US008628799B2

(12) **United States Patent**
Desai et al.

(10) **Patent No.: US 8,628,799 B2**
(45) **Date of Patent: Jan. 14, 2014**

(54) **COATED TABLET FORMULATION AND METHOD**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 49 days.

(21) Appl. No.: **13/094,379**

(22) Filed: **Apr. 26, 2011**

(65) **Prior Publication Data**

US 2011/0200672 A1 Aug. 18, 2011

Related U.S. Application Data

(62) Division of application No. 11/137,068, filed on May 25, 2005, now Pat. No. 7,951,400.

(60) Provisional application No. 60/575,319, filed on May 28, 2004.

(51) **Int. Cl.**
A61K 9/24 (2006.01)
A61K 9/32 (2006.01)

(52) **U.S. Cl.**
USPC **424/472**; 424/482

(58) **Field of Classification Search**
None
See application file for complete search history.

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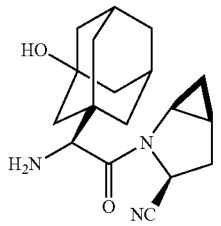
(57) **ABSTRACT**

A coated tablet formulation is provided which includes a medicament such as the DPP4-inhibitor, saxaglipitin



or its HCl salt,

which is subject to intra-molecular cyclization, which formulation includes a tablet core containing one or more fillers, and other conventional excipients, which tablet core includes a coating thereon which may include two or more layers, at least one layer of which is an inner seal coat layer which is formed of one or more coating polymers, a second layer of which is formed of medicament which is the DPP4-inhibitor and one or more coating polymers, and an optional, but preferable third outer protective layer which is formed of one or more coating polymers. A method for forming the coated tablet is also provided.

11 Claims, No Drawings

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COATED TABLET FORMULATION AND METHOD

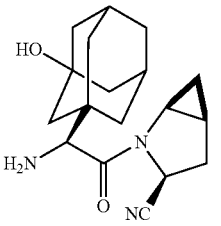
FIELD OF THE INVENTION

This application is a divisional of U.S. patent application Ser. No. 11/137,068, filed May 25, 2005, now U.S. Pat. No. 7,951,400, which 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



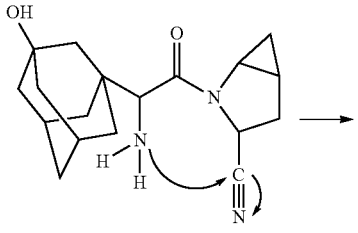
or its HCl salt,

(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. Pat. 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.

Formation of Cyclic Amidine (CA)



DPP4-inhibitor

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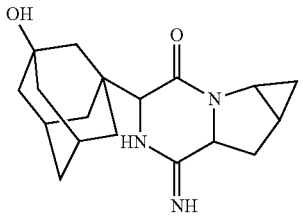


Cyclic amidine

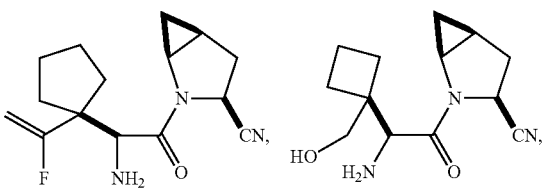
The resultant degradant, cyclic amidine (mainly cis-cyclic amidine (CA)), is not therapeutically active and therefore, its formation is not desirable. This cyclization reaction can occur both in solid state and solution state. The rate of intra-molecular cyclization is accelerated when formulations are 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. Pat. 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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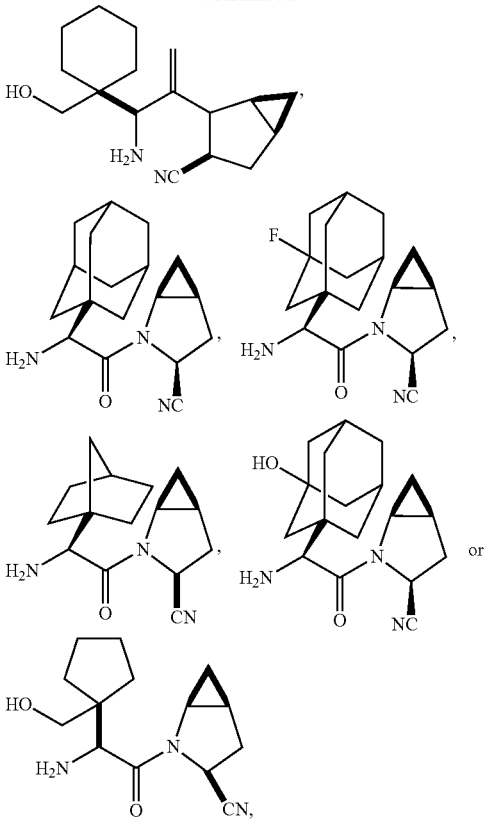

or a pharmaceutically acceptable salt thereof, wherein the pharmaceutically acceptable salt can be the hydrochloride salt or the trifluoroacetic acid salt.

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.

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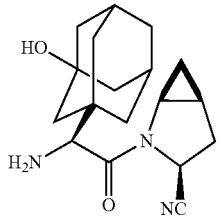

or a pharmaceutically acceptable salt thereof, such as the HCl salt, also referred to as Compound A.

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;

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

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,

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