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(54) Title: ORAL COMPOSITIONS OF SAXAGLIPTIN

(57) Abstract: The present invention relates to oral pharmaceutical compositions comprising saxagliptin and processes for the preparation thereof. It further relates to oral pharmaceutical compositions comprising saxagliptin in combination with other antidiabetic agents.



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ORAL COMPOSITIONS OF SAXAGLIPTIN

Field of the Invention

The present invention relates to oral pharmaceutical compositions comprising saxagliptin and processes for their preparation. It further relates to oral pharmaceutical compositions comprising saxagliptin in combination with other antidiabetic agents.

Background of the Invention

Saxagliptin is a dipeptidyl peptidase IV (DPP-IV) inhibitor used for the treatment of type 2 diabetes mellitus. U.S. Patent No. 6,395,767 discloses the compound saxagliptin.

DPP-IV is an enzyme that catalyses the conversion of glucagon-like peptide-1 (GLP-1) from its active form to its inactive form. Saxagliptin competitively inhibits the DPP-IV enzyme, thereby increasing the endogenous concentration of GLP-1, which further augments insulin secretion and improves the glycemic profile of patients with type 2 diabetes mellitus.

U.S. Patent No. 7,951,400 describes saxagliptin as an unstable compound which easily undergoes intramolecular cyclization to form a cyclic amidine, which is not desirable for therapeutic activity. This process of cyclization is accelerated by the use of common processes of formulation, *e.g.*, granulation or compaction. In order to provide a stable formulation wherein saxagliptin is less prone to cyclization, U.S. Patent No. 7,951,400 provides a coated tablet formulation of saxagliptin containing a polyvinyl alcohol based coating.

The present invention provides alternative oral pharmaceutical compositions comprising saxagliptin.

Summary of the Invention

The present invention provides oral pharmaceutical compositions comprising saxagliptin and processes for their preparation. The oral pharmaceutical compositions are preferably in the form of coated tablets comprising a core and a coating layer surrounding the core, wherein the drug is present in said coating.

The present invention also relates to oral pharmaceutical compositions comprising saxagliptin in combination with other antidiabetic agents.

Detailed Description of the Invention

A first aspect of the present invention provides an oral pharmaceutical composition comprising saxagliptin, wherein said composition comprises:

- (a) a core;
- 5 (b) optionally a seal layer comprising a coating polymer over the core;
- (c) a drug layer comprising saxagliptin and a coating polymer over the core or seal-coated core; and
- (d) an outer layer comprising a coating polymer over the drug layer.

A second aspect of the present invention provides an oral pharmaceutical
10 composition comprising saxagliptin, wherein said composition comprises:

- (a) a core;
- (b) a seal layer comprising a coating polymer over the core;
- (c) a drug layer comprising saxagliptin and a coating polymer over the seal layer;
and
- 15 (d) an outer layer comprising a coating polymer over the drug layer

wherein the polymer in any one of the layers (b), (c), or (d) is not a polyvinyl alcohol based polymer.

A third aspect of the present invention provides an oral pharmaceutical composition comprising saxagliptin, wherein said composition comprises:

- 20 (a) a core;
- (b) a seal layer comprising a coating polymer over the core;
- (c) a drug layer comprising saxagliptin and a coating polymer over the seal layer;
and
- (d) an outer layer comprising a coating polymer over the drug layer

25 wherein the polymer in each of the layers (b), (c), and (d) is not a polyvinyl alcohol based polymer.

The term "saxagliptin," as used herein, refers to saxagliptin and its pharmaceutically acceptable salts or esters. These salts or esters may be prepared from an

inorganic acid selected from the group comprising hydrochloric acid, hydrobromic acid, hydroiodic acid, nitric acid, carbonic acid, bicarbonic acid, sulfuric acid, phosphoric acid, and bisulphonic acid; or an organic acid selected from the group comprising oxalic acid, formic acid, acetic acid, propionic acid, succinic acid, glycolic acid, gluconic acid, lactic acid, malic acid, tartaric acid, citric acid, ascorbic acid, glucuronic acid, maleic acid, fumaric acid, pyruvic acid, aspartic acid, glutamic acid, benzoic acid, anthranilic acid, mesylic acid, salicylic acid, p-hydroxybenzoic acid, phenylacetic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, toluenesulfonic acid, sulfanilic acid, stearic acid, alginic acid, galactaric acid, and galacturonic acid.

10 Saxagliptin used in the composition of the present invention may be present in its crystalline form, amorphous form, anhydrous form, hydrate form, or mixtures thereof.

 The term “core,” as used herein, refers to an inert core or a compressed tablet core optionally containing an additional antidiabetic agent other than saxagliptin. The inert core may include an insoluble, swellable, or soluble core. The insoluble or swellable inert
15 core may be made of dicalcium phosphate, microcrystalline cellulose, or any of the marketed inert cores, *e.g.*, glass beads, silicate beads, sugar spheres, non-pareils, or celphere. The soluble core may include glucose, mannitol, lactose, xylitol, dextrose, or sucrose.

 The compressed tablet core may comprise pharmaceutically acceptable excipients
20 selected from the group comprising binders, fillers, disintegrants, plasticizers, extended-release polymers, lubricants, glidants, or mixtures thereof, and may be prepared by the process of direct compression or granulation.

 According to one embodiment of the present invention, said core optionally contains an additional antidiabetic agent other than saxagliptin.

25 According to another embodiment of the present invention, said core containing an additional antidiabetic agent other than saxagliptin is coated with an extended-release coating.

 According to another embodiment of the present invention, the seal layer optionally contains an additional antidiabetic agent other than saxagliptin.

30 According to another embodiment of the present invention, the drug layer optionally contains an additional antidiabetic agent in addition to saxagliptin.

According to another embodiment of the present invention, the outer layer optionally contains an additional antidiabetic agent other than saxagliptin.

According to another embodiment of the present invention, said oral pharmaceutical composition provides an immediate-release or an extended-release of the
5 additional antidiabetic agent.

The additional antidiabetic agent is selected from the group comprising acarbose, miglitol, repaglinide, nateglinide, chlorpropamide, glibenclamide, gliclazide, glimepiride, glipizide, glycopyramide, tolazamide, tolbutamide, buformin, metformin, phenformin, rosiglitazone, pioglitazone, troglitazone, faraglitazar, englitazone, darglitazone,
10 isaglitazone, reglitazar, rivoglitazone, liraglutide, muraglitazar, peliglitazar, tesaglitazar, sitagliptin, vildagliptin, linagliptin, dutogliptin, alogliptin, canagliflozin, dapagliflozin, remogliflozin, sergliflozin, and pharmaceutically acceptable salts or esters thereof.

According to an embodiment of the present invention, the additional antidiabetic agent is metformin or pharmaceutically acceptable salts or esters thereof. In particular, the
15 additional antidiabetic agent is metformin hydrochloride.

The coating polymer that is not a polyvinyl alcohol based polymer is selected from the group comprising hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxymethyl cellulose, carboxymethyl cellulose, methyl cellulose, sodiumcarboxymethyl cellulose, polyvinyl pyrrolidone, polysaccharides, starch
20 and its derivatives, gums, alginates, acrylic acid derivatives, polyethylene glycol, polyalkylene glycols, mannitol, sucrose, lactose, xylitol, and mixtures thereof. Alternatively, commercially available coating compositions comprising film-forming polymers marketed under various trade names, such as Opadry[®] and Sepifilm[®] LP 010, may also be used for coating.

25 According to another embodiment of the present invention, there is provided an oral pharmaceutical composition comprising saxagliptin wherein said composition is in the form of pellets or tablets. The pellets may further be filled into capsules or compressed into tablets.

According to another embodiment of the present invention, there is provided an
30 oral pharmaceutical composition comprising saxagliptin wherein said composition further comprises pharmaceutically acceptable excipients selected from the group comprising fillers, binders, plasticizers, disintegrants, lubricants, glidants, and mixtures thereof.

The coating suspension optionally contains pharmaceutically acceptable excipients selected from the group comprising plasticizers, colorants, antioxidants, solvents, and mixtures thereof.

Suitable fillers are selected from the group comprising starch, lactose, sucrose,
5 glucose, sorbitol, calcium carbonate, calcium phosphate dibasic, calcium phosphate tribasic, calcium sulfate, microcrystalline cellulose, silicified microcrystalline cellulose, dextrates, dextrans, dextrose, fructose, lactitol, mannitol, sorbitol, pregelatinized starch, and mixtures thereof.

Suitable binders are selected from the group comprising methyl cellulose,
10 hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyvinylpyrrolidone, poloxamer, gelatin, ethyl cellulose, polyvinyl alcohol, pullulan, pregelatinized starch, agar, tragacanth, sodium alginate, propylene glycol, gum arabic, and mixtures thereof.

Suitable plasticizers are selected from the group comprising propylene glycol, triethylene glycol, oleic acid, ethylene glycol monooleate, triethyl citrate, triacetin, diethyl
15 phthalate, glyceryl monostearate, dibutyl sebacate, acetyl triethyl citrate, castor oil, and mixtures thereof.

Suitable disintegrants are selected from the group comprising cross-linked polyvinylpyrrolidone, sodium starch glycolate, cross-linked sodiumcarboxymethyl cellulose, calciumcarboxymethyl cellulose, alginic acid, alginates, pregelatinized starch,
20 starch and its derivatives, low-substituted hydroxypropyl cellulose, and mixtures thereof.

Suitable lubricants and glidants are selected from the group comprising colloidal anhydrous silica, magnesium stearate, calcium stearate, stearic acid, talc, hydrogenated castor oil, sucrose esters of fatty acids, and mixtures thereof.

Suitable antioxidants are selected from the group comprising tocopherol, L-
25 ascorbic acid and its sodium or calcium salts, ascorbyl palmitate, propyl gallate, octyl gallate, dodecyl gallate, butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), and mixtures thereof.

Suitable solvents are selected from aqueous solvents or non-aqueous solvents. The non-aqueous solvents are selected from the group comprising an ester such as ethyl
30 acetate, n-butyl acetate, or n-hexyl acetate; a ketone such as methyl ethyl ketone or methyl

isobutyl ketone; glycol ether; alcohols; hydrocarbons; chlorinated hydrocarbons; and mixtures thereof.

Suitable extended-release polymers are selected from the group comprising cellulose esters, such as cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose acetate propionate, or cellulose acetate butyrate; cellulose ethers, such as
5 hydroxypropylmethyl cellulose, hydroxypropyl cellulose, or ethylcellulose; polyvinyl acetate; methacrylic acid copolymers; and mixtures thereof.

The coloring agents of the present invention may be selected from any FDCA approved colors for oral use.

10 Coating may be carried out using a conventional coating pan, a spray coater, a rotating perforated pan, or an automated system, such as a centrifugal fluidizing granulator, a fluidized bed process, or any other suitable automated coating equipment.

The oral pharmaceutical composition of the present invention may be prepared by a process which comprises the steps of:

- 15 (i) forming core tablets comprising excipients using direct compression;
- (ii) optionally coating the core tablets of step (i) with a coating polymer to obtain seal-coated tablets;
- (iii) coating the seal-coated tablets of step (ii) with a layer comprising saxagliptin and a coating polymer to obtain drug-layered tablets;
- 20 (iv) coating the drug-layered tablets of step (iii) with a coating polymer to form an outer layer.

The oral pharmaceutical composition of the present invention may be prepared by a process which comprises the steps of:

- (i) forming core tablets comprising excipients using direct compression;
- 25 (ii) coating the core tablets of step (i) with a coating polymer to obtain seal-coated tablets;
- (iii) coating the seal-coated tablets of step (ii) with a layer comprising saxagliptin and a coating polymer to obtain drug-layered tablets; and
- (iv) coating the drug-layered tablets of step (iii) with a coating polymer to form
30 an outer layer

wherein the polymer in any one of the layers (ii), (iii), or (iv) is not a polyvinyl alcohol based polymer.

The oral pharmaceutical composition of the present invention may be prepared by a process which comprises the steps of:

- 5 (i) forming core tablets comprising excipients using direct compression;
- (ii) coating the core tablets of step (i) with a coating polymer to obtain seal-coated tablets;
- (iii) coating the seal-coated tablets of step (ii) with a layer comprising saxagliptin and a coating polymer to obtain drug-layered tablets; and
- 10 (iv) coating the drug-layered tablets with a coating polymer to form an outer layer

wherein the polymer in each of the layers (ii), (iii), and (iv) is not a polyvinyl alcohol based polymer.

- 15 The oral pharmaceutical composition of the present invention may be prepared by a process which comprises the steps of:

- (i) forming core tablets comprising excipients and an additional antidiabetic agent other than saxagliptin using wet granulation;
- (ii) optionally coating the core tablets of step (i) with a coating polymer to obtain seal-coated tablets;
- 20 (iii) coating the tablets of step (i) or the seal-coated tablets of step (ii) with a layer comprising saxagliptin and a coating polymer to obtain drug-layered tablets; and
- (iv) coating the drug-layered tablets of step (iii) with a coating polymer to form an outer layer.

- 25 The oral pharmaceutical composition of the present invention may be prepared by a process which comprises the steps of:

- (i) forming core tablets comprising excipients and an additional antidiabetic agent other than saxagliptin using wet granulation;

- (ii) coating the core tablets of step (i) with a coating polymer to obtain seal-coated tablets;
- (iii) coating the seal-coated tablets of step (ii) with a layer comprising saxagliptin and a coating polymer to obtain drug-layered tablets; and
- 5 (iv) coating the drug-layered tablets of step (iii) with a coating polymer to form an outer layer

wherein the polymer in any one of the layers (ii), (iii), or (iv) is not a polyvinyl alcohol based polymer.

The oral pharmaceutical composition of the present invention may be prepared by
10 a process which comprises the steps of:

- (i) forming core tablets comprising excipients and an additional antidiabetic agent other than saxagliptin using direct compression;
- (ii) coating the core tablets of step (i) with a coating polymer to obtain seal-coated tablets;
- 15 (iii) coating the seal-coated tablets of step (ii) with a layer comprising saxagliptin and a coating polymer to obtain drug-layered tablets; and
- (iv) coating the drug-layered tablets of step (iii) with a coating polymer to form an outer layer

wherein the polymer in each of the layers (ii), (iii), and (iv) is not a polyvinyl alcohol
20 based polymer.

The oral pharmaceutical composition of the present invention may be prepared by a process which comprises the steps of:

- (i) coating non-pareil seeds with a layer comprising metformin and a coating polymer to obtain metformin pellets;
- 25 (ii) coating the metformin pellets of step (i) with a layer comprising an extended-release polymer;
- (iii) coating the extended-release metformin pellets of step (ii) with a coating polymer to obtain seal-coated pellets;

- (iv) coating the seal-coated pellets of step (iii) with a layer comprising saxagliptin and a coating polymer to obtain saxagliptin coated pellets;
- (v) coating the saxagliptin coated pellets of step (iv) with a coating polymer to form an outer coating layer over the pellets; and
- 5 (vi) filling the pellets of step (v) into hard gelatin capsules.

The following examples represent various embodiments of the present invention. The examples are given solely for the purpose of illustration and are not to be construed as limitations of the present invention, as many variations thereof are possible without departing from the spirit and scope of the invention.

10

EXAMPLES

Example 1a & Example 1b

Ingredients	Example 1a	Example 1b
	% w/w (5.0 mg)	% w/w (2.5 mg)
Core Tablet		
Lactose monohydrate	42.48	42.94
Microcrystalline cellulose	38.63	39.05
Croscarmellose sodium	4.29	4.34
Magnesium stearate	0.43	0.43
Seal Layer		
Polyvinyl alcohol	0.68	0.69
Titanium dioxide	0.43	0.44
Polyethylene glycol	0.34	0.35
Talc	0.26	0.26
Hydrochloric acid (0.1 N)	q.s.	q.s.
Drug Layer		
Saxagliptin	2.15	1.08
Polyvinyl alcohol	3.43	3.47
Titanium dioxide	2.15	2.17
Polyethylene glycol	1.72	1.74
Talc	1.29	1.30
Hydrochloric acid (0.1 N)	q.s.	q.s.
Outer Layer		
Hydroxypropylmethyl cellulose	1.72	1.74
Hydrochloric acid (0.1 N)	q.s.	q.s.

Procedure:

Core Tablets

- i) Blend lactose monohydrate, croscarmellose sodium, and microcrystalline cellulose together in a blender.
- ii) Lubricate the blend of step i) with magnesium stearate.
- iii) Compress the lubricated blend of step iii) into core tablets.

5 Seal Layer

- iv) Dissolve polyvinyl alcohol and polyethylene glycol in 0.1 N hydrochloric acid to obtain a clear solution and adjust the pH to 2.
- v) Disperse talc and titanium dioxide in 0.1 N hydrochloric acid to obtain a uniform dispersion.
- 10 vi) Add the dispersion of step v) slowly to the solution of step vi) under stirring while maintaining the pH at 2.
- vii) Coat the core tablets of step iii) with the dispersion of step vi) to form a seal layer over the core.

Drug Layer

- 15 viii) Add saxagliptin to 0.1 N hydrochloric acid and adjust the pH to 2.
- ix) Dissolve polyvinyl alcohol and polyethylene glycol in 0.1 N hydrochloric acid to obtain a clear solution and adjust the pH to 2.
- x) Combine the solution of step viii) with the solution of step ix).
- xi) Disperse talc and titanium dioxide in 0.1 N hydrochloric acid to obtain a uniform dispersion.
- 20 xii) Add the dispersion of step xi) slowly to the solution of step x) under stirring, while maintaining the pH at 2.
- xiii) Coat the seal coated tablets of step vii) with the drug dispersion of step xii) to obtain drug-layered tablets.

25 Outer Layer

- xiv) Dissolve hydroxypropylmethyl cellulose in 0.1 N hydrochloric acid to obtain a clear solution.

- xv) Coat the drug-layered tablets of step xiii) with the dispersion of step xiv) to obtain an outer coating layer over the tablets.

Example 2a

Ingredients	Example 2a
	% w/w(5.0 mg)
Core Tablet	
Lactose monohydrate	42.48
Microcrystalline cellulose	38.63
Croscarmellose sodium	4.28
Magnesium stearate	0.43
Seal Coat	
Hydroxypropylmethyl cellulose	1.72
Hydrochloric acid (0.1 N)	q.s.
Drug Layer	
Saxagliptin	2.15
Polyvinyl alcohol	3.43
Titanium dioxide	2.15
Polyethylene glycol	1.72
Talc	1.29
Hydrochloric acid (0.1 N)	q.s.
Outer Layer	
Polyvinyl alcohol	0.69
Titanium dioxide	0.43
Polyethylene glycol	0.34
Talc	0.26
Hydrochloric acid (0.1 N)	q.s.

Procedure:

5 Core Tablets

- i) Lactose monohydrate, croscarmellose sodium, and microcrystalline cellulose were blended together.
- ii) The blend of step i) was lubricated with magnesium stearate.
- iii) The lubricated blend of step ii) was compressed into core tablets.

10 Seal Layer

- iv) Hydroxypropylmethyl cellulose was dissolved in 0.1 N hydrochloric acid to obtain a clear solution.

- v) The core tablets of step iii) were coated with the dispersion of step iv) to form seal-coated tablets.

Drug Layer

- vi) Saxagliptin was added to 0.1 N hydrochloric acid and the pH was adjusted to 2.
- 5 vii) Polyvinyl alcohol and polyethylene glycol were dissolved in 0.1 N hydrochloric acid to obtain a clear solution and the pH was adjusted to 2.
- viii) The solution of step vi) was combined with the solution of step vii).
- ix) Talc and titanium dioxide were dispersed in 0.1 N hydrochloric acid to obtain a uniform dispersion.
- 10 x) The dispersion of step ix) was added slowly to the solution of step viii) under stirring, while maintaining the pH at 2.
- xi) The seal-coated tablets of step v) were coated with the drug dispersion of step x) to obtain drug-layered tablets.

Outer Layer

- 15 xii) Polyvinyl alcohol and polyethylene glycol were dissolved in 0.1 N hydrochloric acid to obtain a clear solution and the pH was adjusted to 2.
- xiii) Talc and titanium dioxide were dispersed in 0.1 N hydrochloric acid to obtain a uniform dispersion.
- xiv) The dispersion of step xiii) was added slowly to the solution of step xii) under stirring, while maintaining the pH at 2.
- 20 xv) The drug-layered tablets of step xi) were coated with the dispersion of step xiv) to obtain an outer coating layer on the tablets.

Example 2b

Ingredients	Example 2b
	% w/w (2.5 mg)
Core Tablet	
Lactose monohydrate	42.94
Microcrystalline cellulose	39.05
Croscarmellose sodium	4.34
Magnesium stearate	0.43
Seal Coat	
Hydroxypropylmethyl cellulose	1.74
Hydrochloric acid (0.1 N)	q.s.
Drug Layer	
Saxagliptin	1.07
Polyvinyl alcohol	3.47
Titanium dioxide	2.17
Polyethylene glycol	1.74
Talc	1.30
Hydrochloric acid (0.1 N)	q.s.
Outer Layer	
Polyvinyl alcohol	0.70
Titanium dioxide	0.44
Polyethylene glycol	0.35
Talc	0.26
Hydrochloric acid (0.1 N)	q.s.

Procedure:Core Tablets

- i) Blend lactose monohydrate, croscarmellose sodium, and microcrystalline cellulose together.
- ii) Lubricate the blend of step i) with magnesium stearate.
- iii) Compress the lubricated blend of step ii) into core tablets.

Seal Layer

- iv) Dissolve hydroxypropylmethyl cellulose in 0.1 N hydrochloric acid to obtain a clear solution.
- v) Coat the core tablets of step iii) with the dispersion of step iv) to form a seal-coated core.

Drug Layer

- vi) Add saxagliptin to 0.1 N hydrochloric acid and adjust the pH to 2.
- vii) Dissolve polyvinyl alcohol and polyethylene glycol in 0.1 N hydrochloric acid to obtain a clear solution and adjust the pH to 2.
- 5 viii) Combine the solution of step vi) with the solution of step vii).
- ix) Disperse talc and titanium dioxide in 0.1 N hydrochloric acid to obtain a uniform dispersion.
- x) Add the dispersion of step ix) slowly to the solution of step viii) under stirring, while maintaining the pH at 2.
- 10 xi) Coat the seal-coated tablets of step v) with the drug dispersion of step x) to obtain drug-layered tablets.

Outer Layer

- xii) Dissolve polyvinyl alcohol and polyethylene glycol in 0.1 N hydrochloric acid to obtain a clear solution and adjust the pH to 2.
- 15 xiii) Disperse talc and titanium dioxide in 0.1 N hydrochloric acid to obtain a uniform dispersion.
- xiv) Add the dispersion of step xiii) slowly to the solution of step xii) under stirring, while maintaining the pH at 2.
- xv) Coat the drug-layered tablets of step xi) with the dispersion of step xiv) to
- 20 obtain an outer coating layer on the tablets.

Example 3a & Example 3b

Ingredients	Example 3a	Example 3b
	% w/w (5.0 mg)	% w/w (2.5 mg)
Core Tablet		
Lactose monohydrate	42.48	42.95
Microcrystalline cellulose	38.63	39.05
Croscarmellose sodium	4.29	4.34
Magnesium stearate	0.43	0.43
Seal Layer		
Polyvinyl alcohol	0.69	0.69
Titanium dioxide	0.43	0.44
Polyethylene glycol	0.34	0.35
Talc	0.26	0.26
Hydrochloric acid (0.1 N)	q.s.	q.s.
Drug Layer		
Saxagliptin	2.15	1.07
Hydroxypropylmethyl cellulose	8.58	8.67
Hydrochloric acid (0.1 N)	q.s.	q.s.
Outer Layer		
Polyvinyl alcohol	0.69	0.70
Titanium dioxide	0.43	0.44
Polyethylene glycol	0.34	0.35
Talc	0.26	0.26
Hydrochloric acid (0.1 N)	q.s.	q.s.

Procedure:Core Tablets

- i) Blend lactose monohydrate, croscarmellose sodium, and microcrystalline cellulose together in a blender.
- ii) Lubricate the blend of step i) with magnesium stearate.
- iii) Compress the lubricated blend of step ii) into core tablets.

Seal Layer

- iv) Dissolve polyvinyl alcohol and polyethylene glycol in 0.1 N hydrochloric acid to obtain a clear solution and adjust the pH to 2.
- v) Disperse talc and titanium dioxide in 0.1 N hydrochloric acid to obtain a uniform dispersion.
- vi) Add the dispersion of step v) slowly to the solution of step iv) under stirring, while maintaining the pH at 2.

- vii) Coat the core tablets of step iii) with the dispersion of step vi) to form a seal layer over the core.

Drug Layer

- viii) Add saxagliptin to 0.1 N hydrochloric acid and adjust the pH to 2.
- 5 ix) Add hydroxypropylmethyl cellulose to the drug dispersion of step viii) and maintain the pH at 2.
- x) Coat the seal-coated tablets of step vii) with the drug dispersion of step ix) to obtain drug-layered tablets.

Outer Layer

- 10 xi) Dissolve polyvinyl alcohol and polyethylene glycol in 0.1 N hydrochloric acid to obtain a clear solution and adjust the pH to 2.
- xii) Disperse talc and titanium dioxide in 0.1 N hydrochloric acid to obtain a uniform dispersion.
- xiii) Add the dispersion of step xii) slowly to the solution of step xi) under stirring,
15 while maintaining the pH at 2.
- xiv) Coat the drug-layered tablets of step x) with the dispersion of step xiii) to obtain an outer coating layer.

Example 4a & Example 4b

Ingredients	Example 4a	Example 4b
	% w/w (5.0 mg)	% w/w (2.5 mg)
Core Tablet		
Lactose monohydrate	42.48	42.95
Microcrystalline cellulose	38.63	39.05
Croscarmellose sodium	4.29	4.34
Magnesium stearate	0.43	0.43
Seal Layer		
Hydroxypropylmethyl cellulose	1.72	1.74
Hydrochloric acid (0.1 N)	q.s.	q.s.
Drug Layer		
Saxagliptin	2.15	1.07
Hydroxypropylmethyl cellulose	8.58	8.68
Hydrochloric acid (0.1 N)	q.s.	q.s.
Outer Layer		
Hydroxypropylmethyl cellulose	1.72	1.74
Hydrochloric acid (0.1 N)	q.s.	q.s.

Procedure:**Core Tablets**

- i) Blend lactose monohydrate, croscarmellose sodium, and microcrystalline cellulose together in a blender.
- 5 ii) Lubricate the blend of step i) with magnesium stearate.
- iii) Compress the lubricated blend of step ii) into core tablets.

Seal Layer

- iv) Dissolve hydroxypropylmethyl cellulose in 0.1 N hydrochloric acid to obtain a uniform mixture and adjust the pH to 2.
- 10 v) Coat the core tablets of step iii) with the dispersion of step iv) to form a seal layer over the core.

Drug Layer

- vi) Add saxagliptin to 0.1 N hydrochloric acid and adjust the pH to 2.
- vii) Add hydroxypropylmethyl cellulose to the drug dispersion of step vi) and
15 maintain the pH at 2.
- viii) Coat the seal-coated tablets of step v) with the drug dispersion of step vii) to obtain drug-layered tablets.

Outer Layer

- ix) Prepare a coating dispersion of hydroxypropylmethyl cellulose in 0.1 N
20 hydrochloric acid.
- x) Coat the drug-layered tablets of step viii) with the dispersion of step ix) to obtain an outer coating layer on the tablets.

Example 5a & Example 5b

Ingredients	Example 5a	Example 5b
	% w/w (5.0 mg)	% w/w (2.5 mg)
Core Tablet		
Lactose monohydrate	43.23	43.71
Microcrystalline cellulose	39.30	39.74
Croscarmellose sodium	4.37	4.42
Magnesium stearate	0.44	0.44
Drug Layer		
Saxagliptin	2.18	1.10
Polyvinyl alcohol	3.49	3.53
Titanium dioxide	2.18	2.21
Polyethylene glycol	1.75	1.76
Talc	1.31	1.32
Hydrochloric acid (0.1 N)	q.s.	q.s.
Outer Layer		
Polyvinyl alcohol	0.70	0.71
Titanium dioxide	0.44	0.44
Polyethylene glycol	0.35	0.35
Talc	0.26	0.27
Hydrochloric acid (0.1 N)	q.s.	q.s.

Procedure:Core Tablets

- i) Blend lactose monohydrate, croscarmellose sodium, and microcrystalline cellulose together in a blender.
- ii) Lubricate the blend of step i) with magnesium stearate.
- iii) Compress the lubricated blend of step ii) into core tablets.

Drug Layer

- iv) Add saxagliptin to 0.1 N hydrochloric acid and adjust the pH to 2.
- v) Dissolve polyvinyl alcohol and polyethylene glycol in 0.1 N hydrochloric acid to obtain a clear solution and adjust the pH to 2.
- vi) Combine the solution of step iv) with the solution of step v).
- vii) Disperse talc and titanium dioxide in 0.1 N hydrochloric acid to obtain a uniform dispersion.
- viii) Add the dispersion of step vii) slowly to the solution of step vi) under stirring, while maintaining the pH at 2.

- ix) Coat the core tablets of step iii) with the drug dispersion of step viii) to obtain drug-layered tablets.

Outer Layer

- 5 x) Dissolve polyvinyl alcohol and polyethylene glycol in 0.1 N hydrochloric acid to obtain a clear solution and adjust the pH to 2.
- xi) Disperse talc and titanium dioxide in 0.1 N hydrochloric acid to obtain a uniform dispersion.
- xii) Add the dispersion of step xi) slowly to the solution of step x) under stirring, while maintaining the pH at 2.
- 10 xiii) Coat the drug-layered tablets of step ix) with the dispersion of step xii) to obtain an outer coating layer on the tablets.

Example 6a & Example 6b

Ingredients	Example 6a	Example 6b
	% w/w (5.0 mg)	% w/w (2.5 mg)
Core		
Non-pareil seeds	85.84	86.76
Seal Layer		
Polyvinyl alcohol	0.68	0.70
Titanium dioxide	0.43	0.44
Polyethylene glycol	0.34	0.35
Talc	0.25	0.25
Hydrochloric acid (0.1 N)	q.s.	q.s.
Drug Layer		
Saxagliptin	2.15	1.07
Polyvinyl alcohol	3.43	3.47
Titanium dioxide	2.15	2.17
Polyethylene glycol	1.72	1.74
Talc	1.29	1.30
Hydrochloric acid (0.1 N)	q.s.	q.s.
Outer Layer		
Polyvinyl alcohol	0.69	0.70
Titanium dioxide	0.43	0.44
Polyethylene glycol	0.34	0.35
Talc	0.26	0.26
Hydrochloric acid (0.1 N)	q.s.	q.s.

Procedure:Seal Layer

- i) Dissolve polyvinyl alcohol and polyethylene glycol in 0.1 N hydrochloric acid to obtain a clear solution and adjust the pH to 2.
- 5 ii) Disperse talc and titanium dioxide in 0.1 N hydrochloric acid to obtain a uniform dispersion.
- iii) Add the dispersion of step ii) slowly to the solution of step i) under stirring, while maintaining the pH at 2.
- iv) Coat non-pareil seeds with the dispersion of step iii) to obtain seal-coated
10 pellets.

Drug Layer

- v) Add saxagliptin to 0.1 N hydrochloric acid and adjust the pH to 2.
- vi) Dissolve polyvinyl alcohol and polyethylene glycol in 0.1 N hydrochloric acid to obtain a clear solution and adjust the pH to 2.
- 15 vii) Combine the solution of step v) with the solution of step vi).
- viii) Disperse talc and titanium dioxide in 0.1 N hydrochloric acid to obtain a uniform dispersion.
- ix) Add the dispersion of step viii) slowly to the solution of step vii) under stirring, while maintaining the pH at 2.
- 20 x) Coat the seal-coated pellets of step iv) with the drug dispersion of step ix) to obtain drug-layered pellets.

Outer Layer

- xi) Dissolve polyvinyl alcohol and polyethylene glycol in 0.1 N hydrochloric acid to obtain a clear solution and adjust the pH to 2.
- 25 xii) Disperse talc and titanium dioxide in 0.1 N hydrochloric acid to obtain a uniform dispersion.
- xiii) Add the dispersion of step xii) slowly to the solution of step xi) under stirring, while maintaining the pH at 2.

- xiv) Coat the pellets of step x) with the dispersion of step xiii) to obtain an outer coating layer.

Capsule Filling

- 5 xv) Fill the coated pellets of step xiv) into hard gelatin capsule shells at a desired fill weight.

Example 7

Ingredients	% w/w
Core Tablet	
Metformin hydrochloride	60.50
Microcrystalline cellulose	4.84
Sodiumcarboxymethyl cellulose	1.51
Hydroxypropylmethyl cellulose	16.64
Purified water	2.72
Colloidal silicon dioxide	1.28
Magnesium stearate	0.23
Seal Layer	
Polyvinyl alcohol	0.70
Talc	0.26
Titanium dioxide	0.44
Polyethylene glycol	0.35
Hydrochloric acid (0.1 N)	q.s.
Drug Layer	
Saxagliptin	0.30
Polyvinyl alcohol	3.39
Talc	1.27
Titanium dioxide	2.13
Polyethylene glycol	1.69
Hydrochloric acid (0.1 N)	q.s.
Outer Layer	
Hydroxypropylmethyl cellulose	1.75
Hydrochloric acid (0.1 N)	q.s.

Procedure:

Core Tablets

- 10 i) Mix metformin hydrochloride with microcrystalline cellulose in a rapid mixer granulator and sprinkle purified water onto the mixture.
- ii) Add hydroxypropylmethyl cellulose and sodiumcarboxymethyl cellulose to the mixture of step i) and mix.
- iii) Add magnesium stearate to the mixture of step ii).

- iv) Compact the blend of step iii) and then pass the compacts through a screen.
- v) Granulate colloidal silicon dioxide with purified water and pass through a screen.
- vi) Mix the granules of step v) with the granules of step iv) to form a blend.
- 5 vii) Compress the final blend to form core tablets.

Seal Layer

- viii) Dissolve polyvinyl alcohol and polyethylene glycol in 0.1 N hydrochloric acid to obtain a clear solution and adjust the pH to 2.
- ix) Disperse talc and titanium dioxide in 0.1 N hydrochloric acid to obtain a
10 uniform dispersion.
- x) Add the dispersion of step ix) slowly to the solution of step viii) under stirring, while maintaining the pH at 2.
- xi) Coat the core tablets of step vii) with the dispersion of step x) to form a seal layer over the core.

15 Drug Layer

- xii) Add saxagliptin to 0.1 N hydrochloric acid and adjust the pH to 2.
- xiii) Dissolve polyvinyl alcohol and polyethylene glycol in 0.1 N hydrochloric acid to obtain a clear solution and adjust the pH to 2.
- xiv) Combine the solution of step xii) with the solution of step xiii).
- 20 xv) Disperse talc and titanium dioxide in 0.1 N hydrochloric acid to obtain a uniform dispersion.
- xvi) Add the dispersion of step xv) slowly to the solution of step xiv) under stirring, while maintaining the pH at 2.
- xvii) Coat the seal-coated tablets of step xi) with the drug dispersion of step xvi) to
25 obtain drug-layered tablets.

Outer Layer

- xviii) Dissolve hydroxypropylmethyl cellulose in 0.1 N hydrochloric acid to obtain a clear solution.

- xix) Coat the drug-layered tablets of step xvii) with the dispersion of step xviii) to obtain an outer coating layer on the tablets.

Example 8

Ingredients	% w/w
Core Tablet	
Metformin hydrochloride	60.50
Microcrystalline cellulose	4.84
Sodiumcarboxymethyl cellulose	1.51
Hydroxypropylmethyl cellulose	16.64
Purified water	2.72
Colloidal silicon dioxide	1.28
Magnesium stearate	0.23
Seal Layer	
Hydroxypropylmethyl cellulose	1.75
Hydrochloric acid (0.1 N)	q.s.
Drug Layer	
Saxagliptin	0.30
Polyvinyl alcohol	3.39
Talc	1.27
Titanium dioxide	2.13
Polyethylene glycol	1.69
Hydrochloric acid (0.1 N)	q.s.
Outer Layer	
Polyvinyl alcohol	0.70
Talc	0.26
Titanium dioxide	0.44
Polyethylene glycol	0.35
Hydrochloric acid (0.1 N)	q.s.

Procedure:

5 Core Tablets

- i) Mix metformin hydrochloride with microcrystalline cellulose in a rapid mixer granulator and sprinkle purified water onto the mixture.
- ii) Add hydroxypropylmethyl cellulose and sodiumcarboxymethyl cellulose to the mixture of step i) and mix.
- 10 iii) Add magnesium stearate to the mixture of step ii).
- iv) Compact the blend of step iii) and then pass the compacts through a screen.
- v) Granulate colloidal silicon dioxide with purified water and pass through a screen.

- vi) Mix the granules of step v) with the granules of step iv) to form a blend.
- vii) Compress the final blend to form core tablets.

Seal Layer

- 5 viii) Dissolve hydroxypropylmethyl cellulose in 0.1 N hydrochloric acid to obtain a clear solution.
- ix) Coat the core tablets of step vii) with the dispersion of step viii) to form a seal layer over the core.

Drug Layer

- x) Add saxagliptin to 0.1 N hydrochloric acid and adjust the pH to 2.
- 10 xi) Dissolve polyvinyl alcohol and polyethylene glycol in 0.1 N hydrochloric acid to obtain a clear solution and adjust the pH to 2.
- xii) Combine the solution of step x) with the solution of step xi).
- xiii) Disperse talc and titanium dioxide in 0.1 N hydrochloric acid to obtain a uniform dispersion.
- 15 xiv) Add the dispersion of step xiii) slowly to the solution of step xii) under stirring, while maintaining the pH at 2.
- xv) Coat the seal-coated tablets of step ix) with the drug dispersion of step xiv) to obtain drug-layered tablets.

Outer Layer

- 20 xvi) Dissolve polyvinyl alcohol and polyethylene glycol in 0.1 N hydrochloric acid to obtain a clear solution and adjust the pH to 2.
- xvii) Disperse talc and titanium dioxide in 0.1 N hydrochloric acid to obtain a uniform dispersion.
- xviii) Add the dispersion of step xvii) slowly to the solution of step xvi) under stirring, while maintaining the pH at 2.
- 25 xix) Coat the drug-layered tablets of step xv) with the dispersion of step xviii) to obtain an outer coating layer on the tablets.

Example 9

Ingredients	% w/w
Core Tablet	
Metformin hydrochloride	60.50
Microcrystalline cellulose	4.84
Sodiumcarboxymethyl cellulose	1.51
Hydroxypropylmethyl cellulose	16.64
Purified water	2.72
Colloidal silicon dioxide	1.29
Magnesium stearate	0.23
Seal Layer	
Polyvinyl alcohol	0.70
Talc	0.26
Titanium dioxide	0.44
Polyethylene glycol	0.35
Hydrochloric acid (0.1 N)	q.s.
Drug Layer	
Saxagliptin	0.30
Hydroxypropylmethyl cellulose	8.47
Hydrochloric acid (0.1 N)	q.s.
Outer Layer	
Polyvinyl alcohol	0.70
Talc	0.26
Titanium dioxide	0.44
Polyethylene glycol	0.35
Hydrochloric acid (0.1 N)	q.s.

Procedure:Core Tablets

- 5 i) Mix metformin hydrochloride with microcrystalline cellulose in a rapid mixer granulator and sprinkle purified water onto the mixture.
- ii) Add hydroxypropylmethyl cellulose and sodiumcarboxymethyl cellulose to the mixture of step i) and mix.
- iii) Add magnesium stearate to the mixture of step ii).
- iv) Compact the blend of step iii) and then pass the compacts through a screen.
- 10 v) Granulate colloidal silicon dioxide with purified water and pass through a screen.
- vi) Mix the granules of step v) with the granules of step iv) to form a blend.
- vii) Compress the final blend to form core tablets.

Seal Layer

- 5
- viii) Dissolve polyvinyl alcohol and polyethylene glycol in 0.1 N hydrochloric acid to obtain a clear solution and adjust the pH to 2.
 - ix) Disperse talc and titanium dioxide in 0.1 N hydrochloric acid to obtain a uniform dispersion.
 - x) Add the dispersion of step ix) slowly to the solution of step viii) under stirring while maintaining the pH at 2.
 - xi) Coat the core tablets of step vii) with the dispersion of step x) to form a seal layer over the core.

10 Drug Layer

- 15
- xii) Add saxagliptin to 0.1 N hydrochloric acid and adjust the pH to 2.
 - xiii) Add hydroxypropylmethyl cellulose to the drug dispersion of step xii) and maintain the pH at 2.
 - xiv) Coat the seal-coated tablets of step xi) with the drug dispersion of step xiii) to obtain drug-layered tablets.

Outer Layer

- 20
- xv) Dissolve polyvinyl alcohol and polyethylene glycol in 0.1 N hydrochloric acid to obtain a clear solution and adjust the pH to 2.
 - xvi) Disperse talc and titanium dioxide in 0.1 N hydrochloric acid to obtain a uniform dispersion.
 - xvii) Add the dispersion of step xvi) slowly to the solution of step xv) under stirring, while maintaining the pH at 2.
 - xviii) Coat the drug-layered tablets of step xiv) with the dispersion of step xvii) to obtain an outer coating layer on the tablets.

Example 10

Ingredients	% w/w
Core Tablet	
Metformin hydrochloride	60.50
Microcrystalline cellulose	4.84
Sodiumcarboxymethyl cellulose	1.51
Hydroxypropylmethyl cellulose	16.64
Purified water	2.72
Colloidal silicon dioxide	1.29
Magnesium stearate	0.23
Seal Layer	
Hydroxypropylmethyl cellulose	1.75
Hydrochloric acid (0.1 N)	q.s.
Drug Layer	
Saxagliptin	0.30
Hydroxypropylmethyl cellulose	8.47
Hydrochloric acid (0.1 N)	q.s.
Outer Layer	
Hydroxypropylmethyl cellulose	1.75
Hydrochloric acid (0.1 N)	q.s.

Procedure:Core Tablets

- i) Mix metformin hydrochloride with microcrystalline cellulose in a rapid mixer granulator and sprinkle purified water onto the mixture.
- ii) Add hydroxypropylmethyl cellulose and sodiumcarboxymethyl cellulose to the mixture of step i) and mix.
- iii) Add magnesium stearate to the mixture of step ii).
- iv) Compact the blend of step iii) and then pass the compacts through a screen.
- v) Granulate colloidal silicon dioxide with purified water and pass through a screen.
- vi) Mix the granules of step v) with the granules of step iv) to form a blend.
- vii) Compress the final blend to form core tablets.

Seal Layer

- viii) Dissolve hydroxypropylmethyl cellulose in 0.1 N hydrochloric acid to obtain a uniform mixture and adjust the pH to 2.
- ix) Coat the core tablets of step vii) with the dispersion of step viii) to form a seal layer over the core.

Drug Layer

- x) Add saxagliptin to 0.1 N hydrochloric acid and adjust the pH to 2.
- xi) Add hydroxypropylmethyl cellulose to the drug dispersion of step x) and maintain the pH at 2.
- 5 xii) Coat the seal-coated tablets of step ix) with the dispersion of step xi) to obtain drug-layered tablets.

Outer Layer

- xiii) Disperse hydroxypropylmethyl cellulose in 0.1 N hydrochloric acid to obtain a coating dispersion.
- 10 xiv) Coat the drug-layered tablets of step xii) with the dispersion of step xiii) to obtain an outer coating layer on the tablets.

Example 11

Ingredients	% w/w
Core Tablet	
Metformin hydrochloride	61.57
Microcrystalline cellulose	4.93
Sodiumcarboxymethyl cellulose	1.54
Hydroxypropylmethyl cellulose	16.93
Purified water	2.77
Colloidal silicon dioxide	1.31
Magnesium stearate	0.23
Drug Layer	
Saxagliptin	0.30
Polyvinyl alcohol	3.45
Talc	1.29
Titanium dioxide	2.15
Polyethylene glycol	1.73
Hydrochloric acid (0.1 N)	q.s.
Outer Layer	
Polyvinyl alcohol	0.72
Talc	0.27
Titanium dioxide	0.45
Polyethylene glycol	0.36
Hydrochloric acid (0.1 N)	q.s.

Procedure:Core Tablets

- i) Mix metformin hydrochloride with microcrystalline cellulose in a rapid mixer granulator and sprinkle purified water onto the mixture.
- 5 ii) Add hydroxypropylmethyl cellulose and sodiumcarboxymethyl cellulose to the mixture of step i) and mix.
- iii) Add magnesium stearate to the mixture of step ii).
- iv) Compact the blend of step iii) and then pass the compacts through a screen.
- v) Granulate colloidal silicon dioxide with purified water and pass through a
10 screen.
- vi) Mix the granules of step v) with the granules of step iv) to form a blend.
- vii) Compress the final blend to form core tablets.

Drug Layer

- viii) Add saxagliptin to 0.1 N hydrochloric acid and adjust the pH to 2.
- 15 ix) Dissolve polyvinyl alcohol and polyethylene glycol in 0.1 N hydrochloric acid to obtain a clear solution and adjust the pH to 2.
- x) Combine the solution of step viii) with the solution of step ix).
- xi) Disperse talc and titanium dioxide in 0.1 N hydrochloric acid to obtain a uniform dispersion.
- 20 xii) Add the dispersion of step xi) slowly to the solution of step x) under stirring, while maintaining the pH at 2.
- xiii) Coat the core tablets of step vii) with the drug dispersion of step xii) to obtain drug-layered tablets.

Outer Layer

- 25 xiv) Dissolve polyvinyl alcohol and polyethylene glycol in 0.1 N hydrochloric acid to obtain a clear solution and adjust the pH to 2.
- xv) Disperse talc and titanium dioxide in 0.1 N hydrochloric acid to obtain a uniform dispersion.
- xvi) Add the dispersion of step xv) slowly to the solution of step xiv) under stirring
30 while maintaining the pH at 2.
- xvii) Coat the drug-layered tablets of step xiii) with the dispersion of step xvi) to obtain an outer coating layer.

Example 12

Ingredients	% w/w
Core	
Non-pareil seeds	13.91
Metformin Layer	
Metformin hydrochloride	69.54
Hydroxypropylmethyl cellulose	0.70
Sodiumcarboxymethylcellulose	1.74
Purified water	q.s.
Extended-release Layer	
Ethyl cellulose	0.96
Hydroxypropylmethyl cellulose	0.42
Seal Layer	
Polyvinyl alcohol	0.70
Talc	0.26
Titanium dioxide	0.44
Polyethylene glycol	0.35
Hydrochloric acid (0.1 N)	q.s.
Drug Layer	
Saxagliptin	0.35
Polyvinyl alcohol	3.48
Talc	1.29
Titanium dioxide	2.17
Polyethylene glycol	1.74
Hydrochloric acid (0.1 N)	q.s.
Outer Layer	
Polyvinyl alcohol	0.78
Talc	0.29
Titanium dioxide	0.49
Polyethylene glycol	0.39
Hydrochloric acid (0.1 N)	q.s.

Procedure:Metformin Layer

- i) Dissolve metformin hydrochloride and hydroxypropylmethyl cellulose in purified water, then disperse sodiumcarboxymethyl cellulose into the purified water to obtain a uniform dispersion.
- ii) Coat non-pareil seeds with the dispersion of step i) to obtain coated pellets.

Extended-Release Layer

- iii) Dissolve ethyl cellulose and hydroxypropylmethyl cellulose in an organic solvent to obtain a clear solution.
- iv) Coat metformin pellets of step ii) with the solution of step iii).

Seal Layer

- v) Dissolve polyvinyl alcohol and polyethylene glycol in 0.1 N hydrochloric acid to obtain a clear solution and adjust the pH to 2.
- 5 vi) Disperse talc and titanium dioxide in 0.1 N hydrochloric acid to obtain a uniform dispersion.
- vii) Add the dispersion of step vi) slowly to the solution of step v) under stirring, while maintaining the pH at 2.
- viii) Coat the extended-release metformin pellets of step iv) with the dispersion of step vii).

10 Drug Layer

- ix) Add saxagliptin to 0.1 N hydrochloric acid and adjust the pH to 2.
- x) Dissolve polyvinyl alcohol and polyethylene glycol in 0.1 N hydrochloric acid to obtain a clear solution and adjust the pH to 2.
- xi) Combine the solution of step ix) with the solution of step x).
- 15 xii) Disperse talc and titanium dioxide in 0.1 N hydrochloric acid to obtain a uniform dispersion.
- xiii) Add the dispersion of step xii) slowly to the solution of step xi) under stirring, while maintaining the pH at 2.
- xiv) Coat the seal-coated pellets of step viii) with the drug dispersion of step xiii).

20 Outer Layer

- xv) Dissolve polyvinyl alcohol and polyethylene glycol in 0.1 N hydrochloric acid to obtain a clear solution and adjust the pH to 2.
- xvi) Disperse talc and titanium dioxide in 0.1 N hydrochloric acid to obtain a uniform dispersion.
- 25 xvii) Add the dispersion of step xvi) slowly to the solution of step xv) under stirring, while maintaining pH at 2.
- xviii) Coat the saxagliptin-coated pellets of step xiii) with the dispersion of step xvii) to obtain an outer coating layer over the pellets.

Capsule Filling

- 30 xix) Fill the pellets of step xviii) into hard gelatin capsule shells at a desired fill weight.

We claim:

- 1 1. An oral pharmaceutical composition comprising saxagliptin, wherein said
2 composition comprises:
 - 3 (a) a core;
 - 4 (b) optionally a seal layer comprising a coating polymer coated over the core;
 - 5 (c) a drug layer comprising saxagliptin and a coating polymer over the core or
6 seal-coated core; and
 - 7 (d) an outer layer comprising a coating polymer over the drug layer.
- 1 2. An oral pharmaceutical composition comprising saxagliptin, wherein said
2 composition comprises:
 - 3 (a) a core;
 - 4 (b) a seal layer comprising a coating polymer over the core;
 - 5 (c) a drug layer comprising saxagliptin and a coating polymer over the seal layer;
6 and
 - 7 (d) an outer layer comprising a coating polymer over the drug layer

8 wherein the polymer in any one of the layers (b), (c), or (d) is not a polyvinyl alcohol
9 based polymer.
- 1 3. An oral pharmaceutical composition comprising saxagliptin, wherein said
2 composition comprises:
 - 3 (a) a core;
 - 4 (b) a seal layer over the core comprising a coating polymer;
 - 5 (c) a drug layer over the seal layer comprising saxagliptin and a coating polymer;
6 and
 - 7 (d) an outer layer over the drug layer comprising a coating polymer;

8 wherein the polymer in each of the layers (b), (c), and (d) is not a polyvinyl alcohol based
9 polymer.
- 1 4. The oral pharmaceutical composition according to claim 1, claim 2, or claim 3,
2 wherein said core is an inert core or a compressed tablet core.

1 5. The oral pharmaceutical composition according to claim 4, wherein the inert core
2 is an insoluble, swellable, or soluble core.

1 6. The oral pharmaceutical composition according to claim 4, wherein the
2 compressed tablet core further comprises pharmaceutically acceptable excipients selected
3 from the group comprising binders, fillers, disintegrants, plasticizers, extended-release
4 polymers, lubricants, glidants, or mixtures thereof.

1 7. The oral pharmaceutical composition according to claim 1, claim 2, or claim 3,
2 wherein said composition further comprises an additional antidiabetic agent.

1 8. The oral pharmaceutical composition according to claim 7, wherein said
2 composition provides an immediate-release or an extended-release of the additional
3 antidiabetic agent.

1 9. The oral pharmaceutical composition according to claim 7, wherein the additional
2 antidiabetic agent is selected from the group comprising acarbose, miglitol, insulin,
3 repaglinide, nateglinide, chlorpropamide, glibenclamide, gliclazide, glimepiride, glipizide,
4 glycopyramide, tolazamide, tolbutamide, buformin, metformin, phenformin,
5 rosiglitazone, pioglitazone, troglitazone, faraglitazar, englitazone, darglitazone,
6 isaglitazone, reglitazar, rivoglitazone, liraglutide, muraglitazar, peliglitazar, tesaglitazar,
7 sitagliptin, vildagliptin, linagliptin, dutogliptin, alogliptin, canagliflozin, dapagliflozin,
8 remogliflozin, sergliflozin, and pharmaceutically acceptable salts or esters thereof.

1 10. The oral pharmaceutical composition according to claim 2 or claim 3, wherein the
2 polymer that is not a polyvinyl alcohol based polymer is selected from the group
3 comprising hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxyethyl
4 cellulose, hydroxymethyl cellulose, carboxymethyl cellulose, methyl cellulose,
5 sodiumcarboxymethyl cellulose, polyvinyl pyrrolidone, polysaccharides, starch and its
6 derivatives, gums, alginates, acrylic acid derivatives, polyethylene glycol, polyalkylene
7 glycols, mannitol, sucrose, lactose, xylitol, and mixtures thereof.

1 11. The oral pharmaceutical composition according to claim 1, wherein said
2 composition is prepared by a process which comprises the steps of:

- 3 (i) forming core tablets comprising excipients using direct compression;
4 (ii) optionally coating the core tablets of step (i) with a coating polymer to obtain
5 seal-coated tablets;

- 6 (iii) coating the tablets of step (i) or the seal-coated tablets of step (ii) with a layer
7 comprising saxagliptin and a coating polymer to obtain drug-layered tablets;
8 and
9 (iv) coating the drug-layered tablets of step (iii) with a coating polymer to form
10 an outer layer.

1 12. The oral pharmaceutical composition according to claim 2, wherein said
2 composition is prepared by a process which comprises the steps of:

- 3 (i) forming core tablets comprising excipients using direct compression;
4 (ii) coating the core tablets of step (i) with a coating polymer to obtain seal-
5 coated tablets;
6 (iii) coating the seal coated tablets of step (ii) with a layer comprising saxagliptin
7 and a coating polymer to obtain drug-layered tablets;
8 (iv) coating the drug-layered tablets of step (iii) with a coating polymer to form
9 an outer layer

10 wherein the polymer in any one of the layers (ii), (iii), or (iv) is not a polyvinyl alcohol
11 based polymer.

1 13. The oral pharmaceutical composition according to claim 3, wherein said
2 composition is prepared by a process which comprises the steps of:

- 3 (i) forming core tablets comprising excipients using direct compression;
4 (ii) coating the core tablets of step (i) with a coating polymer to obtain seal-
5 coated tablets;
6 (iii) coating the seal-coated tablets of step (ii) with a layer comprising saxagliptin
7 and a coating polymer to obtain drug-layered tablets; and
8 (iv) coating the drug-layered tablets of step (iii) with a coating polymer to form
9 an outer layer

10 wherein the polymer in each of the layers (ii), (iii), and (iv) is not a polyvinyl alcohol
11 based polymer.

1 14. The oral pharmaceutical composition according to claim 7, wherein said
2 composition is prepared by a process which comprises the steps of:

- 3 (i) forming core tablets comprising excipients and an additional antidiabetic
4 agent other than saxagliptin using wet granulation;
- 5 (ii) optionally coating the core tablets of step (i) with a coating polymer to obtain
6 seal-coated tablets;
- 7 (iii) coating the tablets of step (i) or the seal coated tablets of step (ii) with a layer
8 comprising saxagliptin and a coating polymer to obtain drug-layered tablets;
9 and
- 10 (iv) coating the drug-layered tablets of step (iii) with a coating polymer to form
11 an outer layer.

1 15. The oral pharmaceutical composition according to claim 7, wherein said
2 composition is prepared by a process which comprises the steps of:

- 3 (i) forming core tablets comprising excipients and an additional antidiabetic
4 agent other than saxagliptin using wet granulation;
- 5 (ii) coating the core tablets of step (i) with a coating polymer to obtain seal-
6 coated tablets;
- 7 (iii) coating the seal-coated tablets of step (ii) with a layer comprising saxagliptin
8 and a coating polymer to obtain drug-layered tablets; and
- 9 (iv) coating the drug-layered tablets with a coating polymer to form an outer layer
- 10 wherein the polymer in any one of the layers (ii), (iii), or (iv) is not a polyvinyl alcohol
11 based polymer.

1 16. The oral pharmaceutical composition according to claim 7, wherein said
2 composition is prepared by a process which comprises the steps of:

- 3 (i) forming core tablets comprising excipients and an additional antidiabetic
4 agent other than saxagliptin using direct compression;
- 5 (ii) coating the core tablets of step (i) with a coating polymer to obtain seal-
6 coated tablets;
- 7 (iii) coating the seal-coated tablets of step (ii) with a layer comprising saxagliptin
8 and a coating polymer to obtain drug-layered tablets; and
- 9 (iv) coating the drug-layered tablets of step (iii) with a coating polymer to form

10 an outer layer

11 wherein the polymer in each of the layers (ii), (iii), and (iv) is not a polyvinyl alcohol
12 based polymer.

1 17. The oral pharmaceutical composition according to claim 9, wherein said
2 composition is prepared by a process which comprises the steps of:

- 3 (i) coating non-pareil seeds with a layer comprising metformin and a coating
4 polymer to obtain metformin pellets;
- 5 (ii) coating the metformin pellets of step (i) with a layer comprising an extended-
6 release polymer;
- 7 (iii) coating the extended-release metformin pellets of step (ii) with a coating
8 polymer to obtain seal-coated pellets;
- 9 (iv) coating the seal-coated pellets of step (iii) with a layer comprising saxagliptin
10 and a coating polymer to obtain saxagliptin coated pellets;
- 11 (v) coating the saxagliptin coated pellets of step (iv) with a coating polymer to
12 form an outer coating layer over the pellets; and
- 13 (vi) filling the pellets of step (v) into hard gelatin capsules.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2014/066137

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K9/24 A61K9/28 A61K31/00 A61K9/50 ADD.		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, BIOSIS, EMBASE, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
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X	WO 2012/031124 A2 (SQUIBB BRISTOL MYERS CO [US]; ASTRAZENECA UK LTD [GB]; NARANG AJIT [US] 8 March 2012 (2012-03-08) claims 1-3 -----	1-17
X	US 2010/074950 A1 (SESHA RAMESH [US]) 25 March 2010 (2010-03-25) paragraph [0100]; examples 1,4; table 8 -----	1-17
X,P	WO 2013/179307 A2 (MYLAN LAB LTD [IN]; SAHOO SATYA SANKAR [IN]; JADAV HARSHAL KUMAR [IN];) 5 December 2013 (2013-12-05) claim 1 -----	1-17
X,P	WO 2014/096982 A1 (WOCKHARDT LTD [IN]) 26 June 2014 (2014-06-26) claim 1 ----- ----- -/-	1-17
☒ 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 26 January 2015		Date of mailing of the international search report 04/02/2015
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 Konter, Jörg

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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