# Description

# Title of Invention: COMPOSITE FORMULATION FOR ORAL ADMINISTRATION COMPRISING EZETIMIBE AND ROSUVASTATIN AND A PROCESS FOR THE PREPARATION THEREOF

## Technical Field

[1] The present disclosure relates to a composite formulation for oral administration including ezetimibe and rosuvastatin (or a pharmaceutically acceptable salt thereof), and more particularly, to a composite formulation for oral administration having improved pharmaceutical characteristics, including improved dissolution rate and dissolution velocity of active ingredients, improved content uniformity, and improved productivity, and a method of preparing the solid composite formulation.

## Background Art

[2] Rosuvastatin or a pharmaceutically acceptable salt thereof is one of HMG-CoA reductase inhibitors that inhibit the synthesis of cholesterol to treatment dyslipidemia. Crestor tablets (i.e., rosuvastatin calcium salts available from AstraZeneca), including rosuvastatin as a main ingredient, have been widely used both domestically and internationally for the treatment of dyslipidemia and dyslipidemia-related disorders. In particular, research has been reporting on excellent effects of rosuvastatin of lowering LDL cholesterol levels in blood and increasing beneficial HDL cholesterol levels in the body, compared to the effects of atorvastatin or simvastatin, which is commercially available as a drug having the same mechanism as rosuvastatin. Accordingly, there is an increasing interest in rosuvastatin formulation.

[3] HMG-CoA reductase inhibitors are generally used in a combination with a therapeutic agent for dyslipidemia having a different mechanism from that of the HMG-CoA reductase inhibitors to enhance therapeutic effects. Among such combinations, due to good drug interaction between the HMG-CoA reductase inhibitor and ezetimibe, which is a drug inhibiting the re-absorption of cholesterol in the small intestine, a composite formulation of these two ingredients are actively being studied. For example, Vytorin™, which is a composite formulation of simvastatin and ezetimibe, has already demonstrated good pharmacological effects and stability thereof, and is currently available in the market with a noticeable sales performance.

[4] Through much research, combined treatment of ezetimibe with rosuvastatin is also reported as having excellent pharmaceutical effects. However, the composite formulation is not yet commercially available ( Brandon Ason et al., J Lipid Res. Apr

2011; 52(4): 679687; Torimoto et al., Lipids in Health and Disease 2013, 12:137). Therefore, there is a need for the development of a composite formulation with improved pharmaceutical characteristics containing a combination of ezetimibe and rosuvastatin whose pharmacological effects are approved.

## Summary

[4a] The present disclosure provides a method of preparing a composite formulation for oral administration, the method comprising: preparing an ezetimibe-wet granule portion comprising ezetimibe by using a fluid-bed granulator; and formulating the ezetimibe-wet granule portion and a rosuvastatin mixture portion together, the rosuvastatin mixture portion comprising rosuvastatin or a pharmaceutically acceptable salt thereof, wherein the preparing of the ezetimibe-wet granule portion is performed while an internal product temperature of the fluid-bed granulator is 20℃ to 40℃.

## Disclosure of Invention

## Technical Problem

[5] The present disclosure provides a solid composite formulation of rosuvastatin and ezetimibe for oral administration that may have improved pharmaceutical characteristics, in terms of dissolution rate and dissolution velocity of active ingredients and content uniformity, and that may be economically prepared with high productivity.

[6] The present disclosure provides a method of preparing the composite formulation of rosuvastatin and ezetimibe for oral administration.

## Solution to Problem

[7] According to an aspect of the present invention, there is provided a solid composite formulation for oral administration including: an ezetimibe-wet granule portion including ezetimibe that is wet-granulated using a fluid-bed granulator; and a rosuvastatin mixture portion including rosuvastatin or a pharmaceutically acceptable salt thereof.

[8] According to another aspect of the present invention, there is provided a method of preparing the solid composite formulation for oral administration including: preparing an ezetimibe-wet granule portion including ezetimibe by using a fluid-bed granulator; and formulating the ezetimibe-wet granule portion and a rosuvastatin mixture portion together, the rosuvastatin mixture portion including rosuvastatin or a pharmaceutically acceptable salt thereof.

## Advantageous Effects of Invention

[9] As described above, according to the one or more embodiments of the present disclosure, a solid composite formulation of ezetimibe and rosuvastatin for oral administration may have a sufficiently improved dissolution rate and dissolution velocity of

the active ingredients without using an excess of a disintegrant, and thus may ensure high bioavailability without the stability reduction of the active ingredients led to by the excessive disintegrant. The solid composite formulation for oral administration may also have good content uniformity. The solid composite formulation for oral administration may have good tableting characteristics, and may be prepared at a low internal temperature of a fluid-bed granulator, leading to high productivity.

## Mode for the Invention

[10] Unless otherwise defined, all terms (including technical and scientific terms) used herein have the same meaning as commonly understood by one of ordinary skill in the

art to which this invention belongs. Although exemplary methods or materials are listed herein, other similar or equivalent ones are also within the scope of the present invention. All publications disclosed as references herein are incorporated in their entirety by reference.

[11] The present inventors researched into the development of a solid composite formulation for oral administration that may have sufficient dissolution rate of active ingredients to ensure good pharmaceutical effects, and which may also be economically prepared with high productivity. As a result, they found that a solid composite formulation prepared as a mixture of ezetimibe-wet granules that are prepared by separate wet granulation using a fluid-bed granulator, with rosuvastatin or a pharmaceutically acceptable salt thereof may have high productivity and markedly improved pharmaceutical characteristics in terms of dissolution rate and dissolution velocity of active ingredients and content uniformity.

[12] According to an aspect of the present disclosure, there is provided a solid composite formulation for oral administration including: an ezetimibe-wet granule portion including ezetimibe that is wet-granulated using a fluid-bed granulator; and a rosuvastatin mixture portion including rosuvastatin or a pharmaceutically acceptable salt thereof.

[13] As used herein, the term "wet granule portion" refers to mixed granules prepared by wet granulation, and the term "mixture-part" refers to a non-granulated mixture.

[14] The ezetimibe-wet granule portion may have a sufficiently high ezetimibe dissolution rate when prepared using a fluid-bed granulator and have high productivity in a tableting process due to good flowability of the wet granules. Accordingly, a solid composite formulation according to any embodiments may have high bioavailability and productivity. However, when the ezetimibe-wet granule portion is prepared using other wet granulation methods available in the pharmaceutical field, it may be difficult to ensure both high dissolution rate and productivity of the solid composite formulation (refer to Experimental Example 1).

[15] When ezetimibe-wet granules are prepared using a high-speed mixer, which is widely used in the art for wet granulation due to short process time and simple process, the resulting solid composite formulation is shown to have a very low dissolution rate of less than about 50% in 10 minutes, as evaluated according to Dissolution method II of the Korean Pharmacopoeia ($10^{th}$ edition). Though the dissolution rate may be increased with reduced amount of solvent used for the preparation, the dissolution rate of ezetimibe in 10 minutes may be still less than about 60%. In addition, the smaller the amount of solvent is, the lower the productivity may become. When ezetimibe-wet granules are prepared using a Consigma which is an advanced mechanical process, though the dissolution rate may be increased with reduced amount of solvent, the dis-

solution rate of ezetimibe in 10 minutes may be still less than about 70%. In addition, the smaller the amount of solvent is, the lower the productivity may become. To improve such dissolution rate reduction of wet granules prepared using a high-speed mixer, Consigma, or the like, the amount of disintegrant may be increased in a granulation process. However, the disintegrant may affect the stability of active ingredients and negatively affect the quality of the medicine when used in excess.

[16] When ezetimibe-wet granules are prepared using a fluid-bed granulator, the dissolution rate may be reduced with increased amount of the solvent used in the preparing process thereof. However, the dissolution rate of ezetimibe in 10 minutes may be high enough as about 80% or greater even when the amount of the solvent is more than about 1 part by weight based on 1 part by weight of a total weight of the ingredients of the ezetimibe-wet granule portion, and the productivity may also be sufficiently high as 100,000 tablets per hour even with reduced amount of the solvent (Experimental Example 1). In common wet granulation using a solvent, the dissolution rate at early phase may be reduced when an amount of the solvent exceeds 0.5 parts by weight or more based on 1 part by weight of the ezetimibe-wet granule portion is used, due to hardening and increased density of the granules. However, in a solid composite formulation according to embodiments of the present disclosure, high dissolution rate may be ensured even when the amount of the solvent is as high as about 0.5 parts by weight or more. Rather, the productivity may be increased due to improved flowability of granules in a tableting process. Thus, when the ezetimibe-wet granule portion is prepared using a fluid-bed granulator as in the present disclosure, both high dissolution rate and productivity may be ensured without using an excessive amount of disintegrant, and consequently medicine with improved quality may be obtained. This is an effect unexpectable in the art, in view that wet granulation using a fluid-bed granulator is conventionally known to reduce the productivity in a tableting process due to poor flowability of wet granules compared to wet granulation using a high-speed mixer.

[17] The solvent may be any available solvent that may dissolve a binder to prepare a binder solution in wet granulation. For example, the solvent may include distilled water, ethanol, or any combination thereof, but is not limited thereto.

[18] A solid composite formulation according to any embodiments of the present disclosure may have markedly improved content uniformity compared to a solid composite formulation including wet granules prepared using any other granulation methods not using a fluid-bed granulator (refer to Experimental Example 2). This is also an effect unexpectable in the art, in view that wet granulation using a fluid-bed granulator is conventionally known to reduce content uniformity compared to wet granulation using a high-speed mixer.

[19] A solid composite formulation according to any embodiments of the present disclosure may reach the saturation solubility at a markedly high rate compared to a solid composite formulation including wet granules prepared using any other granulation methods not using a fluid-bed granulator. Ezetimibe is known as a drug having poor solubility with a low saturation solubility of about 1 ppm or less in either acidic or weak alkali conditions as in the body fluid. The saturation solubility and the dissolution velocity from a dissolution start point to saturation are important indices for bioavailability evaluations of drugs having poor solubility. As a result of experiments, solid composite formulations according to embodiments of the present disclosures were found to reach the saturation solubility at a markedly high rate compared to a solid composite formulation including wet granules prepared using any other granulation methods not using a fluid-bed granulator, and thus to ensure improved bioavailability of ezetimibe as a drug having poor solubility (refer to Experimental Example 3).

[20] In some embodiments, the ezetimibe-wet granule portion of the solid composite formulation may be prepared using about 0.1 parts to about 2 parts by weight of the solvent based on 1 part by weight of a total weight of the ingredients of the ezetimibe-wet granule portion by using a fluid-bed granulator, and in some embodiments, about 0.2 parts to about 1 part by weight of the solvent. As used herein, the expression a total weight of the ingredients of the ezetimibe-wet granule portion refers to a total weight of any active ingredients and additives, except for solvent, used to prepare the ezetimibe-wet granule portion.

[21] When the amount of the solvent is below the lower limit of these ranges, sufficient wet granules may not be obtained, and thus the productivity may be reduced. When the amount of the solvent is above the upper limit of these ranges, the granulation time and consequently the total preparation time may be increased, which may be inefficient.

[22] In some embodiments, the ezetimibe-wet granule portion may include about 0.1 parts to about 2 parts by weight of distilled water, and in some other embodiments, about 0.2 parts to about 1 part by weight, based on 1 part by weight of the total weight of the ingredients of the ezetimibe-wet granule portion.

[23] In some embodiments, the amount of ezetimibe as a first pharmacologically active ingredient in the solid composite formulation may be in a range of about 5 mg to about 20 mg in a unit dosage form, and in some embodiments, about 5 mg to about 10 mg in a unit dosage form.

[24] The solid composite formulation according to any embodiment includes rosuvastatin as a second pharmacologically active ingredient. The rosuvastatin may be in the form of free base or a pharmaceutically acceptable salt thereof. Non-limiting examples of the pharmaceutically acceptable salt include a calcium salt, a magnesium salt, and a

strontium salt. For example, the rosuvastatin may be in the form of calcium salt. However, embodiments are not limited thereto.

[25] Rosuvastatin or a pharmaceutically acceptable salt thereof may inhibit an HMG-CoA reductase, which is required for the synthesis of cholesterol, to lower LDL-cholesterol levels in blood and raise HDL-cholesterol levels in blood, thereby contributing to the treatment of dyslipidemia.

[26] In some embodiments, the amount of the rosuvastatin or a pharmaceutically acceptable salt thereof may be in a range of about 2.5 mg to about 40 mg, and in some embodiments, about 5 mg to about 20 mg, in a unit dosage form of the solid composite formulation.

[27] In some embodiments, the solid composite formulation may further include at least one pharmaceutically acceptable additive, in addition to the pharmacologically active ingredients. For example, the ezetimibe-wet granule portion or rosuvastatin mixture portion may include at least one additive selected from the group consisting of a diluent, a binder, a disintegrant, and a lubricant.

[28] In some embodiments, the ezetimibe-wet granule portion and the rosuvastatin mixture portion may each further include about 0.5 parts to about 50 parts of a diluent, about 0.1 parts to about 20 parts of a binder, about 0.1 parts to about 10 parts by weight of a disintegrant, and about 0.1 parts to about 3 parts by weight of a lubricant based on 1 part by weight of ezetimibe.

[29] Types and amounts of these additives may be appropriately selected by one of ordinary skill in the art depending on a type of a target solid composite formulation. For example, the diluent may be selected from the group consisting of lactose, starch, mannitol, microcrystalline cellulose, carboxymethyl cellulose, and any combinations thereof. The binder may be selected from the group consisting of povidone, hypromellose, hydroxypropyl cellulose, copovidone, and any combinations thereof. The disintegrant may be selected from the group consisting of crospovidone, croscarmellose sodium, sodium starch glycolate, low-substituted hydroxypropyl cellulose, and any combinations thereof. The lubricant may be selected from the group consisting of magnesium stearate, talc, light anhydrous silicic acid, sodium stearyl fumarate, and any combinations thereof. However, embodiments are not limited thereto.

[30] As used herein, the terms solid composite formulation for oral administration refers to a formulation prepared by molding or encapsulating drugs into a predetermined shape. The solid composite formulation for oral administration may be formulated as, but not limited to, a pellet, a capsule, a tablet (including a single-layered tablet, a double-layered tablet, and a pressed core tablet), powder, or granules. For example, the solid composite formulation for oral administration may be in the form of a capsule, a

single-layered tablet, or a double-layered tablet form. When the solid composite formulation is in the form of a capsule, the capsule may contain powder, granules, tablets, syrup, or pellets therein.

[31] In some embodiments, the ezetimibe-wet granule portion may include lactose, microcrystalline cellulose, sodium lauryl sulfate, povidone, and croscarmellose sodium, and the rosuvastatin mixture portion may include microcrystalline cellulose, lactose, mannitol, crospovidone, and magnesium stearate.

[32] In some embodiments, the solid composite formulation may have an ezetimibe dissolution rate of about 85% or greater in 10 minutes, as evaluated in a buffer solution of about pH 4.5 containing about 0.45% of sodium lauryl sulfate at a paddle rotation speed of about 50 rpm according to Dissolution method II of the Korean Pharmacopoeia ($10^{th}$ edition). Therefore, the solid composite formulation may have high bioavailability led to by the increased dissolution rate (refer to Experimental Example 1).

[33] According to another aspect of the present disclosure, there is provided a method of preparing a solid composite formulation for oral administration including: preparing an ezetimibe-wet granule portion including ezetimibe by using a fluid-bed granulator; and formulating the ezetimibe-wet granule portion and a rosuvastatin mixture portion together, the rosuvastatin mixture portion including rosuvastatin or a pharmaceutically acceptable salt thereof.

[34] The detailed descriptions of the solid composite formulations according to embodiments of the present disclosure may be applied to detailed descriptions of methods of preparing such a solid composite formulation according to embodiments of the present disclosure.

[35] In some embodiments, during the preparation of the ezetimibe-wet granule portion, the internal temperature of the fluid-bed granulator may be from about 20℃ to about 40℃.

[36] As used herein, the terms the internal temperature of the fluid-bed granulator refers to an internal temperature of the fluid-bed granulator that is measured when the temperature is maintained constant as a result of sufficient operational stabilization of the fluid-bed granulator, using an electronic thermometer equipped in the container of the fluid-bed granulator.

[37] In general, granulation is performed while maintaining the internal temperature of the fluid-bed granulator at a low temperature of about 30℃ or less, the dissolution rate of active ingredients at early phase tends to be reduced due to increase in granule size and density. However, according to the present disclosure, when the ezetimibe-wet granule portion is prepared at a low internal temperature of the fluid-bed granulator of about 20℃ to about 30℃, the dissolution rate may nearly not be reduced. Accordingly, a

solid composite formulation having a sufficiently high dissolution rate may be prepared at low temperatures. Therefore, according to embodiments of the present disclosure, the ezetimibe-wet granule portion may be prepared at a low internal temperature of the fluid-bed granulator of about 20°C to about 30°C. Accordingly, the source ingredient solution may be more rapidly transported to the fluid-bed granulator, so that the process time may be reduced and the productivity of the solid composite formulation may be increased.

[38] In some embodiments, a method of preparing a solid composite formulation for oral administration according to any of the above-described embodiments may include: i) preparing an ezetimibe-wet granule portion including ezetimibe by using a fluid-bed granulator; ii) preparing a rosuvastatin mixture portion including rosuvastatin or a pharmaceutically acceptable salt thereof; and iii) mixing the ezetimibe-wet granule portion of the step i) and the rosuvastatin mixture portion of the step ii) to obtain a mixture and forming a single-layered tablet of the mixture by using a common tableting method.

[39] In some exemplary embodiments, a method of preparing a solid composite formulation for oral administration according to any of the above-described embodiments may include: i) preparing an ezetimibe-wet granule portion including ezetimibe by using a fluid-bed granulator and tableting the ezetimibe-wet granule portion to obtain a tablet; ii) preparing a rosuvastatin mixture portion including rosuvastatin or a pharmaceutically acceptable salt thereof; and iii) forming a double-layered tablet by using a common double-layered tablet formation method with a tablet press for double-layered tablets, the double-layered tablet including the tablet prepared in the step i) as a first layer, and the rosuvastatin mixture portion of the step ii) as a second layer.

[40] In some other embodiments, a method of preparing a solid composite formulation for oral administration according to any of the above-described embodiments may include: i) preparing an ezetimibe-wet granule portion including ezetimibe by using a fluid-bed granulator; ii) preparing a rosuvastatin mixture portion including rosuvastatin or a pharmaceutically acceptable salt thereof; iii) mixing the ezetimibe-wet granule portion prepared in the step i) and the rosuvastatin mixture portion prepared in the step ii) to obtain a mixture; and iv) encapsulating the mixture to form a capsule according to a common capsulation method.

[41]

[42] [Example]

[43] One or more embodiments of the present disclosure will now be described in detail with reference to the following examples. However, these examples are only for illustrative purposes and are not intended to limit the scope of the one or more embodiments of the present disclosure.

[44]

[45] **Comparative Examples 1 to 6: Preparation of composite formulations by using high-speed mixer**

[46] Composite formulations were prepared as follows according to the compositions in Table 1, in which used ingredients and amounts thereof are shown. Povidone was dissolved in distilled water to prepare a binder solution. Ezetimibe, lactose hydrate, microcrystalline cellulose, sodium lauryl sulfate, and croscarmellose sodium were mixed and the mixture was put into a chamber of a high-speed mixer (P/VAC60, available from Diosna), and then the binder solution above was injected into the chamber while working the high-speed mixer at an agitator speed of about 100 rpm and a chopper speed of about 3000 rpm for about 3 minutes in total to granulate the mixture, followed by drying the resulting granules in a fluid bed dryer. The dried granules were then passed through a sieve having a mesh size of 20. The sieved granules were mixed with a rosuvastatin mixture portion as a mixture of the ingredients in amounts as listed in Table 1, and then the mixture was pressed into tablets having a hardness of 10 kp using a rotary tablet press (MRC-45N, available from Sejong Pharmatech Co., Ltd., Korea).

[47]

[48] **Examples 1 to 6: Preparation of composite formulations by using fluid-bed granulator**

[49] Composite formulations were prepared as follows according to the compositions in Table 1, in which used ingredients and amounts thereof are shown. Povidone was dissolved in distilled water to prepare a binder solution. Ezetimibe, lactose hydrate, microcrystalline cellulose, sodium lauryl sulfate, and croscarmellose sodium were mixed and the mixture was put into a container of a fluid-bed granulator (GRETC-30, available from GR-ENG) and then the binder solution above was injected into the container by spraying while working the fluid-bed granulator at an internal temperature of about 30C, a spray pressure of about 1.2 bar, and a spray speed of about 10 rpm to granulate the mixture until all the binder solution was injected, followed by drying the resulting granules in a fluid bed dryer. The dried granules were then passed through a sieve having a mesh size of 20. The sieved granules were mixed with a rosuvastatin mixture portion as a mixture of the ingredients in amounts as listed in Table 1, and then the mixture was pressed into tablets having a hardness of 10 kp using a rotary tablet press (MRC-45N, available from Sejong Pharmatech Co., Ltd.).

[50]

[51] **Comparative Examples 7 to 12: Preparation of composite formulations by using ConsiGma**

[52] Composite formulations were prepared as follows according to the compositions in Table 1, in which used ingredients and amounts thereof are shown. Povidone was

dissolved in distilled water to prepare a binder solution. Ezetimibe, lactose hydrate, microcrystalline cellulose, sodium lauryl sulfate, and croscarmellose sodium were mixed and the mixture was put into a feeder of a ConsiGma (Consigma-1, available from GEA) while working the ConsiGma at a screw speed of about 700 rpm for about 3 minutes in total to granulate the mixture, followed by drying the resulting granules in a fluid bed dryer. The dried granules were then passed through a sieve having a mesh size of 20. The sieved granules were mixed with a rosuvastatin mixture portion as a mixture of the ingredients in amounts as listed in Table 1, and then the mixture was pressed into tablets having a hardness of 10 kp using a rotary tablet press (MRC-45N, available from Sejong Pharmatech Co., Ltd.).

[53] [Table 1] Preparation of composite formulations

| Example | Wet granulation method | Amount of distilled water (mg) | Types and amounts of additives for ezetimibe-wet granule portion (mg) | Types and amounts of additives for rosuvastatin mixture portion (mg) |
|---|---|---|---|---|
| Comparative Example 1 | High-speed mixer | 15 | Ezetimibe 10<br>Lactose hydrate 30<br>Microcrystalline cellulose 94<br>Sodium lauryl sulfate 2<br>Povidone 4<br>Croscarmellose sodium 10 | Rosuvastatin 20<br>Microcrystalline cellulose 50<br>Lactose hydrate 100<br>Mannitol 100<br>Crospovidone 3<br>Magnesium stearate 4 |
| Comparative Example 2 | | 30 | | |
| Comparative Example 3 | | 70 | | |
| Comparative Example 4 | | 100 | | |
| Comparative Example 5 | | 150 | | |
| Comparative Example 6 | | 200 | | |
| Example 1 | Fluid-bed granulator | 15 | | |
| Example 2 | | 30 | | |
| Example 3 | | 70 | | |
| Example 4 | | 100 | | |
| Example 5 | | 150 | | |
| Example 6 | | 200 | | |
| Comparative Example 7 | ConsiGma | 15 | | |
| Comparative Example 8 | | 30 | | |
| Comparative Example 9 | | 70 | | |
| Comparative Example 10 | | 100 | | |
| Comparative Example 11 | | 150 | | |
| Comparative Example 12 | | 200 | | |

[54] **Experimental Example 1: Dissolution rate and productivity evaluation**

[55] Dissolution rates and productivities of the composite formulations of Examples 1 to 6 and Comparative Examples 1 to 12 were evaluated. The results are shown in Table 2.

[56] The dissolution rate evaluation was performed using tablets of Examples 1 to 6 and Comparative Examples 1 to 12 under the conditions as described below.

[57] The productivity of each composite formulation was evaluated as a total number of tablets produced per hour which was shown as a total weight (g) / an average weight (g/tablet) of when the tablets were prepared under the condition of a rotary tablet press (MRC-45N, available from Sejong Pharmatech Co., Ltd., able to press 45 tablets per revolution and produce 108,000 tablets per hour at a rotation speed of 40 rpm) that is in common use in the art, at a maximum rotation speed that was adjusted to press good tablets having a hardness of about 10 or greater without tableting defects such as capping, sticking, laminating, or the like.

[58]

[59] <Dissolution test conditions>

[60] 1) Dissolution method: Dissolution method II (paddle method) according to the Korean Pharmacopoeia ($10^{th}$ edition)

[61] 2) Dissolution medium: 0.45% sodium lauryl sulfate solution in a 0.025M sodium di-hydrogen phosphate ($NaH_2PO_42H_2O$) buffer (pH 4.5) (obtained by dissolving 3.9 g of sodium dihydrogen phosphate in 900 mL of water, adjusting the pH to 4.5 with 50%(w/w) sodium hydroxide solution or phosphoric acid, filling it with water up to a total volume of 1,000 mL, and then thoroughly mixing the solution)

[62] 3) Amount of dissolution medium: 500 mL

[63] 4) Temperature of dissolution apparatus: 37.5℃

[64] 5) Paddle speed: 50 rpm

[65] 6) Number of test samples in each experimental group: 6

[66] 7) Sampling time: 10 min

[67] [Table 2]

| Example | 10-min dissolution rate (%) | | Production per hour (tablets) |
|---|---|---|---|
| | Average | Standard deviation | |
| Comparative Example 1 | 59.1 | 7.1 | 51,458.7 |
| Comparative Example 2 | 52.7 | 6.6 | 66,157.6 |
| Comparative Example 3 | 45.4 | 10.9 | 75,815.3 |
| Comparative Example 4 | 25.1 | 9.8 | 99,542.5 |
| Comparative Example 5 | Not available | | |
| Comparative Example 6 | Not available | | |
| Example 1 | 90.1 | 2.2 | 119,571.3 |
| Example 2 | 88.9 | 1.7 | 112,414.7 |
| Example 3 | 89.1 | 3.1 | 108.998.6 |
| Example 4 | 90.2 | 1.6 | 105,621.4 |
| Example 5 | 87.8 | 1.1 | 100,527.8 |
| Example 6 | 83.5 | 5.4 | 91,711.7 |
| Comparative Example 7 | 66.9 | 9.7 | 71,421.4 |
| Comparative Example 8 | 62.5 | 5.4 | 79,994.5 |
| Comparative Example 9 | 50.9 | 6.7 | 84,457.8 |
| Comparative Example 10 | 43.7 | 12.5 | 90,515.5 |
| Comparative Example 11 | 21.8 | 13.7 | 108,456.9 |
| Comparative Example 12 | Not available | | |

[68] In Comparative Examples 5, 6, and 12, the density of granules was increased with the increased amount of distilled water, so that excessively hard granules were obtained, which may cause mechanical overload and consequently interrupt smooth production.

[69] The composite formulations of Comparative Examples 1 to 4 prepared using a high-speed mixer were found to have dissolution rates and productivities that are not satisfactorily high compared to those of solid composite formulations prepared using any other methods.

[70] The composite formulations of Comparative Examples 7 to 11 prepared using ConsiGma had improved dissolution rates compared to those of Comparative Examples 1 to 4. However, the dissolution rates did not significantly achieve 85% or more ensuring high bioavailability. The solid composite formulation of Comparative Example 11 had high productivity, but an excessively low dissolution rate.

[71] The solid composite formulations of Examples 1 to 6 prepared using fluid-bed granulator had improved dissolution rates compared to those prepared using any other methods. In particular, the composite formulations of Examples 1 to 5 were found to have a high dissolution rate of about 85% or more after 10 minutes. The solid

composite formulations of Examples 1 to 6 had improved productivity due to good flowabiliity of granules, particularly, the solid composite formulations of Examples 1 to 5 had a significantly high productivity of about 100,000 tablets per hour.

[72]

[73] **Experimental Example 2: Content uniformity test**

[74] A content uniformity test was performed on the composite formulations of Examples 1 to 6 and Comparative Examples 1 to 12 according to the content uniformity test method among general test methods in the Korean Pharmacopoeia ($10^{th}$ edition). The resulting test values (a smaller content uniformity value is desired; quality is generally ensured at 15 or less) are shown in Table 3.

[75] [Table 3]

| Example | Content uniformity value |
|---|---|
| Comparative Example 1 | 21.5 |
| Comparative Example 2 | 16.6 |
| Comparative Example 3 | 10.5 |
| Comparative Example 4 | 12.2 |
| Comparative Example 5 | Not available |
| Comparative Example 6 | Not available |
| Example 1 | 6.2 |
| Example 2 | 6.0 |
| Example 3 | 5.9 |
| Example 4 | 5.8 |
| Example 5 | 5.9 |
| Example 6 | 5.7 |
| Comparative Example 7 | 14.7 |
| Comparative Example 8 | 11.3 |
| Comparative Example 9 | 9.1 |
| Comparative Example 10 | 8.8 |
| Comparative Example 11 | 13.4 |
| Comparative Example 12 | Not available |

[76] Referring to Table 3, with the use of more or less distilled water than appropriate level, content uniformity test values tend to be increased because the diameter of wet granules may become irregular. In the solid composite formulations of Examples 1 to 6 prepared using a fluid-bed granulator, the content uniformity test values were absolutely low, with a small variation from the change in amount of the distilled water. Therefore, the solid composite formulations of Examples 1 to 6 were found to have improved content uniformity, under any preparation conditions.

[77]

[78] **Experimental Example 3: Saturation solubility and dissolution velocity evaluation**

[79] Saturation solubilities and dissolution velocity of solid composite formulations of Comparative Examples 1 and 7 and Example 1 (obtained using the same amount of distilled water) as bioavailability indices of drugs having poor solubility were evaluated. The results are shown in Table 4.

[80] This evaluation was performed under the conditions as described below. The concentration of ezetimibe detected at each sampling time was represented in ppm, and the concentration measured at a certain sampling time was regarded as being saturated whenever the difference between said concentration and a concentration measured at a subsequent sampling time was 0.05 ppm or less. The sampling time at which the concentration of ezetimibe was saturated is represented by a dissolution velocity (time), and the concentration of ezetimibe at said sampling time is represented by a saturation solubility (ppm).

[81] < Test conditions >

[82] 1) Test method: Dissolution method II (paddle method) according to the Korean Pharmacopoeia ($10^{th}$ edition)

[83] 2) Dissolution medium: sodium acetate-acetic acid buffer (pH 4.0) used in a general test method according to the Korean Pharmacopoeia ($10^{th}$ edition)

[84] 3) Amount of dissolution medium: 1000 mL

[85] 4) Temperature of dissolution apparatus: 37.5℃

[86] 5) Paddle speed: 50 rpm

[87] 6) Number of test samples in each experimental group: 6

[88] 7) Sampling time: 0 min, 5 min, 10 min, 15 min, 30 min, and 45 min

[89] [Table 4]

| Example | Saturation solubility (ppm) | Dissolution velocity (time in min) |
|---|---|---|
| Comparative Example 1 | 0.998 | 30 min |
| Example 1 | 1.102 | 5 min |
| Comparative Example 7 | 1.054 | 15 min |

[90] Referring to Table 4, the solid composite formulation of Example 1 prepared using a fluid-bed granulator was found to have improved saturation solubility and about 3 to 6 times higher dissolution velocity, which is defined as the time taken to reach saturation solubility, compared to the solid composite formulations of Comparative Examples 1 and 7 prepared using the same amount of distilled water as in Example 1 but different wet granulation methods. Therefore, the solid composite formulation of Example 1 may also have improved bioavailability due to such increased saturation solubility and

dissolution velocity of ezetimibe.

[91]

[92] **Examples 7 to 11**

[93] Composite formulations were prepared as follows according to the compositions in Table 5, in which used ingredients and amounts thereof are shown. Povidone was dissolved in distilled water to prepare a binder solution. Ezetimibe, lactose hydrate, microcrystalline cellulose, sodium lauryl sulfate, and croscarmellose sodium were mixed and the mixture was put into a container of fluid-bed granulator (GRETC-30, available from GR-ENG), and the internal temperature fluid-bed granulator was set as shown in Table 5. Then, the binder solution was injected into the container by spraying at a spray pressure of about 1.2 bar and a spray speed of about 10 rpm while working the fluid-bed granulator to granulate the mixture, followed by drying the resulting granules in a fluid bed dryer. The dried granules were then passed through a sieve having a mesh size of 20. The sieved granules were mixed with a rosuvastatin mixture portion as a mixture of the ingredients in amounts as listed in Table 5, and then the mixture was pressed into tablets having a hardness of 10 kp using a rotary tablet press (MRC-45N, available from Sejong Pharmatech Co., Ltd.).

[94] [Table 5] Wet granulation at different internal temperatures of fluid-bed granulator

| Example | Wet granulation method | Amount of distilled water (mg) | * Internal Temperature (°C) | Types and amounts of additives for ezetimibe-wet granule portion (mg) | Types and amounts of additives for rosuvastatin mixture portion (mg) |
|---|---|---|---|---|---|
| Example 7 | Fluid-bed granulator | 70 | 15 | Ezetimibe 10<br>Lactose hydrate 32<br>Microcrystalline cellulose 92<br>Sodium lauryl sulfate 2<br>Povidone 4<br>Croscarmellose sodium 10 | Rosuvastatin 20<br>Microcrystalline cellulose 50<br>Lactose hydrate 100<br>Mannitol 100<br>Crospovidone 3<br>Magnesium stearate 4 |
| Example 8 | | | 20 | | |
| Example 9 | | | 25 | | |
| Example 10 | | | 40 | | |
| Example 11 | | | 50 | | |

[95] * This internal temperature indicates an internal temperature of the fluid-bed granulator that was measured when the temperature is maintained constant as a result of sufficient operational stabilization of the fluid-bed granulator, using an electronic thermometer equipped in the container of the fluid-bed granulator.

[96]

[97] **Experimental Example 4: Dissolution rate, productivity, and content uniformity tests at different internal temperatures**

[98] Dissolution rate, productivity, and content uniformity tests were performed on the

solid composite formulations of Example 3 and Examples 7 to 11 in the same manner as in Experimental Examples 1 to 3. The results are shown in Table 6.

[99] [Table 6] Wet granulation at different internal temperatures of fluid-bed granulator

| Example | Internal Temperature (℃) | 10-min dissolution rate (%) | | Production per hour (tablets) | Content uniformity value |
|---|---|---|---|---|---|
| | | Average | Standard deviation | | |
| Example 7 | 15 | 75.5 | 4.4 | 111.317.3 | 16.9 |
| Example 8 | 20 | 86.7 | 2.2 | 108,664.5 | 7.2 |
| Example 9 | 25 | 88.4 | 1.6 | 109.412.9 | 6.6 |
| Example 3 | 30 | 89.1 | 3.1 | 108.998.6 | 5.9 |
| Example 10 | 40 | 89.5 | 2.6 | 100,158.4 | 6.2 |
| Example 11 | 50 | Not available | | | |

[100] According to the results in Table 6, the solid composite formulations of Example 3 and Examples 7 to 11 were all found to have improved ezetimibe dissolution rate, productivity, and content uniformity, particularly when the Internal temperature of the fluid-bed granulator was in the range of about 20℃ to about 40℃.

[101] It should be understood that the exemplary embodiments described therein should be considered in a descriptive sense only and not for purposes of limitation. Descriptions of features or aspects within each embodiment should typically be considered as available for other similar features or aspects in other embodiments. While one or more embodiments of the present invention have been described with reference to the figures, it will be understood by those of ordinary skill in the art that various changes in form and details may be made therein without departing from the spirit and scope of the present invention as defined by the following claims.

# Claims

1. A method of preparing a composite formulation for oral administration, the method comprising:

preparing an ezetimibe-wet granule portion comprising ezetimibe by using a fluid-bed granulator; and

formulating the ezetimibe-wet granule portion and a rosuvastatin mixture portion together, the rosuvastatin mixture portion comprising rosuvastatin or a pharmaceutically acceptable salt thereof,

wherein the preparing of the ezetimibe-wet granule portion is performed while an internal product temperature of the fluid-bed granulator is 20℃ to 40℃.

2. The method of preparing a composite formulation for oral administration of claim 1, wherein the ezetimibe-wet granule portion is prepared by using 0.2 part to 1 part by weight of a solvent based on 1 part by weight of the total raw material weight of the ezetimibe-wet granule portion by using a fluid-bed granulator.

3. The method of preparing a composite formulation for oral administration of claim 2, wherein the solvent is distilled water, ethanol, or any combination thereof.

4. The method of preparing a composite formulation for oral administration of claim 1, wherein the ezetimibe-wet granule portion is prepared by using 0.2 part to 1 part by weight of distilled water based on a total raw material weight of the ezetimibe-wet granule portion by using a fluid-bed granulator.

5. The method of preparing a composite formulation for oral administration of claim 1, wherein the ezetimibe-wet granule portion or the rosuvastatin mixture portion further comprises at least one pharmaceutically acceptable additive selected from the group consisting of an excipient, a binder, a disintegrant, and a lubricant.

6. The method of preparing a composite formulation for oral administration of claim 5, wherein the excipient is selected from the group consisting of lactose, starch, mannitol, microcrystalline cellulose, carboxymethyl cellulose, and any combinations thereof,

the binder is selected from the group consisting of povidone, hypromellose, hydroxypropyl cellulose, copovidone, and any combinations thereof,

the disintegrant is selected from the group consisting of crospovidone, croscarmellose sodium, sodium starch glycolate, low-substituted hydroxypropyl cellulose, and any combinations thereof, and

the lubricant is selected from the group consisting of magnesium stearate, talc, light anhydrous silicic acid, sodium stearyl fumarate, and any combinations thereof.

7. The method of preparing a composite formulation for oral administration of claim 1, wherein the ezetimibe-wet granule portion comprises lactose, microcrystalline cellulose, sodium lauryl sulfate, povidone, and croscarmellose sodium, and the rosuvastatin mixture portion comprises microcrystalline cellulose, lactose, mannitol, crospovidone, and magnesium stearate.

8. The method of preparing a composite formulation for oral administration of claim 1, wherein the amount of ezetimibe is included in a unit dosage form in an amount of 5 mg to 20 mg.

9. The method of preparing a composite formulation for oral administration of claim 1, wherein the amount of rosuvastatin or a pharmaceutically acceptable salt thereof is included in a unit dosage form in an amount of 2.5 mg to 40 mg.

10. The method of preparing a composite formulation for oral administration of claim 1, wherein the composite formulation is in the form of a pellet, a capsule, a single-layered tablet, a double-layered tablet, a press-coated tablet, powder, or granules.

11. The method of preparing a composite formulation for oral administration of claim 1, wherein when a dissolution test of the composite formulation is performed in a pH 4.5 buffer solution containing 0.45% sodium lauryl sulfate at a paddle rotation speed of 50 rpm according to Dissolution Method II in the Korean Pharmacopoeia, the dissolution rate of ezetimibe is 85% or more in 15 minutes.

# COMPOSITE FORMULATION FOR ORAL ADMINISTRATION COMPRISING EZETIMIBE AND ROSUVASTATIN AND A PROCESS FOR THE PREPARATION THEREOF

## ABSTRACT

Provided is a solid composite formulation for oral administration that includes: an ezetimibe-wet granule portion including ezetimibe that is wet-granulated using a fluid-bed granulator; and a rosuvastatin mixture portion including rosuvastatin or a pharmaceutically acceptable salt thereof.

[No suitable figure]