In a first aspect, there is provided a pharmaceutical composition in oral solid dosage form comprising or made from a DPP-4 inhibitor, which has a free or primary amino group, a partner drug, and one or more pharmaceutical excipients, and a nucleophilic and/or basic agent, which is a basic amino acid having an intramolecular amino group and alkaline characteristics, for stabilizing said DPP-4 inhibitor against degradation, wherein the DPP-4 inhibitor is present in a dosage range from about 0.5 mg to about 20 mg; with the proviso that a pharmaceutical composition comprising or made from a DPP-4 inhibitor which is 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine free base, a partner drug which is metformin hydrochloride, and one or more pharmaceutical excipients, and a nucleophilic and/or basic agent for stabilizing said DPP-4 inhibitor against degradation, is disclaimed.

In a second aspect, there is provided a pharmaceutical composition in oral solid dosage form comprising a DPP-4 inhibitor, which has a free or primary amino group, a partner drug, one or more pharmaceutical excipients, and a buffering agent, which is a basic amino acid having an intramolecular amino group and alkaline characteristics, for stabilizing said DPP-4 inhibitor against degradation, wherein the DPP-4 inhibitor is present in a dosage range from about 0.5 mg to about 20 mg; with the proviso that a pharmaceutical composition comprising a DPP-4 inhibitor which is 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine free base, a partner drug which is metformin hydrochloride, and one or more pharmaceutical excipients, and a nucleophilic and/or basic agent for stabilizing said DPP-4 inhibitor against degradation, is disclaimed.

In a third aspect, there is provided a process for preparing a pharmaceutical composition as defined above comprising incorporating the active ingredients and L-arginine in one or more pharmaceutical excipients, such as e.g. one or more pharmaceutical excipients selected from D-mannitol, corn starch, pregelatinized starch, copovidone, magnesium stearate, and colloidal anhydrous silica.

In a fourth aspect, there is provided granules comprising a DPP-4 inhibitor which has a free or primary amino group, metformin hydrochloride, L-arginine, a binder and a filler.

In a fifth aspect, there is provided process for preparing a granulation liquid of a DPP-4 inhibitor which has a free or primary amino group, which comprises combining L-arginine, a binder and the DPP-4 inhibitor in a solvent or mixture of solvents.

Claims

1. A pharmaceutical composition in oral solid dosage form comprising or made from a DPP-4 inhibitor, which has a free or primary amino group, a partner drug, and one or more pharmaceutical excipients, and a nucleophilic and/or basic agent, which is a basic amino acid having an intramolecular amino group and alkaline characteristics, for stabilizing said DPP-4 inhibitor against degradation,
wherein the DPP-4 inhibitor is present in a dosage range from about 0.5 mg to about 20 mg;
with the proviso that
a pharmaceutical composition comprising or made from
a DPP-4 inhibitor which is 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine free base,
a partner drug which is metformin hydrochloride,
and one or more pharmaceutical excipients,
and a nucleophilic and/or basic agent for stabilizing said DPP-4 inhibitor against degradation,
is disclaimed.

2. A pharmaceutical composition in oral solid dosage form comprising a DPP-4 inhibitor, which has a free or primary amino group, a partner drug, one or more pharmaceutical excipients, and a buffering agent, which is a basic amino acid having an intramolecular amino group and alkaline characteristics, for stabilizing said DPP-4 inhibitor against degradation,
wherein the DPP-4 inhibitor is present in a dosage range from about 0.5 mg to about 20 mg;
with the proviso that
a pharmaceutical composition comprising
a DPP-4 inhibitor which is 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine free base,
a partner drug which is metformin hydrochloride,
and one or more pharmaceutical excipients,
and a nucleophilic and/or basic agent for stabilizing said DPP-4 inhibitor against degradation,
is disclaimed.

- the tablet disintegration time is lower than or equal 15 min.

27. The pharmaceutical composition according to any of the claims 22-26, which is an immediate release dosage form, characterized in that in a dissolution test after 45 minutes at least 75 % by weight of each of the active ingredients is dissolved.

28. A process for preparing a pharmaceutical composition according to claim 1, 2, or 19 comprising incorporating the active ingredients and L-arginine in one or more pharmaceutical excipients, such as e.g. one or more pharmaceutical excipients selected from D-mannitol, corn starch, pregelatinized starch, copovidone, magnesium stearate, and colloidal anhydrous silica.

29. The pharmaceutical composition according to any of the claims 1 to 27 which is made by comprising combining said ingredients.

~~30. The pharmaceutical composition according to claim 1 or 2, comprising the active ingredients in an amount of:~~
~~(1) 2.5 mg of 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine, and 500 mg metformin hydrochloride; or~~
~~(2) 2.5 mg of 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine, and 850 mg metformin hydrochloride; or~~
~~(3) 2.5 mg of 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine, and 1000 mg metformin hydrochloride.~~

~~31~~30. The pharmaceutical composition according to any one of claims 1 to 27, or 29 ~~or 30~~ in the dosage form of a coated tablet comprising one or more of the following amounts (% by weight of total coated tablet mass):

0.1-0.5 %	DPP-4 inhibitor,
47-85 %	metformin HCl,
0.07-2.2 %	L-arginine,
3.9-8.1 %	binder (e.g. copovidone),
2.3-5.9 %	filler 1 (e.g. corn starch),
0-4.4 %	filler 2 (e.g. pregelatinized starch),
0-33 %	filler 3 (e.g. D-mannitol),
0.7-1.5 %	lubricant (e.g. magnesium stearate), and
0.1-0.5 %	glidant (e.g. colloidal anhydrous silica).

~~32~~31. Granules comprising a DPP-4 inhibitor which has a free or primary amino group, metformin hydrochloride, L-arginine, a binder and a filler.

~~33~~32. The granules of claim ~~32~~31, prepared by fluid bed granulation.

33. The granules according to claim 31 or 32, wherein the DPP-4 inhibitor is present in a dosage range from about 0.5 mg to about 20 mg, particularly from about 0.5 mg to about 10 mg.

34. The granules according to any of the claims 31 to 33, wherein L-arginine is present from about 1 mg to about 50 mg.

35. The granules according to any of the claims 31 to 34, wherein L-arginine is present from about 1 mg to about 25 mg.

36. The granules according to any of the claims 31 to 35, comprising the active ingredients in an amount of:
(1) 2.5 mg of 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine, and 500 mg metformin hydrochloride; or
(2) 2.5 mg of 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine, and 850 mg metformin hydrochloride; or
(3) 2.5 mg of 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine, and 1000 mg metformin hydrochloride.

~~34~~37. A process for preparing a granulation liquid of a DPP-4 inhibitor which has a free or primary amino group, which comprises combining L-arginine, a binder and the DPP-4 inhibitor in a solvent or mixture of solvents.

~~35. 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine having a particle size distribution of X90 < 200 µm.~~

~~36. 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine having a particle size distribution of X90 > 0.1 µm.~~

~~37. A method for improving drug load of metformin HCl and tablet compactability characterized by surface treatment of metformin HCl with a water-soluble polymer, particularly copolyvidone, such as during fluid-bed granulation.~~