COATED TABLET FORMULATION AND METHOD

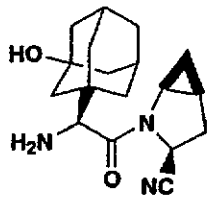
FIELD OF THE INVENTION

This application claims a benefit of priority from U.S. Provisional Application No. 60/575,319, filed May 28, 2004, the entire disclosure of which is herein incorporated by reference.

The present invention relates to a coated tablet formulation which includes a tablet core coated with a medicament such as a DPP4-inhibitor, such as saxagliptin, and to a method for preparing such coated tablet formulation.

BACKGROUND OF THE INVENTION

The compound of the structure

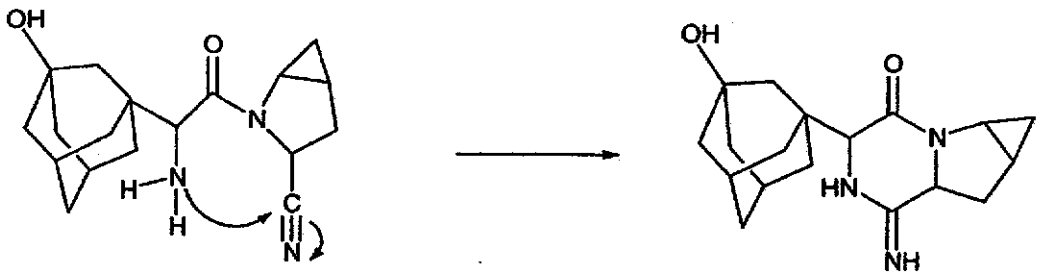


or its HCl salt,

(hereinafter the above DPP4-inhibitor or saxaglipitin) is an orally active reversible dipeptidyl peptidase -4 (DPP4) inhibitor, which is a therapeutic agent for treatment of Type-2 diabetes mellitus which is disclosed in U.S. Patent No. 6,395,767.

After a meal intake, insulinotropic hormone GLP-1 is released which in turn induces insulin release from the pancreas. Some of the GLP-1 is inactivated by the DPP4 present in plasma and intestinal capillary endothelium. Therefore, if the DPP4 is 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, problems of hypoglycemia associated with other diabetes drugs will be less likely with a DPP4 inhibitor.

The above DPP4 inhibitor is a labile compound which is prone to an intra-molecular cyclization as shown below.



DPP4-inhibitor Cyclic amidine

Formation of Cyclic Amidine (CA)

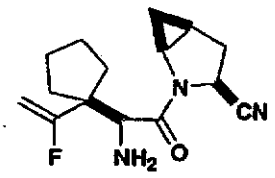
The resultant degradant, cyclic amidine (mainly cis-cyclic amidine (CA)), is not therapeutically active and therefore, its formation is not desirable. This cyclization reaction can occur both in solid state and solution state. The rate of intra-molecular cyclization is accelerated when formulations are subject to commonly used processing activities such as wet granulation, roller compaction, or tabletting. In addition, most commonly used excipients, when mixed with this compound, can accelerate the rate of cyclization. Moreover, the level of cis-cyclic amidine increases when the drug to excipient ratio increases posing more challenges for low strength dosage forms. Given these properties of the molecule, manufacture of a conventional tablet dosage form for the DPP4-inhibitor, which is a preferred dosage form, is not a viable option.

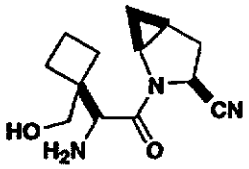
Currently, capsule formulations containing a dry mix of the DPP4-inhibitor and commonly used excipients are manufactured at a small scale and used for clinical studies. The scale up of capsule formulations containing the DPP4-inhibitor will also be problematic since it will involve milling to control the particle size of the DPP4-inhibitor so that capsules of lower strengths are manufactured without content unifomity problems.

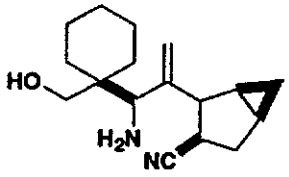
Additionally, most of the therapeutic agents as a single entity or as a combination product for diabetes treatments are available in a tablet dosage form. Since a tablet dosage form using traditional manufacturing process is not feasible for the DPP4-inhibitor, its manufacturing with other therapeutic agents, as a combination tablet will be even more problematic.

Thus, it is seen that there is clearly a need for stable pharmaceutical formulations containing medicaments which are subject to intra-molecular cyclization which results in formation of degradants such as cyclic amidines which are not therapeutically active.

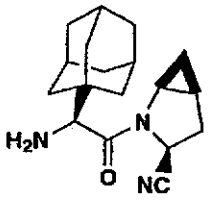
U.S. Patent No. 6,395,767 to Robl et al. (hereinafter Robl et al.) discloses cyclopropyl-fused pyrrolidine-based dipeptidyl peptidase IV inhibitors (DPP4 inhibitors) which include compounds having the structure

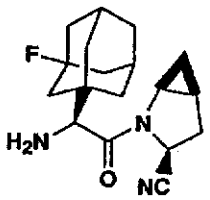


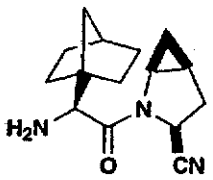
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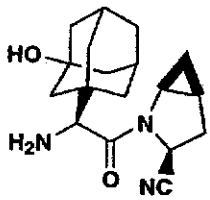
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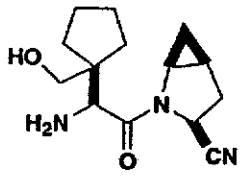
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or


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or a pharmaceutically acceptable salt thereof, wherein the pharmaceutically acceptable salt can be the hydrochloride salt or the trifluoroacetic acid salt.

Robl et al. discloses that the DPP4 inhibitors including those set out above may be formulated as tablets, capsules, granules or powders.

BRIEF DESCRIPTION OF THE INVENTION

In accordance with the present invention a coated tablet is provided which may include a medicament which is subject to intra-molecular cyclization, but is

surprisingly stable under normal storage conditions, that is at 30°C and 60% relative humidity.

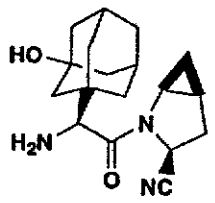
The coated tablet of the invention includes a tablet core (also referred to as a "core", "tablet core", "placebo", "placebo core tablet", "tablet core composition" or "core composition") and

a) a coating layer coated on the core, which coating layer is an inner seal coat formed of at least one coating polymer;

b) a second coating layer, disposed over the inner seal coat, formed of a medicament and at least one coating polymer which preferably is the same coating polymer in the inner seal coat; and optionally

c) an outer protective coating layer, disposed over the second coating layer, formed of at least one coating polymer, which preferably is the same coating polymer in the second coating layer and inner seal coat, but need not necessarily include the same amounts of such polymer.

The medicament will preferably be the DPP4-inhibitor of the structure

A 

or a pharmaceutically acceptable salt thereof, such as the HCl salt, also referred to as Compound A.

In a preferred embodiment, the coated tablet of the invention will include a tablet core which is formed of one or more bulking agents or fillers, optionally one or more binders, optionally one or more disintegrants, and optionally one or more tableting lubricants,

a) an inner seal coating layer which includes at least one coating polymer which preferably is a polyvinyl alcohol (PVA) based polymer;

b) a second coating layer disposed over the seal coating layer a) which includes at least one medicament and at least one coating polymer which is preferably

a PVA based polymer, and preferably the same as the coating polymer of the inner seal coating layer.

The above coating layers are applied to the tablet core preferably by spray coating on to the tablet core.

In a more preferred embodiment of the invention, an outer protective or third coating layer will be coated over the second coating layer (containing the medicament) and will function as a protective layer. The third or protective coating layer may preferably include similar components as in the second coating layer except that it will not include a medicament, but may optionally include one or more colorants, and may not necessarily include the same amounts of such components. Optionally, a fourth layer (which includes similar components as in the third layer) containing colorants and a coating polymer can also be applied to differentiate tablets of various strengths. The first, second , third and fourth coating layers may be formed of the same or different coating polymers .

It has been found that the coated tablets of the invention exhibit superior chemical stability as compared to traditional tablets manufactured using conventional dry granulation or wet granulation techniques.

The coating approach will also facilitate preparation of a combination formulation of a problematic medicament with another drug by using the other drug tablet as a starting tablet (instead of the tablet core or placebo mentioned above) and applying the inner seal coating and the second coating containing the problematic medicament and coating polymer, and optionally but preferably, the outer protective coating over the other drug tablet.

The coated tablets of the invention may be prepared preferably using perforated pan coaters. Fluid bed coating and spray coating may be used as well.

In addition, in accordance with the present invention, a method is provided for preparing the coated tablet of the invention, which method includes the steps of

a) providing a tablet core;

b) coating the tablet with an inner seal coating layer formulation which includes at least one coating polymer;

c) drying the coated tablet to form an inner seal coating thereon;

d) coating the so-coated tablet with a second coating layer formulation which includes medicament and at least one coating polymer;

e) drying the so-coated tablet to form a second coating layer (containing medicament) thereon;

f) optionally, but preferably, coating the so-coated tablet with a third outer protective coating layer formulation which includes at least one coating polymer; and

g) optionally, coating the so-coated tablet with a fourth outer protective coating layer which includes at least one coating polymer and colorant, and

h) drying the so-coated tablet to form the coated tablet of the invention.

In a preferred embodiment of the method of the invention the inner seal coating layer formulation, the second coating layer formulation and the outer protective coating layer(s) formulation(s) each will be applied as a suspension of the coating polymer in a coating solvent.

The third and fourth outer protective coating layers need not include a medicament (although it may, if desired), and may be formed of the other components of the first coating layer and/or second coating layer. The second coating layer may be formed of the components of the first coating layer and/or third/ and or fourth coating layer, but not necessarily the same amounts of such components.

In preparing the coated tablet of the invention, coating suspensions which include coating polymer in water are prepared. Other coating solvents which may be employed include ethanol, methanol, and isopropyl alcohol, with water being preferred. Tablets which are placebos (contain no medicament) and form tablet cores are coated with the inner seal coating suspension and are dried. The second coating layer suspension containing medicament and coating polymer is applied over the so-coated tablets which are then dried.

Where the coated tablet of the invention is to include an outer protective layer, a coating suspension is prepared as in the case of the inner seal coating suspension but without medicament. The coating suspension will then be coated onto the previously coated tablets as described for the inner seal coating and second coating to form a protective coating layer thereon.

The coated tablets of the invention are useful in the treatment of mammals such as humans, dogs and cats for Type II diabetes.

DETAILED DESCRIPTION OF THE INVENTION

The tablet core or placebo employed in the coated tablet of the invention will include conventional pharmaceutical excipients to enable formation of a pharmaceutically acceptable solid tablet core. The tablet core may be in the form of a tablet, bead, beadlet, or pill, all of the above being collectively referred to as a tablet core.

The coated tablet of the invention will contain medicament, such as the above DPP4-inhibitor, saxaglipitin, in an amount within the range from about 0.1 to about 70% by weight and preferably from about 1 to about 50% by weight of the tablet core.

The tablet core employed in the coated tablet of the invention will preferably contain

a) at least one bulking agent or filler;

b) optionally at least one binder;

c) optionally at least one disintegrant; and

d) preferably but optionally at least one lubricant.

wherein

a) the bulking agent or filler is present in an amount within the range from about 1 to about 95% by weight, preferably from about 10 to about 85% by weight;

b) the binder is present in an amount within the range from about 0 to about 20% by weight, preferably from about 1 to about 10% by weight;

c) the disintegrant is present in an amount within the range from about 0 to about 20% by weight, and preferably from about 0.25 to about 10% by weight; and

d) the lubricant is present in an amount within the range from about 0 to about 5% by weight, preferably from about 0.2 to about 2% by weight,

all of the above % by weight being based on the weight of the tablet core.

It is preferred that the bulking agents are microcrystalline cellulose and lactose monohydrate;

the disintegrant is croscarmellose sodium; and

the lubricant is magnesium stearate.

The tablet cores present in the coated tablets of this invention can be prepared by a variety of processes and order of addition of excipients. The utility of these formulations is not limited to a specific dosage form or manufacturing process. Tablet cores may be manufactured by wet granulation, dry granulation, direct blending or any other pharmaceutically acceptable process.

In accordance with the present invention, a preferred method is provided for preparing the tablet cores employed in the coated tablets of the invention which includes the steps of blending the one or more excipients such as bulking agent, optionally binder and optionally disintegrant. A lubricant will be preferably added to the blend to facilitate tablet formation.

The bulking agents or fillers will be present in the tablet core compositions of the invention in an amount within the range from about 1 to about 95% by weight and preferably from about 10 to about 85% by weight of the core composition. Examples of bulking agents or fillers suitable for use herein include, but are not limited to, cellulose derivatives such as microcrystalline cellulose or wood cellulose, lactose, sucrose, starch, pregelatinized starch, dextrose, mannitol, fructose, xylitol, sorbitol, corn starch, modified corn starch, inorganic salts such as calcium carbonate, calcium phosphate, dicalcium phosphate, calcium sulfate, dextrin/dextrates, maltodextrin, compressible sugars, and other known bulking agents or fillers, and/or mixtures of two or more thereof, preferably microcrystalline cellulose.

The binder will be optionally present in the pharmaceutical compositions of the invention in an amount within the range from about 0 to about 20% weight, preferably from about 1 to about 10% by weight of the core composition. Examples of binders suitable for use herein include, but are not limited to, hydroxypropyl cellulose, corn starch, pregelatinized starch, modified corn starch, polyvinyl pyrrolidone (PVP) (molecular weight ranging from about 5,000 to about 1,000,000, preferably about 40,000), hydroxypropyl methylcellulose (HPMC), lactose, gum acacia, ethyl cellulose, cellulose acetate, as well as a wax binder such as carnauba wax, paraffin, spermaceti, polyethylenes or microcrystalline wax, as well as other conventional binding agent and/or mixtures by two or more thereof, preferably hydroxypropyl cellulose.

The disintegrant will be optionally present in the pharmaceutical composition of the invention in an amount within the range from about 0 to about 20% by weight, preferably from about 0.25 to about 10% by weight of the core composition. Examples of disintegrants suitable for use herein include, but are not limited to, croscarmellose sodium, crospovidone, starch, potato starch, pregelatinized starch, corn starch, sodium starch glycolate, microcrystalline cellulose, low substituted hydroxypropyl cellulose or other known disintegrant, preferably croscarmellose sodium.

The lubricant will be optimally present in the pharmaceutical composition of the invention in an amount within the range from about 0.1 to about 5% by weight, preferably from about 0.2 to about 2% by weight of the core composition. Examples of tableting lubricants suitable for use herein include, but are not limited to, magnesium stearate, zinc stearate, calcium stearate, talc, carnauba wax, stearic acid, palmitic acid, sodium stearyl fumarate or hydrogenated vegetable oils and fats, or other known tableting lubricants, and/or mixtures of two or more thereof, preferably magnesium stearate.

The inner seal coating layer formulation (also referred to as the first coating layer) will include up to 95% of polymer based on the weight of the inner seal coating layer, and may be prepared as described hereinbefore. The formulation will contain at least one coating layer polymer and a coating solvent as described above, which preferably is water, which is used for processing and removed by drying. The coating layer polymer may be hydroxypropyl methylcellulose, polyvinyl alcohol (PVA), ethyl cellulose, methacrylic polymers or hydroxypropyl cellulose, preferably PVA. The coating layer may also optionally include a plasticizer such as triacetin, diethyl phthalate, tributyl sebacate or polyethylene glycol (PEG), preferably PEG; and an anti-adherent or glidant such as talc, fumed silica or magnesium stearate, opacifying agent such as titanium dioxide. The coating layer may also include iron oxide based colorants. The coating material is commercially available under the trade name Opadry® HP or Opadry® II white.

The second coating layer formulation will preferably be similar in composition to the first coating layer formulation although it will include medicament, preferably the DPP4-inhibitor in an amount within the range from about 0.5 to about 70%,

preferably from about 30 to about 50% by weight, based on the weight of the second coating layer.

The third outer protective coating layer will preferably be similar in composition to the first coating layer.

The fourth coating layer where present will preferably be similar in composition to the third outer protective coating layer and will include colorant as desired, such as within the range from about 0.5 to about 5.0% by weight, based on the weight of the fourth coating layer.

The inner seal coating layer will preferably be formed of coating layer polymer in an amount within the range from about 10 to about 95%, preferably from about 20 to about 90% by weight of the inner seal coating layer, optionally plasticizer in an amount within the range from about 10 to about 30%, preferably from about 15 to about 20% by weight of the coating layer, and anti-adherent or glidant in an amount within the range for about 15 to about 30%, preferably from about 10 to about 15% by weight of the inner seal coating layer.

The second coating layer will be preferably formed of coating layer polymer in an amount within the range from about 30 to about 99.5%, preferably from about 40 to about 60% by weight of the second coating layer and medicament in an amount within the range from about 0.25% to about 70%, preferably from about 20 to about 50% by weight of the second coating layer.

The coating layer polymer in the second coating layer will be at least about 5 mg with a 200 mg tablet core, and the medicament will be at least about 0.5 mg.

The third outer protective coating layer will preferably be of similar composition to the first coating layer.

The inner seal coating layer will be present in an amount within the range from about 1 to about 5%, preferably from about 1 to about 3% by weight of the finished coated tablet; the second coating layer (containing medicament) will be present in an amount within the range from about 0.25 to about 70%, preferably from about 1 to about 50% by weight of the finished coated tablet, depending on potency; and the third outer protective coating layer and fourth layer where present will each be present in an amount within the range from about 1 to about 10%, preferably from about 1 to about 5% by weight of the finished coated tablet.

Preferred coated tablet formulations in accordance with the invention are set out below.

Material Tablet Placebo	Possible Range %/mg by weight of 200 mg placebo core tablet	Preferred Range %/mg by weight of 200 mg placebo core tablet
Bulking Agent	2 to 95%/4 to 190 mg	10 to 85%/20 to 170 mg
Lactose	0 to 95%/0 to 190 mg	20 to 75%/40 to 150 mg
Microcrystalline cellulose	0 to 95%/0 to 190 mg	20 to 75%/40 to 150 mg
Disintegrant	0 to 20%/0 to 40 mg	0.25 to 10%/0.5 to 20 mg
Croscarmellose sodium	0 to 20%/0 to 40 mg	2 to 10%/4 to 20 mg
Lubricant	0.1 to 5%/0.2 to 10 mg	0.2 to 2%/0.4 to 4 mg
Magnesium Stearate	0.1 to 5%/0.2 to 10 mg	0.2 to 2%/0.4 to 4 mg

First Inner Seal Coating Layer	%/mg by weight of 200 mg placebo core tablet	%/mg by weight of 200 mg placebo core tablet
Coating polymer, and optional plasticizer and glidants	0.5 to 50%/1 to 100 mg	1 to 3%/2 to 6 mg

Second Coating Layer	%/mg by weight of 200 mg placebo core tablet	%/mg by weight of 200 mg placebo core tablet
DPP4-inhibitor (free base or HCl salt)	0.1 to 70%/0.2 to 140 mg	1 to 50%/2 to 100 mg
Coating polymer, and optional plasticizer and glidants	1 to 70%/2 to 140 mg	1 to 50%/2 to 100 mg

Third Outer Protective Coating Layer	%/mg by weight of 200 mg placebo core tablet	%/mg by weight of 200 mg placebo core tablet
Coating polymer, and optional plasticizer, glidants and color	0.5 to 50%/1 to 100 mg	1 to 5%/2 to 10 mg

The following working Example represents a preferred embodiment of the invention.

EXAMPLE

A 500 g batch of 2.5 mg DPP4 coated tablets having the following composition were prepared as described below

Tablet Core	Weight (mg) % by weight of a 200 mg placebo core tablet
Lactose Monohydrate NF	99 mg (49.5%)
Microcrystalline Cellulose NF	90 mg (45%)
Croscarmellose Sodium NF	10 mg (5%)
Magnesium Stearate NF	1 mg (0.5%)
Total	200 mg (100.0%)
Inner Seal Coating Layer	4 mg (2%)
Opadry® HP which contains the following ingredients	
Polyvinyl Alcohol 40%	
PEG 20%	
Talc 15%	
Titanium dioxide 25%	
Middle Layer	
DPP4-inhibitor, Saxaglipitin	2.5 mg (1.25%)
Opadry® HP	20 mg (10%)
Outer Protective Layer	
Opadry® HP	4 mg (2%)

The 500 g of tablet cores were prepared as follows.

Lactose monohydrate, croscarmellose sodium, and microcrystalline cellulose were blended in a planetary mixer. The blend was then lubricated by blending with pre-screened magnesium stearate using a Turbula mixer. The lubricated blend was compressed using a single station press or using a rotary press into 200 mg placebo tablets.

Inner Seal Coating Layer

The inner seal coating suspension was prepared as follows.

0.1 N HCl (about 226.7 g) in a metal container was continuously stirred with a lightening mixer. 40 g Opadry® HP powder was quickly added into the vortex. After

the powder addition was completed, mixing was continued at a low speed until a uniform mixture was visually evident. pH of the resulting suspension was measured and pH was adjusted to 2 using concentrated HCl or NaOH.

A Glatt coater was set up according to the following parameters

Glatt Coater Parameter

Pump rate	3.5-5 ml/min
Pan speed	20 rpm
Air pressure	1.5 bar
Inlet air temperature	50°C
Exhaust air temperature	about 38°C
Air flow	80 m^3/hour
Gun to bed distance	6.5 inch
Nozzle size	0.8 mm

The tablet cores were preheated in a coating pan for about 10 to 15 minutes. 30 heated tablets were weighed. Drying of the tablets was continued until the moisture was driven out of the tablet and tablet weight became constant. The final weight of 30 tablets was designed as A.

The 30 tablets were coated with the inner seal coating suspension as prepared above employing the Glatt coater.

The 30 tablets were weighed every 10 minutes (and the weight recorded) until the tablet weight reached the targeted weight (Equation 1). The coated tablets were dried by heating until the tablet weight became constant. The final weight of the so-coated tablets was designated as B.

Equation 1:

$$\text{Targeted weight} = A \times 1.02 = B$$

Middle (Drug) Coating Layer

The middle drug-containing coating layer suspension was prepared as follows.

12.5 g of the DPP4-inhibitor (free base) was added to 1000 ml of 0.1 N HCl in a metal container. The pH was measured and adjusted to 2. The HCl was continuously stirred and 100 g Opadry® HP was quickly added into the vortex. The

mixture was then stirred at low speed until a uniform mixture was visually evident. The pH of the suspension was maintained at 2 using either concentrated HCl or 1N HCl as necessary.

The seal coated tablet cores prepared above were coated with the coating suspension containing the DPP4-inhibitor prepared above employing the Glatt coater. The 30 seal coated tablets were weighed, initially every 30 minutes, then every 15 minutes and the weight recorded until the targeted weight was reached (Equation 2). The so-coated tablets were dried by heating until the tablet weight became constant. The final weight of 30 tablets was designated as C.

Equation 2:

Targeted weight =

$$B + 30 \times (2.925 \text{ (equivalent to 2.5 mg free base)} + 20 \text{ mg}) = B + 687.75 \text{ mg} = C$$

The amount of drug coated onto the tablets was determined using HPLC, fiber optic probe, or NIR or other suitable means. Coating was stopped when the targeted amount of drug was deposited.

Outer Protective Coating Layer

The so-coated tablets were then coated with a suspension of Opadry® HP as used in forming the inner seal coating. The 30 tablets were weighed every 10 minutes and the weight recorded until tablet weight reached the targeted weight (Equation 3). The tablets were dried by heating until the tablet weight became constant.

The final weight of 30 tablets was designed as D.

Equation 3:

$$\text{Targeted weight} = C + 30 \times 4 \text{ mg} = C + 120 \text{ mg} = D$$

The so-coated tablets were transferred to a suitable container.

The tablets of the invention so-prepared had superior stability to conventional tablet formulations (wherein the drug was in the core) and capsule formulations.

The above 2.5 mg potency coated tablets of the invention were stored at various storage conditions up to and including 41 weeks and stability data related to presence of the degradant cyclic amidine (mainly cis-cyclic amidine (Cis-CA)) were collected. As shown in Table 1 set out below, no cis-CA was detected at 25°C/60% RH storage condition. The cis-CA levels were 0.22% and 0.32% at 30°C/60% RH and 40°C/75% RH storage conditions, respectively. These levels are significantly lower than those observed in the 5 mg and 20 mg potency capsule formulations shown in Table 2.

TABLE 1

Twenty-six weeks stability data on 2.5 mg potency tablets coated with Opadry® HP, free base as starting material, and three coating layers. For stability evaluation, tablets were packaged in HDPE bottles.

Storage Condition	2 wks for all closed conditions			4 wks for all closed conditions 1 wk for two open conditions			8 wks for all closed conditions 5 wks for two open conditions			12 wks for all closed conditions			26 wks for all closed conditions			41 wks for all closed conditions		
	Amide %	Cis-CA %	Trans-CA %	Amide %	Cis-CA %	Trans-CA %	Amide %	Cis-CA %	Trans-CA %	Amide %	Cis-CA %	Trans-CA %	Amide %	Cis-CA %	Trans-CA %	Amide %	Cis-CA %	Trans-CA %
5°C-closed	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
25°C/60% RH-closed	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.03	0	0
30°C/60% RH-closed	0	0	0	0	0	0	0	0	0	0	0	0	0	0.22	0	0.03	0.17	0
40°C/75%RH-closed	0	0	0	0	0.05	0	0	0.09	0	0	0.20	0.05	0	0.32	0	0.03	0.90	0
50°C-closed	0	0.17	0	0	0.33	0.15	0	0.52	0.12	0	0.75	0.15	0	1.00	0	0	1.62	0
30°C/60% RH-open	NA	NA	NA	0	0	0	0	0.20	0.06	NA	NA	NA	NA	NA	NA	NA	NA	NA
40°C/75% RH-open	NA	NA	NA	0	0.68	0.15	0	3.22	0.42	NA	NA	NA	NA	NA	NA	NA	NA	NA

NA denotes "data not available"

TABLE 2

Stability data for capsule formulations (benzoate salt of DPP4 4.8%, Anhydrous lactose 50.2%, lactose hydrous 40%, croscarmellose sodium 2%, and sodium stearyl fumarate 3%, fill weights for 5 mg and 20 mg capsules are 150 mg and 350 mg, respectively.)

Conditions	5 mg capsule				20 mg capsule			
	2 wks	4 wks	13 wks	26 wks	2 wks	4 wks	13 wks	26 wks
	Cis-CA%	Cis-CA%	Cis-CA%	Cis-CA%	Cis-CA%	Cis-CA%	Cis-CA%	Cis-CA%
25°C/60%RH-closed	0.11	0.13	0.20	0.31	0.08	0.05	0.14	0.26
40°C/75%RH-closed	0.23	0.35	0.61	0.95	0.22	0.26	0.46	0.62
50°C-closed	NA	0.73	1.72	NA	NA	0.43	1.19	NA

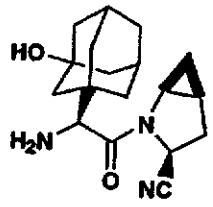
WHAT IS CLAIMED IS:

1. A coated tablet comprising a tablet core and

a) an inner seal coating layer coated on the tablet core;

b) a second coating layer comprising a medicament coated on the inner seal coating of the tablet core; and

c) optionally an outer protective coating layer coated on the second coating layer of the tablet core , wherein the medicament in said second coating layer is saxaglipitin (DPP4 inhibitor)



or a pharmaceutically acceptable salt thereof.

2. The coated tablet as defined in Claim 1 wherein said inner seal coating layer comprises a coating polymer formulation comprising a PVA based polymer, said second coating layer comprises a medicament which is saxaglipitin, and a coating polymer formulation comprising a PVA based polymer, and said other protective coating layer comprises a coating layer formulation comprising a PVA based polymer.

3. The coated tablet as defined in Claim 1 wherein said second coating layer is comprised of from about 0.1 to about 70% by weight medicament and from about 30 to about 99.5% by weight coating polymer, based on the weight of the second coating layer.

4. The coated tablet as defined in Claim 4 wherein the coating polymer formulation in the second coating layer is at least about 2 mg with a 200 mg tablet core, and the medicament is at least about 0.2 mg.

5. The coated tablet as defined in Claim 1 further including a third outer protective coating layer disposed on said second coating layer.

6. The coated tablet as defined in Claim 7 wherein said second coating layer comprises a PVA based polymer.

7. The coated tablet as defined in Claim 7 wherein each of the inner seal coating layer and the outer protective layer comprises a PVA based polymer.

8. The coated tablet as defined in Claim 9 wherein the PVA based polymer in the second coating layer is substantially the same as the PVA based polymer in the other coating layers.

9. The coated tablet as defined in Claim 8 wherein the PVA based polymer is comprised of polyvinyl alcohol.

10. The coated tablet as defined in Claim 1 where in second coating layer the medicament is present in an amount within the range from about 0.2 to about 140 mg and the coating polymer is present in an amount within the range from about 2 to about 140 mg, and in each of the inner seal coating layer and optionally outer protective coating layer, the coating polymer is being present in an amount within the range from about 1 to about 100 mg.

11. The coated tablet as defined in Claim 1 wherein the tablet core is comprised of one or more fillers, optionally one or more binders, optionally one or more disintegrants and optionally one or more tableting lubricants.

12. The coated tablet as defined in Claim 13 wherein the tablet core is comprised of microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, and magnesium stearate.

13. The coated tablet as defined in Claim 1 having the following composition:

Material Tablet Placebo	Range % by weight for 200 mg placebo tablet
Lactose	20 to 75%/40 to 150 mg
Microcrystalline cellulose	20 to 75%/40 to 150 mg
Croscarmellose sodium	2 to 10%/4 to 20 mg
Magnesium Stearate	0.2 to 2%/0.4 to 4 mg

First Inner Seal Coating Layer	% by weight of 200 mg placebo core tablet
Coating polymer, and optional plasticizer and glidants	1 to 3%/2 to 6 mg

Second Coating Layer	% by weight of 200 mg placebo core tablet
DPP4-inhibitor (free base or HCl salt)	0.25 to 70%/0.5 to 140 mg
Coating polymer, and optional plasticizer and glidants	1 to 50%/2 to 100 mg

Third Outer Protective Coating Layer	% by weight of 200 mg placebo core tablet
Coating polymer, and optional plasticizer, glidants and color	1 to 5%/2 to 10 mg

14. The coated tablet as defined in Claim 1 where for a 5 mg potency the second coating layer is comprised of 5 mg medicament and 5 mg polymer based coating and for a 2.5 mg potency the coating layer is comprised of 2.5 mg medicament and 20 mg polymer based coating.

15. A method for preparing a coated tablet comprising:

a) providing a tablet core;

b) coating the tablet with an inner seal coating layer formulation which includes at least one coating polymer;

c) drying the coated tablet to form an inner seal coating thereon;

d) coating the so-coated tablet with a second coating layer formulation which includes medicament which is saxagliptin and at least one coating polymer;

e) drying the so-coated tablet to form a second coating layer (containing medicament) thereon; and

f) optionally coating the so-coated tablet with a third outer protective coating layer formulation which includes at least one coating polymer; and

g) drying the so-coated tablet to form the coated tablet of the invention.

16. The method as defined in Claim 17 wherein the coating layers are applied as a suspension of the coating polymer.