SEAMLESS CAPSULE

Technical Field

[0001]

The present invention relates to a seamless capsule comprising a capsule content and a shell (film) formed by a shell (film) composition comprising gelatin and a plasticizer, which is free of an interfacial tension modifier and a gelling agent, as well as a production method thereof. In addition, the present invention relates to a seamless capsule with extremely small nonuniformity in the thickness, and without an eye or with only an extremely small eye, comprising a shell formed by a shell composition comprising gelatin and a plasticizer, which is free of an interfacial tension modifier and a gelling agent.

[0002]

(Background of the Invention)

Encapsulation techniques have been conventionally used widely in the fields of pharmaceutical products, foods, quasi-drugs, and the like. Among such capsules, seamless capsules are based on an encapsulation technique utilizing the tension produced in the oil-water interface and the gelling property of a shell substrate. While seamless capsule is one kind of soft capsules, it has been widely used in recent years in view of its characteristics such as wide range of selection of particle sizes, thickness and hardness of capsule films and capsule dissolution time, and the like.

As the shell (film)-forming material (shell (film) composition) used for forming such capsules, a material superior in the intracorporeal solubility and capable of releasing the content by being disintegrated rapidly is used. Typical examples of such material include gelatin and a material comprising a composition containing gelatin. Conventionally, seamless capsules have been obtained using an interfacial tension modifier or a gelling agent (e.g., fats

and oils, phospholipid, polar organic solvent such as ethanol and the like) added to a shell composition and/or capsule content in an effort to produce seamless capsules with high quality, which contain a small eye (foam-like defect produced in the shell), and show small nonuniformity in the thickness (significantly varying shell thickness depending on the part of capsule), and the like.

[0003]

Patent reference 1 describes a pharmaceutical composition for the treatment or prophylaxis of cardiovascular diseases, which comprises ω3-fatty acid in a proportion of at least 80 wt% of the total fatty acid, and (all-Z)-5,8,11,14,17-eicosapentaenoic acid (EPA) C20:5 and (all-Z)-4,7,10,13,16,19-docosahexaenoic acid (DHA) C22:6 in a relative amount of 1:2 to 2:1, constituting at least 80 wt% of the total fatty acid. Specifically, EPA ethyl ester capsule, DHA ethyl ester capsule, d-α tocopherol capsule, gelatin capsule, glycerin capsule, red iron oxide capsule and yellow iron oxide capsule are recited and soft·gelatin·capsules (1 g/1 capsules) are recited as preparation examples. These starting materials are filled in oval soft·gelatin·capsules (size 20) using a standard encapsulation machine.

[0004]

Patent reference 2 describes a production method of seamless capsules comprising a shell material wrapping a filling material, which method having a step of preparing a composite nozzle apparatus having outer nozzles and inner nozzles conically arranged, a step of supplying a shell material to the aforementioned outer nozzle and a filling material to the aforementioned inner nozzle, and a step of simultaneously extruding the aforementioned shell material through the aforementioned outer nozzles and the aforementioned filling material through the aforementioned inner nozzles, wherein the aforementioned shell material passing through the aforementioned nozzles has the same flow

flux as that of the aforementioned filling material passing through the aforementioned inner nozzle.

[0005]

Patent reference 3 describes a production method of a seamless capsule comprising curing at least the outermost part of a droplet by contact thereof with a curing liquid, wherein the aforementioned droplet is dropped through at least a part of the aforementioned curing liquid with a helical movement.

[0006]

The above-mentioned prior art references do not describe suppression of formation of the eyes and uneven thickness in a shell, and the relationship between the suppression and use of an interfacial tension modifier and a gelling agent. What should be particularly noted is the absence of description as to the stabilization of the capsule content such as a pharmaceutical ingredient to be enclosed in the capsule and the like, and increase in the amount of the capsule content (e.g., pharmaceutical ingredient).

In the meantime, use of an interfacial tension modifier and a gelling agent adversely affects the stability of the capsule content such as a pharmaceutical ingredient to be enclosed and the like, or prevents increase in the amount of the capsule content (e.g., a pharmaceutical ingredient) (increased content per unit capsule).

[0007]

patent reference 1: JP-B-2810916

patent reference 2: JP-A-10-506841

patent reference 3: JP-B-3159724

Disclosure of the Invention

Problems to be Solved by the Invention

[0008]

An object of the present invention is to provide a seamless capsule superior in the stability of the capsule content, which permits a high content of the capsule content, and a production method thereof, and furthermore, a seamless

capsule free of an eye or with only an extremely small eye if present, and having extremely small nonuniformity in the thickness.

Means of Solving the Problems

[0009]

The present inventors have conducted various studies of constituent components of the shell composition and capsule content, and conditions of seamless capsule production and found that a shell (film) formed by a shell composition containing gelatin and a plasticizer, which is free of an interfacial tension modifier and a gelling agent, and a seamless capsule comprising a capsule content free of an interfacial tension modifier and a gelling agent, solve the above-mentioned problems, and established a production method thereof, which resulted in the completion of the present invention.

[0010]

The present invention is specifically described as follows.

[1] A seamless capsule comprising a shell formed by a shell composition comprising gelatin and a plasticizer, which does not comprise an interfacial tension modifier and a gelling agent, and a capsule content without comprising an interfacial tension modifier and a gelling agent.

[2] The seamless capsule of [1], wherein the gelatin has jelly strength of 200 - 300 g.

[3] The seamless capsule of [1] or [2], wherein the gelatin has a viscosity of 2 - 6 mPa·s.

[4] The seamless capsule of any one of [1] - [3], wherein the gelatin is derived from pigskin.

[5] The seamless capsule of [1], wherein the plasticizer is glycerin.

[6] The seamless capsule of [1], wherein the plasticizer is sorbitol.

[7] The seamless capsule of [1], wherein the plasticizer is a

mixture of glycerin and sorbitol.

[8] The seamless capsule of [7], wherein the weight ratio of glycerin and sorbitol is 1:5 - 5:1.

[9] The seamless capsule of [1], wherein the weight ratio of gelatin and plasticizer is 10:1 - 1:1.

[10] The seamless capsule of [1], wherein the capsule content is a pharmaceutically active ingredient composition.

[11] The seamless capsule of [10], wherein the capsule content comprises a pharmaceutically active ingredient composition with an excessively low or excessively high interfacial tension at a temperature near 25°C.

[12] The seamless capsule of [10], wherein the pharmaceutically active ingredient composition comprises ω3-fatty acid alkyl ester.

[13] The seamless capsule of [12], wherein the pharmaceutically active ingredient composition comprises ω3-fatty acid alkyl ester in a proportion of not less than 90%w/w.

[14] The seamless capsule of [13], wherein the pharmaceutically active ingredient composition comprises EPA ethyl ester (eicosapentaenoic acid ethyl ester) and DHA ethyl ester (docosahexaenoic acid ethyl ester) at a total ratio of the both components of not less than 80%w/w.

[15] The seamless capsule of [14], wherein the pharmaceutically active ingredient composition comprises not less than 40%w/w of EPA ethyl ester and not less than 34%w/w of DHA ethyl ester.

[16] The seamless capsule of [15], wherein the pharmaceutically active ingredient composition comprises OMEGA-3-ACID ETHYL ESTERS 90 in the European Pharmacopoeia.

[17] The seamless capsule of [10], wherein the weight ratio of the pharmaceutically active ingredient composition and the "total of gelatin and a plasticizer" is 10:1 - 1:10.

[18] The seamless capsule of [1], wherein the weight ratio of the shell and the capsule content is 10:1 - 1:10.

[19] A method of producing the seamless capsule of [1] by a

drip in oil method, wherein temperatures of the "capsule content without comprising an interfacial tension modifier and a gelling agent", the "aqueous shell composition solution formed by a shell composition comprising gelatin and a plasticizer, which does not comprise an interfacial tension modifier and a gelling agent" and the "carrier liquid" are each controlled near multiple nozzles of an apparatus used for the drop in oil method.

[20] The production method of [19], wherein the temperature of the "capsule content without comprising an interfacial tension modifier and a gelling agent" is controlled to a value set ± 2°C within the range of 5°C - 25°C.

[21] The production method of [19], wherein the temperature of the "aqueous shell composition solution formed by a shell composition comprising gelatin and a plasticizer, which does not comprise an interfacial tension modifier and a gelling agent" is controlled to a value set ± 2°C within the range of 50°C - 80°C.

[22] The method of [19], wherein the temperature of the "carrier liquid" is controlled to a value set ± 1°C within the range of 1°C - 15°C.

[23] The production method of [19], wherein a difference between the temperature of the "capsule content without comprising an interfacial tension modifier and a gelling agent" and the temperature of the "aqueous shell composition solution formed by a shell composition comprising gelatin and a plasticizer, which does not comprise an interfacial tension modifier and a gelling agent" is not less than 25°C and not more than 75°C.

[24] The production method of [19], wherein a difference between the temperature of the "aqueous shell composition solution formed by a shell composition comprising gelatin and a plasticizer, which does not comprise an interfacial tension modifier and a gelling agent" and the temperature of the "carrier liquid" is not less than 35°C and not more than 79°C.

[25] A seamless capsule produced by a drip in oil method, wherein temperatures of the "capsule content without comprising an interfacial tension modifier and a gelling agent", the "aqueous shell composition solution formed by a shell composition comprising gelatin and a plasticizer, which does not comprise an interfacial tension modifier and a gelling agent" and the "carrier liquid" are each controlled near multiple nozzles of an apparatus used for the drop in oil method.

[26] The seamless capsule of [25], wherein the temperatures are controlled to the following temperatures:
the temperature of the "capsule content" is controlled to a value set ± 2°C within the range of 5 - 25°C;
the temperature of the "aqueous shell composition solution" is controlled to a value set ± 2°C within the range of 50 - 80°C;
the temperature of the "carrier liquid" is controlled to a value set ± 1°C within the range of 1 - 15°C;
the difference between the temperature of the "capsule content" and the temperature of the "aqueous shell composition solution" is not less than 25°C and not more than 75°C; and
the difference between the temperature of the "aqueous shell composition solution" and the temperature of the "carrier liquid" is not less than 35°C and not more than 79°C.

[27] The seamless capsule of [25], wherein the temperatures are controlled to the following temperatures:
the temperature of the "capsule content" is controlled to a value set ± 1°C within the range of 12°C - 22°C;
the temperature of the "an aqueous shell composition solution" is controlled to a value set ± 1°C within the range of 60°C - 70°C;
the temperature of the "carrier liquid" is controlled to a value set ± 0.5°C within the range of 3 - 11°C;
the difference between the temperature of the "capsule content" and the temperature of the "aqueous shell composition solution" is not less than 38°C and not more than 58°C; and

the difference between the temperature of the "aqueous shell composition solution" and the temperature of the "carrier liquid" is not less than 49°C and not more than 67°C.

[28] A seamless capsule comprising a shell formed by a shell composition comprising gelatin and a plasticizer, which does not comprise an interfacial tension modifier and a gelling agent, wherein the shell has a minimum/maximum thickness ratio immediately after encapsulation of not less than 0.6.

[28a] A seamless capsule comprising a shell formed by a shell composition comprising gelatin and a plasticizer, which does not comprise an interfacial tension modifier and a gelling agent, wherein the shell has a minimum/maximum thickness ratio of not less than 0.6.

[29] The seamless capsule of [28], which comprises a capsule content free of an interfacial tension modifier and a gelling agent.

[30] A seamless capsule comprising a shell formed by a shell composition comprising gelatin and a plasticizer, which does not comprise an interfacial tension modifier and a gelling agent, wherein the shell is free of an eye.

[31] The seamless capsule of [30], which comprises a capsule content free of an interfacial tension modifier and a gelling agent.

[32] A seamless capsule comprising a shell formed by a shell composition comprising gelatin and a plasticizer, which does not comprise an interfacial tension modifier and a gelling agent, wherein the diameter of an eye of the shell after encapsulation and before drying is 1/2 or below of the average thickness of shells.

[33] The seamless capsule of [32], which comprises a capsule content free of an interfacial tension modifier and a gelling agent.

[34] A seamless capsule comprising a shell formed by a shell composition comprising gelatin and a plasticizer, which does not comprise an interfacial tension modifier and a gelling

agent, wherein the shell after encapsulation and before drying is free of an eye having a diameter exceeding 1/2 of the average thickness of shells.

[35] The seamless capsule of [34], which comprises a capsule content free of an interfacial tension modifier and a gelling agent.

Effect of the Invention

[0011]

Since the seamless capsule of the present invention does not contain an interfacial tension modifier and a gelling agent, it is superior in the stability of the capsule content, and permits a high content of a capsule content. Moreover, the present invention can provide a high quality seamless capsule free of an eye or with an extremely small eye even if present, which shows extremely small nonuniformity in the thickness.

Since the content can be high, the unit size of a preparation can be minimized, and highly easy administration and small space utility during storage can be realized. Moreover, the stability during preservation can be improved, thus enabling extension of a use-by date.

Brief Description Of The Drawings

[0012]

[Fig. 1] The seamless capsule of the present invention.

[0013]

(Detailed Description Of The Invention)

The present invention is explained in detail in the following by referring to specific examples.

[0014]

(Composition of shell composition)

The shell (film) covering the capsule content of the seamless capsule of the present invention is formed by a shell composition comprising gelatin and a plasticizer, which does not substantially comprise an interfacial tension modifier and a gelling agent.

[0015]

As used herein, the "gelatin" is, for example, one generally used for the production of a seamless capsule, such as the pharmaceutical gelatin defined in the Japanese Pharmacopoeia Fifteenth Edition. The gelatin here is a concept including, for example, modified gelatin such as succinylated gelatin and the like.

Particularly, gelatin preferable for practicing the present invention includes those having the following properties.

1) The jelly strength of gelatin (measured based on the method described in JIS) is 200 - 300 g, preferably 240 - 300 g, more preferably 240 - 280 g.

2) The viscosity of gelatin (measured based on the method described in JIS) is 2 - 6 mPa·s, preferably 3 - 6 mPa·s, more preferably 3 - 5 mPa·s.

3) The gelatin is derived from pigskin.

For the production of the seamless capsule of the present invention, one or more kinds of gelatin may be combined. In this case, the mixed gelatin preferably has the jelly strength of the above-mentioned 1) and/or the gelatin viscosity of the above-mentioned 2).

Most preferred one satisfies one or more of the above-mentioned conditions.

[0016]

As the "plasticizer" here, those generally used for the production of seamless capsules can be mentioned and, for example, polyvalent alcohols such as glycerin, ethylene glycol, polyethylene glycol, propylene glycol, polypropylene glycol and the like, and sugar alcohols such as sorbitol and the like are preferable. These plasticizers are used in a combination of one or more kinds thereof.

Among those, preferred for practicing the present invention are glycerin and sorbitol.

It is also preferable to use them in a mixture. In this case, the weight ratio of glycerin and sorbitol is preferably

within the range of 1:5 - 5:1, particularly preferably 1:3 - 3:1, for practicing the present invention.

[0017]

For practicing the present invention, the shell composition preferably comprises gelatin and a plasticizer at a weight ratio within the range of 10:1 - 1:10, particularly preferably 10:1 - 1:1.

[0018]

(Capsule content)

The content to be encapsulated in the seamless capsule of the present invention is not particularly limited as long as it does not contain an interfacial tension modifier and a gelling agent. As the content, a material desired for the object is used. For example, a pharmaceutically active ingredient, food, flavor, seed, microorganism, plant cell, plant tissue, animal cell, animal tissue (hereinafter to be referred to as the main component) and the like can be mentioned. The capsule content may be the main component itself or a composition containing the main component and other additive. The content of the main component, and the kind and content of the additive, etc. in the seamless capsule can be appropriately determined according to the object of use thereof. The present invention is explained in more detail in the following by taking a "pharmaceutically active ingredient" as an example of the capsule content.

[0019]

While the pharmaceutically active ingredient to be included in the seamless capsule is not particularly limited, for example, a compound having easily oxidizable properties and an oil compound are preferable.

[0020]

One example of such pharmaceutically active ingredient is ω3-fatty acid alkyl ester (e.g., ω3-fatty acid C_{1-6} alkyl ester; preferably ω3-fatty acid ethyl ester). Here, examples of the "ω3-fatty acid" of ω3-fatty acid alkyl ester include

C_{18-22} ω3-fatty acid (e.g., octadecatrienoic acid, octadecatetraenoic acid, eicosatetraenoic acid, eicosapentaenoic acid, heneicosapentaenoic acid, docosapentaenoic acid, docosahexaenoic acid).

Specific examples of the ω3-fatty acid ethyl ester include octadecatrienoic acid ethyl ester, octadecatetraenoic acid ethyl ester, eicosatetraenoic acid ethyl ester, eicosapentaenoic acid (EPA) ethyl ester, heneicosapentaenoic acid ethyl ester, docosapentaenoic acid ethyl ester, docosahexaenoic acid (DHA) ethyl ester, and a mixture of two or more kinds thereof (e.g., OMEGA-3-ACID ETHYL ESTERS 90 in the European Pharmacopoeia, which is useful for the treatment of hyperlipidemia (e.g., hypercholesterolemia, hyper-LDL cholesterolemia, low-HDL cholesterolemia, hypertriglyceride(TG)mia) and the like, prevention of cardiovascular event, and the like).

When a pharmaceutically active ingredient is encapsulated in a seamless capsule, it is included in the form of a "pharmaceutically active ingredient composition". Here, the "pharmaceutically active ingredient composition" encompasses a pharmaceutically active ingredient itself and a mixture of a pharmaceutically active ingredient and additive(s) generally used in the field of pharmaceutical products.

Examples of the specific pharmaceutically active ingredient composition mentioned above are

1) a composition comprising ω3-fatty acid alkyl ester at not less than 90%w/w (e.g., 90 - 100%w/w);

2) the composition of the above-mentioned 1) comprising ω3-fatty acid alkyl ester at not less than 90%w/w (e.g., 90 - 100%w/w), wherein EPA ethyl ester and/or DHA ethyl ester are/is the main component(s);

3) the composition of the above-mentioned 2) comprising both components of EPA ethyl ester and DHA ethyl ester, wherein the total content ratio of the both components is not less than 80%w/w (e.g., 80 - 100%w/w; preferably 80 - 90%w/w) (here, the

composition may contain ω3-fatty acid alkyl ester other than EPA ethyl ester and DHA ethyl ester);

4) the composition of the above-mentioned 3) comprising EPA ethyl ester in not less than 40%w/w (e.g., 40 - 66%w/w; preferably 40 - 50%w/w) and DHA ethyl ester in not less than 34%w/w (e.g., 34 - 60%w/w; preferably 34 - 45%w/w) wherein the total content ratio of the EPA ethyl ester and the DHA ethyl ester is not less than 80%w/w, and the composition may contain ω3-fatty acid alkyl ester other than the EPA ethyl ester and DHA ethyl ester;

5) the composition of the above-mentioned 4) which is OMEGA-3-ACID ETHYL ESTERS 90 defined by the European Pharmacopoeia;

wherein %w/w is the content ratio of the pharmaceutically active ingredient relative to the total weight of the capsule content.

The above-mentioned pharmaceutically active ingredient compositions 1) - 5) may be constituted by ω3-fatty acid alkyl ester alone, which is a pharmaceutically active ingredient, or may further contain additive(s) other than the pharmaceutically active ingredient.

As such additive, those mentioned below can be mentioned. Of those, a stabilizer (preferably, α-tocopherol) is preferable. When a stabilizer is to be used, its content in the pharmaceutically active ingredient composition is 0.3 - 0.5%w/w.

[0021]

The pharmaceutically active ingredient composition can be used for the production of a seamless capsule in the form of a solution, emulsion, suspension or other liquid. When the pharmaceutically active ingredient itself is a liquid, it can also be used as it is.

[0022]

Here, the weight ratio of the weight of the pharmaceutically active ingredient composition and the "total weight of the gelatin and a plasticizer" is generally 10:1 -

1:10, preferably 10:1 - 1:3.

[0023]

The weight ratio of the weight of the shell and the weight of the capsule content is generally 10:1 - 1:10, preferably 3:1 - 1:10.

[0024]

(Interfacial tension modifier and gelling agent)

The seamless capsule of the present invention is constituted by a shell and a capsule content.

In the seamless capsule of the present invention, a shell composition is characteristically free of both an "interfacial tension modifier" and a "gelling agent" conventionally widely used for the production of seamless capsules. Due to the absence of these components in a seamless capsule, the defects of the Prior Art can be avoided. The capsule content does not comprise both an "interfacial tension modifier" and a "gelling agent" in the same manner. Due to the absence, the defects of the Prior Art can also be avoided.

Here, the "interfacial tension modifier" refers to a substance that changes the tension produced in the oil-water interface between the capsule content and the aqueous shell composition solution. Examples thereof include phospholipid, fats and oils, surfactant, polar organic solvents such as alcohol and the like, and the like.

Here, the "gelling agent" refers to a substance that promotes gelling of an aqueous shell composition solution by cooling. Examples thereof include polar organic solvents such as alcohol and the like, polysaccharides and the like.

Here, being "free of an interfacial tension modifier and a gelling agent" means

1) being completely free of both components in a seamless capsule, or

2) even when both components or either component is contained in a seamless capsule, the content thereof being "insufficient to significantly change the interfacial tension" or

"insufficient to significantly shorten the gelling time.

As used herein, the amount "to significantly change the interfacial tension" is, for example, an amount causing a change of not less than 5 mN/m, or an amount causing a change of not less than 10%, as compared to no addition of an "interfacial tension modifier", when a tension produced in the oil-water interface between an aqueous gelatin solution (21.25%w/w, 50°C) and a content liquid (24°C) is measured. The interfacial tension is measured by, for example, a pendant drop method using FTA200 of First Ten Angstroms, Inc.

The "amount to significantly shorten the gelling time" is, for example, an amount that shortens the time necessary for gelling upon dropwise addition of an aqueous gelatin solution (21.25%w/w) heated to 55°C to MCT oil at 4°C, namely, the time necessary for reaching 50% level of elasticity of an aqueous gelatin solution at 4°C, by not less than 10%, as compared to no addition of a "gelling agent".

[0025]

In other words, being "free of an interfacial tension modifier and a gelling agent" means that an "interfacial tension modifier" is not present and a "gelling agent" is not present, either (including being substantially not contained (i.e., substantial absence)). Here, "substantial absence" of an interfacial tension modifier means possible presence thereof in "an amount insufficient to significantly change the interfacial tension", and that of a gelling agent means possible presence thereof in "an amount insufficient to significantly shorten the gelling time".

Accordingly, being "free of an interfacial tension modifier and a gelling agent" includes the following embodiments:

1) the seamless capsule of the present invention is completely free of both an interfacial tension modifier and a gelling agent;

2-1) the seamless capsule of the present invention is

substantially free of both an interfacial tension modifier and a gelling agent;

2-2) the seamless capsule of the present invention is substantially free of an interfacial tension modifier and completely free of a gelling agent; and

2-3) the seamless capsule of the present invention is completely free of an interfacial tension modifier and substantially free of a gelling agent.

[0026]

The seamless capsule of the present invention may contain components other than the "interfacial tension modifier" and "gelling agent" when desired and, for example, may contain a colorant. A colorant to be contained in the composition is not particularly limited and a desired colorant is used as necessary. For example, food colors such as yellow dye No. 5, red dye No. 2, blue dye No. 2 and the like; β carotene; food lake colors; diiron trioxide, yellow ferric oxide; and the like can be mentioned.

When desired, moreover, the seamless capsule of the present invention may contain components such as monosaccharides (e.g., pentose such as arabinose, xylose, ribose, 2-deoxyribose and the like; hexose such as glucose, fructose, galactose, mannose, sorbose, rhamnose, fucose and the like), disaccharides (e.g., malt sugar, cellobiose, α,α-trehalose, lactose, sucrose), celluloses (e.g., crystalline cellulose (including microcrystalline cellulose)), inorganic products (e.g., anhydrous calcium phosphate, precipitated calcium carbonate, calcium silicate) and the like.

When any of the above-mentioned components has an effect of changing the interfacial tension and/or an effect of shortening the gelling time, the seamless capsule of the present invention may even contain a component having such effect in an amount insufficient to significantly change the interfacial tension and an amount insufficient to significantly shorten the gelling time.

[0027]

The seamless capsule of the present invention may further contain, in addition to the above-mentioned components, additive(s) generally used in the field of the pharmaceutical products. Examples of such additive include inactive diluents (e.g., medium-chain triglyceride (MCT) oil, olive oil, soybean oil, corn oil, water, ethanol, a mixture thereof); pH adjusters (e.g., citrate, phosphate, carbonate, tartrate, fumarate, acetate, amino acid salt); surfactants (e.g., sodium lauryl sulfate, polysorbate 80, polyoxyethylene(160)polyoxypropylene(30)glycol); stabilizers (e.g., α-tocopherol, sodium tetraedetate, amide nicotinic acid, cyclodextrins); acidulants (e.g., ascorbic acid, citric acid, tartaric acid, malic acid); flavors (e.g., menthol, peppermint oil, lemon oil, vanillin, blueberry flavor); fluidizers (e.g., light anhydrous silicic acid, hydrated silicon dioxide, talc); and the like.

When any of the above-mentioned additives has an effect of changing the interfacial tension and/or an effect of shortening the gelling time, the seamless capsule of the present invention may even contain an additive having such effect in an amount insufficient to significantly change the interfacial tension and an amount insufficient to significantly shorten the gelling time.

[0028]

Each component of the shell composition above is, for example, blended and dissolved in an aqueous medium and used for the production of a seamless capsule (referred to as an "aqueous shell composition solution").

The concentration of the components (component concentration) other than water in the "aqueous shell composition solution" is preferably 15 - 35%w/w. When a low viscosity gelatin is used, the component concentration can be increased, which in turn shortens the drying time after production of a seamless capsule. Here, the low viscosity

means 2 - 4 mPa·s.

[0029]

(Carrier liquid)

For production of the seamless capsule of the present invention, a "carrier liquid" (e.g., MCT oil, etc.) generally used in this field can be employed.

Examples of the "carrier liquid" generally used in this field include oily substrates such as medium-chain triglyceride (MCT) oil, olive oil, soybean oil, corn oil and the like.

[0030]

(Preparation of seamless capsule)

The seamless capsule of the present invention is prepared using the above-mentioned "aqueous shell composition solution" and "capsule content", and a capsule production apparatus generally used for the production of seamless capsules (e.g., "SPHEREX" manufactured by Freund Corporation) and by a dropping immersed in a carrier liquid using multiple nozzles for the both components.

To be more specific, a capsule content flows out from an inner nozzle of multiple nozzles into a carrier liquid and an aqueous shell composition solution from an outer nozzle thereof into the carrier liquid at constant rates, a fluid of these two layers is cut at given intervals to form droplets with an interfacial tension, and the outer shell layer is gelled by cooling to give seamless capsules. The obtained seamless capsules are cooled for a given time and dried to yield products.

However, production of the seamless capsule of the present invention is not limited to such production method and can also be produced by other method known in this field.

[0031]

The size of the seamless capsule of the present invention can be appropriately adjusted by a known method. A capsule having a diameter within the range of 1 - 10 mm is preferable,

and a capsule having a diameter within the range of 2 - 6 mm is more preferable.

[0032]

For production of the seamless capsule of the present invention, it is preferable to appropriately control the temperature conditions at the capsule formation point (near multiple nozzles) during the production.

When the main component of a capsule content shows an excessively low or excessively high interfacial tension at a temperature near 25°C, as compared to appropriate interfacial tension, (especially when the content of the main component showing an excessively low or excessively high interfacial tension in the capsule content is high), it is particularly preferable for the production of a high quality seamless capsule to appropriately control the temperature.

In the present invention, the appropriate interfacial tension is, for example, 15 - 50 mN/m in the interface with an aqueous gelatin solution (21.25%w/w, 50°C). An interfacial tension below this level can be classified as being "excessively low", and an interfacial tension above this level can be classified as being "excessively high". The interfacial tension can be measured, for example, by the aforementioned method. This numerical value is one index that varies within a reasonable range depending on the capsule content to which the present invention is applied. Those of ordinary skill in the art can consider the necessity of temperature control as appropriate at specific situations where the present invention is applied.

[0033]

In a preferable embodiment, a seamless capsule is produced while keeping various conditions below wherein, near multiple nozzles of an apparatus for seamless capsule production,

1-1) the temperature of the "capsule content" is controlled to a value set ± 2°C within the range of 5 - 25°C;

2-1) the temperature of the "aqueous shell composition solution" is controlled to a value set ± 2°C within the range of 50 - 80°C;

3-1) the temperature of the "carrier liquid" is controlled to a value set ± 1°C within the range of 1 - 15°C;

4-1) the difference between the temperature of the "capsule content" and the temperature of the "aqueous shell composition solution" is not less than 25°C and not more than 75°C; and

5-1) the difference between the temperature of the "aqueous shell composition solution" and the temperature of the "carrier liquid" is not less than 35°C and not more than 79°C.

While a seamless capsule with sufficiently high quality can be obtained under the above temperature conditions, for production of a seamless capsule having still higher quality, a seamless capsule is produced while keeping various conditions below wherein

1-2) the temperature of the "capsule content" is controlled to a value set ± 2°C (preferably ± 1°C) within the range of 12°C - 22°C;

2-2) the temperature of the "an aqueous shell composition solution" is controlled to a value set ± 2°C (preferably ± 1°C) within the range of 60°C - 70°C;

3-2) the temperature of the "carrier liquid" is controlled to a value set ± 1°C (preferably ±0.5°C) within the range of 3 - 11°C;

4-2) the difference between the temperature of the "capsule content" and the temperature of the "aqueous shell composition solution" is not less than 38°C and not more than 58°C; and

5-2) the difference between the temperature of the "aqueous shell composition solution" and the temperature of the "carrier liquid" is not less than 49°C and not more than 67°C.

The aforementioned temperature conditions can be appropriately determined by those of ordinary skill in the art according to the level of quality required of a seamless capsule.

[0034]

When producing the seamless capsule of the present invention, it is particularly advantageous to satisfy all the above conditions 1-1) to 5-1).

While the above-mentioned temperature control can be easily performed by those of ordinary skill in the art by, for example, combining PID control and feedback control, the control method is not limited thereto.

[0035]

The seamless capsule of the present invention comprises a shell formed by a shell composition containing gelatin and a plasticizer, but free of an interfacial tension modifier and a gelling agent (an interfacial tension modifier is not contained and a gelling agent is not contained). The seamless capsule of the present invention preferably does not comprise an interfacial tension modifier and a gelling agent in a capsule content thereof (an interfacial tension modifier is not contained and a gelling agent is not contained), and shows a shell thickness minimum value/maximum value ratio of one capsule of not less than 0.6 immediately after encapsulation (after encapsulation and before drying). Namely, the seamless capsule is a novel capsule since it shows an extremely small nonuniformity in the thickness even though the shell does not contain an interfacial tension modifier and a gelling agent, and the capsule content preferably does not contain these components.

Specifically, the level of uneven thickness of the seamless capsule of the present invention by microscopic observation immediately after encapsulation corresponds to a minimum/maximum ratio of the shell thickness before drying of not less than 0.6, more preferably not less than 0.8, still more preferably not less than 0.9. The thickness can be measured by a general image analysis method. When the shell thickness minimum/maximum ratio is less than 0.6, defectively, the uneven thickness increases, the shell is cracked during

drying and storage after drying, and the capsule content leaks out.

Since shells shrink uniformly during drying, the shell thickness minimum/maximum ratio before drying is maintained even after drying.

[0036]

In addition, the seamless capsule of the present invention comprises a shell formed by a shell composition containing gelatin and a plasticizer, but free of an interfacial tension modifier and a gelling agent. Preferably, its capsule content is free of an interfacial tension modifier and a gelling agent, and the capsule is free of an eye, or with an extremely small eye even if present. When an eye is present, the diameter of the eye is not more than 1/2, more preferably not more than 1/4, still more preferably not more than 1/8, of the average thickness ((maximum + minimum)/2) of the shell before drying, by microscopic observation immediately after encapsulation and before drying. Particularly, the present invention is a seamless capsule comprising a shell formed by a shell composition containing gelatin and a plasticizer, but free of an interfacial tension modifier and a gelling agent (an interfacial tension modifier is not contained and a gelling agent is not contained), which does not contain an eye having a diameter exceeding 1/2 of the average thickness of the shell when measured after encapsulation and before drying, preferably a seamless capsule comprising a capsule content free of an interfacial tension modifier and a gelling agent (an interfacial tension modifier is not contained and a gelling agent is not contained). When the eye has a diameter exceeding 1/2 of the average thickness of the shell ((maximum + minimum)/2), defects such as cracks developed in the shell during drying and storage after drying and leakage of the capsule content occur.

Here, the eye refers to a spherical foam-like defect produced in the shell, and the foam may contain a capsule

content. While the eye is generally a sphere with small distortion, it may be a distorted sphere. In a non-spherical eye, the "eye diameter" refers to the diameter in the maximum direction. A seamless capsule may have multiple eyes, and each diameter is within the above-mentioned range. The thickness and eye diameter can be measured by general image analysis methods as in the measurement of uneven thickness.

In the present specification, when an eye with a diameter of 1/2 or less of the average thickness of the shell is present in a shell, the shell may sometimes be expressed to have "no eye".

[0037]

The seamless capsule of the present invention comprising a pharmaceutically active ingredient as its content can be safely administered to mammals (e.g., mouse, rat, rabbit, cat, dog, bovine, horse, monkey, human).

In this embodiment, the dose of the seamless capsule of the present invention need only be an effective amount of each pharmaceutically active ingredient to be contained in the capsule. While the administration frequency of the seamless capsule of the present invention to the aforementioned mammals in one day varies depending on the properties of the pharmaceutically active ingredient to be contained, it is typically 1 - 3 times a day.

As a specific example, the effective amount of OMEGA-3-ACID ETHYL ESTERS 90 is 100 - 6000 mg/day for an adult (body weight 60 kg).

[0038]

Specific examples of a particularly preferable seamless capsule of the present invention include the following:

1) a seamless capsule containing gelatin, and glycerin and sorbitol as plasticizers, and 25 mg of OMEGA-3-ACID ETHYL ESTERS 90 as a capsule content per capsule;

2) a seamless capsule containing gelatin, and glycerin and sorbitol as plasticizers, and 50 mg of OMEGA-3-ACID ETHYL

ESTERS 90 as a capsule content per capsule;

3) a seamless capsule containing gelatin, and glycerin and sorbitol as plasticizers, and 100 mg of OMEGA-3-ACID ETHYL ESTERS 90 as a capsule content per capsule;

4) a seamless capsule containing gelatin, and glycerin and sorbitol as plasticizers, and 200 mg of OMEGA-3-ACID ETHYL ESTERS 90 as a capsule content per capsule.

Examples

[0039]

The present invention is explained in more detail in the following Examples and Experimental Examples which are not to be construed as limitative.

The various gelatins to be used in the following Examples are commercially available, or even if they are not commercially available, they can be easily obtained by requesting gelatin manufacturers to produce them.

As preparation additives, those listed in the Japanese Pharmacopoeia Fifteenth Edition, the Japanese Pharmacopoeia Pharmaceutical Codex or Pharmaceutical Excipients 2003 were used.

[0040]

Example 1

Gelatin 1 (jelly strength 245 g, viscosity 4.3 mPa·s, 3158 g), gelatin 2 (jelly strength 297 g, viscosity 5.3 mPa·s, 1579 g), concentrated glycerin (559.0 g), sorbitol solution (399.2 g, solid content: 299.4 g) and yellow dye No. 5 (1.17 g) were added to purified water (16610 g) heated to 52°C. The mixture was dissolved, and degassed under reduced pressure (aqueous shell composition solution). The composition ratio when OMEGA-3-ACID ETHYL ESTERS 90 is 1000.00 parts by weight is shown in Table 1.

An apparatus for seamless capsule production (SPHEREX, manufactured by Freund Corporation) was used to prepare seamless capsules. The temperature of "OMEGA-3-ACID ETHYL ESTERS 90" (capsule content) near the nozzle was controlled to

16.3 - 18.9°C, aqueous shell solution was controlled to 67.8 - 68.3°C, MCT oil, which was used as a carrier liquid, was controlled to 5.9 - 7.1°C, and the mixture was encapsulated at a rate of 25 capsules per second.

The encapsulation step could be constantly operated stably by strictly controlling the temperatures.

The obtained capsules were cooled in a refrigerator (5°C, 14 hr), and dried in a drier until the water activity reached not more than 0.2. Then the carrier liquid on the capsule surface was wiped off to give seamless capsules containing 25 mg of OMEGA-3-ACID ETHYL ESTERS 90 per capsule.

The size of the obtained capsules was about 4 mmϕ (variation within the range of 3.5 - 4.5 mmϕ) in the center value.

[0041]

[Table 1]

composition ratio	(-)
OMEGA-3-ACID ETHYL ESTERS 90	1000.00
gelatin 1	242.94
gelatin 2	121.47
concentrated glycerin	43.00
sorbitol	21.50
yellow dye No. 5	0.090
purified water	1287.00

[0042]

Example 2

Gelatin 3 (jelly strength 255 g, viscosity 3.5 mPa·s, 5096.7 g), concentrated glycerin (601.4 g), sorbitol solution (429.2 g, solid content: 300.4 g) and yellow dye No. 5 (1.26 g) were added to purified water (13999.9 g) heated to 55°C. The mixture was dissolved, and degassed under reduced pressure (aqueous shell composition solution). The composition ratio when OMEGA-3-ACID ETHYL ESTERS 90 is 1000.00 parts by weight is shown in Table 2.

An apparatus for seamless capsule production (SPHEREX, manufactured by Freund Corporation) was used to prepare seamless capsules. The temperature of "OMEGA-3-ACID ETHYL ESTERS 90" (capsule content) near the nozzle was controlled to 16.3 - 16.7°C, and the aqueous shell solution was controlled to 70.3 - 70.4°C. MCT oil was used as a carrier liquid and the temperature thereof was controlled to 6.8 - 7.1°C, and the mixture was encapsulated at 25 capsules per second.

The encapsulation step could be constantly operated stably by strictly controlling the temperatures.

The obtained capsules were cooled in a refrigerator (4°C, 28 hr), and dried in a drier until the water activity reached not more than 0.2. Then the carrier liquid on the capsule surface was wiped off to give seamless capsules containing 25 mg of OMEGA-3-ACID ETHYL ESTERS 90 per capsule.

The size of the obtained capsules was about 4 mmϕ (variation within the range of 3.5 - 4.5 mmϕ) in the center value.

[0043]

[Table 2]

composition ratio	(-)
OMEGA-3-ACID ETHYL ESTERS 90	1000.00
gelatin 3	364.41
concentrated glycerin	43.00
sorbitol	21.50
yellow dye No. 5	0.090
purified water	1287.00

[0044]

Example 3

Gelatin 1 (jelly strength 245 g, viscosity 4.3 mPa·s, 3158 g), gelatin 2 (jelly strength 297 g, viscosity 5.3 mPa·s, 1579 g), concentrated glycerin (559.0 g), sorbitol solution (399.2 g, solid content: 299.4 g), and yellow dye No. 5 (1.17 g) were added to purified water (16610 g) heated to 52°C. The

mixture was dissolved, and degassed under reduced pressure (aqueous shell composition solution). The composition ratio when OMEGA-3-ACID ETHYL ESTERS 90 is 1000.00 parts by weight is shown in Table 3.

An apparatus for seamless capsule production (SPHEREX, manufactured by Freund Corporation) was used to prepare seamless capsules. The temperature of "OMEGA-3-ACID ETHYL ESTERS 90" (capsule content) near the nozzle was controlled to 17.7 - 18.8°C, and the aqueous shell solution was controlled to 67.5 - 68.1°C. MCT oil was used as a carrier liquid and the temperature thereof was controlled to 6.4 - 6.8°C, and the mixture was encapsulated at a rate of 25 capsules per second.

The encapsulation step could be constantly operated stably by strictly controlling the temperatures.

The obtained capsules were cooled in a refrigerator (5°C, 14 hr), and dried in a drier until the water activity reached not more than 0.2. Then the carrier liquid on the capsule surface was wiped off to give seamless capsules containing 25 mg of OMEGA-3-ACID ETHYL ESTERS 90 per capsule.

The size of the obtained capsules was about 4 mmϕ (variation within the range of 3.5 - 4.5 mmϕ) in the center value.

[0045]

[Table 3]

composition ratio	(-)
OMEGA-3-ACID ETHYL ESTERS 90	1000.00
gelatin 1	242.94
gelatin 2	121.47
concentrated glycerin	43.00
sorbitol	21.50
yellow dye No. 5	0.090
purified water	1287.00

[0046]

Example 4

Gelatin 4 (jelly strength 264 g, viscosity 4.2 mPa·s, 3398 g), concentrated glycerin (401 g), sorbitol solution (286 g, solid content: 200.2 g), and yellow dye No. 5 (0.84 g) were added to purified water (15914 g) heated to 55°C. The mixture was dissolved, and degassed under reduced pressure (aqueous shell composition solution). The composition ratio when OMEGA-3-ACID ETHYL ESTERS 90 is 1000.00 parts by weight is shown in Table 4.

An apparatus for seamless capsule production (SPHEREX, manufactured by Freund Corporation) was used to prepare seamless capsules. The temperature of "OMEGA-3-ACID ETHYL ESTERS 90" (capsule content) near the nozzle was controlled to 14.7°C, and the aqueous shell solution was controlled to 56.7°C. MCT oil was used as a carrier liquid and the temperature thereof was controlled to 4.4°C, and the mixture was encapsulated at 7 capsules per second.

The encapsulation step could be constantly operated stably by strictly controlling the temperatures.

The obtained capsules were cooled in a refrigerator (4°C, 21 hr), and dried in a drier until the water activity reached not more than 0.2. Then the carrier liquid on the capsule surface was wiped off to give seamless capsules containing 200 mg of OMEGA-3-ACID ETHYL ESTERS 90 per capsule.

The size of the obtained capsules was about 8 mmϕ (variation within the range of 7.5 - 8.5 mmϕ) in the center value.

[0047]

[Table 4]

composition ratio	(-)
OMEGA-3-ACID ETYYL ESTERS 90	1000.00
gelatin 4	195.38
concentrated glycerin	23.06
sorbitol	11.51
yellow dye No. 5	0.048
purified water	919.96

[0048]

Example 5

Gelatin 4 (jelly strength 264 g, viscosity 4.2 mPa·s, 9568.125 g), concentrated glycerin (1128.75 g) and sorbitol solution (806.1 g, solid content: 564.3 g) were added to purified water (33541.5 g) heated to 55°C. The mixture was dissolved, and degassed under reduced pressure (aqueous shell composition solution). The composition ratio when OMEGA-3-ACID ETHYL ESTERS 90 is 1000.00 parts by weight is shown in Table 5.

An apparatus for seamless capsule production (manufactured by Fuji Capsule Co., Ltd.) was used to prepare seamless capsules. The temperature of "OMEGA-3-ACID ETHYL ESTERS 90" (capsule content) near the nozzle was controlled to 22.8 - 23.2°C, and the aqueous shell solution was controlled to 69.9 - 70.3°C. MCT oil was used as a carrier liquid and the temperature thereof was controlled to 6.4 - 6.7°C, and the mixture was encapsulated at 25 capsules per second.

The encapsulation step could be constantly operated stably by strictly controlling the temperatures.

The obtained capsules were cooled in a refrigerator (5°C, 15 hr), and dried in a drier until the water activity reached not more than 0.2. Then the carrier liquid on the capsule surface was wiped off to give seamless capsules containing 25 mg of OMEGA-3-ACID ETHYL ESTERS 90 per capsule.

The size of the obtained capsules was about 4 mmϕ (variation within the range of 3.5 - 4.5 mmϕ) in the center value.

[0049]

[Table 5]

composition ratio	(-)
OMEGA-3-ACID ETYYL ESTERS 90	1000.00
gelatin 4	364.50
concentrated glycerin	43.00
sorbitol	21.50
purified water	1287.00

[0050]

Example 6

Using the seamless capsules obtained in Example 5, aromatized seamless capsules were produced. The composition ratio when OMEGA-3-ACID ETHYL ESTERS 90 is 1000.00 parts by weight is shown in Table 6.

Ethyl alcohol (22.4 g) and blueberry flavor (5.6 g) were mixed to give a flavoring liquid. The flavoring liquid (1.47 g per 300 g of seamless capsules) was dispersed on seamless capsules obtained in Example 5 to aromatize them using a tumbler coating machine (HICOATER: manufactured by Freund Corporation). After aromatization, the ethyl alcohol in the seamless capsules was removed using a tumbler coating machine (HICOATER: manufactured by Freund Corporation) until it reached not more than 5000 ppm to give aromatized seamless capsules.

[0051]

[Table 6]

composition ratio	(-)
OMEGA-3-ACID ETYYL ESTERS 90	1000.0
gelatin 4	364.5
concentrated glycerin	43.0
sorbitol	21.5
purified water	1287.0
ethyl alcohol	224.0
blueberry flavor	56.0

[0052]

Example 7

Gelatin 1 (jelly strength 245 g, viscosity 4.3 mPa·s, 3158 g), gelatin 2 (jelly strength 297 g, viscosity 5.3 mPa·s, 1579 g), concentrated glycerin (559.0 g), sorbitol solution (399.2 g, solid content: 299.4 g) and yellow dye No. 5 (1.17 g) were added to purified water (16610 g) heated to 52°C. The

mixture was dissolved, and degassed under reduced pressure (aqueous shell composition solution). The composition ratio when OMEGA-3-ACID ETHYL ESTERS 90 is 1000.00 parts by weight is shown in Table 7.

An apparatus for seamless capsule production (SPHEREX, manufactured by Freund Corporation) was used to prepare seamless capsules. The temperature of "OMEGA-3-ACID ETHYL ESTERS 90" (capsule content) near the nozzle was controlled to 17.7 - 18.8°C, and the aqueous shell solution was controlled to 67.5 - 68.1°C. MCT oil was used as a carrier liquid and the temperature thereof was controlled to 6.4 - 6.8°C, and the mixture was encapsulated at a rate of 25 capsules per second.

The encapsulation step could be constantly operated stably by strictly controlling the temperatures.

The obtained capsules were cooled in a refrigerator (5°C, 21 hr), and dried in a drier until the water activity reached not more than 0.2. Then the carrier liquid on the capsule surface was wiped off to give seamless capsules containing 25 mg of OMEGA-3-ACID ETHYL ESTERS 90 per capsule.

The operation up to this point was repeated 3 times, and the obtained seamless capsules were mixed using a tumbler drier (manufactured by Freund Corporation). Ethyl alcohol (224 g) and blueberry flavor (56 g) were mixed to give a flavoring liquid. The flavoring liquid (199.1 g per 40655 g of seamless capsules) was dispersed on the mixed seamless capsules to aromatize them using a tumbler drier (manufactured by Freund Corporation). After aromatization, the ethyl alcohol in the seamless capsules was removed until it reached not more than 5000 ppm using a tumbler drier (manufactured by Freund Corporation) to give aromatized seamless capsules.

The size of the obtained capsules was about 4 mmϕ (variation within the range of 3.5 - 4.5 mmϕ) in the center value.

[0053]

[Table 7]

composition ratio	(-)
OMEGA-3-ACID ETYYL ESTERS 90	1000.00
gelatin 1	242.94
gelatin 2	121.47
concentrated glycerin	43.00
sorbitol	21.50
yellow dye No. 5	0.086
purified water	1290.00
ethyl alcohol	224.0
blueberry flavor	56.0

[0054]

The OMEGA-3-ACID ETHYL ESTERS 90 used in each of Examples 1 - 7 is a product compatible with the European Pharmacopoeia. The quality thereof is shown in Table 8.

[0055]

[Table 8]

	Ex. 1	Ex. 2	Ex. 3	Ex. 4	Ex. 5	Ex. 6	Ex. 7
content rate of EPA ethyl ester	45.3% w/w	45.7% w/w	45.3% w/w	47.3% w/w	47.0% w/w	47.0% w/w	47.1% w/w
content rate of DHA ethyl ester	37.7% w/w	37.6% w/w	37.7% w/w	36.9% w/w	35.8% w/w	35.8% w/w	37.2% w/w
total content rate of EPA ethyl ester and DHA ethyl ester	83.0% w/w	83.3% w/w	83.0% w/w	84.2% w/w	82.8% w/w	82.8% w/w	84.3% w/w
content rate of ω3-fatty acid alkyl ester	92% w/w	91% w/w	92% w/w	93% w/w	91% w/w	91% w/w	92% w/w
content of α-tocopherol	3.8 mg/g	3.8 mg/g	3.8 mg/g	4.0 mg/g	3.9 mg/g	3.9 mg/g	3.7 mg/g
European Pharmacopoeia	compa-tible	compa-tible	compa-tible	compa-tible	compa-tible	compa-tible	compa-tible

* The content rate and content in the table indicate the values

in a capsule content (pharmaceutically active ingredient composition).

[0056]

Experimental Example 1

The seamless capsules (200 g) obtained in Example 3 were evaluated by a Digital Image Processing Particle Size Analyzer (Camsizer, manufactured by Horiba, Ltd.). The aspect ratio was not less than 0.95, which confirmed they were almost spherical.

[0057]

Experimental Example 2

In Example 3, as the content, OMEGA-3-ACID ETHYL ESTERS 90 could be contained at a high content of 100%. In addition, by capsule evaluation using a digital microscope (VHX-200, KEYENCE CORPORATION) before drying, it was observed that eyes were absent (which permits a conclusion that an eye having a size exceeding 1/2 of the average thickness of the shell was not present), and encapsulation with a good shell showing extremely less uneven thickness was achieved, as shown in Fig. 1. The thickness of the shell was 0.84 mm at maximum and 0.82 mm at minimum (minimum/maximum 0.98).

Industrial Applicability

[0058]

The seamless capsule of the present invention is superior in the stability of the capsule content, and can contain a large amount of the capsule content. Furthermore, the present invention affords high quality seamless capsules free of an eye or with only an extremely small eye even if present, which show extremely small nonuniformity in the thickness. Since the content can be high, the unit size of a preparation can be minimized, and highly easy administration and small space utility during storage can be realized. Moreover, the stability during preservation can be improved, thus enabling extension of a use-by date.

[0059]

This application is based on patent application No. 2007-173198 filed in Japan, the contents of which are incorporated in full herein by this reference.

CLAIMS

1. A seamless capsule comprising a shell formed by a shell composition comprising gelatin and a plasticizer, which does not comprise an interfacial tension modifier and a gelling agent, and a pharmaceutically active ingredient composition without comprising an interfacial tension modifier and a gelling agent, wherein the pharmaceutically active ingredient composition comprises not less than 40%w/w of EPA ethyl ester and not less than 34%w/w of DHA ethyl ester.

2. The seamless capsule of claim 1, wherein the gelatin has jelly strength of 200 - 300 g.

3. The seamless capsule of claim 1 or 2, wherein the gelatin has a viscosity of 2 - 6 mPa·s.

4. The seamless capsule of any one of claims 1 - 3, wherein the gelatin is derived from pigskin.

5. The seamless capsule of claim 1, wherein the plasticizer is glycerin.

6. The seamless capsule of claim 1, wherein the plasticizer is sorbitol.

7. The seamless capsule of claim 1, wherein the plasticizer is a mixture of glycerin and sorbitol.

8. The seamless capsule of claim 7, wherein the weight ratio of glycerin and sorbitol is 1:5 - 5:1.

9. The seamless capsule of claim 1, wherein the weight ratio of gelatin and plasticizer is 10:1 - 1:1.

10. The seamless capsule of claim 1, wherein the pharmaceutically active ingredient composition comprises OMEGA-3-ACID ETHYL ESTERS 90 in the European Pharmacopoeia.

11. The seamless capsule of claim 1, wherein the weight ratio of the pharmaceutically active ingredient composition and the "total of gelatin and a plasticizer" is 10:1 - 1:10.

12. The seamless capsule of claim 1, wherein the weight ratio of the shell and the capsule content is 10:1 - 1:10.

13. A method of producing a seamless capsule comprising a shell formed by a shell composition comprising gelatin and a plasticizer, which does not comprise an interfacial tension modifier and a gelling agent, and a capsule content without comprising an interfacial tension modifier and a gelling agent by a drip in oil method,

wherein the capsule content is a pharmaceutically active ingredient composition,

wherein the pharmaceutically active ingredient composition comprises not less than 40%w/w of EPA ethyl ester and not less than 34%w/w of DHA ethyl ester,

wherein temperatures of the "capsule content without comprising an interfacial tension modifier and a gelling agent", the "aqueous shell composition solution formed by a shell composition comprising gelatin and a plasticizer, which does not comprise an interfacial tension modifier and a gelling agent" and the "carrier liquid" are each controlled near multiple nozzles of an apparatus used for the drop in oil method, wherein the temperature of the "capsule content without comprising an interfacial tension modifier and a gelling agent" is controlled to a value set ± 2°C within the range of 5°C - 25°C,

wherein the temperature of the "aqueous shell composition solution formed by a shell composition comprising gelatin and a plasticizer, which does not comprise an interfacial tension modifier and a gelling agent" is controlled to a value set ± 2°C within the range of 50°C - 80°C, wherein the temperature of the "carrier liquid" is controlled to

a value set ± 1°C within the range of 1°C - 15°C, wherein a difference between the temperature of the "capsule content without comprising an interfacial tension modifier and a gelling agent" and the temperature of the "aqueous shell composition solution formed by a shell composition comprising gelatin and a plasticizer, which does not comprise an interfacial tension modifier and a gelling agent" is not less than 25°C and not more than 75°C,

and wherein a difference between the temperature of the "aqueous shell composition solution formed by a shell composition comprising gelatin and a plasticizer, which does not comprise an interfacial tension modifier and a gelling agent" and the temperature of the "carrier liquid" is not less than 35°C and not more than 79°C.

14. A seamless capsule produced by a drip in oil method, wherein temperatures of the "capsule content without comprising an interfacial tension modifier and a gelling agent", the "aqueous shell composition solution formed by a shell composition comprising gelatin and a plasticizer, which does not comprise an interfacial tension modifier and a gelling agent" and the "carrier liquid" are each controlled near multiple nozzles of an apparatus used for the drop in oil method,

wherein the capsule content is a pharmaceutically active ingredient composition,

wherein the pharmaceutically active ingredient composition comprises not less than 40%w/w of EPA ethyl ester and not less than 34%w/w of DHA ethyl ester, and wherein the temperatures are controlled to the following temperatures:

the temperature of the "capsule content" is controlled to a value set ± 2°C within the range of 5 - 25°C;

the temperature of the "aqueous shell composition solution" is controlled to a value set ± 2°C within the range of 50 - 80°C;

the temperature of the "carrier liquid" is controlled to a value set ± 1°C within the range of 1 - 15°C;

the difference between the temperature of the "capsule content" and the temperature of the "aqueous shell composition solution" is not less than 25°C and not more than 75°C; and

the difference between the temperature of the "aqueous shell

composition solution" and the temperature of the "carrier liquid" is not less than 35°C and not more than 79°C.

15. The seamless capsule of claim 14, wherein the temperatures are controlled to the following temperatures:

the temperature of the "capsule content" is controlled to a value set ± 1°C within the range of 12°C - 22°C;

the temperature of the "an aqueous shell composition solution" is controlled to a value set ± 1°C within the range of 60°C - 70°C;

the temperature of the "carrier liquid" is controlled to a value set ± 0.5°C within the range of 3 - 11°C;

the difference between the temperature of the "capsule content" and the temperature of the "aqueous shell composition solution" is not less than 38°C and not more than 58°C; and

the difference between the temperature of the "aqueous shell composition solution" and the temperature of the "carrier liquid" is not less than 49°C and not more than 67°C.

16. A seamless capsule comprising a shell formed by a shell composition comprising gelatin and a plasticizer, which does not comprise an interfacial tension modifier and a gelling agent, and a pharmaceutically active ingredient composition without comprising an interfacial tension modifier and a gelling agent,

wherein the pharmaceutically active ingredient composition comprises not less than 40%w/w of EPA ethyl ester and not less than 34%w/w of DHA ethyl ester,

wherein the shell has a minimum/maximum thickness ratio of not less than 0.6.

17. The seamless capsule of claim 16, which comprises the pharmaceutically active ingredient composition free of an interfacial tension modifier and a gelling agent.

18. A seamless capsule comprising a shell formed by a shell composition comprising gelatin and a plasticizer, which does not comprise an interfacial tension modifier and a gelling agent, and a

pharmaceutically active ingredient composition without comprising an interfacial tension modifier and a gelling agent,

wherein the pharmaceutically active ingredient composition comprises not less than 40%w/w of EPA ethyl ester and not less than 34%w/w of DHA ethyl ester,

wherein the shell is free of an eye.

19. The seamless capsule of claim 18, which comprises the pharmaceutically active ingredient composition free of an interfacial tension modifier and a gelling agent.

20. A seamless capsule comprising a shell formed by a shell composition comprising gelatin and a plasticizer, which does not comprise an interfacial tension modifier and a gelling agent, and a pharmaceutically active ingredient composition without comprising an interfacial tension modifier and a gelling agent,

wherein the pharmaceutically active ingredient composition comprises not less than 40%w/w of EPA ethyl ester and not less than 34%w/w of DHA ethyl ester,

wherein the diameter of an eye of the shell after encapsulation and before drying is 1/2 or below of the average thickness of shells.

21. The seamless capsule of claim 20, which comprises a capsule content free of an interfacial tension modifier and a gelling agent.

22. A seamless capsule comprising a shell formed by a shell composition comprising gelatin and a plasticizer, which does not comprise an interfacial tension modifier and a gelling agent, and a pharmaceutically active ingredient composition without comprising an interfacial tension modifier and a gelling agent,

wherein the pharmaceutically active ingredient composition comprises not less than 40%w/w of EPA ethyl ester and not less than 34%w/w of DHA ethyl ester,

wherein the shell after encapsulation and before drying is free of an eye having a diameter exceeding 1/2 of the average thickness of shells.

23. The seamless capsule of claim 22, which comprises the pharmaceutically active ingredient composition free of an interfacial tension modifier and a gelling agent.