Claims

[Claim 1] A solid composite formulation for oral administration, the solid composite formulation comprising:

an ezetimibe granules-part comprising ezetimibe, said ezetimibe having a particle size distribution wherein the average particle size $d_{(0.9)}$ for the bottom 90% is about 10 μm or less; and

a rosuvastatin mixture-part comprising rosuvastatin or a pharmaceutically acceptable salt thereof,

wherein

the ezetimibe granules-part further comprises

water;

a diluent selected from the group consisting of lactose, starch, mannitol, microcrystalline cellulose, carboxymethyl cellulose, and any combinations thereof; a binder selected from the group consisting of povidone, hypromellose, hydroxypropyl cellulose, copovidone, and any combinations thereof; and

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

the rosuvastatin mixture-part further comprises

a weakly basic stabilizer selected from the group consisting of sodium hydrogen carbonate, potassium hydrogen carbonate, magnesium hydrogen carbonate, ammonium hydrogen carbonate, and any combinations thereof, in an amount of about 0.05 parts to about 0.5 parts by weight based on 1 part by weight of rosuvastatin;

mannitol;

a diluent selected from the group consisting of lactose, starch, microcrystalline cellulose, carboxymethyl cellulose, and any combinations thereof; a binder selected from the group consisting of povidone, hypromellose, hydroxypropyl cellulose, copovidone, and any combinations thereof;

a disintegrant selected from the group consisting of crospovidone, croscarmellose sodium, sodium starch glycolate, low-substituted hydroxypropyl cellulose, and any combinations thereof; and a glidant selected from the group consisting of magnesium stearate, talc, light anhydrous silicic acid, sodium stearyl fumarate, and any combinations thereof.

[Claim 2] The solid composite formulation of claim 1, wherein the ezetimibe granules-part is a wet granules-part.

[Claim 3] The solid composite formulation of claim 1 or 2,
wherein the ezetimibe granules-part or the rosuvastatin mixture-part comprises, based on 1 part by weight of ezetimibe, a diluent in an amount of about 0.5 to about 50 parts by weight, a binder in an amount of about 0.1 to about 20 parts by weight, a disintegrant in an amount of about 0.1 to about 40 parts by weight, a glidant in an amount of about 0.1 to about 3 parts by weight, or any combinations thereof.

[Claim 4] The solid composite formulation of any one of claims 1 to 3, wherein the average particle size $d_{(0.9)}$ for the bottom 90% of ezetimibe is in a range of about 0.8 μm to about 10 μm.

[Claim 5] The solid composite formulation of any one of claims 1 to 4, wherein the amount of ezetimibe is in a range of about 5 mg to about 20 mg in a unit dosage form.

[Claim 6] The solid composite formulation of any one of claims 1 to 5, wherein the amount of rosuvastatin or a pharmaceutically acceptable salt thereof is in a range of about 2.5 mg to about 40 mg in a unit dosage form.

[Claim 7] The solid composite formulation of any one of claims 1 to 6, wherein the dissolution rate of ezetimibe is about 85% or more in about 15 minutes when the composite formulation is subjected to a dissolution test at a paddle rotation speed of about 50 rpm in a buffer solution of a pH of about 4.5 containing about 0.45% sodium lauryl sulfate according to Dissolution method II in the

Korean Pharmacopoeia.

[Claim 8] The solid composite formulation of any one of claims 1 to 7, wherein

(3R,6E)-7-[4-(4-fluorophenyl)-2-(N-methylmethanesulfonamido)-6-(propane-2-yl)pyrimidine-5-yl]-3-hydroxy-5-oxo-hept-6-enoate calcium, or

N-[4-(4-fluorophenyl)-6-(1-methylethyl)-5-[(1E)-2-[(2S,4R)tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethenyl]-2-pyrimidinyl]-N-methylmethanesulfonamide which is a rosuvastatin-related compound, is in an amount of less than 1.0% after long-term storage of the composite formulation for about 24 months under conditions of a temperature of about 25°C and a relative humidity of about 60%.

[Claim 9] The solid composite formulation of any one of claims 1 to 8, wherein the amount of total ezetimibe-related compounds is less than about 1.0% after long-term storage of the composite formulation for about 24 months under conditions of a temperature of about 25°C and a relative humidity of about 60%.

[Claim 10] A method of preparing a solid composite formulation for oral administration, the method comprising:

preparing an ezetimibe granules-part comprising ezetimibe, said ezetimibe having a particle size distribution wherein the average particle size $d_{(0.9)}$ for the bottom 90% is about 10 μm or less; and

formulating the ezetimibe granules-part and a rosuvastatin mixture-part together, wherein the rosuvastatin mixture-part comprises rosuvastatin or a pharmaceutically acceptable salt thereof,

wherein

the ezetimibe granules-part further comprises

water;

a diluent selected from the group consisting of lactose, starch, mannitol, microcrystalline cellulose, carboxymethyl cellulose, and any combinations thereof; a binder selected from the group

consisting of povidone, hypromellose, hydroxypropyl cellulose, copovidone, and any combinations thereof; and

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

the rosuvastatin mixture-part further comprises

a weakly basic stabilizer selected from the group consisting of sodium hydrogen carbonate, potassium hydrogen carbonate, magnesium hydrogen carbonate, ammonium hydrogen carbonate, and any combinations thereof, in an amount of about 0.05 parts to about 0.5 parts by weight based on 1 part by weight of rosuvastatin;

mannitol;

a diluent selected from the group consisting of lactose, starch, microcrystalline cellulose, carboxymethyl cellulose, and any combinations thereof;

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

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

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

[Claim 11] The method of claim 10, wherein the ezetimibe granules-part is prepared by wet granulation.