

Description
Gelatin Capsule

Technical Field

[0001]

The present invention relates to a gelatin capsule having disintegration delay suppressed.

Background Art

[0002]

A capsule having a shell made of gelatin has advantages such that it is nontoxic to a human body and is rapidly dissolved in a human body and thereby is a dosage form most widely used, particularly in the field of food. However, there is a problem such that gelatin becomes insoluble due to thermal denaturalization, crosslinked structures of gelatin molecules are formed due to oxidization, which results in disintegration delay. Particularly, when the filled contents contain an unsaturated fatty acid such as DHA or EPA, an oily ingredient formed of oil and fat having unsaturated fatty acid residues, a vitamin, a polyphenol, etc., gelatin molecules in the shell interact with the filled contents, the insolubilization of gelatin shell results with time, and the disintegration of a formulation is considerably delayed, which is disadvantageous. If such disintegration delay occurs, bioavailability of the formulation decreases, and an expected effect cannot be fully obtained.

[0003]

As methods for preventing disintegration delay, a method of adding amino acid to gelatin shell (Patent Document 1), a method of adding citric acid to gelatin shell (Patent Document 2), a method of adding inositol hexaphosphate (phytic acid) to gelatin shell (Patent Document 3), a method of adding tartaric acid to gelatin shell (Patent Document 4), etc. have been reported.

However, the effects of preventing disintegration delay by these methods are not fully satisfied. Further, it has been concerned that if an organic acid is added, the viscosity is lowered, resulting in the deterioration of the strength of the shell, and the outer appearance is impaired.

Prior Art Documents

Patent Documents

[0004]

Patent Document 1: JP-B-1982-30088

Patent Document 2: JP-A-1984-39834

Patent Document 3: JP-A-2006-328044

Patent Document 4: Japanese Patent No. 5829607

Summary of the Invention

Problems to be Solved by the Invention

[0005]

The present invention relates to providing a gelatin capsule having disintegration delay suppressed.

Means for Solving the Problems

[0006]

Under such circumstances, the present inventors have

conducted extensive studies and have found that, by incorporating malic acid or a salt thereof into a capsule shell containing gelatin, the drop in solubility of the shell in water can be effectively suppressed without causing a considerable decrease in viscosity.

[0007]

That is, the present invention is directed to the following 1) to 6).

1) A capsule having a capsule shell which comprises gelatin as a base material, and malic acid or a salt thereof.

2) The capsule according to 1), wherein the content of malic acid or a salt thereof in the shell is from 0.5 to 12 parts by mass, per 100 parts by mass of gelatin.

3) The capsule according to 1) or 2), which is a soft capsule.

4) The capsule according to any one of 1) to 3), which encloses one or more members selected from a) an unsaturated fatty acid, b) a fat and oil containing an unsaturated fatty acid as a component fatty acid, c) a vitamin, d) a polyphenol, e) a natural material containing any one or more members of a) to d), f) a fungus, g) a fermentation extract, h) a flavor, i) a mineral, j) an amino acid, k) a protein or peptide and l) a microorganism or its metabolite.

5) A capsule shell composition comprising gelatin, malic acid or a salt thereof, and a plasticizer.

6) A method for suppressing disintegration delay of a capsule comprising a gelatin as a base material, which

comprises incorporating malic acid or a salt thereof into a capsule shell.

Effects of the Invention

[0008]

According to the present invention, it is possible to provide a capsule having disintegration delay suppressed in the body and being excellent in quality and stability.

Modes for Carrying Out the Invention

[0009]

The capsule of the present invention is a capsule comprising gelatin as a base material (i.e., a gelatin capsule) and having a capsule shell containing malic acid or a salt thereof.

In the present invention, the gelatin as a base material is a modified collagen which is obtained by treating a material derived from collagen, which is a main protein component of skin, bone, tendon, etc. of cow, sheep, pig, chicken, fish, etc. with an acid or an alkali, followed by extracting with hot water. As the gelatin used in the present invention, the origin of collagen and the treatment method are not particularly restricted.

[0010]

The content of the gelatin in the capsule shell is not particularly restricted. For example, the content is preferably from 60 to 90 mass%, more preferably from 65 to 85 mass%, per the total mass of the capsule shell.

[0011]

Malic acid is also called "2-hydroxybutanedioic acid" and is an organic compound classified into the hydroxyacid. Malic acid or a salt thereof is used as an acidulant in a variety of foods and beverages.

In the present invention, malic acid may be any of D form, L form, or DL form (a mixture of D form and L form). However, DL-malic acid is preferably used. Further, malic acid may be an anhydride or a hydride.

[0012]

The malic acid salt may, for example, be an alkali metal salt such as sodium or potassium, an alkaline earth metal salt such as calcium or a magnesium salt but is not limited thereto, and a sodium salt and a potassium salt are preferred, and the sodium salt is more preferred.

[0013]

As shown in the Examples described after, in the case of the capsule having a shell containing malic acid, the drop over time in solubility of the capsule in water can be effectively suppressed. As a result, a gelatin capsule having a shell containing malic is a capsule having disintegration delay suppressed. Further, malic acid or a salt thereof serves as a disintegration delay inhibitor for a gelatin capsule, particularly a soft capsule. Thus, by incorporating malic acid or a salt thereof into the shell of a capsule comprising gelatin as a base material, the disintegration delay of the capsule can be suppressed.

The effect of suppressing disintegration delay can be

evaluated by storing a capsule under specific conditions (e.g., at 40°C and humidity of 75% for 1 to 3 months) and measuring the disintegration time in accordance with "Dissolution test" as defined in "The Japanese Pharmacopoeia 17th edition."

[0014]

The added amount of malic acid or a salt thereof in the capsule shell may be appropriately determined in consideration of effects to be expected, etc. The added amount of malic acid (as free acid form) suitably used is from 0.5 to 12 parts by mass, preferably from 1 to 8 parts by mass, more preferably from 2 to 6 parts by mass, per 100 parts by mass of gelatin.

[0015]

For imparting flexibility and elasticity, a plasticizer may be appropriately added to the capsule shell. The plasticizer may, for example, be glycerins (e.g., glycerin, diglycerin and polyglycerin); sugar alcohols (such as sorbitol, xylitol, erythritol, maltitol, mannitol and cyclitol), glycols (such as propylene glycol, dipropylene glycol, 1,3-butylene glycol, ethylene glycol and polyethylene glycol); disaccharides; or oligo saccharides.

The mixing ratio of the plasticizer, per 100 parts by mass of gelatin, is, for example, from 5 to 150 parts by mass, preferably from 10 to 80 parts by mass, more preferably from 20 to 50 parts by mass.

[0016]

So long as the effects of the present invention are not impaired, the capsule shell may contain a pigment, an anti-sticking agent (e.g., processed starch or silica) or the like, as a case requires.

[0017]

The form of the capsule of the present invention may be a hard capsule having a capsule shell filled with contents or a soft capsule formed by encapsulating contents with a capsule shell, and a soft capsule is preferred.

[0018]

In the capsule of the present invention, contents in the capsule are not particularly restricted and may, for example, be medicine, quasi drugs, cosmetic products, ingredients employed in foods (such as health foods, foods for specific health uses, foods with functional claims, and supplements, seasonings, flavors, fungi, fermentation extracts, minerals, amino acids, proteins, microorganisms or a metabolite produced therewith, which are generally charged into capsule shells. The capsule shell of the present invention is particularly effective for encapsulating one or more species selected from among a) unsaturated fatty acid, b) a fat and oil containing an unsaturated fatty acid as a component fatty acid, c) a vitamin, d) a polyphenol, e) a natural material containing any one or more species of a) to d), (f) a fungus, g) a fermentation extract, h) a flavor, i) a mineral, j) an amino acid, k) a protein or peptide, and l) a microorganism or a metabolite produced therewith.

[0019]

Here, as the unsaturated fatty acid, ω 3 polyunsaturated fatty acids such as α -linolenic acid, stearidonic acid, docosahexanoic acid (DHA) and eicosapentanoic acid (EPA); ω 6 polyunsaturated fatty acids such as linoleic acid, γ -linolenic acid and arachidonic acid; and ω 9 monobasic unsaturated fatty acids such as oleic acid, may be mentioned.

Further, as the fat and oil containing an unsaturated fatty acid as a component fatty acid, plant-derived fat and oils such as soy bean oil, rapeseed oil, safflower oil, rice bran oil, corn oil, sunflower oil, cotton oil, olive oil, sesame oil, peanut oil, adlay oil, wheat germ oil, perilla (*shiso*) oil, linseed oil, perilla (*egoma*) oil, sacha inchi oil, walnut oil, kiwi seed oil, salvia seed oil, grape seed oil, macadamia nut oil, hazel nut oil, pumpkin seed oil, camellia oil, teaberry oil, borage oil, palm oil, palm olein, palm stealin, coconut oil, palm kernel oil, cacao fat, *Shorea robusta* fat, Shea fat and Algae oil; animal-derived fat and oils such as fish oil, lard, beef tallow oil and butter; and other fat and oils such as transesterified products thereof, hydrogenated product thereof and separated products thereof, may be mentioned. Among them, fish oil containing a large amount of ω 3 fatty acids such as DHA and EPA is preferred.

[0020]

The polyphenol may, for example, be flavonol, isoflavone, tannin, catechin, quercetin, anthocyanine, flavangenol or flavonoid, and among them, anthocyanine

contained in bilberry and cassis and rhodanthenone B contained in mangosteen extract are preferred.

[0021]

Further, the fungus may, for example, be a powder obtained by drying and pulverizing *Agaricus*, *Phellinus linteus*, *Ganoderma lucidum* (Mannen-take), Enoki mushroom, *Skizophyllum commune*, Shiitake mushroom, hen of the woods, Chaga (*Inonotus obliquus*), mushroom, *Lyophyllum decastes*, *Trametes versicolor*, *Crepidotus mollis* Peck, Polypore, Caterpillar fungus or *Ganoderma lucidum* (Reishi) as it is, or an extract thereof

[0022]

The fermentation extract may, for example, be a fermentation extract prepared by fermenting a plant such as vegetable, fruit, bean or cereal), a seaweed, a fungus, a sugar or the like with a microorganism such as yeast, *Lactobacillus*, *Aspergillus*, *Monascus purpureus*, *Acetobacter*, or *Bacillus subtilis*.

[0023]

The mineral may, for example, be calcium, phosphorus, sodium, potassium, magnesium, zinc, selenium, iron or copper, and they may be used as inorganic or organic salts.

[0024]

The amino acid may, for example, be functional amino acids such as GABA (γ -aminobutyric acid), HMB (3-hydroxyisovaleric acid), theanine, 5-ALA (5-aminolevulinic acid), β -alanine, cystine, ergothioneine, selenoneine,

cysteine, ornithine or citrulline.

[0025]

The protein or peptide may, for example, be a functional protein or a peptide such as elastin, collagen, carnosine, anserine, balenine or glutathione.

[0026]

The microorganism may, for example, be Lactobacilli belonging to *Lactobacillus* employed in fermented food and the like, *Lactococcus*, *Streptococcus*, *Enterococcus* or *Leuconostoc*; *Bifidobacterium* bacteria; *Eubacterium* bacteria; *Propionibacterium* bacteria; or a microorganism belonging to *Bacillus*, *Acetobacter* or the like.

[0027]

Generally, the capsule of the present invention can be produced by filling the capsule shell with contents or encapsulating contents with the capsule shell.

The capsule shell is formed by adding an appropriate amount of water to the above mentioned capsule shell composition containing gelatin, malic acid or a salt thereof and a plasticizer and mixing and stirring the mixture under heating (at 70 to 90°C, preferably at about 80°C) to prepare a liquid for forming a capsule shell (a gelatin solution), followed by molding and drying.

[0028]

The soft capsule may be a rotary die soft capsule prepared by while charging contents in a space between two shell material sheets, forming and punching out the sheets by

means of a rotary die, a seamless capsule prepared by a drop method by means of a dual nozzle or the like. The capsule of the present invention may have any form.

In the preparation of the rotary die soft capsule, a liquid for forming a shell is prepared from a capsule shell composition, the liquid is formed into sheets, and then the sheets are punched out by rotating two die rollers, while the liquid contents are charged into capsules. By pressing the capsule shell with die rollers, the capsule is tightly closed.

[0029]

The shell of the capsule may be dried by means of, for example, a rotary drum-type drier. Drying conditions such as temperature and time may be appropriately adjusted depending on types of ingredients contained in the contents and ingredients contained in the capsule shell. For example, the drying temperature is from about 15° to 35°C, the humidity is from about 10%RH to 50%RH, and the drying time is from about 0.5 to 2 days.

[0030]

Accordingly, the capsule of the present invention thus produced is a capsule which is excellent in quality and stability, since the drop over time in solubility of the capsule in water is suppressed, and the drop in viscosity of gelation as the base material of the shell is also suppressed, whereby the delay of disintegration is suppressed when taken.

Examples

[0031]

Example 1: Production of soft capsule <1>

(1) Soft capsule A (vitamin C-including soft capsule)

1) Preparation of liquid for forming capsule shell

Respective ingredients shown in Table 1 were mixed at the predetermined proportions and dissolved by stirring under heating in a water bath at about 80°C, to prepare gelatin solutions for forming a malic acid-added shell and a malic acid-non-added shell.

[0032]

[Table 1]

		(parts by mass)	
		Malic acid-added shell	Malic acid-non-added shell
Gelatin:	BCN200S (Nitta gelatin)	100	100
Glycerin:	Food additive glycerin (Sakamoto Yakuhin Kogyo)	35	35
Purified water:		70	70
Malic acid:	Malic acid Fuso Type S (Fuso Chemical)	3	-

[0033]

2) Preparation of capsule contents

Beeswax, Poem S-100 and sunflower oil shown in Table 2 were mixed at the predetermined proportions and heated at about 70°C for dissolution, followed by cooling to 40°C or lower, adding vitamin C thereto and stirring. Then, wet pulverization (colloid mill) treatment, sieving, and

defoaming were conducted to prepare capsule contents.

[0034]

[Table 2]

		(mg/capsule)
Vitamin C:	Vitamin C (micropowder) (Fuso Chemical)	100
Sunflower oil:	Sunflower oil (High olein) (Nissin Boeki)	117.5
Beeswax:	White beeswax AR-100 (Yokozeki Yushi)	12.5
Emulsifier:	Poem S-100 (Riken Vitamin)	20.0
Total:		250

[0035]

3) Production of soft capsule

The gelatin solution (80°C) prepared in 1) was defoamed and left to stand at about 10 hours. The gelatin solution was formed into a thin film having a thickness of from 0.8 to 0.9 mm by means of a rotary die soft capsule filler (Oval No. 5), and the thin film was cooled, to prepare gelatin sheets. The prepared gelatin sheets were passed through a roller die in a left-to-right direction, and while heating at about 40°C by means of a segment to bond the gelatin sheets, the capsule contents prepared in 2) were charged by means of a pump just before punching, followed by punch molding and drying to produce a soft capsule A.

[0036]

(2) Soft capsule B (mangosteen extract-including soft capsule)

1) Preparation of liquid for forming capsule shell

In the same manner as in the above (1), gelatin solutions for forming a malic acid-added shell and a malic

acid-non-added shell were prepared.

2) Preparation of capsule contents

Beeswax, Poem S-100, linseed oil and olive oil shown in Table 3 were heated at about 70°C for dissolution, followed by cooling to 40°C or lower, adding a mangosteen extract thereto and stirring. Then, wet pulverization (colloid mill) treatment, sieving, and defoaming were conducted to prepare capsule contents.

[0037]

[Table 3]

		(mg/capsule)
Mangosteen extract:	Mangosteen aqua (Nippon Shinyaku)	100
Linseed oil:	Linseed oil (Summit oil mill)	85
Olive oil:	Extravergine olive oil (DSP Gokyo Food & Chmical)	82
Beeswax:	White beeswax AR-100 (Yokozeki Yushi)	12
Emulsifier:	Poem S-100 (Riken Vitamin)	21
Total:		300

[0038]

3) Production of soft capsule

Gelatin sheets were prepared in the same manner as in the above (1). The gelatin sheets were passed through a roller die in a left-to-right direction, and while heating at about 40°C by means of a segment to bond the gelatin sheets, the capsule contents prepared in 2) were charged by means of a pump just before punching, followed by punch molding and drying to produce a soft capsule B.

[0039]

Test Example 1: Disintegration test

(1) Each of the soft capsules A and B produced in Example 1 was placed in a glass bottle, and the bottle was tightly closed with a metallic cap (with a packing provided with a rubber liner). The bottle was stored in a thermostat bath at 40°C and 75%Rh for a period of 1, 2, and 3 months, and the disintegration time was analyzed in a comparative manner. The disintegration time was determined by means of a disintegration tester (an autosensing disintegration tester ZT720, manufactured by ERWEKA) in accordance with "Dissolution test" as defined in "The Japanese Pharmacopoeia 17th edition."

[0040]

(2) Results

Table 4 shows the results.

All the soft capsules A and B having a capsule shell containing intentionally added malic acid were found to complete disintegration within 20 minutes after storage at 40°C and 3M under the conditions stipulated by "The Japanese Pharmacopoeia 17th edition." In contrast, soft capsules having a capsule shell containing no malic acid were found to require 20 minutes or longer for the completion of disintegration after storage at 40°C and 1M, or to be absolutely insoluble after storage.

[0041]

[Table 4]

Storage period	Soft capsule A		Soft capsule B	
	Capsule shell		Capsule shell	
	Malic acid	No malic acid	Malic acid	No malic acid

INI	10 min 42 sec	11 min 26 sec	9 min 14 sec	11 min 46 sec
40°C.1M	10 min 10 sec	33 min 18 sec	11 min 40 sec	insol
40°C.2M	9 min 38 sec	36 min 01 sec	12 min 06 sec	insol
40°C.3M	11 min 50 sec	39 min 00 sec	17 min 06 sec	insol

[0042]

Test Example 2: Dissolution test of gelatin shell sheet

(1) Preparation of gelatin shell sheet

i) 100 g of purified water was added to a 500 ml-glass beaker, and 100 g of gelatin (BCN200S (Nitta Gelatin Inc.)) and 35 g of glycerin (food additive glycerin) were added thereto. The contents were swollen by water, and then the mixture was dissolved by stirring under heating in a water bath at about 80°C, to prepare a gelatin solution. The prepared gelatin solution was uniformly spread so as to be a thickness of about 1 mm and dried at room temperature of 25°C for 24 hours, to form a gelatin shell sheet ("reference sheet" in Table 5).

ii) 100 g of purified water was added to a 500 ml-glass beaker, and 100 g of gelatin (BCN200S (Nitta Gelatin Inc.)) and 35 g of glycerin (food additive glycerin) were added thereto. The contents were swollen by water. Then, 3 g of an organic acid shown in Table 5 was added, and then the mixture was dissolved by stirring under heating in a water bath at about 80°C, to prepare a gelatin solution containing the organic acid. In the same manner similar as in i), gelatin shell sheets A to F were prepared.

[0043]

Here, in Table 5, glycerin is a "food additive glycerin"; malic acid is "malic acid Fuso type S (Fuso Chemical Co., Ltd.)"; phytic acid is a 50% aqueous solution of "food additive phytic acid (Fuso Chemical Co., Ltd.)"; citric acid is "citric anhydride"; and gluconic acid is "gluconic acid solution (50% aqueous solution."

[0044]

[Table 5]

(g)

Ingredients		Capsule shell sheet					
		Ref.	A	B	C	D	E
Gelatin		100	100	100	100	100	100
Glycerin		35	35	35	35	35	35
Purified water		100	100	97	100	97	100
Organic acid	Malic acid	-	3	-	-	-	-
	Phytic acid	-	-	6	-	-	-
	Citric acid	-	-	-	3	-	-
	Gluconic acid	-	-	-	-	6	-
	Succinic acid	-	-	-	-	-	3

[0045]

(2) Dissolution test

Under the assumption of a capsule containing fish oil as the capsule contents, 10 g of a fish oil (DHA-46G: Nissui Corporation) was put into a screw tube, and a sheet piece of each gelatin shell sheet cut into 7 mm × 7 mm was immersed therein, and the screw tube was maintained in a thermostat bath at 50°C.

The maintained piece of the gelatin shell sheet was sampled at several points of time, and attached fish oil was wiped off. Then, the piece of the gelatin shell sheet was

put into 150 ml of hot water at 60°C, and stirring was performed by means of a stirrer (a magnetic stirrer, 600 rpm) for 3 minutes. The system was left to stand, and the presence of an insoluble matter was visually observed, to determine the time (days) to start insolubilization. The solubility was evaluated based on the following standard. Table 6 shows the results.

[0046]

<Evaluation standard>

- Complete dissolution of capsule shell pieces with no insoluble matter: -
- Dissolution of capsule shell pieces with slight insoluble matters: ±
- Dissolution of capsule shell pieces with a small number of insoluble pieces: +
- Dissolution of capsule shell pieces with a certain number of insoluble pieces: ++
- Dissolution of capsule shell pieces with a substantial number of insoluble pieces: +++
- Complete insolubilization of capsule shell pieces: ++++

[0047]

[Table 6]

Presence of insoluble matter

Shell sheet	Ref. shell	A	B	C	D	E
Days after treatment						
Day 1	++	±	±	±	±	+
Day 2	++	±	±	±	+	++

Day 3	+++	+	+	+	++	++
Day 4	+++	++	+	++	+++	+++
Day 5	++++	++	++	+++	++++	++++
Day 6		+++	+++	+++		
Day 7		+++	+++	++++		
Day 8		+++	++++			
Day 9		+++				
Day 10		++++				

[0048]

Shell sheet D containing gluconic acid and shell sheet E containing succinic acid were found to be insolubilized on day 5, similar to the reference shell sheet, and no effect of preventing insolubilization was confirmed. Shell sheet A containing malic acid, shell sheet B containing phytic acid, and shell sheet C containing citric acid were found to exhibit an effect of suppressing insolubilization, and among them, the shell sheet A containing malic acid exhibited the highest effect.

[0049]

Test Example 3: Drop in viscosity of gelatin shell solution in storage under heating

Generally, in the production of soft capsules, 1) glycerin and purified water are added to gelatin, and the mixture is stirred under heating at from 70 to 80°C for dissolution, followed by defoaming in vacuum to prepare a gelatin solution (having a viscosity adjusted to 20,000 mPa·s) and storing the gelatin solution at 60°C under heating for from 4 to 10 hours. 2) Then, the gelatin shell solution

heated at 60°C is fed to a capsule filling apparatus, and the content liquid is charged, followed by shaping. Thus, the gelatin solution is heated at 60°C for about 40 hours of from the preparation of the gelatin solution to the completion of capsule filling and shaping. Here, the viscosity of the gelatin solution is known to decrease over time during storage at 60°C. An initial viscosity of 20,000 mPa·s is reduced to at most 14,000 mPa·s (at most 70% from the initial value), and the strength of the gelatin shell thereby deteriorates, whereby mechanical troubles when filling and fatal failures such as cracking and deformation due to the insufficient strength of molded soft capsules result. The drop in viscosity is concerned due to the addition of an organic acid to the gelatin solution. Thus, the following tests were conducted for the above concern.

[0050]

1) Preparation of gelatin solution

112 g of purified water was added to a 500 ml-glass beaker, and 7 g of an organic acid weighed and shown in Table 7 was dissolved with stirring (Tartaric acid and succinic acid were heated in a water bath at about 80°C after added in the purified water and thereby dissolved.). Then, 140 g of gelatin (BCN200S (Nitta Gelatin Inc.) and 49 g of glycerin (food additive glycerin) were added thereto and swollen by water. Then, the mixture was dissolved by stirring under heating in a water bath at about 80°C to prepare a gelatin solution. Here, in Table 7, malic acid is "malic acid Fuso

type S (Fuso Chemical Co., Ltd.)"; tartaric acid is "L-tartaric acid S (Fuso Chemical Co., Ltd.)"; citric acid is "citric anhydride" (Iwata Chemical Co., Ltd.), and succinic acid is "succinic acid (Fuso Chemical Co., Ltd.)."

[0051]

[Table 7]

(g)

Ingredients		Gelatin solution				
		Ref. solution	F	G	H	I
Gelatin		140	140	140	140	140
Glycerin		49	49	49	49	49
Purified water		112	112	112	112	112
Organic acid	Malic acid	-	7	-	-	-
	Tartaric acid	-	-	7	-	-
	Citric acid	-	-	-	7	-
	Succinic acid	-	-	-		7

[0052]

2) Viscosity measurement

The prepared gelatin solutions was subjected to viscosity measurement by means of a type B viscometer (rotor rotation: 12 rpm). Then, the gelatin solution was fractionated by 90 g into a glass bottle (size No. 10), and the bottles were stored in a thermostat bath at 60°C.

After 48 hours, each of the stored gelatin solution was sampled, and the viscosity was measured. Table 8 shows the results.

[0053]

[Table 8]

Viscosity of gelatin solution in storage at 60°C

Shell solution Storage time	Ref. solution	F	G	H	I
After treatment	100%	100%	100%	100%	100%
48 hours	71%	70%	59%	63%	62%

[0054]

The viscosity of the gelatin solution F containing malic acid decreased to 70% after storage at 60°C for 48 hours, however, the viscosity decrease ratio was almost the same as that of a reference solution containing no malic acid, and the viscosity was at least the lower target limit value of 14,000 mPa·s. The viscosity decrease ratio of the gelatin solution G containing tartaric acid, the gelatin solution H containing citric acid and the gelatin solution I containing succinic acid were 30% or higher, which was less than 14,000 mPa·s, and adversely effects on capsule molding, capsule strength, etc. were concerned.

[0055]

Example 2: Production of soft capsule <2>

(1) Soft capsule C (fungus extract-including soft capsule)

1) Preparation of liquid for forming capsule shell

Components shown in Table 9 were mixed at the predetermined proportions, stirred under heating in a water bath at about 80°C and thereby dissolved to prepare gelatin

solutions for forming a malic acid-added shell and a malic acid-non-added shell.

[0056]

[Table 9]

(parts by weight)

		Malic acid-added shell	Malic acid-non-added shell
Gelatin:	BCN200S (Nitta gelatin)	100	100
Glycerin:	Food additive glycerin (Sakamoto Yakuhin Kogyo)	35	35
Purified water:		70	70
Malic acid:	Malic acid Fuso Type S (Fuso Chemical)	8	-

[0057]

2) Preparation of capsule contents

Sunflower oil, beeswax, and an emulsifier shown in Table 10 were heated at about 70°C for dissolution, and then cooled to 40°C or lower, and reishi was added thereto, followed by stirring. Then, wet pulverization (colloid mill) treatment, sieving, and defoaming were conducted to prepare capsule contents.

[0058]

[Table 10]

(mg/capsule)

Reishi:	Reishi extract powder (Maruzen Pharmaceuticals)	100
Sunflower oil:	Sunflower oil (High olein) (Nissin Boeki)	120
Beeswax:	White beeswax AR-100 (Yokozeki Yushi)	15
Emulsifier:	Poem S-100 (Riken Vitamin)	15
Total:		250

[0059]

3) Production of soft capsule

Gelatin sheets were prepared in the same manner as in (1) in Example 1. The gelatin sheets were passed through a roller die in a left-to-right direction, and while heating at about 40°C by means of a segment to bond the gelatin sheets, the capsule contents prepared in 2) were charged by means of a pump just before punching, followed by punch molding and drying to produce a soft capsule C.

[0060]

(b) Soft capsule D (live bacteria-including soft capsule)

1) Preparation of liquid for forming capsule shell

In the same manner as in the above (1), gelatin solutions for forming a malic acid-added shell and a malic acid-non-added shell were prepared.

[0061]

[Table 11]

(parts by weight)

		Malic acid-added shell	Malic acid-non-added shell
Gelatin:	BCN200S (Nitta gelatin)	100	100
Glycerin:	Food additive glycerin (Sakamoto Yakuhin Kogyo)	35	35
Purified water:		70	70
Malic acid:	Malic acid Fuso Type S (Fuso Chemical)	3	-

[0062]

2) Preparation of capsule contents

Sunflower oil, beeswax, and an emulsifier shown in Table 12 were heated at about 70°C for dissolution and then cooled to 40°C or lower, and *Bifidobacterium* and *Bacillus subtilis* were added thereto, followed by stirring. Then, wet pulverization (colloid mill) treatment, sieving, and defoaming were conducted to prepare capsule contents.

[0063]

[Table 12]

(mg/capsule)

Bifidobacterium:	BB536-EX (Morinaga Milk Industry)	50
Bacillus sub.:	Bacillus sub. culture extract NSK-SD (Japan Bio Science Laboratory)	50
Sunflower oil:	Sunflower oil (High olein) (Nissin Boeki)	120
Beeswax:	White beeswax AR-100 (Yokozeki Yushi)	15
Emulsifier:	Poem S-100 (Riken Vitamin)	15
Total:		250

[0064]

3) Production of soft capsule

Gelatin sheets were prepared in the same manner as in (2). The gelatin sheets were passed through a roller die in a left-to-right direction, and while heating at about 40°C by means of a segment to bond the gelatin sheets, the capsule contents prepared in 2) were charged by means of a pump just before punching, followed by punch molding and drying to produce a soft capsule D.

[0065]

(3) Soft capsule E (amino acid-including soft capsule)

1) Preparation of liquid for forming capsule shell

In the same manner as in the above (1), gelatin

solutions for forming a malic acid-added shell and a malic acid-non-added shell were prepared.

[0066]

[Table 13]

(parts by weight)

		Malic acid-added shell	Malic acid-non-added shell
Gelatin:	BCN200S (Nitta gelatin)	100	100
Glycerin:	Food additive glycerin (Sakamoto Yakuhin Kogyo)	35	35
Purified water:		70	70
Malic acid:	Malic acid Fuso Type S (Fuso Chemical)	3	-

[0067]

2) Preparation of capsule contents

Sunflower oil, beeswax, and an emulsifier shown in Table 14 were heated at about 70°C for dissolution and then cooled to 40°C or lower, and GABA was added thereto, followed by stirring. Then, wet pulverization (colloid mill) treatment, sieving, and defoaming were conducted to prepare capsule contents.

[0068]

[Table 14]

(mg/capsule)

GABA:	Barley-origin lactic acid fermentation liquid GABA 90% (Sanwa Shurui)	100
Sunflower oil:	Sunflower oil (High olein) (Nissin Boeki)	120
Beeswax:	White beeswax AR-100 (Yokozeki Yushi)	15
Emulsifier:	Poem S-100 (Riken Vitamin)	15
Total:		250

[0069]

3) Production of soft capsule

Gelatin sheets were prepared in the same manner as in (2). The gelatin sheets were passed through a roller die in a left-to-right direction, and while heating at about 40°C by means of a segment to bond the gelatin sheets, the capsule contents prepared in 2) were charged by means of a pump just before punching, followed by punch molding and drying to produce a soft capsule E.

[0070]

(4) Soft capsules F, G, and H (bilberry- and DHA-including soft capsules)

1) Preparation of liquid for forming capsule shell

In the same manner as in the above (1), gelatin solutions for forming a malic acid-added shell and a malic acid-non-added shell were prepared.

[0071]

[Table 15]

(parts by weight)

		Malic acid-added shell			Malic acid-non-added shell
		Soft capsule F	Soft capsule G	Soft capsule H	Soft capsule I
Gelatin:	BCN200S (Nitta gelatin)	100	100	100	100
Glycerin:	Food additive glycerin (Sakamoto Yakuhin Kogyo)	35	35	35	35
Purified water:		70	70	70	70

Malic acid:	Malic acid Fuso Type S (Fuso Chemical)	3	5	8	-
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[0072]

2) Preparation of capsule contents

DHA, beeswax, and an emulsifier shown in Table 16 were heated at about 70°C for dissolution and then cooled to 40°C or lower, and bilberry was added thereto, followed by stirring. Then, wet pulverization (colloid mill) treatment, sieving and defoaming were conducted to prepare capsule contents.

[0073]

[Table 16]

(mg/capsule)

Bilberry:	Bilberry dry extract (Indena Japan)	70
DHA:	DHA-55MK (Maruha Nichiro)	150
Beeswax:	White beeswax AR-100 (Yokozeki Yushi)	15
Emulsifier:	Poem S-100 (Riken Vitamin)	15
Total:		250

[0074]

3) Production of soft capsule

Gelatin sheets were prepared in the same manner as in (2). The gelatin sheets were passed through a roller die in a left-to-right direction, and while heating at about 40°C by means of a segment to bond the gelatin sheets, the capsule contents prepared in 2) were charged by means of a pump just before punching, followed by punch molding and drying to produce soft capsules. Among the malic acid-added shells, a soft capsule F was produced from a gelatin solution

containing 3 parts by weight of malic acid, a soft capsule G was produced from a gelatin solution containing 5 parts by weight of malic acid, a soft capsule H was produced from a gelatin solution containing 8 parts by weight of malic acid, and a soft capsule I was produced from a gelatin solution containing no malic acid.

[0075]

Test Example 4: Disintegration test

(1) Test procedure

Each of the soft capsules F, G, and H produced in Example 2 was put in a glass bottle, and the bottle was tightly closed with a metallic cap (with a packing provided with a rubber liner) and stored in a thermostat bath at 40°C and 75%Rh for a period of 1, 2, 3, and 4 months, and the disintegration time was compared. The disintegration time was measured by means of a disintegration tester (an autosensing disintegration tester ZT720, manufactured by ERWEKA) in accordance with "the dissolution test" as defined in "The Japanese Pharmacopoeia 17th edition."

[0076]

(2) Results

Table 17 shows the results.

All of the soft capsules F, G, and H having a capsule shell containing malic acid were found to complete disintegration within 20 minutes after storage at 40°C and 3M under the conditions stipulated by "The Japanese Pharmacopoeia 17th edition." On the other hand, the soft

capsule I having a capsule shell containing no malic acid was found to require 20 minutes or longer for the completion of disintegration or to be absolutely insoluble after storage at 40°C and 2M.

[0077]

[Table 17]

	Soft capsule F	Soft capsule G	Soft capsule H	Soft capsule I
	malic acid : 3 parts by wt.	malic acid : 5 parts by wt.	malic acid : 8 parts by wt.	—
INI	7 min 02 sec	6 min 50 sec	6 min 06 sec	11 min 02 min
40°C.1M	9 min 30 sec	8 min 24 sec	7 min 58 sec	19 min 31 sec
40°C.2M	10 min 00 sec	9 min 33 sec	9 min 00 sec	Insoluble
40°C.3M	12 min 48 sec	12 min 21 sec	11 min 46 sec	Insoluble
40°C.4M	13 min 22 sec	13 min 05 sec	12 min 47 sec	insoluble

Claims

1. A capsule having a capsule shell which comprises gelatin as a base material and malic acid or a salt thereof.

2. The capsule according to Claim 1, wherein the content of malic acid or a salt thereof in the shell is from 0.5 to 12 parts by mass, per 100 parts by mass of gelatin.

3. The capsule according to Claim 1 or 2, which is a soft capsule.

4. The capsule according to any one of Claims 1 to 3, which encloses one or more members selected from a) an unsaturated fatty acid, b) a fat and oil containing an unsaturated fatty acid as a component fatty acid, c) a vitamin, d) a polyphenol, e) a natural material containing any one or more members of a) to d), f) a fungus, g) a fermentation extract, h) a flavor, i) a mineral, j) an amino acid, k) a protein or peptide and l) a microorganism or its metabolite.

5. A capsule shell composition comprising gelatin, malic acid or a salt thereof, and a plasticizer.

6. A method for suppressing disintegration delay of a capsule comprising a gelatin as a base material, which comprises incorporating malic acid or a salt thereof into a capsule shell.