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

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.