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(54) **Tetracalcium phosphate-based materials and processes for their preparation**

(57) The invention provides (i) apatite-coated tetracalcium phosphate particles; (ii) a process for preparing the apatite-coated tetracalcium phosphate particles by hydration; (iii) a tetracalcium phosphate-based setting composition; (iv) a composition for forming a hardening material using coated tetracalcium phosphate particles and an acidic aqueous solution; and (v) the composition as defined in (iv) in which the acidic aqueous solution can satisfy the concentration relationships as represented below:

(a) $25\% \leq \text{citric acid} \leq 50\%$

(b) $30\% \leq \text{citric acid} + \text{phosphoric acid} \leq 70\%$

(c) $10\% \text{ citric acid} - \text{phosphoric acid} \leq 50\%$

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FIG. 1

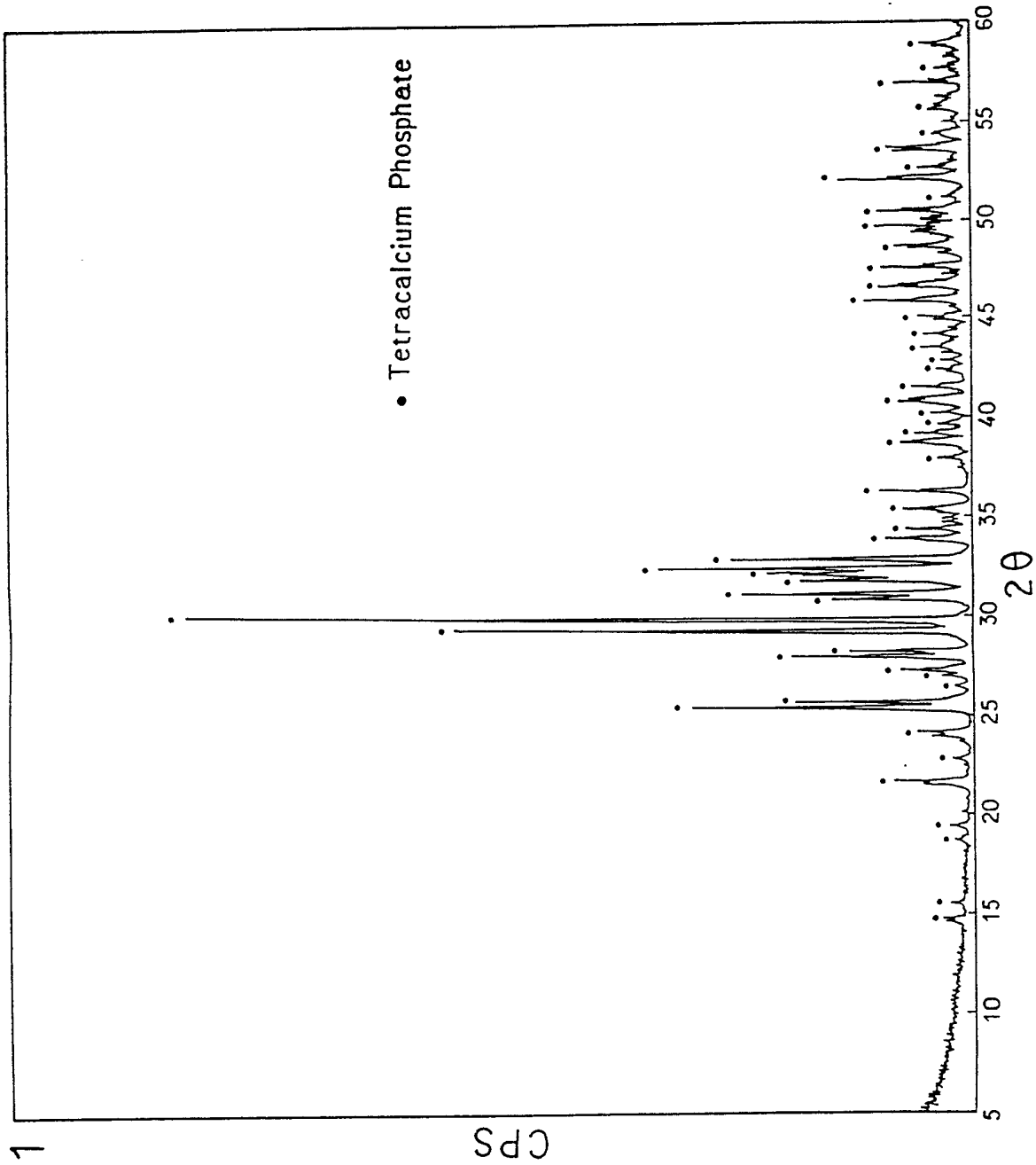


FIG. 2

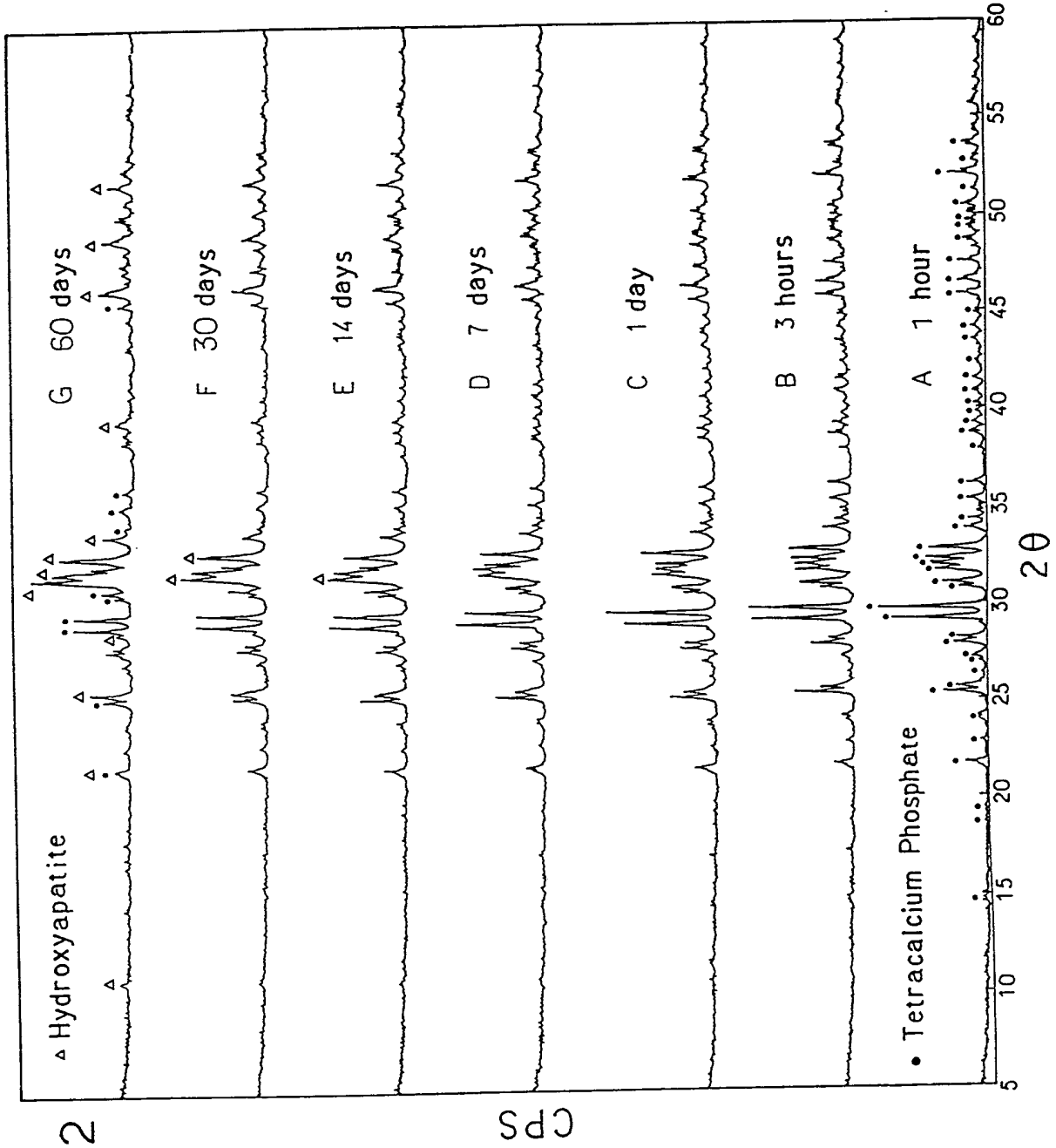


FIG. 3

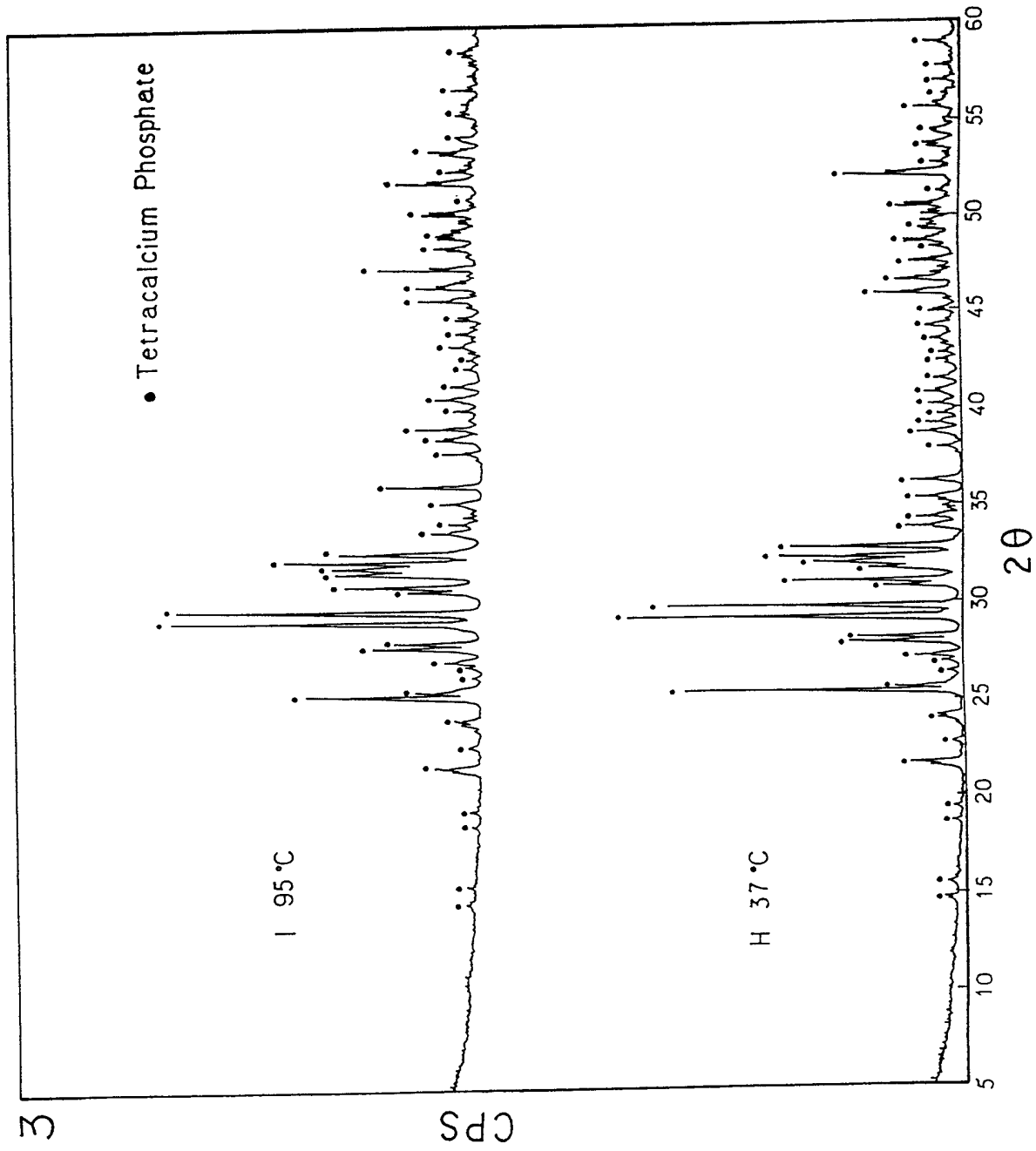
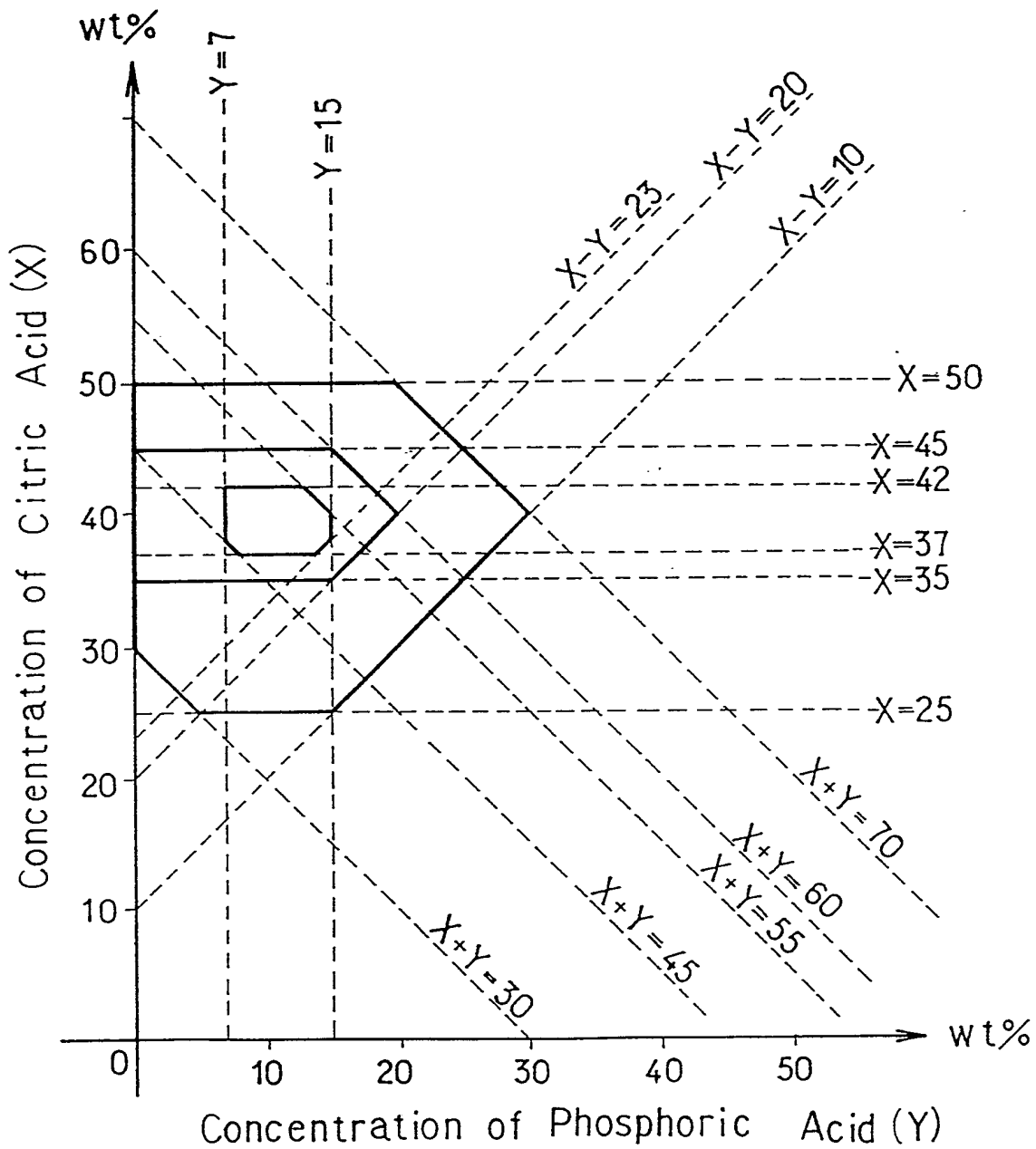


FIG. 4



- 1 -

TETRACALCIUM PHOSPHATE-BASED MATERIALS AND
PROCESSES FOR THEIR PREPARATION

Industrial Field of the Invention

The present invention concerns with tetracalcium
5 phosphate particles coated with a material, such as apatite,
having an affinity for the living body and useful as
osteosynthetic materials, dental materials and the like,
processes for preparing the same, and compositions for
producing hardened or cured materials or products which
10 contain such tetracalcium phosphate particles.

The parts and the percentages used herein are all by
weight unless otherwise specified.

Prior Art

Tetracalcium phosphate ($\text{Ca}_4(\text{PO}_4)_2\text{O}$) is a phosphoric acid
15 compound which is the main inorganic component of bones,
teeth and so on. Tetracalcium phosphate has a high chemical
activity and reacts at room temperature with an aqueous
solution of, e.g. inorganic acid, saturated or unsaturated
organic acid or a homopolymer or a copolymer of unsaturated
20 organic acid, or a physiological saline or the like to
undergo setting. The obtained hardening material or product
has an affinity for the living body and is useful as an
osteosynthetic material, a dental material and so on.

In preparation of tetracalcium phosphate, CaCO_3 , CaO ,
25 $\text{Ca}(\text{OH})_2$ or the like has been used as a Ca source, P_2O_5 , H_3PO_4 ,

$\text{NH}_4\text{H}_2\text{PO}_4$, $(\text{NH}_4)_2\text{HPO}_4$ or the like as a P source, and CaHPO_4 ,
 $\text{Ca}(\text{H}_2\text{PO}_4)_2$ or the like as a Ca and P sources. Tetracalcium
phosphate can be prepared by various processes depending on
the kinds of the materials used. Most predominantly
5 employed is a dry process as shown below in which a mixture
of CaCO_3 and CaHPO_4 is calcined:



This process requires calcination of a mixture of the
starting particles at a temperature of about 1,300 to about
10 1,600°C and rapidly cooling of the obtained product to about
400°C (at a cooling rate of not lower than about 10°C/min),
and gives a product of phosphoric acid compounds containing
a predominant amount of tetracalcium phosphate. When the
mixture is calcined at not lower than 1,600°C in this
15 process, the obtained product is composed of a phase mixture
of a porous portion and a semi-fused portion, posing the
problem that the obtained product (tetracalcium phosphate)
has an irregular quality. Furthermore, the tetracalcium
phosphate produced by calcination even at about 1,300 to
20 about 1,600°C is highly reactive and very unstable, so that
the product being cooled at a low cooling rate is caused to
absorb water vapor in the atmosphere at 1,200 to 400°C,
readily producing hydroxyapatite. With these problems, the
process necessitates rigid control of calcining temperature,
25 moisture content in the atmosphere within the calciner

during cooling and cooling rate in order to obtain a tetracalcium phosphate of stable quality in a higher yield.

However, it is difficult to remove the moisture in the atmosphere within the calciner from the viewpoint of practical operation. Forced cooling of the product in the calciner is technically difficult and causes damage to refractory materials of calciner wall due to rapid cooling.

Given below are proposed processes for preparing a setting composition containing tetracalcium phosphate particles for use as osteosynthetic materials, osteosynthetic fillers, dental cement and so on:

- (1) a process comprising admixing tetracalcium phosphate particles with an aqueous solution of TCA cycle-type organic acid;
- (2) a process comprising admixing tetracalcium phosphate particles with an aqueous solution which is similar in composition to a tissue fluid in the living body, such as a physiological saline, a phosphate buffer or the like;
- (3) a process comprising admixing tetracalcium phosphate particles with an aqueous solution of polysaccharide;
- (4) a process comprising admixing tetracalcium phosphate particles with an aqueous solution of a homopolymer or a copolymer of unsaturated organic acid; and
- (5) a process comprising conducting a suitable combination of above processes (1) to (4).

These setting compositions are provided to clinicians in the form of a powder-liquid pack product comprising a combination of powder and liquid materials. In treatment, clinicians must knead the powder and liquid materials to obtain a paste or a clay-like mixture for use in any desired form. Moreover, after application to the affected part, the composition must be rapidly set (or cured) and firmly fixed thereto to exhibit a high biological activity. Yet these requirements can not be fully met by the setting (or curable) compositions produced by any of the above processes (1) to (5). The tetracalcium phosphate, which is the main component of the powder material, has a high chemical activity and is alkaline. It rapidly undergoes setting reaction when mixed with an acidic aqueous solution and thus is difficult to make into a homogeneous composition which can retain a suitable softness for a specific period of time.

In view of these drawbacks, attempts have been made to assure a sufficient treating time and enhance the operational efficiency in treatment. For example, an acid concentration in the liquid material has been reduced or the water content of the composition has been increased to improve the properties of the composition to be set or to control the setting time. In respect of the powder material, attempts have been made to inhibit the setting

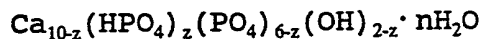
reaction of tetracalcium phosphate to the greatest extent possible by admixing therewith apatite, tricalcium phosphate, calcium monohydrogenphosphate, citrate, alkali phosphate or the like. However, these attempts have
5 resulted in considerable impairment of properties of tetracalcium phosphate-based setting composition, and have failed to enhance the properties for setting reaction sufficiently to make up for the impairment. In short, the attempts have provided no complete solution to the problem.

10 Tetracalcium phosphate particles have been tentatively mixed with a neutral or substantially neutral aqueous solution. The attempt, however, has markedly decreased the setting reaction rate, whereby the tetracalcium phosphate-based composition has become unlikely to exhibit the
15 required mechanical and physical characteristics and has been made alkaline, causing the hazard of acting as an irritant in the living body.

For the foregoing reasons, tetracalcium phosphate, although suitable for use as medical materials, dental
20 materials or the like, has not been industrially provided in the form of a setting (or curable) tetracalcium phosphate-based composition having satisfactory properties, because of difficulties in handling and inability to fully exhibit the desired properties.

25 Hydroxyapatite is a calcium phosphate compound

represented by the formula



wherein $n=0-2.5$, $z=0-1$, and is also useful as an osteosynthetic material, a dental material and so on due to its affinity to the living body.

However, hydroxyapatite is not a material clinically easy to handle since it is chemically highly stable. In clinical use, it must be previously shaped or molded in a required form or finely divided to be used as a filling material because it does not set even when mixed with a solution of organic or inorganic acid, or a physiological saline, etc.

Means for Solving the Problems

In view of the foregoing state of the art, the present inventors conducted extensive research and found the following. When the surface of tetracalcium phosphate particles is coated with apatite, the coated particles have the combined properties of the two materials, and can markedly mitigate or substantially overcome the prior art problems. In addition, a setting composition prepared from the obtained tetracalcium phosphate particles coated with apatite is equivalent or superior in properties to conventional setting compositions.

According to the invention, there are provided:

(i) tetracalcium phosphate particles coated with apatite;

(ii) a process for preparing tetracalcium phosphate particles coated with apatite, the process comprising subjecting tetracalcium phosphate particles to hydration reaction; and

5 (iii) a tetracalcium phosphate-based setting composition comprising 100 parts by weight of the tetracalcium phosphate particles as defined above in (i) and about 5 to about 80 parts by weight of an aqueous solution of an acid, calculated as an acid.

10 What are stated above in (i), (ii) and (iii) will be hereinafter referred to as "first invention".

The present inventors' additional research revealed the following. When an acidic aqueous solution predominantly containing citric acid and phosphoric acid is kneaded with
15 a powder mixture predominantly containing tetracalcium phosphate particles having a double structure (the term "double structure" used herein refers to a structure wherein the tetracalcium phosphate particles are coated with apatite or like substance which is harmless to the living body or
20 which has an affinity for the living body), the mixture can pronouncedly moderate or substantially solve the prior art problems.

In other words, according to the invention, there are also provided:

25 (i) a composition capable of forming a hardening material of

high strength, the composition comprising 100 parts by weight of a powder mixture predominantly containing tetracalcium phosphate particles coated with a substance which is harmless to the living body and which has an affinity for the living body, and about 5 to about 80 parts by weight, calculated as an acid, of an acidic aqueous solution predominantly containing citric acid and phosphoric acid; and

(ii) a composition capable of forming a hardening material of high strength as defined above in (i) in which the acidic aqueous solution is able to satisfy all the concentration relations given below

(a) $25\% \leq \text{citric acid} \leq 50\%$

(b) $30\% \leq \text{citric acid} + \text{phosphoric acid} \leq 70\%$

(c) $10\% \leq \text{citric acid} - \text{phosphoric acid} \leq 50\%$.

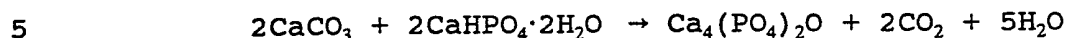
What are stated above in (i) and (ii) will be hereinafter referred to as "second invention".

The first and second inventions will be described below in greater detail.

I. First Invention

The tetracalcium phosphate for use in the first invention is not specifically limited, e.g. to those prepared by specific processes. A preferred tetracalcium phosphate is one which contains apatite, calcium oxide or the like in the smallest amount possible. Such high-purity

tetracalcium phosphate can be prepared as by a solid phase reaction method as represented below in which a CaCO_3 powder is admixed with a $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$ powder and the mixture is calcined.



For preparation of tetracalcium phosphate particles coated with apatite according to the invention, tetracalcium phosphate is pulverized to a desired particle size. The particle size of the powder is not specifically limited but desirably about $20 \mu\text{m}$ or less and about $5 \mu\text{m}$ on the average, for use as the powder for a setting composition.

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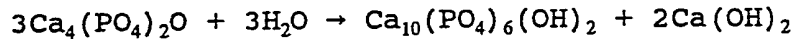
Next, the tetracalcium phosphate powder is subjected to hydration reaction. The hydration reaction proceeds merely by contact of the tetracalcium phosphate powder with water. Yet, to accelerate the reaction, the powder may be heated to a temperature of about 80 to about 100°C , preferably to about 95°C , or a reaction accelerator may be added. Useful reaction accelerators include organic acids such as citric acid, lactic acid, tartaric acid, succinic acid, etc.; salts thereof; inorganic acids such as hydrochloric acid, phosphoric acid, sulfuric acid, etc.; salts thereof; phosphate buffer solution and like pH adjusting agents for adjustment to neutrality or weak alkalinity; etc. These reaction accelerators are used in the form of an aqueous solution having a concentration of 1% or less. In the

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hydration reaction, apatite coating is formed on the surface of tetracalcium phosphate particles by the reaction as illustrated below:



5 Since apatite is highly stable in an alkaline aqueous solution, the water to be used in the reaction is preferably alkaline insofar as apatite coating can be formed. When the water to be used has a pH of 8 or less, octacalcium phosphate as well as apatite can be produced. Because
10 octacalcium phosphate is a precursor of apatite, the coating is not necessarily formed of a high-purity apatite. For example, even if the coating is formed of a mixture of apatite and octacalcium phosphate or of a high-purity octacalcium phosphate, no practical problem would occur. In
15 the above reaction, the calcium hydroxide is dissolved out in the water at the same time as the production of apatite, so that this eliminates the need to add a basic substance. Apatite coating can be satisfactorily produced even in an aqueous solution adjusted to alkalinity. On formation of
20 apatite coating, the reaction rate is rapidly decreased, and the surface of particles would not be activated without addition of water or an aqueous solution of an acid. Therefore the quality of tetracalcium phosphate particles is not impaired due to the excessive progress of reaction.

25 The hydration reaction can be effectively conducted by

other methods as listed below:

- (a) by contact of tetracalcium phosphate with steam;
- (b) by reaction at high temperatures utilizing the moisture in the atmosphere;
- 5 (c) by conducting a combination of the methods (a) and (b).

In the method (a), the treating time is substantially the same as in the treatment with water when the steam has a temperature of 100°C or less. At a temperature of 100°C or higher, the treating time is shortened as the temperature rises. For example, when steam of 300°C is blended in air with tetracalcium phosphate powder, the treating time is 1 to 120 seconds, preferably about 30 to about 60 seconds.

The method (b) is carried out utilizing the characteristic of tetracalcium phosphate which can be converted into apatite by its positive absorption of moisture in the atmosphere at a temperature of about 300 to about 1,200°C. For example, when air superheated to 500°C is blended with tetracalcium phosphate powder, the treating time is about 1 to about 120 seconds, preferably about 30 to about 60 seconds.

In the method (c), the surface treatment is effected while controlling the partial pressure of steam and the temperature in the atmosphere. In other words, the method (c) is a combination of methods (a) and (b). For example, when air of 350°C adjusted to a partial pressure of steam to

15 Torr is blended with tetracalcium phosphate powder, the treating time is about 1 to about 120 seconds, preferably about 30 to about 60 seconds.

5 A tetracalcium phosphate powder having a double structure can be effectively produced by the following methods without resort to hydration reaction.

- a) a method in which ultrafine apatite is adsorbed and fixed on the surface of tetracalcium phosphate particles; and
- b) a method in which apatite in a liquid form is adhered to
10 (or deposited on) and fixed on the surface of the tetracalcium phosphate particles.

These methods have the advantage that coating materials are not limited to apatite. Usable, in other words, is any material which can be gradually dissolved in an acidic
15 aqueous solution. For use as a biological material, it is desirable to use materials which are harmless to the living body (such as tricalcium phosphate, dicalcium phosphate dihydrate, etc.).

The tetracalcium phosphate-based setting composition
20 according to the first invention can be prepared by admixing the tetracalcium phosphate particles coated with apatite in the above manner with an aqueous solution of organic acid in an amount of about 5 to about 80%, calculated as an acid, based on the weight of the tetracalcium phosphate particles.
25 The tetracalcium phosphate particles coated with apatite

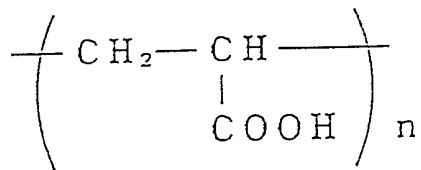
preferably have a particle size of about 20 μm or less and about 5 μm on the average.

Examples of useful organic acids are:

(a) citric acid, tartaric acid, malonic acid, malic acid, maleic acid, lactic acid, succinic acid, fumaric acid, ascorbic acid, gluconic acid, glutaric acid, pyruvic acid and like TCA cycle-type carboxylic acids;

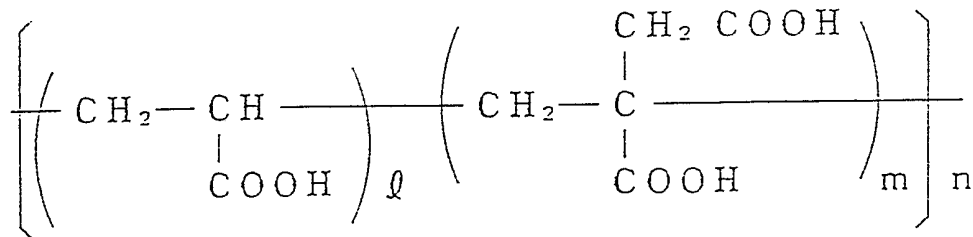
(b) phosphoric acid;

(c) homopolymers of acrylic acid represented by the formula



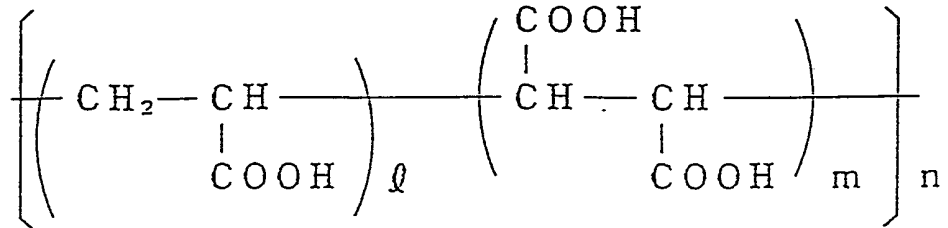
wherein n is 50 to 50,000;

(d) copolymers of acrylic acid and itaconic acid represented by the formula



wherein l is 5 to 10, m is 1 to 5 and n is 50 to 50,000;

(e) copolymers of acrylic acid and fumaric acid represented by the formula



wherein ℓ is 5 to 10, m is 1 to 5, and n is 50 to 50,000.

These acids are usable singly or at least two of them can be used in mixture. The acid is usually used in the form of an aqueous solution having the materials dissolved in pure water used as a solvent in a concentration of about 30 to about 70%.

The tetracalcium phosphate-based setting composition thus obtained can fully exhibit any of the inherent properties of tetracalcium phosphate not at an impaired level but an improved level unlike conventional setting compositions. Therefore these setting compositions are particularly useful as medical materials, dental materials and like biological materials.

II. Second Invention

The hardening material prepared by mixing the powder material and liquid material according to the second invention is equivalent or superior in properties to conventional biological materials, and also comparable or superior in physical and mechanical properties to hardening materials of known compositions having no affinity for the

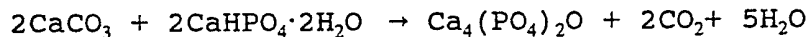
living body (such as zinc phosphate cement).

We discuss below in more detail the powder material and liquid material constituting the setting composition of the second invention and the process for preparing a hardening material.

A. Powder Material

The powder material for use in the second invention is tetracalcium phosphate particles coated with a material which is harmless to the living body and which has an affinity therefor.

A tetracalcium phosphate powder to be used can be prepared by any suitable process and is desirably a high-purity product (more preferably 98% or higher purity) having the lowest possible contents of apatite, calcium oxide and the like. Such high-purity tetracalcium phosphate can be prepared by a solid phase reaction method as illustrated below, as in the first invention, in which a mixture of CaCO_3 powder and $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$ powder is calcined:



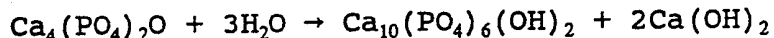
In the solid phase reaction method, a tetracalcium phosphate of higher quality can be obtained by adding an alumina powder (Al_2O_3) to tetracalcium phosphate, and heating the mixture to a sintered state (Japanese Unexamined Patent Publication No.180705/1990).

A tetracalcium phosphate powder having a double

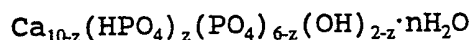
structure which is used in the second invention can be produced as follows. First a tetracalcium phosphate is pulverized to a desired particle size and classified. The particle size of tetracalcium phosphate particles for use herein may be varied according to a particular utility of the setting composition and is not specifically limited. It is preferred to adjust tetracalcium phosphate particles to a particle size of about 20 μm or less and about 5 μm on the average.

Subsequently a coating material lower in chemical activity than tetracalcium phosphate is applied to the surface of the above-obtained tetracalcium phosphate particles to form a coating thereon. The coating material is not specifically limited provided that it is stable in storage and is able to gradually dissolve or to release from the surface of tetracalcium phosphate particles on contact with the liquid material to be described below. The coating material for use in preparing medical materials, dental materials, etc. is required to be harmless to the living body or to have an affinity therefor. The surface of tetracalcium phosphate particles can be coated by methods not specifically limited. When apatite coating having an affinity for the living body is formed, a liquid-solid phase hydration reaction as represented below is carried out to obtain tetracalcium phosphate particles having a double

structure:



Apatite or hydroxyapatite which can be used in the invention include those having a chemical composition represented by the formula



wherein $n=0$ to 2.5 and $z=0$ to 1.

Also useful are apatites other than hydroxyapatite such as fluorine-containing apatite having OH group substituted by fluorine, carboxyapatite having OH group substituted by carbonate, etc. which can produce the same level of effect. The term "apatite" used herein includes these apatites.

The thickness of the apatite coating is not specifically limited, usually in the range of about 0.01 to about 1 μm .

B. Liquid Material

The liquid material for use in the second invention is an aqueous solution comprising citric acid and phosphoric acid which can satisfy all of the concentration relationships represented by:

(a) $25\% \leq \text{citric acid} \leq 50\%$

(b) $30\% \leq \text{citric acid} + \text{phosphoric acid} \leq 70\%$

(c) $10\% \leq \text{citric acid} - \text{phosphoric acid} \leq 50\%$

If citric acid or phosphoric acid is singly used, the desired result is not obtained, of course, in the invention.

Even if these two acids are used, the desired setting compositions can not be obtained unless the concentration relationships as shown above in (a) to (c) are completely fulfilled. In the case of not fulfilling them, the obtained
5 compositions can not give a hardening material having improved properties, or quickly set or are brought into sand-like or semi-dried clay-like state.

Given below are preferred concentration relationships of citric acid and phosphoric acid in the aqueous solution
10 as the liquid material:

(d) $35\% \leq \text{citric acid} \leq 45\%$

(e) $35\% \leq \text{citric acid} + \text{phosphoric acid} \leq 60\%$

(f) $20\% \leq \text{citric acid} - \text{phosphoric acid} \leq 45\%$

The most preferred concentration relationships of
15 citric acid and phosphoric acid in the aqueous solution are as follows:

(g) $37\% \leq \text{citric acid} \leq 42\%$

(h) $45\% \leq \text{citric acid} + \text{phosphoric acid} \leq 55\%$

(i) $23\% \leq \text{citric acid} - \text{phosphoric acid} \leq 42\%$

20 (j) $7\% \leq \text{phosphoric acid} \leq 15\%$

Insofar as citric acid and phosphoric acid in the aqueous solution satisfy all of the concentration relationships (a) to (c), the solution may incorporate therein up to 10% of at least one of other organic acids or
25 inorganic acids. Useful organic and inorganic acids are

hydrochloric acid, nitric acid, ascorbic acid, polycarboxylic acid, etc.

Optionally malic acid and/or lactic acid can partially replace citric acid (up to 40%) although the use thereof slightly deteriorates the properties of hardening material such as compressive strength, solubility in water, etc.

The phosphoric acid to be incorporated in the acidic aqueous solution is at least one acid selected from the group consisting of orthophosphoric acid, pyrophosphoric acid, polyphosphoric acid, metaphosphoric acid and phosphorus acid.

C. Process for Forming A Hardening Material

The setting composition according to the second invention can be prepared by admixing about 5 to about 80 parts, calculated as an acid, of the liquid material with 100 parts of the powder material immediately before use. The obtained setting composition is applied in the conventional manner to the affected part to be treated, as it is or, when required, as admixed with barium phosphate, calcium fluoride, X-ray contrast medium, other anti-fungus, medical materials, etc.

In this case, phosphoric acid is reacted with tetracalcium phosphate in the presence of citric acid, producing apatite and contributing to marked increase of strength. In conventional setting compositions, phosphoric

acid is present as a substance which is detrimental to the living body, and has been considered a minor component of biological compositions from biological, physical and mechanical viewpoints. In contrast, phosphoric acid exhibits a unique action in the second invention.

According to the first invention, the following remarkable results can be obtained.

(1) Apatite coating can be formed on the surface of tetracalcium phosphate particles by means of simple procedure without need for special apparatus.

(2) The tetracalcium phosphate particles coated with apatite remain stable in quality for an extended period and excellent in resistance to weathering and in storage properties.

(3) The apatite-coated tetracalcium phosphate particles have improved mechanical and physical properties while retaining the properties of tetracalcium phosphate as biological materials.

(4) Setting compositions having various setting properties can be obtained by adjusting the conditions for surface treatment and thus can be used for an extended range of applications of tetracalcium phosphate as biological materials.

According to the second invention, the following remarkable results can be achieved.

(1) The finally obtained hardening material is given pronouncedly enhanced mechanical and physical properties (compressive strength, setting time, film thickness, etc.) without being impaired in the excellent properties of tetracalcium phosphate as biological materials.

(2) The obtained setting composition gives hardening materials equivalent or superior in mechanical and physical properties to those formed from conventional biologically inactive setting compositions (such as zinc phosphate cement).

(3) The obtained setting composition provides a hardening material of high strength, and thus are usable for a wider range of applications as biological materials.

(4) Phosphoric acid which has found a narrow range of utility as biological materials in conventional materials specifically improves the properties of setting compositions due to the synergistic effect produced by conjoint use with citric acid.

(5) The obtained setting composition is set after a suitable period (neither too long nor too short), thereby facilitating the operation.

(6) The hardening material has a suitable hardness which leads to enhancement of operational efficiency.

Examples

Given below are Examples and Comparison Examples to

clarify the features of the invention in further detail.

Reference Example 1

Powdery CaCO_3 and $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$ having an average particle size of about $5 \mu\text{m}$ were mixed together in a Ca/P molar ratio of 2/1. The mixture was shaped and calcined in the atmosphere at 1600°C for 3 hours to obtain a sintered body. The sintered body was pulverized into particles having the maximum particle size of up to $20 \mu\text{m}$ and an average particle size of about $5 \mu\text{m}$, giving powdery tetracalcium phosphate.

The product obtained was subjected to X-ray diffractometry with the results shown in Fig. 1. The results of Table 1 show that the product obtained is a high-purity one substantially consisting of tetracalcium phosphate alone.

In the following examples, the high-purity tetracalcium phosphate thus obtained was used.

Example 1

A 20 g quantity of purified water heated to 95°C was added to 10 g of powdery tetracalcium phosphate. The resulting mixture was separated into seven portions to provide seven hermetically sealed samples. The samples were treated in a constant-temperature bath maintained at 95°C and withdrawn therefrom 1 hour, 3 hours, 24 hours, 7 days, 14 days, 30 days and 60 days after the initiation of the treatment, respectively. Each sample was dried at 105°C and the particles obtained were subjected to X-ray diffractometry.

metry. The results are shown with symbols A to G in Fig. 2.

The results A to G in Fig. 2 indicate that the tetracalcium phosphate was gradually transformed into hydroxyapatite and that the tetracalcium phosphate remained present even in hot water relatively stably for a prolonged period of time.

Example 2

A 2 g quantity of powdery tetracalcium phosphate was dispersed in 1 l of purified water and heated at 37°C and 95°C for 5 hours, respectively. The powder was separated by filtration and was dried by standing for 24 hours. The obtained powder was subjected to X-ray diffractometry.

The results of the X-ray diffraction are indicated at H and I in Fig. 3.

The results of Fig. 3 show that the tetracalcium phosphate obtained according to the present invention can be stably present in an excessive quantity of water.

Example 3

A 20 g quantity of purified water was added to 10 g of powdery tetracalcium phosphate. The resulting mixture was subjected to surface treatment under the conditions (temperature and time) as shown in Table 1 and separated by filtration. The cake was allowed to stand for drying for 24 hours, giving powder for setting composition. In Table 1, the figures 1 to 40 designate the sample numbers.

Thereafter an aqueous solution of citric acid at a concentration of 40% was mixed with the above powder to give setting compositions. The setting time of each composition was determined. The powder was mixed with the aqueous solution in a powder to liquid ratio of 2.3 g/ml.

Table 2 shows the results.

Table 1

Treatment Time	Treatment temperature			
	23°C	37°C	50°C	95°C
1 min	1	11	21	31
5 min	2	12	22	32
10 min	3	13	23	33
30 min	4	14	24	34
1 hr	5	15	25	35
3 hrs	6	16	26	36
6 hrs	7	17	27	37
12 hrs	8	18	28	38
24 hrs	9	19	29	39
72 hrs	10	20	30	40

Table 2

Sample No.	Setting time	
1	Within 20 sec	
2	Within 20 sec	
5	3	Within 20 sec
4	Within 20 sec	
5	30 sec	
6	1 min	
7	4 min 30 sec	
10	8	4 min 45 sec
9	6 min 15 sec	
10	7 min 50 sec	
11	Within 20 sec	
12	40 sec	
15	13	1 min 50 sec
14	3 min 45 sec	
15	4 min 30 sec	

Table 2 (continued)

Sample No.	Setting time
16	4 min 55 sec
17	5 min 10 sec
5 18	5 min 30 sec
19	6 min 45 sec
20	7 min 40 sec
21	Within 20 sec
22	30 sec
10 23	45 sec
24	2 min
25	4 min
26	4 min 20 sec
27	4 min 30 sec
15 28	4 min 40 sec
29	6 min
30	7 min 40 sec

Table 2 (continued)

Sample No.	Setting time
31	1 min 30 sec
32	2 min
33	4 min 45 sec
34	5 min 30 sec
35	5 min 40 sec
36	5 min 45 sec
37	5 min 50 sec
38	6 min
39	7 min 45 sec
40	11 min 15 sec

Example 4

A 100 g quantity of powdery tetracalcium phosphate was stirred for 3 hours in 200 g of distilled water heated to 95°C and the resulting mixture was subjected to filtration. The cake was dried at 105°C for 24 hours. The obtained powdery tetracalcium phosphate coated with apatite was mixed with aqueous solutions under the following conditions, giving setting compositions:

(a) the powder was mixed with an aqueous solution of 40% citric acid in a ratio of the powder/liquid = 2.4 (g/ml);

(b) the powder was mixed with an aqueous solution containing 40% citric acid and 5% polyacrylic acid in a ratio of powder/liquid = 2.2 (g/ml);

(c) the powder was mixed with an aqueous solution of 38%

citric acid, 1% tartaric acid and 2.5% polyacrylic acid in a ratio of powder/liquid = 2.2 (g/ml);

(d) the powder was mixed with an aqueous solution of 29% citric acid, 10% malonic acid and 2.5% polyacrylic acid in a ratio of powder/liquid = 2.3 (g/ml); and

(e) the powder was mixed with an aqueous solution of 40% citric acid and 20% phosphoric acid in a ratio of powder/liquid = 2.0 (g/ml).

The setting compositions thus obtained were tested for (1) setting time, (2) compressive strength after 24 hours (kgf/cm²) and (3) film thickness, all by the test methods according to JIS T6602.

Table 3 shows the results.

Table 3

Mixing conditions	(1)	(2)	(3)
(a)	6 min 30 sec	984	24 μm
(b)	6 min 30 sec	1239	29 μm
(c)	5 min 30 sec	1019	38 μm
(d)	5 min 30 sec	1123	25 μm
(e)	4 min 45 sec	1472	41 μm

Comparison Example 1

Setting compositions were prepared in the same manner as in Example 4 with the exception of using tetracalcium phosphate particles not surface treated.

Setting compositions were tested by the same methods as in Example 4 with the results shown below in Table 4. In Table 4, the symbols (a) to (e) and (1) to (3) have the same meaning as in Table 3.

5

Table 4

Mixing conditions	(1)	(2)	(3)
(a)	Within 30 sec	Impossible to measure	Impossible to measure
(b)	Within 30 sec	Impossible to measure	Impossible to measure
(c)	Within 30 sec	Impossible to measure	Impossible to measure
(d)	Within 30 sec	Impossible to measure	Impossible to measure
(e)	Within 30 sec	Impossible to measure	Impossible to measure

10

15

As clear from the results shown in Table 4, the compositions prepared under the same mixing conditions as in Example 4 are set within a very short period of time, i.e. are set substantially instantaneously, thus failing to obtain a soft setting composition which is easy to handle.

Comparison Example 2

20

Setting compositions were produced under the same mixing conditions as in Example 4 except that tetracalcium phosphate not surface treated were used and that an increased amount of the acidic aqueous solution was used to obtain setting compositions having physical properties which

can be measured.

The mixing conditions (f) to (j) in Table 5 are as follows.

5 (f) the aqueous solution (a) in Example 4 was mixed in a ratio of powder/liquid = 1.5 (g/ml)

(g) the aqueous solution (b) in Example 4 was mixed in a ratio of powder/liquid = 1.5 (g/ml)

(h) the aqueous solution (c) in Example 4 was mixed in a ratio of powder/liquid = 1.5 (g/ml)

10 (i) the aqueous solution (d) in Example 4 was mixed in a ratio of powder/liquid = 1.5 (g/ml)

(j) the aqueous solution (e) in Example 4 was mixed in a ratio of powder/liquid = 1.5 (g/ml)

Table 6 shows the results.

15

Table 5

Mixing conditions	(1)	(2)	(3)
(f)	4 min	593	46 μm
(g)	3 min 50 sec	612	52 μm
20 (h)	3 min 05 sec	623	73 μm
(i)	2 min 40 sec	671	107 μm
(j)	1 min 55 sec	819	113 μm

Example 5

25 Used as a powder material was a powdery tetracalcium phosphate (having a maximum particle size of 20 μm and an

average particle size of 5 μm) having a double structure wherein the surface of particles was coated with apatite by subjecting the tetracalcium phosphate to hydration reaction. Used as a liquid material was an acidic aqueous solution containing citric acid and phosphoric acid. Using these materials, a setting composition sample was obtained by mixing the powder material and the liquid material in a ratio of powder/liquid = 2.4 g/ml.

The concentrations of citric acid and phosphoric acid in the liquid material used for preparing the samples were as follows.

- No. 41 -- citric acid = 35%, orthophosphoric acid = 7%
- No. 42 -- citric acid = 40%, orthophosphoric acid = 5%
- No. 43 -- citric acid = 45%, orthophosphoric acid = 5%
- No. 44 -- citric acid = 40%, orthophosphoric acid = 10%
- No. 45 -- citric acid = 35%, orthophosphoric acid = 15%
- No. 46 -- citric acid = 40%, orthophosphoric acid = 15%
- No. 47 -- citric acid = 45%, orthophosphoric acid = 15%

The setting compositions thus obtained were tested for (1) setting time, (2) compressive strength (kgf/cm^2) after 24 hours and (3) film thickness, all by the test methods according to JIS T 6602.

Table 6 shows the results.

Table 6

	(1)	(2)	(3)
No. 41	6 min 10 sec	1130	20 μm
No. 42	5 min 50 sec	1231	21 μm
No. 43	4 min 45 sec	1339	27 μm
No. 44	5 min 20 sec	1828	22 μm
No. 45	5 min 10 sec	1243	30 μm
No. 46	4 min 50 sec	1619	24 μm
No. 47	4 min 5 sec	1283	23 μm

Example 6

10 Used as a powder material was a mixture of a 100-part
of the same apatite-coated, double-structured tetracalcium
phosphate particles as in Example 5, 25 parts of barium
sulfate (X-ray contrast medium) and 2.5 parts of calcium
fluoride (anti-fungus agent). The powder material was mixed
15 with an acidic aqueous solution containing citric acid and
phosphoric acid as a liquid material, giving a setting
composition sample.

 Given below are the concentrations of citric acid and
phosphoric acid in the liquid material, and the ratio of the
20 powdery/liquid employed for preparation of samples.

No. 48 -- citric acid = 42%, orthophosphoric acid = 10%
 ratio of powder/liquid = 2.5 g/ml

No. 49 -- citric acid = 41%, orthophosphoric acid = 11%
 ratio of powder/liquid = 2.6 g/ml

No. 50 -- citric acid = 38%, orthophosphoric acid = 8%
ratio of powder/liquid = 2.7 g/ml

The setting compositions thus obtained were tested for
(1) setting time, (2) compressive strength (kgf/cm²) after 24
5 hours and (3) film thickness in the same manner as in
Example 5.

Table 7 shows the results.

Table 7

	(1)	(2)	(3)
No. 48	4 min 30 sec	1654	30 μm
No. 49	4 min 40 sec	1792	29 μm
No. 50	4 min 20 sec	1823	30 μm

As clear from the results of Tables 6 and 7, the
setting time of the samples Nos. 41 to 50 is in an ideal
range of 4 to 8 minutes and the film thickness is about 30
15 μm, which means that the samples are neither too hard nor
too soft, hence are easy to handle.

Since the average compressive resistance of natural
bones is about 1500 kgf/cm², evidently the products of the
invention have a sufficient strength for use as their
20 substitutes.

Comparison Example 3

The same apatite-coated, double-structured powdery
tetracalcium phosphate as used in Example 5 as a powder

material was mixed with an acidic aqueous solution as a liquid material containing citric acid and phosphoric acid, giving a setting composition sample.

5 The concentrations of citric acid and phosphoric acid in the liquid material and the ratio of powder material to liquid material for preparation of samples were as follows.

No. 51 -- citric acid = 51%, phosphoric acid = 5%

powder/liquid ratio = 2.0 g/ml

No. 52 -- citric acid = 46%, phosphoric acid = 26%

10 powder/liquid ratio = 2.0 g/ml

No. 53 -- citric acid = 35%, phosphoric acid = 30%

powder/liquid ratio = 2.0 g/ml

No. 54 -- citric acid = 30%, phosphoric acid = 25%

powder/liquid ratio = 2.0 g/ml

15 No. 55 -- citric acid = 24%, phosphoric acid = 15%

powder/liquid ratio = 2.2 g/ml

No. 56 -- citric acid = 23%, phosphoric acid = 7%

powder/liquid ratio = 2.2 g/ml

No. 57 -- phosphoric acid = 10%

20 powder/liquid ratio = 2.4 g/ml

The setting compositions thus obtained were tested for (1) setting time, (2) compressive strength after 24 hours (kgf/cm²) and (3) film thickness in the same manner as in Example 5.

25 Table 8 shows the results.

Table 8

	(1)	(2)	(3)
No. 51	Less than 30 seconds	Impossible to measure	Impossible to measure
No. 52	Less than 30 seconds	Impossible to measure	Impossible to measure
No. 53	Less than 30 seconds	Impossible to measure	Impossible to measure
No. 54	Not set	Impossible to measure	Impossible to measure
No. 55	Not set	Impossible to measure	Impossible to measure
No. 56	Not set	Impossible to measure	Impossible to measure
No. 57	Not set	Impossible to measure	Impossible to measure

As clear from the results of Table 8, when the ratio of citric acid to phosphoric acid in a liquid material is outside the range specified in the invention, the obtained samples were set in an exceedingly short period of time, or were not cured, or were apparently set, but the hardening materials exhibited a fatal defect of, e.g. having substantially no mechanical strength, hence unsuited for use.

Comparison Examples 4 to 7

The following commercially available or known setting compositions for medical or dental use which consisted of powder material and liquid material were checked for physical properties in the same manner as in Example 5.

[Comparison Example 4]

* Apatite-coated commercially available product A:

powder material: α -tricalcium phosphate

liquid material: aqueous solution of organic high-
molecular weight acid

5 powder/liquid ratio = 1.3 g/g

[Comparison Example 5]

* Product disclosed in Japanese Unexamined Patent Publica-
tion No. 72363/1987:

powder material: tetracalcium phosphate

10 liquid material: aqueous solution of citric acid

powder/liquid ratio = 2.0 g/g

[Comparison Example 6]

* Product disclosed in Japanese Unexamined Patent Publica-
tion No. 176252/1989:

15 powder material: tetracalcium phosphate + dibasic
calcium phosphate

liquid material: aqueous solution of phosphoric acid

powder/liquid ratio = 3.8 g/g

[Comparison Example 7]

20 * Product disclosed in Japanese Unexamined Patent Publica-
tion No. 100049/1989

powder material: α -tricalcium phosphate + tetracalcium
phosphate

liquid material: aqueous solution of a mixture of citric

25 acid, saccharose and chitosan

powder/liquid ratio = 2.0 g/g

The setting compositions thus obtained were tested for (1) setting time, (2) compressive strength after 24 hours (kgf/cm²) and (3) film thickness in the same manner as in

5 Example 5.

Table 9 shows the results.

Table 9

Comp. Ex.	(1)	(2)	(3)
5	6 min 10 sec	541	20 μm
6	2 min 50 sec	910	57 μm
7	35 min	342	22 μm
8	8 min 50 sec	623	39 μm

10

15

20

As clear from the results of Table 9, none of the obtained products had all of the following properties, namely an appropriate setting time (preferably about 2 to about 10 minutes), a compressive strength sufficient for use as substitutes for bones, teeth and the like (preferably 1000 kgf/cm² or higher), a softness which facilitates handling (preferably film thickness up to 30 μm) and like properties. In general, when any of the products was outstanding in a specific property, but poor in other properties.

Reference Example 2

25

Fig. 4 graphically represents the relationships in quantity between citric acid and phosphoric acid in the

liquid material for setting compositions of the invention,
more specifically the relationship therebetween which
results in improvement of properties (the range according to
the invention), the relationship therebetween which results
5 in increase of compressive strength (more preferred range
according to the invention), and the relationship there-
between which results in highest degree of increase of
compressive strength (most preferred range according to the
invention).

10 The area surrounded by the outermost line indicates the
ordinary range of the invention, the area surrounded by the
intermediate line indicates the preferred range of the
invention and the area surrounded by the innermost line
indicates the most preferred range of the invention.

15 Example 7

The same procedure as in Example 5 was repeated with
the exception of using citric acid and phosphoric acids in
the following ratios, giving setting compositions wherein
the ratio of powder/liquid was 2.4 g/ml.

20 No. 58 -- citric acid = 40%, pyrophosphoric acid = 10%

No. 59 -- citric acid = 40%, polyphosphoric acid = 10%

No. 60 -- citric acid = 40%, metaphosphoric acid = 10%

No. 61 -- citric acid = 40%, phosphorous acid = 10%

The setting compositions thus obtained were tested for
25 (1) setting time, (2) compressive strength (kgf/cm²) after 24

hours and (3) film thickness (μm), in the same manner as in Example 5.

Table 11 shows the results.

Table 10

	Setting time	Compressive strength	Thickness	
5	No. 58	5 min 10 sec	1750	25
	No. 59	5 min 15 sec	1782	27
	No. 60	5 min 45 sec	1611	28
	No. 61	6 min 10 sec	1815	21

Example 8

10 Setting compositions were prepared in the same manner as in Example 5 except that citric acid and phosphoric acids were used in the following ratios and that the ratios of powder/liquid were as follows.

15 No. 62 -- citric acid = 25%, orthophosphoric acid = 5%
 powder/liquid ratio = 3.0 g/ml

 No. 63 -- citric acid = 45%, phosphorous acid = 25%
 powder/liquid ratio = 1.0 g/ml

 No. 64 -- citric acid = 30%, phosphorous acid = 20%
 powder/liquid ratio = 2.2 g/ml

20 No. 65 -- citric acid = 48%, orthophosphoric acid = 5%
 powder/liquid ratio = 2.0 g/ml

 The setting compositions thus obtained were tested for (1) setting time, (2) compressive strength (kgf/cm^2) after 24

hours and (3) film thickness (μm), in the same manner as in Example 5.

Table 11 shows the results.

Table 11

	Setting time	Compressive strength	Thickness
No. 62	7 min 30 sec	1186	11
No. 63	7 min 50 sec	1027	12
No. 64	6 min 15 sec	1250	24
No. 65	4 min 10 sec	1247	26

5

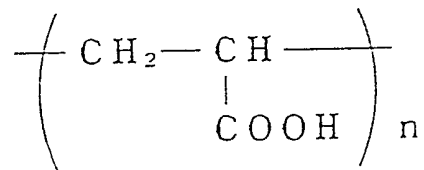
CLAIMS:

1. Tetracalcium phosphate particles coated with apatite.

2. A process for preparing tetracalcium phosphate particles coated with apatite, the process comprising
5 subjecting tetracalcium phosphate particles to hydration reaction.

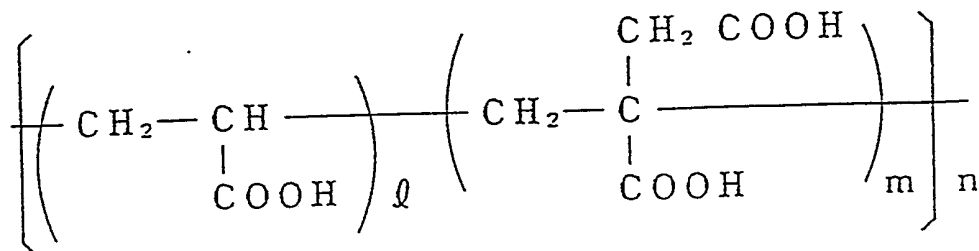
3. A tetracalcium phosphate-based setting composition comprising 100 parts by weight of the tetracalcium phosphate particles as defined in claim 1 and about 5 to about 80
10 parts by weight of an aqueous solution of an acid, calculated as an acid.

4. A setting composition according to claim 3 wherein the aqueous solution of acid contains about 30 to about 70%
15 of at least one acid selected from the group consisting of:
(a) TCA cycle-type carboxylic acids;
(b) phosphoric acid;
(c) homopolymers of acrylic acid represented by the formula

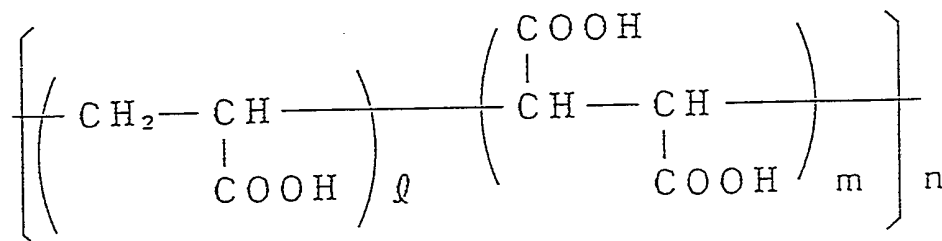


wherein n is 50 to 50,000;

20 (d) copolymers of acrylic acid and itaconic acid represented by the formula



wherein l is 5 to 10, m is 1 to 5 and n is 50 to 50,000; and
 (e) copolymers of acrylic acid and fumaric acid represented
 by the formula



wherein l is 5 to 10, m is 1 to 5, and n is 50 to 50,000.

5 5. A composition for forming a hardening material of
 high strength, the composition comprising 100 parts by
 weight of a powder mixture predominantly containing
 tetracalcium phosphate particles coated with a substance
 which is harmless to the living body and which has an
 10 affinity for the living body, and about 5 to about 80 parts
 by weight, calculated as an acid, of an acidic aqueous
 solution predominantly containing citric acid and phosphoric
 acid.

15 6. A composition according to claim 5 wherein the
 acidic aqueous solution comprising citric acid and
 phosphoric acid as the main components which satisfies all

the concentration relationships given below:

(a) $25\% \leq \text{citric acid} \leq 50\%$

(b) $30\% \leq \text{citric acid} + \text{phosphoric acid} \leq 70\%$

(c) $10\% \leq \text{citric acid} - \text{phosphoric acid} \leq 50\%$

5 7. A composition according to claim 5 wherein the phosphoric acid in the acidic aqueous solution is at least one acid selected from the group consisting of orthophosphoric acid, pyrophosphoric acid, polyphosphoric acid, metaphosphoric acid and phosphorus acid.

10 8. A composition according to claim 5 wherein the citric acid and phosphoric acid in the aqueous solution satisfy the concentration relationships represented by:

(d) $35\% \leq \text{citric acid} \leq 45\%$

(e) $35\% \leq \text{citric acid} + \text{phosphoric acid} \leq 60\%$

15 (f) $20\% \leq \text{citric acid} - \text{phosphoric acid} \leq 45\%$

9. A composition according to claim 5 wherein the citric acid and phosphoric acid in the aqueous solution satisfy the concentration relationships represented by:

(g) $37\% \leq \text{citric acid} \leq 42\%$

20 (h) $45\% \leq \text{citric acid} + \text{phosphoric acid} \leq 55\%$

(i) $23\% \leq \text{citric acid} - \text{phosphoric acid} \leq 42\%$

(j) $7\% \leq \text{phosphoric acid} \leq 15\%$

25 10. A composition according to claim 5 wherein the acidic aqueous solution contains up to 10% of at least one acid selected from the group consisting of hydrochloric

acid, nitric acid, ascorbic acid and polycarboxylic acid.

11. A composition according to claim 5 wherein the coating having an affinity for the living body is formed of apatite.

5 12. A composition according to claim 5 wherein the apatite coating has a thickness of about 0.01 to about 1 μm .