

DESCRIPTION

Agent for Preventing, Improving or Treating Phosphorus-
related Disorder, Oral Preparation for Adsorbing
5 Phosphate Ions in Foods and Beverages or Pharmaceuticals
and Process for Production Thereof

TECHNICAL FIELD

[0001]

The present invention relates to agents and oral
10 preparations capable of efficiently adsorbing phosphate
ions for which excessive intake causes problems. More
specifically, the present invention relates to (1) agents
for preventing, improving or treating organ disorders due
to phosphorus, which are capable of improving blood
15 concentrations of phosphorus of patients with kidney
failures and controlling accumulations of phosphorus in
the body and (2) oral preparations for preventing various
diseases related to phosphorus, which are capable of
eliminating problems with excessive intake of phosphorus
20 from foods and beverages or the like.

BACKGROUND ART

[0002]

Phosphorus is an essential substance for living
organisms. Man decomposes foods into phosphate ions
25 throughout the digestive tract (small intestine, in
particular) and subsequently absorbed. The average
Japanese adult has a daily phosphorus intake of
approximately 1,000 mg. It is reported that, for a
normal person, approximately 80% of such phosphorus is
30 absorbed and approximately 80% of that absorbed portion
is excreted by the kidney. If the kidney dysfunctions
(renal failure), phosphorus excretion decreases and
causes an increased serum phosphorus concentration (a
hyperphosphatemia). A healthy human maintains a
35 phosphorus serum concentration range of 0.25 to 4.5

mg/dl; concentrations at or over 4.5 mg/dl are defined as hyperphosphatemia.

[0003]

Hyperphosphatemia induces abnormal calcium metabolism
5 and/or hyperparathyroidism and causes modifications of
the bones throughout the body (renal osteodystrophy)
and/or calcium deposits formed in various organs -
especially to the cardiac valves, aortae, lungs and the
like (heterotopic calcinosis). Such disorders not only
10 impair the QoL (quality of life) of patients with renal
failures but also cause fatal complications such as
cardiac infarction and exacerbating life prognoses.
Furthermore, hyperphosphatemia is known to be a promoting
factor of renal disorders. Thus, the ability to maintain
15 a normal (healthy) phosphorus blood concentration is a
crucial problem for patients with renal failures.

[0004]

As described above, the absolute amount of phosphorus
that the kidney can excrete will decrease under renal
20 failure. Hence, under renal failure, when the amount of
phosphorus absorbed via the digestive tract exceeds the
capacity of the kidney, phosphorus will accumulate in the
body. As such, the standard treatment for patients with
kidney failures has been to limit the total amount of
25 phosphorus absorbed through the digestive tract; an
amount that may not exceed the capacity of the kidney.
In addition to alimentary therapy through phosphorus
restricting diet, phosphorus adsorbents (agents capable
of reducing the amount of absorbed phosphorus by
30 adsorbing phosphate ions generated from foods in the
digestive tract, especially in the small intestine and
excreting them directly with stool) have been used in
combination for renal failure treatment (Patent
References 1 to 4, for example).

35 [0005]

However, phosphorus adsorbents, which have been put into practical use or which are under review for clinical applications, suffer from such disadvantages as described below.

5 [0006]

Firstly, aluminum preparations (aluminum hydroxide gels) are highly adsorptive to phosphate ions in the digestive tract and reduce phosphorus serum concentration. However, aluminum - once absorbed through the digestive
10 tract - will not be excreted outside the body and can cause aluminum poisoning due to the accumulation of aluminum in the body (aluminum encephalopathy, aluminum osteopathy and anemia). For this reason, administration of the aluminum preparations has been contraindicated for
15 dialysis patients in our nation (Japan) since June, 1992. [0007]

Secondly, calcium preparations (such as calcium carbonate and calcium acetate) are still widely used in place of aluminum preparations. However, they too have
20 disadvantages such as they require large doses to improve hyperphosphatemia and they are usually regarded as distasteful and hard to be taken; furthermore, calcium is in turn absorbed through the digestive tract and can cause hypercalcemia which may bring about additional
25 exacerbations such as heterotopic calcification. [0008]

Thirdly, novel substances have been introduced in recent years as phosphorus adsorbents and are now under review for use. One of them, known as Sevelamer HCl™, is
30 a polymer of prop-2-en-1-amine and 1-chloro-2,3-epoxypropane in the hydrochloride form. Sevelamer HCl™ is a phosphorus binding polymer developed in the United States, and approved in Japan in January, 2003 and currently used. However, this agent often needs to be
35 administered in large doses in order to improve

hyperphosphatemia. In addition, there are still a number of problems yet to be solved such as frequent complications with the digestive tract (i.e. constipation). Another reagent, lanthanum carbonate, is under review for use in the United States and Europe. Since the influences of lanthanum on living organisms are not yet sufficiently understood, which may have similar problems as aluminum preparations, its practical application appears very questionable.

10 Patent Reference 1: Japanese Unexamined Patent Publication No. 1990-77266

 Patent Reference 2: Japanese Unexamined Patent Publication No. 1991-182259

15 Patent Reference 3: Japanese Unexamined Patent Publication No. 1995-2903

 Patent Reference 4: PCT Publication WO 01/66607

DISCLOSURE OF THE INVENTION

PROBLEMS TO BE SOLVED BY THE INVENTION

[0009]

20 Further, since 1999, various iron compounds (stabilized polynuclear iron hydroxide, iron(3)-saccharide complex, iron(3)-sucrose complex, ferric polymaltose complex, ferric citrate) have been under review for use as phosphorus adsorbents. However, these iron compounds suffer from the disadvantages that they are insufficient in phosphorus adsorptive power and need to be administered in large doses in order to improve hyperphosphatemia, as in the case of calcium carbonate and Sevelamer HCl™. These iron substances do not accumulate in the body (iron poisoning) differently from aluminum gel and do not create serious digestive tract complications differently from Sevelamer HCl, when clinically applied. As such, focusing attention on iron compounds having such advantages, the first object of the present invention is to provide agents for preventing,

35

improving or treating phosphorus-related disorders;
agents which are biostable and more potent, by enhancing
phosphorus adsorptive power of the iron compounds to the
degrees equal to or higher than that of conventional
5 adsorbents.

[0010]

In addition, when phosphorus-containing foods,
beverages are taken in large quantities or phosphate-
containing agents are taken, high phosphate ions will
10 emerge through the digestive tract. The large quantities
of phosphoric acid produced in the digestive tract will
then be absorbed in large quantities through the mucosa
of the digestive tract and, when the excretion capacity
of the kidney becomes exceeded, phosphorus can start
15 accumulating in the body; a condition resulting in the
phosphorus-related disorders previously described above.
As such, it is a second object of the present invention
to provide oral preparations (food and beverage additives,
food and beverage adjuvants, pharmaceutical additives or
20 pharmaceutical adjuvants, for example) having as an
active principle an iron compound with high adsorptive
power to phosphate ions that are effective in preventing
various diseases directly or indirectly related to
phosphate ions by adsorbing phosphate ions produced by
25 digestion and decomposition of foods and beverages or
pharmaceuticals.

MEANS FOR SOLVING THE PROBLEMS

[0011]

The present invention (1) is an agent for preventing,
30 improving or treating a phosphorus-related disorder,
which contains ferric hydroxide as produced under such
conditions that a ferrous species is present.

[0012]

The present invention (2) is the agent for preventing,
35 improving or treating a phosphorus-related disorder

according to the invention (1) wherein the ferric hydroxide is produced by adding to an aqueous solution of ferrous iron an oxidizing agent in an amount less than the equivalent amount of the ferrous iron and then adding
5 an alkali in such a manner that its pH at the end of the reaction may be adjusted in the range of 1.5 to 5.5 (preferably 1.5 to 4.0 and more preferably 2.0 to 3.5).
[0013]

The present invention (3) is the agent for preventing,
10 improving or treating a phosphorus-related disorder according to the invention (1) wherein the ferric hydroxide is produced by adding an oxidizing agent to an aqueous solution of ferrous iron in such a manner that its redox potential may be brought in the range of +400
15 to 770 mV (preferably +500 to 730 mV and more preferably +600 to 700 mV) and then adding an alkali in such a manner that its pH at the end of the reaction may be adjusted in the range of 1.5 to 5.5 (preferably 1.5 to 4.0 and more preferably 2.0 to 3.5).
20 [0014]

The present invention (4) is the agent for preventing, improving or treating a phosphorus-related disorder according to the invention (1) wherein the ferric hydroxide is produced by adding to an aqueous solution of
25 ferrous iron an oxidizing agent in an amount less than the equivalent amount of the ferrous iron in such a manner that its redox potential may be brought in the range of +400 to 770 mV and then adding an alkali in such a manner that its pH at the end of the reaction may be
30 adjusted in the range of 1.5 to 5.5.
[0015]

The present invention (5) is the agent for preventing, improving or treating a phosphorus-related disorder according to any one of the inventions (2) to (4) wherein
35 the oxidizing agent is a hypochlorite.

[0016]

The present invention (6) is the agent for preventing, improving or treating a phosphorus-related disorder according to any one of the inventions (1) to (5) wherein
5 the ferric hydroxide is amorphous.

[0017]

The present invention (7) is the agent for preventing, improving or treating a phosphorus-related disorder according to any one of the inventions (1) to (6) further
10 including glycerin.

[0018]

The present inventions (8) is the agent for preventing, improving or treating a phosphorus-related disorder according to any one of the inventions (1) to
15 (7) wherein the disorder is hyperphosphatemia.

[0019]

The present invention (9) is a process for producing an agent for preventing, improving or treating a phosphorus-related disorder, the agent containing ferric
20 hydroxide, which comprises the steps of adding to an aqueous solution of ferrous iron an oxidizing agent in an amount less than the equivalent amount of the ferrous iron and then adding an alkali in such a manner that its pH may be adjusted in the range of 1.5 to 5.5 (preferably
25 1.5 to 4.0 and more preferably 2.0 to 3.5).

[0020]

The present invention (10) is a process for producing an agent for preventing, improving or treating a phosphorus-related disorder, the agent containing ferric
30 hydroxide, which comprises the steps of adding an oxidizing agent to an aqueous solution of ferrous iron in such a manner that its redox potential may be brought in the range of +400 to 770 mV (preferably +500 to 730 mV and more preferably +600 to 700 mV) and then adding an
35 alkali in such a manner that its pH may be adjusted in

the range of 1.5 to 5.5 (preferably 1.5 to 4.0 and more preferably 2.0 to 3.5).

[0021]

The present invention (11) is a process for producing
5 an agent for preventing, improving or treating a
phosphorus-related disorder, the agent containing ferric
hydroxide, which comprises the steps of adding to an
aqueous solution of ferrous iron an oxidizing agent in an
amount less than the equivalent amount of the ferrous
10 iron in such a manner that its redox potential may be
brought in the range of +400 to 770 mV (preferably +500
to 730 mV and more preferably +600 to 700 mV) and then
adding an alkali in such a manner that its pH may be
adjusted in the range of 1.5 to 5.5 (preferably 1.5 to
15 4.0 and more preferably 2.0 to 3.5).

[0022]

The present invention (12) is the process according
to any one of the inventions (9) to (11) wherein the
oxidizing agent is a hypochlorite.

20 [0023]

The present invention (13) is the process according
to any one of the inventions (9) to (12) wherein the
ferric hydroxide is amorphous.

[0024]

25 The present invention (14) is the process according
to any one of the inventions (9) to (13) further
including the step of adding glycerin.

[0025]

The present invention (15) is the process according
30 to any one of the inventions (9) to (14) further
including the step of dehydration, freeze-drying or
spray-drying.

[0026]

The present invention (16) is the process according
35 to the invention (15) wherein, after the step for pH

adjustment, the step of adding glycerin is performed before, during or after the step of dehydration, freeze-drying or spray-drying.

[0027]

5 The present invention (17) is the process according to any one of the inventions (9) to (16) wherein the disorder is hyperphosphatemia.

[0028]

10 The present invention (18) is an oral preparation for adsorbing phosphate ions in foods and beverages or pharmaceuticals, which contains ferric hydroxide as produced under such conditions that a ferrous species is present.

[0029]

15 The present invention (19) is the oral preparation according to the invention (18) wherein the ferric hydroxide is produced by adding to an aqueous solution of ferrous iron an oxidizing agent in an amount less than the equivalent amount of the ferrous iron and then adding
20 an alkali in such a manner that its pH at the end of the reaction may be adjusted in the range of 1.5 to 5.5 (preferably 1.5 to 4.0 and more preferably 2.0 to 3.5).

[0030]

25 The present invention (20) is the oral preparation according to the invention (18) wherein the ferric hydroxide is produced by adding an oxidizing agent to an aqueous solution of ferrous iron in such a manner that its redox potential may be brought in the range of +400 to 770 mV (preferably +500 to 730 mV and more preferably
30 +600 to 700 mV) and then adding an alkali in such a manner that its pH at the end of the reaction may be adjusted in the range of 1.5 to 5.5 (preferably 1.5 to 4.0 and more preferably 2.0 to 3.5).

[0031]

35 The present invention (21) is the oral preparation

according to the invention (18) wherein the ferric hydroxide is produced by adding to an aqueous solution of ferrous iron an oxidizing agent in an amount less than the equivalent amount of the ferrous iron in such a manner that its redox potential may be brought in the range of +400 to 770 mV (preferably +500 to 730 mV and more preferably +600 to 700 mV) and then adding an alkali in such a manner that its pH at the end of the reaction may be adjusted in the range of 1.5 to 5.5 (preferably 1.5 to 4.0 and more preferably 2.0 to 3.5).

[0032]

The present invention (22) is the oral preparation according to any one of the inventions (19) to (21) wherein the oxidizing agent is a hypochlorite.

[0033]

The present invention (23) is the oral preparation according to any one of the inventions (18) to (22) wherein the ferric hydroxide is amorphous.

[0034]

The present invention is the oral preparation according to any one of the inventions (18) to (23) further including glycerin.

[0035]

The present invention (25) is the oral preparation according to any one of the inventions (18) to (24) which is a food and beverage additive, food and beverage adjuvant, pharmaceutical additive or pharmaceutical adjuvant.

[0036]

The present invention (26) is a process for producing an oral preparation for adsorbing phosphate ions in foods and beverages or pharmaceuticals, the preparation containing ferric hydroxide, which comprises the steps of adding to an aqueous solution of ferrous iron an oxidizing agent in an amount less than the equivalent

amount of the ferrous iron and then adding an alkali in such a manner that its pH may be adjusted in the range of 1.5 to 5.5 (preferably 1.5 to 4.0 and more preferably 2.0 to 3.5).

5 [0037]

The present invention (27) is a process for producing an oral preparation for adsorbing phosphate ions in foods and beverages or pharmaceuticals, the preparation containing ferric hydroxide, which comprises the steps of
10 adding an oxidizing agent to an aqueous solution of ferrous iron in such a manner that its redox potential may be brought in the range of +400 to 770 mV (preferably +500 to 730 mV and more preferably +600 to 700 mV) and then adding an alkali in such a manner that its pH may be
15 adjusted in the range of 1.5 to 5.5 (preferably 1.5 to 4.0 and more preferably 2.0 to 3.5).

[0038]

The present invention (28) is a process for producing an oral preparation for adsorbing phosphate ions in foods
20 and beverages or pharmaceuticals, which comprises the steps of adding to an aqueous solution of ferrous iron an oxidizing agent in an amount less than the equivalent amount of the ferrous iron in such a manner that its redox potential may be brought in the range of +400 to
25 770 mV (preferably +500 to 730 mV and more preferably +600 to 700 mV) and then adding an alkali in such a manner that its pH may be adjusted in the range of 1.5 to 5.5 (preferably 1.5 to 4.0 and more preferably 2.0 to 3.5).

30 [0039]

The present invention (29) is the process according to any one of the inventions (26) to (28) wherein the oxidizing agent is a hypochlorite.

[0040]

35 The present invention (30) is the process according

to any one of the inventions (26) to (29) wherein the ferric hydroxide is amorphous.

[0041]

The present invention (31) is the process according
5 to any one of the inventions (26) to (30) further including the step of adding glycerin.

[0042]

The present invention (32) is the process according
to any one of the inventions (26) to (31) further
10 including the step of dehydration, freeze-drying or spray-drying.

[0043]

The present invention (33) is the process according
to the invention (32) wherein, after the step for pH
15 adjustment, the step of adding glycerin is performed before, during or after the step of dehydration, freeze-drying or spray-drying.

[0044]

The present invention (34) is the process according
20 to any one of the inventions (26) to (33) wherein the oral preparation is a food and beverage additive, food and beverage adjuvant, pharmaceutical additive or pharmaceutical adjuvant.

[0045]

25 Terms as used herein will now be defined. The term "ferrous species" refers to a substance in which iron is present as having a valence of two, such as a ferrous ion or ferrous compound (ferrous hydroxide, for example). The term "aqueous solution of ferrous iron" is not
30 particularly limited as long as it is an aqueous solution in which ferrous ions are present and may contain other substances. The term "oxidizing agent" is not particularly limited, examples of which may include hypochlorites, hydrogen peroxide and calcium
35 hydroperoxide, hypochlorites being preferred. The term

"phosphorus-related disorder" refers to a disorder affecting various organs due to an excessive accumulation of phosphorus in the body, often attributable to chronic renal failures. Examples of such diseases and symptoms may include osteopathy, calcium deposits to the organs, such as the heart, aortae and lungs, anemia and secondary hyperparathyroidism. The term "agent for preventing, improving or treating a phosphorus-related disorder" refers to an agent to be used for the purpose of at least one of prevention, improvement and treatment. The term "oral preparation" is not particularly limited as long as it is orally administered, including one to be added to foods or beverages (food and beverage additive), one to be taken separately from foods or beverages (food and beverage adjuvant such as supplement), one to be added to pharmaceuticals (pharmaceutical additive) and one to be taken separately from pharmaceuticals (pharmaceutical adjuvant).

BEST MODE FOR CARRYING OUT THE INVENTION

[0046]

A best mode of the present invention will be described below. The agent for preventing, improving or treating a phosphorus-related disorder and the oral preparation for adsorbing phosphate ions in foods and beverages or pharmaceuticals differ partly in terms of use (sharing a common purpose of preventing phosphorus-related disorders) but share a common ingredient (phosphate adsorbent). Therefore, description will be made first on the phosphorus adsorbent and then on the respective uses in detail.

[0047]

The present phosphorus adsorbent includes amorphous ferric hydroxide as produced under such conditions that a ferrous species (ferrous hydroxide, for example) is present. Although the active ingredient exhibiting a

high phosphorus adsorptive power is amorphous ferric hydroxide, not any ferric hydroxide can achieve such an effect. For example, ferric hydroxide produced by adding caustic soda to a solution of ferric iron or commercially available ferric hydroxide will not exhibit such a high phosphorus adsorptive power (see Examples). On the basis of Eh (redox potential) vs pH charts for Fe^{2+} - $\text{Fe}(\text{OH})_3$ systems, the present ferric hydroxide is produced under extremely unstable conditions where iron ions are present as ferric ions while remaining under Eh vs pH conditions where they remain as ferrous iron when they are present as stable chemical species. The present ferric hydroxide therefore includes ferrous iron in ferric hydroxide in the produced precipitate and is in an unstable and extremely high amorphous state. The present ferric hydroxide is therefore characterized in that the bond - Fe-O-Fe-O-Fe- is unstable and easily cleaved and it is presumed that newly produced Fe-OH groups react with phosphate ions and the like while bonds are cleaved, exhibiting remarkably high adsorptive power.

[0048]

The chemical structure of ferric hydroxide is unclear. On the basis of experimentation results and the like, however, it has presumably the structure as described below (the ferric hydroxide according to the present invention is not, however, limited to such a presumed formation). Specifically, the present ferric hydroxide essentially contains ferric iron and has oxygen atoms or hydroxyl groups that are hexacoordinated to iron atoms so that the hexacoordinated irons are presumably linked via oxygen atoms. It is then presumed that certain water molecules present around such iron atoms will have some influence on the bond between the iron atoms and the oxygen atoms, consequently destabilizing the bond. It is then believed that, as a result of replacement of the

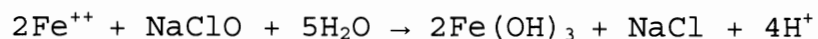
hydroxyl groups or the destabilized oxygen atoms coordinated to the iron atoms with anions (phosphate ions, for example) the iron atoms will bond with those anions (phosphate ions). Under such assumption, a preferred
5 formation is one in which -Fe-O-Fe-O-Fe- (cluster) has a moderate size due to the presence of moderate hydroxyl groups.

[0049]

In a process for producing the present phosphorus
10 adsorbent, ferrous iron is reacted with an oxidizing agent (sodium hypochlorite, for example) to obtain ferric hydroxide as described below. The reaction scheme for such a redox reaction is shown below, wherein ferric hydroxide is abbreviated as "Fe(OH)₃" for ease of
15 understanding.

Formula 1

[0050]



[0051]

20 As shown above, one mole of hypochlorite reacts with two moles of ferrous iron (in other words, one mole of hypochlorite is equivalent in amount to two moles of ferrous iron). In the process for production, such conditions are then established that the ferrous iron may
25 not completely be oxidized into the ferric iron by reducing the amount of the oxidizing agent to less than the equivalent amount of the ferrous iron (to less than one mole of hypochlorite, in the case of two moles of ferrous iron, for example) as described below.

30 [0052]

The term such as "amorphous" or "extremely high in amorphousness" means that X-ray powder diffraction using K α ray of Cu as an X-ray source shows at least one non-crystalline halo pattern in the range of 5° to 80° by 2 θ
35 value, with no apparent crystalline peaks. Slight

crystalline peaks may be observed in non-crystalline halo patterns depending on starting materials or the like during production. In such cases, the crystalline peak intensities observed in the range of 5° to 80° by 2θ value in X-ray powder diffraction using $K\alpha$ ray of Cu as an X-ray source may be allowed if they are at or below 5% in relation to crystalline peaks for a corresponding crystalline reference material (% X-ray diffraction intensity/reference material). Specific % X-ray diffraction intensity/reference materials which may be used include those given by the formula below in accordance with ASTM (American Society for Testing and Materials) D3906. The number of crystalline peaks used for calculation of integrated reflection intensities is not particularly limited, but is preferably in the range of 1 to 8.

Formula 2

[0053]

$$(\% \text{ X-ray diffraction intensity/reference material}) = \{ (S_X) / (S_R) \} \times 100$$

wherein S_X represents an integrated reflection intensity of a sample, and

S_R represents an integrated reflection intensity of a reference material.

[0054]

Thus, although the active ingredient is ferric hydroxide, ferrous species are inevitably contained since the production is performed under such conditions that ferrous species (ferrous hydroxide, for example) are present. The content of such ferrous species (ferrous hydroxide, for example) is not particularly limited and usually 5% by weight or less, preferably from 0.01 to 4% by weight and more preferably from 0.1 to 2% by weight on the basis of dry weight (furnace-dried at 105°C for 2 h). The ferrous species are inevitably contained during

production and such ingredients may, however, be removed by washing.

[0055]

Further, the present phosphorus adsorbent may contain
5 crystalline ferric hydroxide as long as amorphous ferric hydroxide as the active ingredient is present. In such cases, the amorphous ingredient comprises preferably 30% or more, more preferably 50% or more and even more preferably 75% or more.

10 [0056]

It is preferred that the present phosphorus adsorbent further contains glycerin. Depending on the method of drying or aging (extended storage), the ferric hydroxide causes its OH groups attached to irons of -Fe-O-Fe-O-Fe-
15 to be dehydrated and assumes a stable condition through growth of clusters or otherwise, possibly decreasing its adsorptive power. Therefore, admixing glycerin to wetted ferric hydroxide makes it difficult for dehydration of OH groups to occur even when it gets dry so that a decrease
20 in adsorptive power may remarkably be inhibited. The content of glycerin is preferably 20% by weight or less on the basis of dry weight (furnace-dried at 105°C for 2 h).

[0057]

25 A process for producing the phosphorus adsorbent according to the best mode will then be described. The present phosphorus adsorbent is obtained by (Step 1A) adding to an aqueous solution of ferrous iron an oxidizing agent (an aqueous hypochlorite solution, for
30 example) in an amount less than the equivalent amount of the ferrous iron (preferably from 0.3 to 0.95 and more preferably from 0.4 to 0.8) or (Step 1B) adding an oxidizing agent (an aqueous hypochlorite solution, for example) to an aqueous solution of ferrous iron in such a
35 manner that its redox potential may be brought in the

range of +400 to 770 mV (preferably in the range of +500 to 730 mV and more preferably in the range of +600 to 700 mV) and then (Step 2) adding an alkali (preferably a caustic alkali) in such a manner that its pH may be
5 adjusted in the range of 1.5 to 5.5 (preferably in the range of 1.5 to 4.0 and more preferably in the range of 2.0 to 3.5). The order of Step 1A or Step 1B and Step 2 is important. If reversed, phosphorus adsorbents having high adsorptive power could not be obtained. Each
10 condition will be described below.

[0058]

First, ferrous salts which may be used in the aqueous solution of ferrous iron are not particularly limited as long as they are water-soluble, examples of which may
15 include ferrous sulfate, ferrous chloride and ferrous nitrate. Ferrous sulfate is preferred because filtration of precipitate is easy. Further, the concentration of ferrous ions in the aqueous solution of ferrous iron is preferably from 0.05 to 2M.

20 [0059]

Next, oxidizing agents which may be used are not particularly limited and are preferably hypochlorites. Examples of hypochlorites may include sodium hypochlorite and calcium hypochlorite, sodium hypochlorite being
25 particularly preferred. The concentration of a hypochlorite in an aqueous hypochlorite solution is not particularly limited and commercially available solutions with concentrations of 5 to 10 % are usable.

[0060]

30 When Step 1A is adopted, the amount of an oxidizing agent is to be less than the equivalent amount of ferrous iron in an aqueous solution of ferrous iron. The amount of the oxidizing agent is preferably from 0.3 to 0.95 and more preferably from 0.4 to 0.8 in equivalence ratio
35 relative to the amount of the ferrous iron.

[0061]

Also, when Step 1B is adopted, an oxidizing agent (an aqueous hypochlorite solution, for example) is added to an aqueous solution of ferrous iron in such a manner that
5 its redox potential may be brought in the range of +400 to 770 mV (preferably in the range of +500 to 730 mV and more preferably in the range of +600 to 700 mV). It is preferred that the addition of a solution of oxidizing agent (an aqueous hypochlorite solution, for example) is
10 made dropwise while stirring.

[0062]

Steps 1A and 1B may not necessarily be independent steps, so that embodiments in which performing Step 1A results in performing Step 1B and vice versa may be
15 included.

[0063]

Next, after adding a predetermined amount of oxidizing agent in Step 1A or after confirming that the redox potential has settled within the specified range in
20 Step 1B, Step 2 of adding an alkali will be performed. Alkalies are not particularly limited and preferably are caustic alkalies. Examples of caustic alkalies may include caustic soda and caustic potassium, caustic soda being preferred. In addition, the concentration of an alkali
25 (preferably, the concentration of a caustic alkali) is from 0.5 to 5 N, for example. Then, to the solution to which the predetermined amount of oxidizing agent has been added (Step 1A) or the solution whose redox potential has settled within the specified range (Step
30 1B) an aqueous alkali solution (preferably, an aqueous caustic alkali solution) is added in such a manner that its pH may be brought in the range of 1.5 to 5.5 (preferably in the range of 1.5 to 4.0 and more preferably in the range of 2.0 to 3.5). Through this
35 procedure, amorphous ferric hydroxide will precipitate,

providing the present phosphorus adsorbent.

[0064]

The present phosphorus adsorbent is preferably in dry form for the ease of handling. A method for drying is preferably dehydration, freeze-drying or spray-drying, through which dehydration from the Fe-OH bond is reduced during drying so that phosphorus adsorptive power may remain high.

[0065]

Further, admixing glycerin before, during or after drying can minimize a decrease in phosphorus adsorptive power. The amount of glycerin added is 20% or less (preferably from 3 to 7%) on the basis of dry weight (furnace-dried at 105°C for 2 h). The timing for admixing glycerin is not particularly limited and is preferably after pH adjustment and before drying.

[0066]

Next, description will be made on uses and methods for use of the present phosphorus adsorbent. The present phosphorus adsorbent is useful in various fields where excessive phosphorus and biosafety may cause problems, such as for patients with chronic renal failures and artificial dialysis. Specific description will be made below.

[0067]

First, when the present phosphorus adsorbent is used as an agent for preventing, improving or treating phosphorus-related disorders (phosphorus absorption inhibitor) for patients with chronic renal failures and artificial dialysis, it is believed optimum that the agent is filled in an enteric capsule to be orally administered. Doses are from 1 to 5 g a day depending on the conditions of patients, especially the severity of renal failures and the blood concentration of phosphorus. Thus, when the present ferric hydroxide is used for

patients with chronic renal failures and artificial dialysis, the ferric hydroxide will bond with phosphate ions to form water-insoluble iron phosphate, which will be excreted with stool. The reaction of the ferric hydroxide with the water-soluble phosphate ions will complete within one minute. Therefore, almost 100 % of phosphate ions produced when foodstuff passes through the small intestine for two to three hours will be adsorbed by the iron hydroxide to be excreted. In addition, when the agent is orally administered in practical doses, it is unlikely that iron ions derived from the substance according to the present invention are absorbed in the digestive tract.

[0068]

The present phosphorus adsorbent may be used as an oral preparation in view of preventing various diseases attributable to excessive phosphorus intake. Specifically, when the present preparation is orally taken along with foods and beverages or pharmaceuticals containing phosphorus, phosphoric acid produced in the intestines will be adsorbed by the present substance. Thus, the present preparation is extremely effective in preventing phosphorus-related disorders due to the intake of phosphates in large quantities. Doses are from 1 to 5 g a day, for example, depending on the age and weight of a person and the kind and quantity of a food or beverage to be taken or the like. The preparation may be added to foods and beverages or pharmaceuticals to be orally taken into the body (additive, for example) or may be taken in a physically separate form (supplement, for example).

EXAMPLES

[0069]

Production of Phosphorus Adsorbent (Agent for Preventing, Improving or Treating Phosphorus-related Disorders, Oral Preparation)

A 6% sodium hypochlorite (active chlorine 5%) solution was added dropwise while stirring to 800 ml of a 0.1 M aqueous ferrous sulfate solution (amount added dropwise = 29.8 g, equivalent ratio = 0.588) in such a manner that its redox potential was 650 mV and the solution was left for three minutes while stirring. Next, 1N caustic soda was added to the solution until its pH was stabilized at 2.7 to obtain the phosphorus adsorbent according to the example. The pH at the end of the reaction was 2.7 and the redox potential was +584 mV.
[0070]

Component Analysis

(1) Quantitative Analysis according to Fe Formation

For the phosphorus adsorbent obtained above, quantitative analysis was performed with respect to T-Fe, M-Fe, Fe^{2+} and Fe^{3+} ("T" means total and "M" means metal). For T-Fe, stannous chloride reduction-potassium dichromate titration was used for measurement, for M-Fe, mercuric chloride dissolution-potassium dichromate titration was used for measurement, for Fe^{2+} , inert gas-filled acid dissolution-potassium dichromate titration was used for measurement and, for Fe^{3+} , calculations were made according to the equation [$\text{Fe}^{3+} = \text{T-Fe} - (\text{M-Fe} + \text{Fe}^{2+})$]. The results are summarized in Table 1. Sample No. 1 is a paste-like phosphorus adsorbent and Sample No. 2 is a freeze-dried phosphorus adsorbent.

[0071]

[Table 1]

Quantitative Analysis Results (unit: wt%)

sample	T-Fe	M-Fe	Fe^{2+}	Fe^{3+}
No. 1	43.6	less than 0.1	0.5	43.1
No. 2	43.8	less than 0.1	1.0	42.7

[0072]

(2) Identification of Compositional Phase by X-ray Diffractometry (XRD)

Equipment: Type RINT-2200, Rigaku Corporation

Tube: Cu

Voltage-Current: 40 kV-40 mA

Scan Rate: 4°/min

5 Scan Range: 5° to 80° (2θ)

X-ray diffraction experiment was performed under the measurement conditions above. X-ray diffraction charts are shown in Figs. 1 to 4 and the results of analysis are summarized in Table 2.

10 [0073]

[Table 2]

X-ray Diffraction Results

compositional phase/sample name	relative intensity	
	No. 1	No. 2
Lepidocrocite γ -FeOOH	(+)	(+)
amorphous ingredient	+++	+++

relative intensity: ++++ very high, +++ high, ++ moderate, + low, (+) very low, - undetectable

15 [0074]

Based on the analysis results, lepidocrocite (γ -FeOOH) was detected as very low in intensity for both Samples No. 1 and No. 2. Also, the both samples showed generally broadened profiles except the diffraction peaks obtained in the X-ray diffraction charts, eliciting extremely high amorphousness.

[0075]

Phosphorus Adsorption Test

For determining phosphorus absorptive power, 20 ml of an ammonium phosphate solution (5.9 g P/l) were added to 0.5 g (dry weight) of the phosphorus adsorbent according to the example and the solution was left for 24 hours with occasional shaking. The solution was then filtrated and the concentration of phosphorus in the filtrate was determined and calculated. For comparison, adsorptive power was also tested in a similar procedure for ferric hydroxide produced by rapidly stirring 1N NaOH into a 1M

aqueous FeCl_3 solution in such a manner that its pH may be brought in the range of 7.5 to 8.0 and hydrous iron oxide (commercial product) produced through dehydration of ferric hydroxide. The results are summarized in Table 3.

[0076]

[Table 3]

	Example	ferric hydroxide	commercial product (hydrous iron oxide)
phosphorus adsorptive power	156 g/kg	56 g/kg	14.8 g/kg

[0077]

Example of Addition of Glycerin, etc.

Glycerin, ethanol and skimmed milk were added to the 70% hydrous phosphorus adsorbent produced according to the above procedure each at 5% by weight based on the phosphorus adsorbent and were freeze-dried. Phosphorus adsorptive power of each of these dried products is summarized in Table 4.

[0078]

[Table 4]

	hydrous	freeze-dried	5% glycerin added, freeze-dried	5% EtOH added, freeze-dried	5% skimmed milk added, freeze-dried
phosphorus adsorptive power	156 g/kg	102 g/kg	130 g/kg	117 g/kg	123 g/kg

[0079]

Test Example 1 (Test for Confirming Action of Reducing Blood Concentration of Phosphorus Using Rats)

Groups each consisting of three male SD rats (eight weeks old) were bred for a week by dietary administration of a feed to which the present phosphorus adsorbent (agent for preventing, improving or treating phosphorus-related disorders) was added. Blood was sampled before the administration (Day 1), two days after the administration (Day 3), four days after the administration (Day 5) and seven days after the

administration (Day 8) to determine blood concentrations of phosphorus. The group with a feed not containing the present phosphorus adsorbent was designated as Control and the groups with feeds containing 1%, 3% and 5% of the present phosphorus adsorbent were designated respectively as Phosphorus Adsorbent 1%, Phosphorus Adsorbent 3% and Phosphorus Adsorbent 5% in the drawing (Fig. 5). Also, a significant difference in phosphorus concentration from Control at each time point was indicated by ** ($P < 0.01$).

10 [0080]

Test Example 2 (Small Intestine Fluid and Phosphorus Adsorption Test in Small Intestine System)

In order to simulate the composition of the enteral fluid with the composition of a test solution, 187 g/700 ml of an aqueous solution of an enteral nutrition Elental (AJINOMOTO PHARMA Co., Ltd.) was mixed with 1 L of Ringer solution adjusted to pH 7.2 as a small intestine fluid model to provide a test solution. To 100 ml of the test solution, 0.178 g (dry weight) of the phosphorus adsorbent (oral preparation) of the example was added and the concentration of water-soluble P in the system was determined. Also, for comparison, similar determinations were made for cases without the phosphorus adsorbent (Tests 1 and 2). Further, similar determinations were made for cases where water-soluble phosphoric acid was added (in the amount based on the assumption that the total amount of organic P in the enteric nutrition was digested in the intestines) to the test solution (Tests 3 and 4). The results are shown in the table below. As can be seen from the table, the water-soluble P was eliminated by the present phosphorus adsorbent (oral preparation) and, when a large quantity of additional water-soluble P was added, the amount of phosphorus eliminated by the present phosphorus adsorbent (oral preparation) increased. In other words, the lower the

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water-soluble phosphorus concentration, the less the amount adsorbed was and the higher the water-soluble phosphorus concentration, the more the amount adsorbed was. The "total P" in the table represents a total value
 5 of water-soluble and water-insoluble phosphorus. Also, the "water-insoluble phosphorus" refers to phosphorus that is not water-soluble, such as that found in proteins.
 [0081]

[Table 5]

		added water-soluble P, ppm	water-soluble P, ppm	amount of P eliminated by P adsorbent	total P, ppm
1	test solution	-	29.8	-	155.6
2	test solution + P adsorbent	-	21.1	8.7	155.6
3	test solution + added water-soluble P	155.6	185.4	-	311.2
4	test solution + added water-soluble P + P adsorbent	155.6	83.7	102.7	311.2

10 BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a chart illustrating X-ray diffraction for Sample No. 1;

Fig. 2 is a chart illustrating X-ray diffraction for Sample No. 1;

15 Fig. 3 is a chart illustrating X-ray diffraction for Sample No. 2;

Fig. 4 is a chart illustrating X-ray diffraction for Sample No. 2; and

20 Fig. 5 shows the results of Test Example 1 (action by phosphorus adsorbent of reducing blood concentration of phosphorus using rats).

CLAIMS

1. An agent for preventing, improving or treating a phosphorus-related disorder, which contains ferric
5 hydroxide as produced under such conditions that a ferrous species is present.

2. The agent for preventing, improving or treating a phosphorus-related disorder according to Claim 1, wherein
10 the ferric hydroxide is produced by adding to an aqueous solution of ferrous iron an oxidizing agent in an amount less than the equivalent amount of the ferrous iron and then adding an alkali in such a manner that its pH at the end of the reaction may be adjusted in the range of 1.5
15 to 5.5.

3. The agent for preventing, improving or treating a phosphorus-related disorder according to Claim 1, wherein the ferric hydroxide is produced by adding an oxidizing
20 agent to an aqueous solution of ferrous iron in such a manner that its redox potential may be brought in the range of +400 to 770 mV and then adding an alkali in such a manner that its pH at the end of the reaction may be adjusted in the range of 1.5 to 5.5.

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4. The agent for preventing, improving or treating a phosphorus-related disorder according to Claim 1, wherein the ferric hydroxide is produced by adding to an aqueous solution of ferrous iron an oxidizing agent in an amount
30 less than the equivalent amount of the ferrous iron in such a manner that its redox potential may be brought in the range of +400 to 770 mV and then adding an alkali in such a manner that its pH at the end of the reaction may be adjusted in the range of 1.5 to 5.5.

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5. The agent for preventing, improving or treating a phosphorus-related disorder according to any one of Claims 2 to 4, wherein the oxidizing agent is a hypochlorite.

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6. The agent for preventing, improving or treating a phosphorus-related disorder according to any one of Claims 1 to 5, wherein the ferric hydroxide is amorphous.

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7. The agent for preventing, improving or treating a phosphorus-related disorder according to any one of Claims 1 to 6, further including glycerin.

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8. The agent for preventing, improving or treating a phosphorus-related disorder according to any one of Claims 1 to 7, wherein the disorder is hyperphosphatemia.

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9. A process for producing an agent for preventing, improving or treating a phosphorus-related disorder, the agent containing ferric hydroxide, which comprises the steps of adding to an aqueous solution of ferrous iron an oxidizing agent in an amount less than the equivalent amount of the ferrous iron and then adding an alkali in such a manner that its pH may be adjusted in the range of 1.5 to 5.5.

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10. A process for producing an agent for preventing, improving or treating a phosphorus-related disorder, the agent containing ferric hydroxide, which comprises the steps of adding an oxidizing agent to an aqueous solution of ferrous iron in such a manner that its redox potential may be brought in the range of +400 to 770 mV and then adding an alkali in such a manner that its pH may be adjusted in the range of 1.5 to 5.5.

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11. A process for producing an agent for preventing, improving or treating a phosphorus-related disorder, the agent containing ferric hydroxide, which comprises the steps of adding to an aqueous solution of ferrous iron an oxidizing agent in an amount less than the equivalent amount of the ferrous iron in such a manner that its redox potential may be brought in the range of +400 to 770 mV and then adding an alkali in such a manner that its pH may be adjusted in the range of 1.5 to 5.5.

12. The process according to any one of Claims 9 to 11, wherein the oxidizing agent is a hypochlorite.

13. The process according to any one of Claims 9 to 12, wherein the ferric hydroxide is amorphous.

14. The process according to any one of Claims 9 to 13, further including the step of adding glycerin.

15. The process according to any one of Claims 9 to 14, further including the step of dehydration, freeze-drying or spray-drying.

16. The process according to Claim 15, wherein, after the step for pH adjustment, the step of adding glycerin is performed before, during or after the step of dehydration, freeze-drying or spray-drying.

17. The process according to any one of Claims 9 to 16, wherein the disorder is hyperphosphatemia.

18. An oral preparation for adsorbing phosphate ions in foods and beverages or pharmaceuticals, which contains ferric hydroxide as produced under such conditions that a ferrous species is present.

19. The oral preparation according to Claim 18,
wherein the ferric hydroxide is produced by adding to an
aqueous solution of ferrous iron an oxidizing agent in an
5 amount less than the equivalent amount of the ferrous
iron and then adding an alkali in such a manner that its
pH at the end of the reaction may be adjusted in the
range of 1.5 to 5.5.

10 20. The oral preparation according to Claim 18,
wherein the ferric hydroxide is produced by adding an
oxidizing agent to an aqueous solution of ferrous iron in
such a manner that its redox potential may be brought in
the range of +400 to 770 mV and then adding an alkali in
15 such a manner that its pH at the end of the reaction may
be adjusted in the range of 1.5 to 5.5.

21. The oral preparation according to Claim 18,
wherein the ferric hydroxide is produced by adding to an
20 aqueous solution of ferrous iron an oxidizing agent in an
amount less than the equivalent amount of the ferrous
iron in such a manner that its redox potential may be
brought in the range of +400 to 770 mV and then adding an
alkali in such a manner that its pH at the end of the
25 reaction may be adjusted in the range of 1.5 to 5.5.

22. The oral preparation according to any one of
Claims 19 to 21, wherein the oxidizing agent is a
hypochlorite.

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23. The oral preparation according to any one of
Claims 18 to 22, wherein the ferric hydroxide is
amorphous.

35 24. The oral preparation according to any one of

Claims 18 to 23, further including glycerin.

25. The oral preparation according to any one of Claims 18 to 24, which is a food and beverage additive,
5 food and beverage adjuvant, pharmaceutical additive or pharmaceutical adjuvant.

26. A process for producing an oral preparation for adsorbing phosphate ions in foods and beverages or
10 pharmaceuticals, the preparation containing ferric hydroxide, which comprises the steps of adding to an aqueous solution of ferrous iron an oxidizing agent in an amount less than the equivalent amount of the ferrous iron and then adding an alkali in such a manner that its
15 pH may be adjusted in the range of 1.5 to 5.5.

27. A process for producing an oral preparation for adsorbing phosphate ions in foods and beverages or pharmaceuticals, the preparation containing ferric
20 hydroxide, which comprises the steps of adding an oxidizing agent to an aqueous solution of ferrous iron in such a manner that its redox potential may be brought in the range of +400 to 770 mV and then adding an alkali in such a manner that its pH may be adjusted in the range of
25 1.5 to 5.5.

28. A process for producing an oral preparation for adsorbing phosphate ions in foods and beverages or pharmaceuticals, which comprises the steps of adding to
30 an aqueous solution of ferrous iron an oxidizing agent in an amount less than the equivalent amount of the ferrous iron in such a manner that its redox potential may be brought in the range of +400 to 770 mV and then adding an alkali in such a manner that its pH may be adjusted in
35 the range of 1.5 to 5.5.

29. The process according to any one of Claims 26 to 28, wherein the oxidizing agent is a hypochlorite.

5 30. The process according to any one of Claims 26 to 29, wherein the ferric hydroxide is amorphous.

31. The process according to any one of Claims 26 to 30, further including the step of adding glycerin.

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32. The process according to any one of Claims 26 to 31, further including the step of dehydration, freeze-drying or spray-drying.

15 33. The process according to Claim 32, wherein, after the step for pH adjustment, the step of adding glycerin is performed before, during or after the step of dehydration, freeze-drying or spray-drying.

20 34. The process according to any one of Claims 26 to 33, wherein the oral preparation is a food and beverage additive, food and beverage adjuvant, pharmaceutical additive or pharmaceutical adjuvant.