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(71) Applicant *(for all designated States except US)*: **CALCITEC, INC.** [US/US]; 20057 Glen Arbor Court, Saratoga, CA 95070 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **LIN, Jiin-Huey, Chern** [US/US]; 911 Tower Road, Winnetka, IL 60093 (US). **JU, Chien-Ping** [US/US]; 16 Pinewood Drive, Carbondale, IL 62901 (US). **CHEN, Wen-Cheng**; No. 12, Bau-Shing Street, Gueiren Shiang, Tainan (TW). **LIN, Kuan-Liang**; No. 27, Lane 69 Shian Street, Fengyuan City, Taichung (TW). **WANG, I-Chang**; No. 114, Jinhu Tsuen, Beimen Shiang, Tainan (TW).

(74) Agent: **HAILE, Lisa, A.**; Gray Cary Ware & Freidenrich LLP, Suite 1100, 4365 Executive Drive, San Diego, CA 92121-2133 (US).

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(54) Title: CALCIUM PHOSPHATE CEMENT, USE AND PREPARATION THEREOF

(57) Abstract: Monophasic TTCP particles having surfaces covered with whiskers or fine crystals with a width ranging from 2 to 500 nm and a length ranging from 5 to 5000 nm are provided and methods for their preparation. In another embodiment, methods are provided for using such monophasic TTCP particles to prepare a calcium phosphate cement having the consistency of paste that sets to form a substance with a compressive strength of about 10 MPa after setting for about 30 minutes and a compressive strength of about 25 MPa within 24 hours of exposure to in vivo conditions. The paste can be used directly to treat a defect in a bone or a tooth in a patient or the paste can be shaped and implanted into the defect.

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CALCIUM PHOSPHATE CEMENT, USE AND PREPARATION THEREOF

FIELD OF THE INVENTION

[0001] The present invention relates generally to a calcium phosphate cement, and particularly to a fast-setting calcium phosphate cement, for use in dental and bone prosthesis.

BACKGROUND OF THE INVENTION

[0002] A calcium phosphate cement (abbreviated as CPC) has been widely used as an implant or filling material in dental and bone prostheses, and details of its technical description can be found in many patents, for example, U.S. Patent Nos. 4,959,104; 5,092,888; 5,180,426; 5,262,166; 5,336,264; 5,525,148; 5,053,212; 5,149,368; 5,342,441; 5,503,164; 5,542,973; 5,545,254; 5,695,729 and 5,814,681. In general, the prior art calcium phosphate cements suffer one or more drawbacks as follows: 1) requiring additives with a relatively poor bioactivity; 2) a complicated preparation process; 3) an undesired setting time or working time for the CPC that is difficult to adjust; 4) being incapable of setting to a desired shape in water, blood or body fluid; and 5) having poor initial strength after setting of the CPC.

SUMMARY OF THE INVENTION

[0003] The present invention is based on the discovery that monophasic particles of tetracalcium phosphate (TTCP) having whiskers or fine crystals on surfaces of the particles can be prepared and used to make a calcium phosphate cement suitable for preparation of bone and tooth prosthesis.

[0004] In one embodiment, the invention provides calcium phosphate cement particles comprising monophasic tetracalcium phosphate (TTCP) particles, wherein said TTCP

particles on their surfaces have whiskers or fine crystals with a width ranging from 2 to 500 nm and a length ranging from 5 to 5000 nm.

[0005] In another embodiment, the invention provides methods for preparing a paste for use in treating a defect in a bone or a tooth in a patient by introducing said paste into a bone defect or bone cavity of said patient or shaping said paste and implanting the resulting shaped paste into a bone defect or a bone cavity of said patient, said method comprising mixing invention TTCP particles and a hardening aqueous solution sufficient to form a paste.

[0006] In still another embodiment, the invention provides methods for preparing TTCP particles comprising mixing a powder or small pieces of invention TTCP particles with a wetting agent, and controlling growth of whiskers or fine crystals of TTCP on surfaces of said TTCP powder or small pieces of TTCP by a controlling treatment, to provide whiskers or fine crystals of TTCP having a width ranging from 1 nm to 100 nm and a length ranging from 1 nm to 5000 nm.

DETAILED DESCRIPTION OF THE INVENTION

[0007] The present invention provides a calcium phosphate cement comprising monophasic TTCP particles having a diameter of 0.05 to 100 microns, wherein said TTCP particles on their surfaces have whiskers or fine crystals having a width ranging from 2 to 500 nm and a length ranging from 5 to 5000 nm, for example a width ranging from 2 to 100 nm and a length ranging from 5 to 1000 nm, or a width ranging from 2 nm to about 200 nm and a length ranging from 10 nm to about 2000 nm.

[0008] By adjusting the diameter of the TTCP particles, the width and/or the length of the whiskers or fine crystals, the working time and/or the setting time of the calcium phosphate cement of can be adjusted to conform to requirements for various purposes. Moreover, the calcium phosphate cement of the present invention is fast-setting, and is non-dispersive in water or an aqueous solution.

[0009] A suitable process for preparing the calcium phosphate cement of the present invention comprises mixing a TTCP powder or small pieces of monophasic TTCP with a wetting agent, and controlling growth of whiskers or fine crystals on surfaces of said TTCP powder or small pieces of TTCP by an controlling treatment. The shape of the monophasic small pieces of TTCP or grains of TTCP powder are not limited, and can include spherical or irregular shapes; and the crystal structure thereof can be single crystal, polycrystal, mixed crystals, semi-crystal, or amorphous.

[0010] Suitable wetting agents used to wet the powder or small pieces of TTCP include any aqueous solution comprising alkaline ions (for example, sodium(Na) or potassium(K) ions);alkaline earth ions (for example, magnesium(Mg) or calcium(Ca) ions); fluorine(F) ion; chlorine $(Cl)^{-1}$ ion; carbonate $(CO_3)^{-2}$ ion, nitrate $(NO_3)^{-1}$ ion, acetate $(CH_3COO)^{-1}$ ion; phosphate $(PO_4)^{-3}$ ion; ammonium ion $(NH_4)^{+}$, hydrogen $(H)^{+}$ ion, or hydroxyl $(OH)^{-}$ ion. Preferably, however, the wetting agent used is a diluted aqueous solution containing phosphoric acid or phosphate.

[0011] The amount of the wetting agent mixed with the monophasic TTCP powder or small pieces, in general, should be enough to substantially wet all the TTCP powder or small pieces of TTCP. However, it is not necessarily the case when the controlling treatment is the organic solvent treatment, where a water miscible organic solvent is added to the mixture of said wetting agent and the TTCP powder or small pieces of TTCP to form a paste for a subsequent processing step. For example, a dilute aqueous solution containing more than 20 ppm of phosphoric acid or phosphate, more preferably more than 50 ppm, and most preferably more than 100 ppm of phosphoric acid or phosphate can be mixed with the monophasic TTCP particles or powder prior to the controlling treatment.

[0012] The controlling treatment is selected from a vacuuming treatment, an organic solvent treatment, a microwave treatment, a heating treatment, or any other treatments that can control growth of whiskers or fine crystals on surfaces of monophasic TTCP powder or small pieces. Due to its simplicity and effectiveness, the most frequently used controlling treatment is heating to about 50 °C for 1 day.

[0013] The process for preparing the calcium phosphate cement can further comprise grinding the resulting product from the controlling treatment to form TTCP particles having a diameter of 0.05 to 100 microns, wherein said whiskers or fine crystals of TTCP have a width ranging from 1 to 100 nm and a length ranging from 1 to 1000 nm.

[0014] Preferably, the process for preparing the calcium phosphate cement of the present invention comprises soaking said TTCP powder or said small pieces of TTCP with a diluted aqueous solution containing more than 100 ppm of phosphoric acid or phosphate, and carrying out (a) a heating treatment comprising drying the resulting soaked TTCP powder or soaked small pieces of TTCP at a temperature in the range from about 50°C to about ; (b) a vacuuming treatment comprising drying the resulting soaked TTCP powder or soaked small pieces of TTCP under vacuum; or (c) a microwave treatment comprising drying the resulting soaked-TTCP powder or soaked small pieces of TTCP by microwave heating. More preferably, the resulting soaked TTCP powder or soaked small pieces of TTCP are well mixed to form a uniform mixture prior to being subjected to treatment (a), (b) or (c).

[0015] Alternatively, the process for preparing the calcium phosphate cement of the present invention comprises mixing the TTCP powder or the small pieces of TTCP with the diluted aqueous solution containing more than 100 ppm of phosphoric acid or phosphate, and carrying out the organic solvent treatment comprising mixing the mixture of the wetting agent and the TTCP powder or small pieces of TTCP with a water miscible organic solvent, and drying the resulting mixture under vacuum. Preferably, the organic solvent treatment is carried out while stirring, and more preferably, the mixture of the diluted aqueous solution containing more than 100 ppm of phosphoric acid or phosphate and the TTCP powder or small pieces of TTCP is well mixed prior to being subjected to the organic solvent treatment.

[0016] Preferably, the TTCP particles of the calcium phosphate cement of the present invention have a diameter of 0.2 to 80 microns, and more preferably 0.5 to 50 microns.

[0017] As used herein, the" width" of a whisker means an average value of lateral cross-sectional diameters of the whisker, and the "width" of a fine crystal means an average

value of the first 30% of the diameters of the fine crystal, which are shorter than the other 70% thereof. As used herein, the "length" of a fine crystal means an average value of the last 30% of the diameters of the fine crystal, which are longer than the other 70% thereof.

[0018] Preferably, the whiskers or fine crystals of TTCP have a width ranging from 2 to 70 nm and a length ranging from 5 to 800 nm, and more preferably a length ranging from 10 to 700 nm.

[0019] Preferably, the TTCP particles have a molar ratio of calcium to phosphate ranging from 0.5 to 2.5, more preferably 0.8 to 2.3, and most preferably 1.0 to 2.2.

[0020] The calcium phosphate cement of the present invention is biocompatible and a paste made therefrom is non-dispersive in water. The paste has a working time from several minutes to hours and a setting time from a few minutes to hours. Consequently, the calcium phosphate cement of the present invention is extremely suitable for use as an implant or filling material in dental or bone prostheses, where the paste must contact water, blood or body fluid when implanted. In one embodiment, the paste made from the calcium phosphate cement of the invention is suitable for direct injection into a bone defect or cavity as an implant or filling material.

[0021] The present invention also discloses a method of treating a defect in bone or a tooth in a patient, by mixing the calcium phosphate cement of the present invention with a hardening -promoter-containing aqueous solution to form a paste, and a) injecting the paste into a bone defect or cavity of said patient or b) shaping the paste and implanting the resulting shaped paste into a bone defect or cavity of the patient.

[0022] In one embodiment of the invention methods, the calcium phosphate cement may further comprise an agent that promotes bone growth, such as a growth factor, a bone morphology protein or a pharmaceutical carrier, or the hardening-promoter-containing aqueous solution can further comprises such an agent, for example, a growth factor, a bone morphology protein or a pharmaceutical carrier.

[0023] The hardening-promoter-containing aqueous solution can further comprise any known compound or composition that promotes the solidification of calcium phosphate,

for example phosphates, calcium salts, and fluorides. For example, the hardening-promoter-containing aqueous solution may be an aqueous solution comprising phosphate ions, calcium ions, fluorine ions, or phosphate ions together with additional fluorine ions as a hardening promoter.

[0024] The amount of the hardening promoter in the hardening-promoter-containing aqueous solution has no special limitation, but preferably the concentration of the hardening promoter therein ranges from 0.1 M to 8 M, and more preferably from 1 M to 6 M.

[0025] The mixing ratio of the calcium phosphate cement of the present invention and the hardening-promoter-containing aqueous solution is not restricted to any particular ranges; however, the amount of said hardening-promoter-containing aqueous solution in the mixture should be sufficient to provide substantial wetting of the calcium phosphate cement of the present invention. It should be noted that more water can be supplied in-situ from saliva or body fluid when the paste is injected or implanted into the bone defect or cavity. Furthermore, the amount of the hardening promoter in the hardening-promoter-containing aqueous solution should be adjusted to a higher level when a lesser amount of said hardening-promoter-containing aqueous solution is used in the mixture.

[0026] A "subject" as the term is used herein is any mammal, including zoo, farm and domestic animals and humans.

[0027] An "effective amount" of the injectable calcium-phosphate-based bone substitute as the term is used herein is an amount effective to accomplish fusion of vertebrae adjacent to the interbody site in the subject.

[0028] "Setting time" as the term is used herein is the time after which a 1 mm diameter pin with a load of 1/4 pound can be inserted only 1 mm deep into the surface of a CPC paste, as determined using ISO 1566, a method commonly used for measuring the setting time of dental zinc phosphate cements as well as CPC

[0029] "Working time" as the term is used herein means the time after which a CPC paste becomes too viscous to be stirred. Generally working time is a few minutes shorter than setting time.

[0030] After setting for about 30 minutes, the CPC paste made by the invention methods has a minimum compressive strength of about 10 MPa and a minimum compressive strength of 25 MPa is obtained within 24 hours after exposure to physiological conditions. The compressive strength herein is as determined using ASTM F451-99, a method, that is commonly used for the compressive strength measurement of CPC.

[0031] An injectable formulation of the invention CPC paste can be introduced into a defect in a bone or tooth using any method known in the art and will have working and setting times of about 5 to about 30 minutes. About 30 minutes after introduction into the defect or after exposure to biological conditions, the invention CPC paste will form a substance with a minimum compressive strength of about 10 MPa, or a minimum of 25 MPa compressive strength within 24 hours. Additionally, when solidified, the bone substitute produced from the invention CPC paste can have a porosity of about 20% to about 50% by volume as measured using ASTM C830-00 water saturation technique.

[0032] The CPC paste having these characteristics can consist essentially of calcium phosphate, for example being a substantially monophasic TTCP, and is made from invention particles of monophasic TTCP having surface whiskers or fine needles of calcium phosphate, said whiskers having a length ranging from 1 to about 1000 nm and a width ranging from 1 to about 100 nm as described herein.

[0033] The following examples are meant to illustrate an embodiment of the invention and not to limit the scope of the invention.

EXAMPLE 1

[0034] The most-frequently used wetting agent used in preparation of the invention TTCP monophasic particles is $(NH_4)_2HPO_4$ with a concentration range 0.1 – 8M, preferably 1 - 6M. The length of exposure to the wetting agent will also affect the composition of the particles. For example, when TTCP monophasic particles are treated

by exposure to $(NH4)_2HPO_4$ for 10 min, the whiskers formed are of monophasic TTCP. However, when the same TTCP monophasic particles are treated by exposure to $(NH_4)_2HPO_4$ for 24 hours the whiskers become pure hydroxyapatite.

[0035] The working and setting times for the CPC cement derived from TTCP particles being treated in $(NH_4)_2HPO_4$ for 5-10 min (maximum strength obtained) are about 7 and 9 min, respectively. The water solubility for such CPC paste is only about 0.65% in weight after immersing the hardened cement in 37 °C deionized water for 568 hours.

EXAMPLE 2

[0036] The following tables demonstrate the relationship between compressive strength of CPC paste subjected to physiological conditions (exposure to Hank's solution for one day) when the TTCP particles used to make the CPC paste are treated for growth of whiskers for varying amounts of time resulting in whiskers of various size.

Compressive strength (CS) of CPC derived from TTCP particles whisker-treated in HCl solution

Whisker-treating time	10min	1h	4h	12h	24h
CS (MPa)	21.1±2.6	22.7±2.8	33.1±3.3	48±4.3	29±4.1

Compressive strength of CPC derived from TTCP particles whisker-treated in $(NH_4)_2HPO_4$ solution

	5min	10min	30min	24hr
CS(MPa)	41±6.2	43.9±5.6	26.8±3.2	6.3±1.6

The CPC was immersed in Hanks' solution for one day before being tested for compressive strength. These studies show the compressive strength of CPC prepared from the whisker-treated TTCP powder increases with treating time until a maximum strength is obtained. When treated further, the strength declines due to "overgrowing" of the whiskers.

[0037] Although the invention has been described with respect to specific embodiments, it will be understood that modifications and variations are encompassed

within the spirit and scope of the invention. Accordingly, the invention is limited only by the following claims.

WHAT IS CLAIMED IS:

1. Calcium phosphate cement particles comprising monophasic tetracalcium phosphate (TTCP) particles, wherein said TTCP particles on their surfaces have whiskers or fine crystals with a width ranging from 2 to 500 nm and a length ranging from 5 to 5000 nm.

2. The calcium phosphate cement particles of claim 1, wherein said TTCP particles have a diameter of 0.2 to 80 microns.

3. The calcium phosphate cement particles of claim 2, wherein said TTCP particles have a diameter of 0.5 to 50 microns.

4. The calcium phosphate cement particles of claims 1, 2 or 3, wherein said whiskers or fine crystals have a width ranging from 2 to about 100 nm. and a length ranging from 5 to 1000 nm.

5. The calcium phosphate cement particles of claim 4, wherein said whiskers or fine crystals of TTCP have a width ranging from about 2 nm to about 200 nm and a length ranging from 10 nm to about 2000 nm.

6. The calcium phosphate cement particles of claim 1, wherein the whiskers are monophasic TTCP.

7. A method of preparing a paste for use in treating a defect in a bone or a tooth in a patient by introducing said paste into a bone defect or a bone cavity of said patient or shaping said paste and implanting the resulting shaped paste into a bone defect or a bone cavity of said patient, said method comprising mixing calcium phosphate cement particles of claim 1 and a hardening aqueous solution sufficient to form a paste.

8. The method of claim 7, wherein said hardening aqueous solution comprises phosphate ions, calcium ions, fluorine ions, or phosphate ions together with fluorine ions as a hardening promoter.

9. The method of claims 7 or 8, wherein said hardening aqueous solution has a concentration of 1 mM to 10 M of said hardening promoter.

10. The method of claim 9, wherein said hardening aqueous solution has a concentration of 10 mM to 6 M of said hardening promoter and the hardening promoter is $(NH_4)_2HPO_4$.

11. The method according to any claim of claims 7 to 10, wherein said particles have a diameter of 0.2 to 80 microns, and said whiskers or fine crystals have a width ranging from 2 to 70 nm and a length ranging from 5 to 800 nm.

12. The method of claim 11, wherein said particles have a diameter of 0.5 to 50 microns, and said whiskers or fine crystals have a length ranging from 10 to 700 nm.

13. The method according to any claim of claims 7 to 10, further comprising introducing a growth factor, a bone morphology protein or a pharmaceutical carrier into the hardening aqueous solution or said TTCP cement.

14. The method of claim 13, wherein the paste has a minimum compressive strength of 10 MPa or about 30 minutes after being introduced to a defect in a bone or tooth in a patient.

15. The method of claim 13, wherein the paste has a minimum compressive strength of about 25 MPa about 24 hours after being introduced to a defect in a bone or tooth in a patient

16. A method comprising mixing a powder or small pieces of monophasic TTCP with a wetting agent, and controlling growth of whiskers or fine crystals on surfaces of said powder or small pieces of TTCP by a controlling treatment, to provide whiskers or fine crystals having a width ranging from 1 nm to 100 nm and a length ranging from 1 nm to 5000 nm.

17. The method of claim 16, wherein growth of said whiskers or fine crystals is controlled to a length ranging from 10 nm to 700 nm.

18. The method of claim 16 further comprising grinding the product resulting from the controlling treatment to form monophasic TTCP particles having a diameter of 0.05 to 100 microns.

19. The method of claim 18, wherein said TTCP particles have a diameter of 0.2 to 80 microns.

20. The method of claim 19, wherein said TTCP particles have a diameter of 0.5 to 50 microns.

21. The method according to any claim of claims 7 to 20, wherein said wetting agent is an aqueous solution comprising more than 20 ppm of phosphoric acid or phosphate.

22. The method of claim 21, wherein said wetting agent is an aqueous solution comprising about 1 to 6 M $(NH_4)_2HPO_4$ and the controlling treatment is exposure to the solution for about 5 to 10 minutes.

23. The method according to any claim of claims 16 to 22, wherein said controlling treatment is selected from a vacuum treatment, an organic solvent treatment, a microwave treatment, and a heating treatment.

24. The method of claim 23, wherein said TTCP powder or said small pieces of TTCP are soaked with said wetting agent, and said controlling treatment is a heating treatment comprising drying the resulting soaked powder or small pieces of TTCP at a temperature from 45 °C to about 1000 °C.

25. The method of claim 23, wherein said TTCP powder or said small pieces of TTCP are soaked with said wetting agent, and said controlling treatment is a vacuum treatment comprising drying the soaked powder or small pieces of TTCP under vacuum.

26. The method of claim 23, wherein said TTCP powder or said small pieces of TTCP are soaked with said wetting agent, and said controlling treatment is a microwave treatment comprising drying the soaked powder or small pieces of TTCP by microwave heating.

27. The method of claim 23, wherein said controlling treatment is an organic solvent treatment comprising mixing said wetting agent and said powder or small pieces of TTCP with a water miscible organic solvent, and drying the resulting mixture under vacuum.

28. The method of claim 13, wherein said calcium phosphate cement further comprises a growth factor, a bone morphology protein or a pharmaceutical carrier.

29. The method of claim 13, wherein said hardening-promoter-containing aqueous solution further comprises a growth factor, a bone morphology protein or a pharmaceutical carrier.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/11637

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C04B 12/02; A61L 24/02
US CL : 106/35,690; 623/23.62
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)
U.S. : 106/35,690; 623/23.62

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,496,399 A (ISON et al) 5 March 1996 (05.03.1996), col. 2, line 42-col. 9, line 67.	1-10 and 16-20

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

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

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Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (703) 305-3230

Authorized officer
C. Melissa Koslow
Telephone No. (571) 272-1700

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INTERNATIONAL SEARCH REPORT

International application No.
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Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 11-15 and 21-29
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.