provided an injectable ceramic slurry, which is obtained by mixing the precursor composition and a curing liquid, i.e. water, in a specified water-to-cement-ratio. The injectable ceramic slurry is defined in claim 14.

According to a third aspect, there is provided a cured ceramic material, which is obtained by mixing the precursor composition and a curing liquid, i.e. water, such that a slurry is formed, and allowing said slurry to cure. The cured ceramic material is defined in claim 17.

According to a fourth aspect, there is provided a method of manufacturing the cured ceramic material from the ceramic precursor composition. The method is defined in claim 32.

According to a fifth aspect, there is provided a medical implant which comprises the non-cured precursor composition or cured material. Said medical implant is defined in claim 30.

- 5 According to a sixth aspect, there is provided a carrier material for drug delivery comprising the non-cured precursor composition or cured material. Said carrier material is defined in claim 31.

10 The major advantages of the present invention precursor composition, cured material and product, after having been inserted or injected into a body, is that they have a resorbability, such that a high in-growth rate of a bone is achieved. The resorption rate is less or equal to that of the bone in-growth rate. The material sets within 20 minutes and have a static immersion pH (i.e. a pH in a medium without stirring the material (slurry, paste)) of less than 11.

15 The compressive strength level obtained with the cured material according to the present invention is within the interval more than 50 MPa – to be compared with that of other resorbable biomaterials with a compressive strength in the interval 20-50 MPa.

20 The ceramic materials according to the invention have been especially developed for biomaterials used as bone void filler materials for orthopaedic applications, but can also be used as resorbable filler materials within odontology including endodontics.

25 **Detailed description of the invention**

The present invention deals with bioactive ceramics based on resorbable ceramics. Accordingly, the present invention aims at providing materials, preferably biomaterials, having early and maintained strength, which with time dissolves and interacts with the body system to yield new tissue.

30 In a basic embodiment of the present invention, the ceramic precursor composition according to the invention comprises main binding phase(s) of chemically bonded

ceramics, preferably Ca-silicates, with Ca as the main cation. The Ca-silicate preferably comprises one or more of the following phases:

C3S = $3\text{CaO} \cdot \text{SiO}_2$, C2S = $2\text{CaO} \cdot \text{SiO}_2$, and CS = $\text{CaO} \cdot \text{SiO}_2$. The main binding phase(s) of the ceramic precursor composition comprises 40-70 wt-% of one or more Ca-

5 silicate. In a preferred embodiment, the main binding phase comprises $3\text{CaO} \cdot \text{SiO}_2$. In a preferred embodiment, the main binding phase(s) of the cured ceramic material comprises hydrates of $3\text{CaO} \cdot \text{SiO}_2$. Said main binding phase(s) also comprise a Ca-based sulphate.

10 The use of soluble chemically bonded ceramic based on $3\text{CaO} \cdot \text{SiO}_2$ is preferred, since it offers both resorbability, and a high initial consumption or up-take of water that reduces the porosity, whereby a high strength is achieved early after the application of the ceramic precursor composition mixed with a curing liquid.

15 In order to further enhance early strength properties, a phase is included which improves initial closure of pores in the ceramic material by pure water up-take, e.g. the non-hydrated pure CaSO_4 , the semi-hydrate $\text{CaSO}_4 \cdot \frac{1}{2}\text{H}_2\text{O}$ and/or mixtures of these and the hydrated $\text{CaSO}_4 \cdot 2\text{H}_2\text{O}$ (gypsum). These phases will not contribute to the medium-term or long-term properties, only enhance the initial pore closure and
20 initial strength.

The ceramic precursor composition comprises 40-20 wt-% of the Ca-based sulphate. The composition preferably comprises 35-22 wt-% of the Ca-based sulphate.

25 The initial high pH can be reduced by the addition of an acidic soluble Ca salt, selected from compounds having the molecular composition $[\text{CaHX}]$, where the anion X^- is a phosphate and/or carbonate. One example of such salt is mono calcium phosphate monohydrate (MCPM), $(\text{Ca}(\text{H}_2\text{PO}_4)_2 \cdot \text{H}_2\text{O})$. By the addition of
30 more than zero wt-% to 10 wt-% of such a salt, the pH is reduced from 12 to below 10 during static immersion tests in water. Said salt is preferably present in an amount greater than 0 wt-% to 5 wt-%.

The ceramic precursor composition may also comprise additional Ca-based phosphates and carbonates, having calcium as the major cation, in an amount greater than 0 wt-% to 30 wt-%, preferably greater than 0 wt-% to 20 wt-%.

Examples of such calcium phosphates are calcium phosphates, β -TCP,
5 hydroxyapatites, etc.

The ceramic precursor composition may further comprise particles of hydrated chemically bonded ceramics of the same or similar composition as that of main the binding phase(s) and in amounts greater than zero wt-% to 40 wt-%. The preferred
10 amount is 10-30 wt-%. This improves the homogeneity of the microstructure and enhances the binding between reacting chemically bonded ceramics and the filler material in the early stage of curing.

The viscosity of the ceramic material prior to curing can be controlled within a wide
15 range, upon initial mixing of the powdered material and the hydration liquid, from moist granules to an injectable slurry. However it is preferable to decrease the water-to-cement (w/c) ratio as much as possible in order to obtain the appropriate viscosity for any given application. The w/c ratio should be equal to or less than 0,55, more preferably equal to or less than 0,45, but not less than 0,2. For
20 orthopaedic applications the use of a somewhat higher w/c ratio than that for dental filling materials is possible and desirable to ensure an easily injectable biomaterial. The slurry should be injectable through a surgical needle, and preferably a size 11 Gauge needle.

25 The materials also show slow disintegration rate in water and body liquid, i.e. that more than 95% of the inserted mass is intact after a setting time of 5 minutes, more preferably after a setting time of 10 minutes, which is beneficial since it is important to allow the material to have time for setting without being too much mixed with the surrounding liquid. The time for defined partial and complete
30 disintegration can be varied within the interval of some months up to a few years.

The cured ceramic material, after having been inserted into a body, has a low disintegration rate in water and body liquid throughout the setting time.

The cured ceramic material exhibits a compressive strength exceeding 50 MPa. It has a compressive strength within 24 hours of at least 40 MPa, preferably more than 50 MPa.

5

The pressure the material exerts during setting and curing (hardening) is less than 5 MPa, in some cases less than 3 MPa, on the surrounding environment, i.e. normally the body tissue. This is due to the fact that the expansion of the material during curing is very moderate.

10

The cured ceramic product according to the present invention, after having been inserted into a body, has a resorption rate that is less or equal to that of the bone in-growth rate. More than 60 wt-% of the material is resorbed within 3 years, preferably more than 50 wt-% within 2 years, and more preferably more than 40 wt-% within 1 year.

15

With the term "bioelement", is intended all types of ceramic objects or coated objects intended for insertion into a body, such as medical implants, and particularly orthopaedic implants. The ceramic precursor composition according to the invention, mixed with a curing liquid, may also be inserted as a slurry, paste or putty, which after curing, forms said bioelement.

20

For the purposes of the invention, the term "cured" when used to describe the ceramic material, is taken to mean the ceramic material in any stage of the curing period, i.e. from the moment that a slurry, paste or putty is manufactured from the precursor composition and a hydration liquid, to the completion of the curing period and the obtaining of a fully cured material. Therefore, when the properties of the cured material is described in the specification, the referral to injection of a "cured" material actually means that a not fully cured slurry, paste or putty made from the precursor composition has been injected or inserted. The properties of the cured material thus reflects its properties from the moment it is inserted or injected.

25

30

Examples

Example 1

An animal study was performed to study the inflammatory response to calcium silicate-based materials.

A pure calcium silicate $3\text{CaO}_3 \cdot \text{SiO}_2$ -based paste was injected into predrilled hole in the left femur of 6 New Zealand white rabbits. In the right femur control materials Norian SRS (Synthes) was injected. The inflammatory response in the tissue surrounding the implant was studied macroscopically and on paraffin sections after 14 days implantation time.

The results showed a marked inflammation in the tissue surrounding the calcium silicate-based material. The inflammatory response could be coupled to the high pH of the calcium silicate material.

Example 2

Tests were performed to lower the reaction pH of injectable biomaterials containing calcium silicate $\text{CaO}_3 \cdot \text{SiO}_2$. The setting time and compressive strength should be controlled to be within 20 minutes and more than 50 MPa.

Compositions 5-9 below represent comparative examples that do not fall within the scope of the present invention.

Precursor formulations were mixed according to:

Formulation number	$3\text{CaO} \cdot 3\text{SiO}_2$	Calcium sulphate	MCPM	β -TCP
1	63,75	33,75	2,5	0
2	58,75	28,75	2,5	10
3	56,25	26,25	2,5	15
4	53,75	23,75	2,5	20
5 (Comparative)	100	0	0	0
6 (Comparative)	85	0	0	15

7 (Comparative)	25	70	5	0
8 (Comparative)	70	15	0	15
9 (Comparative)	40	30	0	30

The setting time were measured by static immersion testing in water with a water – to-cement ratio of 0.2. The setting time was measured using the Gillmore needle method and the compressive strength according to ISO 9917. All powders were mixed with water to a w/c of 0.4.

The results can be viewed in the table below.

Formulation number	Setting time (min)	Maximum pH	Compressive strength, 24 hours (MPa)
1	9	10.54	62
2	11	10.46	64
3	14	10.39	59
4	14	10.20	57
5 (Comparative)	45	12.3	70
6 (Comparative)	37	12.1	78
7 (Comparative)	9	9.5	32
8 (Comparative)	14	12	69
9 (Comparative)	17	11.5	23

The results show that the compressive strength is lowered (but still within therapeutically acceptable limits), but the pH and setting time are improved, via the addition of sulphate and phosphate to the formulation.

Example 3

An animal study was performed to study the inflammatory response to formulation 3 in Example 2.

The paste was injected into predrilled hole in the left femur of 6 New Zealand white rabbits. In the right femur control materials Norian SRS (Synthes) was injected. The inflammatory response in the tissue surrounding the implants was studied macroscopically and on paraffin sections after 14 days implantation time.

5

No inflammatory response could be detected in the tissue surrounding the implants.

CLAIMS

1. A ceramic precursor composition for resorbable or partly resorbable high-strength bioelements, wherein the precursor composition comprises 40-70 wt-
5 % of one or more silicate with Ca as the main cation, 40-20 wt-% of a Ca-sulphate, and greater than 0 wt-% to less than 10 wt-% of an acidic soluble Ca-salt, the remainder, if any, comprises additives.
2. The composition according to claim 1, wherein the Ca-silicate is selected from
10 the group consisting of $3\text{CaO}\cdot\text{SiO}_2$, $2\text{CaO}\cdot\text{SiO}_2$, and $\text{CaO}\cdot\text{SiO}_2$.
3. The composition according to claim 2, wherein the Ca-silicate is $3\text{CaO}\cdot\text{SiO}_2$.
4. The composition according to claim 1, wherein the Ca-sulphate is selected
15 from the group consisting of non-hydrated pure CaSO_4 , the semi-hydrate $\text{CaSO}_4\cdot\frac{1}{2}\text{H}_2\text{O}$ and/or mixtures of these and the hydrated $\text{CaSO}_4\cdot 2\text{H}_2\text{O}$ (gypsum).
5. The composition according to any of the preceding claims, wherein it
20 comprises 35-22 wt-% of the Ca-based sulphate.
6. The composition according to any of the preceding claims, wherein the acidic
soluble Ca-salt is selected from compounds having the molecular composition $[\text{CaHX}]$, where the anion X^- is a phosphate and/or carbonate.
25
7. The composition according to claim 6, wherein the acidic Ca-salt is mono
calcium phosphate monohydrate.
8. The composition according to any of the preceding claims, wherein the acidic
30 soluble Ca-salt is present in an amount greater than 0 wt-% to 5 wt-%.

9. The composition according to any of the preceding claims, wherein the composition further comprises phosphates and carbonates of calcium, and combinations thereof in an amount greater than 0 wt-% to 30 wt-%.
- 5 10. The composition according to any of the preceding claims, wherein the composition comprises phosphates and carbonates of calcium, and combinations thereof in an amount greater than 0 wt-% to 20 wt-%.
- 10 11. The composition according to claim 9 or 10, wherein said phosphates and carbonates of calcium are selected from the group consisting of calcium phosphates, β -TCP, and hydroxyapatites.
- 15 12. The composition according to any of the preceding claims, wherein it further comprises hydrated particles of the same or of similar non-hydrated phases as those used for the main binding phase and in an amount greater than 0 wt-% to 40 wt-%.
- 20 13. The composition according claim 12, wherein it comprises 10-30 wt-% of said hydrated phase.
- 25 14. A ceramic slurry comprising the ceramic precursor composition defined in claims 1-13 and water, in a water-to-cement ratio of equal to or less than 0,55, but not less than 0,2, said slurry being injectable through a surgical needle.
- 30 15. The slurry according to claim 14, wherein said slurry is injectable through a size 11 Gauge needle.
16. The slurry according to claim 14 or 15, wherein said water-to-cement ratio is equal to or less than 0,45, but not less than 0,2.
17. A cured ceramic material for high-strength bioelements used as resorbable or partly resorbable biomaterials, said cured ceramic material being based on the

ceramic precursor composition defined in any of claims 1-13, in hydrated and cured form, or the slurry defined in any of claims 14-16, in cured form.

18. The cured material according to claim 17, wherein the material has a
5 compressive strength exceeding 50 MPa.
19. The cured material according to claim 17 or 18, wherein the material, during a static immersion test, results in a pH value of less than 11.
- 10 20. The cured material according to any of claims 17-19, wherein the material has a setting time of less than 20 minutes according to the Gillmore needle method.
- 15 21. The cured material according to any of claims 17-20, wherein the material has a compressive strength within 24 hours of at least 40 MPa.
22. The cured material according to any of claims 17-21, wherein the material has a compressive strength within 24 hours of at least 50 MPa.
- 20 23. The cured material according to any of claims 17-22, wherein the material, after having been inserted or injected into a body, has a slow disintegration rate in water and body liquid throughout the setting time, i.e. that more than 95% of the inserted mass is intact after a setting time of 5 minutes.
- 25 24. The cured material according to any of claims 17-23, wherein the material, after having been inserted or injected into a body, has a slow disintegration rate in water and body liquid throughout the setting time, i.e. that more than 95% of the inserted mass is intact after a setting time of 10 minutes.
- 30 25. The cured material according to any of claims 17-24, wherein more than 60 wt-% of the material, after having been inserted into a body, is resorbed within 3 years.

26. The cured material according to any of claims 17-25, wherein more than 50 wt-% of the material, after having been inserted into a body, is resorbed within 2 years.
- 5 27. The cured material according to any of claims 17-26, wherein more than 40 wt-% of the material, after having been inserted into a body, is resorbed within 1 year.
- 10 28. The cured material according to any of claims 17-27, wherein the material during setting and curing exerts a pressure of less than 5 MPa on the surrounding environment.
- 15 29. The cured material according to any of claims 17-28, wherein the material during setting and curing exerts a pressure of less than 3 MPa on the surrounding environment.
30. A medical implant comprising a non-cured ceramic precursor composition defined in claims 1-13 or a cured ceramic material defined in claims 17-29.
- 20 31. A carrier material for drug delivery comprising a non-cured ceramic precursor composition defined in claims 1-13 or a cured ceramic material defined in claims 17-29.
- 25 32. A method of manufacturing a cured chemically bonded ceramic material for high-strength bioelements used as a resorbable or partly resorbable biomaterial, wherein the method comprises the step of mixing the ceramic precursor composition defined in claims 1-13 and water, in a water-to-cement ratio of equal to or less than 0,55, but not less than 0,2, such that a slurry is formed, and allowing said slurry to cure.
- 30 33. The method according to claim 32, wherein the water-to-cement ratio is equal to or less than 0,45, but not less than 0,2.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2007/050745

A. CLASSIFICATION OF SUBJECT MATTER

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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 20060078590 A1 (HERMANSSON, LEIF ET AL), 13 April 2006 (13.04.2006), claims 1-28, abstract, paragraphs [0020], [0022], [0025], [0029], [0030], [0040], table 1:1 --	1-33
Y	US 20060213395 A1 (LU, DONGHUI ET AL), 28 Sept 2006 (28.09.2006), abstract, paragraphs [0039]-[0042] --	1-33
A	ZHAO, WENYUAN et al, "The self-setting properties and in vitro bioactivity of tricalcium silicate", Biomaterials, 2005, Vol. 26, page 6113 - page 6121 --	1-33

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

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INTERNATIONAL SEARCH REPORT

International application No.

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Gou, Zhongru et al, "Study on the Self-Setting Property and the In Vitro Bioactivity of Beta-Ca ₂ SiO ₄ ", J. Biomed Mater Res Part B: Appl Biomater, 2005, Vol. 73B, page 244 - page 251 --	1-33
A	Fernández, Enrique et al, "Modulation of porosity in apatitic cements by the use of alpha-tricalcium phosphate-calcium sulphate dihydrate mixtures", Biomaterials, 2005, Vol. 26, page 3395 - page 3404 --	1-33
P,A	HUAN, ZHIGUANG et al, "Self-setting properties and in vitro bioactivity of calcium sulfate hemihydrate-tricalcium silicate composite bone cements", Acta Biomaterialia, 2007, Vol. 3, page 952 - page 960 --	1-33
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P,A	STN International, File CAPLUS, CAPLUS accession no. 2007:261815, Document no. 146:365819, Shanghai Institute of Ceramics, Chinese Academy of Sciences, Peop. Rep. China, "Manufacture and application of bioactive self-curing calcium sulfate hemihydrate/tricalcium silicate composite for bone repair"; & CN1923302,A,20070307 --	1-33
P,A	STN International, File CAPLUS, CAPLUS accession no. 2007:205735, Document no. 146:302390, Shanghai Institute of Ceramics, Chinese Academy of Sciences, Peop. Rep. China, "Bone and dental fillings containing bioactive self-curing tricalcium silicate and calcium sulfate hemihydrate composites"; & CN1911458,A,20070214 -- -----	1-33

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Information on patent family members

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