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(54) Title: AN ORAL OSMOTIC PHARMACEUTICAL COMPOSITION OF VILDAGLIPTIN

(57) Abstract: There is provided an osmotic pharmaceutical composition comprising: (a) a core, comprising: (i) a drug layer comprising vildagliptin or salt thereof, and one or more pharmaceutically acceptable excipients; (ii) a push layer comprising polyethylene oxide having molecular weight of about 5,000,000 to about 8,000,000, wherein weight ratio of vildagliptin or salt thereof and polyethylene oxide ranges from about 1:1 to about 1:5; (b) a seal coat surrounding the core; (c) a sustained release coat cellulose acetate surrounding the seal coat; (d) an immediate release drug layer comprising vildagliptin or salt thereof surrounding the sustained release coat. Also provided is process of preparing such compositions.



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AN ORAL OSMOTIC PHARMACEUTICAL COMPOSITION OF VILDAGLIPTIN

TECHNICAL FIELD OF THE INVENTION

5 The invention relates to a novel osmotic pharmaceutical composition comprising vildagliptin or salt thereof. The invention further provides a process of preparing such compositions.

BACKGROUND OF THE INVENTION

10 Diabetes mellitus is a common disorder more prevalent in developed countries. It is characterized by its clinical manifestations, namely the non-insulin-dependent or maturity onset form, also known as type 2 diabetes and the insulin-dependent or juvenile onset form, also known as type 1 diabetes. It is a metabolic disease in which there is a high blood sugar level over a prolonged period. This disorder is associated with high morbidity and mortality.

15 Dipeptidyl-peptidase-IV (DPP-IV) inhibitors are an oral drug class that was introduced in 2006 and that seems easy to use and do not require regular glucose monitoring or dose adjustments. DPP-IV inhibitors act by inhibiting DPP-IV enzyme, a multifunctional transmembrane glycoprotein enzyme that cleaves N-terminal dipeptides from polypeptides with L-proline or L-alanine at the penultimate position. Vildagliptin is an orally active inhibitor of the DPP-IV
20 enzyme. After a meal intake, insulinotropic hormone glucagon-like peptide-1 (GLP-1) is released which in turn induces insulin release from the pancreas. Some of the GLP-1 is inactivated by the DPP-IV present in plasma and intestinal capillary endothelium. Therefore, if the DPP-IV inhibited, more GLP-1 will be available to activate insulin release from the pancreas. The advantage of this mechanism of insulin release is that insulin is secreted only in response to a meal. Therefore,
25 problems of hypoglycemia associated with other diabetes drugs are less likely with a DPP-IV inhibitor. Vildagliptin alone or in combination with other anti-diabetic agents is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type-2 diabetes mellitus in multiple clinical conditions. Vildagliptin is marketed by Novartis in the Europe in the form of tablets under the trademark GALVUS®. The recommended daily dose of Vildagliptin is 100mg,
30 administered as one dose of 50mg in the morning and one dose of 50mg in the evening.

U.S. Patent No. 6,166,063 discloses a DPP-IV inhibitor compound vildagliptin, its use in treating type-2 diabetes mellitus and its pharmaceutical composition. U.S. Patent No. 6,303,661 discloses methods of using an oral inhibitor of DPP-IV or DPP IV-like enzyme activity to reduce blood
35 glucose levels after food intake. U.S. Patent No. 8,143,217 discloses methods of using vildagliptin in combination with insulin to treat hypoglycemic events in a patient with diabetes. European Patent Application, EP 1,537,880 A1 relates to a sustained release formulation of DPP-IV inhibitor

(Vildagliptin) comprising a hydrophilic polymer. European Patent No. EP 2,191,824 B1 discloses sustained release formulation of DPP-IV inhibitor (Vildagliptin) comprising hydroxypropyl methylcellulose. European Patent Application, EP 2,578,208 A1 discloses solid dosage formulation obtained with briquette pressing or compression between rollers and characterized in that it comprises DPP-IV inhibitor. PCT Publication No. WO 2014/029841 A1 discloses extended release compositions of an amino-C2-C6-alkyl nitrate and fixed dose combinations with vildagliptin.

The existing vildagliptin product is a direct compression tablet with a 25% drug load. Patient adherence to a drug regimen indirectly correlates with frequency of dosing i.e. greater adherence is seen with a once daily dosing regimen compared to a twice daily dosing regimen. The majority of data currently available for vildagliptin is derived from studies based on the immediate release formulation (GALVUS[®]) having twice daily dosing regimen. There is a need to provide a once a daily formulation of vildagliptin which will provide ease, convenience and reduced side effects profile.

SUMMARY OF THE INVENTION

A general aspect of the invention discloses an osmotic pharmaceutical composition comprising: (a) a core, comprising: (i) a drug layer comprising vildagliptin or salt thereof, and one or more pharmaceutically acceptable excipients; (ii) a push layer comprising polyethylene oxide having molecular weight of about 5,000,000 to about 8,000,000, wherein weight ratio of vildagliptin or salt thereof and polyethylene oxide ranges from about 1:1 to about 1:5; (b) a seal coat surrounding the core; (c) a sustained release coat comprising cellulose acetate surrounding the seal coat; (d) an immediate release drug layer comprising vildagliptin or salt thereof surrounding the sustained release coat.

In another aspect of the invention, there is provided an osmotic pharmaceutical composition comprising: (a) a core, comprising: (i) a drug layer comprising about 35 mg to about 95 mg of vildagliptin or salt thereof, and one or more pharmaceutically acceptable excipients; (ii) a push layer comprising polyethylene oxide having molecular weight of about 5,000,000 to about 8,000,000, wherein weight ratio of vildagliptin or salt thereof and polyethylene oxide ranges from about 1:1 to about 1:5; (b) a seal coat surrounding the core; (c) a sustained release coat comprising about 70% to about 95% by weight cellulose acetate surrounding the seal coat; (d) an immediate release drug layer comprising about 15 mg to about 35 mg of vildagliptin or salt thereof surrounding the sustained release coat.

In another aspect of the invention, there is provided an osmotic pharmaceutical composition comprising: (a) a core, comprising: (i) a drug layer comprising about 35 mg to about 95 mg of vildagliptin or salt thereof, and one or more pharmaceutically acceptable excipients; (ii) a push layer comprising polyethylene oxide having molecular weight of about 5,000,000 to about 8,000,000, wherein weight ratio of vildagliptin or salt thereof and polyethylene oxide ranges from about 1:1 to about 1:5; (b) a seal coat surrounding the core; (c) a sustained release coat comprising about 70% to about 95% by weight cellulose acetate surrounding the seal coat; (d) an immediate release drug layer comprising about 15 mg to about 35 mg of vildagliptin or salt thereof surrounding the sustained release coat; and wherein the composition exhibits an in-vitro release profile such that about 10% to about 30% of vildagliptin or salt thereof is released at 2 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, 0.1N HCl at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. In another embodiment, the composition exhibits an in-vitro release profile such that about 70% to about 95% of vildagliptin or salt thereof is released at 24 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, phosphate buffer of pH 6.8 at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$.

In another embodiment, the composition is storage stable for a period of 3 months at about $30^{\circ}\text{C}/65\%$ relative humidity and exhibits an in-vitro release profile such that about 20% to about 30% of vildagliptin or salt thereof is released at 2 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, 0.1N HCl at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. In another embodiment, the composition is storage stable for a period 3 months at $40^{\circ}\text{C}/75\%$ relative humidity and exhibits an in-vitro release profile such that about 20% to about 30% of vildagliptin or salt thereof is released at 2 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, 0.1N HCl at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. In another embodiment, the composition is storage stable for a period 3 months at $30^{\circ}\text{C}/65\%$ relative humidity and exhibits an in-vitro release profile such that about 85% to about 95% of vildagliptin or salt thereof is released at 24 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, phosphate buffer of pH 6.8 at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. In another embodiment, the composition is storage stable for a period 3 months at $40^{\circ}\text{C}/75\%$ relative humidity and exhibits an in-vitro release profile such that about 85% to about 95% of vildagliptin or salt thereof is released at 24 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, phosphate buffer of pH 6.8 at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$.

In another embodiment, the composition provides a mean plasma concentration of vildagliptin or salt thereof in the range of about 5 ng/ml to about 250 ng/ml over a period of at least 24 hours after once daily oral administration. In another embodiment, the composition provides a mean plasma concentration of vildagliptin or salt thereof of about 5 ng/ml to about 30 ng/ml at 24 hours after once daily oral administration.

In another embodiment, the composition can decrease DPP-IV enzyme activity in blood plasma by about 60% to about 90% over the period of 24 hours. In another embodiment, the composition can decrease DPP-IV enzyme activity in blood plasma by about 80% over the period of 24 hours.

- 5 In another aspect of the invention, there is provided an osmotic pharmaceutical composition comprising: (a) a core, comprising: (i) a drug layer comprising about 75 mg of vildagliptin or salt thereof, and one or more pharmaceutically acceptable excipients; (ii) a push layer comprising about 80 mg to about 90 mg of polyethylene oxide having molecular weight of about 5,000,000 to about 8,000,000; (b) a seal coat surrounding the core; (c) a sustained release coat comprising about
10 35 mg to about 45 mg of cellulose acetate surrounding the seal coat; (d) an immediate release drug layer comprising about 25 mg of vildagliptin or salt thereof surrounding the sustained release coat; and wherein the composition exhibits an in-vitro release profile such that about 20% to about 30% of vildagliptin or salt thereof is released at 2 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, 0.1N HCl at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ and/or about 85% to about 95% of vildagliptin
15 or salt thereof is released at 24 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, phosphate buffer of pH 6.8 at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$.

- In another aspect of the invention, there is provided a kit comprising an osmotic pharmaceutical composition comprising: (a) a core, comprising: (i) a drug layer comprising vildagliptin or salt
20 thereof, and one or more pharmaceutically acceptable excipients; (ii) a push layer comprising polyethylene oxide having molecular weight of about 5,000,000 to about 8,000,000, wherein weight ratio of vildagliptin or salt thereof and polyethylene oxide ranges from about 1:1 to about 1:5; (b) a seal coat surrounding the core; (c) a sustained release coat cellulose acetate surrounding the seal coat; (d) an immediate release drug layer comprising vildagliptin or salt thereof
25 surrounding the sustained release coat.

- In another aspect of the invention, there is provided a kit comprising an osmotic pharmaceutical composition comprising: (a) a core, comprising: (i) a drug layer comprising about 35 mg to about 95 mg of vildagliptin or salt thereof, and one or more pharmaceutically acceptable excipients; (ii) a
30 push layer comprising polyethylene oxide having molecular weight of about 5,000,000 to about 8,000,000, wherein weight ratio of vildagliptin or salt thereof and polyethylene oxide ranges from about 1:1 to about 1:5; (b) a seal coat surrounding the core; (c) a sustained release coat comprising about 70% to about 95% by weight cellulose acetate surrounding the seal coat; (d) an immediate release drug layer comprising about 15 mg to about 35 mg of vildagliptin or salt thereof
35 surrounding the sustained release coat; and wherein the composition exhibits an in-vitro release profile such that about 10% to about 30% of vildagliptin or salt thereof is released at 2 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, 0.1N HCl at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$.

In another aspect of the invention, there is provided a method of treating type 2 diabetes, said method comprises administering to a patient in a need thereof an osmotic pharmaceutical composition comprising: (a) a core, comprising: (i) a drug layer comprising vildagliptin or salt thereof, and one or more pharmaceutically acceptable excipients; (ii) a push layer comprising polyethylene oxide having molecular weight of about 5,000,000 to about 8,000,000, wherein weight ratio of vildagliptin or salt thereof and polyethylene oxide ranges from about 1:1 to about 1:5; (b) a seal coat surrounding the core; (c) a sustained release coat cellulose acetate surrounding the seal coat; (d) an immediate release drug layer comprising vildagliptin or salt thereof surrounding the sustained release coat.

In another aspect of the invention, there is provided a method of treating type 2 diabetes, said method comprises administering to a patient in a need thereof an osmotic pharmaceutical composition comprising: (a) a core, comprising: (i) a drug layer comprising about 35 mg to about 95 mg of vildagliptin or salt thereof, and one or more pharmaceutically acceptable excipients; (ii) a push layer comprising polyethylene oxide having molecular weight of about 5,000,000 to about 8,000,000, wherein weight ratio of vildagliptin or salt thereof and polyethylene oxide ranges from about 1:1 to about 1:5; (b) a seal coat surrounding the core; (c) a sustained release coat comprising about 70% to about 95% by weight cellulose acetate surrounding the seal coat; (d) an immediate release drug layer comprising about 15 mg to about 35 mg of vildagliptin or salt thereof surrounding the sustained release coat; and wherein the composition exhibits an in-vitro release profile such that about 10% to about 30% of vildagliptin or salt thereof is released at 2 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, 0.1N HCl at 37°C ± 0.5°C.

In another aspect of the invention, there is provided a process of preparing an osmotic pharmaceutical composition comprising: (a) a core, comprising: (i) a drug layer comprising about 35 mg to about 95 mg of vildagliptin or salt thereof, and one or more pharmaceutically acceptable excipients; (ii) a push layer comprising polyethylene oxide having molecular weight of about 5,000,000 to about 8,000,000, wherein weight ratio of vildagliptin or salt thereof and polyethylene oxide ranges from about 1:1 to about 1:5; (b) a seal coat surrounding the core; (c) a sustained release coat comprising about 70% to about 95% by weight cellulose acetate surrounding the seal coat; (d) an immediate release drug layer comprising about 15 mg to about 35 mg of vildagliptin or salt thereof surrounding the sustained release coat; and wherein the composition exhibits an in-vitro release profile such that about 10% to about 30% of vildagliptin or salt thereof is released at 2 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, 0.1N HCl at 37°C ± 0.5°C, and wherein said process comprises steps of:

- (a) preparing the drug layer in the form of a granules comprising vildagliptin or salt thereof, and one or more pharmaceutically acceptable excipients,
- (b) preparing a push layer in the form of a granules comprising polyethylene oxide,
- (c) compressing the granules of the drug layer and the push layer to form the core,
- 5 (d) seal coating the core of step (c),
- (e) coating the seal coat of step (d) with the sustained release coat comprising about 70% to about 95% by weight cellulose acetate, and
- (f) coating the sustained release coat of step (e) with the immediate release drug layer comprising vildagliptin or salt thereof to obtain the osmotic pharmaceutical composition.

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BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1A and Figure 1B shows in-vitro dissolution profile of vildagliptin composition 1A and composition 1B respectively, at acid stage and buffer stage.

15 Figure 2A shows % DPP-IV inhibition after administration of invention composition 1A and GALVUS[®].

Figure 2B shows Plasma-drug concentration profile after administration of invention composition 1A and GALVUS[®].

Figure 3A shows % DPP-IV inhibition after administration of invention composition 1B and GALVUS[®].

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Figure 3B shows Plasma-drug concentration profile after administration of invention composition 1B and GALVUS[®].

Figure 4 shows in-vitro dissolution profile of comparative vildagliptin composition 6A and 6B at acid stage and buffer stage.

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DETAILED DESCRIPTION OF THE INVENTION

A general aspect of the invention discloses an osmotic pharmaceutical composition comprising: (a) a core, comprising: (i) a drug layer comprising vildagliptin or salt thereof, and one or more pharmaceutically acceptable excipients; (ii) a push layer comprising polyethylene oxide having molecular weight of about 5,000,000 to about 8,000,000, wherein weight ratio of vildagliptin or salt thereof and polyethylene oxide ranges from about 1:1 to about 1:5; (b) a seal coat surrounding the core; (c) a sustained release coat comprising cellulose acetate surrounding the seal coat; (d) an immediate release drug layer comprising vildagliptin or salt thereof surrounding the sustained release coat.

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The term “osmotic pharmaceutical composition” refers to an advanced controlled release solid drug delivery system with a sustained release coat and one or more small laser drilled bores in it.

The term “core” refers to a matrix or a bilayer or a trilayer or a multilayer component having a drug, osmotic agent and one or more pharmaceutically acceptable excipients.

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The term “sustained release coat” refers to a semi-permeable membrane controlling drug release.

In another aspect of the invention, there is provided an osmotic pharmaceutical composition comprising: (a) a core, comprising: (i) a drug layer comprising about 35 mg to about 95 mg of vildagliptin or salt thereof, and one or more pharmaceutically acceptable excipients; (ii) a push layer comprising polyethylene oxide having molecular weight of about 5,000,000 to about 8,000,000, wherein weight ratio of vildagliptin or salt thereof and polyethylene oxide ranges from about 1:1 to about 1:5; (b) a seal coat surrounding the core; (c) a sustained release coat comprising about 70% to about 95% by weight cellulose acetate surrounding the seal coat; (d) an immediate release drug layer comprising about 15 mg to about 35 mg of vildagliptin or salt thereof surrounding the sustained release coat.

In another aspect of the invention, there is provided an osmotic pharmaceutical composition comprising: (a) a core, comprising: (i) a drug layer comprising about 35 mg to about 95 mg of vildagliptin or salt thereof, and one or more pharmaceutically acceptable excipients; (ii) a push layer comprising polyethylene oxide having molecular weight of about 5,000,000 to about 8,000,000, wherein weight ratio of vildagliptin or salt thereof and polyethylene oxide ranges from about 1:1 to about 1:5; (b) a seal coat surrounding the core; (c) a sustained release coat comprising about 70% to about 95% by weight cellulose acetate surrounding the seal coat; (d) an immediate release drug layer comprising about 15 mg to about 35 mg of vildagliptin or salt thereof surrounding the sustained release coat; and wherein the composition exhibits an in-vitro release profile such that about 10% to about 30% of vildagliptin or salt thereof is released at 2 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, 0.1N HCl at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$.

In one embodiment, the composition exhibits an in-vitro release profile such that about 15% to about 25% of vildagliptin or salt thereof is released at 2 hours when measured in 0.1N HCl at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. Alternatively, the composition exhibits an in-vitro release profile such that about 18% to about 22% of vildagliptin or salt thereof is released at 2 hours when measured in 0.1N HCl at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. Alternatively, the composition exhibits an in-vitro release profile such that about 20% of vildagliptin or salt thereof is released at 2 hours when measured in 0.1N HCl at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$.

In another embodiment, the composition exhibits an in-vitro release profile such that about 70% to about 95% of vildagliptin or salt thereof is released at 24 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, phosphate buffer of pH 6.8 at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. In another embodiment of this aspect, the composition exhibits an in-vitro release profile such that about 85% to about 95% of vildagliptin or salt thereof is released at 24 hours when measured in phosphate buffer of pH 6.8 at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. Alternatively, the composition exhibits an in-vitro release profile such that about 80% to about 90% of vildagliptin or salt thereof is released at 24 hours when measured in phosphate buffer of pH 6.8 at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. Alternatively, the composition exhibits an in-vitro release profile such that about 85% of vildagliptin or salt thereof is released at 24 hours when measured in phosphate buffer of pH 6.8 at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$.

In another embodiment, the composition is storage stable for a period of 3 months at about $30^{\circ}\text{C}/65\%$ relative humidity and exhibits an in-vitro release profile such that about 20% to about 30% of vildagliptin or salt thereof is released at 2 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, 0.1N HCl at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. Alternatively, the composition is storage stable for a period of 3 months at about $30^{\circ}\text{C}/65\%$ relative humidity and exhibits an in-vitro release profile such that about 25% of vildagliptin or salt thereof is released at 2 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, 0.1N HCl at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$.

In another embodiment, the composition is storage stable for a period 3 months at $40^{\circ}\text{C}/75\%$ relative humidity and exhibits an in-vitro release profile such that about 20% to about 30% of vildagliptin or salt thereof is released at 2 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, 0.1N HCl at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. Alternatively, the composition is storage stable for a period 3 months at $40^{\circ}\text{C}/75\%$ relative humidity and exhibits an in-vitro release profile such that about 25% of vildagliptin or salt thereof is released at 2 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, 0.1N HCl at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$.

In another embodiment, the composition is storage stable for a period 3 months at $30^{\circ}\text{C}/65\%$ relative humidity and exhibits an in-vitro release profile such that about 85% to about 95% of vildagliptin or salt thereof is released at 24 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, phosphate buffer of pH 6.8 at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. Alternatively, the composition is storage stable for a period 3 months at $30^{\circ}\text{C}/65\%$ relative humidity and exhibits an in-vitro release profile such that about 90% of vildagliptin or salt thereof is released at 24 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, phosphate buffer of pH 6.8 at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$.

In another embodiment, the composition is storage stable for a period 3 months at $40^{\circ}\text{C}/75\%$ relative humidity and exhibits an in-vitro release profile such that about 85% to about 95% of

vildagliptin or salt thereof is released at 24 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, phosphate buffer of pH 6.8 at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. Alternatively, the composition is storage stable for a period 3 months at $40^{\circ}\text{C}/75\%$ relative humidity and exhibits an in-vitro release profile such that about 90% of vildagliptin or salt thereof is released at 24 hours, when measured in
5 USP apparatus Type I, at 100 rpm using 900 ml, phosphate buffer of pH 6.8 at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$.

In another embodiment, the composition provides a mean plasma concentration of vildagliptin or salt thereof in the range of about 5 ng/ml to about 250 ng/ml over a period of at least 24 hours after once daily oral administration. In another embodiment, the composition provides a mean plasma
10 concentration of vildagliptin or salt thereof in the range of about 10 ng/ml to about 200 ng/ml, or about 20 ng/ml to about 150 ng/ml, or about 30 ng/ml to about 100 ng/ml, or about 40 ng/ml to about 50 ng/ml over a period of at least 24 hours after once daily oral administration. In another embodiment, the composition provides a mean plasma concentration of vildagliptin or salt thereof of about 5 ng/ml to about 30 ng/ml at 24 hours after once daily oral administration. Alternatively,
15 the composition provides a mean plasma concentration of vildagliptin or salt thereof of about 10 ng/ml to about 20 ng/ml at 24 hours after once daily oral administration.

In another embodiment, the composition can decrease DPP-IV enzyme activity in blood plasma by about 60% to about 90% over the period of 24 hours. Alternatively, the composition can decrease
20 DPP-IV enzyme activity in blood plasma by about 70% to about 80% over the period of 24 hours. Alternatively, the composition can decrease DPP-IV enzyme activity in blood plasma by about 80% over the period of 24 hours. In another embodiment, the composition can decrease DPP-IV enzyme activity in blood plasma by about 80% over the period of 24 hours. In another embodiment, the composition can decrease DPP-IV enzyme activity in blood plasma by about
25 80% over the period of 20 hours. In another embodiment, the composition can decrease DPP-IV enzyme activity in blood plasma by about 80% over the period of 18 hours. In another embodiment, the composition can decrease DPP-IV enzyme activity in blood plasma by about 80% over the period of 16 hours. In another embodiment, the composition can decrease DPP-IV enzyme activity in blood plasma by about 80% over the period of 14 hours. In another
30 embodiment, the composition can decrease DPP-IV enzyme activity in blood plasma by about 80% over the period of 12 hours. In another embodiment, the composition can decrease DPP-IV enzyme activity in blood plasma by about 80% over the period of 10 hours.

In another embodiment, the core comprises a drug layer comprising about 35 mg to about 95 mg of
35 vildagliptin or salt thereof. In another embodiment, the drug layer comprises about 45 mg to about 90 mg, or about 55 mg to about 85 mg, or about 65 mg to about 75 mg of vildagliptin or salt thereof. Alternatively, the drug layer comprises about 40 mg, or about 45 mg, or about 50 mg, or

about 55 mg, or about 60 mg, or about 65 mg, or about 70 mg, or about 75 mg, or about 80 mg, or about 85 mg, or about 90 mg of vildagliptin or salt thereof. Alternatively, in another embodiment the drug layer comprises about 75 mg of vildagliptin or salt thereof.

- 5 In further embodiment, the drug layer further comprises pharmaceutically acceptable excipients such as swelling polymer like polyethylene oxide having molecular weight of about 100,000 to 200,000, osmotic agents selected from the group consisting of sucrose, xylitol, glucose, lactose, mannitol, sodium chloride, potassium chloride, cellulose ethers, maltodextrins, and cyclodextrins. The preferred osmotic agent is mannitol and lubricants like magnesium stearate, zinc stearate,
10 sodium stearyl fumarate. In another embodiment, the drug layer comprises polyethylene oxide having molecular weight of about 100,000 to 200,000 is present in about 170 mg to about 200 mg, or about 188 mg or about 190 mg or about 195 mg. In another embodiment, the drug layer comprises osmotic agent that is mannitol present in about 30 mg to about 50 mg or about 36 mg.
- 15 In another embodiment, the core comprises the push layer comprising polyethylene oxide having molecular weight of about 5,000,000 to about 8,000,000. In another embodiment, the push layer comprises polyethylene oxide having molecular weight of about 5,000,000 to about 8,000,000 and is present in about 70 mg to about 100 mg, or about 80 mg to about 90 mg. Alternatively, the push layer comprises polyethylene oxide having molecular weight of about 5,000,000 to about
20 8,000,000 and is present in about 85 mg, or 90 mg or 95 mg.

In another embodiment, the push layer further comprises pharmaceutically acceptable excipients such osmotic agents selected from the group consisting of sucrose, xylitol, glucose, lactose, mannitol, sodium chloride, potassium chloride, cellulose ethers, maltodextrins, and cyclodextrins.

- 25 The preferred osmotic agent is sodium chloride, binder such as hydroxypropyl methylcellulose (HPMC) having viscosity of 3cP to 6cP when present in 2% solution, and lubricants like magnesium stearate, zinc stearate, sodium stearyl fumarate. In another embodiment, the push layer comprises osmotic agent that is sodium chloride present in about 30 mg to about 50 mg or about 45 mg. In another embodiment, the osmotic agent present in drug layer is different than push layer.
- 30 In another embodiment, the push layer further comprises hydroxypropyl methylcellulose in an about 3% to about 7% by weight.

- In another embodiment, the weight ratio of vildagliptin or salt thereof and polyethylene oxide having molecular weight of about 5,000,000 to about 8,000,000 in the core ranges from about 1:1
35 to about 1:10. In another embodiment, the weight ratio of vildagliptin or salt thereof and polyethylene oxide having molecular weight of about 5,000,000 to about 8,000,000 in the core ranges from about 1:1 to about 1:3. Alternatively, the weight ratio of vildagliptin or salt thereof

and polyethylene oxide having molecular weight of about 5,000,000 to about 8,000,000 in the core is about 1:1.10, or about 1:1.15, or about 1:1.20, or about 1:1.25.

5 In another embodiment, the core is surrounded by a seal coat selected from commercially available coating system such as Opadry®. In another embodiment, the seal coat is surrounded by a sustained release coat comprising about 80% to about 90% by weight cellulose acetate. In another embodiment, the seal coat is surrounded by a sustained release coat comprising about 90% by weight cellulose acetate.

10 In another embodiment, the sustained release coat includes at least one bore suitable for providing the osmotic delivery of the vildagliptin or salt thereof from the core, wherein said bore has cross section of about 0.1 to about 1 mm² or about 0.7 mm².

15 In another embodiment, the sustained release coat is surrounded by an immediate release drug layer comprising about 20 mg to about 30 mg of vildagliptin or salt thereof, or about 25 mg of vildagliptin or salt thereof.

In another embodiment, the total amount of vildagliptin or salt thereof present in composition is about 100 mg or about 150 mg or about 200 mg or about 250 mg or about 300 mg, wherein about 20 90%, or about 80%, or about 70% or about 60% or about 50% of vildagliptin or salt thereof is present in the core of composition and about 10%, or about 20%, or about 30%, or about 40%, or about 50% of vildagliptin or salt thereof is present in the immediate release drug layer.

25 In another embodiment, the invention compositions are present in the form of an oral formulation such as a tablet, capsule (including a microcapsule), granule, or powder; of these forms, an oral formulation such as a tablet is preferred.

In another aspect of the invention, there is provided an osmotic pharmaceutical composition comprising: (a) a core, comprising: (i) a drug layer comprising about 75 mg of vildagliptin or salt 30 thereof, and one or more pharmaceutically acceptable excipients; (ii) a push layer comprising about 80 mg to about 90 mg of polyethylene oxide having molecular weight of about 5,000,000 to about 8,000,000; (b) a seal coat surrounding the core; (c) a sustained release coat comprising about 35 mg to about 45 mg of cellulose acetate surrounding the seal coat; (d) an immediate release drug layer comprising about 25 mg of vildagliptin or salt thereof surrounding the sustained release coat; 35 and wherein the composition exhibits an in-vitro release profile such that about 20% to about 30% of vildagliptin or salt thereof is released at 2 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, 0.1N HCl at 37°C ± 0.5°C. In one embodiment of this aspect, about 15% to

about 25% of vildagliptin or salt thereof is released at 2 hours when measured in 0.1N HCl at 37°C ± 0.5°C.

5 In another embodiment of this aspect, the composition exhibits an in-vitro release profile such that about 70% to about 95% of vildagliptin or salt thereof is released at 24 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, phosphate buffer of pH 6.8 at 37°C ± 0.5°C. In another embodiment of this aspect, about 85% to about 95% of vildagliptin or salt thereof is released at 24 hours when measured in phosphate buffer of pH 6.8 at 37°C ± 0.5°C.

10 In another embodiment of this aspect, the composition is storage stable for a period of 3 months at about 30°C/65% relative humidity and exhibits an in-vitro release profile such that about 20% to about 30% of vildagliptin or salt thereof is released at 2 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, 0.1N HCl at 37°C ± 0.5°C. In another embodiment of this aspect, the composition is storage stable for a period 3 months at 40°C/75% relative humidity and exhibits
15 an in-vitro release profile such that about 20% to about 30% of vildagliptin or salt thereof is released at 2 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, 0.1N HCl at 37°C ± 0.5°C. In another embodiment of this aspect, the composition is storage stable for a period 3 months at 30°C/65% relative humidity and exhibits an in-vitro release profile such that about 85% to about 95% of vildagliptin or salt thereof is released at 24 hours, when measured in
20 USP apparatus Type I, at 100 rpm using 900 ml, phosphate buffer of pH 6.8 at 37°C ± 0.5°C. In another embodiment of this aspect, the composition is storage stable for a period 3 months at 40°C/75% relative humidity and exhibits an in-vitro release profile such that about 85% to about 95% of vildagliptin or salt thereof is released at 24 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, phosphate buffer of pH 6.8 at 37°C ± 0.5°C.

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In another embodiment of this aspect, the composition provides a mean plasma concentration of vildagliptin or salt thereof in the range of about 5 ng/ml to about 250 ng/ml over a period of at least 24 hours after once daily oral administration. In another embodiment of this aspect, the composition provides a mean plasma concentration of vildagliptin or salt thereof of about 5 ng/ml
30 to about 30 ng/ml at 24 hours after once daily oral administration.

In another embodiment of this aspect, the composition can decrease DPP-IV enzyme activity in blood plasma by about 60% to about 90% over the period of 24 hours. In another embodiment of this aspect, the composition can decrease DPP-IV enzyme activity in blood plasma by about 80%
35 over the period of 24 hours.

In another embodiment of this aspect, the push layer further comprises hydroxypropyl methylcellulose in an about 3% to about 7% by weight. In another embodiment of this aspect, the core further comprises at least one osmotic agent selected from the group consisting of sucrose, xylitol, glucose, lactose, mannitol, sodium chloride, potassium chloride, cellulose ethers, maltodextrins, and cyclodextrins. In another embodiment, the osmotic agent present in drug layer is different than push layer. In another embodiment of this aspect, the sustained release coat comprises about 40 mg cellulose acetate. In another embodiment of this aspect, the sustained release coat includes at least one bore suitable for providing the osmotic delivery of the vildagliptin or salt thereof from the core, wherein said bore has cross section of about 0.1 to about 1 mm² or about 0.7 mm².

In another aspect of the invention, there is provided an osmotic pharmaceutical composition comprising: (a) a core, comprising: (i) a drug layer comprising about 75 mg of vildagliptin or salt thereof, and one or more pharmaceutically acceptable excipients; (ii) a push layer comprising about 95 mg of polyethylene oxide having molecular weight of about 5,000,000 to about 8,000,000; (b) a seal coat surrounding the core; (c) a sustained release coat comprising about 35 mg to about 45 mg of cellulose acetate surrounding the seal coat; (d) an immediate release drug layer comprising about 25 mg of vildagliptin or salt thereof surrounding the sustained release coat; and wherein the composition exhibits an in-vitro release profile such that about 20% to about 30% of vildagliptin or salt thereof is released at 2 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, 0.1N HCl at 37°C ± 0.5°C. In one embodiment of this aspect, about 15% to about 25% of vildagliptin or salt thereof is released at 2 hours when measured in 0.1N HCl at 37°C ± 0.5°C.

In another embodiment of this aspect, the composition exhibits an in-vitro release profile such that about 70% to about 95% of vildagliptin or salt thereof is released at 24 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, phosphate buffer of pH 6.8 at 37°C ± 0.5°C. In another embodiment of this aspect, about 85% to about 95% of vildagliptin or salt thereof is released at 24 hours when measured in phosphate buffer of pH 6.8 at 37°C ± 0.5°C.

In another embodiment of this aspect, the composition is storage stable for a period of 3 months at about 30°C/65% relative humidity and exhibits an in-vitro release profile such that about 20% to about 30% of vildagliptin or salt thereof is released at 2 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, 0.1N HCl at 37°C ± 0.5°C. In another embodiment of this aspect, the composition is storage stable for a period 3 months at 40°C/75% relative humidity and exhibits an in-vitro release profile such that about 20% to about 30% of vildagliptin or salt thereof is released at 2 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, 0.1N HCl

at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. In another embodiment of this aspect, the composition is storage stable for a period 3 months at $30^{\circ}\text{C}/65\%$ relative humidity and exhibits an in-vitro release profile such that about 85% to about 95% of vildagliptin or salt thereof is released at 24 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, phosphate buffer of pH 6.8 at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. In
5 another embodiment of this aspect, the composition is storage stable for a period 3 months at $40^{\circ}\text{C}/75\%$ relative humidity and exhibits an in-vitro release profile such that about 85% to about 95% of vildagliptin or salt thereof is released at 24 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, phosphate buffer of pH 6.8 at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$.

10 In another embodiment of this aspect, the composition provides a mean plasma concentration of vildagliptin or salt thereof in the range of about 5 ng/ml to about 250 ng/ml over a period of at least 24 hours after once daily oral administration. In another embodiment of this aspect, the composition provides a mean plasma concentration of vildagliptin or salt thereof of about 5 ng/ml to about 30 ng/ml at 24 hours after once daily oral administration.

15 In another embodiment of this aspect, the composition can decrease DPP-IV enzyme activity in blood plasma by about 60% to about 90% over the period of 24 hours. In another embodiment of this aspect, the composition can decrease DPP-IV enzyme activity in blood plasma by about 80% over the period of 24 hours.

20 In another embodiment of this aspect, the push layer further comprises hydroxypropyl methylcellulose in an about 3% to about 7% by weight. In another embodiment of this aspect, the core further comprises at least one osmotic agent selected from the group consisting of sucrose, xylitol, glucose, lactose, mannitol, sodium chloride, potassium chloride, cellulose ethers,
25 maltodextrins, and cyclodextrins. In another embodiment of this aspect, the osmotic agent present in drug layer is different than push layer. In another embodiment of this aspect, the sustained release coat comprises about 40 mg cellulose acetate. In another embodiment of this aspect, the sustained release coat includes at least one bore suitable for providing the osmotic delivery of the vildagliptin or salt thereof from the core, wherein said bore has cross section of about 0.1 to about
30 1 mm^2 or about 0.7 mm^2 .

In another aspect of the invention, there is provided an osmotic pharmaceutical composition comprising: (a) a core, comprising: (i) a drug layer comprising about 75 mg of vildagliptin or salt thereof, and one or more pharmaceutically acceptable excipients; (ii) a push layer comprising
35 about 85 mg of polyethylene oxide having molecular weight of about 5,000,000 to about 8,000,000; (b) a seal coat surrounding the core; (c) a sustained release coat comprising about 35 mg to about 45 mg of cellulose acetate surrounding the seal coat; (d) an immediate release drug

layer comprising about 25 mg of vildagliptin or salt thereof surrounding the sustained release coat; and wherein the composition exhibits an in-vitro release profile such that about 20% to about 30% of vildagliptin or salt thereof is released at 2 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, 0.1N HCl at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. In one embodiment of this aspect, about 15% to
5 about 25% of vildagliptin or salt thereof is released at 2 hours when measured in 0.1N HCl at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$.

In another embodiment of this aspect, the composition exhibits an in-vitro release profile such that about 70% to about 95% of vildagliptin or salt thereof is released at 24 hours, when measured in
10 USP apparatus Type I, at 100 rpm using 900 ml, phosphate buffer of pH 6.8 at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. In another embodiment of this aspect, about 85% to about 95% of vildagliptin or salt thereof is released at 24 hours when measured in phosphate buffer of pH 6.8 at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$.

In another embodiment of this aspect, the composition is storage stable for a period of 3 months at
15 about $30^{\circ}\text{C}/65\%$ relative humidity and exhibits an in-vitro release profile such that about 20% to about 30% of vildagliptin or salt thereof is released at 2 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, 0.1N HCl at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. In another embodiment of this aspect, the composition is storage stable for a period 3 months at $40^{\circ}\text{C}/75\%$ relative humidity and exhibits an in-vitro release profile such that about 20% to about 30% of vildagliptin or salt thereof is
20 released at 2 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, 0.1N HCl at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. In another embodiment of this aspect, the composition is storage stable for a period 3 months at $30^{\circ}\text{C}/65\%$ relative humidity and exhibits an in-vitro release profile such that about 85% to about 95% of vildagliptin or salt thereof is released at 24 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, phosphate buffer of pH 6.8 at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. In
25 another embodiment of this aspect, the composition is storage stable for a period 3 months at $40^{\circ}\text{C}/75\%$ relative humidity and exhibits an in-vitro release profile such that about 85% to about 95% of vildagliptin or salt thereof is released at 24 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, phosphate buffer of pH 6.8 at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$.

In another embodiment of this aspect, the composition provides a mean plasma concentration of
30 vildagliptin or salt thereof in the range of about 5 ng/ml to about 250 ng/ml over a period of at least 24 hours after once daily oral administration. In another embodiment of this aspect, the composition provides a mean plasma concentration of vildagliptin or salt thereof of about 5 ng/ml to about 30 ng/ml at 24 hours after once daily oral administration.

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In another embodiment of this aspect, the composition can decrease DPP-IV enzyme activity in blood plasma by about 60% to about 90% over the period of 24 hours. In another embodiment of

this aspect, the composition can decrease DPP-IV enzyme activity in blood plasma by about 80% over the period of 24 hours.

In another embodiment of this aspect, the push layer further comprises hydroxypropyl methylcellulose in an about 3% to about 7% by weight. In another embodiment of this aspect, the core further comprises at least one osmotic agent selected from the group consisting of sucrose, xylitol, glucose, lactose, mannitol, sodium chloride, potassium chloride, cellulose ethers, maltodextrins, and cyclodextrins. In another embodiment of this aspect, the osmotic agent present in drug layer is different than push layer. In another embodiment of this aspect, the sustained release coat comprises about 40 mg cellulose acetate. In another embodiment of this aspect, the sustained release coat includes at least one bore suitable for providing the osmotic delivery of the vildagliptin or salt thereof from the core, wherein said bore has cross section of about 0.1 to about 1 mm² or about 0.7 mm².

In another aspect of the invention, there is provided an osmotic pharmaceutical composition comprising: (a) a core, comprising: (i) a drug layer comprising about 75 mg of vildagliptin or salt thereof, and one or more pharmaceutically acceptable excipients; (ii) a push layer comprising about 90 mg of polyethylene oxide having molecular weight of about 5,000,000 to about 8,000,000; (b) a seal coat surrounding the core; (c) a sustained release coat comprising about 35 mg to about 45 mg of cellulose acetate surrounding the seal coat; (d) an immediate release drug layer comprising about 25 mg of vildagliptin or salt thereof surrounding the sustained release coat; and wherein the composition exhibits an in-vitro release profile such that about 20% to about 30% of vildagliptin or salt thereof is released at 2 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, 0.1N HCl at 37°C ± 0.5°C. In one embodiment of this aspect, about 15% to about 25% of vildagliptin or salt thereof is released at 2 hours when measured in 0.1N HCl at 37°C ± 0.5°C.

In another embodiment of this aspect, the composition exhibits an in-vitro release profile such that about 70% to about 95% of vildagliptin or salt thereof is released at 24 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, phosphate buffer of pH 6.8 at 37°C ± 0.5°C. In another embodiment of this aspect, about 85% to about 95% of vildagliptin or salt thereof is released at 24 hours when measured in phosphate buffer of pH 6.8 at 37°C ± 0.5°C.

In another embodiment of this aspect, the composition is storage stable for a period of 3 months at about 30°C/65% relative humidity and exhibits an in-vitro release profile such that about 20% to about 30% of vildagliptin or salt thereof is released at 2 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, 0.1N HCl at 37°C ± 0.5°C. In another embodiment of this aspect,

the composition is storage stable for a period 3 months at 40°C/75% relative humidity and exhibits an in-vitro release profile such that about 20% to about 30% of vildagliptin or salt thereof is released at 2 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, 0.1N HCl at 37°C ± 0.5°C. In another embodiment of this aspect, the composition is storage stable for a period 3 months at 30°C/65% relative humidity and exhibits an in-vitro release profile such that about 85% to about 95% of vildagliptin or salt thereof is released at 24 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, phosphate buffer of pH 6.8 at 37°C ± 0.5°C. In another embodiment of this aspect, the composition is storage stable for a period 3 months at 40°C/75% relative humidity and exhibits an in-vitro release profile such that about 85% to about 95% of vildagliptin or salt thereof is released at 24 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, phosphate buffer of pH 6.8 at 37°C ± 0.5°C.

In another embodiment of this aspect, the composition provides a mean plasma concentration of vildagliptin or salt thereof in the range of about 5 ng/ml to about 250 ng/ml over a period of at least 24 hours after once daily oral administration. In another embodiment of this aspect, the composition provides a mean plasma concentration of vildagliptin or salt thereof of about 5 ng/ml to about 30 ng/ml at 24 hours after once daily oral administration.

In another embodiment of this aspect, the composition can decrease DPP-IV enzyme activity in blood plasma by about 60% to about 90% over the period of 24 hours. In another embodiment of this aspect, the composition can decrease DPP-IV enzyme activity in blood plasma by about 80% over the period of 24 hours.

In another embodiment of this aspect, the push layer further comprises hydroxypropyl methylcellulose in an about 3% to about 7% by weight. In another embodiment of this aspect, the core further comprises at least one osmotic agent selected from the group consisting of sucrose, xylitol, glucose, lactose, mannitol, sodium chloride, potassium chloride, cellulose ethers, maltodextrins, and cyclodextrins. In another embodiment of this aspect, the osmotic agent present in drug layer is different than push layer. In another embodiment of this aspect, the sustained release coat comprises about 40 mg cellulose acetate. In another embodiment of this aspect, the sustained release coat includes at least one bore suitable for providing the osmotic delivery of the vildagliptin or salt thereof from the core, wherein said bore has cross section of about 0.1 to about 1 mm² or about 0.7 mm².

In another aspect of the invention, there is provided a kit comprising an osmotic pharmaceutical composition comprising: (a) a core, comprising: (i) a drug layer comprising vildagliptin or salt thereof, and one or more pharmaceutically acceptable excipients; (ii) a push layer comprising

polyethylene oxide having molecular weight of about 5,000,000 to about 8,000,000, wherein weight ratio of vildagliptin or salt thereof and polyethylene oxide ranges from about 1:1 to about 1:5; (b) a seal coat surrounding the core; (c) a sustained release coat cellulose acetate surrounding the seal coat; (d) an immediate release drug layer comprising vildagliptin or salt thereof
5 surrounding the sustained release coat.

In another aspect of the invention, there is provided a kit comprising an osmotic pharmaceutical composition comprising: (a) a core, comprising: (i) a drug layer comprising about 35 mg to about 95 mg of vildagliptin or salt thereof, and one or more pharmaceutically acceptable excipients; (ii) a
10 push layer comprising polyethylene oxide having molecular weight of about 5,000,000 to about 8,000,000, wherein weight ratio of vildagliptin or salt thereof and polyethylene oxide ranges from about 1:1 to about 1:5; (b) a seal coat surrounding the core; (c) a sustained release coat comprising about 70% to about 95% by weight cellulose acetate surrounding the seal coat; (d) an immediate release drug layer comprising about 15 mg to about 35 mg of vildagliptin or salt thereof
15 surrounding the sustained release coat; and wherein the composition exhibits an in-vitro release profile such that about 10% to about 30% of vildagliptin or salt thereof is released at 2 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, 0.1N HCl at 37°C ± 0.5°C.

In one embodiment of this aspect, about 15% to about 25% of vildagliptin or salt thereof is
20 released at 2 hours when measured in 0.1N HCl at 37°C ± 0.5°C. In another embodiment of this aspect, the composition exhibits an in-vitro release profile such that about 70% to about 95% of vildagliptin or salt thereof is released at 24 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, phosphate buffer of pH 6.8 at 37°C ± 0.5°C. In another embodiment of this aspect, about 85% to about 95% of vildagliptin or salt thereof is released at 24 hours when
25 measured in phosphate buffer of pH 6.8 at 37°C ± 0.5°C.

In another embodiment of this aspect, the composition is storage stable for a period of 3 months at about 30°C/65% relative humidity and exhibits an in-vitro release profile such that about 20% to about 30% of vildagliptin or salt thereof is released at 2 hours, when measured in USP apparatus
30 Type I, at 100 rpm using 900 ml, 0.1N HCl at 37°C ± 0.5°C. In another embodiment of this aspect, the composition is storage stable for a period 3 months at 40°C/75% relative humidity and exhibits an in-vitro release profile such that about 20% to about 30% of vildagliptin or salt thereof is released at 2 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, 0.1N HCl at 37°C ± 0.5°C. In another embodiment of this aspect, the composition is storage stable for a
35 period 3 months at 30°C/65% relative humidity and exhibits an in-vitro release profile such that about 85% to about 95% of vildagliptin or salt thereof is released at 24 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, phosphate buffer of pH 6.8 at 37°C ± 0.5°C. In

another embodiment of this aspect, the composition is storage stable for a period 3 months at 40°C/75% relative humidity and exhibits an in-vitro release profile such that about 85% to about 95% of vildagliptin or salt thereof is released at 24 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, phosphate buffer of pH 6.8 at 37°C ± 0.5°C.

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In another embodiment of this aspect, the composition provides a mean plasma concentration of vildagliptin or salt thereof in the range of about 5 ng/ml to about 250 ng/ml over a period of at least 24 hours after once daily oral administration. In another embodiment of this aspect, the composition provides a mean plasma concentration of vildagliptin or salt thereof of about 5 ng/ml

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to about 30 ng/ml at 24 hours after once daily oral administration.

In another embodiment of this aspect, the composition can decrease DPP-IV enzyme activity in blood plasma by about 60% to about 90% over the period of 24 hours. In another embodiment of this aspect, the composition can decrease DPP-IV enzyme activity in blood plasma by about 80%

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over the period of 24 hours.

In another embodiment of this aspect, the core comprises about 75 mg of vildagliptin or salt thereof. In another embodiment of this aspect, the weight ratio of vildagliptin or salt thereof and polyethylene oxide in the core ranges from about 1:1 to about 1:3. In another embodiment of this aspect, the push layer further comprises hydroxypropyl methylcellulose in an about 3% to about 7% by weight. In another embodiment of this aspect, the core further comprises at least one osmotic agent selected from the group consisting of sucrose, xylitol, glucose, lactose, mannitol, sodium chloride, potassium chloride, cellulose ethers, maltodextrins, and cyclodextrins. In another embodiment of this aspect, the sustained release coat comprises about 90% by weight cellulose acetate. In another embodiment of this aspect, the sustained release coat includes at least one bore suitable for providing the osmotic delivery of the vildagliptin or salt thereof from the core, wherein said bore has cross section of about 0.1 to about 1 mm² or about 0.7 mm².

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In another aspect of the invention, there is provided a method of treating type 2 diabetes, said method comprises administering to a patient in a need thereof an osmotic pharmaceutical composition comprising: (a) a core, comprising: (i) a drug layer comprising vildagliptin or salt thereof, and one or more pharmaceutically acceptable excipients; (ii) a push layer comprising polyethylene oxide having molecular weight of about 5,000,000 to about 8,000,000, wherein weight ratio of vildagliptin or salt thereof and polyethylene oxide ranges from about 1:1 to about 1:5; (b) a seal coat surrounding the core; (c) a sustained release coat cellulose acetate surrounding the seal coat; (d) an immediate release drug layer comprising vildagliptin or salt thereof surrounding the sustained release coat.

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In another aspect of the invention, there is provided a method of treating type 2 diabetes, said method comprises administering to a patient in a need thereof an osmotic pharmaceutical composition comprising: (a) a core, comprising: (i) a drug layer comprising about 35 mg to about 95 mg of vildagliptin or salt thereof, and one or more pharmaceutically acceptable excipients; (ii) a
5 push layer comprising polyethylene oxide having molecular weight of about 5,000,000 to about 8,000,000, wherein weight ratio of vildagliptin or salt thereof and polyethylene oxide ranges from about 1:1 to about 1:5; (b) a seal coat surrounding the core; (c) a sustained release coat comprising about 70% to about 95% by weight cellulose acetate surrounding the seal coat; (d) an immediate
10 release drug layer comprising about 15 mg to about 35 mg of vildagliptin or salt thereof surrounding the sustained release coat; and wherein the composition exhibits an in-vitro release profile such that about 10% to about 30% of vildagliptin or salt thereof is released at 2 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, 0.1N HCl at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$.

In one embodiment of this aspect, about 15% to about 25% of vildagliptin or salt thereof is
15 released at 2 hours when measured in 0.1N HCl at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. In another embodiment of this aspect, the composition exhibits an in-vitro release profile such that about 70% to about 95% of vildagliptin or salt thereof is released at 24 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, phosphate buffer of pH 6.8 at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. In another embodiment of this aspect, about 85% to about 95% of vildagliptin or salt thereof is released at 24 hours when
20 measured in phosphate buffer of pH 6.8 at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$.

In another embodiment of this aspect, the composition is storage stable for a period of 3 months at about $30^{\circ}\text{C}/65\%$ relative humidity and exhibits an in-vitro release profile such that about 20% to about 30% of vildagliptin or salt thereof is released at 2 hours, when measured in USP apparatus
25 Type I, at 100 rpm using 900 ml, 0.1N HCl at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. In another embodiment of this aspect, the composition is storage stable for a period 3 months at $40^{\circ}\text{C}/75\%$ relative humidity and exhibits an in-vitro release profile such that about 20% to about 30% of vildagliptin or salt thereof is released at 2 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, 0.1N HCl at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. In another embodiment of this aspect, the composition is storage stable for a
30 period 3 months at $30^{\circ}\text{C}/65\%$ relative humidity and exhibits an in-vitro release profile such that about 85% to about 95% of vildagliptin or salt thereof is released at 24 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, phosphate buffer of pH 6.8 at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. In another embodiment of this aspect, the composition is storage stable for a period 3 months at $40^{\circ}\text{C}/75\%$ relative humidity and exhibits an in-vitro release profile such that about 85% to about
35 95% of vildagliptin or salt thereof is released at 24 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, phosphate buffer of pH 6.8 at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$.

In another embodiment of this aspect, the composition provides a mean plasma concentration of vildagliptin or salt thereof in the range of about 5 ng/ml to about 250 ng/ml over a period of at least 24 hours after once daily oral administration. In another embodiment of this aspect, the composition provides a mean plasma concentration of vildagliptin or salt thereof of about 5 ng/ml
5 to about 30 ng/ml at 24 hours after once daily oral administration.

In another embodiment of this aspect, the composition can decrease DPP-IV enzyme activity in blood plasma by about 60% to about 90% over the period of 24 hours. In another embodiment of this aspect, the composition can decrease DPP-IV enzyme activity in blood plasma by about 80%
10 over the period of 24 hours.

In another embodiment of this aspect, the core comprises about 75 mg of vildagliptin or salt thereof. In another embodiment of this aspect, the weight ratio of vildagliptin or salt thereof and polyethylene oxide in the core ranges from about 1:1 to about 1:3. In another embodiment of this
15 aspect, the push layer further comprises hydroxypropyl methylcellulose in an about 3% to about 7% by weight. In another embodiment of this aspect, the core further comprises at least one osmotic agent selected from the group consisting of sucrose, xylitol, glucose, lactose, mannitol, sodium chloride, potassium chloride, cellulose ethers, maltodextrins, and cyclodextrins. In another embodiment of this aspect, the sustained release coat comprises about 90% by weight cellulose
20 acetate. In another embodiment of this aspect, the sustained release coat includes at least one bore suitable for providing the osmotic delivery of the vildagliptin or salt thereof from the core, wherein said bore has cross section of about 0.1 to about 1 mm² or about 0.7 mm².

In another aspect of the invention, there is provided a process of preparing an osmotic
25 pharmaceutical composition comprising: (a) a core, comprising: (i) a drug layer comprising about 35 mg to about 95 mg of vildagliptin or salt thereof, and one or more pharmaceutically acceptable excipients; (ii) a push layer comprising polyethylene oxide having molecular weight of about 5,000,000 to about 8,000,000, wherein weight ratio of vildagliptin or salt thereof and polyethylene oxide ranges from about 1:1 to about 1:5; (b) a seal coat surrounding the core; (c) a sustained
30 release coat comprising about 70% to about 95% by weight cellulose acetate surrounding the seal coat; (d) an immediate release drug layer comprising about 15 mg to about 35 mg of vildagliptin or salt thereof surrounding the sustained release coat; and wherein the composition exhibits an in-vitro release profile such that about 10% to about 30% of vildagliptin or salt thereof is released at 2 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, 0.1N HCl at 37°C ±
35 0.5°C, and wherein said process comprises steps of:

(a) preparing the drug layer in the form of a granules comprising vildagliptin or salt thereof, and one or more pharmaceutically acceptable excipients,

- (b) preparing a push layer in the form of a granules comprising polyethylene oxide,
- (c) compressing the granules of the drug layer and the push layer to form the core,
- (d) seal coating the core of step (c),
- (e) coating the seal coat of step (d) with the sustained release coat comprising about 70%
5 to about 95% by weight cellulose acetate, and
- (f) coating the sustained release coat of step (e) with the immediate release drug layer comprising vildagliptin or salt thereof to obtain the osmotic pharmaceutical composition.

10 In one embodiment of this aspect, about 15% to about 25% of vildagliptin or salt thereof is released at 2 hours when measured in 0.1N HCl at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. In another embodiment of this aspect, the composition exhibits an in-vitro release profile such that about 70% to about 95% of vildagliptin or salt thereof is released at 24 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, phosphate buffer of pH 6.8 at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. In another embodiment of this aspect, about 85% to about 95% of vildagliptin or salt thereof is released at 24 hours when
15 measured in phosphate buffer of pH 6.8 at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$.

In another embodiment of this aspect, the composition is storage stable for a period of 3 months at about $30^{\circ}\text{C}/65\%$ relative humidity and exhibits an in-vitro release profile such that about 20% to about 30% of vildagliptin or salt thereof is released at 2 hours, when measured in USP apparatus
20 Type I, at 100 rpm using 900 ml, 0.1N HCl at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. In another embodiment of this aspect, the composition is storage stable for a period 3 months at $40^{\circ}\text{C}/75\%$ relative humidity and exhibits an in-vitro release profile such that about 20% to about 30% of vildagliptin or salt thereof is released at 2 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, 0.1N HCl at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. In another embodiment of this aspect, the composition is storage stable for a
25 period 3 months at $30^{\circ}\text{C}/65\%$ relative humidity and exhibits an in-vitro release profile such that about 85% to about 95% of vildagliptin or salt thereof is released at 24 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, phosphate buffer of pH 6.8 at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. In another embodiment of this aspect, the composition is storage stable for a period 3 months at $40^{\circ}\text{C}/75\%$ relative humidity and exhibits an in-vitro release profile such that about 85% to about
30 95% of vildagliptin or salt thereof is released at 24 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, phosphate buffer of pH 6.8 at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$.

In another embodiment of this aspect, the composition provides a mean plasma concentration of vildagliptin or salt thereof in the range of about 5 ng/ml to about 250 ng/ml over a period of at
35 least 24 hours after once daily oral administration. In another embodiment of this aspect, the composition provides a mean plasma concentration of vildagliptin or salt thereof of about 5 ng/ml to about 30 ng/ml at 24 hours after once daily oral administration.

In another embodiment of this aspect, the composition can decrease DPP-IV enzyme activity in blood plasma by about 60% to about 90% over the period of 24 hours. In another embodiment of this aspect, the composition can decrease DPP-IV enzyme activity in blood plasma by about 80% over the period of 24 hours.

In another embodiment of this aspect, the core comprises about 75 mg of vildagliptin or salt thereof. In another embodiment of this aspect, the weight ratio of vildagliptin or salt thereof and polyethylene oxide in the core ranges from about 1:1 to about 1:3. In another embodiment of this aspect, the push layer further comprises hydroxypropyl methylcellulose in an about 3% to about 7% by weight. In another embodiment of this aspect, the core further comprises at least one osmotic agent selected from the group consisting of sucrose, xylitol, glucose, lactose, mannitol, sodium chloride, potassium chloride, cellulose ethers, maltodextrins, and cyclodextrins. In another embodiment of this aspect, the sustained release coat comprises about 90% by weight cellulose acetate. In another embodiment of this aspect, the sustained release coat includes at least one bore suitable for providing the osmotic delivery of the vildagliptin or salt thereof from the core, wherein said bore has cross section of about 0.1 to about 1 mm² or about 0.7 mm².

In another aspect of the invention, there is provided a process of preparing an osmotic pharmaceutical composition comprising: (a) a core, comprising: (i) a drug layer comprising about 75 mg of vildagliptin or salt thereof, and one or more pharmaceutically acceptable excipients; (ii) a push layer comprising about 80 mg to about 90 mg of polyethylene oxide having molecular weight of about 5,000,000 to about 8,000,000; (b) a seal coat surrounding the core; (c) a sustained release coat comprising about 35 mg to about 45 mg of cellulose acetate surrounding the seal coat; (d) an immediate release drug layer comprising about 25 mg of vildagliptin or salt thereof surrounding the sustained release coat; and wherein the composition exhibits an in-vitro release profile such that about 20% to about 30% of vildagliptin or salt thereof is released at 2 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, 0.1N HCl at 37°C ± 0.5°C, and wherein said process comprises steps of:

- (a) preparing the drug layer in the form of a granules comprising vildagliptin or salt thereof, and one or more pharmaceutically acceptable excipients,
- (b) preparing a push layer in the form of a granules comprising polyethylene oxide,
- (c) compressing the granules of the drug layer and the push layer to form the core,
- (d) seal coating the core of step (c),
- (e) coating the seal coat of step (d) with the sustained release coat comprising cellulose acetate, and

(f) coating the sustained release coat of step (e) with the immediate release drug layer comprising vildagliptin or salt thereof to obtain the osmotic pharmaceutical composition.

In another aspect of the invention, there is provided a process of preparing an osmotic pharmaceutical composition comprising: (a) a core, comprising: (i) a drug layer comprising about 75 mg of vildagliptin or salt thereof, and one or more pharmaceutically acceptable excipients; (ii) a push layer comprising about 90 mg of polyethylene oxide having molecular weight of about 5,000,000 to about 8,000,000; (b) a seal coat surrounding the core; (c) a sustained release coat comprising about 35 mg to about 45 mg of cellulose acetate surrounding the seal coat; (d) an immediate release drug layer comprising about 25 mg of vildagliptin or salt thereof surrounding the sustained release coat; and wherein the composition exhibits an in-vitro release profile such that about 20% to about 30% of vildagliptin or salt thereof is released at 2 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, 0.1N HCl at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$, and wherein said process comprises steps of:

- 15 (a) preparing the drug layer in the form of a granules comprising vildagliptin or salt thereof, and one or more pharmaceutically acceptable excipients,
- (b) preparing a push layer in the form of a granules comprising polyethylene oxide,
- (c) compressing the granules of the drug layer and the push layer to form the core,
- (d) seal coating the core of step (c),
- 20 (e) coating the seal coat of step (d) with the sustained release coat comprising cellulose acetate, and
- (f) coating the sustained release coat of step (e) with the immediate release drug layer comprising vildagliptin or salt thereof to obtain the osmotic pharmaceutical composition.

25 While the invention has been described in term of its specific embodiments, certain modification and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the invention.

EXAMPLES

EXAMPLE 1: Osmotic compositions of vildagliptin

Sr. No	Ingredients	Unit Quantity (mg)	
		1A	1B
Drug layer			
1	Vildagliptin	75.00	75.00
2	Polyethylene oxide (WSR N80)	198.00	188.00
3	Mannitol 25	26.00	36.00
4	Magnesium stearate	1.00	1.00
5	IPA (Isopropyl alcohol)	q.s.	q.s.
Total		300.00	300.0
Push layer			
6	Polyethylene oxide (WSR 303)	90.00	90.00
7	Iron oxide red	1.00	1.00
8	HPMC E5 (Hydroxypropyl methyl cellulose)	8.00	8.00
9	NaCl (Sodium Chloride)	45.00	45.00
10	Magnesium stearate	1.00	1.00
11	IPA	q.s.	q.s.
Total		145.00	145.00
Wt of Core Tablet		445.00	445.00
Seal coating (3%)			
12	Opadry 03K19229(clear)	13.35	13.35
13	IPA	q.s.	q.s.
14	MDC (Methylene Dichloride)	q.s.	q.s.
Total Tab. wt.		458.35	458.35
Sustained Release (SR) coat (10%)			
15	Cellulose acetate 398-10	41.26	41.26
16	PEG3350 (Polyethylene Glycol)	4.58	4.58
17	Water	q.s.	q.s.
18	Acetone	q.s.	q.s.

Total Tab. wt.		504.19	504.19
Drug coating (immediate release)			
19	Vildagliptin	25.00	25.00
20	Opadry 03A690050 (clear)	25.00	25.00
21	IPA	94.00	94.00
22	MDC	219.00	219.00
Total Tab. wt.		554.19	554.19
Actual Total Tab. wt.		554.19	554.19
Top Coat			
23	Opadry 03K19229(clear)	16.63	16.63
24	Water	220.00	-
25	IPA	-	q.s.
26	MDC	-	q.s.
Final Tab. wt.		570.82	570.82

Manufacturing process:

Drug Layer:

- I. Vildagliptin and Polyox N 80 were passed thorough #40 sieve.
- 5 II. Separately passed mannitol thorough #40 sieve and geometrically blended with Step I mixture.
- III. The Step II powder blend was granulated with IPA in a rapid mixer granulator by spraying IPA on the dry mix to get uniform sized granules.
- IV. The above granules were dried in a fluid bed dryer at an inlet temperature of $40\pm 5^{\circ}\text{C}$ for
10 appropriate time till an LOD of less than 2 % is attained.
- V. The dried granules were passed thorough #40 mesh sieve and further lubricated the granules with pre- sifted magnesium stearate for 5 minutes.

Push Layer:

- I. Polyox WSR 303 and HPMC E-5 were passed thorough #60 mesh sieve.
- 15 II. Iron Oxide passed thorough #60 mesh mixed with the step I mixture for 5 minutes.
- III. The Step II powder blend was granulated with IPA in a rapid mixer granulator by spraying IPA on the dry mix to get uniform sized granules.
- IV. The above granules were dried in a fluid bed dryer at an inlet temperature of $40\pm 5^{\circ}\text{C}$ for appropriate time till an LOD of less than 2 % is attained.
- 20 V. The dried granules were passed thorough #40 mesh sieve and further lubricated the granules with pre- sifted magnesium stearate for 5 minutes.

Compression:

- I. The above two lubricated granules of drug layer and push layer were compressed into a bilayered tablet using 10.00 mm round shallow concave tooling in a rotary bilayered compression machine.

5

Seal Coating:

- I. Opadry 03K19229 (clear) was dispersed in IPA and stir for 30 minutes. Added MDC to the above solution and mix for 10 minutes.

- II. The bilayered tablets were seal coated with the above solution till a weight gain of 3% w/w is attained.

10

Micro-porous Semi-Permeable membrane (SPM) (Extended release) coating:

- I. Cellulose acetate 398-10 in was dispersed in acetone under stirring. PEG 3350 was dissolved in water and mixed the solution with cellulose acetate solution for 40 minutes.

- II. Seal coated tablets were coated with step I solution until a weight gain of 10% w/w is attained.

15

Drug Layering:

- I. Vildagliptin was dissolved in 60% MDC under stirring.

- II. Separately Opadry 03A690050 (clear) was dispersed in IPA for 10 minutes and remaining 40% of MDC added in the solution.

20

- III. Opadry solution was added to the drug solution under stirring and mixed for 30 minutes.

- IV. Further the SPM coated tablets layered with the above solution of drug and binder till the desired concentration of drug (25 mg) was layered on the tablet as a loading dose.

Drilling

- I. The drug layer side of the above tablet was drilled by with a 0.6 mm needle using a tablet laser drilling machine.

25

Top coat:

- I. Opadry 03K19229 (clear) was dispersed in IPA and stirred for 30 minutes. MDC was added to the above solution and mixed for 10 minutes.

- II. Top coated the above tablets (drilled on the drug layer side) with the above solution till a weight gain of 2.5-3% w/w was attained.

30

EXAMPLE 2: Dissolution testing of osmotic pharmaceutical compositions of Example 1.

In-vitro percentage drug release was estimated using the following change over dissolution method.

35

ACID STAGE:

Dissolution parameters:

	Medium	:	0.1N Hydrochloric acid
	Volume	:	900 mL
	Apparatus	:	USP Type I (basket)
	Rotational speed	:	100 RPM
5	Temperature	:	37°C±0.5°C
	Time	:	1 h, 2 h
	Diluent	:	Use dissolution medium as diluent.

After completion of dissolution in acid stage, the acid medium was discarded or decanted carefully and the tablets were dried to preserve for buffer stage.

BUFFER STAGE:

Dissolution parameters:

	Medium	:	Phosphate buffer pH 6.8
	Volume	:	900 mL
15	Apparatus	:	USP Type I (basket)
	Rotational speed	:	100 RPM
	Temperature	:	37°C±0.5°C
	Time	:	1, 2, 4, 8, 12, 16, 18, 22 hours
	Diluent	:	Use dissolution medium as diluent.

Composition of example 1A and 1B, when subjected to acid stage, about 25% of vildagliptin or salt thereof was released at 2 hours and when subjected buffer stage, about 80% of vildagliptin or salt thereof was released at 24 hours as shown in Fig 1A and Fig 1B.

EXAMPLE 3: Measurement of DPP-IV inhibition by administration of osmotic pharmaceutical composition of Example 1.

Preclinical studies were carried out on male beagle dogs to evaluate the PK/PD profile of Example 1 (1A and 1B) compositions. Plasma drug concentrations and DPP-IV enzyme activity were assessed and compared with GALVUS[®]. Dogs weighing 10.5 to 13.2 kg were received from the

Dog House Facility, Wockhardt Research Centre, Aurangabad. Dogs were housed under controlled kennel condition with a 12h light and 12h dark cycle and given access to food once in a day with water ad-libitum. Animals were fasted for 14 hours before the test drug administration, randomized in different treatment arms (n = 4 - 5) with comparable average body weight. Following fasting, animals were treated with single oral dose of example 1 (1A and 1B) compositions (100 mg) and two doses of GALVUS[®] (50 mg) at 0 and 10 hour. Blood samples were collected at 0 (before) and 0.5, 1, 2, 3, 3.25, 3.5, 4, 6, 8, 10, 10.5, 11, 12, 14, 16, 20, 24 and 30 h post-dose. Blood collected was centrifuged, plasma was separated and stored in two aliquots

at -80°C for DPP-IV enzyme activity and drug concentration measurement. DPP-IV enzyme activity assay was performed by measuring fluorescence velocities released from fluorogenic substance 7-Amino-4-methylcoumarin (AMC) cleaved from substrate Gly-Pro-AMC by the activity of DPP-IV enzyme at λ_{ex} = 360 nm and λ_{em} = 460 nm wavelength. Percent inhibition of DPP-IV was calculated as $100 \times (1 - A_t/A_0)$, where A_0 was the enzyme activity measured predose and A_t was the activity measured post-dose at time t in the same treatment period. Plasma drug concentrations were measured using LC-MS method. The results obtained are presented in the form of mean $\pm$ SEM in Fig 2A and Fig 2B for example 1A and Fig 3A and Fig 3B for example 1B composition.

As shown in Fig 2A and Fig 2B, GALVUS[®] showed >80% DPP-IV inhibition from 0.5 - 6 hour during first dose and 10.5-16 hour during second dose. Overall, GALVUS[®] maintained >80 % DPP-IV inhibition for 6 hour after each dose. After 6 hour of administration, GALVUS[®] showed DPP-IV inhibition below 80% which correlates with plasma drug concentration. Example 1A composition reported >80% DPP-IV inhibition up to 14 hours which is in alignment with plasma drug concentrations. The drop in DPP-IV inhibition after 20 hours may be attributed to incomplete drug release. Example 1A composition showed consistent and longer DPP-IV inhibition compared with GALVUS[®].

As shown in Fig 3A and Fig 3B, example 1B composition showed > 80% DPP-IV inhibition up to 8 hour and more than 70% up to 14 hour. DPP-IV activity correlated with plasma drug concentrations and in-vitro results. Relative Bioavailability of 95% achieved against GALVUS[®]. The similar and consistent PK/PD outcomes can be anticipated in human volunteers in view of drug half-life and clearance correlations between humans and dogs.

EXAMPLE 4: Stability testing of composition of vildagliptin

Tablets of composition Example 1B were packed in Alu Alu blisters and were loaded on stability under the 40°C $\pm$ 2°C & 75%RH $\pm$ 5%RH and 30°C $\pm$ 2°C & 65%RH $\pm$ 5%RH and evaluated for assay, dissolution and impurity profile.

Test	Initial	30°C $\pm$ 2°C & 65%RH $\pm$ 5%RH		Initial	40°C $\pm$ 2°C & 75%RH $\pm$ 5%RH	
		1M	3M		1M	3M
Assay	105.8	104.5	102.5	105.8	102.9	98.6
DISSOLUTION						
2 h (acid stage)	28	27	28	28	28	28

Buffer stage (6.8 pH)						
3 h	32	-	34	32	-	33
4 h	35	-	40	35	-	38
6 h	42	39	52	42	42	46
10 h	59	-	74	59	-	60
14h	78	-	90	78	-	72
20 h	87	78	94	87	89	82
24 h	91	92	96	91	93	87
RELATED SUBSTANCES						
Highest Unknown impurities	0.04	0.08	0.16	0.04	0.15	0.23
Total Related substances	0.19	0.24	0.68	0.19	0.59	1.35

As shown in above table, the invention composition (example 1B) remain storage stable at 40°C± 2°C & 75%RH ± 5%RH and 30°C± 2°C & 65%RH ± 5%RH conditions. The compositions were also proved to dissolution stable at these conditions.

5

EXAMPLE 5: Osmotic compositions of vildagliptin

Sr. No	Ingredients	Unit Quantity (mg)		
		5A	5B	5C
Drug layer				
1	Vildagliptin	75.00	75.00	75.00
2	Polyethylene oxide (WSR N80)	193.00	193.00	188.00
3	Mannitol 25	31.00	31.00	36.00
4	Magnesium stearate	1.00	1.00	1.00
5	IPA	q.s.	q.s.	q.s.
Total		300.00	300.0	300.0
Push layer				
6	Polyethylene oxide (WSR 303)	90.00	95.00	85.00
7	Iron oxide red	1.00	1.00	1.00
8	HPMC E5	8.00	8.00	8.00
9	NaCl	45.00	40.00	40.00

10	Magnesium stearate	1.00	1.00	1.00
11	IPA	q.s.	q.s.	q.s.
Total		145.00	145.00	135.00
Wt of core Tablet		445.00	445.00	435.00
Seal coating (3%)				
12	Opadry 03K19229(clear)	13.35	13.35	13.35
13	IPA	q.s.	q.s.	q.s.
14	MDC	q.s.	q.s.	q.s.
Total Tab. wt.		458.35	458.35	448.35
Sustain release coat (10%)				
15	Cellulose acetate 398- 10	41.26	41.26	41.26
16	PEG3350	4.58	4.58	4.58
17	Water	q.s.	q.s.	q.s.
18	Acetone	q.s.	q.s.	q.s.
Total Tab. wt.		504.19	504.19	494.19
Drug coating (immediate release)				
19	Vildagliptin	25.00	25.00	25.00
20	Opadry 03A690050(clear)	25.00	25.00	25.00
21	IPA	94.00	94.00	94.00
22	MDC	219.00	219.00	219.00
Total Tab. wt.		554.19	554.19	544.19
Actual Total Tab. wt.		554.19	554.19	544.19
Top Coat				
23	Opadry 03K19229(clear)	16.63	16.63	16.63
24	Water	-	-	-
25	IPA	q.s.	q.s.	q.s.
26	MDC	q.s.	q.s.	q.s.
Final Tab. wt.		570.82	570.82	560.82

Manufacturing process:

The compositions of Example 5 were prepared by the process as described in Example 1.

EXAMPLE 6: Comparative examples

Sr. No	Ingredients	Unit Quantity (mg)		
		Invention composition Example 1A	Comparative Example 6A	Comparative Example 6B
Drug layer				
1	Vildagliptin	75.00	75.00	75.00
2	Polyethylene oxide (WSR N80)	198.00	198.00	198.00
3	Mannitol 25	26.00	26.00	26.00
4	Magnesium stearate	1.00	1.00	1.00
5	IPA	q.s.	q.s.	q.s.
Total		300.00	300.00	300.00
Push layer				
6	Polyethylene oxide (WSR 303)	90.00	750.00	50.00
7	Iron oxide red	1.00	1.00	1.00
8	HPMC E5	8.00	8.00	8.00
9	NaCl	45.00	45.00	45.00
10	Magnesium stearate	1.00	1.00	1.00
11	IPA	q.s.	q.s.	q.s.
Total		145.00	805.00	105.00
Weight of Core Tablet		445.00	1105.00	405.00
Seal coating (3%)				
12	Opadry 03K19229(clear)	13.35	13.35	13.35
13	IPA	q.s.	q.s.	q.s.
14	MDC	q.s.	q.s.	q.s.
Total Tab. wt.		458.35	1118.35	405.35
Sustained Release (SR) coat (10%)				
15	Cellulose acetate 398-10	41.26	41.26	41.26
16	PEG3350	4.58	4.58	4.58
17	Water	q.s.	q.s.	q.s.
18	Acetone	q.s.	q.s.	q.s.

Total Tab. wt.		504.19	1164.19	451.19
Drug coating (immediate release)				
19	Vildagliptin	25.00	25.00	25.00
20	Opadry 03A690050(clear)	25.00	25.00	25.00
21	IPA	94.00	94.00	94.00
22	MDC	219.00	219.00	219.00
Total Tab. wt.		554.19	1214.19	501.19
Actual Total Tab. wt.		554.19	1214.19	501.19
Top Coat				
23	Opadry 03K19229(clear)	16.63	16.63	16.63
24	Water	220.00	220.00	220.00
25	IPA	-	-	-
26	MDC	-	-	-
Final Tab. wt.		570.82	1230.82	517.82

The comparative example compositions of Example 6 were prepared by the process described in Example 1. The comparative example compositions 6A and 6B were subjected to in-vitro dissolution testing at the condition provided in example 2 and compared with invention composition 1A.

Figure 4 shows in-vitro dissolution profile of comparative vildagliptin composition 6A and 6B at acid stage and buffer stage and following table points out the difference between invention composition and comparative examples:

Composition	In-vitro Vildagliptin release	
	Acid stage (at 2 hours)	Buffer stage (at 24 hours)
Composition of Example 1A	25%	80%
Composition 6A	<5%	<50%
Composition 6B	50%	100% at 14 hrs

CLAIMS

We claim:

1. An osmotic pharmaceutical composition comprising: (a) a core, comprising: (i) a drug layer comprising about 35 mg to about 95 mg of vildagliptin or salt thereof, and one or more pharmaceutically acceptable excipients; (ii) a push layer comprising polyethylene oxide having molecular weight of about 5,000,000 to about 8,000,000, wherein weight ratio of vildagliptin or salt thereof in the drug layer to polyethylene oxide in the push layer ranges from about 1:1 to about 1:5; (b) a seal coat surrounding the core; (c) a sustained release coat comprising about 70% to about 95% by weight cellulose acetate surrounding the seal coat; and (d) an immediate release drug layer comprising about 15 mg to about 35 mg of vildagliptin or salt thereof surrounding the sustained release coat; wherein the pharmaceutical composition exhibits an in-vitro release profile such that about 10% to about 30% of vildagliptin or salt thereof is released at 2 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, 0.1N HCl at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$.
2. The pharmaceutical composition of claim 1, wherein about 15% to about 25% of vildagliptin or salt thereof is released at 2 hours when measured in 0.1N HCl at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$.
3. The pharmaceutical composition of claim 1, wherein the composition exhibits an in-vitro release profile such that about 70% to about 95% of vildagliptin or salt thereof is released at 24 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, phosphate buffer of pH 6.8 at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$.
4. The pharmaceutical composition of claim 3, wherein about 85% to about 95% of vildagliptin or salt thereof is released at 24 hours when measured in phosphate buffer of pH 6.8 at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$.
5. The pharmaceutical composition of claim 1, wherein the composition is storage stable for a period of 3 months at about $30^{\circ}\text{C}/65\%$ relative humidity and exhibits an in-vitro release profile such that about 20% to about 30% of vildagliptin or salt thereof is released at 2 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, 0.1N HCl at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$.
6. The pharmaceutical composition of claim 1, wherein the composition is storage stable for a period 3 months at $40^{\circ}\text{C}/75\%$ relative humidity and exhibits an in-vitro release profile such

that about 20% to about 30% of vildagliptin or salt thereof is released at 2 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, 0.1N HCl at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$.

7. The pharmaceutical composition of claim 1, wherein the composition is storage stable for a period 3 months at $30^{\circ}\text{C}/65\%$ relative humidity and exhibits an in-vitro release profile such that about 85% to about 95% of vildagliptin or salt thereof is released at 24 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, phosphate buffer of pH 6.8 at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$.
8. The pharmaceutical composition of claim 1, wherein the composition is storage stable for a period 3 months at $40^{\circ}\text{C}/75\%$ relative humidity and exhibits an in-vitro release profile such that about 85% to about 95% of vildagliptin or salt thereof is released at 24 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, phosphate buffer of pH 6.8 at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$.
9. The pharmaceutical composition of claim 1, wherein the composition provides a mean plasma concentration of vildagliptin or salt thereof in the range of about 5 ng/ml to about 250 ng/ml over a period of at least 24 hours after once daily oral administration to a human subject.
10. The pharmaceutical composition of claim 9, wherein the composition provides a mean plasma concentration of vildagliptin or salt thereof of about 5 ng/ml to about 30 ng/ml at 24 hours after once daily oral administration to a human subject.
11. The pharmaceutical composition of claim 1, wherein the composition can decrease DPP-IV enzyme activity in blood plasma by about 60% to about 90% over the period of 24 hours.
12. The pharmaceutical composition of claim 1, wherein the core comprises about 75 mg of vildagliptin or salt thereof.
13. The pharmaceutical composition of claim 1, wherein weight ratio of vildagliptin or salt thereof and polyethylene oxide in the core ranges from about 1:1 to about 1:3.
14. An osmotic pharmaceutical composition comprising: (a) a core, comprising: (i) a drug layer comprising about 75 mg of vildagliptin or salt thereof, and one or more pharmaceutically acceptable excipients; (ii) a push layer comprising about 80 mg to about 90 mg of polyethylene oxide having molecular weight of about 5,000,000 to about 8,000,000; (b) a seal coat surrounding the core; (c) a sustained release coat comprising about 35 mg to about 45 mg

of cellulose acetate surrounding the seal coat; and (d) an immediate release drug layer comprising about 25 mg of vildagliptin or salt thereof surrounding the sustained release coat; wherein the pharmaceutical composition exhibits an in-vitro release profile such that about 20% to about 30% of vildagliptin or salt thereof is released at 2 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, 0.1N HCl at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$.

15. The pharmaceutical composition of claim 14, wherein the composition exhibits an in-vitro release profile such that about 85% to about 95% of vildagliptin or salt thereof is released at 24 hours, when measured in USP apparatus Type I, at 100 rpm using 900 ml, phosphate buffer of pH 6.8 at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$.

Figure 1A

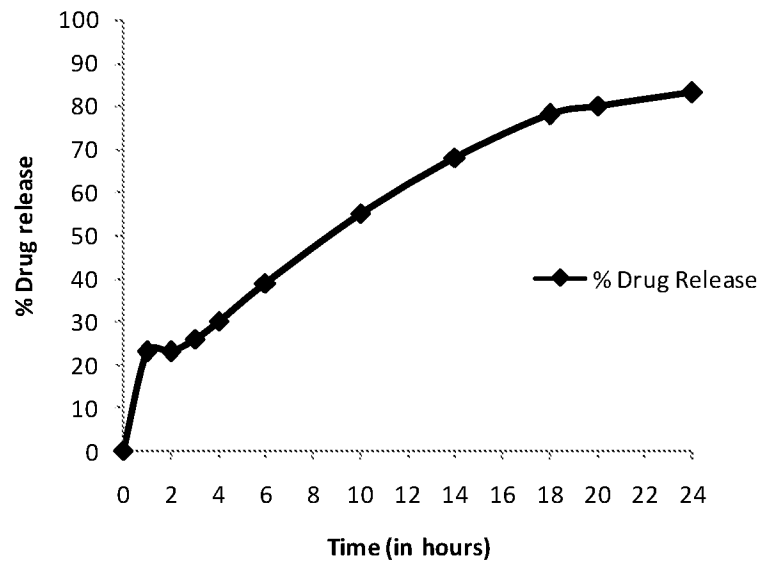


Figure 1B

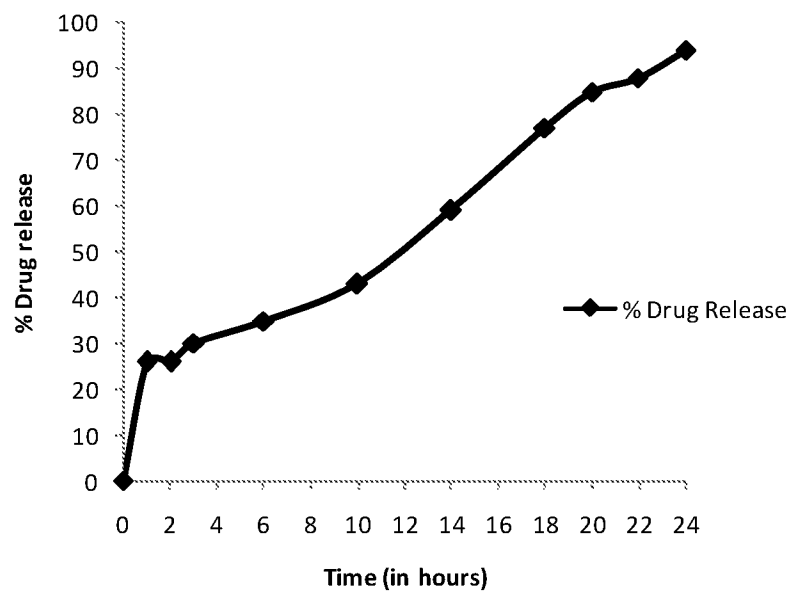


Figure 2A

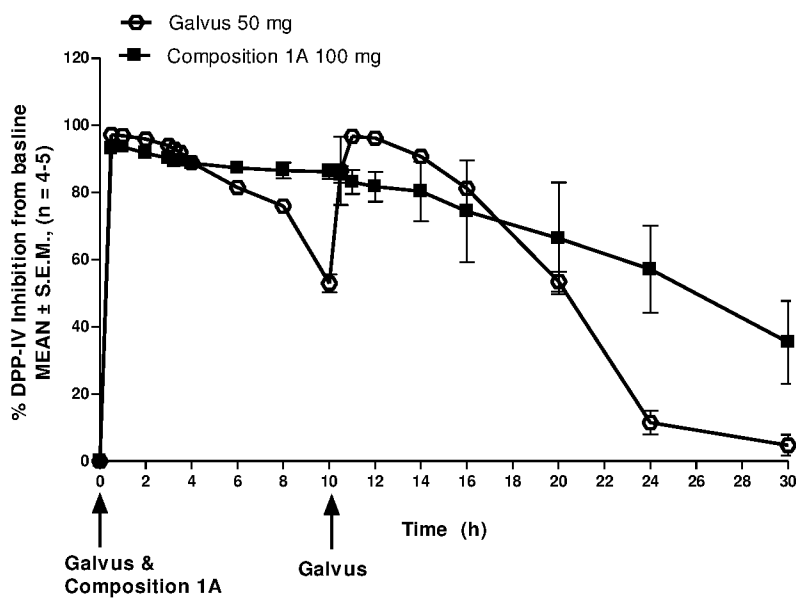


Figure 2B

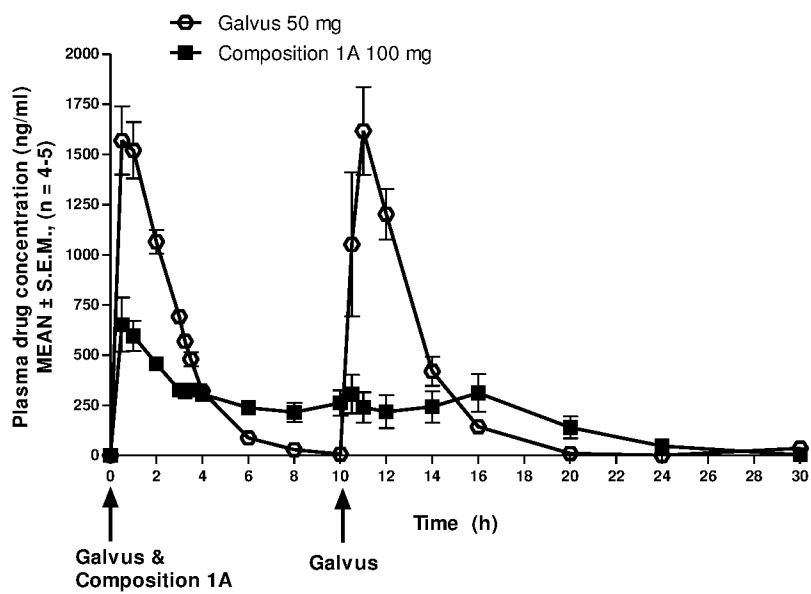


Figure 3A

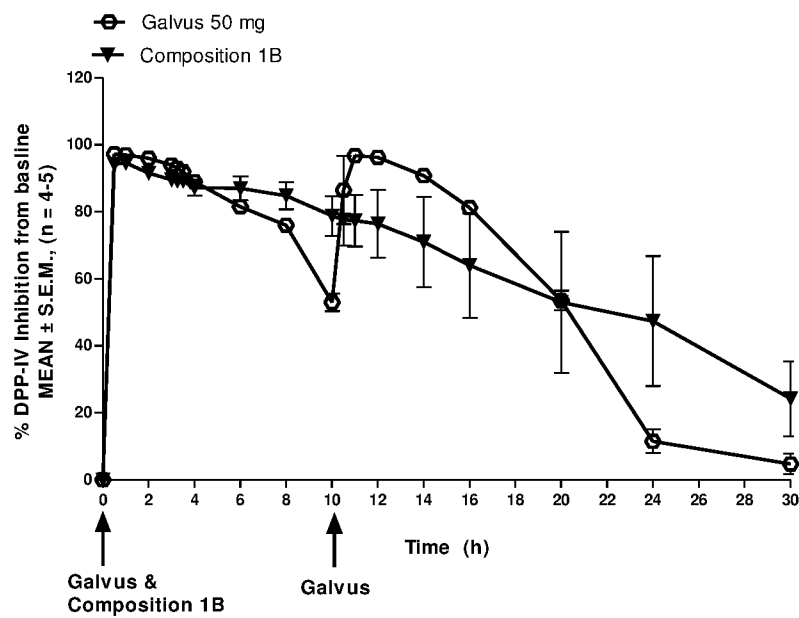


Figure 3B

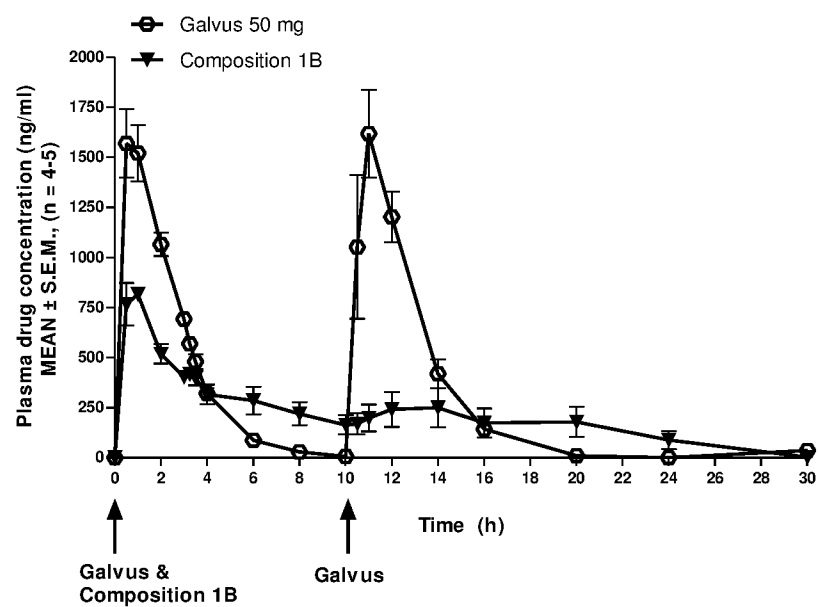
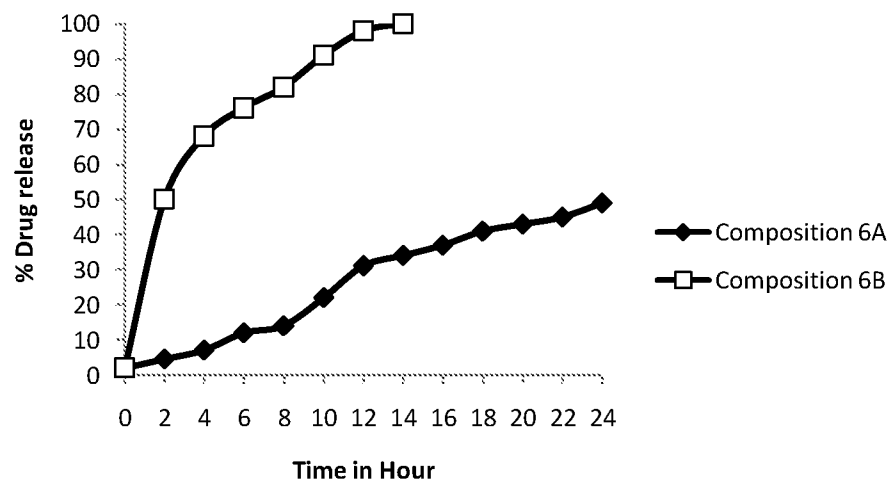


Figure 4



INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2016/057975

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K9/00 A61K9/20 A61K9/28 A61K31/40 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, WPI Data, BIOSIS, EMBASE		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 2 191 824 A1 (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]) 2 June 2010 (2010-06-02) paragraphs [0007], [0008], [0016] - [0019], [0172] - [0173], [0198] - [0214] -----	1-15
A	EP 1 537 880 A1 (TAKEDA PHARMACEUTICAL [JP]) 8 June 2005 (2005-06-08) paragraphs [0001], [0009], [0010]; claims 1-14; examples 1-38 -----	1-15
A	WO 2009/111200 A1 (MERCK & CO INC [US]; POURKAVOOS NAZANEEN [US]) 11 September 2009 (2009-09-11) the whole document -----	1-15
A	US 2007/172525 A1 (SESHA RAMESH [US]) 26 July 2007 (2007-07-26) the whole document -----	1-15
☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search	Date of mailing of the international search report	
23 March 2017	07/04/2017	
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Toulacis, C	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2016/057975

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 2191824	A1	02-06-2010	AR 054383 A1 20-06-2007
			AT 444748 T 15-10-2009
			AT 549019 T 15-03-2012
			AU 2006257947 A1 21-12-2006
			BR PI0613499 A2 11-01-2011
			CA 2610422 A1 21-12-2006
			CY 1109719 T1 13-08-2014
			DK 1898904 T3 21-12-2009
			EC SP077987 A 23-01-2008
			EP 1898904 A2 19-03-2008
			EP 2191824 A1 02-06-2010
			ES 2334261 T3 08-03-2010
			ES 2385129 T3 18-07-2012
			GT 200600246 A 28-03-2007
			HK 1117037 A1 23-04-2010
			HK 1143094 A1 24-08-2012
			HR P20090680 T1 28-02-2010
			IL 187420 A 31-01-2013
			JO 2584 B 27-02-2011
			JP 5579986 B2 27-08-2014
			JP 2008543773 A 04-12-2008
			JP 2013177428 A 09-09-2013
			JP 2015091864 A 14-05-2015
			JP 2016222675 A 28-12-2016
			KR 20080028364 A 31-03-2008
			MA 29564 B1 02-06-2008
			MY 152185 A 29-08-2014
			NZ 563447 A 24-02-2012
			PE 00572011 A1 15-02-2011
			PE 06912007 A1 06-08-2007
			PE 07282015 A1 01-06-2015
			PT 1898904 E 23-12-2009
			PT 2191824 E 18-06-2012
			SI 1898904 T1 29-01-2010
			TW I381835 B 11-01-2013
			US 2010021539 A1 28-01-2010
			US 2011086096 A1 14-04-2011
			WO 2006135723 A2 21-12-2006
EP 1537880	A1	08-06-2005	AU 2003262059 A1 30-04-2004
			EP 1537880 A1 08-06-2005
			US 2006039974 A1 23-02-2006
			WO 2004024184 A1 25-03-2004
WO 2009111200	A1	11-09-2009	AU 2009220444 A1 11-09-2009
			CA 2716130 A1 11-09-2009
			CN 101959406 A 26-01-2011
			EP 2259676 A1 15-12-2010
			JP 2011513408 A 28-04-2011
			US 2010323011 A1 23-12-2010
			WO 2009111200 A1 11-09-2009
US 2007172525	A1	26-07-2007	NONE