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(54) **DPP IV INHIBITOR FORMULATIONS**

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(57) **ABSTRACT**

The present invention relates to pharmaceutical compositions of DPP IV inhibitors with an amino group, their preparation and their use to treat diabetes mellitus.

DPP IV INHIBITOR FORMULATIONS

BACKGROUND OF THE INVENTION

[0001] This Application claims priority of EP 06 009 201, which is hereby incorporated by reference in its entirety.

[0002] 1. Field of the Invention

[0003] The present invention relates to pharmaceutical compositions of selected DPP IV inhibitors, their preparation and their use to treat selected medical conditions.

[0004] 2. Description of the Prior Art

[0005] The enzyme DPP-IV (dipeptidyl peptidase IV) also known as CD26 is a serine protease known to lead to the cleavage of a dipeptide from the N-terminal end of a number of proteins having at their N-terminal end a prolin or alanin residue. Due to this property DPP-IV inhibitors interfere with the plasma level of bioactive peptides including the peptide GLP-1 and are considered to be promising drugs for the treatment of diabetes mellitus.

DETAILED DESCRIPTION OF THE INVENTION

[0006] In attempts to prepare pharmaceutical compositions of selected DPP-IV inhibitors it has been observed, that the DPP-IV inhibitors with a primary or secondary amino group show incompatibilities, degradation problems, or extraction problems with a number of customary excipients such as microcrystalline cellulose, sodium starch glycolate, croscarmellose sodium, tartaric acid, citric acid, glucose, fructose, saccharose, lactose, maltodextrines. Though the compounds themselves are very stable, they react with many excipients used in solid dosage forms and with impurities of excipients, especially in tight contact provided in tablets and at high excipient/drug ratios. The amino group appears to react with reducing sugars and with other reactive carbonyl groups and with carboxylic acid functional groups formed for example at the surface of microcrystalline cellulose by oxidation. These unforeseen difficulties are primarily observed in low dosage ranges which are required due to the surprising potency of the selected inhibitors. Thus, pharmaceutical compositions are required so solve these technical problems associated with the unexpected potency of selected DPP-IV inhibitor compounds.

[0007] A pharmaceutical composition according to the present invention is intended for the treatment of to achieve glycemic control in a type 1 or type 2 diabetes mellitus patient and comprises a DPP-IV inhibitor with an amino group, especially a free or primary amino group, as an active ingredient, a first and second diluent, a binder, a disintegrant and a lubricant. An additional disintegrant and an additional glidant are a further option. Additionally the compositions can be used to treat rheumatoid arthritis, obesity and osteoporosis as well as to support allograft transplantation.

[0008] Diluents suitable for a pharmaceutical composition according to the invention are cellulose powder, dibasic calciumphosphate anhydrous, dibasic calciumphosphate dihydrate, erythritol, low substituted hydroxypropyl cellulose, mannitol, pregelatinized starch or xylitol. Among those diluents mannitol and pregelatinized starch are preferred.

[0009] Diluents preferred as the second diluent are the above mentioned diluents pre-gelatinized starch and low-substituted hydroxypropylcellulose (L-HPC) which show additional binder properties.

[0010] Lubricants suitable for a pharmaceutical composition according to the invention are sodium stearyl fumarate, calcium behenate, calcium stearate, hydrogenated castor oil or magnesium stearate. The preferred lubricant is magnesium stearate.

[0011] Binders suitable for a pharmaceutical composition according to the invention are copovidone (copolymerisates of vinylpyrrolidon with other vinylderivates), hydroxypropyl methylcellulose (HPMC), hydroxypropylcellulose (HPC), polyvinylpyrrolidon (povidone), pregelatinized starch, low-substituted hydroxypropylcellulose (L-HPC), copovidone and pregelatinized starch being preferred.

[0012] The above mentioned binders pregelatinized starch and L-HPC show additional diluent and disintegrant properties and can also be used as the second diluent or the disintegrant.

[0013] Disintegrants suitable for a pharmaceutical composition according to the present invention are corn starch, crospovidone, low-substituted hydroxypropylcellulose (L-HPC) or pregelatinized starch, corn starch being preferred.

[0014] As an optional glidant colloidal silicon dioxide can be used.

[0015] An exemplary composition according to the present invention comprises the diluent mannitol, pregelatinized starch as a diluent with additional binder properties, the binder copovidone, the disintegrant corn starch, and magnesium stearate as the lubricant.

[0016] Dosage forms prepared with a pharmaceutical compositions according to the present invention contain active ingredients in dosage ranges of 0.1-100 mg. Preferred dosages are 0.5 mg, 1 mg, 2.5 mg, 5 mg and 10 mg.

[0017] Typical pharmaceutical compositions comprise (% by weight)

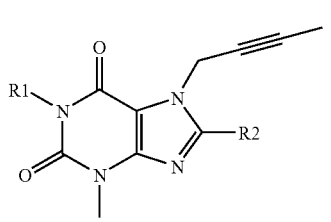
0.5-20%	active ingredient
40-88%	diluent 1,
3-40%	diluent 2,
1-5%	binder,
5-15%	disintegrant, and
0.1-4%	lubricant.

[0018] Preferred pharmaceutical compositions comprise (% by weight)

0.5-7%	active ingredient
50-75%	diluent 1,
5-15%	diluent 2,
2-4%	binder,
8-12%	disintegrant, and
0.5-2%	lubricant

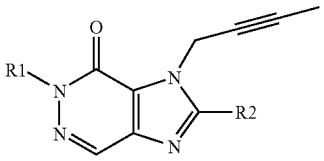
[0019] The pharmaceutical compositions according to the invention are intended for oral use and can be used in the dosage form of a capsule, a tablet or a film-coated tablet. Typically the film coat represents 2-4%, preferably 3% of the composition and comprises a film-forming agent, a plasticizer, a glidant and optionally one or more pigments. An exemplary coat composition may comprise hydroxypropyl-

[0020] Preferred active ingredients in the context of the present invention are DPP-IV inhibitors with a primary amino group and salts thereof such as any DPP-IV inhibitor and salt thereof defined by formula (I)



(I)

or formula (II)

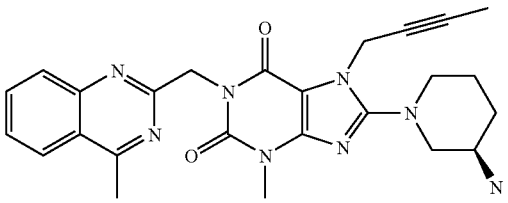


(II)

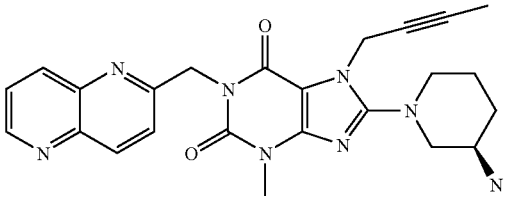
wherein R1 is ([1,5]naphthyridin-2-yl)methyl, (quinazolin-2-yl)methyl], (quinoxalin-6-yl)methyl, (4-Methyl-quinazolin-2-yl)methyl, 2-Cyano-benzyl, (3-Cyano-quinolin-2-yl) methyl, (3-Cyano-pyridin-2-yl)methyl, (4-Methyl-pyrimidin-2-yl)methyl, or (4,6-Dimethyl-pyrimidin-2-yl) methyl, and R2 is 3-(R)-amino-piperidin-1-yl, (2-amino-2-methyl-propyl)-methylamino or (2-(S)-amino-propyl)-methylamino.

[0021] Preferred DPP IV inhibitor compounds are the following compounds and salts thereof:

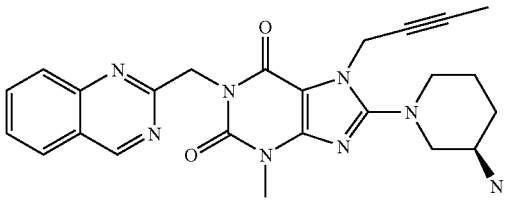
[0022] 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine (compare WO 2004/018468, example 2(142):



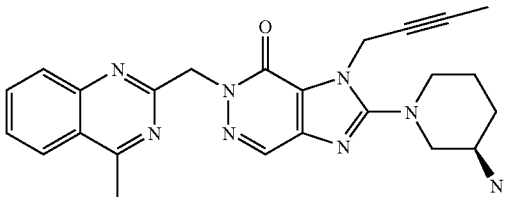
[0023] 1-[([1,5]naphthyridin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-((R)-3-amino-piperidin-1-yl)-xanthine (compare WO 2004/018468, example 2(252)):



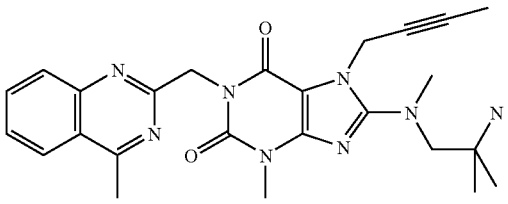
[0024] 1-[(Quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-((R)-3-amino-piperidin-1-yl)-xanthine (compare WO 2004/018468, example 2(80)):



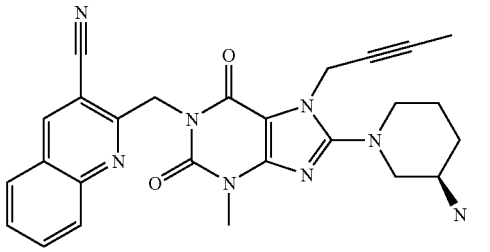
[0025] 2-((R)-3-Amino-piperidin-1-yl)-3-(but-2-yinyl)-5-(4-methyl-quinazolin-2-ylmethyl)-3,5-dihydro-imidazo[4,5-d]pyridazin-4-one (compare WO 2004/050658, example 136):



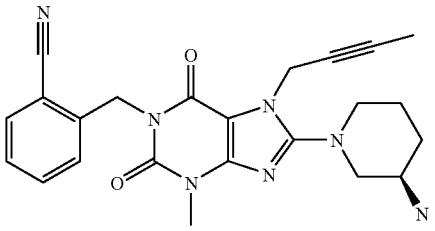
[0026] 1-[(4-Methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyin-1-yl)-8-[(2-amino-2-methyl-propyl)-methylamino]-xanthine (compare WO 2006/029769, example 2(1)):



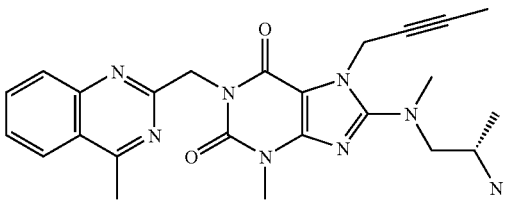
[0027] 1-[(3-Cyano-quinolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-((R)-3-amino-piperidin-1-yl)-xanthine (compare WO 2005/085246, example 1(30)):



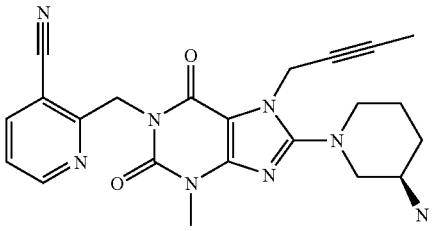
[0028] 1-(2-Cyano-benzyl)-3-methyl-7-(2-butyn-1-yl)-



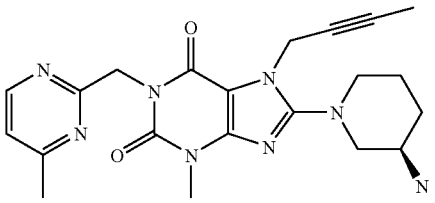
[0029] 1-[(4-Methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-[(S)-(2-amino-propyl)-methylamino]-xanthine (compare WO 2006/029769, example 2(4)):



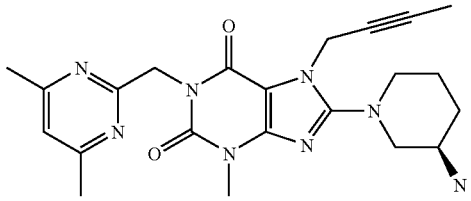
[0030] 1-[(3-Cyano-pyridin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-((R)-3-amino-piperidin-1-yl)-xanthine (compare WO 2005/085246, example 1(52)):



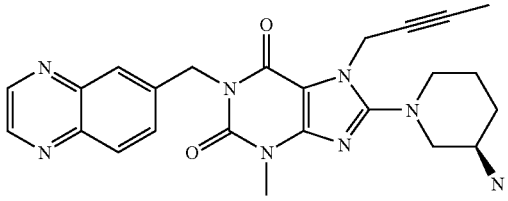
[0031] 1-[(4-Methyl-pyrimidin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-((R)-3-amino-piperidin-1-yl)-xanthine (compare WO 2005/085246, example 1(81)):



[0032] 1-[(4,6-Dimethyl-pyrimidin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-((R)-3-amino-piperidin-1-yl)-



[0033] 1-[(Quinoxalin-6-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-((R)-3-amino-piperidin-1-yl)-xanthine (compare WO 2005/085246, example 1(83)):



[0034] To prepare compositions according to the invention a granulate can be prepared by a wet granulation process. Alternative methods for granulation of active ingredient and excipients with a granulation liquid are fluid bed granulation or one-pot granulation.

[0035] In the wet granulation process the granulation liquid is a solvent such as water, ethanol, methanol, isopropanol, acetone, preferably purified water, and contains a binder such as copovidone. The solvent is a volatile component, which does not remain in the final product. The active ingredient and the other excipients with exception of the lubricant are premixed and granulated with the aqueous granulation liquid using a high shear granulator. The wet granulation step is followed by an optional wet sieving step, drying and dry sieving of the granules. For example a fluid bed dryer can then be used for drying.

[0036] The dried granules are sieved through an appropriate sieve. After addition of the other excipients with exception of the lubricant the mixture is blended in a suitable conventional blender such as a free fall blender followed by addition of the lubricant such as magnesium stearate and final blending in the blender.

[0037] Thus an exemplary wet granulation process for the preparation of a pharmaceutical composition according to the present invention comprises

[0038] a. dissolving a binder such as copovidone in a solvent such as purified water at ambient temperature to produce a granulation liquid;

[0039] b. blending a DPP-IV inhibitor, a diluent, and a disintegrant in a suitable mixer, to produce a pre-mix;

[0040] c. moistening the pre-mix with the granulation liquid and subsequently granulating the moistened pre-mix for example in a high shear mixer;

[0041] d. optionally sieving the granulated pre-mix through a sieve with a mesh size of at least 1.0 mm and preferably 3 mm;

[0042] e. drying the granulate at about 40-75° C. and preferably 55-65° C. inlet air temperature for example in

[0043] f. delumping the dried granulate for example by sieving through a sieve with a mesh size of 0.6 mm-1.6 mm, preferably 1.0 mm; and

[0044] g. adding preferably sieved lubricant to the granulate for final blending for example in a cube mixer.

[0045] In an alternative process part of the exipients such as part of a disintegrant (e.g. corn starch) or a diluent (e.g. pregelatinized starch) or an additional disintegrant (crospovidone) can be added extragranular prior to final blending of step g.

[0046] In another alternative version of the process the granulate produced in steps a to e is produced in a one pot high shear granulation process and subsequent drying in a one pot granulator.

[0047] For the preparation of capsules the final blend is further filled into capsules.

[0048] For the preparation of tablets or tablet cores the final blend is further compressed into tablets of the target tablet core weight with appropriate size and crushing strength, using an appropriate tablet press.

[0049] For the preparation of film-coated tablets a coating suspension is prepared and the compressed tablet cores are coated with the coating suspension to a weight gain of about 2-4%, preferably about 3%, using a standard film coater. The film-coating solvent is a volatile component, which does not remain in the final product. To reduce the required amount of lubricant in the tablets it is an option to use an external lubrication system.

EXAMPLES

Example 1

Formulation for Direct Compression

[0050] An active DPP IV inhibitor ingredient with a primary amino group and all other excipients with exception of magnesium stearate are blended in a high shear blender. This pre-mix is sieved through a 1 mm sieve. After addition of magnesium stearate the pre-mix is blended in a free fall blender to produce the final blend. The final blend is compressed into tablets using a suitable tablet press. The following compositions can be obtained:

Component	mg/tablet	%/tablet	mg/tablet	%/tablet
Active ingredient	1.000	2.000	2.500	2.000
Mannitol	43.250	86.500	108.125	86.500
Pregelatinized starch	5.000	10.000	12.500	10.000
Magnesium stearate	0.750	1.500	1.875	1.500
Total	50.000	100.000	125.000	100.000

Component	mg/tablet	%/tablet	mg/tablet	%/tablet
Active ingredient	5.000	2.000	10.000	2.000
Mannitol	216.250	86.500	432.500	86.500
Pregelatinized starch	25.000	10.000	50.000	10.000
Magnesium stearate	3.750	1.500	7.500	1.500
Total	250.000	100.000	500.000	100.000

Example 2

Alternative Formulation for Direct Compression

[0051] An active DPP IV inhibitor ingredient with a primary amino group and all other excipients with exception of magnesium stearate are blended in a high shear blender. This pre-mix is sieved through a 1 mm sieve. After addition of magnesium stearate the pre-mix is blended in a free fall blender to produce the final blend. The final blend is compressed into tablets using a suitable tablet press. The following compositions can be obtained:

Component	mg/tablet	%/tablet	mg/tablet	%/tablet
Active ingredient	1.000	1.667	0.500	0.833
Dibasic calciumphosphate, anhydrous	46.400	77.333	46.900	78.177
Low-substituted hydroxypropylcellulose	12.000	20.000	12.000	20.000
Magnesium stearate	0.600	1.000	0.600	1.000
Total	60.000	100.000	60.000	100.000

Component	mg/tablet	%/tablet	mg/tablet	%/tablet
Active ingredient	10.000	1.667	10.000	2.222
Dibasic calciumphosphate, anhydrous	464.000	77.333	344.000	76.788
Low-substituted hydroxypropylcellulose	120.000	20.000	90.000	20.000
Magnesium stearate	6.000	1.000	6.000	1.000
Total	600.000	100.000	450.000	100.000

Example 3

Tablet Formulation

[0052] Copovidone is dissolved in purified water at ambient temperature to produce a granulation liquid. An active DPP IV inhibitor ingredient with a primary amino group, mannitol and part of the pregelatinized starch are blended in a suitable mixer, to produce a pre-mix. The pre-mix is moistened with the granulation liquid and subsequently granulated. The moist granulate is optionally sieved through a sieve with a mesh size of 1.6-3.0 mm. The granulate is dried at 55 ° C. in a suitable dryer to a residual moisture content corresponding to 2-5% loss on drying. The dried granulate is sieved through a sieve with a mesh size of 1.0 mm. The granulate is blended with part of the pregelatinized starch in a suitable mixer. Magnesium stearate is added to this blend after passing through a 1.0 mm sieve for delumping. Subsequently the final blend is produced by final blending in a suitable mixer and compressed into tablets. The following tablet composition

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