DIRECT COMPRESSION FORMULATION AND PROCESS

This invention relates to tablets especially tablets formed by direct compression of a dipeptidylpeptidase IV (DPP-IV) inhibitor compound, a process for the preparation thereof, to new pharmaceutical formulations , and new tableting powders comprising DPP-IV inhibitor formulations capable of being directly compressed into tablets. The invention relates further to a process for preparing the tablets by blending the active ingredient and specific excipients into the new formulations and then directly compressing the formulations into the direct compression tablets.

The preferred DPP-IV inhibitor compounds to which this invention is primarily directed are described below:

In the present context "a DPP-IV inhibitor" is also intended to comprise active metabolites and prodrugs thereof, such as active metabolites and prodrugs of DPP-IV inhibitors. A "metabolite" is an active derivative of a DPP-IV inhibitor produced when the DPP-IV inhibitor is metabolised. A "prodrug" is a compound that is either metabolised to a DPP-IV inhibitor or is metabolised to the same metabolite(s) as a DPP-IV inhibitor.

DPP-IV inhibitors are known in the art. For example, DPP-IV inhibitors are in each case generically and specifically disclosed e.g. in WO 98/19998,DE19616 486 A1, WO 00/34241, WO 95/15309, WO 01/72290, WO 01/52825, WO 9310127, WO 9925719, WO 9938501, WO 9946272, WO 9967278 and WO 9967279.

Preferred DPP-IV inhibitors are described in the following patent applications; WO 02053548 especially compounds 1001 to 1293 and examples 1 to 124, WO 02067918 especially compounds 1000 to 1278 and 2001 to 2159, WO 02066627 especially the described examples, WO 02/068420 especially all the compounds specifically listed in the examples I to LXIII and the described corresponding analogues, even preferred compounds are 2(28), 2(88), 2(119), 2(136) described in the table reporting IC50, WO 02083128 especially examples 1 to 13, US 2003096846 especially the specifically described compounds, WO 2004/037181 especially examples 1 to 33 and compounds of claims 3 to 5, WO 0168603 especially compounds of examples 1 to 109, EP1258480 especially compounds of examples 1 to 60, WO 0181337 especially examples 1 to 118, WO 02083109 especially examples 1A to 1D, WO 030003250 especially compounds of examples 1 to 166, most preferably 1 to 8, WO 03035067 especially the compounds described in the examples, WO 03/035057 especially the compounds described in the examples, US2003216450 especially examples 1

to 450, WO 99/46272 especially compounds of claims 12, 14, 15 and 17, WO 0197808 especially compounds of claim 2, WO 03002553 especially compounds of examples 1 to 33, WO 01/34594 especially the compounds described in the examples 1 to 4, WO 02051836 especially examples 1 to 712, EP1245568 especially examples 1 to 7, EP1258476 especially examples 1 to 32, US 2003087950 especially the described examples, WO 02/076450 especially examples 1 to 128, WO 03000180 especially examples 1 to 162, WO 03000181 especially examples 1 to 66, WO 03004498 especially examples 1 to 33, WO 0302942 especially examples 1 to 68, US 6482844 especially the described examples, WO 0155105 especially the compounds listed in the examples 1 and 2, WO 0202560 especially examples 1 to 166, WO 03004496 especially examples 1 to 103, WO 03/024965 especially examples 1 to 54, WO 0303727 especially examples 1 to 209, WO 0368757 especially examples 1 to 88, WO 03074500 especially examples 1 to 72, examples 4.1 to 4.23, examples 5.1 to 5.10, examples 6.1 to 6.30, examples 7.1 to 7.23, examples 8.1 to 8.10, examples 9.1 to 9.30, WO 02038541 especially examples 1 to 53, WO 02062764 especially examples 1 to 293, preferably the compound of example 95 (2-{{3-(Aminomethyl)-4-butoxy-2-neopentyl-1-oxo-1,2 dihydro-6-isoquinolinyl}oxy}acetamide hydrochloride), WO 02308090 especially examples 1-1 to 1-109, examples 2-1 to 2-9, example 3, examples 4-1 to 4-19, examples 5-1 to 5-39, examples 6-1 to 6-4, examples 7-1 to 7-10, examples 8-1 to 8-8, examples 7-1 to 7-7 of page 90, examples 8-1 to 8-59 of pages 91 to 95, examples 9-1 to 9-33, examples 10-1 to 10-20, US 2003225102 especially compounds 1 to 115, compounds of examples 1 to 121,preferably compounds a) to z), aa) to az), ba) to bz), ca) to cz) and da) to dk), WO 0214271 especially examples 1 to 320 and US 2003096857, WO 2004/052850 especially the specifically described compounds such as examples 1 to 42 and compounds of claim 1, DE 102 56 264 A1 especially the described compounds such as examples 1 to 181 and the compounds of claim 5, WO 04/076433 especially the compounds specifically described, such as listed in table A, preferably the compounds listed in table B, preferably compounds I to XXXXVII, or compounds of claims 6 to 49, WO 04/071454 especially the specifically described compounds e.g. compounds 1 to 53 or compounds of tables Ia to If , or compounds of claims 2 to 55, WO 02/068420 especially the compounds specifically described, such as the compounds I to LXIII or Beispiele I and analogues 1 to 140 or Beispiele 2 and analogues 1 to 174 or Beispiele 3 and analogues 1, or Beispiele 4 to 5, or Beispiele 6 and analogues 1 to 5, or Beispiele 7 and analogues 1-3, or Beispiele 8 and analogue 1, or Beispiele 9, or Beispiele 10 and analogues 1 to 531 even preferred are compounds of claim 13, WO 03/000250 especially the compounds specifically described,

such as the compounds 1 to 166, preferably compounds of examples 1 to 9, WO 03/024942 especially the compounds specifically described, such compounds 1 to 59, compounds of table 1 (1 to 68), compounds of claims 6, 7, 8, 9, WO 03024965 especially the compounds specifically described, such compounds 1 to 54, WO 03002593 especially the compounds specifically described, such compounds table 1 or of claims 2 to 15, WO 03037327 especially the compounds specifically described, such compounds of examples 1 to 209 WO 03/000250 especially the compounds specifically described, such as the compounds 1 to 166, preferably compounds of examples 1 to 9, WO 03/024942 especially the compounds specifically described, such compounds 1 to 59, compounds of table 1 (1 to 68), compounds of claims 6, 7, 8, 9, WO 03024965 especially the compounds specifically described, such compounds 1 to 54, WO 03002593 especially the compounds specifically described, such compounds table 1 or of claims 2 to 15, WO03037327 especially the compounds specifically described, such compounds of examples 1 to 209, WO 0238541, WO 0230890, U.S. application Serial No. 09/788,173 filed February 16, 2001 (attorney file LA50) especially the described examples, WO99/38501 especially the described examples, W099/46272 especially the described examples and DE19616 486 A1 especially val-pyr, val-thiazolidide, isoleucyl-thiazolidide, isoleucyl-pyrrolidide, and fumar salts of isoleucyl-thiazolidide and isoleucyl-pyrrolidide, WO 0238541 especially the compounds specifically described, such compounds of examples 1 to 53, WO 03/002531 especially the compounds specifically described preferably the compounds listed on page 9 to 13, most preferably the compounds of examples 1 to 46 and even preferred compound of example 9, U.S. Patent No. 6,395,767 preferably compound of examples 1 to 109 most preferably compound of example 60.

Further preferred DPP-IV inhibitors include the specific examples disclosed in United States Patent Numbers 6124305 and US 6107317, International Patent Applications, Publication Numbers WO 9819998, WO 95153 09 and WO 9818763; such as 1[2- [(5 eyanopyridin-2-yl)aminoethylamino]acetyl-2-cyano-(S)-pyrrolidine and (2S)- I-[(2S)-2 arnino-3,3-dimethylbutanoyl]-2-pyrrolidinecarbonitrile.

WO 9819998 discloses N-(N'-substituted glycyl)-2-cyano pyrrolidines, in particular 1-[2-[5-Cyanopyridin-2-yl] amino]- ethylamino] acetyl-2-cyano- (S)- pyrrolidine. Preferred compounds described in WO03/002553 are listed on pages 9 to 11 and are incorporated into the present application by reference. Published patent application WO 0034241 and published patent US 6110949 disclose N-substituted adamantyl-amino-acetyl-2-cyano pyrrolidines and N-(substituted glycyl)-4-cyano pyrrolidines respectively. DPP-IV inhibitors of

interest are specially those cited in claims 1 to 4. In particular these applications describe the compound 1-[[(3-Hydroxy-1-adamantyl) amino]acetyl]-2-cyano-(S)-pyrrolidine (also known as LAF237).

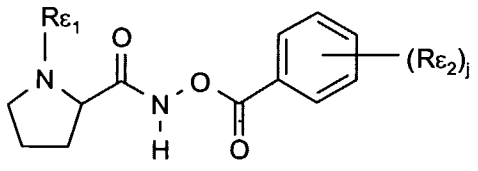
WO 9515309 discloses amino acid 2- cyanopyrrolidine amides as inhibitors of DPP-IV and WO 9529691 discloses peptidyl derivates of diesters of alpha-aminoalkylphosphonic acids, particularly those with proline or related structures. DPP-IV inhibitors of interest are specially those cited in Table 1 to 8. In WO 01/72290 DPP-IV inhibitors of interest are specially those cited in example 1 and claims 1, 4,and 6. WO 9310127 discloses proline boronic esters useful as DPP-IV inhibitors. DPP-IV inhibitors of interest are specially those cited in examples 1 to 19. Published patent application WO 9925719 discloses sulphostin, a DPP-IV inhibitor prepared by culturing a Streptomyces microorganism. WO 9938501 discloses N-substituted 4- to 8-membered heterocyclic rings. DPP-IV inhibitors of interest are specially those cited in claims 15 to 20.

WO 9946272 discloses phosphoric compounds as inhibitors of DPP-IV. DPP-IV inhibitors of interest are specially those cited in claims 1 to 23.

Other preferred DPP-IV inhibitors are the compounds of formula I, II or III disclosed in the patent application WO 03/057200 on page 14 to 27. Most preferred DPP-IV inhibitors are the compounds specifically described on pages 28 and 29.

Published patent applications WO 9967278 and WO 9967279 disclose DPP-IV prodrugs and inhibitors of the form A-B-C where C is either a stable or unstable inhibitor of DPP-IV.

Preferably, the N-peptidyl-O-aroyl hydroxylamine is a compound of formula VII



(VII)

wherein

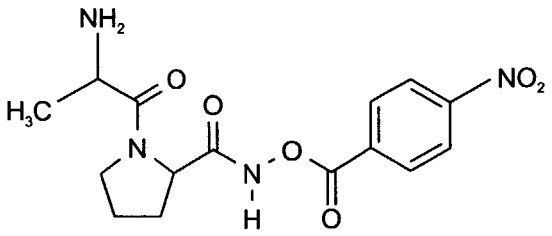
j is 0, 1 or 2;

$R\varepsilon_1$ represents the side chain of a natural amino acid; and

$R\varepsilon_2$ represents lower alkoxy, lower alkyl, halogen or nitro;

or a pharmaceutically acceptable salt thereof.

In a very preferred embodiment of the invention, the N-peptidyl-O-aroyl hydroxylamine is a compound of formula VIIa

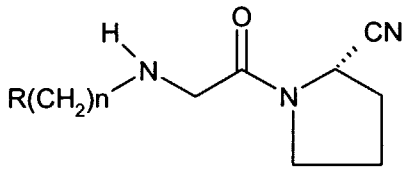


(VIIa)

or a pharmaceutically acceptable salt thereof.

N-Peptidyl-O-aroyl hydroxylamines, e.g. of formula VII or VIIa, and their preparation are described by H.U. Demuth et al. in J. Enzyme Inhibition 1988, Vol. 2, pages 129-142, especially on pages 130-132.

Most preferably the inhibitors are *N*-(substituted glycyl)-2-cyanopyrrolidines of formula (I)



(I)

wherein

R is substituted adamantyl; and

n is 0 to 3; in free form or in acid addition salt form.

The term "substituted adamantly" refers to adamantyl, i.e., 1- or 2-adamantyl, substituted by one or more, e.g., two substituents selected from alkyl, $-OR_1$ or $-NR_2R_3$, where R_1, R_2 and R_3 are independently hydrogen, alkyl, (C_1-C_8alkanoyl), carbamyl, or $-CO-NR_4R_5$, where R_4 and R_5 are independently alkyl, unsubstituted or substituted aryl and where one of R_4 and R_5 additionally is hydrogen or R_4 and R_5 together represent C_2-C_7alkylene.

The term "aryl" preferably represents phenyl. Substituted phenyl preferably is phenyl substituted by one or more, e.g., two, substitutents selected from, e.g., alkyl, alkoxy, halogen and trifluoromethyl.

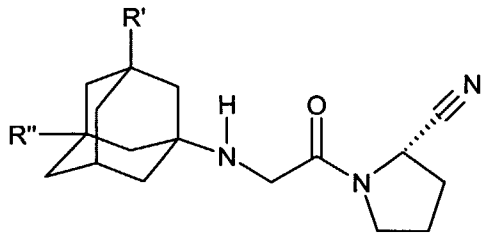
The term "alkoxy" refers to alkyl-O-.

The term "halogen" or "halo" refers to fluorine, chlorine, bromine and iodine.

The term "alkylene" refers to a straight chain bridge of 2 to 7 carbon atoms, preferably of 3 to 6 carbon atoms, most preferably 5 carbon atoms.

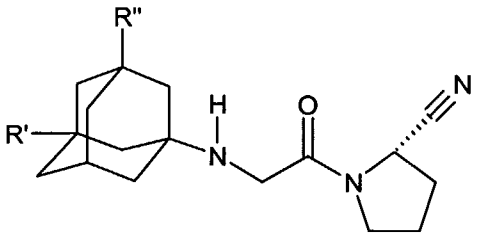
A preferred group of compounds of the invention is the compounds of formula (I), wherein the substituent on the adamantyl is bonded on a bridgehead or a methylene adjacent to a bridgehead. Compounds of formula (I), wherein the glycyl-2-cyanopyrrolidine moiety is bonded to a bridgehead, the R' substituent on the adamantyl is preferably 3-hydroxy. Compounds of formula (I), wherein the glycyl-2-cyanopyrrolidine moiety is bonded at a methylene adjacent to a bridgehead, the R' substituent on the adamantyl is preferably 5-hydroxy.

The present invention especially relates to a compound of formula (IA) or (IB)



(IA)

or



(IB)

wherein

R' represents hydroxy, C_1-C_7alkoxy, C_1-C_8alkanoyloxy or R_5R_4N-CO-O-, where R_4 and R_5 independently are C_1-C_7alkyl or phenyl which is unsubstituted or substituted by a substitutent selected from C_1-C_7alkyl, C_1-C_7alkoxy, halogen and trifluoromethyl and where R_4 additionally is hydrogen; or R_4 and R_5 together represent C_3-C_6alkylene; and

R" represents hydrogen; or

R' and R" independently represent C_1-C_7alkyl;

in free form or in form of a pharmaceutically acceptable acid addition salt.

These DPP-IV inhibitor compounds of formula (I), (IA) or (IB) are known and described in U.S. Patent No. 6,166,063, issued December 26, 2000 and WO 01/52825. Specially disclosed is (S)-1 -{2-[5-cyanopyridin-2yl)amino]ethyl-aminoacetyl)-2-cyano- pyrrolidine or (S)-1 -[(3-hydroxy-1 adamantyl)amino]acetyl-2-cyano-pyrrolidine (LAF237). They can exist in free form or in acid addition salt form. Pharmaceutically acceptable, i.e., non-toxic and physiologically acceptable, salts are preferred, although other salts are also useful, e.g., in isolating or purifying the compounds of this invention. Although the preferred acid addition salts are the hydrochlorides, salts of methanesulfonic, sulfuric, phosphoric, citric, lactic and acetic acid may also be utilized.

Preferred DPP-IV inhibitors are those described by Mona Patel and col. (Expert Opinion Investig Drugs. 2003 Apr;12(4):623-33) on the paragraph 5, especially P32/98, K-364, FE-

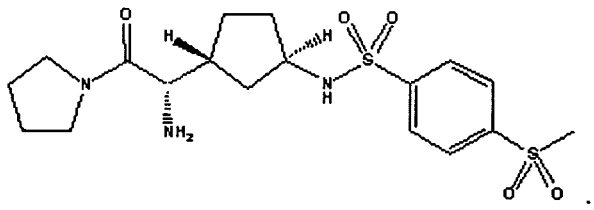
999011, BDPX, NVP-DDP-728 and others, which publication is hereby incorporated by reference especially the described DPP-IV inhibitors.

FE-999011 is described in the patent application WO 95/15309 page 14, as compound No. 18.

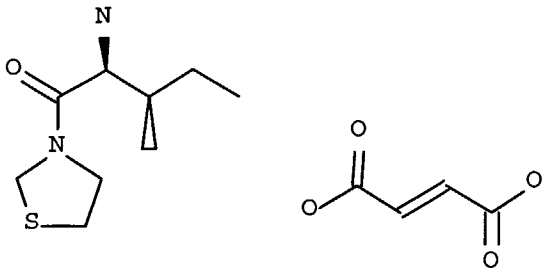
Another preferred inhibitor is the compound BMS-477118 disclosed in U.S. Patent No. 6,395,767 (compound of example 60) also known as is (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.1^{3,7}]dec-1-yl)-1-oxoethyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile, benzoate (1:1) as depicted in Formula M of the patent application WO 2004/052850 on page 2, and the corresponding free base, (IS,3S,5S)-2-[(2S)-2-amino-2- (3-hydroxy-tricyclo[3.3.1.1^{3,7}]dec-1-yl)-1-oxoethyl]-2-azabicyclo-[3.1.0]hexane-3-carbonitrile (M') and its monohydrate (M") as depicted in Formula M of the patent application WO 2004/052850 on page 3.

Another preferred inhibitor is the compound GSK23A disclosed in WO 03/002531 (example 9) also known as (2S,4S)- 1- ((2R)-2-Amino-3-[(4-methoxybenzyl)sulfonyl]-3-methylbutanoyl)-4-fluoropyrrolidine-2-carbonitrile hydrochloride.

Other very preferred DPP-IV inhibitors of the invention are described in the International patent application WO 02/076450 (especially the examples 1 to 128) and by Wallace T. Ashton (Bioorganic & Medicinal Chemistry Letters 14 (2004) 859-863) especially the compound 1 and the compounds listed in the tables 1 and 2. The preferred compound is the compound 21e (table 1) of formula



P32/98 or P3298 (CAS number: 251572-86-8) also known as 3-[(2S,3S)-2-amino-3-methyl-1-oxopentyl]thiazolidine can be used as 3-[(2S,3S)-2-amino-3-methyl-1-oxopentyl]thiazolidine and (2E)-2-butenedioate (2:1) mixture such as shown below

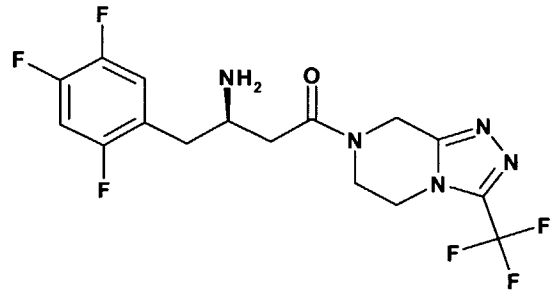


and is described in WO 99/61431 in the name of Probiodrug and also the compound P 93/01.

Other preferred DPP-IV inhibitors are the compounds disclosed in the patent application WO 02/083128 such as in the claims 1 to 5. Most preferred DPP-IV inhibitors are the compounds specifically described by the examples 1 to 13 and the claims 6 to 10.

Other preferred DPP-IV inhibitors are described in the patent applications WO 2004/037169 especially those described in the examples 1 to 48 and WO 02/062764 especially the described examples 1 to 293, even preferred are the compounds 3-(aminomethyl)-2-isobuthyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinecarboxamide and 2-{[3-(aminomethyl)-2-isobuthyl-4-phenyl-1-oxo-1,2-dihydro-6-isoquinolyl]oxy}acetamide described on page 7 and also in the patent application WO2004/024184 especially in the reference examples 1 to 4.

Other preferred DPP-IV inhibitors are described in the patent application WO 03/004498 especially examples 1 to 33 and most preferably the compound of the formula



MK-0431

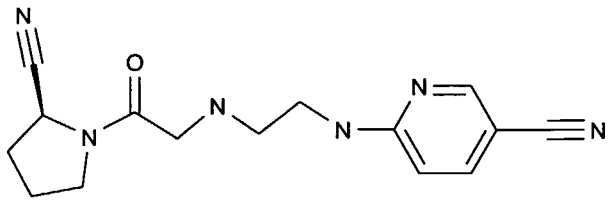
described by the example 7 and also known as MK-0431.

Preferred DPP-IV inhibitors are also described in the patent application WO 2004/037181 especially examples 1 to 33, most preferably the compounds described in the claims 3 to 5.

Preferred DPP-IV inhibitors are N-substituted adamantyl-amino- acetyl-2-cyano pyrrolidines, N (substituted glycyl)-4-cyano pyrrolidines, N- (N'-substituted glycyl)-2-cyanopyrrolidines, N-aminoacyl thiazolidines, N-aminoacyl pyrrolidines, L-allo-isoleucyl thiazolidine, L-threo-

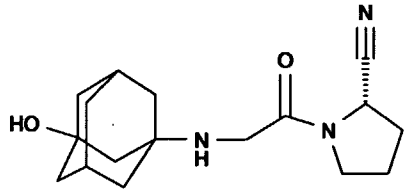
isoleucyl pyrrolidine, and L-allo-isoleucyl pyrrolidine, 1-[2-[(5-cyanopyridin-2-yl) amino] ethylamino] acetyl-2-cyano- (S)-pyrrolidine and pharmaceutical salts thereof.

Especially preferred are 1-{2-[(5-cyanopyridin-2-yl) amino] ethylamino} acetyl-2 (S)- cyano-pyrrolidine dihydrochloride (DPP728), of formula



especially the dihydrochloride thereof,

and (S)-1-[(3-hydroxy-1-adamantyl)amino]acetyl-2-cyano-pyrrolidine (LAF237) of formula



,

and L-threo-isoleucyl thiazolidine (compound code according to Probiodrug: P32/98 as described above), MK-0431, GSK23A, BMS-477118, 3-(aminomethyl)-2-isobuthyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinecarboxamide and 2-{[3-(aminomethyl)-2-isobuthyl-4-phenyl-1-oxo-1,2-dihydro-6-isoquinolyl]oxy}acetamide and optionally in any case pharmaceutical salts thereof.

DPP728 and LAF237 are the very preferred compounds and are specifically disclosed in Example 3 of WO 98/19998 and Example 1 of WO 00/34241, respectively. The DPP-IV inhibitor P32/98 (see above) is specifically described in Diabetes 1998, 47, 1253-1258. DPP728 and LAF237 can be formulated as described on page 20 of WO 98/19998 or in WO 00/34241. The preferred formulations for the administration of LAF237 are described in the US provisional application No. 60/604274.

Especially preferred are orally active DPP-IV inhibitors.

In each case in particular in the compound claims and the final products of the working examples, the subject matter of the final products, the pharmaceutical preparations and the claims are hereby incorporated into the present application by reference to the herein mentioned publications or patent applications.

The DPP-IV inhibitor compounds e.g. those of formula (I), and their corresponding pharmaceutically acceptable acid addition salts, may be combined with one or more pharmaceutically acceptable carriers and, optionally, one or more other conventional pharmaceutical adjuvants and administered enterally, e.g., orally, in the form of tablets, capsules, caplets, etc. or parenterally, e.g., intravenously, in the form of sterile injectable solutions or suspensions. The enteral and parenteral compositions may be prepared by conventional means.

The DPP-IV inhibitor compounds e.g. those of formula (I), and their corresponding pharmaceutically acceptable acid addition salts, may be formulated into enteral and parenteral pharmaceutical compositions containing an amount of the active substance that is effective for treating conditions mediated by DPP-IV inhibition, such compositions in unit dosage form and such compositions comprising a pharmaceutically acceptable carrier.

The DPP-IV inhibitor compounds e.g. those of formula (I), including those of each of the sub-scopes thereof and each of the examples, may be administered in enantiomerically pure form, e.g., >98%, preferably >99%; or together with the R enantiomer, e.g., in racemic form. The above dosage ranges are based on the compounds of formula (I), excluding the amount of the R enantiomer.

In view of their ability to inhibit DPP-IV, the DPP-IV inhibitor compounds e.g. those of formula (I), and their corresponding pharmaceutically acceptable acid addition salts, are useful in treating conditions mediated by DPP-IV inhibition. Based on the above and findings in the literature, it is expected that the compounds disclosed herein are useful in the treatment of conditions, such as non-insulin-dependent diabetes mellitus, arthritis, obesity, allograft transplantation and calcitonin-osteoporosis. In addition, based on the roles of glucagon-like peptides, such as GLP-1 and GLP-2, and their association with DPP-IV inhibition, it is expected that the compounds disclosed herein are useful for example, to produce a sedative or anxiolytic effect, or to attenuate post-surgical catabolic changes and hormonal responses to stress, or to reduce mortality and morbidity after myocardial infarction, or in the treatment of conditions related to the above effects which may be mediated by GLP-1 and/or GLP-2 levels.

More specifically, e.g., the DPP-IV inhibitor compounds e.g. those of formula (I), and their corresponding pharmaceutically acceptable acid addition salts, improve early insulin response to an oral glucose challenge and, therefore, are useful in treating non-insulin-dependent diabetes mellitus.

The DPP-IV inhibitor compounds especially compounds of formula I, IA or IB, useful in this invention are hygroscopic, presents stability problems, and are not inherently compressible. Consequently, there is a need to provide a free-flowing and cohesive composition capable of being directly compressed into strong tablets with an acceptable *in vitro* dissolution profile. Tablets may be defined as solid dosage pharmaceutical forms containing drug substances with or without suitable fillers. They are produced by compression or compaction of a formulation containing the active ingredient and certain excipients selected to aid in the processing and to improve the properties of the product. Tablets may be coated or uncoated and are made from powdered, crystalline materials. They may include various diluents, binders, disintegrants, lubricants, glidants and in many cases, colorants. Excipients used are classified according to the function they perform. For example, a glidant may be used to improve the flow of powder blend in the hopper and into the tablet die.

There has been widespread use of tablets since the latter part of the 19th century and the majority of pharmaceutical dosage forms are marketed as tablets. Major reasons of tablet popularity as a dosage form are simplicity, low cost and the speed of production. Other reasons include stability of drug product, convenience in packaging, shipping and dispensing. To the patient or consumer, tablets offer convenience of administration, ease of accurate dosage, compactness, portability, blandness of taste, ease of administration and elegant distinctive appearance.

Tablets may be plain, film or sugar coated bisected, embossed, layered or sustained-release. They can be made in a variety of sizes, shapes and colors. Tablets may be swallowed, chewed or dissolved in the buccal cavity or beneath the tongue. They may be dissolved in water for local or topical application. Sterile tablets are normally used for parenteral solutions and for implantation beneath the skin.

In addition to the active or therapeutic ingredients, tablets may contain a number of inert materials known as excipients. They may be classified according to the role they play in the final tablet. The primary composition includes a filler, binder, lubricant and glidant. Other excipients which give physical characteristics to the finished tablet are coloring agents, and flavors in the case of chewable tablets. Without excipients most drugs and pharmaceutical ingredients cannot be directly-compressed into tablets. This is primarily due to the poor flow and cohesive properties of most drugs. Typically, excipients are added to a formulation to impart good flow and compression characteristics to the material being

compressed. Such properties are imparted to these excipients through pretreatment steps, such as wet granulation, slugging, spray drying spheronization or crystallization.

Lubricants are typically added to prevent the tableting materials from sticking to punches, minimize friction during tablet compression, and allow for removal of the compressed tablet from the die. Such lubricants are commonly included in the final tablet mix in amounts usually less than 1% by weight.

In addition, tablets often contain diluents which are added to increase the bulk weight of the blend resulting in a practical size for compression. This is often necessary where the dose of the drug is relatively small.

Another commonly used class of excipients in tablets is binders. Binders are agents, which impart cohesive qualities to the powdered material. Commonly used binders include starch, and sugars, such as sucrose, glucose, dextrose and lactose.

Disintegrants are often included to ensure that the tablet has an acceptable rate of disintegration. Typical disintegrants include starch derivatives and salts of carboxymethylcellulose.

Other desirable characteristics of excipients include the following:

- High-compressibility to allow strong tablets to be made at low compression forces;
- Good flow properties that can improve the flow of other excipients in the formula; and
- Cohesiveness (to prevent tablet from crumbling during processing, shipping and handling).

There are three commercially important processes for making compressed tablets: wet granulation, direct compression and dry granulation (slugging or roller compaction). The method of preparation and type of excipients are selected to give the tablet formulation the desired physical characteristics that allow for the rapid compression of the tablets. After compression, the tablets must have a number of additional attributes, such as appearance, hardness, disintegrating ability and an acceptable dissolution profile. Choice of fillers and other excipients will depend on the chemical and physical properties of the drug, behavior of the mixture during processing and the properties of the final tablets. Preformulation studies are done to determine the chemical and physical compatibility of the active component with proposed excipients.

The properties of the drug, its dosage forms and the economics of the operation will determine selection of the best process for tableting. Generally, both wet granulation and direct compression are used in developing a tablet.

The dry granulation method may be used where one of the constituents, either the drug or the diluent, has sufficient cohesive properties to be tabletted. The method consists of blending, slugging the ingredients, dry screening, lubrication and compression.

The wet granulation method is used to convert a powder mixture into granules having suitable flow and cohesive properties for tableting. The procedure consists of mixing the powders in a suitable blender followed by adding the granulating solution under shear to the mixed powders to obtain a granulation. The damp mass is then screened through a suitable screen and dried by tray drying or fluidized bed drying. Alternately, the wet mass may be dried and passed through a mill. The overall process includes weighing, dry powder blending, wet granulating, drying, milling, blending lubrication and compression.

In general, powders do not have sufficient adhesive or cohesive properties to form hard, strong granules. A binder is usually required to bond the powder particles together due to the poor cohesive properties of most powders. Heat and moisture sensitive drugs cannot usually be manufactured using wet granulation. The large number of processing steps and processing time are problems due to high level manufacturing costs. Wet granulation has also been known to reduce the compressibility of some pharmaceutical excipients, such as microcrystalline cellulose.

Direct compression is regarded as a relatively quick process where the powdered materials are compressed directly without changing the physical and chemical properties of the drug. The active ingredient(s), direct compression excipients and other auxiliary substances, such as a glidant and lubricant are blended in a twin shell blender or similar low shear apparatus before being compressed into tablets. This type of mixing was believed to be essential in order to prepare "pharmaceutically acceptable" dosage forms. Some pharmaceutical scientists believe that the manner in which a lubricant is added to a formulation must be carefully controlled. Accordingly, lubricants are usually added to a granulation by gentle mixing. It is also believed that prolonged blending of a lubricant with a granulation can materially affect hardness and disintegration time for the resulting tablets. Excessive blending of lubricants with the granulate ingredients can cause water proofing of the granule and reduces tablet hardness or strength of the compressed tablet. For these

reasons, high-shear mixing conditions have not been used to prepare direct compression dosage forms.

The advantages of direct compression include uniformity of blend, few manufacturing steps involved, i.e., the overall process involves weighing of powders, blending and compression, hence less cost; elimination of heat and moisture, prime particle dissociation and physical stability.

Pharmaceutical manufacturers would prefer to use direct compression techniques over wet or dry granulation methods because of quick processing time and cost advantages. However, direct compression is usually limited to those situations where the drug or active ingredient has physical characteristics required to form pharmaceutically acceptable tablets. However, one or more excipients must often be combined with the active ingredient before the direct-compression method can be used since many ingredients do not have the necessary properties. Since each excipient added to the formulation increases the tablet size of the final product, manufacturers are often limited to using the direct-compression method in formulations containing a low dose of the active ingredient per compressed tablet.

A solid dosage form containing a high-dose drug, i.e., the drug itself comprises a substantial portion of the total compressed tablet weight, could only be directly compressed if the drug itself has sufficient physical characteristics, e.g., cohesiveness, for the ingredients to be directly compressed.

For an example, the DPP-IV inhibitor e.g. those of formula (I) is considered a high-dose drug. Most tablet formulations include a range of 70-85% by weight of DPP-IV inhibitor per tablet. This high-dose drug, combined with its rather poor physical characteristics for direct compression, has not permitted direct compression as a method to prepare the final tablet. In addition, the active ingredients have poor stability in presence of water, another factor militating against the use of the wet granulation method.

Another limitation of direct compression as a method of tablet manufacturing is the potential size of the compressed tablets. If the amount of active ingredient is high, a pharmaceutical formulator may choose to wet granulate the active ingredient with other excipients to attain an acceptable sized tablet with the desired amount of active ingredient. The amount of filler, binder or other excipients needed in wet granulation is less than that required for direct compression since the process of wet granulation contributes toward the desired physical properties of the tablet.

Hydroxypropyl methylcellulose has been utilized in the pharmaceutical industry as a direct compression excipient for solid dose forms. Hydroxypropyl methylcellulose is a processed cellulose and controls drug release from solid dosage forms.

Despite the advantages of the direct compression, such as reduced processing time and cost, wet granulation is widely-used in the industry to prepare solid dosage forms. Wet granulation is often preferred over direct compression because wet granulation has a greater chance of overcoming any problems associated with the physical characteristics of various ingredients in the formulation. This provides material which has the required flow and cohesive properties necessary to obtain an acceptable solid dosage form.

The popularity of wet granulation compared to direct compression is based on at least three advantages. First, wet granulation provides the material to be compressed with better wetting properties, particularly in the case of hydrophobic drug substances. The addition of hydrophilic excipients makes the surface of the hydrophobic drug more hydrophilic, reducing disintegration and dissolution problems. Second, the content uniformity of the solid dosage form is generally improved with wet granulation because all of the granules usually contain the same amount of drug. Lastly, the segregation of drug(s) from excipients is avoided.

Segregation could be a potential problem with direct compression. The size and shape of particles comprising the granulate to be compressed are optimized through the wet granulation process. This is because when a dry solid is wet granulated the binder "glues" particles together, so that they agglomerate into spherical granules.

In spite of the advantages afforded by wet granulation in general, due to the instability of the compounds in the presence of water, it is desirable to directly compress tablets containing high-dose DPP-IV inhibitor, e.g. as that defined in formula (I). There is a need in the industry for techniques and pharmaceutical excipients which will allow manufacturers to prepare high-dose DPP-IV inhibitor tablets by direct compression.

It is an object of the invention to provide a DPP-IV inhibitor formulation in the form of a free-flowing, cohesive tableting powder, capable of being directly compressed into a tablet.

It is a further object of the invention to provide a direct compressed DPP-IV inhibitor tablet in unit dosage form having an acceptable dissolution profile, as well as acceptable degrees of hardness and resistance to chipping, as well as a short disintegration time.

It is a further object of the invention to provide a process for preparing a compressed DPP-IV inhibitor tablet by direct compression in unit dosage form.

The present invention provides a direct tableting, free-flowing particulate DPP-IV inhibitor formulation in the form of a tableting powder, capable of being directly compressed into a tablet having adequate hardness, rapid disintegration time and an acceptable dissolution pattern.

In addition to the active ingredient, the tableting powder contains a number of inert materials known as excipients. They may be classified according to the role they play in the final tablet. The primary composition includes fillers, binders or diluents, lubricants, disintegrants and glidants. Other excipients which give physical characteristics to the finished tablet are coloring agents, and flavors in the case of chewable tablets. Typically, excipients are added to a formulation to impart good flow and compression characteristics to the material being compressed.

The preferred formulation of this invention comprises the following: the active ingredient which is the DPP-IV inhibitor compound, the binders or diluents which are microcrystalline cellulose and lactose, the disintegrant which is sodium starch glycolate and the lubricant which is magnesium stearate.

One, two, three or more diluents can be selected. Examples of pharmaceutically acceptable fillers and pharmaceutically acceptable diluents include, but are not limited to, confectioner's sugar, compressible sugar, dextrates, dextrin, dextrose, lactose, mannitol, microcrystalline cellulose, powdered cellulose, sorbitol, sucrose and talc. The filler and/or diluent, e.g., may be present in an amount from about 15% to about 40% by weight of the composition. The preferred diluents include microcrystalline cellulose which is manufactured by the controlled hydrolysis of alpha-cellulose, obtained as a pulp from fibrous plant materials, with dilute mineral acid solutions. Following hydrolysis, the hydrocellulose is purified by filtration and the aqueous slurry is spray dried to form dry, porous particles of a broad size distribution. Suitable microcrystalline cellulose will have an average particle size of from about 20 nm to about 200 nm. Microcrystalline cellulose is available from several suppliers. Suitable microcrystalline cellulose includes Avicel PH 101, Avicel PH 102, Avicel PH 103, Avicel PH 105 and Avicel PH 200, manufactured by FMC Corporation. Particularly preferred in the practice of this invention is Avicel PH 102, which has the smallest surface area and pore structure. Preferably the microcrystalline cellulose is present in a tablet formulation in an amount of from about 25% to about 70% by weight. Another preferred range of this material is from about 30% to about 35% by weight; yet another preferred range of from about 30% to about 32% by weight.

Another diluent is lactose. Preferably, the lactose is ground to have an average particle size of between about 50 μm and about 500 μm prior to formulating. The lactose is present in the tablet formulation in an amount of from about 5% to about 40% by weight, and can be from about 18% to about 35% by weight, and most preferred, can be from about 20% to about 25% by weight.

One, two, three or more disintegrants can be selected. Examples of pharmaceutically acceptable disintegrants include, but are not limited to, starches; clays; celluloses; alginates; gums; cross-linked polymers, e.g., cross-linked polyvinyl pyrrolidone, cross-linked calcium carboxymethylcellulose and cross-linked sodium carboxymethylcellulose; soy polysaccharides; and guar gum. The disintegrant, e.g., may be present in an amount from about 2% to about 20%, e.g., from about 5% to about 10%, e.g., about 7% about by weight of the composition. A disintegrant is also an optional but useful component of the tablet formulation. Disintegrants are included to ensure that the tablet has an acceptable rate of disintegration. Typical disintegrants include starch derivatives and salts of carboxymethylcellulose. Sodium starch glycolate is the preferred disintegrant for this formulation. Preferably the disintegrant is present in the tablet formulation in an amount of from about 0% to about 10% by weight, and can be from about 1% to about 4% by weight, and most preferred, can be from about 1.5% to about 2.5% by weight.

One, two, three or more lubricants can be selected. Examples of pharmaceutically acceptable lubricants and pharmaceutically acceptable glidants include, but are not limited to, colloidal silica, magnesium trisilicate, starches, talc, tribasic calcium phosphate, magnesium stearate, aluminum stearate, calcium stearate, magnesium carbonate, magnesium oxide, polyethylene glycol, powdered cellulose and microcrystalline cellulose. The lubricant, e.g., may be present in an amount from about 0.1% to about 5% by weight of the composition; whereas, the glidant, e.g., may be present in an amount from about 0.1% to about 10% by weight. Lubricants are typically added to prevent the tableting materials from sticking to punches, minimize friction during tablet compression and allow for removal of the compressed tablet from the die. Such lubricants are commonly included in the final tablet mix in amounts usually less than 1% by weight. The lubricant component may be hydrophobic or hydrophilic. Examples of such lubricants include stearic acid, talc and magnesium stearate. Magnesium stearate reduces the friction between the die wall and tablet mix during the compression and ejection of the tablets. It helps prevent adhesion of tablets to the punches and dies. Magnesium stearate also aids in the flow of the powder in the hopper and into the die. It has a particle size range of 450-550 microns and a density range of 1.00-1.80 g/mL. It is stable and does not polymerize within the tableting mix. The

preferred lubricant, magnesium stearate is also employed in the formulation. Preferably, the lubricant is present in the tablet formulation in an amount of from about 0.25% to about 6%; also preferred is a level of about 0.5% to about 4% by weight; and most preferably from about 0.1% to about 2% by weight. Other possible lubricants include talc, polyethylene glycol, silica and hardened vegetable oils. In an optional embodiment of the invention, the lubricant is not present in the formulation, but is sprayed onto the dies or the punches rather than being added directly to the formulation.

Other conventional solid fillers or carriers, such as, cornstarch, calcium phosphate, calcium sulfate, calcium stearate, magnesium stearate, stearic acid, glyceryl mono- and distearate, sorbitol, mannitol, gelatin, natural or synthetic gums, such as carboxymethyl cellulose, methyl cellulose, alginate, dextran, acacia gum, karaya gum, locust bean gum, tragacanth and the like, diluents, binders, lubricants, disintegrators, coloring and flavoring agents could optionally be employed.

Examples of pharmaceutically acceptable binders include, but are not limited to, starches; celluloses and derivatives thereof, e.g., microcrystalline cellulose, hydroxypropyl cellulose hydroxylethyl cellulose and hydroxylpropylmethyl cellulose; sucrose; dextrose; corn syrup; polysaccharides; and gelatin. The binder, e.g., may be present in an amount from about 10% to about 40% by weight of the composition.

Additional examples of useful excipients are described in the Handbook of pharmaceutical excipients, 3rd edition , Edited by A.H.Kibbe, Published by: American Pharmaceutical Association, Washington DC, ISBN: 0-917330-96-X, or Handbook of Pharmaceutical Excipients (4^{th} edition), Edited by Raymond C Rowe – Publisher: Science and Practice which are incorporated herewith by reference.

Thus, in a first embodiment, the present invention concerns a pharmaceutical composition comprising;

(a) a DPP-IV inhibitor in free form or in acid addition salt form, preferably LAF237;

(b) a pharmaceutically acceptable diluent,

wherein in the unit dosage form, the weight of DPP-IV inhibitor preferably LAF237 on a dry weight basis to tablet weight of diluent ratio is of 0.5 to 0.25, preferably 0.4 to 0.28.

Composition as described above, wherein at least one diluent is a microcrystalline cellulose and wherein in the unit dosage form, the weight of DPP-IV inhibitor preferably LAF237 on a dry weight basis to tablet weight of microcrystalline cellulose ratio is of 2 to 0.333, preferably 1 to 0.333, most preferably of 0.7 to 0.333.

Composition as described above comprising between 20 and 120 mg of LAF237 preferably between 25 and 100m of LAF237 or a pharmaceutically acceptable acid addition salt thereof.

Composition as described above wherein the diluent is selected from a microcrystalline cellulose and lactose, preferably microcrystalline cellulose and lactose are in the composition.

Composition as described above which comprises in addition;
(c) 0-20% by weight on a dry weight basis of a pharmaceutically acceptable disintegrant;
(d) 0.1-10% by weight on a dry weight basis of a pharmaceutically acceptable lubricant.

Preferably composition as described above which comprises in addition;;
(c) 1-6% by weight on a dry weight basis of a pharmaceutically acceptable disintegrant;
(d) 0.25-6% by weight on a dry weight basis of a pharmaceutically acceptable lubricant.

The above ratios have been obtained on a dry weight basis for the DPP-IV inhibitors and diluents.

The unit dosage form, is any kind of pharmaceutical dosage form such as capsules, tablets, granules, chewable tablets, etc.

In a further, embodiment, the present invention concerns a pharmaceutical composition comprising;

(a) 5-60% by weight on a dry weight basis of a DPP-IV inhibitor in free form or in acid addition salt form, preferably LAF237;
(b) 40-95% by weight on a dry weight basis of a pharmaceutically acceptable diluent;
(c) 0-20% by weight on a dry weight basis of a pharmaceutically acceptable disintegrant; and optionally
(d) 0.1-10% by weight on a dry weight basis of a pharmaceutically acceptable lubricant.

Preferably the present invention concerns a pharmaceutical composition comprising;

(a) 20-40% by weight on a dry weight basis of a DPP-IV inhibitor in free form or in acid addition salt form, preferably LAF237;
(b) 40-95% by weight on a dry weight basis of a pharmaceutically acceptable diluent;
(c) 0-10% by weight on a dry weight basis of a pharmaceutically acceptable disintegrant; and optionally
(d) 0.25-6% by weight on a dry weight basis of a pharmaceutically acceptable lubricant.

Most preferably the present invention concerns a pharmaceutical composition comprising;

(a) 20-35% by weight on a dry weight basis of a DPP-IV inhibitor in free form or in acid addition salt form, preferably LAF237;

(b) 40-95% by weight on a dry weight basis of a pharmaceutically acceptable diluent;

(c) 0-10% by weight on a dry weight basis of a pharmaceutically acceptable disintegrant; and optionally

(d) 0.25-6% by weight on a dry weight basis of a pharmaceutically acceptable lubricant.

Most preferably the present invention concerns a pharmaceutical composition comprising;

(a) 20-35% by weight on a dry weight basis of a DPP-IV inhibitor in free form or in acid addition salt form, preferably LAF237;

(b) 62-78% by weight on a dry weight basis of a pharmaceutically acceptable diluent;

(c) 0-10% by weight on a dry weight basis of a pharmaceutically acceptable disintegrant; and optionally

(d) 0.1-10% by weight on a dry weight basis of a pharmaceutically acceptable lubricant.

Most preferably the present invention concerns a pharmaceutical composition comprising;

(a) 20-35% by weight on a dry weight basis of a DPP-IV inhibitor in free form or in acid addition salt form, preferably LAF237;

(b) 62-78% by weight on a dry weight basis of a pharmaceutically acceptable diluent;

(c) 1-6% by weight on a dry weight basis of a pharmaceutically acceptable disintegrant; and optionally

(d) 0.25-6% by weight on a dry weight basis of a pharmaceutically acceptable lubricant.

Most preferably the present invention concerns a pharmaceutical composition comprising;

(a) 22-28% by weight on a dry weight basis of a DPP-IV inhibitor in free form or in acid addition salt form, preferably LAF237;

(b) 66-76% by weight on a dry weight basis of a pharmaceutically acceptable diluent;

(c) 0-6% by weight on a dry weight basis of a pharmaceutically acceptable disintegrant; and optionally

(d) 0.25-6% by weight on a dry weight basis of a pharmaceutically acceptable lubricant.

Most preferably the present invention concerns a pharmaceutical composition comprising;

(a) 22-28% by weight on a dry weight basis of a DPP-IV inhibitor in free form or in acid addition salt form, preferably LAF237;

(b) 66-76% by weight on a dry weight basis of a pharmaceutically acceptable diluent;

(c) 1-6% by weight on a dry weight basis of a pharmaceutically acceptable disintegrant; and optionally

(d) 0.25-6% by weight on a dry weight basis of a pharmaceutically acceptable lubricant.

In the present application the reference to a pharmaceutically acceptable diluent means at least one diluent, a mixture of e.g. 2 or 3 diluents is also covered.

Preferably the above described compositions comprise;

i) one or two diluents selected from microcrystalline cellulose and lactose

ii) the two diluents microcrystalline cellulose and lactose,

iii) 25-70% preferably 35-55% by weight on a dry weight basis of a pharmaceutically acceptable microcrystalline cellulose, or

iv) 25-70% preferably 35-55% by weight on a dry weight basis of a pharmaceutically acceptable microcrystalline cellulose and 5-40% preferably 18-35% of lactose.

Most preferably the above described compositions comprise one or two diluents selected from microcrystalline cellulose such as Avicel PH 102 and lactose.

Most preferably the pharmaceutical composition comprises the pharmaceutically acceptable lubricant (d).

In the present application the reference to a pharmaceutically acceptable disintegrant means at least one disintegrant, a mixture of e.g. 2 or 3 disintegrants is also covered.

In the present application the reference to a pharmaceutically acceptable lubricant means at least one lubricant, a mixture of e.g. 2 or 3 lubricants is also covered.

Preferred DPP-IV inhibitor is LAF237, preferred diluents are microcrystalline cellulose or lactose or preferably a combination of microcrystalline cellulose and lactose, preferred disintegrant is sodium starch glycolate, and preferred lubricant is magnesium stearate.

The particular components in the preferred composition are the following:

(a) 20-35% by weight on a dry weight basis of DPP-IV inhibitor e.g. LAF237;

(b) 25-70% by weight on a dry weight basis of a pharmaceutically acceptable microcrystalline cellulose;

(c) 5-40% by weight on a dry weight basis of a pharmaceutically acceptable lactose;

(d) 0-10% by weight on a dry weight basis of a pharmaceutically acceptable sodium starch glycolate;

(e) 0.25-6% by weight on a dry weight basis of magnesium stearate.

The particular components in the preferred composition are the following:

(a) 25-35% by weight on a dry weight basis of DPP-IV inhibitor e.g. LAF237;

(b) 25-70% by weight on a dry weight basis of a pharmaceutically acceptable microcrystalline cellulose;

(c) 5-40% by weight on a dry weight basis of a pharmaceutically acceptable lactose;

(d) 0-10% by weight on a dry weight basis of a pharmaceutically acceptable sodium starch glycolate;

(e) 0.25-6% by weight on a dry weight basis of magnesium stearate.

Another preferred composition is the following:

(a) from about 30% to about 32% by weight on a dry weight basis of a DPP-IV inhibitor or a DPP-IV inhibitor of formula (I);

(b) from about 40% to about 45% by weight on a dry weight basis of a pharmaceutically acceptable microcrystalline cellulose;

(c) from about 20% to about 25% by weight on a dry weight basis of a pharmaceutically acceptable lactose;

(d) from about 1.5% to about 2.5% by weight on a dry weight basis of a pharmaceutically acceptable sodium starch glycolate; and

(e) from about 0.1% to about 2% by weight on a dry weight basis of magnesium stearate.

Another preferred composition is the following:

(a) 20-35% preferably 22-28% by weight on a dry weight basis of DPP-IV inhibitor e.g. LAF237;

(b) 35-55% by weight on a dry weight basis of a pharmaceutically acceptable microcrystalline cellulose;

(c) 18-35% by weight on a dry weight basis of a pharmaceutically acceptable lactose;

(d) 1-4% by weight on a dry weight basis of a pharmaceutically acceptable sodium starch glycolate; and

(e) 0.5-4% by weight on a dry weight basis of magnesium stearate.

Still another preferred composition is the following:

(a) from about 22% to about 28% preferably 24-26% by weight on a dry weight basis of a DPP-IV inhibitor or a DPP-IV inhibitor of formula (I);

(b) from about 45% to about 50% by weight on a dry weight basis of a pharmaceutically acceptable microcrystalline cellulose;

(c) from about 20% to about 25% by weight on a dry weight basis of a pharmaceutically acceptable lactose;

(d) from about 1.5% to about 2.5% by weight on a dry weight basis of a pharmaceutically acceptable sodium starch glycolate; and

(e) from about 0.1% to about 2% by weight on a dry weight basis of magnesium stearate.

Still another preferred composition is the following:

(a) from 24-26% by weight on a dry weight basis of a DPP-IV inhibitor or a DPP-IV inhibitor of formula (I);

(b) from about 46% to about 48% by weight on a dry weight basis of a pharmaceutically acceptable microcrystalline cellulose;

(c) from about 23% to about 24.5% by weight on a dry weight basis of a pharmaceutically acceptable lactose;

(d) from about 1.5% to about 2.5% by weight on a dry weight basis of a pharmaceutically acceptable sodium starch glycolate; and

(e) from about 0.1% to about 2% by weight on a dry weight basis of magnesium stearate.

Still another preferred composition is the following:

(a) 30-35% by weight on a dry weight basis of DPP-IV inhibitor e.g. LAF237;

(b) 35-50% by weight on a dry weight basis of a pharmaceutically acceptable microcrystalline cellulose;

(c) 18-35% by weight on a dry weight basis of a pharmaceutically acceptable lactose;

(d) 1-4% by weight on a dry weight basis of a pharmaceutically acceptable sodium starch glycolate; and

(e) 0.5-4% by weight on a dry weight basis of magnesium stearate.

In a further embodiment, the present invention concerns any one of the above described compositions wherein the pharmaceutically acceptable lubricant (d) is only optionally comprised in the formulation. But preferably the pharmaceutically acceptable lubricant (d) is comprised in the composition.

Preferably for compressed tablets especially for direct compressed tablets, the above described compositions comprise between 20 and 35% most preferably between 22 and 28% by weight on a dry weight basis of a DPP-IV inhibitor especially LAF237, in free form or in acid addition salt form.

Additional conventional excipients can optionally be added to the herein described formulations such as the conventional solid fillers or carriers described hereinabove.

The above described formulations are particularly adapted for the production of pharmaceutical tablets e.g compressed tablets or preferably direct compressed tablets, caplets or capsules and provides the necessary physical characteristics, dissolution and drug release profiles as required by one of ordinary necessary physical skill in the art. Therefore in an additional embodiment, the present invention concerns the use of any of the above described formulations, for the manufacture of pharmaceutical tablets, caplets or capsules in particular for granulation, direct compression and dry granulation (slugging or roller compaction).

The above formulations are also particularly useful for the production of tablets especially compressed tablets and very preferably direct compressed tablets.

In particular the tablets obtained with the above described formulations especially when processed in the form of direct compressed tablets or the below described direct compressed tablets, have very low friability problems, very good breaking strength, improved manufacturing robustness, optimal tablet thickness to tablet weight ratios (direct compressed tablets), less water in the formulation especially directed compressed tablet, good Dispersion Disintegration time DT according to the British Pharmacopoeia 1988, good Dispersion Quality.

This present invention of direct compression of DPP-IV inhibitor involves blending and compression. The choice of grades of excipients took into consideration particle size maintained within a range that allows homogeneity of the powder mix and content uniformity

of DPP-IV inhibitor. It prevents segregation of powders in the hopper during direct compression. The advantages of using these excipients are that they impart compressibility, cohesiveness and flowability of the powder blend. In addition, the use of direct compression provides competitive unit production cost, shelf life, eliminates heat and moisture, allows for prime particle dissociation, physical stability and ensures particle size uniformity.

The described advantages of the claimed compositions are also very useful for e.g. roller compaction or wet granulation or to fill capsules.

In the development of the herein described pharmaceutical compositions, the applicant has discovered that the compressed tablets especially direct compressed tablet is particularly advantageous if;

i) the particles comprising the DPP-IV inhibitor have a particle size distribution of less than 250 μm preferably between 10 to 250 μm, and/or

ii) the water content of the tablet at less than 10% after 1 week at 25°C and 60% room humidity (RH), and/or

iii) tablet thickness to tablet weight ratios is of 0.002 to 0.06 mm/mg.

Thus, the present invention concerns a compressed pharmaceutical tablet preferably a direct compressed pharmaceutical tablet, comprising a DPP-IV inhibitor, in free form or in acid addition salt form, having physical properties that render the tableting into direct compressed pharmaceutical tablet unlikely or very difficult. Preferred DPP-IV inhibitor is LAF237.

Thus in a first embodiment (a), the present invention concerns compressed tablets preferably direct compressed pharmaceutical tablets, wherein the dispersion contains particles comprising DPP-IV inhibitor preferably LAF237, in free form or in acid addition salt form, and wherein at least 60%, preferably 80% and most preferably 90% of the particle size distribution in the tablet is less than 250 μm or preferably between 10 to 250 μm.

The present invention concerns compressed tablets preferably direct compressed pharmaceutical tablets, wherein the dispersion contains particles comprising DPP-IV inhibitor preferably LAF237, in free form or in acid addition salt form, and wherein at least 60%, preferably 80% and most preferably 90% of the particle size distribution in the tablet is greater than 10 μm.

The term "wherein at least 60%, preferably 80% and most preferably 90%" means at least 60%, preferably at least 80% and most preferably at least 90%.

The term "wherein at least at least 25%, preferably 35% and most preferably 45%" means at least 25%, preferably at least 35% and most preferably at least 45%.

In particular the present invention concerns compressed tablets preferably direct compressed pharmaceutical tablets, wherein the dispersion contains particles comprising DPP-IV inhibitor preferably LAF237, in free form or in acid addition salt form, and wherein at least 25%, preferably 35% and most preferably 45% of the particle size distribution in the tablet is between 50 to 150 μm.

In a second embodiment (b), this invention concerns a compressed tablet, preferably a direct compressed pharmaceutical tablet wherein the dispersion contains particles comprising DPP-IV inhibitor preferably LAF237, in free form or in acid addition salt form, and wherein tablet thickness to tablet weight ratios is of 0.002 to 0.06 mm/mg preferably of 0.01 to 0.03 mm/mg.

The combination of the above first and second embodiments (a) and (b), provide compressed tablets preferably direct compressed tablets with good compaction characteristics.

Thus this invention concerns also a compressed tablet, preferably a direct compressed tablet wherein the dispersion contains particles comprising DPP-IV inhibitor preferably LAF237, in free form or in acid addition salt form, and wherein;

i) at least 60%, preferably 80% and most preferably 90% of the particle size distribution in the tablet is less than 250 μm or preferably between 10 to 250 μm, and

ii) tablet thickness to tablet weight ratios is of 0.002 to 0.06 mm/mg or of 0.01 to 0.03 mm/mg

preferably wherein;

i) at least 25 %, preferably 35% and most preferably 45% of the particle size distribution in the tablet is between 50 to 150 μm, and

ii) tablet thickness to tablet weight ratios is of 0.002 to 0.06 mm/mg or of 0.01 to 0.03 mm/mg.

In a third embodiment, this invention concerns a compressed tablet preferably a direct compressed pharmaceutical tablet wherein the dispersion contains particles comprising DPP-IV inhibitor preferably LAF237, in free form or in acid addition salt form, and wherein;

i) at least 60%, preferably 80% and most preferably 90% of the particle size distribution in the tablet is less than 250 μm preferably between 10 to 250 μm,

ii) the water content of the tablet is less than 10% after 1 week at 25°C and 60% RH, and

iii) tablet thickness to tablet weight ratios is of 0.002 to 0.06 mm/mg.

Preferably this invention concerns a compressed tablet most preferably a direct compressed tablet wherein the dispersion contains particles comprising DPP-IV inhibitor preferably LAF237, in free form or in acid addition salt form, and wherein;

i) at least 25%, preferably 35% and most preferably 45% of the particle size distribution in the tablet is between 50 to 150 μm,

ii) the water content of the tablet is less than 10% after 1 week at 25°C and 60% RH, and

iii) tablet thickness to tablet weight ratios is of 0.002 to 0.06 mm/mg.

Preferably this invention concerns a compressed tablet most preferably a direct compressed tablet wherein the dispersion contains particles comprising DPP-IV inhibitor preferably LAF237, in free form or in acid addition salt form, and wherein;

i) at least 25%, preferably 35% and most preferably 45% of the particle size distribution in the tablet is between 50 to 150 μm,

ii) the water content of the tablet is less than 5% after 1 week at 25°C and 60% RH, and

iii) tablet thickness to tablet weight ratios is of 0.002 to 0.06 mm/mg.

Preferably this invention concerns a compressed tablet, most preferably a direct compressed tablet wherein the dispersion contains particles comprising DPP-IV inhibitor preferably LAF237, in free form or in acid addition salt form, and wherein;

i) at least 25%, preferably 35% and most preferably 45% of the particle size distribution in the tablet is between 50 to 150 μm,

ii) the water content of the tablet is less than 5% after 1 week at 25°C and 60% RH, and

iii) tablet thickness to tablet weight ratios is of 0.01 to 0.03 mm/mg

In a very preferred aspect, the above described three embodiments i.e. compressed tablets and direct compressed tablets contain the herein described compositions such as a pharmaceutical composition comprising;

(a) 20-35% by weight on a dry weight basis of a DPP-IV inhibitor in free form or in acid addition salt form, preferably LAF237;

(b) 40-95% by weight on a dry weight basis of a pharmaceutically acceptable diluent;

(c) 0-10% by weight on a dry weight basis of a pharmaceutically acceptable disintegrant;

(d) 0.25-6% by weight on a dry weight basis of a pharmaceutically acceptable lubricant.

Preferably the DPPIV particles especially the LAF237 particles comprise more than 70% of DPPIV inhibitor, most preferably more than 90% or 95% and even more preferably more than 98% of DPPIV inhibitor.

Preferably the LAF237 particles comprise more than 70% of LAF237, most preferably more than 90% or 95% and even more preferably more than 98% of LAF237.

It has been discovered that the selected particle size distribution of DPPIV inhibitor especially LAF237 were particularly important to provide the best compaction of the tablets.

In an additional preferred embodiment, the particle size distribution of the selected excipients (b), (c) and/or (d) is similar to the particle size distribution of the DPP-IV inhibitor particles preferably LAF237 particles.

The term "similar", means that the particle size distribution of the excipient in the tablet is between 5 and 400μm, or between 10 and 300 μm, preferably between 10 to 250 μm.

The preferred excipients with an adapted particle size distribution can be picked from e.g. Handbook of Pharmaceutical Excipients (4th edition), Edited by Raymond C Rowe – Publisher: Science and Practice.

Particle size of drug, e.g. LAF237 particles size, is controlled by crystallisazion, drying and/or milling/sieving (non limiting examples are described below). Particle size can also be comminuted using roller compaction and milling/sieving. Producing the right particle size is well known and described in the art such as in "Pharmaceutical dosage forms: volume 2, 2nd edition, Ed.: H.A.Lieberman, L.Lachman, J.B.Schwartz (Chapter 3: SIZE REDUCTION)".

Multiple particle sizes have been studied and it has been discovered that the herein described specific size range provides unexpected good results for direct compaction.

PARTICLE SIZE DISTRIBUTION ESTIMATION BY ANALYTICAL SIEVING: Particle size distribution is measured using Sieve analysis, Photon Correlation Spectroscopy or laser diffraction (international standart ISO 13320-1), or electronic sensing zone, light obstruction, sedimentation or microscopy which are procedures well known by the person skilled in the art. Sieving is one of the oldest methods of classifying powders by particle size distribution. Such methods are well known and described in the art such as in any analytical chemistry text book or by the United State Pharmacopeia's (USP) publication USP-NF (2004 - Chapter 786 - (The United States Pharmacopeial Convention, Inc., Rockville, MD)) which describes the US Food and Drug Administration (FDA) enforceable standards. The used techniques are e.g. described in Pharmaceutical dosage forms: volume 2, 2nd edition, Ed.: H.A.Lieberman, L.Lachman, J.B.Schwartz is a good example. It also mentions (page 187) additional methods: Electronic sensing zone, light obstruction, air permeation, sedimentation in gas or liquid.

In an air jet sieve measurement of particle size, air is drawn upwards, through a sieve, from a rotating slit so that material on the sieve is fluidised. At the same time a negative pressure is applied to the bottom of the sieve which removes fine particles to a collecting device. Size analyses and determination of average particle size are performed by removal of particles from the fine end of the size distribution by using single sieves consecutively. See also "Particle Size Measurement", 5th Ed. , p 178, vol. 1; T. Allen, Chapman & Hall, London, UK, 1997, for more details on this. For a person skilled in the art, the size measurement as such is thus of conventional character.

Water content of the tablet can be measured using Loss on drying method or Karl-Fischer method which are well known methods to the person skilled in the art (e.g. water content can be measured by loss on drying by thermogrametry). Such methods are well known and described in the art such as in any analytical chemistry text book (J.A. Dean, Analytical Chemistry Handbook, Section 19, McGraw-Hill, New York, 1995) or by the United State Pharmacopeia's (USP) publication USP-NF (2004) which describes the US Food and Drug Administration (FDA) enforceable standards ((2004 – USP - Chapter 921).

Tablet thickness is measurable using a ruler, vernier caliper, a screw gauge or any electronic method to measure dimensions. We take the tablet thickness in mm and divide by tablet weight in mg to get the ratio. Such methods are well known and described in the art such as in any analytical chemistry text book or by the United State Pharmacopeia's (USP) publication USP-NF (2004) which describes the US Food and Drug Administration (FDA) enforceable standards.

This invention provides in particular a compressed tablet or direct compressed tablet which is capable of dispersing in water within a period of 5 to 15 minutes to provide a dispersion which is capable of passing through a sieve screen with a mesh aperture of 710 μm in accordance with the herein defined British Pharmacopoeia test for dispersible tablets.

A tablet according to the invention, as well as being quickly dispersible in water, has the added advantage that it meets the British Pharmacopoeia (B.P.) test for dispersible tablets in respect of dispersion times and dispersion quality (i.e. passage through a 710 μ m sieve).

Preferably the dispersion time of a tablet according to the invention is less than 15 minutes, more preferably less than 12 minutes and most preferably less than 10 minute.

A further advantage of the tablets according to invention is that because a relatively fine dispersion is formed the tablet will have a lower dissolution time and thus the drug may be absorbed into the blood stream much faster. Furthermore the fast dispersion times and relatively fine dispersions obtained with tablets according to the invention are also advantageous for swallowable tablets. Thus tablets according to the invention can be presented both for dispersion in water and also for directly swallowing. Those tablets according to the invention that are intended for swelling are preferably film-coated to aid swallowing.

In a further embodiment the present invention concerns a compressed tablet with improved dissolution rates (dissolution of the drug), wherein the dispersion contains particles i.e. DPPIV particles especially LAF237 particles comprising DPP-IV inhibitor preferably LAF237, in free form or in acid addition salt form, wherein at least 60%, preferably 80% and most preferably 90% of the particle size distribution in the tablet is between 10 to 250 mm,

and wherein

i) between 0 and 10 minutes 85 to 99.5 % of the active ingredient is released, and

ii) between 10 and 15 minutes 90 to 99.5 % of the active ingredient is released,

preferably wherein,

i) between 0 and 10 minutes 88 to 99.5 % of the active ingredient is released, and

ii) between 10 and 15 minutes 95 to 99.5 % of the active ingredient is released,

or preferably

i) between 0 and 10 minutes 89 to 94 % of the active ingredient is released, and

ii) between 10 and 15 minutes 96 to 99 % of the active ingredient is released

The Paddle method to measure the drug dissolution rate (% of release) is used with 1000ml of 0.01N HCl. Such methods are well known and described in the art such as in any analytical chemistry text book or by the United State Pharmacopeia's (USP) publication USP-NF (2004 - Chapter 711) which describes the US Food and Drug Administration (FDA) enforceable standards.

The invention also provides a process for preparing a compressed DPP-IV inhibitor tablet in unit dosage form, wherein;

i) at least 60%, preferably 80% and most preferably 90% of the particles comprising DPP-IV inhibitor preferably LAF237, in free form or in acid addition salt form, in the tablet have a particle size distribution of between 10 to 250 μm,

ii) the water content of the tablet is less than 10% after 1 week at 25°C and 60% RH, and

iii) tablet thickness to tablet weight ratios is of 0.002 to 0.06 mm

which comprises:

(a) blending as a % by weight on a dry weight basis:

(i) 5-60% by weight on a dry weight basis of DPP-IV inhibitor e.g. LAF237; and

(ii) and at least one excipient selected from a diluent, a disintegrant and a lubricant,

to form a DPP-IV inhibitor formulation in the form of a tableting powder, capable of being directly compressed into a tablet; and

(b) compressing the formulation prepared during step (a) to form the compressed DPP-IV inhibitor tablet in unit dosage form.

Preferably the above described process comprises:

(a) blending as a % by weight on a dry weight basis:

(i) 5-60% by weight, on a dry weight basis of DPP-IV inhibitor e.g. LAF237;

(ii) 40-95% by weight on a dry weight basis of a pharmaceutically acceptable diluent;

(iii) 0-20% by weight on a dry weight basis of a pharmaceutically acceptable disintegrant; and

(iv) 0.1-10% by weight on a dry weight basis of a pharmaceutically acceptable lubricant,

to form a DPP-IV inhibitor formulation in the form of a tableting powder, capable of being directly compressed into a tablet; and

(b) compressing the formulation prepared during step (a) to form the compressed DPP-IV inhibitor tablet in unit dosage form.

Most preferably the process comprises:

(a) blending as a % by weight on a dry weight basis:

(i) 25-35% by weight on a dry weight basis of DPP-IV inhibitor e.g. LAF237;

(ii) 40-95% by weight on a dry weight basis of a pharmaceutically acceptable diluent;

(iii) 0-10% by weight on a dry weight basis of a pharmaceutically acceptable disintegrant; and

(iv) 0.25-6% by weight on a dry weight basis of a pharmaceutically acceptable lubricant,

to form a DPP-IV inhibitor formulation in the form of a tableting powder, capable of being directly compressed into a tablet; and

(b) compressing the formulation prepared during step (a) to form the compressed DPP-IV inhibitor tablet in unit dosage form.

Preferably the blended composition used in step (a) is selected from the herein described preferred formulations.

Preferred DPP-IV inhibitor is LAF237, preferred diluents are microcrystalline cellulose or lactose or preferably a combination of microcrystalline cellulose and lactose, preferred disintegrant is sodium starch glycolate, and preferred lubricant is magnesium stearate.

In a best embodiment the process comprises:

(a) blending as a % by weight on a dry weight basis:

(i) 20-35% or preferably 25-30% by weight by weight on a dry weight basis of DPP-IV inhibitor preferably LAF237, in free form or in acid addition salt form;

(ii) 25-70% by weight or preferably 35-50% by weight on a dry weight basis of a pharmaceutically acceptable microcrystalline cellulose such as Avicel PH 102;

(iii) 5-40% by weight or preferably 18-35% by weight on a dry weight basis of a pharmaceutically acceptable lactose;

(iv) 0-10% by weight or preferably 1-4% by weight on a dry weight basis of a pharmaceutically acceptable sodium starch glycolate; and

(v) 0.25- 6% by weight or preferably 0.5-4% by weight on a dry weight basis of a pharmaceutically acceptable magnesium stearate.

to form a DPP-IV inhibitor formulation in the form of a tableting powder, capable of being directly compressed into a tablet; and

(b) compressing the formulation prepared during step (a) to form the compressed DPP-IV inhibitor tablet in unit dosage form.

The invention also provides a process for preparing a compressed DPP-IV inhibitor tablet in unit dosage form which comprises:

(a) blending as a % by weight on a dry weight basis:

(i) 30-32% by weight on a dry weight basis of DPP-IV inhibitor preferably LAF237, in free form or in acid addition salt form;

(ii) 40-45% by weight on a dry weight basis of a pharmaceutically acceptable microcrystalline cellulose (Avicel PH 102);

(iii) 20-25% by weight on a dry weight basis of a pharmaceutically acceptable lactose;

(iv) 1.5-2% by weight on a dry weight basis of a pharmaceutically acceptable sodium starch glycolate; and

(v) 0.1-2% by weight on a dry weight basis of magnesium stearate,

to form a DPP-IV inhibitor formulation in the form of a tableting powder, capable of being directly compressed into a tablet; and

(b) compressing the formulation prepared during step (a) to form the compressed DPP-IV inhibitor tablet in unit dosage form.

The invention also provides a process for preparing a compressed DPP-IV inhibitor tablet in unit dosage form which comprises:

(a) blending as a % by weight on a dry weight basis:

(i) 23-28% by weight on a dry weight basis of DPP-IV inhibitor preferably LAF237, in free form or in acid addition salt form;

(ii) 45-50% by weight on a dry weight basis of a pharmaceutically acceptable microcrystalline cellulose (Avicel PH 102);

(iii) 20-25% by weight on a dry weight basis of a pharmaceutically acceptable lactose;

(iv) 1.5-2% by weight on a dry weight basis of a pharmaceutically acceptable sodium starch glycolate; and

(v) 0.1-2% by weight on a dry weight basis of magnesium stearate,

to form a DPP-IV inhibitor formulation in the form of a tableting powder, capable of being directly compressed into a tablet; and

(b) compressing the formulation prepared during step (a) to form the compressed DPP-IV inhibitor tablet in unit dosage form.

Before the compression step (b) a sieving step is preferably applied to the formulation for basic delumping i.e. to get rid of any agglomerates/cakes.

In an other embodiment, the present invention covers capsule comprising the above described pharmaceutical compositions, and preferably wherein;

i) at least 60%, preferably 80% and most preferably 90% of the particles comprising the DPP-IV inhibitor preferably LAF237, in free form or in acid addition salt form, in the capsule have a particle size distribution between 10 to 500 μm,

ii) the water content of the tablet is less than 10% after 1 week at 25°C and 60% RH.

More preferably capsule comprising the above described pharmaceutical compositions, and preferably wherein;

i) at least 60%, preferably 80% and most preferably 90% of the particles comprising the DPP-IV inhibitor preferably LAF237, in free form or in acid addition salt form, in the capsule have a particle size distribution 10 to 250 μm,

ii) the water content of the tablet is less than 5% after 1 week at 25°C and 60% RH.

The final product is prepared in the form of tablets, capsules or the like by employing conventional tableting or similar machinery.

Most preferably the DPP-IV inhibitor for the herein described formulations, compressed tablets or processes is selected from 1-{2-[(5-cyanopyridin-2-yl) amino] ethylamino} acetyl-2 (S)- cyano-pyrrolidine dihydrochloride, (S)-1-[(3-hydroxy-1-adamantyl)amino]acetyl-2-cyano-pyrrolidine, L-threo-isoleucyl thiazolidine, MK-0431, GSK23A, BMS-477118, 3-(aminomethyl)-2-isobuthyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinecarboxamide and 2-{[3-(aminomethyl)-2-isobuthyl-4-phenyl-1-oxo-1,2-dihydro-6-isoquinolyl]oxy}acetamide and optionally in any case pharmaceutical salts thereof.

Most preferably the DPP-IV inhibitor is 1-[3-hydroxy-adamant-1-ylamino)-acetyl]-pyrrolidine-2(*S*)-carbonitrile (LAF237 or vildagliptin).

In a further aspect, the present invention concerns the use of the herein described formulations, capsules, tablets, compressed tables, direct compressed tablets for the treatment of conditions, such as non-insulin-dependent diabetes mellitus, arthritis, obesity, allograft transplantation, calcitonin-osteoporosis, Heart Failure, Impaired Glucose Metabolism), IGT (Impaired Glucose Tolerance), neurodegenerative diseases such as Alzheimer's and Parkinson disease, modulating hyperlipidemia, modulating conditions associated with hyperlipidemia or for lowering VLDL, LDL and Lp(a) levels, cardiovascular or renal diseases e.g. diabetic cardiomyopathy, left or right ventricular hypertrophy, hypertrophic medial thickening in arteries and/or in large vessels, mesenteric vasculature hypertrophy, mesanglial hypertrophy, neurodegenerative disorders and cognitive disorders, to produce a sedative or anxiolytic effect, to attenuate post-surgical catabolic changes and hormonal responses to stress, to reduce mortality and morbidity after myocardial infarction, the treatment of conditions related to the above effects which may be mediated by GLP-1 and/or GLP-2 levels.

In each case in particular in the compound claims, the final products of the working examples, the subject matter of the final products, the analytical and measurement methods (e.g. USP documents) the methods to obtain the right particles size, the pharmaceutical

preparations, the excipients and the claims are hereby incorporated into the present application by reference to the herein mentioned publications or patent applications.

This invention is further illustrated by the following example:

Example 1

To prepare the 25 mg tablet size (directly compressed tablet), a batch size of 7 kg is prepared using amounts corresponding to the following per unit: 25 mg per unit of the compound 1-[3-hydroxy-adamant-1-ylamino)-acetyl]-pyrrolidine-2(*S*)-carbonitrile is mixed with 35.1 mg of microcrystalline cellulose, 17.5 mg anhydrous lactose and 1.6 mg sodium starch glycolate. The ingredients are pre-blended together in a commercial bin blender, then sieved through a 500 µm or 850 µm screen. The mix is blended again in the bin blender, then the necessary amount of the magnesium stearate to yield the 0.8 mg magnesium stearate per 25 mg tablet size, is added. Blending in each step is conducted at about 150-450 rotations, to ensure homogeneity of the mixture. Following blending again in the bin blender, the mix can be tabletted in a conventional tableting machine. The individual tablet weight for the 25 mg tablet is 80 mg. Tablets having 50 mg active ingredient weigh 160 mg, and 100 mg active ingredient tablets weigh 320 mg, respectively. The blend is a powder which has excellent compressibility into the desired tablet size.

Example 2

The same process as described above in example 1, can be applied to produce the below described preferred 50 mg tablet (directly compressed).

Components	**Composition per unit (mg)**	**Quantity per batch (kg)**
LAF 237 drug substance	50.00	65.0
Microcrystalline cellulose, PH102 (Ph.Eur., NF)	95.68	124.38
Lactose anhydrous DT (USP, Ph.Eur.)	47.82	62.17
Sodium starch glycolate (USP, Ph.Eur.)	4.00	5.2
Magnesium stearate (Ph.Eur, NF)	2.50	3.25
Total weight, per tablet or per batch	200.0	260.0

Example 3: The tablets prepared in accordance with the above Description and examples can be tested as follows.

Tablet Evaluation Methods

1. Average tablet weight. Twenty tablets are weighed on an analytical balance and the average tablet weight calculated.

2. Tablet breaking strength (kilo bond-kp). 5 tablets are individually tested using a Schleuniger crushing strength tester, and the average breaking strength calculated.

3. Friability (% loss). 10 tablets, accurately weighed, are subjected to 10 minutes friability testing using a Roche Friabilator. The tablets are dedusted, reweighed, and the weight loss due to the friability is calculated as a percentage of the initial weight.

4. Dispersion Disintegration time DT (The test for dispersible tablets defined in the British Pharmacopoeia, 1988, Volume II, page 895 - BP 1988). 6 tablets are tested in accordance to the above-defined BP test (without discs) for dispersible tablets. This utilizes water at a temperature of 19°- 21° C.

5. Dispersion Quality. In accordance with the BP uniformity of dispersion test for dispersible tablets (BP 1988 Volume II page 895), two tablets are placed in 100 ml of water at 19°-21° C. and allowed to disperse.

Granule Evaluation Methods

1. Loss on Drying (LOD). The residual moisture content of the granule (LOD) can be determined on a 3-4 g sample using a Computrac moisture analyser set at 90° C. operated in accordance with the manufacturer's procedure.

2. Weight Median Diameter (WMD). A 10 g sample of granule is sifted for 2 minutes at suitable pulse and sift amplitudes in an Allen Bradley sonic sifter in accordance with manufacturer's instructions. Sieves of 300 µm, 250 µm, 200 µm, 150 µm, 100 µm, 53 µm and 40 µm are used. The WMD is calculated from the cumulative percentage undersize size distribution using a computer program.

Example 4:

Improved manufacturing robustness

A preliminary compactibility assessment is carried out on a Carver press using different formulations as well as binary mixtures of LAF 237 with different excipients e.g. microcrystalline cellulose (Avicel PH102).

Data demonstrate that our claimed compositions on being compressed with increasing levels of pressure (compression force) show a substantially useful increase in tablet strength. In particular e.g. mixture of LAF237 and Avicel show a substantially useful increase in tablet strength. These results indicated that from compactibility point of view microcrystalline cellulose e.g. Avicel would a preferred excipient to be combined with LAF237. With increasing pressure (compression force) our claimed formulations and selected ranges show a substantially useful increase in tablet strength.

A compactibility study (D. Becker, personal communication) is carried out on an instrumented Korsch single station press with force and displacement sensors on both upper and lower punches.

A clear indication is afforded from these data that LAF237 tablets are very likely to have poor tablet hardness/crushing strength unless diluted out using sufficient filler with excellent compactibility. Our claimed formulations and selected ranges are particularly adapted to provide the required compactibility. Microcrystalline cellulose e.g. Avicel is a good choice for a filler in this respect.

Example 5: Friability

Evaluation is carried out using a Manesty Betapress at 6 different settings: strain rate settings of 66-90 rpm (63,000-86,000 TPH) and force of 7.5-15 kN. The trials uses Flat-faced Beveled-edge (FFBE) tooling of 9 mm diameter for 250 mg tablets and 10 mm diameter for 310 mg tablets (other diameters are used depending on the weight of the tested tablet) . Total tablet weights were selected so that both the 9 and 10 mm FFBE tablets would have 100 mg of LAF237 and identical tablet thickness. Friability, Compression profile, Strain rate profile and Weight variation are the measured outcomes. Study design and the friability results obtained from the study are used to determine the variables (particle size distribution in the formulation, tablet weight, tablet thickness and weight, water content in the tablet etc) impacting the outcome of hardness.

Example 6: Mechanical stress (particle size distribution)

The material in the desired particle size range can be produced from any form of vildagliptin e.g. amorphous vildagliptin, by mechanical stress. This stress can be mediated by impact, shear or compression. In most commercially available grinding equipment a combination of these principles occurs. For vildagliptin preferably a mechanical impact or jet mill is used.

The most preferable mechanical impact mill can be equipped with different kind of beaters, screens, liners or with pin plates. For our process preferably an impact mill with plate beater and a slit screen 5 * 2.5 cm is used. The impact speed should be variable between 20 and 100 m/s (as peripheral speed) to adapt to any batch to batch variation. In our case a peripheral speed of the beater of about 40 - 50 m/s is used.

What is claimed is:

1. A pharmaceutical composition comprising;

(a) 5-60% by weight on a dry weight basis of a DPP-IV inhibitor in free form or in acid addition salt form;

(b) 40-95% by weight on a dry weight basis of a pharmaceutically acceptable diluent;

(c) 0-20% by weight on a dry weight basis of a pharmaceutically acceptable disintegrant; and optionally

(d) 0.1-10% by weight on a dry weight basis of a pharmaceutically acceptable lubricant.

2. A composition according to claim 1 comprising;

(a) 20-40% preferably 20-35% by weight on a dry weight basis of a DPP-IV inhibitor in free form or in acid addition salt form;

(b) 40-95% by weight on a dry weight basis of a pharmaceutically acceptable diluent;

(c) 0-10% by weight on a dry weight basis of a pharmaceutically acceptable disintegrant; and optionally

(d) 0.25-6% by weight on a dry weight basis of a pharmaceutically acceptable lubricant.

3. A composition according to claim 1 or claim 2, comprising;

(a) 20-35% by weight on a dry weight basis of a DPP-IV inhibitor in free form or in acid addition salt form;

(b) 62-78% by weight on a dry weight basis of a pharmaceutically acceptable diluent;

(c) 0-10% by weight on a dry weight basis of a pharmaceutically acceptable disintegrant; and optionally

(d) 0.1-10% by weight on a dry weight basis of a pharmaceutically acceptable lubricant.

4. A composition according to any one of claims 1 to 3 comprising;

(a) 22-28% by weight on a dry weight basis of a DPP-IV inhibitor in free form or in acid addition salt form.

5. A composition according to any one of claims 1 to 2 comprising;

(a) 30-35 % by weight on a dry weight basis of a DPP-IV inhibitor in free form or in acid addition salt form, and

(b) 58-72% by weight on a dry weight basis of a pharmaceutically acceptable diluent;

6. A composition according to any one of claims 1 to 5 comprising;

i) one or two diluents selected from microcrystalline cellulose and lactose

ii) the two diluents microcrystalline cellulose and lactose,

iii) 25-70% preferably 35-55% by weight on a dry weight basis of a pharmaceutically acceptable microcrystalline cellulose, or

iv) 25-70% preferably 35-55% by weight on a dry weight basis of a pharmaceutically acceptable microcrystalline cellulose and 5-40% preferably 18-35% by weight on a dry weight basis of lactose.

7. A composition according to any one of claims 1 to 6 comprising;

(c) 1-6% by weight on a dry weight basis of a pharmaceutically acceptable disintegrant, and/or (d) 0.1-10% by weight on a dry weight basis of a pharmaceutically acceptable lubricant.;

8. A composition according to any one of claims 1 to 5 comprising;

(a) 20-35% by weight on a dry weight basis of DPP-IV inhibitor;

(b) 25-70% by weight on a dry weight basis of a pharmaceutically acceptable microcrystalline cellulose;

(c) 5-40% by weight on a dry weight basis of a pharmaceutically acceptable lactose;

(d) 0-10% by weight on a dry weight basis of a pharmaceutically acceptable sodium starch glycolate;

(e) 0.25-6% by weight on a dry weight basis of magnesium stearate.

9. A composition according to any one of claims 1 to 5 comprising;

(a) 25-35% by weight on a dry weight basis of a DPP-IV inhibitor in free form or in acid addition salt form;

(b) 25-70% by weight on a dry weight basis of a pharmaceutically acceptable microcrystalline cellulose;

(c) 5-40% by weight on a dry weight basis of a pharmaceutically acceptable lactose;

(d) 0-10% by weight on a dry weight basis of a pharmaceutically acceptable sodium starch glycolate;

(e) 0.25-6% by weight on a dry weight basis of magnesium stearate.

10. A composition according to any one of claims 1 to 5 comprising;

(a) 30-35% preferably 30-32% by weight on a dry weight basis of DPP-IV inhibitor e.g. LAF237;

(b) 35-50% preferably 40-45% by weight on a dry weight basis of a pharmaceutically acceptable microcrystalline cellulose;

(c) 18-35% preferably 20-25% by weight on a dry weight basis of a pharmaceutically acceptable lactose;

(d) 1-4% preferably 1.5-2.5% by weight on a dry weight basis of a pharmaceutically acceptable sodium starch glycolate; and

(e) 0.5-4% preferably 0.1-2% by weight on a dry weight basis of magnesium stearate.

11. A composition according to any one of claims 1 to 5 comprising;

(a) 20-35% preferably 22-28% by weight on a dry weight basis of DPP-IV inhibitor e.g. LAF237;

(b) 35-55% by weight on a dry weight basis of a pharmaceutically acceptable microcrystalline cellulose;

(c) 18-35% by weight on a dry weight basis of a pharmaceutically acceptable lactose;

(d) 1-4% by weight on a dry weight basis of a pharmaceutically acceptable sodium starch glycolate; and

(e) 0.5-4% by weight on a dry weight basis of magnesium stearate.

12. A composition according to any one of claims 1 to 5 comprising;

(a) from about 22% to about 28% by weight on a dry weight basis of a DPP-IV inhibitor or a DPP-IV inhibitor of formula (I);

(b) from about 45% to about 50% by weight on a dry weight basis of a pharmaceutically acceptable microcrystalline cellulose;

(c) from about 20% to about 25% by weight on a dry weight basis of a pharmaceutically acceptable lactose;

(d) from about 1.5% to about 2.5% by weight on a dry weight basis of a pharmaceutically acceptable sodium starch glycolate; and

(e) from about 0.1% to about 2% by weight on a dry weight basis of magnesium stearate.

13. A composition according to any one of claims 1 to 12, wherein the DPP-IV inhibitor is selected from 1-{2-[(5-cyanopyridin-2-yl) amino] ethylamino} acetyl-2 (S)- cyano-pyrrolidine dihydrochloride, (S)-1-[(3-hydroxy-1-adamantyl)amino]acetyl-2-cyano-pyrrolidine, L-threo-isoleucyl thiazolidine, MK-0431, GSK23A, BMS-477118, 3-(aminomethyl)-2-isobuthyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinecarboxamide and 2-{[3-(aminomethyl)-2-isobuthyl-4-phenyl-1-oxo-1,2-dihydro-6-isoquinolyl]oxy}acetamide and optionally in any case pharmaceutical salts thereof.

14. A composition according to any one of claims 1 to 12, wherein the DPP-IV inhibitor is 1-[3-hydroxy-adamant-1-ylamino)-acetyl]-pyrrolidine-2(*S*)-carbonitrile or a pharmaceutical salt thereof.

15. A compressed pharmaceutical tablet or a direct compressed pharmaceutical tablet, wherein the dispersion contains particles comprising a DPP-IV inhibitor, in free form or in acid addition salt form, and wherein at least 60% of the particle size distribution in the tablet is less than 250 μm.

16. A compressed pharmaceutical tablet or a direct compressed pharmaceutical tablet wherein the dispersion contains particles comprising DPP-IV inhibitor, in free form or in acid

addition salt form, and wherein tablet thickness to tablet weight ratios is of 0.002 to 0.06 mm/mg preferably of 0.01 to 0.03 mm/mg.

17. A compressed pharmaceutical tablet or a direct compressed pharmaceutical tablet wherein the dispersion contains particles comprising DPP-IV inhibitor, in free form or in acid addition salt form, and wherein;

i) at least 60% of the particle size distribution in the tablet is less than 250 μm preferably between 10 to 250 μm, and

ii) tablet thickness to tablet weight ratios is of 0.002 to 0.06 mm/mg or of 0.01 to 0.03 mm/mg

18. A compressed pharmaceutical tablet or a direct compressed pharmaceutical tablet wherein the dispersion contains particles comprising DPP-IV inhibitor preferably LAF237, in free form or in acid addition salt form, and wherein;

i) at least 60% of the particle size distribution in the tablet is less than 250 μm preferably between 10 to 250 μm,

ii) the water content of the tablet is less than 10% after 1 week at 25°C and 60% RH, and

iii) tablet thickness to tablet weight ratios is of 0.002 to 0.06 mm/mg.

19. A compressed pharmaceutical tablet or a direct compressed pharmaceutical tablet according to any one of claims 15 to 18, wherein the particle size distribution in the tablet is between 50 to 150 μm.

20. A compressed pharmaceutical tablet or a direct compressed pharmaceutical tablet according to any one of claims 15 to 19, wherein the water content of the tablet is less than 5% after 1 week at 25°C and 60% RH

21. A compressed pharmaceutical tablet or a direct compressed pharmaceutical tablet according to any one of claims 15 to 20, wherein tablet thickness to tablet weight ratios is of 0.01 to 0.03 mm/mg

22. A compressed pharmaceutical tablet or a direct compressed pharmaceutical tablet according to any one of claims 15 to 21, wherein at least 60% or at least 80% of the particle size distribution in the tablet is between 10 to 250 μm.

23. A compressed pharmaceutical tablet or a direct compressed pharmaceutical tablet according to any one of claims 15 to 21, wherein at least 25% or at least 35% of the particle size distribution in the tablet is between 50 to 150 μm.

24. A compressed pharmaceutical tablet or a direct compressed pharmaceutical tablet according to any one of claims 15 to 23 wherein the tablet comprises a composition according to any one of claims 1 to 14.

25. A compressed pharmaceutical tablet or a direct compressed pharmaceutical tablet according to any one of claims 15 to 24, wherein

i) between 0 and 10 minutes 85 to 99.5 % of the active ingredient is released, and

ii) between 10 and 15 minutes 90 to 99.5 % of the active ingredient is released.

26. A compressed pharmaceutical tablet or a direct compressed pharmaceutical tablet according to any one of claims 15 to 24, wherein the particle size distribution of the pharmaceutical excipients in the tablet is between 5 and 400μm.

27. The compressed pharmaceutical tablet or a direct compressed pharmaceutical tablet according to any one of claims 15 to 26, in which the DPP-IV inhibitor is selected from 1-{2-[(5-cyanopyridin-2-yl) amino] ethylamino} acetyl-2 (S)- cyano-pyrrolidine dihydrochloride, (S)-1-[(3-hydroxy-1-adamantyl)amino]acetyl-2-cyano-pyrrolidine, L-threo-isoleucyl thiazolidine, MK-0431, GSK23A, BMS-477118, 3-(aminomethyl)-2-isobuthyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinecarboxamide and 2-{[3-(aminomethyl)-2-isobuthyl-4-phenyl-1-oxo-1,2-dihydro-6-isoquinolyl]oxy}acetamide and optionally in any case pharmaceutical salts thereof.

28. The compressed pharmaceutical tablet or a direct compressed pharmaceutical tablet according to any one of claims 15 to 26, in which the DPP-IV inhibitor is *N*-(substituted glycyl)-2-cyanopyrrolidine is 1-[3-hydroxy-adamant-1-ylamino)-acetyl]-pyrrolidine-2(*S*)-carbonitrile or a pharmaceutical salts thereof.

29. A compressed pharmaceutical tablet according to any one of claims 15 to 28, which is a direct compressed tablet.

30. A solid dosage form of the composition according to any one of Claims 1 to 14.

31. The solid dosage form of Claim 30 which is a tablet.

32. The solid dosage form of Claim 30 which is a capsule.

33. A solid dosage form of the composition according to any one of Claims 1 to 14 which is a compressed tablet preferably a direct compressed tablet.

34. Process for preparing a direct compressed tablet according to any one of claims 15 to 29, in unit dosage form, which comprises:

(a) blending as a % by weight on a dry weight basis:

(i) 6-60% by weight on a dry weight basis of DPP-IV inhibitor e.g. LAF237; and
(ii) and at least one excipient selected from a diluent, a disintegrant and a lubricant,

to form a DPP-IV inhibitor formulation in the form of a tableting powder, capable of being directly compressed into a tablet; and

(b) compressing the formulation prepared during step (a) to form the compressed DPP-IV inhibitor tablet in unit dosage form.

35. Process for preparing a direct compressed tablet according to any one of claims 15 to 29, in unit dosage form, which comprises:

(a) blending as a % by weight on a dry weight basis:

(i) 25-35% by weight on a dry weight basis of DPP-IV inhibitor e.g. LAF237;
(ii) 40-95% by weight on a dry weight basis of a pharmaceutically acceptable diluent;

(iii) 0-10% by weight on a dry weight basis of a pharmaceutically acceptable disintegrant; and

(iv) 0.25-6% by weight on a dry weight basis of a pharmaceutically acceptable lubricant,

to form a DPP-IV inhibitor formulation in the form of a tableting powder, capable of being directly compressed into a tablet; and

(b) compressing the formulation prepared during step (a) to form the compressed DPP-IV inhibitor tablet in unit dosage form.

36. Process according to claim 35 wherein the blended formulation comprises:

(i) 20-35% or preferably 25-30% by weight by weight on a dry weight basis of DPP-IV inhibitor preferably LAF237, in free form or in acid addition salt form;
(ii) 25-70% by weight or preferably 35-50% by weight on a dry weight basis of a pharmaceutically acceptable microcrystalline cellulose such as Avicel PH 102;

(iii) 5-40% by weight or preferably 18-35% by weight on a dry weight basis of a pharmaceutically acceptable lactose;

(iv) 0-10% by weight or preferably 1-4% by weight on a dry weight basis of a pharmaceutically acceptable sodium starch glycolate; and

(v) 0.25- 6% by weight or preferably 0.5-4% by weight on a dry weight basis of a pharmaceutically acceptable magnesium stearate.

37. Process according to claim 34, wherein the blended composition used in step (a) is selected from the compositions of claims 1 to 14.

38. The process according to any one of claims 34 to 37, in which the DPP-IV inhibitor is selected from 1-{2-[(5-cyanopyridin-2-yl) amino] ethylamino} acetyl-2 (S)- cyano-pyrrolidine dihydrochloride, (S)-1-[(3-hydroxy-1-adamantyl)amino]acetyl-2-cyano-pyrrolidine, L-threo-isoleucyl thiazolidine, MK-0431, GSK23A, BMS-477118, 3-(aminomethyl)-2-isobuthyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinecarboxamide and 2-{[3-(aminomethyl)-2-isobuthyl-4-phenyl-1-oxo-1,2-dihydro-6-isoquinolyl]oxy}acetamide and optionally in any case pharmaceutical salts thereof.

39. The process according to any one of claims 34 to 37, in which the which the DPP-IV inhibitor is 1-[3-hydroxy-adamant-1-ylamino)-acetyl]-pyrrolidine-2(*S*)-carbonitrile or pharmaceutical salts thereof.

40. A pharmaceutical composition comprising;

(a) a DPP-IV inhibitor in free form or in acid addition salt form,

(b) a pharmaceutically acceptable diluent,

wherein in the unit dosage form, the weight of DPP-IV inhibitor on a dry weight basis to tablet weight of diluent ratio is of 0.5 to 0.25, preferably 0.4 to 0.28.

41. A composition according to claim 40 wherein the diluent is selected from a microcrystalline cellulose and lactose.

42. A composition according to claim 40 or claim 41, wherein at least one diluent is a microcrystalline cellulose and wherein in the unit dosage form, the weight of DPP-IV inhibitor on a dry weight basis to tablet weight of microcrystalline cellulose ratio is of 2 to 0.333, preferably 1 to 0.333, most preferably of 0.7 to 0.333.

43. A composition according to claim 42 or claim 40 comprising lactose as diluent in addition to a microcrystalline cellulose.

44. Composition according to any of claims 40 to 43 wherein the DPP-IV inhibitor is selected from 1-{2-[(5-cyanopyridin-2-yl) amino] ethylamino} acetyl-2 (S)- cyano-pyrrolidine dihydrochloride, (S)-1-[(3-hydroxy-1-adamantyl)amino]acetyl-2-cyano-pyrrolidine, L-threo-isoleucyl thiazolidine, MK-0431, GSK23A, BMS-477118, 3-(aminomethyl)-2-isobuthyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinecarboxamide and 2-{[3-(aminomethyl)-2-isobuthyl-4-phenyl-1-oxo-1,2-dihydro-6-isoquinolyl]oxy}acetamide and optionally in any case pharmaceutical salts thereof.

45. Composition according to any of claims 40 to 43 wherein the DPP-IV inhibitor is 1-[3-hydroxy-adamant-1-ylamino)-acetyl]-pyrrolidine-2(*S*)-carbonitrile or pharmaceutical salts thereof.

46. Composition according to any of claims 1 to 33 or 40 to 45, comprising between 20 and 120 mg preferably between 25 and 100 mg of 1-[3-hydroxy-adamant-1-ylamino)-acetyl]-pyrrolidine-2(*S*)-carbonitrile or a pharmaceutically acceptable acid addition salt thereof.

47. Composition according to any of claims 40 to 46, which further comprises;
(c) 0-20% by weight on a dry weight basis of a pharmaceutically acceptable disintegrant;
(d) 0.1-10% by weight on a dry weight basis of a pharmaceutically acceptable lubricant.

48. Composition according to any of claims 40 to 47, which further comprises;
(c) 1-6% by weight on a dry weight basis of a pharmaceutically acceptable disintegrant;
(d) 0.25-6% by weight on a dry weight basis of a pharmaceutically acceptable lubricant.

49. Composition according to any of claims 40 to 48, which further comprises;
(c) 1-4% by weight on a dry weight basis of a pharmaceutically acceptable sodium starch glycolate; and
(d) 0.5-4% by weight on a dry weight basis of magnesium stearate.

50. A compressed pharmaceutical tablet according to any one of claims 15 to 29 comprising a composition of claims 40 to 49.

52. The Composition according to any of claims 40 to 48 which is a tablet.

53. The composition according to any of claims 40 to 48 which is a capsule.

54. A compressed pharmaceutical tablet, preferably a direct compressed tablet, comprising a DPP-IV inhibitor, in free form or in acid addition salt form.

55. A compressed pharmaceutical tablet according to claim 54, wherein the DPP-IV inhibitor is selected from 1-{2-[(5-cyanopyridin-2-yl) amino] ethylamino} acetyl-2 (S)- cyano-pyrrolidine dihydrochloride, (S)-1-[(3-hydroxy-1-adamantyl)amino]acetyl-2-cyano-pyrrolidine, L-threo-isoleucyl thiazolidine, MK-0431, GSK23A, BMS-477118, 3-(aminomethyl)-2-isobuthyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinecarboxamide and 2-{[3-(aminomethyl)-2-isobuthyl-4-phenyl-1-oxo-1,2-dihydro-6-isoquinolyl]oxy}acetamide and optionally in any case pharmaceutical salts thereof.