Claims

1. A pharmaceutical composition 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 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.

~~3. A pharmaceutical composition comprising or made from a DPP-4 inhibitor, a partner drug, and one or more pharmaceutical excipients, and a nucleophilic and/or basic agent for stabilizing said DPP-4 inhibitor against degradation, for the treatment of diabetes.~~

~~4. A pharmaceutical composition comprising a DPP-4 inhibitor, a partner drug, one or more pharmaceutical excipients, and a buffering agent for stabilizing said DPP-4 inhibitor against degradation, for the treatment of diabetes.~~

~~5. A pharmaceutical composition comprising or made from a DPP-4 inhibitor, a partner drug, and one or more pharmaceutical excipients, and a nucleophilic and/or basic agent for stabilizing said DPP-4 inhibitor against degradation;~~
~~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,~~
~~for the treatment of diabetes.~~

~~6. A pharmaceutical composition comprising a DPP-4 inhibitor, a partner drug, one or more pharmaceutical excipients, and a buffering agent for stabilizing said DPP-4 inhibitor against degradation;~~
~~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,~~
~~for the treatment of diabetes.~~

~~7~~3. The pharmaceutical composition according to ~~any of the~~ claim~~s~~ 1 ~~to 6~~or 2, wherein said DPP-4 inhibitor is stabilized against chemical degradation.

~~8~~4. The pharmaceutical composition according to ~~any of the~~ claim~~s~~ 1, 2 or 3 ~~to 7~~, wherein the partner drug is selected from the group consisting of biguanides including metformin hydrochloride, thiazolidinones including pioglitazone hydrochloride, statines including atorvastatin, and ARBs including telmisartan.

~~9~~5. The pharmaceutical composition according to any of the claims 1 to ~~8~~4, wherein the nucleophilic and/or basic agent or the buffering agent is a basic amino acid having an intramolecular amino group and alkaline characteristics having isoelectric point, pI: 7.59-10.76, such as e.g. L-arginine, L-lysine and L-histidine.

~~10~~6. The pharmaceutical composition according to any of the claims 1 to ~~9~~5, wherein the DPP-4 inhibitor has an intramolecular free primary or secondary amino group.

~~117~~. The pharmaceutical composition according to any of the claims 1 to ~~106~~, wherein the DPP-4 inhibitor is selected from vildagliptin, saxagliptin and alogliptin.

~~128~~. The pharmaceutical composition according to any of the claims 1 to ~~106~~, wherein the DPP-4 inhibitor 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.

~~13~~9. The pharmaceutical composition according to any of the claims 1 to ~~12~~8, 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.

~~14~~10. The pharmaceutical composition according to claim ~~12~~8 or ~~13~~9, wherein the DPP-4 inhibitor is present in a dosage strength of 0.5, 1, 2.5, 5 or 10 mg.

~~15~~11. The pharmaceutical composition according to claim ~~12~~8, ~~13~~9 or ~~14~~10, wherein the DPP-4 inhibitor is present in a dosage strength of 2.5 mg.

~~16~~12. The pharmaceutical composition according to any of the claims 1 to ~~15~~11, wherein the partner drug is metformin hydrochloride.

~~17~~13. The pharmaceutical composition according to claim ~~16~~12, wherein metformin hydrochloride is present in a dosage range from about 100 mg to about 1500 mg.

~~18~~14. The pharmaceutical composition according to claim ~~16~~12 or ~~17~~13, wherein metformin hydrochloride is present in a dosage strength of 250, 500, 625, 750, 850 or 1000 mg.

~~19~~15. The pharmaceutical composition according to claim ~~16~~12, ~~17~~13 or ~~18~~15, wherein metformin hydrochloride is present in a dosage strength of 500 mg, 850 mg or 1000 mg.

~~20~~16. The pharmaceutical composition according to any of the claims 1 to ~~19~~15, wherein the nucleophilic and/or basic agent or the buffering agent is L-arginine.

~~21~~17. The pharmaceutical composition according to claim ~~20~~16, wherein L-arginine is present from about 1 mg to about 50 mg, preferably from about 1 mg to about 25 mg.

~~22~~18. The pharmaceutical composition according to claim ~~20~~16 or ~~21~~17, wherein the DPP-4 inhibitor and L-arginine are present in a weight ratio from about 1:20 to about 10:1, or from about 1:15 to about 10:1, preferably from about 1:10 to about 10:1.

~~23~~19. The pharmaceutical composition according to any of the claims 1 to ~~22~~18, wherein the excipients are selected from the group consisting of one or more fillers including D-mannitol,

corn starch and pregelatinized starch; a binder including copovidone; a lubricant including magnesium stearate; and a glidant including colloidal anhydrous silica.

~~24~~20. The pharmaceutical composition according to any of the claims 1 to ~~23~~19 comprising copovidone as binder.

~~25~~21. The pharmaceutical composition according to claim ~~24~~20 further comprising one or more of the following: the filler corn starch, the lubricant magnesium stearate, and the glidant colloidal anhydrous silica.

~~26~~22. The pharmaceutical composition according to any of the claims 1 to ~~25~~21 in the dosage form of a tablet.

~~27~~23. The pharmaceutical composition according to claim ~~26~~22, wherein the tablet is selected from a mono-layer tablet, a bi-layer tablet, a press-coated tablet (including a tablet-in-tablet and a Bull's eye tablet), and a tablet which is film-coated for drug-loading.

~~28~~24. The pharmaceutical composition according to claim ~~26~~22 or ~~27~~23, wherein the tablet comprises a film-coat.

~~29~~25. The pharmaceutical composition according to claim ~~28~~24, wherein the film-coat comprises a film-coating agent, such as e.g. hypromellose; a plasticizer, such as e.g. propylene glycol; optionally a glidant, such as e.g. talc, and optionally one or more pigments, such as e.g. titanium dioxide, iron oxide red and/or iron oxide yellow.

~~30~~26. The pharmaceutical composition according to any of the preceding claims, in which the pharmaceutical composition is a mono-layer tablet, wherein one or more of the following may apply:

- the percentage of metformin hydrochloride is about 85 % by weight of total tablet core,
- the percentage of DPP-4 inhibitor is about 0.2 % - 0.4 % by weight of total tablet core,
- the percentage of L-arginine is about 2 % by weight of total tablet core,
- the tablet crushing strength is higher than or equal 100 N,
- the tablet friability is lower than or equal 0.5 %,
- the tablet thickness is from about 5.7 to about 8.4 mm,
- the tablet core weight is from about 590 to about 1180 mg, and

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

~~31~~27. The pharmaceutical composition according to any of the claims ~~26~~22-~~30~~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.

~~32. A solid pharmaceutical composition comprising or made from~~
~~1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine,~~
~~metformin hydrochloride,~~
~~L-arginine,~~
~~and one or more fillers, one or more binders, one or more glidants and/or one or more lubricants;~~
~~for the treatment of diabetes.~~

~~33. The pharmaceutical composition according to claim 12 or 32, wherein 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine has a particle size distribution of X90 < 200 µm.~~

~~34~~28. A process for preparing a pharmaceutical composition according to claim 1, 2, ~~3, 4, 5, 6, 23~~ or 19 ~~or 32~~ 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.

~~35~~29. The pharmaceutical composition according to any of the claims 1 to ~~33~~27 which is made by comprising combining said ingredients.

~~36~~30. The pharmaceutical composition according to claim 1~~,~~ or 2, ~~3, 4, 5, 6 or 32~~ 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.

~~37~~31. The pharmaceutical composition according to any one of claims 1 to ~~33~~27, ~~35~~ 29 or ~~36~~ 30 comprising one or more of the following amounts:

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).

~~38~~32. Granules comprising a DPP-4 inhibitor, metformin hydrochloride, L-arginine, a binder and a filler.

~~39~~33. The granules of claim ~~38~~32, prepared by fluid bed granulation.

~~40~~34. A process for preparing a granulation liquid of a DPP-4 inhibitor, which comprises combining L-arginine, a binder and the DPP-4 inhibitor in a solvent or mixture of solvents.

~~41~~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.

~~42~~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.

~~43~~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.