

DESCRIPTION

TITLE OF INVENTION

5 COATING COMPOSITION, COATING FILM, AND COATING PREPARATION
AND METHOD FOR PRODUCING SAME

TECHNICAL FIELD

10 [0001]

The present invention relates to coating compositions that can be used for coating foods, drugs or the like, coating films, and coated preparations as well as methods for producing the same.

15

BACKGROUND ART

[0002]

There exists a desire for enteric-coated preparations which have active ingredients, such as lactic acid bacteria, enzymes and other protein-based functional ingredients, that exhibit a high functionality by preventing decomposition in the stomach, keeping the structure intact and delivery to the intestines, which preparations dissolve in the intestines but not in the stomach, enabling the active ingredients to reach the intestines.

[0003]

Ingredients which do not dissolve under the pH conditions in the stomach (acidic) but do dissolve under the pH conditions in the small intestine (neutral to alkaline) are used as the coating film for enabling the active ingredients to reach the intestines. Examples of such ingredients include methacrylic acid-based polymeric compounds, shellac, zein and alginate. However, methacrylic acid-based polymeric compounds are limited to drug applications, and shellac and zein are generally sprayed on using organic solvents. Therefore, the use of alginate, which can be used not only in drug applications but also in food applications and which enables coating to be carried using water --the environmental impact of which is minimal-- has been growing recently.

[0004]

However, enteric-coated preparations obtained using alginate, when stored in a high-temperature, high-humidity environment, incur degradation of the coating film that is thought to be caused by hydrolysis of the alginate, and sometimes thus undergo a decline in the gastric juice resistance. Hence, there exists a desire for coating technology that can suppress a decline in gastric juice resistance even when the preparation is stored in a high-temperature, high-humidity environment.

[0005]

Prior-art literature relating to the present invention includes that cited below.

PRIOR ART DOCUMENTS

PATENT DOCUMENTS

[0006]

Patent Document 1: JP-A 2002-193792

SUMMARY OF INVENTION

TECHNICAL PROBLEM

[0007]

The objects of the present invention are to provide a coating composition that not only can be uniformly coated without chipping or peeling and thus has excellent coating properties, but also imparts a coating film of excellent durability in high-temperature, high-humidity environments; a coating film that can be obtained using this coating composition; and a coated preparation that has been coated with this coating composition as well as a method for producing the coated preparation.

SOLUTION TO PROBLEM

[0008]

The inventors have conducted extensive investigations in order to achieve the above objects. As a result, they have discovered that a coating composition which includes alginate and divalent cations in a specific ratio not only can be uniformly coated without chipping or peeling and thus has excellent coating properties, but also imparts a coating film of excellent durability in high-temperature, high-humidity environments; and that a

preparation which is coated using this composition undergoes little decrease in gastric juice resistance even when stored in a high-temperature, high-humidity environment, and thus has an excellent storage stability. They have also found that a coating film containing alginate and divalent cations in a given ratio has an excellent durability in high-temperature, high-humidity environments; and that a coated preparation covered with such a coating film, even when stored in a high-temperature, high-humidity environment, undergoes little decrease in gastric juice resistance and has an excellent storage stability. These findings ultimately led to the present invention.

[0009]

10 Accordingly, the invention provides the following.

[1] A coating composition which includes (A) an alginate and (B) a divalent cation, wherein the weight ratio of component (B) included relative to component (A), expressed as $(B)/(A) \times 100$, is from 0.015 to 0.25.

15 [2] The coating composition of [1], wherein component (A) is an alginate having a viscosity, measured as a 1 wt% aqueous solution at 20°C, of not more than 600 mPa·s.

[3] The coating composition of [1] or [2], further including (C) a plasticizer.

[4] The coating composition of [3], wherein the weight ratio of component (B) included relative to component (C), expressed as $(B)/(C) \times 100$, is from 0.02 to 5.

20 [5] The coating composition of any of [1] to [4], further including (D) a film-forming ingredient.

[6] A coated preparation which includes a substrate and a coating film formed on the substrate from the coating composition of any of [1] to [5].

25 [7] A method for producing a coated preparation, which method includes the step of forming a coating film on a surface of a substrate by spraying a coating solution containing the coating composition of any of [1] to [5] and water onto the substrate and then drying.

[8] A coating film that is formed on a surface of a substrate and includes (A) an alginate and (B) a divalent cation, wherein the weight ratio of component (B) included relative to component (A), expressed as $(B)/(A) \times 100$, is from 0.015 to 0.25.

[9] The coating film of [8], further including (C) a plasticizer.

30 [10] The coating film of [9], wherein the weight ratio of component (B) included relative to component (C), expressed as $(B)/(C) \times 100$, is from 0.02 to 5.

[11] The coating film of any of [8] to [10], further including (D) a film-forming ingredient.

ADVANTAGEOUS EFFECTS OF INVENTION

[0010]

This invention makes it is possible to provide a coating composition which not only has excellent coating properties but also gives a coating film having an excellent durability in high-temperature, high-humidity environments, a coating film that can be obtained using this coating composition, and a coated preparation of excellent storage stability that has been coated with this coating composition as well as a method for producing the coating preparation. This invention is also able to provide a coating film which has an excellent durability in high-temperature, high-humidity environments, as well as a method for producing such a coating film.

DESCRIPTION OF EMBODIMENTS

[0011]

The invention is described more fully below.

(I) Coating Composition

The coating composition of the invention includes (A) an alginate and (B) a divalent cation.

[0012]

(A) Alginate

The alginate is preferably a monovalent alginate such as an alkali metal salt or ammonium salt or a water-soluble alginate, more preferably an alkali metal salt, even more preferably a sodium salt or a potassium salt, and still more preferably a sodium salt. The alginate may be of one type having a suitable viscosity that is used alone, or may be of two or more types of suitable viscosity that are used in combination. The overall alginate has a viscosity, measured as a 1 wt% aqueous solution at 20°C, that is preferably not more than 600 mPa·s, and more preferably at least 25 mPa·s and not more than 400 mPa·s. In addition, it is even more preferable to use in combination: (A-1) an alginate having a viscosity, measured as a 1 wt% aqueous solution at 20°C, of at least 50 mPa·s, and (A-2) an alginate having a viscosity, measured as a 1 wt% aqueous solution at 20°C, of less than 50 mPa·s.

[0013]

The (A-1) alginate which has a viscosity, measured as a 1 wt% aqueous solution at 20°C, of at least 50 mPa·s is preferably an alginate with a viscosity of at least 50 mPa·s

and not more than 600 mPa·s, and more preferably an alginate with a viscosity of at least 50 mPa·s and not more than 400 mPa·s. The (A-1) alginate is preferably a sodium alginate. [0014]

5 The (A-2) alginate having a viscosity, measured as a 1 wt% aqueous solution at 20°C, of less than 50 mPa·s is preferably one whose viscosity is at least 5 mPa·s and less than 50 mPa·s, and more preferably one whose viscosity is at least 10 mPa·s and less than 50 mPa·s. The (A-2) alginate is preferably a sodium alginate. [0015]

10 In this invention, by setting the viscosity of component (A) in the above range, the coating properties and enteric properties can be further enhanced. [0016]

The component (A) content within the coating composition is preferably from 5 to 85 wt% (solids content; here and below, “solids content” refers to the proportion relative to the weight of all ingredients other than the solvent, and is the same as the proportion within
15 the coating film), more preferably from 10 to 80 wt% (solids content), even more preferably from 10 to 70 wt% (solids content), and still more preferably in the range of 10 to 60 wt% (solids content). By setting the component (A) content to at least the lower limit of the above range, good enteric properties can be obtained; by setting the content to not more than the upper limit, good coating properties can be obtained. In this invention, the
20 component (A) content signifies the amount of sodium alginate. When component (A) is an alginate other than sodium alginate, the content signifies the amount converted to the amount of sodium alginate. For example, when component (A) is potassium alginate, the value obtained by multiplying the potassium alginate content by 0.92 is treated as the component (A) content. When component (A) is ammonium alginate, the value obtained
25 by multiplying the ammonium alginate content by 1.03 is treated as the component (A) content. The same applies also in the subsequently described weight ratios with component (A-1), component (A-2) and other ingredients. [0017]

30 When alginate (A-1) is included, the content thereof within the coating composition is preferably from 5 to 85 wt% (solids content), more preferably from 10 to 60 wt% (solids content), and even more preferably from 20 to 50 wt% (solids content). By setting the content to at least the lower limit, good enteric properties can be better obtained; by setting

the content to not more than the upper limit, sticking and peeling during coating are prevented, enabling a good coating performance to be obtained.

[0018]

When alginate (A-2) is included, the content thereof within the coating composition
5 is preferably not more than 85 wt% (solids content), more preferably from 5 to 50 wt% (solids content), and even more preferably from 10 to 40 wt% (solids content). Within this range, the enteric properties improve and good coating properties are obtained.

[0019]

In this invention, alginate (A-1) is preferably used as the alginate (A). By thus using
10 an alginate having at least a given molecular weight, the coating properties are good and a high acid resistance can be imparted to the coating film that has formed. Also, by using alginate (A-1) and alginate (A-2) together, the coating performance can be further improved while maintaining the enteric properties.

[0020]

Regarding the use of two types of alginate having differing viscosities such as above
15 alginate (A-1) and alginate (A-2), two types of alginate were selected not merely to adjust the viscosity of the coating solution but also from the standpoint of the enteric properties and the coating properties. The weight ratio (A-1):(A-2) ((A-1)/(A-2)) is preferably from 1:5 to 10:1 (0.2 to 10), more preferably from 1:3 to 5:1 (0.33 to 5), and even more preferably
20 from 1:1.8 to 3:1 (0.56 to 3). By setting this weight ratio to at least the bottom limit, the film performance under acidity becomes even higher, and so the non-dissolvability is good. By setting the weight ratio to not more than the upper limit, the coating properties become even better.

[0021]

25 In this invention, alginate viscosity measurements are carried out using a rotational viscometer (BM type). Viscosities below 200 mPa·s are measured using a No. 1 rotor, and viscosities of at least 200 mPa·s and up to but less than 1,000 mPa·s are measured with a No. 2 rotor. Measurement is carried out on a 1 wt% aqueous solution at 20°C and 30 rpm, and the value obtained after 60 seconds is treated as the measured value.

30 [0022]

The alginate viscosity is substantially proportional to the molecular weight of the alginate. For example, the weight-average molecular weight (Mw) of (A-1) is at least

800,000, preferably at least 800,000 and less than 3,000,000, and more preferably at least 800,000 and less than 1,900,000. The weight-average molecular weight (M_w) of (A-2) is at least 200,000 and less than 800,000, and more preferably at least 300,000 and less than 800,000. The method for measuring the weight-average molecular weight (M_w) of alginate in this invention by gel permeation chromatography (GPC) is described below.

[0023]

(1) Sample Preparation

The alginate is dissolved in a mobile phase (0.1 M (mol/L) NaNO_3 aqueous solution) to a concentration of 0.1 wt%, and this is used as the sample.

A working curve is prepared using reference standards of various molecular weights (pullulan: $M_w = 1,660,000$, $M_w = 380,000$, $M_w = 100,000$, $M_w = 12,200$; each of these is dissolved in the mobile phase to a concentration of 0.1 wt%).

(2) GPC Measurement Conditions

Column: Shodex OHpak SB-806M HQ (8 mm (I.D.) $\times$ 300 mm (L); 13 μm)

Mobile phase: 0.1 M (mol/L) NaNO_3 aqueous solution

Flow rate: 0.5 mL/min

Temperature: 40°C

Injection rate: 200 μL (0.1% in mobile phase)

Detector: differential refractive index (RI) detector

(3) Method of Analysis

A working curve formula is determined using the working curve samples, and the pullulan-equivalent weight-average molecular weight (M_w) is determined from the GPC analysis results for the sample.

[0024]

(B) Divalent Cations

It is preferable to include magnesium ions and calcium ions as the divalent cations, with calcium ions being more preferred. The divalent cations can be incorporated in the coating composition of the invention by including divalent cation-containing metal salts. Specific examples include food ingredients such as calcium chloride, calcium lactate, calcium glutamate, calcium citrate, calcium gluconate, magnesium chloride, calcium hydroxide, magnesium sulfate, milk casein, bittern and sea salt. In this invention, of these, preferred use can be made of calcium chloride, calcium lactate and magnesium chloride.

[0025]

The content of component (B) as a proportion of the coating composition is preferably from 0.005 to 0.10 wt% (solids content), more preferably from 0.01 to 0.08 wt% (solids content), and even more preferably from 0.03 to 0.06 wt% (solids content). By setting
5 the component (B) content in this range, the stability of the coating film further improves. In addition, good enteric properties can be obtained. The component (B) content can be calculated by multiplying the ratio of divalent cations included in a divalent cation-containing metal salt by the actual amount of the divalent cation-containing metal salt used. For example,
10 the ratio of calcium ions in calcium chloride dihydrate is 27.27 wt%, the ratio of calcium ions in calcium lactate pentahydrate is 13.00 wt%, and the ratio of magnesium ions in magnesium chloride hexahydrate is 11.96 wt%. The content of component (B) can be calculated by multiplying these ratios by the amounts of the respective metal salts used.

The divalent cation content can be checked using methods and apparatuses commonly used in the field of science and technology. Examples of such methods include, but are not
15 limited to, inductively coupled plasma emission spectrometry, inductively coupled plasma mass spectrometry, electron beam microanalysis, x-ray photoelectron spectroscopy, secondary ion mass spectrometry, ion chromatography and atomic absorption spectrophotometry.

[0026]

20 The weight ratio of (B) included relative to component (A), expressed as $(B)/(A) \times 100$, is from 0.015 to 0.25, preferably from 0.02 to 0.20, more preferably from 0.06 to 0.20, and most preferably from 0.09 to 0.16. When this weight ratio is less than 0.015 or more than 0.25, the resulting coating film readily deteriorates and has a low durability. Tablets with such a coating film have a poor storage stability.

25 [0027]

(C) Plasticizer

Examples of plasticizers include surfactants such as sucrose fatty acid esters, glycerol fatty acid esters, monoglycerol fatty acid esters and polyoxyethylene sorbitan fatty acid esters; polyhydric alcohols such as glycerol, propylene glycol and polyethylene glycol;
30 sugars such as glucose, high-fructose corn syrup and sucrose; sugar alcohols such as sorbitol, maltitol, mannitol, erythritol and xylitol; higher alcohols (preferably having 6 to 22 carbon atoms) such as dodecanol, tridecanol, tetradecanol, pentadecanol, hexadecanol, heptadecanol,

octadecanol, hexadecyl alcohol, isostearyl alcohol and 2-octyldodecanol; and fatty oils such as medium-chain fatty acid esters (preferably having 6 to 12 carbon atoms). These may be used singly or two or more may be used in suitable combination. Of these, glycerol is preferred from the standpoint of the coating film plasticizing effect, and a surfactant is preferred from the standpoint of the enteric properties. Glycerol and/or a sucrose fatty acid ester are more preferred.

[0028]

The content of component (C) within the coating composition is preferably from 0.1 to 70 wt% (solids content), and more preferably from 2 to 50 wt% (solids content).

By setting the component (C) content within this range, the stability of the coating is further improved. Also, by setting the content to at least the lower limit of this range, peeling of the film during coating is better suppressed; by setting the content to not more than the upper limit, tackiness during coating is suppressed, making coating treatment easier and also enabling good enteric properties to be obtained.

[0029]

The weight ratio of component (C) included relative to component (A), expressed as (C)/(A), is preferably in the range of 0.001 to 3, more preferably from 0.05 to 3, and even more preferably from 0.05 to 2. Within this range, the film performance under acidity becomes even higher and the stability of the coating film improves further.

[0030]

The weight ratio of component (B) included relative to component (C), expressed as (B)/(C) $\times$ 100, is preferably from 0.02 to 5, more preferably from 0.04 to 1.6, and even more preferably from 0.06 to 1.6. By setting the weight ratio within this range, the stability of the coating film further improves.

[0031]

(D) Film-Forming Ingredient

A film-forming ingredient other than component (A) may be included in the coating composition of the invention. The film-forming ingredient (D) is preferably a water-soluble polymer. Specific examples include natural water-soluble polysaccharides such as gelatin, pectin, curdlan, pullulan, gum arabic, xanthan gum and gellan gum; water-soluble cellulose derivatives such as hydroxypropyl methylcellulose, carboxymethylcellulose sodium and hydroxypropyl cellulose; and agar, chitosan, tamarind seed gum, locust bean gum,

polyvinyl alcohol and ethyl cellulose aqueous dispersions. These may be used singly or two or more may be used in suitable combination. Of these, an ingredient selected from gelatin, curdlan, pullulan, gum arabic, xanthan gum, gellan gum, hydroxypropyl methylcellulose and hydroxypropyl cellulose is preferred from the standpoint of the coating properties and combination with component (A).

[0032]

The content of component (D) is preferably from 1 to 80 wt% (solids content), and more preferably from 5 to 75 wt% (solids content), of the coating composition. By setting the content within this range, the advantageous effects of including component (D) can be better obtained. Including component (D) in an amount in excess of this range may adversely affect the enteric properties.

[0033]

In this case, the weight ratio of components (A) and (D) included, expressed as (A):(D) ((A)/(D)), is preferably from 1:10 to 20:1 (0.1 to 20), more preferably from 1:5 to 20:1 (0.2 to 20), and even more preferably from 1:1 to 10:1 (1 to 10). By setting the ratio within this range, in addition to maintaining good coating properties and an attractive appearance, tablets can be obtained which have a higher film performance, especially under acidic conditions, and thus an excellent enteric performance.

[0034]

The coating composition may include (E) fine particles. By including fine particles, peeling of the coating film due to tablets sticking to each other at the time of coating treatment can be prevented. Examples of component (E) include talc, calcium stearate, silicon dioxide and titanium oxide; one type may be used alone or two or more types may be used in suitable combination. The particle size of the fine particles is from 0.01 to 50 μm , and preferably from 0.1 to 20 μm . Particle size measurement is carried out using a laser diffraction-type particle size analyzer (dry measurement).

[0035]

The component (E) content within the coating composition is preferably from 1 to 80 wt% (solids content), more preferably from 3 to 60 wt% (solids content), and even more preferably from 5 to 40 wt% (solids content). By setting the content within this range, the advantageous effects of including component (E) can be better obtained. Including component (E) in an amount in excess of this range may adversely affect the film formability.

[0036]

In addition to above components (A) to (E), the coating composition of the invention may suitably include one, two or more ingredients commonly used in coating compositions. Examples of such optional ingredients include antifoaming agents and colorants.

5 [0037]

Illustrative examples of antifoaming agents include glycerol fatty acid esters, dimethylpolysiloxanes, dimethylpolysiloxane-silicon dioxide mixtures, hydrated silicon dioxide and silicon dioxide. These may be used singly or two or more may be used in suitable combination.

10 [0038]

Illustrative examples of colorants include catechu tannin powder, turmeric root extract, yellow iron sesquioxide, orange essence, brown iron oxide, carbon black, caramel, carmine, carotene solution, β -carotene, glycyrrhiza extract, gold foil, black iron oxide, light silicic anhydride, titanium oxide, iron sesquioxide, Food Blue No. 1, Food Yellow No. 4, Food Yellow No. 4 aluminum lake, Food Yellow No. 5, Food Red No. 2, Food Red No. 3, Food Red No. 102, sodium hydroxide, sodium copper chlorophyllin, copper chlorophyll, rye green leaf extract, medicinal carbon, riboflavin butyrate, riboflavin, green tea powder and riboflavin sodium phosphate.

[0039]

20 Water and organic solvents such as ethanol may be included in the coating composition of the invention within a range that does not detract from the advantageous effects of the invention. The solvent content within the coating composition is suitably selected within a range of 1 to 98 wt%, preferably 50 to 98 wt%, and more preferably 70 to 96 wt%.

25 [0040]

(II) Coated Preparation

In the present invention, "coating" refers to a process that includes forming a film by applying or spraying a coating solution onto the surface of a substrate, or dipping a substrate in a coating solution, and then drying the coating solution on the substrate to hardness. In this invention, a coated preparation can be obtained by using the above-described coating composition to form a coating film composed of the coating composition on a substrate.

30

[0041]

(1) Coating Substrate

In this invention, the shape and dosage form of the substrate are not particularly limited, so long as the substrate has a shape that enables a coating film to be formed on a solid surface, such as tablets, medicinal powders, fine granules, granules, hard capsules, soft capsules and powders. The tablets may have a single layer or two or more layers. Of these, in order to better elicit enteric properties, it is preferable for the substrate to be in the form of tablets. Although the tablet dimensions are not particularly limited, from the standpoint of the ease of handling the tablets and swallowability, the tablet diameter is preferably from 5 to 14 mm, and more preferably from 7 to 12 mm. Also, it is suitable for the weight per tablet to be from about 150 mg to about 700 mg.

[0042]

The coating substrate is exemplified by, without particular limitation, the active ingredients of foods, drugs and the like. Specific examples include lactic acid bacteria, cysteine, iron, proteins such as antibodies and lactoferrin, peptides and ATP-2Na. These may be used singly or two or more may be used in suitable combination. Of these, high-molecular-weight ingredients such as proteins and water-insoluble ingredients are preferred.

[0043]

(2) Coating Film

In this invention, when only a coating film obtained using the coating composition of the invention (which film is sometimes referred to below as the “main coating film”) is formed, “coating film” refers to this main coating film. However, in cases where, in addition to this main coating film, the subsequently described precoat film and/or topcoat film is formed, “coating film” refers to the overall coating film which includes these as well.

[0044]

The main coating film, precoat film and topcoat film may each be formed of a single layer or of two or more layers. For example, the main coating film may have two or more layers obtained by using coating solutions having differing ratios of (A) alginate and (B) divalent cations to carry out coating. In cases where coating has been consecutively carried two or more times using coating solutions of the same composition, even when a

plurality of coating films have been formed, the range over which consecutive layers of the same composition are consecutively arranged shall be counted as a single layer overall.

[0045]

(2-1) Main Coating Film

5 The coating film formed using the coating composition of the invention (main coating film) contains above component (A); as subsequently described, a water-soluble film is formed with direct drying of an aqueous solution of alginic acid. This water-soluble film has the following properties: under acidic conditions, monovalent cations are replaced with hydrogen ions, so that component (A) changes to alginic acid, forming an insoluble film;
10 under neutral to alkaline conditions, the water-soluble film dissolves.

[0046]

 The coating composition of the invention and the coating film formed from this coating composition have enteric properties, meaning that they dissolve in the intestines but do not dissolve in the stomach, enabling the substrate to reach the intestines. By using
15 the coating composition of the invention having enteric properties to coat the substrate, an enteric-coated preparation which has an enteric coating film formed of the coating composition can be easily obtained.

[0047]

 In the present invention, “enteric” refers to an agent that delivers a functional
20 ingredient to the intestines. This means, carrying out tests in accordance with the Dissolution Test method in the Japanese Pharmacopoeia, a dissolution rate over 2 hours of less than 50% (preferably less than 30%) in a dissolution test solution corresponding to gastric juice (pH 1.2), and a dissolution rate over 2 hours of at least 70% in a dissolution test solution corresponding to intestinal juice (pH 6.8).

25 [0048]

 The thickness of the main coating film, although not particularly limited, is preferably from 5 μm to 2.5 mm, more preferably from 10 μm to 2.0 mm, and even more preferably from 50 μm to 1.5 mm. By setting the coating film thickness to at least 5 μm , a sufficient gastric resistance over time can be obtained; by setting the thickness to not more than 2.5 mm,
30 the dissolution properties in an intestinal environment are good. The substrate release profile can be adjusted by varying the thickness of the coating film.

[0049]

Confirmation that the substrate is coated with the coating composition of the invention and of the thickness of the coating film can be carried out using methods and apparatuses commonly employed in the field of science and technology.

5 Such methods are exemplified by, but not limited to, the following methods (i) and (ii).

(i) Examining with a digital microscope or a scanning electron microscope the cross-section of a coated preparation that has been cut with a cutter, measuring the thickness of the coating film in several places, and treating the average of these measured values as the film thickness.

10 (ii) Using a near-infrared/mid-infrared/far-infrared imaging system, a terahertz imaging system and an OCT imaging system (optical coherence tomography) to non-invasively measure the film thickness distribution of the coated preparation in accordance with the measurement methods for the respective systems, and treating the average of these measured values as the film thickness.

15 [0050]

In cases where the substrate is a tablet, hard capsule or soft capsule, the weight per unit surface area of the main coating film, although not particularly limited, is preferably from 3.0 to 25 mg/cm², and more preferably from 5.0 to 20 mg/cm². By setting the weight per unit surface area of the main coating film to 3.0 mg/cm² or more, a sufficient gastric resistance over time can be obtained; by setting this to 25 mg/cm² or less, the dissolution properties in an intestinal environment are good.

[0051]

Also, in the case of tablets, hard capsules or soft capsules, the main coating film is set to preferably 0.5 to 20 wt%, and more preferably 1 to 15 wt%, of the coated preparation.

25 In the case of medicinal powders, fine granules, granules or powders, the main coating film is set to preferably 10 to 60 wt%, and more preferably 15 to 50 wt%, of the coated preparation. Also, the contents (solids contents) of the respective ingredients in the main coating film are the same as those in the coating composition.

[0052]

30 (2-2) Precoating Film

In this invention, prior to forming the main coating film, precoating may be carried out on the substrate so as to form a layer below the main coating film.

[0053]

The precoating composition is not particularly limited, although a composition that includes the film-forming ingredient (D) can be suitably used. The content of component (D) in the precoating composition is preferably 10 to 90 wt% (solids content), and more preferably 20 to 80 wt% (solids content) of the composition.

[0054]

In addition, (C) a plasticizer may be included in the precoating composition.

When component (C) is included, the content thereof is preferably 1 to 40 wt% (solids content) of the composition.

[0055]

The thickness of the precoating film, although not particularly limited, is preferably from 1 to 500 μm , and more preferably from 10 to 300 μm . By setting the precoating film thickness to at least 1 μm , sufficient gastric resistance over time can be obtained; by setting the thickness to not more than 500 μm , the dissolution properties in an intestinal environment are good.

[0056]

In cases where the substrate is a tablet, hard capsule or soft capsule, the weight per unit surface area of the precoating film, although not particularly limited, is preferably from 0.5 to 10 mg/cm^2 , and more preferably from 1 to 5 mg/cm^2 . By setting the weight per unit surface area of the precoating film to at least 0.5 mg/cm^2 , a sufficient gastric resistance over time can be obtained; by setting this to not more than 10 mg/cm^2 , the dissolution properties in an intestinal environment are good.

[0057]

Also, in the case of tablets, hard capsules or soft capsules, the precoating film is set to preferably 0.5 to 20 wt%, and more preferably 1 to 12 wt%, of the coated preparation. In the case of medicinal powders, fine granules, granules or powders, the precoating film is set to preferably 10 to 60 wt%, and more preferably 15 to 50 wt%, of the coated preparation.

[0058]

(2-3) Topcoating Film

In this invention, after forming the main coating film using the above coating composition, topcoating may additionally be carried out on the main coating film.

The topcoating composition is not particularly limited, although a composition that includes components (C), (D) and (E) may be used. Carnauba wax, white beeswax, beeswax, shellac and the like may be included as optional ingredients.

[0059]

5 The thickness of the topcoating film, as well as its weight per unit area and its weight ratio relative to the coated preparation are not particularly limited, but may be set in the same ranges as for the precoating film. By forming a topcoating film on the coated preparation, it is possible to prevent fissuring and crack initiation, provide coloration (primarily by means of component (E)), mask odors, suppress the oxidation of substances
10 included in uncoated tablets, and impart gloss with a polishing wax.

[0060]

(2-4) Overall Coating Film

Suitable contents (proportions) of the various ingredients in the overall coating film are as indicated below. In cases where the coating film is simply a main coating film, the
15 following contents indicate the content in the main coating film. In cases where a precoating film or a topcoating film or both are included, the following contents indicate the content in the overall coating film which includes the main coating film and these other coating films. Apart from the suitable contents indicated below, suitable ingredients and physicochemical properties (viscosity as a 1% aqueous solution, molecular weight, particle size) of the various
20 ingredients are the same as for the ingredients in the coating composition. In addition, aside from components (A) to (E) below, optional ingredients that may be included are likewise the same as for the coating composition.

[0061]

The content of alginate (A) relative to the weight of the overall coating film is
25 preferably from 5 to 85 wt%, more preferably from 10 to 80 wt%, even more preferably from 10 to 70 wt%, and still more preferably in the range of 10 to 60 wt%. By setting the component (A) content in the above range, good enteric properties and coating properties can be obtained.

[0062]

30 In cases where alginate (A-1) is included, the content relative to the weight of the overall coating film is preferably 5 to 85 wt%, more preferably 10 to 60 wt%, and even more preferably 20 to 50 wt%. By setting the component (A-1) content to at least this lower limit,

good enteric properties can be better obtained; by setting the content to not more than this upper limit, the stability of the coating film improves.

[0063]

In cases where alginate (A-2) is included, the content relative to the weight of the overall coating film is preferably not more than 85 wt%, more preferably 5 to 50 wt%, and even more preferably 10 to 40 wt%. By setting the content within this range, the enteric properties improve and the stability of the coating film further improves.

[0064]

The weight ratio (A-1):(A-2) ((A-1)/(A-2)) between alginate (A-1) and alginate (A-2) is preferably from 1:5 to 10:1 (0.2 to 10), more preferably from 1:3 to 5:1 (0.33 to 5), and even more preferably from 1:1.8 to 3:1 (0.56 to 3). By setting the weight ratio to at least this lower limit, the film performance under acidic conditions becomes even higher and the non-dissolvability is good; by setting the weight ratio to not more than this upper limit, the stability of the coating film becomes even better.

[0065]

The content of divalent cations (B) relative to the weight of the overall coating film is preferably from 0.005 to 0.10 wt%, more preferably from 0.01 to 0.08 wt%, and even more preferably from 0.03 to 0.06 wt%. By setting the component (B) content within this range, the stability of the coating film further improves and good enteric properties are obtained.

The amount of divalent cations used can be checked using methods and apparatuses commonly used in the field of science and technology. Examples of such methods include, but are not limited to, inductively coupled plasma emission spectrometry, inductively coupled plasma mass spectroscopy, electron beam microanalysis, x-ray photoelectron spectroscopy, secondary ion mass spectrometry, ion chromatography and atomic absorption spectrophotometry.

[0066]

The content of plasticizer (C) with respect to the weight of the overall coating film is preferably 0.1 to 70 wt%, and more preferably 2 to 50 wt%. By setting the component (C) content in the above range, the coating stability further improves. Also, good enteric properties are obtained.

[0067]

The content of film-forming ingredient (D) with respect to the weight of the overall coating film is preferably 1 to 80 wt%, and more preferably 5 to 75 wt%. By setting the component (D) content in the above range, good enteric properties can be obtained.

5 [0068]

The content of fine particles (E) with respect to the weight of the overall coating film is preferably 1 to 80 wt%, more preferably 3 to 60 wt%, and even more preferably 5 to 40 wt%. By setting the content within this range, the advantageous effect of including component (E) (the prevention of peeling of the coating film due to the sticking of coated preparation units to each other) can be better obtained. Including component (E) in an amount in excess of this range may adversely affect the film formability.

10 [0069]

Solvent that is included in the coating composition sometimes remains in the coating film, although the amount of this remaining solvent is not particularly limited so long as it is in a range that does not detract from the advantageous effects of the invention. In this invention, the amount of solvent with respect to the weight of the overall coating film is preferably not more than 30 wt%, and more preferably not more than 10 wt%. It is even more preferable for no solvent to be present (0 wt%).

[0070]

20 In the overall coating film, the weight ratio of component (C) included relative to component (A), which ratio is expressed as (C)/(A), is preferably in the range of 0.001 to 3, more preferably from 0.05 to 3, and even more preferably from 0.15 to 2. By setting the weight ratio of (C) included within this range, the film performance under acidic properties becomes higher and the stability of the coating film further improves.

25 [0071]

The weight ratio of component (B) included relative to component (C), expressed as $(B)/(C) \times 100$, is preferably from 0.02 to 5, more preferably from 0.04 to 1.6, and still more preferably from 0.06 to 1.6. By setting the weight ratio of component (B) included to at least the lower limit, the film performance under acidic properties becomes higher, resulting in good non-dissolvability; by setting the weight ratio to not more than the upper limit, the stability of the coating film becomes better.

[0072]

The weight ratio of component (D) included relative to component (A), which ratio is expressed as (A):(D) ((A)/(D)), is preferably from 1:10 to 20:1 (0.1 to 20), more preferably from 1:5 to 20:1 (0.2 to 20), and even more preferably from 1:1 to 10:1 (1 to 10). By setting
5 the weight ratio within this range, the coating film stability and the attractiveness of the appearance are maintained, in addition to which the film performance under acidic properties in particular is higher and tablets having an even higher enteric performance can be obtained.

[0073]

When precoating is carried out, the ratio of the precoating film with respect to the
10 weight of the overall coating, although not particularly limited, is preferably 5 to 60 wt%, and more preferably 10 to 50 wt%. By setting the above ratio of the precoating film to at least the lower limit of this range, a sufficient gastric resistance over time can be obtained. By setting this ratio to not more than the upper limit, the dissolvability in an enteric environment is good.

15 [0074]

When topcoating is carried out, the ratio of the topcoating film with respect to the weight of the overall coating, although not particularly limited, is preferably 5 to 60 wt%, and more preferably 10 to 50 wt%. By setting the above ratio of the topcoating film to at least the lower limit of this range, a sufficient gastric resistance over time can be obtained.
20 By setting this ratio to not more than the upper limit, the dissolvability in an enteric environment is good.

[0075]

The overall coating film has a thickness which, although not particularly limited, is preferably from 5 μm to 2.5 mm, more preferably from 10 μm to 2.0 mm, and even more
25 preferably from 50 μm to 1.5 mm. By setting the thickness of the overall coating film to at least 5 μm , a sufficient gastric resistance over time can be obtained. By setting the thickness to not more than 2.5 mm, the dissolvability in an enteric environment is good. The substrate release profile can be adjusted by varying the thickness of the overall coating film.

[0076]

30 In cases where the substrate is a tablet, hard capsule or soft capsule, the weight per unit surface area of the overall coating film, although not particularly limited, is preferably from 3.0 to 25 mg/cm^2 , and more preferably from 5.0 to 20 mg/cm^2 . By setting the weight

per unit surface area of the overall coating film to 3.0 mg/cm² or more, a sufficient gastric resistance over time can be obtained; by setting this to 25 mg/cm² or less, the dissolvability in the intestinal environment is good.

[0077]

Also, in the case of tablets, hard capsules or soft capsules, the overall coating film is set to preferably 0.5 to 20 wt%, and more preferably 1 to 15 wt%, of the coated preparation. In the case of medicinal powders, fine granules, granules or powders, the overall coating film is set to preferably 10 to 60 wt%, and more preferably 15 to 50 wt%, of the coated preparation.

[0078]

When the coated preparation is a sugar-coated tablet, as described above, in addition to components (A), (B) and (C), components (D) and (E) may also be suitably included in the main coating film. Component (C) is preferably a sugar such as glucose, high-fructose corn syrup or sucrose, or a sugar alcohol such as sorbitol, maltitol, mannitol, erythritol or xylitol. Component (D) is preferably gelatin, pectin, pullulan, gum arabic, hydroxypropyl methylcellulose or polyvinyl alcohol. Component (E) is preferably talc or titanium oxide. In addition, a colorant may also be included. Moreover, the coated preparation may also have a precoating film and/or a topcoating film that include component (C) and component (D). When the coated preparation is a sugar-coated tablet, the proportions or ratios of components (A) to (E) included in the overall coating film are the same as described above.

[0079]

(III) Method for Producing Coated Preparation

The coating composition can be obtained by mixing together the essential ingredients mentioned above. The coated preparation can be obtained by spraying the substrate with the coating composition itself or with a coating solution obtained by adding water to the coating composition, and then drying so as to form a coating film on the surface of the substrate. Because the coating composition of the invention is aqueous, coating with the use of water is possible and a coating film forms.

[0080]

The method of preparing a coating solution for the main coating film (sometimes referred to below as the “main coating solution”) is not particularly limited, provided that the various ingredients can be ultimately rendered into a mixed state on the surface of the substrate.

In this invention, the coating solution may be a one-part system prepared beforehand as a solution containing component (A), component (B) and all the optional ingredients, or may be a two-part or multi-part system prepared by separating the ingredients into a plurality of solutions.

5 [0081]

An example of a one-part main coating solution is one that includes the coating composition and water, the water content of the coating solution being preferably from 50 to 98 wt%, and more preferably from 70 to 96 wt%. Organic solvents such as ethanol may be included, provided that doing so does not detract from the advantageous effects of the invention.

10 [0082]

Examples of methods for preparing two-part and multi-part main coating solutions include, but are not limited to, the following methods:

- (i) the method of respectively preparing a solution containing component (A) and a solution containing component (B);
- 15 (ii) the method of respectively preparing a solution containing component (A) and optional ingredients and a solution containing component (B);
- (iii) the method of respectively preparing a solution containing component (A) and a solution containing component (B) and optional ingredients;
- (iv) the method of respectively preparing a solution containing component (A) and
20 optional ingredients and a solution containing component (B) and optional ingredients;
- (v) the method of respectively preparing a solution containing components (A) and (B) and a solution containing optional ingredients;
- (vi) the method of respectively preparing a solution containing component (A), a solution containing component (B), and a solution containing optional ingredients;
- 25 (vii) the method of respectively preparing a solution $\alpha 1$ containing component (A), component (B) and optional ingredients, and a solution $\alpha 2$ containing component (A), component (B) and optional ingredients (solutions $\alpha 1$ and $\alpha 2$ containing the various ingredients in differing proportions);
- (viii) the method of respectively preparing a solution α containing component (A),
30 component (B) and optional ingredients, and a solution β containing component (B) and optional ingredients;

- (ix) the method of respectively preparing a solution α containing component (A), component (B) and optional ingredients, and a solution γ containing component (A) and optional ingredients.

[0083]

5 The coater is not particularly limited. Use can be made of, for example, a pan coater, a fluidized bed coater, a tumbling coater, a draft tube spouted bed or a spray drying granulator, so long as the coater is one that is commonly used in the field of the art.

[0084]

10 The coating method is not particularly limited. For example, the method may be one that involves spraying the main coating solution onto the substrate and drying by warming so as to render the main coating solution into a film on the surface of the substrate. The main coating solution can be suitably warmed, the warming temperature being preferably from 30 to 80°C and the drying temperature being preferably from 40 to 80°C. The rate of addition of the main coating solution is preferably from 1 to 5 g/min with respect to a
15 drying air flow rate of 1 m³/min. Aside from the above, it is also possible to employ a dip coating method that dips the substrate in the main coating solution and then dries the solution. Drying is preferably carried out until the moisture content in the coated preparation becomes 0.1 to 20 wt%.

[0085]

20 When the main coating solution is a two-part or multi-part system, the respective solutions may be mixed together prior to delivery to the coater, or may be delivered to the coater and then mixed together just prior to coating or spraying onto the substrate.

 In addition, the respective solutions can be mixed together in a coating or spraying step within the coater. Examples include, but are not limited to, methods such as the
25 following:

- (i) the method of simultaneously spraying a coating solution containing component (A) and a coating solution containing component (B);
- (ii) the method of spraying a coating solution containing component (B) onto the substrate, and then spraying a coating solution containing component (A);
- 30 (iii) the method of applying a coating solution containing component (A) onto the substrate, and then spraying a coating solution containing component (B);

- (iv) the method of spraying a coating solution containing component (B) onto the substrate, and then spraying a coating solution containing components (A) and (B);
- (v) the method of spraying a coating solution containing component (A) onto the substrate, and then spraying a coating solution containing components (A) and (B);
- 5 (vi) the method of spraying a first coating solution containing components (A) and (B) onto the substrate, and then spraying a second coating solution containing components (A) and (B) in a different proportion than the first coating solution.

The coating composition and coating film of the invention can be prepared by these methods on the surface of a substrate.

10 [0086]

In cases where precoating is carried out prior to carrying out the main coating, a precoating film can be formed on the surface of the substrate by spraying the precoating composition itself, or a coating solution obtained by adding water thereto, and then drying. When forming the precoating film, an apparatus and method similar to those used in forming
15 the main coating film can be employed.

[0087]

In cases where topcoating is carried out, a topcoating film can be formed on the surface of the substrate by spraying the topcoating composition itself, or a coating solution obtained by adding water thereto, and then drying. An apparatus and method similar to those
20 used in forming the main coating film can be employed when forming the topcoating film.

[0088]

Coating may be either complete coating which covers the entire surface of the substrate, or may be partial coating which covers only part of the substrate. For example, in the case of two-layer tablets, partially coated tablets can be obtained by dipping only the
25 layer on one side of the tablets into the coating solution.

EXAMPLES

[0089]

The invention is illustrated more fully below by way of Examples and Comparative Examples, although the invention is not limited by these Examples. In the Examples that
5 follow, unless noted otherwise, all references to “%” or “ratio” of a composition are by weight.

[0090]

[Examples 1 to 34, Comparative Examples 1 to 4]

Coated tablets were produced by preparing the following uncoated tablets below, preparing coating solutions having the compositions shown in Tables 1 to 11 below, and
10 coating the uncoated tablets by the method described below. With regard to the proportion in which component (B) is included, the calcium content in calcium chloride dihydrate was calculated as 27.27 wt%, the calcium content in calcium lactate pentahydrate was calculated as 13.00 wt%, and the magnesium content in magnesium chloride hexahydrate was calculated as 11.96 wt%.

15 [Uncoated Tablets]

The starting materials shown below were mixed together and tableting was carried out using a tablet press so as to form tablets (300 mg; 9.0 mm diameter; 5.3 mm thick).

<Composition of Uncoated Tablets>

	Lactoferrin:	1,156 g
20	Dextrin:	500 g
	Crystalline cellulose:	649 g
	Maltitol:	600 g
	Carboxymethylcellulose calcium:	60 g
	Finely divided silicon dioxide:	30 g
25	Calcium stearate:	5 g

[0091]

[Preparation of Coating Solutions]

(1) Preparation of Precoating Solutions

Precoating solutions were obtained by mixing/stirring and uniformly dissolving all
30 the ingredients in accordance with the compositions in Tables 1 to 10. The right-hand columns in the tables indicate the solids content (%) (the same applies below).

(2) Preparation of Main Coating Solutions

Solution A was prepared by dispersing and uniformly dissolving components (A) and (B) in a portion of the water in accordance with the coating solution compositions in Tables 1 to 10. Next, Solution B was prepared by dispersing the other ingredients in the remaining water. Solution B was then added to Solution A and mixing/stirring was carried out, giving the main coating solution.

[0092]

[Coating]

(1) Precoating

A coater (Hicoater FZ-Lab, from Freund Corporation) was used to carry out precoating at a product temperature of about 50°C by spraying 45 g of precoating solution (25°C) onto 200 g of uncoated tablets at an average of 4 g/min. After spraying, the precoating solution was dried at about 45°C for 2 minutes, giving a coated preparation (tablets). The thickness of the precoating film was 10 to 30 µm and the weight of the precoating film per unit surface area was in the range of 1.0 to 2.0 mg/cm². In Example 32, a precoating film was not formed; only the subsequently described main coating was carried out.

(2) Main Coating

A coater (Hicoater FZ-Lab, from Freund Corporation) was used to carry out main coating at a product temperature of about 50°C by spraying 200 g of main coating solution (60°C) onto 200 g of uncoated tablets at an average of 4 g/min. After spraying, the main coating solution was dried at about 45°C for 2 minutes, giving a coated preparation (tablets). The thickness of the main coating film was 50 to 200 µm and the weight of the main coating film per unit surface area was in the range of 5 to 20 mg/cm². The thickness of the overall coating film which includes the precoating film and the main coating film was from 80 to 230 µm, the weight per unit surface area of the overall coating film which includes the precoating film and the main coating film was in the range of 7 to 21 mg/cm², and the moisture content in the coated preparation was from 2 to 7 wt%.

[0093]

[Examples 35 to 37]

Coated tablets were produced by preparing uncoated tablets in the same way as in Example 1, preparing a two-part coating solution having the composition shown in Table 11, and coating the uncoated tablets by the method described below.

[Preparation of Two-Part Coating Solution]

(1) Preparation of Main Coating Solution I

Solution A was prepared by dispersing and uniformly dissolving, in accordance with the composition shown in Table 11, component (B) in a portion of the water. Next, Solution B was prepared by dispersing the other ingredients in the remaining water. Solution B was then added to Solution A and mixing/stirring was carried out, giving Main Coating Solution I.

(2) Preparation of Main Coating Solution II

Solution A was prepared by dispersing and uniformly dissolving, in accordance with the composition shown in Table 11, component (A) in a portion of the water. Next, Solution B was prepared by dispersing the other ingredients in the remaining water. Solution B was then added to Solution A and mixing/stirring was carried out, giving Main Coating Solution II.

[0094]

[Example 38]

Coated tablets were produced by preparing uncoated tablets in the same way as in Example 1, preparing a two-part coating solution having the composition shown in Table 11, and coating the uncoated tablets by the method described below.

[Preparation of Two-Part Coating Solution]

(1) Preparation of Main Coating Solution I

Solution A was prepared by dispersing and uniformly dissolving, in accordance with the composition shown in Table 11, component (B) in a portion of the water. Next, Solution B was prepared by dispersing the other ingredients in the remaining water. Solution B was then added to Solution A and mixing/stirring was carried out, giving Main Coating Solution I.

(2) Preparation of Main Coating Solution II

Solution A was prepared by dispersing and uniformly dissolving, in accordance with the composition shown in Table 11, component (A) and component (B) in a portion of the water. Next, Solution B was prepared by dispersing the other ingredients in the remaining water. Solution B was then added to Solution A and mixing/stirring was carried out, giving Main Coating Solution II.

[0095]

[Coating]

(1) Coating I Layer (First Layer of Main Coating)

5 A coater (Hicoater FZ-Lab, from Freund Corporation) was used to carry out Coating I at a product temperature of about 50°C by spraying 45 g of Main Coating Solution I (25°C) onto 200 g of uncoated tablets at an average of 4 g/min. After spraying, drying was carried out at about 45°C for 2 minutes. The thickness of the Coating I film was 10 to 30 μm and the weight of the Coating I film per unit surface area was in the range of 1.5 to 2 mg/cm².

(2) Coating II Layer (Second Layer of Main Coating)

10 A coater (Hicoater FZ-Lab, from Freund Corporation) was used to carry out Coating II at a product temperature of about 50°C by spraying 200 g of Main Coating Solution II (60°C) onto 200 g of uncoated tablets at an average of 4 g/min. After spraying, drying was carried out at about 45°C for 2 minutes, giving a coated preparation (tablets). The thickness of the Coating II film was 50 to 200 μm and the weight of the Coating II
15 film per unit surface area was in the range of 6.5 to 9 mg/cm². The thickness of the overall coating film which includes Coatings I and II was from 80 to 230 μm, the weight per unit surface area of the overall coating film which includes Coatings I and II was in the range of 8 to 11 mg/cm², and the moisture content in the coated preparation was from 2 to 7 wt%.

20 The moisture content within the coated preparations in the Examples of the invention was measured by the following method.

[Measurement of Moisture Content in Coated Preparations]

The coated preparation was pulverized in a mortar or grinder, about 5 g of pulverized sample was placed on the weighing dish of a heating-type moisture meter, and the moisture
25 value after 20 minutes of heating at 105°C was recorded.

Moisture content (%) =

(sample weight prior to drying after pulverization - sample weight after heating) /
(sample weight prior to drying after pulverization) × 100

[0096]

[Non-Dissolvability Test at Acidic pH]

Using Japanese Pharmacopoeia (JP) Solution 1 (pH 1.2), a dissolution test by the Paddle Method (rate of rotation, 50 rpm) was carried out in accordance with “General Tests, Processes and Apparatuses” in the Japanese Pharmacopoeia and the amount of lactoferrin in the dissolution test solution sampled after 2 hours 30 minutes was assayed by the procedure described below. The test was carried out on six tablets, and the average value for these was calculated.

- ◎: Less than 1% dissolution in 2 hours 30 minutes
- : At least 1% but less than 10% dissolution in 2 hours 30 minutes
- △: At least 10% but less than 30% dissolution in 2 hours 30 minutes
- ×: At least 30% dissolution in 2 hours 30 minutes

[0097]

[Dissolution Test at Neutral to Alkaline pH]

Using JP Solution 2 (pH 6.8), a dissolution test by the Paddle Method (rate of rotation, 50 rpm) was carried out in accordance with “General Tests, Processes and Apparatuses” in the Japanese Pharmacopoeia and the amount of lactoferrin in the dissolution test solution sampled after 2 hours was assayed by the procedure described below. The test was carried out on six tablets, and the average value for these was calculated.

- ◎: At least 90% dissolution in 2 hours
- : At least 70% but less than 90% dissolution in 2 hours
- △: At least 50% but less than 70% dissolution in 2 hours
- ×: Less than 50% dissolution in 2 hours

In the above non-dissolvability test at acidic pH, △, ◎ or ○ was acceptable. In the dissolution test at neutral to alkaline pH, △, ◎ or ○ was acceptable.

[0098]

[Lactoferrin Assay]

Lactoferrin assays were carried out in accordance with the method in the proposed 9th edition of Japan's Specifications and Standards for Food Additives.

5 <Assay>

The solution obtained after two hours in the above dissolution test was used as the sample solution. Twenty microliters was collected from the sample solution and from each of three standard solutions having different concentrations, and liquid chromatography was carried out under the following operating conditions. The surface area of the lactoferrin peak for each standard solution was measured and a working curve was prepared. The lactoferrin concentration in the sample solution was determined from this working curve and the lactoferrin peak surface area of the sample solution, and the lactoferrin dissolution ratio with respect to 100 mg of lactoferrin/tablet was calculated from the following formula.

15 Lactoferrin dissolution ratio (%) =

$$\text{lactoferrin concentration (mg/mL) in sample solution} \times 900 \text{ (mL)} \times \\ \text{purity (\%)} \text{ of lactoferrin for assay} \times 1/100 \times 1/100 \text{ (mg)} \times 100$$

[0099]

Chromatography Conditions

- 20 Detector: Ultraviolet absorptiometer (Measurement wavelength: 280 nm)
Column packing: 5 µm butylated polyvinyl alcohol polymer gel for liquid chromatography (Shodex Asahipak C4P-50 4D)
Column tube: Stainless steel tube with inside diameter of 4.6 mm and length of 15 cm
Guard column: Shodex Asahipak C4P-50G 4A
25 Column temperature: 35°C

Mobile Phase A:

0.093 w/v% trifluoroacetic acid-containing acetonitrile/sodium chloride solution
(3 → 100) mixture (10:90)

Mobile Phase B:

- 30 0.03 w/v% trifluoroacetic acid-containing acetonitrile/sodium chloride solution
(3 → 100) mixture (50:50)

A linear concentration gradient from a concentration gradient A:B of 50:50 to 0:100 was carried out for 25 minutes.

Flow rate: 0.8 mL/min

Lactoferrin for assay: Bovine milk-derived lactoferrin for biochemistry, from Wako Pure
5 Chemical Industries, Ltd.

Purity (%) of lactoferrin for assay:

Numerical value of content (HPLC) on Wako Pure Chemical
Industries, Ltd. inspection report

[0100]

10 [Coating Properties]

The coating properties were evaluated based on the following criteria.

◎: Coating was carried out uniformly without any apparent chipping or peeling,
and coating surface was glossy.

○: Coating was carried out uniformly with substantially no apparent chipping
15 or peeling, but coating surface was slightly rough.

△: Chipping of coating was apparent on some tablets.

[0101]

[Storage Stability Test]

The tablets were packed under the conditions below, and stored for two months at
20 50°C and 75% relative humidity.

Packaging: bottle

Number of tablets: 60

Drying agent: one packet

A non-dissolvability test under acidic pH was carried out by the same procedure as
25 above on the tablets following storage, and the dissolution properties were evaluated.

[0102]

[Table 1]

Composition (% / solids content %)			Example									
			1		2		3		4		5	
Precoating	(C)	glycerin	2	25	2	25	2	25	2	25	2	25
	(D)	hydroxypropyl methylcellulose	6	75	6	75	6	75	6	75	6	75
	Water		92	-	92	-	92	-	92	-	92	-
	Total		100	100	100	100	100	100	100	100	100	100
Main coating	(A-1)	sodium alginate (50 to 80 mPa·s)	3.20	47.39	3.20	47.39	3.20	47.37	3.20	47.34	3.20	47.32
	(B)	calcium chloride dihydrate	0.002	0.03	0.003	0.04	0.006	0.09	0.009	0.13	0.012	0.18
		calcium lactate pentahydrate	-	-	-	-	-	-	-	-	-	-
		magnesium chloride hexahydrate	-	-	-	-	-	-	-	-	-	-
	(C)	glycerin	1.50	22.22	1.50	22.21	1.50	22.20	1.50	22.19	1.50	22.18
	(D)	hydroxypropyl methylcellulose	1.05	15.55	1.05	15.55	1.05	15.54	1.05	15.53	1.05	15.53
	(E)	silicon dioxide	0.50	7.41	0.50	7.40	0.50	7.40	0.50	7.40	0.50	7.39
		talc	0.50	7.41	0.50	7.40	0.50	7.40	0.50	7.40	0.50	7.40
	Water		93.248	-	93.247	-	93.244	-	93.241	-	93.238	-
	Total		100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Precoating	Component (C) content (%)		25.0		25.0		25.0		25.0		25.0	
	Component (D) content (%)		75.0		75.0		75.0		75.0		75.0	
	Precoating film weight (mg)		5.4		5.4		5.4		5.4		5.4	
	Precoating film content (%) in overall coating film		21.0		21.0		21.0		21.0		21.0	
Main coating	Component (A) content (%)		47.39		47.39		47.37		47.34		47.32	
	Component (B) content (%)		0.008		0.012		0.024		0.036		0.048	
	Component (C) content (%)		22.22		22.21		22.20		22.19		22.18	
	Component (D) content (%)		15.55		15.55		15.54		15.53		15.53	
	Main Coating film weight (mg)		20.3		20.3		20.3		20.3		20.3	
	Main Coating film content (%) in overall coating film		79.0		79.0		79.0		79.0		79.0	
	(B)/(A) × 100		0.02		0.03		0.05		0.08		0.10	
	(B)/(C) × 100		0.04		0.06		0.11		0.16		0.22	
Overall coating film	Component (A) content (%)		37.4		37.4		37.4		37.4		37.4	
	Component (B) content (%)		0.006		0.010		0.019		0.029		0.038	
	Component (C) content (%)		22.8		22.8		22.8		22.8		22.8	
	Component (D) content (%)		28.1		28.1		28.1		28.0		28.0	
	(B)/(A) × 100		0.017		0.026		0.051		0.077		0.102	
	(B)/(C) × 100		0.028		0.042		0.084		0.126		0.168	
Evaluations	Coating properties		○		○		○		○		○	
	Initial	Dissolvability (pH 6.8)	○		○		○		○		○	
		Non-dissolvability (pH 1.2)	◎		◎		◎		◎		◎	
	After 2 months storage at 50°C/75%RH	Non-dissolvability (pH 1.2)	△		○		○		○		◎	

[0103]

[Table 2]

Composition (% / solids content %)			Example							
			6		7		8		9	
Precoating	(C)	glycerin	2	25	2	25	2	25	2	25
	(D)	hydroxypropyl methylcellulose	6	75	6	75	6	75	6	75
	Water		92	-	92	-	92	-	92	-
	Total		100	100	100	100	100	100	100	100
Main coating	(A-1)	sodium alginate (50 to 80 mPa·s)	3.20	47.28	3.20	47.24	3.20	47.23	3.20	47.22
	(B)	calcium chloride dihydrate	0.018	0.27	0.024	0.35	-	-	-	-
		calcium lactate pentahydrate	-	-	-	-	0.025	0.37	-	-
		magnesium chloride hexahydrate	-	-	-	-	-	-	0.027	0.40
	(C)	glycerin	1.50	22.16	1.50	22.14	1.50	22.14	1.50	22.13
	(D)	hydroxypropyl methylcellulose	1.05	15.51	1.05	15.50	1.05	15.50	1.05	15.49
	(E)	silicon dioxide	0.50	7.39	0.50	7.38	0.50	7.38	0.50	7.38
		talc	0.50	7.39	0.50	7.38	0.50	7.38	0.50	7.38
	Water		93.232	-	93.226	-	93.225	-	93.223	-
	Total		100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Precoating	Component (C) content (%)		25.0		25.0		25.0		25.0	
	Component (D) content (%)		75.0		75.0		75.0		75.0	
	Precoating film weight (mg)		5.4		5.4		5.4		5.4	
	Precoating film content (%) in overall coating film		21.0		21.0		21.0		21.0	
Main coating	Component (A) content (%)		47.28		47.24		47.23		47.22	
	Component (B) content (%)		0.073		0.097		0.048		0.048	
	Component (C) content (%)		22.16		22.14		22.14		22.13	
	Component (D) content (%)		15.51		15.50		15.50		15.49	
	Main Coating film weight (mg)		20.3		20.3		20.3		20.3	
	Main Coating film content (%) in overall coating film		79.0		79.0		79.0		79.0	
	(B)/(A) × 100		0.15		0.20		0.10		0.10	
	(B)/(C) × 100		0.33		0.44		0.22		0.22	
Overall coating film	Component (A) content (%)		37.3		37.3		37.3		37.3	
	Component (B) content (%)		0.057		0.076		0.038		0.038	
	Component (C) content (%)		22.8		22.7		22.7		22.7	
	Component (D) content (%)		28.0		28.0		28.0		28.0	
	(B)/(A) × 100		0.153		0.204		0.102		0.101	
	(B)/(C) × 100		0.252		0.336		0.167		0.166	
Evaluations	Coating properties		○		○		○		○	
	Initial	Dissolvability (pH 6.8)	○		○		○		○	
		Non-dissolvability (pH 1.2)	◎		◎		◎		◎	
	After 2 months storage at 50°C/75%RH	Non-dissolvability (pH 1.2)	◎		○		◎		◎	

[0104]

[Table 3]

Composition (% / solids content %)			Comparative Example							
			1		2		3		4	
Precoating	(C)	glycerin	2	25	2	25	2	25	2	25
	(D)	hydroxypropyl methylcellulose	6	75	6	75	6	75	6	75
	Water		92	-	92	-	92	-	92	-
	Total		100	100	100	100	100	100	100	100
Main coating	(A-1)	sodium alginate (50 to 80 mPa·s)	-	-	-	-	3.20	47.41	3.20	47.20
	(A-2)	sodium alginate (at least 20 mPa·s but less than 50 mPa·s)	-	-	-	-	-	-	-	-
	Comparative products for (A)	xanthan gum	3.20	47.32	-	-	-	-	-	-
		gellan gum	-	-	3.20	47.32	-	-	-	-
	(B)	calcium chloride dihydrate	0.012	0.18	0.012	0.18	0.00	0.00	0.03	0.44
	(C)	glycerin	1.50	22.18	1.50	22.18	1.50	22.22	1.50	22.12
	(D)	hydroxypropyl methylcellulose	1.05	15.53	1.05	15.53	1.05	15.56	1.05	15.49
	(E)	silicon dioxide	0.50	7.39	0.50	7.39	0.50	7.41	0.50	7.37
		talc	0.50	7.39	0.50	7.39	0.50	7.41	0.50	7.37
	Water		93.238	-	93.238	-	93.250	-	93.220	-
	Total		100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Precoating	Component (C) content (%)		25.0		25.0		25.0		25.0	
	Component (D) content (%)		75.0		75.0		75.0		75.0	
	Precoating film weight (mg)		5.4		5.4		5.4		5.4	
	Precoating film content (%) in overall coating film		21.0		21.0		21.1		21.0	
Main coating	Component (A) or comparative product (A) content (%)		47.32		47.32		47.41		47.20	
	Component (B) content (%)		0.05		0.05		0.00		0.12	
	Component (C) content (%)		22.18		22.18		22.22		22.12	
	Component (D) content (%)		15.53		15.53		15.56		15.49	
	Main Coating film weight (mg)		20.3		20.3		20.2		20.3	
	Main Coating film content (%) in overall coating film		79.0		79.0		78.9		79.0	
	(B)/(A) × 100		0.10		0.10		0.00		0.26	
	(B)/(C) × 100		0.22		0.22		0.00		0.55	
Overall coating film	Component (A) or comparative product (A) content (%)		37.4		37.4		37.4		37.3	
	Component (B) content (%)		0.038		0.038		0.000		0.095	
	Component (C) content (%)		22.8		22.8		22.8		22.7	
	Component (D) content (%)		28.0		28.0		28.1		28.0	
	(B)/((A) or comparative product (A)) × 100		0.102		0.102		0.000		0.256	
	(B)/(C) × 100		0.168		0.168		0.000		0.419	
Evaluations	Coating properties		×		×		○		○	
	Initial	Dissolvability (pH 6.8)	◎		◎		○		△	
		Non-dissolvability (pH 1.2)	×		×		◎		◎	
	After 2 months storage at 50°C/75%RH	Non-dissolvability (pH 1.2)	×		×		×		×	

[0105]

[Table 4]

Composition (% / solids content %)			Example									
			10		11		12		13		14	
Precoating	(C)	glycerin	2	25	2	25	2	25	2	25	2	25
	(D)	hydroxypropyl methylcellulose	6	75	6	75	6	75	6	75	6	75
	Water		92	-	92	-	92	-	92	-	92	-
	Total		100	100	100	100	100	100	100	100	100	100
Main coating	(A-1)	sodium alginate (50 to 80 mPa·s)	1.60	23.66	1.80	26.62	1.40	20.70	-	-	-	-
	(A-2)	sodium alginate (at least 20 mPa·s but less than 50 mPa·s)	1.60	23.66	1.40	20.70	1.80	26.62	3.20	47.32	-	-
	(A-1)	sodium alginate (300 to 400 mPa·s)	-	-	-	-	-	-	-	-	3.20	47.32
	(B)	calcium chloride dihydrate	0.012	0.18	0.012	0.18	0.012	0.18	0.012	0.18	0.012	0.18
	(C)	glycerin	1.50	22.18	1.50	22.18	1.50	22.18	1.50	22.18	1.50	22.18
	(D)	hydroxypropyl methylcellulose	1.05	15.53	1.05	15.53	1.05	15.53	1.05	15.53	1.05	15.53
	(E)	silicon dioxide	0.50	7.39	0.50	7.39	0.50	7.39	0.50	7.39	0.50	7.39
		talc	0.50	7.39	0.50	7.39	0.50	7.40	0.50	7.39	0.50	7.39
	Water		93.238	-	93.238	-	93.238	-	93.238	-	93.238	-
	Total		100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Precoating	Component (C) content (%)		25.0		25.0		25.0		25.0		25.0	
	Component (D) content (%)		75.0		75.0		75.0		75.0		75.0	
	Precoating film weight (mg)		5.4		5.4		5.4		5.4		5.4	
	Precoating film content (%) in overall coating film		21.0		21.0		21.0		21.0		21.0	
Main coating	Component (A) content (%)		47.3		47.3		47.3		47.3		47.3	
	Component (B) content (%)		0.05		0.05		0.05		0.05		0.05	
	Component (C) content (%)		22.18		22.18		22.18		22.18		22.18	
	Component (D) content (%)		15.53		15.53		15.53		15.53		15.53	
	Main Coating film weight (mg)		20.3		20.3		20.3		20.3		20.3	
	Main Coating film content (%) in overall coating film		79.0		79.0		79.0		79.0		79.0	
	(B)/(A) × 100		0.10		0.10		0.10		0.10		0.10	
	(B)/(C) × 100		0.22		0.22		0.22		0.22		0.22	
Overall coating film	Component (A) content (%)		37.4		37.4		37.4		37.4		37.4	
	Component (B) content (%)		0.038		0.038		0.038		0.038		0.038	
	Component (C) content (%)		22.8		22.8		22.8		22.8		22.8	
	Component (D) content (%)		28.0		28.0		28.0		28.0		28.0	
	(B)/(A) × 100		0.102		0.102		0.102		0.102		0.102	
	(B)/(C) × 100		0.168		0.168		0.168		0.168		0.168	
Evaluations	Coating properties		◎		◎		◎		◎		○	
	Initial	Dissolvability (pH 6.8)	◎		◎		◎		◎		○	
		Non-dissolvability (pH 1.2)	◎		◎		◎		○		◎	
	After 2 months storage at 50°C/ 75%RH	Non-dissolvability (pH 1.2)	◎		◎		◎		○		◎	

[0106]

[Table 5]

Composition (% / solids content %)			Example			
			15		16	
Precoating	(C)	glycerin	2	25	2	25
	(D)	hydroxypropyl methylcellulose	6	75	6	75
	Water		92	-	92	-
	Total		100	100	100	100
Main coating	(A-1)	sodium alginate (50 to 80 mPa·s)	0.70	8.33	2.50	49.84
	(A-2)	sodium alginate (at least 20 mPa·s but less than 50 mPa·s)	0.20	2.38	1.50	29.90
	(B)	calcium chloride dihydrate	0.004	0.05	0.016	0.32
	(C)	glycerin	1.50	17.85	-	-
	(D)	hydroxypropyl methylcellulose	5.00	59.50	-	-
	(E)	silica	0.50	5.95	0.50	9.97
		talc	0.50	5.95	0.50	9.97
	Water		91.596	-	94.984	-
	Total		100.0	100.0	100.0	100.0
Precoating	Component (C) content (%)		25.0		25.0	
	Component (D) content (%)		75.0		75.0	
	Precoating film weight (mg)		5.4		5.4	
	Precoating film content (%) in overall coating film		17.6		26.4	
Main coating	Component (A) content (%)		10.7		79.7	
	Component (B) content (%)		0.01		0.09	
	Component (C) content (%)		17.85		-	
	Component (D) content (%)		59.50		0.00	
	Main Coating film weight (mg)		25.2		15.0	
	Main Coating film content (%) in overall coating film		82.4		73.6	
	(B)/(A) × 100		0.12		0.11	
	(B)/(C) × 100		0.07		-	
Overall coating film	Component (A) content (%)		8.8		58.7	
	Component (B) content (%)		0.011		0.064	
	Component (C) content (%)		19.1		6.6	
	Component (D) content (%)		62.2		19.8	
	(B)/(A) × 100		0.121		0.109	
	(B)/(C) × 100		0.056		0.969	
Evaluations	Coating properties		⊙		○	
	Initial	Dissolvability (pH 6.8)	⊙		⊙	
		Non-dissolvability (pH 1.2)	○		○	
	After 2 months storage at 50°C/75%RH		○		△	

[0107]

[Table 6]

Composition (% / solids content %)			Example											
			17		18		19		20		21		22	
Precoating	(C)	glycerin	2	25	2	25	2	25	2	25	2	25	2	25
	(D)	hydroxypropyl methylcellulose	6	75	6	75	6	75	6	75	6	75	6	75
	Water		92	-	92	-	92	-	92	-	92	-	92	-
	Total		100	100	100	100	100	100	100	100	100	100	100	100
Main coating	(A-1)	sodium alginate (50 to 80 mPa·s)	1.40	26.61	1.40	25.58	1.40	24.30	1.40	22.18	1.40	19.02	2.00	17.60
	(A-2)	sodium alginate (at least 20 mPa·s but less than 50 mPa·s)	1.80	34.21	1.80	32.89	1.80	31.24	1.80	28.52	1.80	24.45	1.00	8.80
	(B)	calcium chloride dihydrate	0.012	0.23	0.012	0.22	0.012	0.21	0.012	0.19	0.012	0.16	0.012	0.11
	(C)	glycerin	-	-	0.21	3.84	0.50	8.68	1.05	16.63	2.10	28.52	6.30	55.45
	(D)	hydroxypropyl methylcellulose	1.05	19.95	1.05	19.19	1.05	18.22	1.05	16.63	1.05	14.26	1.05	9.24
	(E)	silica	0.50	9.50	0.50	9.14	0.50	8.68	0.50	7.92	0.50	6.79	0.50	4.40
		talc	0.50	9.50	0.50	9.14	0.50	8.68	0.50	7.92	0.50	6.79	0.50	4.40
	Water		94.738	-	94.528	-	94.238	-	93.688	-	92.638	-	88.638	-
	Total		100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Precoating	Component (C) content (%)		25.0		25.0		25.0		25.0		25.0		25.0	
	Component (D) content (%)		75.0		75.0		75.0		75.0		75.0		75.0	
	Precoating film weight (mg)		5.4		5.4		5.4		5.4		5.4		5.4	
	Precoating film content (%) in overall coating film		25.5		24.8		23.8		22.2		19.6		13.7	
Main coating	Component (A) content (%)		60.8		58.5		55.5		50.7		43.5		26.4	
	Component (B) content (%)		0.06		0.06		0.06		0.05		0.04		0.03	
	Component (C) content (%)		-		3.84		8.68		16.63		28.52		55.45	
	Component (D) content (%)		19.95		19.19		18.22		16.63		14.26		9.24	
	Main Coating film weight (mg)		15.8		16.4		17.3		18.9		22.1		34.1	
	Main Coating film content (%) in overall coating film		74.5		75.2		76.2		77.8		80.4		86.3	
	(B)/(A) × 100		0.10		0.10		0.10		0.10		0.10		0.11	
	(B)/(C) × 100		-		1.56		0.65		0.31		0.16		0.05	
Overall coating film	Component (A) content (%)		45.3		44.0		42.3		39.4		34.9		22.8	
	Component (B) content (%)		0.046		0.045		0.043		0.040		0.036		0.025	
	Component (C) content (%)		6.4		9.1		12.6		18.5		27.8		51.3	
	Component (D) content (%)		34.0		33.0		31.7		29.6		26.2		18.2	
	(B)/(A) × 100		0.102		0.102		0.102		0.102		0.102		0.109	
	(B)/(C) × 100		0.727		0.496		0.344		0.218		0.128		0.048	
Evaluations	Coating properties		⊙		⊙		⊙		⊙		⊙		⊙	
	Initial	Dissolvability (pH 6.8)	⊙		⊙		⊙		⊙		⊙		⊙	
		Non-dissolvability (pH 1.2)	⊙		⊙		⊙		⊙		⊙		⊙	
	After 2 months storage at 50°C/ 75%RH	Non-dissolvability (pH 1.2)	○		⊙		⊙		⊙		⊙		○	

[0108]

[Table 7]

Composition (% / solids content %)			Example			
			23		24	
Precoating	(C)	glycerin	2	25	2	25
	(D)	hydroxypropyl methylcellulose	6	75	6	75
	Water		92	-	92	-
	Total		100	100	100	100
Main coating	(A-1)	sodium alginate (50 to 80 mPa·s)	1.40	22.18	1.40	22.18
	(A-2)	sodium alginate (at least 20 mPa·s but less than 50 mPa·s)	1.80	28.52	1.80	28.52
	(B)	calcium chloride dihydrate	0.012	0.19	0.012	0.19
	(C)	sucrose stearate	1.05	16.63	-	-
		sorbitol	-	-	1.05	16.63
	(D)	hydroxypropyl methylcellulose	1.05	16.63	1.05	16.63
	(E)	silica	0.50	7.92	0.50	7.92
		talc	0.50	7.92	0.50	7.92
	Water		93.688	-	93.688	-
	Total		100.0	100.0	100.0	100.0
Precoating	Component (C) content (%)		25.0		25.0	
	Component (D) content (%)		75.0		75.0	
	Precoating film weight (mg)		5.4		5.4	
	Precoating film content (%) in overall coating film		22.2		22.2	
Main coating	Component (A) content (%)		50.7		50.7	
	Component (B) content (%)		0.05		0.05	
	Component (C) content (%)		16.63		16.63	
	Component (D) content (%)		16.63		16.63	
	Main Coating film weight (mg)		18.9		18.9	
	Main Coating film content (%) in overall coating film		77.8		77.8	
	(B)/(A) × 100		0.10		0.10	
	(B)/(C) × 100		0.31		0.31	
Overall coating film	Component (A) content (%)		39.4		39.4	
	Component (B) content (%)		0.040		0.040	
	Component (C) content (%)		18.5		18.5	
	Component (D) content (%)		29.6		29.6	
	(B)/(A) × 100		0.102		0.102	
	(B)/(C) × 100		0.218		0.218	
Evaluations	Coating properties		◎		◎	
	Initial	Dissolvability (pH 6.8)	◎		◎	
		Non-dissolvability (pH 1.2)	◎		◎	
	After 2 months storage at 50°C/75%RH		◎		◎	

[0109]

[Table 8]

Composition (% / solids content %)			Example									
			25		26		27		28		29	
Precoating	(C)	glycerin	2	25	2	25	2	25	2	25	2	25
	(D)	hydroxypropyl methylcellulose	6	75	6	75	6	75	6	75	6	75
	Water		92	-	92	-	92	-	92	-	92	-
	Total		100	100	100	100	100	100	100	100	100	100
Main coating	(A-1)	sodium alginate (50 to 80 mPa·s)	1.40	26.61	1.40	25.63	1.40	19.02	1.40	13.64	1.00	8.29
	(A-2)	sodium alginate (at least 20 mPa·s but less than 50 mPa·s)	1.80	34.21	1.80	32.95	1.80	24.45	1.80	17.54	1.00	8.29
	(B)	calcium chloride dihydrate	0.012	0.23	0.012	0.22	0.012	0.16	0.012	0.12	0.008	0.07
	(C)	glycerin	1.05	19.95	1.05	19.22	1.05	14.26	1.05	10.23	1.05	8.71
	(D)	hydroxypropyl methylcellulose	-	-	0.20	3.66	2.10	28.52	5.00	48.72	8.00	66.35
		pullulan	-	-	-	-	-	-	-	-	-	-
		gelatin	-	-	-	-	-	-	-	-	-	-
	(E)	silica	0.50	9.50	0.50	9.15	0.50	6.79	0.50	4.87	0.50	4.15
		talc	0.50	9.50	0.50	9.15	0.50	6.79	0.50	4.87	0.50	4.15
	Water		94.738	-	94.538	-	92.638	-	89.738	-	87.942	-
	Total		100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Precoating	Component (C) content (%)		25.0		25.0		25.0		25.0		25.0	
	Component (D) content (%)		75.0		75.0		75.0		75.0		75.0	
	Precoating film weight (mg)		5.4		5.4		5.4		5.4		5.4	
	Precoating film content (%) in overall coating film		25.5		24.8		19.6		14.9		13.0	
Main coating	Component (A) content (%)		60.8		58.6		43.5		31.2		16.6	
	Component (B) content (%)		0.06		0.06		0.04		0.03		0.02	
	Component (C) content (%)		19.95		19.22		14.26		10.23		8.71	
	Component (D) content (%)		0.0		3.7		28.5		48.7		66.3	
	Main Coating film weight (mg)		15.8		16.4		22.1		30.8		36.2	
	Main Coating film content (%) in overall coating film		74.5		75.2		80.4		85.1		87.0	
	(B)/(A) × 100		0.10		0.10		0.10		0.10		0.11	
	(B)/(C) × 100		0.31		0.31		0.31		0.31		0.21	
Overall coating film	Component (A) content (%)		45.3		44.1		34.9		26.5		14.4	
	Component (B) content (%)		0.046		0.045		0.036		0.027		0.016	
	Component (C) content (%)		21.2		20.7		16.4		12.4		10.8	
	Component (D) content (%)		19.1		21.3		37.7		52.6		67.5	
	(B)/(A) × 100		0.102		0.102		0.102		0.102		0.109	
	(B)/(C) × 100		0.218		0.218		0.218		0.218		0.145	
Evaluations	Coating properties		◎		◎		◎		◎		◎	
	Initial	Dissolvability (pH 6.8)	◎		◎		◎		◎		◎	
		Non-dissolvability (pH 1.2)	○		◎		◎		◎		◎	
	After 2 months storage at 50°C/ 75%RH	Non-dissolvability (pH 1.2)	○		◎		◎		◎		◎	

[0110]

[Table 9]

Composition (% / solids content %)			Example			
			30		31	
Precoating	(C)	glycerin	2	25	2	25
	(D)	hydroxypropyl methylcellulose	6	75	6	75
	Water		92	-	92	-
	Total		100	100	100	100
Main coating	(A-1)	sodium alginate (50 to 80 mPa·s)	1.40	22.18	1.40	22.18
	(A-2)	sodium alginate (at least 20 mPa·s but less than 50 mPa·s)	1.80	28.52	1.80	28.52
	(B)	calcium chloride dihydrate	0.012	0.19	0.012	0.19
	(C)	glycerin	1.05	16.63	1.05	16.63
	(D)	hydroxypropyl methylcellulose	-	-	-	-
		pullulan	1.05	16.63	-	-
		gelatin	-	-	1.05	16.63
	(E)	silica	0.50	7.92	0.50	7.92
		talc	0.50	7.92	0.50	7.92
	Water		93.688	-	93.688	-
	Total		100.0	100.0	100.0	100.0
Precoating	Component (C) content (%)		25.0		25.0	
	Component (D) content (%)		75.0		75.0	
	Precoating film weight (mg)		5.4		5.4	
	Precoating film content (%) in overall coating film		22.2		22.2	
Main coating	Component (A) content (%)		50.7		50.7	
	Component (B) content (%)		0.05		0.05	
	Component (C) content (%)		16.63		16.63	
	Component (D) content (%)		16.6		16.6	
	Main Coating film weight (mg)		18.9		18.9	
	Main Coating film content (%) in overall coating film		77.8		77.8	
	(B)/(A) × 100		0.10		0.10	
	(B)/(C) × 100		0.31		0.31	
Overall coating film	Component (A) content (%)		39.4		39.4	
	Component (B) content (%)		0.040		0.040	
	Component (C) content (%)		18.5		18.5	
	Component (D) content (%)		29.6		29.6	
	(B)/(A) × 100		0.102		0.102	
	(B)/(C) × 100		0.218		0.218	
Evaluations	Coating properties		◎		◎	
	Initial	Dissolvability (pH 6.8)	◎		◎	
		Non-dissolvability (pH 1.2)	◎		◎	
	After 2 months storage at 50°C/75%RH		◎		◎	

[0111]

[Table 10]

Composition (% / solids content %)			Example					
			32		33		34	
Precoating	(C)	glycerin	-	-	2	25	2	25
	(D)	pullulan	-	-	6	75	-	-
		gelatin	-	-	-	-	6	75
	Water		-	-	92	-	92	-
	Total		0	0	100	100	100	100
Main coating	(A-1)	sodium alginate (50 to 80 mPa·s)	1.40	22.18	1.40	22.18	1.40	22.18
	(A-2)	sodium alginate (at least 20 mPa·s but less than 50 mPa·s)	1.80	28.52	1.80	28.52	1.80	28.52
	(B)	calcium chloride dihydrate	0.012	0.19	0.012	0.19	0.012	0.19
	(C)	glycerin	1.05	16.63	1.05	16.63	1.05	16.63
	(D)	hydroxypropyl methylcellulose	1.05	16.63	1.05	16.63	1.05	16.63
	(E)	silica	0.50	7.92	0.50	7.92	0.50	7.92
		talc	0.50	7.92	0.50	7.92	0.50	7.92
	Water		93.688	-	93.688	-	93.688	-
	Total		100.0	100.0	100.0	100.0	100.0	100.0
Precoating	Component (C) content (%)		-		25.0		25.0	
	Component (D) content (%)		-		75.0		75.0	
	Precoating film weight (mg)		0.0		5.4		5.4	
	Precoating film content (%) in overall coating film		0.0		22.2		22.2	
Main coating	Component (A) content (%)		50.7		50.7		50.7	
	Component (B) content (%)		0.05		0.05		0.05	
	Component (C) content (%)		16.6		16.6		16.6	
	Component (D) content (%)		16.6		16.6		16.6	
	Main Coating film weight (mg)		18.9		18.9		18.9	
	Main Coating film content (%) in overall coating film		100.0		77.8		77.8	
	(B)/(A) × 100		0.10		0.10		0.10	
	(B)/(C) × 100		0.31		0.31		0.31	
Overall coating film	Component (A) content (%)		50.7		39.4		39.4	
	Component (B) content (%)		0.052		0.040		0.040	
	Component (C) content (%)		16.6		18.5		18.5	
	Component (D) content (%)		16.6		29.6		29.6	
	(B)/(A) × 100		0.102		0.102		0.102	
	(B)/(C) × 100		0.312		0.218		0.218	
Evaluations	Coating properties		◎		◎		◎	
	Initial	Dissolvability (pH 6.8)	◎		◎		◎	
		Non-dissolvability (pH 1.2)	○		◎		◎	
	After 2 months storage at 50°C/75%RH	Non-dissolvability (pH 1.2)	○		◎		◎	

[0112]

[Table 11]

Composition (% / solids content %)			Example							
			35		36		37		38	
Coating I	(B)	calcium chloride dihydrate	0.008	0.10	0.040	0.50	0.120	1.48	0.040	0.50
	(C)	glycerin	2.000	24.98	2.000	24.88	2.000	24.63	2.000	24.88
	(D)	hydroxypropyl methylcellulose	6.000	74.93	6.000	74.63	6.000	73.89	6.000	74.63
	Water		91.99	-	91.96	-	91.88	-	91.96	-
	Total		100	100	100	100	100	100	100	100
Coating II	(A-1)	sodium alginate (50 to 80 mPa·s)	1.40	22.22	1.40	22.22	1.40	22.22	1.40	22.19
	(A-2)	sodium alginate (at least 20 mPa·s but less than 50 mPa·s)	1.80	28.57	1.80	28.57	1.80	28.57	1.80	28.53
	(B)	calcium chloride dihydrate	-	0.00	-	0.00	-	0.00	0.01	0.16
	(C)	glycerin	1.05	16.67	1.05	16.67	1.05	16.67	1.05	16.64
	(D)	hydroxypropyl methylcellulose	1.05	16.67	1.05	16.67	1.05	16.67	1.05	16.64
	(E)	silica	0.500	7.94	0.500	7.94	0.500	7.94	0.500	7.92
		talc	0.50	7.94	0.50	7.94	0.50	7.94	0.50	7.92
	Water		93.700	-	93.700	-	93.700	-	93.690	-
	Total		100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Coating I	Coating I film weight (mg)		5.4		5.4		5.4		5.4	
	Coating I film content (%) in overall coating film		22.2		22.2		22.2		22.2	
Coating II	Coating II film weight (mg)		18.9		18.9		18.9		18.9	
	Coating II film content (%) in overall coating film		77.8		77.8		77.8		77.8	
Overall coating film	Component (A) content (%)		39.5		39.5		39.5		39.5	
	Component (B) content (%)		0.006		0.030		0.090		0.064	
	Component (C) content (%)		18.5		18.5		18.4		18.5	
	Component (D) content (%)		29.6		29.5		29.4		29.5	
	(B)/(A) × 100		0.015		0.076		0.227		0.162	
	(B)/(C) × 100		0.033		0.163		0.486		0.345	
Evaluations	Coating properties		◎		◎		◎		◎	
	Initial	Dissolvability (pH 6.8)	◎		◎		◎		◎	
		Non-dissolvability (pH 1.2)	◎		◎		◎		◎	
	After 2 months storage at 50°C/75%RH	Non-dissolvability (pH 1.2)	○		○		○		◎	

[0113]

The starting materials used for preparation in the Examples and Comparative Examples are shown below.

5 [Table 12]

Starting material	Manufacturer	Trade name
Lactoferrin	Morinaga Milk Industry Co., Ltd.	
Dextrin	Roquette	MALTRIN M040
Crystalline cellulose	Asahi Kasei Chemicals	Ceolus UF-F711
Maltitol	Mitsubishi Shoji Foodtech Co., Ltd.	G-3
Carboxymethylcellulose calcium	Nichirin Chemical Industries, Ltd.	ECG-FA
Finely divided silicon dioxide	DSL. Japan Co., Ltd.	Carplex FPS-500
Calcium stearate	Taihei Chemical Industrial Co., Ltd.	food additive
Sodium alginate (300 to 400 mPa·s)	KIMICA Corporation	KIMICA ALGIN I-3
Sodium alginate (50 to 80 mPa·s)	KIMICA Corporation	KIMICA ALGIN IL-6
Sodium alginate (at least 20 mPa·s but less than 50 mPa·s)	KIMICA Corporation	KIMICA ALGIN IL-2
Calcium chloride dihydrate	Tokuyama Corporation	food additive
Calcium lactate pentahydrate	Taihei Chemical Industrial Co., Ltd.	calcium lactate (using fermented lactic acid)
Magnesium chloride hexahydrate	Naikai Salt Industries Co., Ltd.	food additive
Xanthan gum	DSP Gokyo Food & Chemical Co., Ltd.	Echo Gum
Gellan gum	DSP Gokyo Food & Chemical Co., Ltd.	Kelcogel
Glycerin	Sakamoto Yakuhin Kogyo Co., Ltd.	food additive glycerin
Sucrose stearate	Mitsubishi Kagaku Foods Corporation	Ryoto Sugar Ester S-370F
Sorbitol	Mitsubishi Shoji Foodtech Co., Ltd.	Sorbit D-70
Hydroxypropyl methylcellulose	Shin-Etsu Chemical Co., Ltd.	Metolose SE-06
Pullulan	Hayashibara Co., Ltd.	food additive pullulan
Gelatin	Nitta Gelatin Inc.	Ixos HDL-50F
Silica	Fuji Silysia Chemical Ltd.	Silopage 720
Talc	Kihara Kasei KK	LisBlanc

[0014]

[Table 13]

	Weight-average molecular weight	Manufacturer	Trade name
Sodium alginate (300 to 400 mPa·s)	1,850,000	KIMICA Corporation	KIMICA ALGIN I-3
Sodium alginate (50 to 80 mPa·s)	1,000,000	KIMICA Corporation	KIMICA ALGIN IL-6
Sodium alginate (at least 20 mPa·s but less than 50 mPa·s)	720,000	KIMICA Corporation	KIMICA ALGIN IL-2

CLAIMS:

1. A coating composition comprising (A) an alginate and (B) a divalent cation, wherein the weight ratio of component (B) included relative to component (A), expressed as $(B)/(A) \times 100$, is from 0.015 to 0.25.
2. The coating composition of claim 1, wherein component (A) is an alginate having a viscosity, measured as a 1 wt% aqueous solution at 20°C, of not more than 600 mPa·s.
3. The coating composition of claim 1 or 2, further comprising (C) a plasticizer.
4. The coating composition of claim 3, wherein the weight ratio of component (B) included relative to component (C), expressed as $(B)/(C) \times 100$, is from 0.02 to 5.
5. The coating composition of any one of claims 1 to 4, further comprising (D) a film-forming ingredient.
6. A coated preparation comprising a substrate and a coating film formed on the substrate from the coating composition of any one of claims 1 to 5.
7. A method for producing a coated preparation, comprising the step of forming a coating film on a surface of a substrate by spraying a coating solution containing the coating composition of any one of claims 1 to 5 and water onto the substrate and then drying.
8. A coating film that is formed on a surface of a substrate and comprises (A) an alginate and (B) a divalent cation, wherein the weight ratio of component (B) included relative to component (A), expressed as $(B)/(A) \times 100$, is from 0.015 to 0.25.
9. The coating film of claim 8, further comprising (C) a plasticizer.
10. The coating film of claim 9, wherein the weight ratio of component (B) included relative to component (C), expressed as $(B)/(C) \times 100$, is from 0.02 to 5.

11. The coating film of any one of claims 8 to 10, further comprising (D) a film-forming ingredient.