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(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING VILDAGLIPTIN AND METFORMIN AND METHOD OF PREPARATION THEREOF

(57) Abstract: The present invention relates to a solid pharmaceutical formulation of Vildagliptin or a pharmaceutically acceptable salt thereof in combination with Metformin or a pharmaceutically acceptable salt thereof, to be used for the treatment of Type2 diabetes.

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# PHARMACEUTICAL COMPOSITION COMPRISING VILDAGLIPTIN AND METFORMIN AND METHOD OF PREPARATION THEREOF

## TECHNICAL FIELD OF THE INVENTION

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The present invention relates to a solid pharmaceutical formulation of Vildagliptin or a pharmaceutically acceptable salt thereof in combination with Metformin or a pharmaceutically acceptable salt thereof, to be used for the treatment of Type 2 diabetes. The main objective of the present invention is to provide a formulation that is stable and robust and it overcomes the  
10 difficulties encountered in formulating combination products.

## BACKGROUND OF THE INVENTION

Diabetes mellitus is a common disorder with higher prevalence in developed countries. It is  
15 considered a metabolic disease wherein the patient has high blood sugar level over a prolonged period of time. The disease has three different types. Type 1 diabetes, wherein the pancreas fails to produce enough insulin, therefore it requires immediate and life-long treatment with insulin. Type 2 diabetes, a chronic and progressive disease with a complex pathophysiology involving the dual endocrine defects of insulin resistance and impaired insulin secretion. Typical treatment  
20 begins with diet and exercise, however, it will be followed by oral antidiabetic monotherapy, before moving into a combination regime. Most patients find it hard to sufficiently control glycaemia during long-term treatment with diet and exercise alone. And the third form of the disease is gestational diabetes occurs when pregnant women develop high blood sugar levels and is treated with diet and exercise and in some cases insulin.

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Drugs of choice for therapy include biguanides, Dipeptidyl peptidase-IV (DPP-IV) inhibitors, sulfonylurea, thiazolidinedione, alphaglucoSIDase inhibitor, amylin analog, glucagon-like peptide-1 (GLP-1) or incretin mimetic, meglitinide and insulin. DPP-IV inhibitors represent a class of agents that are being developed for the treatment or improvement in glycemic control in  
30 patients with type 2 diabetes. More specifically, Vildagliptin, also known as LAF-237 is the generic name for (S)-1-[(3-hydroxy-1-adamantyl)amino]acetyl-2-cyano-pyrrolidine has been disclosed specifically in US patent no 6,166,063; it was introduced in 2006, it is easy to use and does not require regular glucose monitoring or dose adjustments. Vildagliptin has been found to reduce fasting glucose and postprandial glucose excursion in association with significantly  
35 reduced HbA<sub>1c</sub> levels.

It is well known in the art that DPP-IV inhibitors with primary or secondary amino group show incompatibilities, degradation problems or extraction problems with some excipients especially excipients that have acidic properties. Vildagliptin has also a secondary amino group on its chemical structure. In solid dosage forms, it may react with many excipients or impurities of excipients, although it is very stable it has high susceptibility to air and humidity. This leads to formation of impurities and incorporation of undesired components into the composition. EP 2468361 discloses a pharmaceutical composition, comprising Vildagliptin granules which are coated with at least one coating layer and one or more than one excipients. In patent applications EP1841413 and EP2165703, direct compression is used to develop tablet formulation of DPP-IV inhibitor compounds, especially Vildagliptin or an acid addition salt thereof.

The biguanide antihyperglycemic agent Metformin has also been widely prescribed for lowering blood glucose in patients with Type 2 diabetes and is marketed in 500, 750, 850 and 1000 mg strengths. However, because it is a short acting drug, metformin requires twice-daily or three-times-daily dosing (500 - 850 mg tab 2-3/day or 1000 mg bid with meals). Metformin is disclosed in U.S. 3,174,901 is currently marketed in the U.S. in the form of its hydrochloride salt (Glucophage<sup>®</sup>, BMS), The preparation of metformin (dimethyldiguanide) and its hydrochloride salt is state of the art and was disclosed first by Emil A. Werner and James Bell, J. Chem. Soc. 121, 1922, 1790-1794 .

Metformin increases the sensitivity to insulin in peripheral tissues of the hosts and it is also involved in inhibition of glucose absorption from the intestine, suppression of hepatic gluconeogenesis, and inhibition of fatty acid oxidation. Suitable dosage regimens of Metformin include unit doses of 500 mg two to three time's daily and can even be build up to five times daily or 850 mg once or twice daily.

Combination products offer several advantages. First, they have concentrations for the active agents that are consistently maintained within an optimal therapeutic range for both active agents. Second, combination products have been shown to improve patient compliance. Most healthcare practitioners now agree that within an ageing population, compliance becomes less certain and, therefore, more important. Third, particularly for treatment of Type 2 diabetes where single treatment along with diet and exercise fails quickly a combination product can have more advantages.

The present invention relates to a combination product comprising Vildagliptin and Metformin that overcomes the difficulties in the manufacturing process of such product, and a process for preparation thereof.

## 5 SUMMARY OF THE INVENTION

It is, therefore, an object of the present invention to provide an immediate release pharmaceutical formulation comprising a combination of Vildagliptin or a pharmaceutically acceptable salt thereof and Metformin or pharmaceutically acceptable salt thereof.

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A further object of the present invention is to provide a manufacturing process that is easy and cost effective and overcomes the added problems of impurities due to reaction of Vildagliptin with excipients present in the formulation. During the manufacturing process Metformin granules are formed after granulation with an appropriate binder and Vildagliptin is then added  
15 in order to avoid formation of impurities.

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The main objective of the present invention is to provide a composition comprising the combination of Vildagliptin or pharmaceutical acceptable salt thereof and Metformin or a pharmaceutically acceptable salt thereof, prepared by a suitable manufacturing process in order  
20 to obtain a stable and efficacious dosage form with good physicochemical characteristics.

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According to the present invention, a process for the preparation of a stable dosage form of Vildagliptin and Metformin is provided, comprising the following steps:

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- wet granulation of Metformin with a binder in an aqueous solution,
- addition of a glidant and mixing,
- addition of Vildagliptin and mixing,
- addition of a lubricant and mixing,
- compression to tablets and coating

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Other objects and advantages of the present invention will become apparent to those skilled in the art in view of the following detailed description.

## DETAILED DESCRIPTION OF THE INVENTION

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(s), 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 tableted. 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 time create 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. 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 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.

As there is an important amount of Metformin present in the formulation of the invention, the size and shape of the resulting tablet should be considered since an easy oral administration to a patient is required, as well as an easy tablet manufacturing process which meets all the herein described requirements. Thus there is a need in the industry for techniques and pharmaceutical formulations which will allow preparation of high-dose Vildagliptin and Metformin combination tablets (high drug load). The high-dose Vildagliptin and Metformin tablets have to meet all the herein listed requirements with preferably a limited number and amount of pharmaceutical excipients to reduce the size of the tablet.

Pre-formulation testing was the first step in the development of dosage forms for the drug substance. The physical and chemical properties of the drug substance combined with excipients were investigated. Pre-formulation testing generated useful information in developing stable and bioavailable dosage forms that can be scaled up. Based on compatibility and pre-formulation studies the selected commonly used Ph.Eur grade excipients were shown compatible with the active substance.

The main objective of the present invention is to develop a robust and stable immediate release film-coated tablet comprising Vildagliptin/Metformin HCl in two strengths 50/850mg and 50/1000mg respectively. The excipients were selected to enhance dissolution, physicochemical properties and stability of drug substances in the finished dosage form and thus were subjected to compatibility study with the APIs.

Binders such as Hydroxypropylcellulose, Hydroxypropylmethylcellulose Copovidone, vinylpyrrolidone-vinyl acetate copolymer and Povidone were tested in order to promote granules during granulation and to provide mechanical strength to the tablet. Colloidal silicon dioxide was tested as glidant to improve the flow property of the formulation due to the reduction of the friction between the particles during granulation and compaction. Magnesium Stearate was used in formulations as lubricant to prevent any sticking during compression. Wet (aqueous and solvent) granulation and melt granulation were tested in manufacturing process.

Formulation trials were performed in order to study the physicochemical properties of the tablets as well as dissolution properties and result in the final drug product with the optimum quality. The target characteristics were set to hardness from 150 to 250N, disintegration time from 12'00'' to 17'00'' and dissolution was set to >85% at 30 minutes.

The preferred formulation of this invention comprises the following: Vildagliptin and Metformin HCl as the active ingredients, one or more binders, optionally a diluent, one or more lubricants, optionally a disintegrant and a lubricant which is magnesium stearate. The excipients have been carefully selected after many optimization steps.

Binder excipients are formulated to act as an adhesive, to literally "bind together" powders, granules and other dry ingredients to impart to the product the necessary mechanical strength. Binders are added to create a more effective and predictable granule formation. Examples of pharmaceutically acceptable binders include, but are not limited to, starches; celluloses and

derivatives thereof, e.g., vinylpyrrolidone-vinyl acetate copolymer, microcrystalline cellulose, hydroxypropyl cellulose hydroxyethyl cellulose and hydroxypropylmethyl 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.

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Polyvinylpyrrolidone VA64 (PVP VA64), also known as Kollidon® VA 64, is a vinylpyrrolidone-vinyl acetate copolymer. It is used in a variety of manufacturing processes such as a dry binder for direct compression, as a granulating agent, as a retarding agent and as a film-forming agent as well as in taste-masking applications. Kollidon® VA 64 can be used as a dry binder for direct compression tableting and as a soluble binder for granulation and it is ideal as a solubilizer in hot-melt extrusion processes because of its excellent binding capacity. Another important property of Kollidon® VA 64 is the plasticity, which distinguishes the products from povidone (e.g. Kollidon® 30). This property often gives granules and mixtures that are less susceptible to capping during tableting, and tablets that are less brittle. These properties in total make it an attractive and cost-effective alternative to natural binders. In addition, Kollidon® VA 64 is especially suitable for processes with higher humidity exposure.

Kollidon® VA 64 is an excellent binder in wet granulation for the production of tablets and granules, since it is readily soluble in all the usual solvents. It can then be added either as a solution during granulation, or dry to the other ingredients, in which case the solvent is added alone during granulation. Trials so far conducted with both methods, using equal quantities of liquid, produced tablets of much the same hardness. A combination of the two methods, i.e. mixing some of the Kollidon® VA 64 with the active ingredient, and dissolving the rest in the solvent, sometimes gives the best results. This is particularly recommended if the active ingredient does not readily absorb the solvent. Since it is less hygroscopic than povidone (e.g. Kollidon® 25 or Kollidon® 30), Kollidon® VA 64 gives granules that have less tendency to stick to the punches of the tableting machine, when operating under humid conditions.

In the present invention the use of Kollidon VA64 as binder showed the best results when used in an amount from about 5% to about 25% by weight of the composition, more preferably from about 10% to about 20%.

Many stability problems can be encountered during development and can be attributed to inadequate matching of the excipients to the active ingredient and the complexity of chemical and physical interactions between them. Drug-excipient interactions may take a long time to be

manifested and are not always predicted by pre-formulation studies. In the case of Vildagliptin, it is well known that because of its amino group it shows incompatibility and degradation problems when in contact with a wide range of excipients. In addition, Vildagliptin is susceptible to humidity. To overcome these problems the inventors tested the use of a glidant, in this case colloidal silicon dioxide such as Aerosil®. Different percentages of externally added Aerosil® were tested. Surprisingly, a higher percentage of Aerosil® added during the external phase showed the best results. Those results suggest that Aerosil®, when added during the external phase protects Vildagliptin and minimizes its degradation. This is most likely due to the formation of a protective film around Vildagliptin and minimization of its interaction with the Metformin granules. The preferred amount of Aerosil® in the present invention is from about 0.1% to about 7% of the total weight of the composition and most preferably from about 1% to about 5% of the total weight of the composition.

Optionally the formulation may contain diluents. 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 may be present in an amount from about 15% to about 40% by weight of the composition. The preferred diluent is 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.

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. 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 calcium carboxymethylcellulose and cross-linked sodium carboxymethylcellulose (croscarmellose sodium or croscarmellose); soy polysaccharides; and guar gum, sodium starch glycolate. The disintegrant may be present preferably in an amount from about 2% to about 20%, more preferably from about 5% to about 10%, and most preferably from 7% to about 9% by weight of the composition.

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. 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  
5 cellulose and microcrystalline cellulose. The lubricant may be present in an amount preferably from about 0.1% to about 5% by weight of the composition and most preferably from about 0.1% to about 2% by weight of the composition.

Magnesium stearate was the choice for the present invention. It reduces the friction between the  
10 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.

15 Unless the context clearly indicates otherwise, throughout the description and the claims, the words “comprise”, “comprising”, and the like are to be taken into as an inclusive sense as opposed to an exclusive or exhaustive sense, that is to say, in the sense of “including, but not limited to”.

20 The inventors of the invention have surprisingly found that it is possible to formulate a stable pharmaceutical composition comprising a combination of Vildagliptin or pharmaceutically acceptable salt thereof and Metformin or a pharmaceutically acceptable salt thereof, which can exhibit superior chemical and physical stability by wet granulation, a manufacturing process that is easy and cost effective.

25 The tablet as described in the present invention is obtained by wet granulation of the Metformin granules in the presence of a binder, drying and subsequent addition of a lubricant and Vildagliptin and optionally at least one pharmaceutically acceptable excipient.

30 The tablet as described in the present invention comprises as active ingredients,  
i) between 0.5 to 35% or between 1.5 to 35%, preferably between 0.5 to 20% or 1.5 to 20% of Vildagliptin or a pharmaceutically acceptable salt thereof,  
ii) between 65 to 98.5%, preferably between 80 to 98.5% of metformin or a pharmaceutically acceptable salt thereof, and wherein metformin is in the form of granules comprising between 1  
35 to 25% of a binder.

According to the present invention, the process for the preparation of a stable dosage form of Vildagliptin and Metformin HCl is provided, comprising the following steps:

- wet granulation of Metformin with a binder which is PVP in an aqueous solution,
- addition of colloidal silicon dioxide and mixing,
- addition of Vildagliptin and mixing,
- addition of a lubricant, which is Magnesium stearate and mixing,
- compression to tablets and coating

The following Examples illustrate aspects of the present invention but are not in any way limiting the scope of invention.

## EXAMPLES

### Example 1

The main objective of the present invention was to develop a robust and stable immediate release film-coated tablet comprising Vildagliptin/Metformin HCl in two strengths 50/850mg and 50/1000 mg with respect to both active ingredients.

The excipients were selected to enhance dissolution, physicochemical properties and stability of drug substances in the finished dosage form and thus were subjected to compatibility study with the active ingredients.

Formulation trials were performed in order to study the physicochemical properties of the tablets as well as dissolution properties and result in the final drug product with the optimum quality. below.

For the initialization of the formulation development different processes were tested that incorporate HPC as a binder with the two active agents Vildagliptin and Metformin. The first step of the manufacturing process is the binding of Metformin and HPC to form granulates. Subsequently, Vildagliptin is added to the granulated mixture and then Magnesium stearate for the lubrication of the final mixture. The tested formulations 1.1, 1.2, 1.3 and 1.4 are presented below in Table 1 manufactured respectively with dry mixing, wet (aqueous), solvent and melt granulation. These trials were performed for the 50/850 mg strength and the proportions were

kept constant. Concerning the dry mixing process, all the excipients were mixed with both Metformin and Vildagliptin to form a blend that after lubrication was compressed. For the wet and solvent granulation, the respective solvent (purified water and ethanol) was used to form the Metformin granulate. Then, Vildagliptin was added to granulate and lubrication took place.

- 5 Finally, melt granulation was performed with the binder (HPC) and Metformin. Similarly, Vildagliptin was then added to the melt metformin granulate. Coating with Opadry® premix of the produced tablets is the final stage of the manufacturing process.

Compression of the dry mixed blend did not performed well and tablet capping was observed.

- 10 Tablets obtained by wet (aqueous) and solvent granulation were characterized by reduced physical properties compared to the tablets obtained by melt granulation. Apparently, HPC is more suitable for melt granulation due to its thermoplastic properties.

Table 1: Formulations 1.1 – 1.4

| Composition                            | 1.1            | 1.2              | 1.3             | 1.4            |
|----------------------------------------|----------------|------------------|-----------------|----------------|
| <b>Manufacturing process</b>           | Dry mixing     | Wet granul.(aq.) | Ethanol granul. | Melt granul.   |
| <b>Metformin granulate</b>             |                |                  |                 |                |
| <b>Metformin HCl</b>                   | <b>850.00</b>  | <b>850.00</b>    | <b>850.00</b>   | <b>850.00</b>  |
| Hydroxypropylcellulose (Klucel EXF)    | <b>84.15</b>   | <b>84.15</b>     | <b>84.15</b>    | <b>84.15</b>   |
| Purified water                         | -              | q.s.             | -               | -              |
| Ethanol                                | -              | -                | q.s.            | -              |
| <b>External phase</b>                  |                |                  |                 |                |
| <b>Vildagliptin</b>                    | <b>50.00</b>   | <b>50.00</b>     | <b>50.00</b>    | <b>50.00</b>   |
| <b>Lubrication</b>                     |                |                  |                 |                |
| Magnesium Stearate                     | <b>8.85</b>    | <b>8.85</b>      | <b>8.85</b>     | <b>8.85</b>    |
| <b>Total for uncoated tablet</b>       | <b>993.00</b>  | <b>993.00</b>    | <b>993.00</b>   | <b>993.00</b>  |
| Opadry premix                          |                |                  |                 |                |
| Purified water                         | q.s.           | q.s.             | q.s.            | q.s.           |
| <b>Total for coated tablet</b>         | <b>1023.00</b> | <b>1023.00</b>   | <b>1023.00</b>  | <b>1023.00</b> |
| <b>Physicochemical characteristics</b> |                |                  |                 |                |
| Disintegration time                    | -              | 11'20''          | 3'13''          | 15'53''        |
| Hardness (N)                           | capping        | 127              | 87              | 270            |

For the formulations 1.2, 1.3 and 1.4 a stability study was conducted. The results of this study for both Vildagliptin and Metformin HCl in zero time and after six months, is recorded in Tables 2 and 3.

Table 2. Total impurities for Vildagliptin in zero time and after 6 months

| <b>Comp. 1.2</b>        |             | Zero time | 25°C 6months | 40°C 6months |
|-------------------------|-------------|-----------|--------------|--------------|
| <b>Impurity C</b>       | <b>0.2%</b> | 0.11%     | 0.14%        | 0.16%        |
| <b>Impurity E</b>       |             | 0.04%     | 0.06%        | 0.07%        |
| <b>Total Impurities</b> | <b>1.5%</b> | 0.25%     | 0.30%        | 0.49%        |
| <b>Comp. 1.3</b>        |             | Zero time | 25°C 6months | 40°C 6months |
| <b>Impurity C</b>       | <b>0.2%</b> | 0.14%     | 0.26%        | 0.27%        |
| <b>Impurity E</b>       |             | 0.05      | 0.06%        | 0.06%        |
| <b>Total Impurities</b> | <b>1.5%</b> | 0.32%     | 0.43%        | 0.87%        |
| <b>Comp. 1.4</b>        |             | Zero time | 25°C 6months | 40°C 6months |
| <b>Impurity C</b>       | <b>0.2%</b> | 0.14%     | 0.16%        | 0.18%        |
| <b>Impurity E</b>       |             | 0.05%     | 0.07%        | 0.08%        |
| <b>Total Impurities</b> | <b>1.5%</b> | 0.33%     | 0.44%        | 0.92%        |

Table 3. Total impurities for Metformin HCl in zero time and after 6 months

| <b>Comp. 1.2</b>        |             | Zero time | 25°C 6months | 40°C 6months |
|-------------------------|-------------|-----------|--------------|--------------|
| <b>Impurity F</b>       | <b>0.2%</b> | ND        | ND           | ND           |
| <b>Total Impurities</b> | <b>1.0%</b> | 0.03%     | 0.02%        | 0.04%        |
| <b>Comp. 1.3</b>        |             | Zero time | 25°C 6months | 40°C 6months |
| <b>Impurity F</b>       | <b>0.2%</b> | ND        | ND           | 0.06%        |
| <b>Total Impurities</b> | <b>1.0%</b> | 0.08%     | 0.12%        | 0.25%        |
| <b>Comp. 1.4</b>        |             | Zero time | 25°C 6months | 40°C 6months |
| <b>Impurity F</b>       | <b>0.2%</b> | ND        | 0.04%        | 0.06%        |
| <b>Total Impurities</b> | <b>1.0%</b> | 0.06%     | 0.10%        | 0.30%        |

- 5 The stability data for compositions 1.2 – 1.4 show a rather stable behavior except from formulation 1.3 with the ethanol granulation where the total impurities after the six months are above the limit. Based upon the stability data and the physical attributes of the studied compositions, the manufacturing process of formulation 1.3 was not further utilized, while the process of formulations 1.2 and 1.4 were qualified as more appropriate for the development.

10

### Example 2

Wet granulation is a standard and cost-effective manufacturing process that incorporates common raw materials and requires standard equipment. On the contrary, melt granulation may require non-typical equipment i.e. hot melt extruder (HME) which means that the potential excipients for such process are limited. For that reason, melt granulation was not further utilized and wet granulation remained as the prevalent manufacturing process

Subsequently, the next step of the formulation development incorporated the use of alternative excipients (PVP/K30, PVP/VA64, MCC, Aerosil and HPMC) with different proportions in each

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composition, in order to study any effect on the physical attributes of the final tablet. Wet granulation in a high shear granulator performed as the selected manufacturing process to form metformin granulates for all formulations. The composition, for each compression mixture categorized by the binder type and the internal phase excipients, is tabulated below (Table 4).

- 5 Hardness and disintegration time for each formulation after compression and coating were measured and listed in Table 4.

Table 4: Formulation compositions 2.1 – 2.9

| Composition                            | 2.1    | 2.2    | 2.3    | 2.4    | 2.5     | 2.6     | 2.7     | 2.8    | 2.9     |
|----------------------------------------|--------|--------|--------|--------|---------|---------|---------|--------|---------|
| <b>Components (mg)</b>                 |        |        |        |        |         |         |         |        |         |
| <b>Metformin granulate</b>             |        |        |        |        |         |         |         |        |         |
| Metformin HCl                          | 1000.0 | 1000.0 | 1000.0 | 1000.0 | 1000.0  | 1000.0  | 1000.0  | 1000.0 | 1000.0  |
| PVP/VA64                               | -      | -      | 100.0  | 100.0  | 280.0   | 100.0   | 250.0   |        |         |
| PVP/K30                                | 100.0  | 280.0  | -      | -      | -       | -       | -       | -      | -       |
| HPMC                                   | -      | -      | -      | -      | -       | -       | -       | 100.0  | 100.0   |
| Purified water                         | q.s.   | q.s.   | q.s.   | q.s.   | q.s.    | q.s.    | q.s.    | q.s.   | q.s.    |
| <b>External phase</b>                  |        |        |        |        |         |         |         |        |         |
| MCC                                    | 295.0  | -      | 295.0  | -      | -       | -       | -       | 295.0  | -       |
| Aerosil                                | -      | -      | -      | -      | -       | 30.0    | 27.0    | -      | 35.0    |
| Vildagliptin                           | 50.0   | 50.0   | 50.0   | 50.0   | 50.0    | 50.0    | 50.0    | 50.0   | 50.0    |
| <b>Lubrication</b>                     |        |        |        |        |         |         |         |        |         |
| Magnesium stearate                     | 15.0   | 15.0   | 15.0   | 11.0   | 15.0    | 15.0    | 15.0    | 15.0   | 15.0    |
| <b>Physicochemical characteristics</b> |        |        |        |        |         |         |         |        |         |
| Hardness (N)                           | 184    | caping | 191    | 94     | 158     | 188     | 157     | 150    | 85      |
| Disintegration                         | 2'51'' | -      | 5'23'' | 8'11'' | 10'03'' | 12'44'' | 11'20'' | 0'22'' | 15'20'' |

- 10 Tablets with adequate physical attributes were obtained from all the above formulations except that of 2.2. Formulations 2.5, 2.6 and 2.7 presented the best hardness value in combination with an acceptable disintegration time for a high load drug combination. Flowability of the said formulations 2.5, 2.6 and 2.7 was measured by the Carr's index and found to be 26, 19 and 23, respectively. In conclusion, PVP/VA64 performed well as a binding agent, to form a Metformin granulate that provides adequate physical properties to the final tablet.
- 15

### Example 3

Further formulation trials incorporated the optimization of formulation 2.6 with DOE approach.

- 20 The idea was to keep PVP/VA64 as the main binder for the wet granulation, while Aerosil was added with Vildagliptin in predetermined percentages. For that, two numerical factors such as PVP/VA64 and Aerosil percentages were varied. The methodology for this DOE was the full factorial design that included 3 center points for a total of 8 runs. Likely operating ranges of the

independent variables were established (Table 5). The factors that were selected for this DOE with the respective constraints are presented in Table 5 and 6.

Table 5. Factors selected to perform factorial design

| Factors in total internal phase excipients  | Level |      |
|---------------------------------------------|-------|------|
|                                             | Low   | High |
| X <sub>1</sub> = percentage of PVP/VA64 (%) | 5.0   | 12.0 |
| X <sub>2</sub> = percentage of Aerosil (%)  | 0.0   | 5.0  |

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Table 6. DOE parameter settings including ingredients and proportions in the mixture

| Run | PVP/VA64 (X <sub>1</sub> ) | Aerosil (X <sub>2</sub> ) |
|-----|----------------------------|---------------------------|
| 3.1 | 5.0                        | 0.0                       |
| 3.2 | 12.0                       | 0.0                       |
| 3.3 | 8.5                        | 2.5                       |
| 3.4 | 8.5                        | 2.5                       |
| 3.5 | 5.0                        | 5.0                       |
| 3.6 | 8.5                        | 2.5                       |
| 3.7 | 12.0                       | 5.0                       |
| 3.8 | 12.0                       | 1.0                       |

The design points were generated by Minitab® statistical software and the respective tablet formulations are based upon Table 6 with a fixed final uncoated tablet weight of 1189 mg. A summarization of the DOE experimental results regarding the physical characterization of the uncoated tablets are presented in Table 7. Additionally, Carr's indices have been included in the factorial responses as in all formulations and found to be in the range of 10-26.

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Table 7. Average tablet hardness, disintegration time and flowability of the blend

| Formulation | Disintegration (min) | Hardness (N) | Carr's index |
|-------------|----------------------|--------------|--------------|
| Comp 3.1    | 4                    | 114          | 20           |
| Comp 3.2    | 12                   | 158          | 10           |
| Comp 3.3    | 21                   | 163          | 26           |
| Comp 3.4    | 8                    | 120          | 26           |
| Comp 3.5    | 6                    | 90           | 10           |
| Comp 3.6    | 10                   | 129          | 20           |
| Comp 3.7    | 14                   | 163          | 11           |
| Comp 3.8    | 12                   | 155          | 10           |

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For the preferred response limits (Hardness: 100-180 N, Disintegration: 6-14 min and Carr's index: 8-18%) the best design seems to be with a percentage range of 7 to 9% of PVP/VA64 (X<sub>1</sub>) and a range of 2 and 3% Aerosil (X<sub>2</sub>) to develop an acceptable formulation

Example 4

Further formulation development was initiated in order to optimize the proportion of PVP/VA64 for the formation of Metformin granulates together with the percentage of the externally added Aerosil. With regard to the optimal design space of the previous section three formulations were conducted with a constant PVP/VA64 percentage of ~8% and a range of 1-3% for Aerosil. For that reason, replicates of compositions 2.6, 3.6 and 3.7 were conducted and numerated as 2.6.1, 3.6.1 and 3.7.1 with 2%, 1% and 3% Aerosil, respectively. The formulations are presented in the following Table 8 as well as their physical attributes.

Table 8. Formulations 2.6.1, 3.6.1 and 3.7.1 and physicochemical characteristics

| Composition                            | 2.6.1         | 3.6.1         | 3.7.1         |
|----------------------------------------|---------------|---------------|---------------|
| <b>Components (mg)</b>                 |               |               |               |
| <b>Metformin granulate</b>             |               |               |               |
| Metformin HCl                          | 1000.0        | 1000.0        | 1000.0        |
| PVP/VA64                               | 100.0         | 100.0         | 100.0         |
| <i>Purified water</i>                  | q.s.          | q.s.          | q.s.          |
| <b>External phase</b>                  |               |               |               |
| Aerosil                                | 24.0          | 12.0          | 36.0          |
| Vildagliptin                           | 50.0          | 50.0          | 50.0          |
| <b>Lubrication</b>                     |               |               |               |
| Magnesium stearate                     | 15.0          | 15.0          | 15.0          |
| <b>Total for uncoated tablet</b>       | <b>1189.0</b> | <b>1177.0</b> | <b>1201.0</b> |
| Opadry premix                          | 35.7          | 35.3          | 36.0          |
| <i>Purified water</i>                  | q.s.          | q.s.          | q.s.          |
| <b>Total for coated tablet</b>         | <b>1224.7</b> | <b>1212.3</b> | <b>1237.0</b> |
| <b>Physicochemical characteristics</b> |               |               |               |
| Disintegration (min)                   | 14            | 12            | 17            |
| Hardness (N)                           | 226           | 173           | 201           |
| Carr's index                           | 13            | 20            | 10            |

The in-vitro Vildagliptin and Metformin release from film-coated tablets was evaluated using apparatus II (rotating paddle method) of the USP 2 on a dissolution tester. The test for the film-coated tablets was performed at  $37 \pm 0.5^\circ\text{C}$  with a rotation speed of 100 rpm using as dissolution medium 900 mL of buffer solution at pH 6.8 for 60 mins.

Formulation 2.6.1 with 8.4% PVP/VA64 and 2% Aerosil showed Metformin and Vildagliptin release rates that were satisfying. Although, Metformin release rate for formulations 3.6.1 and 3.7.1 exhibited similar behaviour, the respective Vildagliptin release rate showed a slower

profile. The Carr's index for formulations 2.6.1 and 3.7.1 characterized the bulk flowability as good and for formulation 3.6.1 as poor.

### Example 5

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Further optimization procedure was utilized due to prior art that involve the total percentage of both active agents in the final formulation. The percentage of active agents has impact on the final tablet weight and for that the DOE approach was used. A series of formulation runs was initiated, where the main goal was to optimize the PVP/VA64 and Aerosil percentages while the total tablet weight is increased. The methodology for this DOE was the full factorial design that included 1 center point for a total of 4 runs (Formulation 4.1, 4.2, 4.3, 4.4). Likely operating ranges of the independent variables were established (Table 9). The factors that were selected for this DOE with the respective constraints are presented in Tables 9 and 10.

15 Table 9. Factors selected to perform factorial design

| Factors in total internal phase excipients  | Level |      |
|---------------------------------------------|-------|------|
|                                             | Low   | High |
| X <sub>1</sub> = percentage of PVP/VA64 (%) | 8.0   | 16.0 |
| X <sub>2</sub> = percentage of Aerosil (%)  | 2.0   | 9.0  |

Table 10. DOE parameter settings including ingredients and proportions in the mixture

| Run | PVP/VA64 (X <sub>1</sub> ) | Aerosil (X <sub>2</sub> ) |
|-----|----------------------------|---------------------------|
| 4.1 | 16.0                       | 2.0                       |
| 4.2 | 12.0                       | 5.5                       |
| 4.3 | 16.0                       | 9.0                       |
| 4.4 | 8.0                        | 9.0                       |

20 The design points were generated by Minitab® statistical software and the respective tablet formulations are based upon Table 10 with a fixed final uncoated tablet weight of 1311 mg. A summarization of the DOE experimental results regarding the physical characterization of the uncoated tablets are presented in Table 10. The DOE experimental results regarding the physical characterization of the uncoated tablets are presented in Table 11.

Table 11. Average tablet hardness, disintegration time and flowability of the blend

| Composition | Disintegration (min) | Hardness (N) |
|-------------|----------------------|--------------|
| Comp 4.1    | 12                   | 213          |
| Comp 4.2    | 25                   | 96           |
| Comp 4.3    | 18                   | 89           |
| Comp 4.4    | 16                   | 183          |

Example 6

- 5 According to the results from the previous experiments the inventors determined that the PVP/VA64 and Aerosil percentages are defined at around 15.5% and 3.4%, respectively. Finally, formulation 4.5 was tested that was manufactured according to these findings shown in table 12.

Table 12. Composition 4.5 for 50/850 and 50/1000 mg strength and physicochemical characteristics

| Composition 4.5                        | 50/850 mg                  |                | 50/1000 mg    |               |
|----------------------------------------|----------------------------|----------------|---------------|---------------|
| Ingredients                            | %                          | mg per tablet  | %             | mg per tablet |
|                                        | <b>Metformin granulate</b> |                |               |               |
| Metformin HCl                          | 75.22                      | 850.00         | 75.87         | 1000.0        |
| PVP/VA64                               | 15.49                      | 175.00         | 15.40         | 203.0         |
| <i>Purified water</i>                  | q.s.                       | q.s.           | q.s.          | q.s.          |
|                                        | <b>External Phase</b>      |                |               |               |
| Aerosil                                | 3.36                       | 38.00          | 3.41          | 45.0          |
| Vildagliptin                           | 4.42                       | 50.00          | 3.79          | 50.0          |
|                                        | <b>Lubrication</b>         |                |               |               |
| Magnesium Stearate                     | 1.50                       | 17.00          | 1.52          | 20.0          |
| <b>Total for uncoated tablet</b>       | <b>100.00</b>              | <b>1130.00</b> | <b>100.00</b> | <b>1318.0</b> |
| Opadry premix                          | 3.00                       |                | 3.00          |               |
| <i>Purified water</i>                  | q.s.                       | q.s.           | q.s.          | q.s.          |
| <b>Total for coated tablet</b>         |                            | <b>1163.9</b>  |               | <b>1357.5</b> |
| <b>Physicochemical characteristics</b> |                            |                |               |               |
| Disintegration (min)                   |                            | 15'30''        |               | 15'45''       |
| Hardness (N)                           |                            | 235            |               | 237           |
| Carr's index                           |                            | 15             |               | 15            |

The manufacturing process comprises wet granulation of Metformin HCl with a kneading aqueous solution of PVP/VA64. Then, for the external phase Vildagliptin and Aerosil are added successively and Magnesium Stearate for the lubrication.

The drug release profile is similar for formulations 4.5 compared to 2.6.1, a fact that underlines the unchangeable in-vitro behaviour even in case of different final tablet weight.

The 6 months stability data for the final composition 4.5 are shown below in Table 13 and 14. Regarding the final composition 4.5, the stability data are within the specified limits for both active ingredients

5 Table 13. Vildagliptin stability data in zero time and after 6 months for Comp 4.5

| <b>Comp 4.5</b>         | <b>Limit</b> | <b>Zero time</b> | <b>25°C</b> | <b>40°C</b> |
|-------------------------|--------------|------------------|-------------|-------------|
| <b>Impurity C</b>       | <b>0.2%</b>  | 0.09%            | 0.11%       | 0.14%       |
| <b>Impurity E</b>       |              | 0.03%            | 0.04%       | 0.05%       |
| <b>Total Impurities</b> | <b>1.5%</b>  | 0.22%            | 0.23%       | 0.42%       |

Table 14. Metformin HCl stability data in zero time and after 6 months for Comp 4.5

| <b>Comp 4.5</b>         | <b>Limit</b> | <b>Zero time</b> | <b>25°C</b> | <b>40°C</b> |
|-------------------------|--------------|------------------|-------------|-------------|
| <b>Impurity F</b>       | <b>0.2%</b>  | ND               | ND          | ND          |
| <b>Total Impurities</b> | <b>1.0%</b>  | 0.02%            | 0.03%       | 0.04%       |

Finally, Metformin HCl and Vildagliptin sustain their crystallinity form after the manufacturing process.

## CLAIMS

1. A pharmaceutical composition comprising Vildagliptin and Metformin or a pharmaceutically acceptable salt thereof, wherein said composition comprises a granulate of Metformin or a pharmaceutically acceptable salt thereof with a vinylpyrrolidone-vinyl acetate copolymer.
2. The pharmaceutical composition according to claim 1, wherein the vinylpyrrolidone-vinyl acetate copolymer is in an amount of from 5% to about 25% of the total weight of the composition, preferably from 10% to about 20% of the total weight of the composition.
3. The pharmaceutical composition according to any of claims 1 or 2, further comprising colloidal silicon dioxide.
4. The pharmaceutical composition according to claim 3, comprising colloidal silicon dioxide in amount from 1% to 5% of the total weight of the composition.
5. The pharmaceutical composition according to any of the preceding claims comprises at least one optional pharmaceutically acceptable excipient selected from a diluent, a lubricant and a disintegrant.
6. The pharmaceutical composition according to any of the preceding claims comprises a lubricant.
7. The pharmaceutical composition according to claim 6, wherein the lubricant is magnesium stearate.
8. The solid pharmaceutical composition according to any of claims 6 and 7, wherein the lubricant is in a percentage from 1% to 5% of the total weight of the composition.
9. A process for the preparation of a pharmaceutical composition of Vildagliptin and Metformin or a pharmaceutically acceptable salt thereof, comprising the following steps:
  - wet granulation of Metformin or a pharmaceutically acceptable salt thereof with a vinylpyrrolidone-vinyl acetate copolymer in an aqueous solution to form a granulate,
  - Drying of the granulate,
  - addition of Vildagliptin or a pharmaceutically acceptable salt thereof & a glidant and mixing,
  - addition of a lubricant and mixing,
  - compression to tablets and coating
10. The process according to claim 9, wherein the vinylpyrrolidone-vinyl acetate copolymer is in an amount of from 5% to about 25% of the total weight of the composition, preferably from 10% to about 20% of the total weight of the composition.

11. The process according to claim 9, wherein the glidant is colloidal silicon dioxide.
12. The process according to claim 9, wherein the lubricant is selected from magnesium stearate.

# INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2019/025314

A. CLASSIFICATION OF SUBJECT MATTER  
INV. A61K31/155 A61P3/08  
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, EMBASE, WPI Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                                     | Relevant to claim No. |
|-----------|----------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X         | WO 2015/097234 A1 (KRKA D D NOVO MESTO [SI]) 2 July 2015 (2015-07-02)<br>page 10, line 1; claims 1, 12<br>page 6, lines 26-30<br>----- | 1-12                  |



Further documents are listed in the continuation of Box C.



See patent family annex.

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2019/025314

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s) | Publication<br>date |
|-------------------------------------------|---------------------|----------------------------|---------------------|
| W0 2015097234 A1                          | 02-07-2015          | EA 201691322 A1            | 31-10-2016          |
|                                           |                     | EP 3086781 A1              | 02-11-2016          |
|                                           |                     | W0 2015097234 A1           | 02-07-2015          |
| -----                                     |                     |                            |                     |