Description

Title of Invention: GRANULAR PREPARATION

Technical Field

[0001]

The present invention relates to a granular preparation. Specifically, the present invention relates to a granular preparation containing isoleucine, leucine and valine.

Background Art

[0002]

LIVACT (registered trademark, the same applies to the following) Granules, a therapeutic drug effective for hepatic diseases, etc., are commercially available as a drug containing isoleucine, leucine and valine.

LIVACT Granules contain 4 g of active ingredients in one package (4.15 g) and are used to improve hypoalbuminemia in patients with decompensated hepatic cirrhosis who exhibit hypoalbuminemia despite adequate dietary intake (Non Patent Literature 1).

Citation List

Non Patent Literature

[0003]

Non Patent Literature 1: Package Insert Branched-chain Amino Acid Formula, the Japanese Pharmacopoeia

Isoleucine·leucine·valine Granules LIVACT (registered trademark) Granules, revised April 2016 (17th Edition)

Summary of Invention

Technical Problem

[0004]

LIVACT Granules are a granular preparation containing large amounts of amino acid ingredients, and thus required to be further improved in unpalatability such as bitterness due to amino acids and granules' property of remaining in the mouth.

[0005]

An object to be achieved by the present invention is to provide a granular preparation containing isoleucine, leucine and valine with improved unpalatability.

Solution to Problem

[0006]

As a result of intensive studies, the present inventors have discovered that the above object can be achieved by combining a granular preparation containing isoleucine, leucine and valine with a gelling agent, and thus have completed the present invention.

[0007]

Specifically, the present invention is as follows.

(1) A granular preparation containing isoleucine, leucine and valine as active ingredients, wherein the preparation contains a gelling agent.

(2) The granular preparation according to (1), wherein the gelling agent is a carboxyvinyl polymer or a polyethylene oxide.

(3) The granular preparation according to (1) or (2), wherein the gelling agent is a polyethylene oxide having an average molecular weight of 500,000 or more.

(4) The granular preparation according to any one of (1) to (3), wherein the gelling agent is added in the form of powder.

(5) The granular preparation according to any one of (1) to (4), wherein the gelling agent is added at 0.05% to 2% based on the total amount of the granular preparation.

(6) The granular preparation according to any one of (1) to (5), wherein contains isoleucine, leucine, and valine are contained at a weight ratio of 1/(1.9–2.2)/(1.1–1.3).

(7) The granular preparation according to any one of (1) to (6), wherein isoleucine, leucine and valine are contained at 80% or more based on the total amount of the granular preparation.

(8) The granular preparation according to any one of (1) to (7), further containing a binder and/or a corrigent.

(9) A method for producing a granular preparation containing isoleucine, leucine and valine as active ingredients, comprising the step of adding a gelling

agent to granules containing isoleucine, leucine and valine.

(10) The production method according to (9), wherein the gelling agent is added in the form of powder.

Advantageous Effects of Invention

[0008]

According to the present invention, a granular preparation containing isoleucine, leucine and valine with improved unpalatability can be provided.

Brief Description of Drawings

[0009]

[Figure 1] Figure 1 shows the results of dissolution test on the granular preparation in Example 1.

[Figure 2] Figure 2 shows the results of dissolution test on the granular preparation in Comparative Example 1.

Description of Embodiments

[0010]

The present invention will be described in detail with reference to Description of Embodiments. The present invention is not limited to the following embodiments and various modifications of the present invention can be implemented.

[0011]

The granular preparation of the present invention contains isoleucine, leucine and valine as active ingredients and contains a gelling agent.

In the granular preparation of the present invention, isoleucine, leucine and valine to be used as active ingredients are amino acids known as branched-chain amino acids.

In the present invention, D-amino acids, L-amino acids, mixtures of D-amino acids and L-amino acids at arbitrary ratios, or DL-amino acids may be used.

Isoleucine, leucine and valine may each be a chemically synthesized product or a fermentation product.

As isoleucine, leucine and valine, those satisfying the specifications for L-isoleucine, L-leucine and L-valine described in the Japanese Pharmacopoeia, Seventeenth Edition (pages 483, 1711 to 1712, and 1248, respectively) are preferably used.

[0012]

In the present invention, the expression "containing (contains) isoleucine, leucine and valine as active ingredients" means that the granular preparation of the present invention contains isoleucine, leucine and valine as ingredients exhibiting efficacy, when used as a drug.

As the indication of a drug containing isoleucine, leucine and valine as active ingredients, in Japan, the indication of a commercially available product, LIVACT Granules, that is, "improvement of hypoalbuminemia in

patients with decompensated hepatic cirrhosis who exhibit hypoalbuminemia despite adequate dietary intake" is known. The indication of the granular preparation of the present invention containing isoleucine, leucine and valine as active ingredients is not limited to such an indication alone.

In the present invention, the granular preparation may contain other ingredients as active ingredients, but preferably contains only isoleucine, leucine and valine as active ingredients.

The granular preparation of the present invention contains isoleucine, leucine and valine as active ingredients, and thus can be used as a pharmaceutical granular preparation.

[0013]

In the granular preparation of the present invention, the content ratio of isoleucine, leucine and valine is not particularly limited and is preferably isoleucine/leucine/valine=1/(1.9–2.2)/(1.1–1.3) as a weight ratio.

The content of isoleucine, leucine and valine is determined as appropriate, and the lower limit of the content is preferably 80% or more, more preferably 90% or more, and further preferably 95% or more, as mass% based on the total amount of the granular preparation.

The upper limit of the content of isoleucine, leucine and valine is not particularly limited. The

content of isoleucine, leucine and valine is preferably less than 100%, more preferably 99% or less, further preferably 98% or less, and even more preferably 97% or less.

The content of isoleucine, leucine and valine may be within the range obtained by combining values described as the preferable upper limits and lower limits.

[0014]

The granular preparation of the present invention contains a gelling agent.

In the present invention, the term "gelling agent" refers to an additive for a preparation, which is a base material that is gelled when it contains water.

Examples of the gelling agent include, but are not particularly limited to, hypromellose, methylcellulose, hydroxypropylcellulose, carboxyvinyl polymer, sodium alginate, carrageenan, xanthan gum, tamarind gum, pectin, locust bean gum, gellangum, agar and a polyethylene oxide.

In view of gelling ability and gelling rate, a carboxyvinyl polymer and a polyethylene oxide are preferable, and a polyethylene oxide is more preferable.

One gelling agent may be used and a mixture of two or gelling agents may also be used.

[0015]

The average molecular weight of a gelling agent is adequately determined depending on the type of the

gelling agent in view of indices such as gelling ability and gelling rate.

Gelling ability can be confirmed through observation of the appearance of a gelling agent when it is dissolved in water at a high concentration or a low concentration.

Moreover, a gelling rate can be confirmed by adding and dissolving a gelling agent in water, stirring the resultant, and then observing the gelling conditions over time.

Examples of the concentration for determining gelling ability include a high concentration (10 w/v%) and a low concentration (1 w/v%). Examples of the concentration for determining gelling rate include 10 w/v% and the like.

[0016]

Polyethylene oxide has preferably an average molecular weight of 150,000 or more, more preferably an average molecular weight of 500,000 or more, further preferably an average molecular weight of 1,000,000 or more, and even more preferably an average molecular weight of 2,000,000 or more, in terms of the lower limit of the average molecular weight.

The upper limit of the average molecular weight of polyethylene oxide is not particularly limited. The average molecular weight of polyethylene oxide is preferably 10,000,000 or less, and more preferably 5,000,000 or less.

The average molecular weight of polyethylene oxide may be within the range obtained by combining values described as the preferable upper and lower limits.

[0017]

In the present invention, the average molecular weight of a gelling agent may be a value denoted on a relevant product and can be measured as a viscosity-average molecular weight through measurement of the viscosity of the solution of the gelling agent.

[0018]

A gelling agent contained in the granular preparation of the present invention is preferably added in the form of powder and thus is present in the granular preparation.

The gelling agent is added in the form of powder to uncoated granules containing isoleucine, leucine and valine. Through addition of the gelling agent in the form of powder to uncoated granules, the resulting granular preparation contains the gelling agent existing in the form of powder added over the surface of the granules.

[0019]

When a gelling agent is added in the form of powder to the granular preparation of the present invention, the gelling agent is present in the form of powder added over the surface of the granules. Hence, the granular preparation of the present invention differs from

granular preparations with a surface coated with a gelling agent, as so-called coated granules.

In the case of coated granules, uncoated granules containing isoleucine, leucine and valine are coated with a coating liquid. In this case, a gelling agent is contained in the coating liquid.

In the granular preparation, the presence of a gelling agent after addition thereof in the form of powder can be confirmed by evaluating the gelling ability etc., of powder obtained by separation such as sieving, for example, but the confirmation method is not particularly limited thereto. Moreover, the presence of a gelling agent after addition thereof in the form of powder can also be confirmed by observation of spectral images, for example.

[0020]

The content of a gelling agent is adequately determined depending on the type of the gelling agent, and is, in view of gelling ability and gelling rate, preferably 0.01 to 5%, more preferably 0.05 to 2%, and further preferably 0.05 to 1%, as mass% based on the total amount of the granular preparation. The content of a gelling agent may be 0.1 mass% or more within the above range.

[0021]

The granular preparation of the present invention can be produced by adding a gelling agent to granules

containing isoleucine, leucine and valine, which have been produced by a conventionally known method.

[0022]

In the present invention, the particle sizes of isoleucine, leucine and valine may be adjusted by mixing and pulverizing solid raw-material amino acids, which are isoleucine, leucine and valine, by the method described in Japanese Patent No. 3228288.

For mixing and pulverization, both a method that involves mixing in advance isoleucine, leucine and valine and then pulverizing the mixture, and a method that involves pulverizing isoleucine, leucine and valine while mixing them can be used.

[0023]

For mixing of solid raw-material amino acids, container rotary type mixers such as a container mixer, pneumatic mixers such as a fluidized-bed mixer, convection mixers for mixing with the use of the rotation of agitation blades and agitation ribbons, line mixers for mixing in the powder transport line or feeder mixers provided at ports for feeding raw materials of pulverizers or the like can be used, for example, but the examples thereof are not particularly limited thereto.

[0024]

For pulverization of solid raw-material amino acids, impact (high rpm) pulverizers such as a hammer mill and a pin mill, tumbler (medium type) pulverizers such as a

ball mill or fluid energy (airflow) pulverizers such as a jet mill can be used, for example, but the examples thereof are not particularly limited thereto.

[0025]

Upon production of the granules containing isoleucine, leucine and valine of the present invention, a high-speed agitation granulator, a fluidized bed granulator, a planetary mixer, a dry press granulator, a crushing granulator, an extruding granulator, a tumbling granulator, spray drying granulator, or a coating granulator can be used, for example, but the examples thereof are not particularly limited thereto.

Granules are preferably produced using a high-speed agitation granulator or an extruding granulator.

Examples of the extruding granulator include, but are not particularly limited to, a pre-extruding granulator, a disc pelleter, a ring die granulator, a basket granulator, an oscillating granulator and a cylinder granulator.

[0026]

When granules are produced, known pharmaceutically applicable additives that meet the specifications of the Japanese Pharmacopoeia or the Japanese Pharmaceutical Excipients, for example, can be mixed therewith.

Examples of such additives include, but are not particularly limited to, additives known as a binder, a lubricant, a colorant, a plasticizer, a surfactant, a

sweetener, a corrigent, an odor improving agent, and an flavoring agent, etc. Of these examples, a binder and/or a corrigent is preferable.

A single type of additive or a mixture of two or more types of additive may be used.

[0027]

Examples of the binder include, but are not particularly limited to, cellulose derivatives such as methylcellulose, hydroxypropylcellulose, hydroxypropyl methylcellulose, and hydroxypropyl methylcellulose phthalate, starches such as corn starch and wheat starch, synthetic polymers such as polyvinylpyrrolidone (povidone), polyvinyl alcohol, and acrylic acid polymers, and natural polymers such as gum Arabic and gelatin.

Examples of the corrigent include, but are not particularly limited to, citric acid, tartaric acid, aspartame, saccharin, saccharin sodium, erythritol, xylitol, mannitol and stevia. Examples of a corrigent also include an additive known as a sweetener.

Examples of the odor improving agents and the flavoring agents include, but are not particularly limited to, menthol, lemon flavor, sugarless flavor, sweet flavor and strawberry oil.

[0028]

In the present invention, preferably, a corrigent and/or an odor improving agent is adhered onto the surface of the granules containing isoleucine, leucine

and valine by the method described in Japanese Patent No. 3405342.

The particle size of granules to which a corrigent and/or an odor improving agent is adhered is not particularly limited, as long as the fluid state can be easily maintained at a general fluidization device, and is generally 100 to 2000 μm, and preferably about 200 to 1700 μm.

[0029]

Examples of a fluidization device for adhesion of a corrigent and/or an odor improving agent onto granules include, but are not particularly limited to, a fluid dryer "flow dryer" (Freund Corporation), fluidized bed granulator/coater "flow coater" (Freund Corporation), "Glatt GPCG" (Powrex Corporation), "Malmeriser" (Dalton), and "Multiprocessor" (Kikusui Seisakusho Ltd.).

[0030]

In the present invention, granules containing isoleucine, leucine and valine, preferably granules to which a corrigent and/or an odor improving agent is adhered are mixed with a gelling agent.

In the present invention, a gelling agent is preferably added in the form of powder to granules containing isoleucine, leucine and valine, preferably, granules to which a corrigent and/or an odor improving agent is adhered, and then the resultant is mixed.

Examples of such a mixing method include, but are not particularly limited to, as long as it enables approximately uniform mixing, methods using general container rotating mixers (e.g., V type, double conical type, and a rotating and oscillating type), container fixed mixers (e.g., ribbon type, and conical screw type) or pneumatic mixers, for example.

A method that may be used herein involves adding a specified amount of each preparation into a predetermined container and then mixing using a dividing and packing machine etc.

[0031]

A gelling agent is added in the form of powder to granules containing isoleucine, leucine and valine, and then mixing the resultant, so that a granular preparation on which the gelling agent is present after addition thereof in the form of powder can be obtained.

The granular preparation of the present invention comprises granules to which a gelling agent is added. Such granules are “Granules” as specified in the Japanese Pharmacopoeia (see page 11 in the case of the Japanese Pharmacopoeia, Seventeenth Edition.).

In the present invention, the particle size of the granular preparation is generally 100 μm to 2000 μm, and preferably about 200 μm to 1700 μm.

[0032]

In the present invention, the term "particle size" refers to the mean particle diameter of particles and can be measured according to General Tests, Processes and Apparatus 3.04 "Particle Size Determination", Method 2 "Analytical Sieving Method" described in the Japanese Pharmacopoeia, Seventeenth Edition (pages 95 to 97). Note that the particle size may also be measured according to General Tests, Processes and Apparatus 6.03 "Particle Size Distribution Test for Preparations" (page 135) described in the Japanese Pharmacopoeia, Seventeenth Edition.

[0033]

The granular preparation of the present invention can be a granular preparation obtained by the method for producing the granular preparation of the present invention.

The granular preparation of the present invention exhibits improvement in unpalatability such as bitterness due to amino acids and granules' property of remaining in the mouth.

[0034]

In the present invention, a method for improving the unpalatability of a granular preparation containing isoleucine, leucine and valine as active ingredients through addition of a gelling agent in the form of powder in advance is provided. Examples of the improvement of unpalatability include improvement in bitterness due to

amino acids and improvement in the granular preparation's property of remaining in the mouth.

Examples

[0035]

The present invention is described specifically based on Examples, but is not limited thereto. Persons skilled in the art can change the present invention into various modes without departing from the significance of the present invention. Such changes are included within the scope of present invention.

[0036]

Example 1

On the basis of formulations described in Table 1, a granular preparation was prepared.

To a mixture of L-isoleucine, L-leucine and L-valine, an aqueous solution of povidone (kollidon, 90F), polyvinyl alcohol (partially saponified product), tartaric acid and saccharin sodium hydrate was added. The mixture was granulated using an agitation granulator, and then the granules were subjected to particle sizing and drying, thereby obtaining uncoated granules.

A flavoring agent was spread over the uncoated granules. After particle sizing, polyethylene oxide (average molecular weight: 5,000,000) was added in the form of powder, thereby preparing a granular preparation.

[0037]

Comparative Example 1

On the basis of formulations described in Table 1, a granular preparation was prepared.

Uncoated granules were obtained in the same manner as in Example 1.

After the uncoated granules were coated using an aqueous solution of povidone (kollidon, 90F), a flavoring agent was spread, and then particle sizing was performed, thereby preparing a granular preparation.

[0038]

[Table 1]

Ingredient name	Example 1	Comparative Example 1
L-isoleucine	952	952
L-leucine	1904	1904
L-valine	1144	1144
Povidone	40	81
Polyvinyl alcohol (partially hydronized)	33	33
Tartaric acid	20	20
Saccharin sodium hydrate	17	17
Flavoring agent	Trace amount	Trace amount
Polyethylene oxide	20	-

[0039]

With the use of granular preparations prepared in Example 1 and Comparative Example 1, sensory assessment was carried out using ease of swallowing, granules' property of being hard to remain in the mouth, and weakness of bitterness as indices. (n=9)

Regarding the ease of swallowing, the two granular preparations were compared when taken, and then the one

better than the other in terms of the ease of swallowing was selected.

Regarding granules' property of being hard to remain in the mouth, the two granular preparations were compared when taken, and then the one better than the other in terms of the property of being hard to remain in the mouth was selected.

Regarding the weakness of bitterness, the two granular preparations were compared when taken, and then the one exhibiting bitterness weaker than that of the other was selected.

The results are shown in Table 2.

[0040]

[Table 2]

Assessment of:	Comparative Example 1	Example 1	No change
Ease of swallowing	0	9	0
Granules' property of being hard to remain	0	9	0
Weakness of bitterness	1	6	2

[0041]

The granular preparation of Example 1 was found to be excellent in unpalatability, since it was better than the granular preparation of Comparative Example 1 prepared according to the formulation of LIVACT Granules, in terms of the ease of swallowing, granules' property of being hard to remain in the mouth, and bitterness.

[0042]

With the use of the granular preparations prepared in Example 1 and Comparative Example 1, dissolution was assessed by dissolution test according to the Paddle Method using the 2nd fluid for dissolution test described in the Japanese Pharmacopoeia, Seventeenth Edition (pages 141 to 145, General Tests, Processes and Apparatus 6.10 "dissolution test").

The results are shown in Figure 1 and Figure 2.

[0043]

The granular preparation of Example 1 was confirmed to exhibit a lower dissolution than the granular preparation of Comparative Example 1 at an early stage (the value at 5 minutes). However, at 15 minutes or later, both preparations were confirmed to exhibit a dissolution rate of almost 100%. The granular preparation of Example 1 was also considered to exhibit a beneficial effect similar to that of LIVACT Granules.

[0044]

Examples 2 to 4

Granular preparations were prepared in the same manner as in Example 1, except that the content of polyethylene oxide (average molecular weight: 5,000,000) was 0.1%, 1% or 2% based on the total amount of each granular preparation.

[0045]

Examples 5 to 7

Granular preparations were prepared in the same manner as in Example 1, except that polyethylene oxide having an average molecular weight of 500,000, 1,000,000 or 2,000,000 was used.

[0046]

With the use of the granular preparations prepared in Examples 1 to 7, sensory assessment was carried out using foreign body sensation in mouth, bitterness, and ease of swallowing as indices. (n=10)

Points were assigned for each index, such that 1 point was assigned when "noticed none", 2 points were assigned when "noticed almost none", 3 points were assigned when "noticed reasonably", and 4 points were assigned when "noticed clearly", and then average values were found. The results are shown in Table 3.

[0047]

[Table 3]

Assessment of:	Example 1	Example 2	Example 3	Example 4	Example 5	Example 6	Example 7
Ease of swallowing	2.4	2.7	3.0	2.4	2.5	2.5	3.0
Foreign body sensation in mouth	2.8	2.4	2.2	2.8	2.7	2.7	2.5
Bitterness	2.8	2.6	2.3	2.3	2.4	2.3	2.2

Industrial Applicability

[0048]

The granular preparation of the present invention is considered to have improved unpalatability compared with a current preparation, LIVACT Granules, and thus has

industrial applicability as a pharmaceutical granular preparation.

Claims

[Claim 1]

A granular preparation containing isoleucine, leucine and valine as active ingredients, wherein the preparation contains a gelling agent.

[Claim 2]

The granular preparation according to claim 1, wherein the gelling agent is a carboxyvinyl polymer or a polyethylene oxide.

[Claim 3]

The granular preparation according to claim 1 or 2, wherein the gelling agent is a polyethylene oxide having an average molecular weight of 500,000 or more.

[Claim 4]

The granular preparation according to any one of claims 1 to 3, wherein the gelling agent is added in the form of powder.

[Claim 5]

The granular preparation according to any one of claims 1 to 4, wherein the gelling agent is contained at 0.05% to 2% based on the total amount of the granular preparation.

[Claim 6]

The granular preparation according to any one of claims 1 to 5, wherein isoleucine, leucine, and valine are contained at a weight ratio of 1/(1.9–2.2)/(1.1–1.3).

[Claim 7]

The granular preparation according to any one of claims 1 to 6, wherein isoleucine, leucine and valine are contained at 80% or more based on the total amount of the granular preparation.

[Claim 8]

The granular preparation according to any one of claims 1 to 7, further containing a binder and/or a corrigent.

[Claim 9]

A method for producing a granular preparation containing isoleucine, leucine and valine as active ingredients, comprising the step of adding a gelling agent to granules containing isoleucine, leucine and valine.

[Claim 10]

The production method according to claim 9, wherein the gelling agent is added in the form of powder.