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(54) **Title:** A FILM COATED TABLET OF SAXAGLIPTIN AND AT LEAST ONE ANTIOXIDANT PROCESSED WITH WET GRANULATION

(57) **Abstract:** The present invention relates to a film coated tablet comprising a granulate comprising saxagliptin or a pharmaceutically acceptable salt thereof or crystalline polymorph thereof and at least one antioxidant, wherein the granulate is obtained by wet-granulation using ethanol.

A FILM COATED TABLET OF SAXAGLIPTIN AND AT LEAST ONE ANTIOXIDANT PROCESSED WITH WET GRANULATION

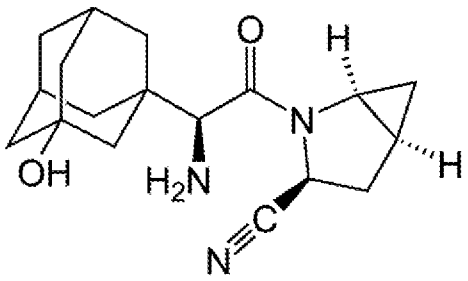
Field of the Invention

The present invention relates to a film coated tablet comprising a granulate comprising saxagliptin or a pharmaceutically acceptable salt thereof or crystalline polymorph thereof and at least one antioxidant, wherein the granulate is obtained by wet-granulation using ethanol.

Background of the Invention

DPP-IV (dipeptidyl peptidase IV) is an enzyme that catalyzes the conversion of glucagon like peptide-1 (GLP-1) from its active form to its inactive form. DPP-IV inhibitors, also commonly known as gliptins, competitively inhibit the enzyme DPP-IV, thereby increasing the endogenous concentration of GLP-1, which further augments insulin secretion and improves the glycemic profile of patients with diabetes.

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.



Formula I: Saxagliptin

There are also several patent applications which disclose orally administered saxagliptin formulations, but none of them includes orally disintegrating tablets of saxagliptin.

It is well known in the art that saxagliptin is an unstable compound and it can undergo a thermodynamically favored cyclization to form the corresponding cyclic amidine. This cyclization reaction can occur both in solid state and solution state. The challenge of minimizing or preventing the cyclization reaction during manufacture of saxagliptin formulations is particularly significant.

Also, saxagliptin or a pharmaceutically acceptable salt thereof or crystalline polymorph thereof is used small proportion that can lead to considerable problems during the manufacture of the composition with regard to the uniformity of the content of active agent in the individual composition units.

US 6,395,767 discloses a DPP4 inhibiting compound, saxagliptin and its use in treating type-II diabetes mellitus.

WO 2011/052825 discloses a composition of DPP4 inhibitors and anti-diabetic compounds for use in the treatment of diabetes.

US 7,951,400 discloses a coated tablet formulation of saxagliptin containing a polyvinyl alcohol based coating.

Several studies have been conducted to address providing stabilite of saxagliptin and attempts have also been made to improve the formulation. However, despite the stability problem of saxagliptin, pharmacotechnical properties, such as flowability, compressibility and content uniformity of saxagliptin in the tablet has not been disclosed.

The present invention discloses a film coated tablet comprising a granulate comprising saxagliptin or a pharmaceutically acceptable salt thereof or crystalline polymorph thereof and at least one antioxidant, wherein the granulate is obtained by wet-granulation using ethanol. The film coated tablet is created to overcome the above problems and provides additional advantages to the relevant field of art. Other advantages and embodiments of the present invention will be clarified in the following description.

Detailed Description of the Invention

The present invention relates to a film coated tablet comprising a granulate comprising saxagliptin or a pharmaceutically acceptable salt thereof or crystalline polymorph thereof and at least one antioxidant, wherein the granulate is obtained by wet-granulation using ethanol. So, this way eliminates the problems stability of active agent and provides additional advantages to the relevant field of art. Based on the state of the art, the main object of the present invention is to obtain stable a tablet with improved stability and content uniformity and compressibility, flowability by wet granulation.

Another object of the present invention is to provide a film coated tablet having the desired dissolution profile.

Another object of the present invention is to provide a method for preparing a film coated tablet having the desired stability, content uniformity, dissolution profile, flowability, hardness and compressibility.

Saxagliptin or a pharmaceutically acceptable salt thereof or crystalline polymorph thereof is used small proportion that can lead to considerable problems during the manufacture of the composition with regard to the uniformity of the content of active agent in the individual composition units. In this invention, to eliminate this problem, wet granulation is preferred in terms of pharmacotechnical properties, such as flowability, compressibility and content uniformity of saxagliptin. Especially, using ethanol also provides the desired stability.

According to one embodiment of the present invention, a film coated tablet comprises a granulate comprising saxagliptin or a pharmaceutically acceptable salt thereof or crystalline polymorph thereof and at least one antioxidant, wherein the granulate is obtained by wet-granulation using ethanol.

Both wet and dry granulation processes improved compressibility. However, unexpectedly, when the granulation process was scaled up to an industrial scale, the flowability of the saxagliptin or a pharmaceutically acceptable salt thereof was unsatisfactory when using the dry granulation method; only the wet granulation process improved flowability. In addition, this method provides the desired compressibility and flowability without loss of active substance.

Although the wet granulation process is effective to solve the flowability problems associated with dry granulation, there can be problems with binding when the process is scaled up to an industrial scale. It has been found that these problems can be solved by using a wet granulation process using ethanol granulation liquid as in which part of the antioxidant is mixed with the saxagliptin, for example in a powder form, and the remaining part is present in the granulation liquid.

According to one embodiment of the present invention, the weight ratio of antioxidant to saxagliptin or a pharmaceutically acceptable salt thereof or crystalline polymorph thereof is between 2.0 and 10.0, preferably is between 4.0 and 8.0.

According to one embodiment of the present invention, the weight ratio of antioxidant to saxagliptin or a pharmaceutically acceptable salt thereof or crystalline polymorph thereof is between 5.0 and 6.5.

Suitable antioxidants are selected from the group comprising ascorbic acid, sodium ascorbate, ascorbyl palmitate, erythorbic acid, butylated hydroxy anisole, butylated hydroxy toluene, propyl gallate, sodium sulfite, sodium metabisulfite, sodium bisulfite, thioglycollic acid, alpha tocopherol, tocopherol, thioglycerols, thiogallic acid, cysteine, glutathione, cysteamine, dihydrolipoic acid, lipoic acid, thioredoxin, propyl gallate, ethyl gallate, methyl gallate, lauryl gallate or mixtures thereof.

According to one embodiment of the present invention, the antioxidant is alpha tocopherol, ascorbic acid, sodium ascorbate, ascorbyl palmitate, erythorbic acid, propyl gallate, ethyl gallate, methyl gallate, lauryl gallate or mixtures thereof.

According to one embodiment of the present invention, the antioxidant is gallates, for example; propyl gallate, ethyl gallate, methyl gallate, lauryl gallate.

According to one embodiment of the present invention, the antioxidant is ascorbic acid.

According to one embodiment of the present invention, the antioxidant is alpha tocopherol.

According to one embodiment of the present invention, the antioxidant is sodium ascorbate.

According to one embodiment of the present invention, the antioxidant is ascorbyl palmitate.

According to one embodiment of the present invention, the antioxidant is erythorbic acid.

Too little or too much antioxidant can affect the stability of the tablet of saxagliptin or a pharmaceutically acceptable salt thereof or crystalline polymorph thereof and an appropriate amount of antioxidant must therefore be present in this tablet.

According to one embodiment of the present invention, the amount of antioxidant is between 0.2% and 4.0% by weight in the total film coated tablet. Preferably, the amount of antioxidant is between 0.5% and 2.50% by weight in the total film coated tablet.

According to one embodiment of the present invention, the amount of saxagliptin or a pharmaceutically acceptable salt thereof or crystalline polymorph thereof is between 1.0% and 15.0% by weight in the total film coated tablet. Preferably, it is between 3.0% and 10.0% by weight in the total film coated tablet.

According to one embodiment of the present invention, saxagliptin or a pharmaceutically acceptable salt thereof or crystalline polymorph thereof is present as saxagliptin hydrochloride dihydrate. The use of this form of saxagliptin helps to achieve the desired stability.

According to one embodiment of the present invention, the amount of saxagliptin hydrochloride dihydrate is between 1.0% and 15.0% by weight in the total film coated tablet. Preferably, it is between 3.0% and 10.0% by weight in the total film coated tablet.

In general terms, excipients provided in a composition may positively or negatively influence the physicochemical and pharmacokinetic properties, e.g. the solubility, stability, absorption, bioavailability of an active agent. For this reason, the excipients which accompany an active agent have to be selected in a careful and conscious manner while a composition is developed because saxagliptin or a pharmaceutically acceptable salt thereof or crystalline polymorph thereof is a low dose drug and hence the ratio of excipients to drug is high. The composition should have no physicochemical incompatibility between the active agents and the excipients. If active agent is incompatible of excipients, stability and psychochemical problems may be during or after the process.
According to one embodiment of the present invention, the tablet comprises at least one pharmaceutically acceptable excipient selected from the group comprising fillers, disintegrants or mixtures thereof.

Suitable disintegrants are selected from the group comprising mannitol, starch, crospovidone, croscarmellose sodium, low-substituted hydroxypropyl cellulose, carboxymethyl cellulose, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, sodium carboxymethyl starch, hydroxymethyl starch or mixtures thereof.

According to one embodiment of the present invention, the disintegrant is mannitol.

Suitable fillers are selected from group comprising talc, lactose anhydrous, microcrystalline cellulose, dicalcium phosphate dihydrate, ammonium alginate, calcium carbonate, calcium phosphate, calcium sulfate, cellulose, cellulose acetate, dextrates, dextrin, dextrose, erythritol, ethylcellulose, mannitol, magnesium carbonate, magnesium oxide, maltodextrin, polydextrose, polymethacrylates, sodium alginate, sodium chloride, starch, sugar spheres, sulfobutylether beta-cyclodextrin, polysorbate 80, xylitol or mixtures thereof.

According to one embodiment of the present invention, the filler is talc or lactose anhydrous or mixtures thereof. Preferably, both talc and lactose anhydrous are used. It's important to choose diluent and use the diluent in a specific amount for providing a good uniformity of content and avoiding stability problems. Since the tablet has porous characteristics, it's sensitive to humidity and fragility which may be lead to stability problems. Furthermore, this stability problem becomes a big challenge due to cyclization reaction problem of saxagliptin.

According to one embodiment of the present invention, the tablet further comprises at least one lubricant.

Suitable lubricants are selected from the group comprising stearic acid, sodium stearyl fumarate, magnesium stearate, sodium lauryl sulphate, zinc stearate, calcium stearate, mineral oil, talc, polyethylene glycol, glyceryl monostearate, glyceryl palmitostearate, magnesium lauryl sulphate, fumaric acid, zinc stearate or mixtures thereof.

According to one embodiment of the present invention, the lubricant is stearic acid. Using the described lubricant helps to provide the desired flowability and compressibility.

According to one embodiment of the present invention, the obtained tablet by wet granulation comprises;

- Saxagliptin HCl Dihydrate
- Ascorbic acid as antioxidant
- Ethanol
- Lactose anhydrate
- Mannitol
- Talc
- Stearic acid

According to one embodiment of the present invention, the obtained tablet by wet granulation comprises;

- 1.0-15.0% by weight of saxagliptin HCl Dihydrate
- 0.2-4.0% by weight of an antioxidant
- 40.0-60.0% by weight of lactose anhydrate
- 23.0-37.0% by weight of mannitol
- 1.0-10.0% by weight of talc
- 0.2-3.0% by weight of stearic acid
- Ethanol.

According to this embodiment of the invention, a method for preparing a film coated tablet comprises the following steps:

a) Mixing saxagliptin HCl Dihydrate, at least one filler and at least one antioxidant,
b) Granulating the mixture with ethanol,
c) Adding at least one disintegrant and at least one filler and then mixing,
d) Adding at least one lubricant and then mixing,

e) Compressing to form of tablets,

f) Coating tablets with film coating.

According to this embodiment of the invention, a method for preparing a film coated tablet comprises the following steps:

a) Mixing saxagliptin HCl Dihydrate, the half of lactose anhydrate and at least one antioxidant,

b) Granulating the mixture with ethanol,

c) Adding the remaining part of lactose anhydrate, mannitol and talc and then mixing,

d) Adding stearic acid and then mixing,

e) Compressing to form of tablets,

f) Coating tablets with film coating.

Example 1:

Ingredients	**Amount (% by weight of the total formulation)**
Saxagliptin HCl Dihydrate	1.0 – 15.0
At least one antioxidant	0.2 – 4.0
Ethanol	q.s.
At least one filler	40.0 – 70.0
At least one disintegrant, preferably mannitol	20.0 – 40.0
At least one lubricant, preferably stearic acid	0.2 – 4.0
Film coating*	3.0 – 10.0
TOTAL	**100**

q.s.: sufficient quantity

A process for example 1;

a) Mixing saxagliptin HCl Dihydrate, at least one filler and at least one antioxidant,

b) Granulating the mixture with ethanol,

c) Adding at least one disintegrant and at least one filler and then mixing,

d) Adding at least one lubricant and then mixing,

e) Compressing to form of tablets,

f) Coating tablets with film coating.

Example 2:

Ingredients	**Amount (% by weight of the total formulation)**
Saxagliptin HCl Dihydrate	1.0 – 15.0
alpha tocopherol, ascorbic acid, sodium ascorbate, ascorbyl palmitate, erythorbic acid, propyl gallate, ethyl gallate, methyl gallate, lauryl gallate as antioxidant	0.2 – 4.0
Ethanol	q.s.
Lactose anhydrate	40.0 – 60.0
Mannitol	23.0 – 37.0
Talc	1.0 – 10.0
Stearic acid	0.2 – 3.0
Film coating*	2.0 – 8.0
TOTAL	**100**

q.s.: sufficient quantity

Example 3:

Ingredients	**Amount (% by weight of the total formulation)**
Saxagliptin HCl Dihydrate	5.9
Ascorbic acid as antioxidant	1.0
Ethanol	q.s.
Lactose anhydrate	50.8
Mannitol	28.8
Talc	4.8
Stearic acid	1.0
Film coating*	5
TOTAL	**100**

q.s.: sufficient quantity

A process for example 2 or 3;

a) Mixing saxagliptin HCl Dihydrate, the half of lactose anhydrate and at least one antioxidant,
b) Granulating the mixture with ethanol,
c) Adding the remaining part of lactose anhydrate, mannitol and talc and then mixing,
d) Adding stearic acid and then mixing,
e) Compressing to form of tablets,
f) Coating tablets with film coating.

*Film coating; copovidone, polydextrose, talc, hydroxypropylcellulose, titanium dioxide, polyethylene glycol, caprylic/capric triglyceride.

CLAIMS

1- A film coated tablet comprising a granulate comprising saxagliptin or a pharmaceutically acceptable salt thereof or crystalline polymorph thereof and at least one antioxidant, wherein the granulate is obtained by wet-granulation using ethanol.

2- The film coated tablet according to claim 1, wherein the weight ratio of antioxidant to saxagliptin or a pharmaceutically acceptable salt thereof or crystalline polymorph thereof is between 2.0 and 10.0, preferably is between 4.0 and 8.0.

3- The film coated tablet according to claim 1, wherein the weight ratio of antioxidant to saxagliptin or a pharmaceutically acceptable salt thereof or crystalline polymorph thereof is between 5.0 and 6.5.

4- The film coated tablet according to claim 1, wherein antioxidants are selected from the group comprising ascorbic acid, sodium ascorbate, ascorbyl palmitate, erythorbic acid, butylated hydroxy anisole, butylated hydroxy toluene, propyl gallate, sodium sulfite, sodium metabisulfite, sodium bisulfite, thioglycollic acid, alpha tocopherol, tocopherol, thioglycerols, thiogallic acid, cysteine, glutathione, cysteamine, dihydrolipoic acid, lipoic acid, thioredoxin, propyl gallate, ethyl gallate, methyl gallate, lauryl gallate or mixtures thereof.

5- The film coated tablet according to claim 4, wherein the antioxidant is alpha tocopherol, ascorbic acid, sodium ascorbate, ascorbyl palmitate, erythorbic acid, propyl gallate, ethyl gallate, methyl gallate, lauryl gallate or mixtures thereof.

6- The film coated tablet according to claim 4, wherein the amount of antioxidant is between 0.2% and 4.0% by weight in the total film coated tablet.

7- The film coated tablet according to claim 1, wherein the amount of saxagliptin or a pharmaceutically acceptable salt thereof or crystalline polymorph thereof is between 1.0% and 15.0% by weight in the total film coated tablet.

8- The film coated tablet according to claim 1, wherein saxagliptin or a pharmaceutically acceptable salt thereof or crystalline polymorph thereof is present as saxagliptin hydrochloride dihydrate.

9- The film coated tablet according to claim 1, wherein the amount of saxagliptin hydrochloride dihydrate is between 1.0% and 15.0% by weight in the total film coated tablet.

10- The film coated tablet according to claim 1, wherein the tablet comprising at least one pharmaceutically acceptable excipient selected from the group comprising fillers, disintegrants or mixtures thereof.

11- The film coated tablet according to claim 10, wherein disintegrants are selected from the group comprising mannitol, starch, crospovidone, croscarmellose sodium, low-substituted hydroxypropyl cellulose, carboxymethyl cellulose, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, sodium carboxymethyl starch, hydroxymethyl starch or mixtures thereof.

12- The film coated tablet according to claim 10, wherein fillers are selected from group comprising talc, lactose anhydrous, microcrystalline cellulose, dicalcium phosphate dihydrate, ammonium alginate, calcium carbonate, calcium phosphate, calcium sulfate, cellulose, cellulose acetate, dextrates, dextrin, dextrose, erythritol, ethylcellulose, mannitol, magnesium carbonate, magnesium oxide, maltodextrin, polydextrose, polymethacrylates, sodium alginate, sodium chloride, starch, sugar spheres, sulfobutylether beta-cyclodextrin, polysorbate 80, xylitol or mixtures thereof.

13- The film coated tablet according to claim 12, wherein the filler is talc or lactose anhydrous or mixtures thereof.

14- The film coated tablet according to claim 10, wherein the tablet further comprising at least one lubricant.

15- A method for preparing a film coated tablet comprises the following steps:

a) Mixing saxagliptin HCl Dihydrate, at least one filler and at least one antioxidant,
b) Granulating the mixture with ethanol,
c) Adding at least one disintegrant and at least one filler and then mixing,
d) Adding at least one lubricant and then mixing,
e) Compressing to form of tablets,
f) Coating tablets with film coating.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/TR2022/051467

A. CLASSIFICATION OF SUBJECT MATTER

A61P 3/10 (2006.01)i; A61K 9/14 (2006.01)i; A61K 9/20 (2006.01)i

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)

A61P 3/10; A61K 9/14; A61K 9/20

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN 102379869 A (FEI LIN) 21 March 2012 (2012-03-21) Claims, examples, method 9	1-15
X	CN 102086172 A (GUOCHAO LIAO) 08 June 2011 (2011-06-08) Abstract, claims, example 12	1-15

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
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"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
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Date of the actual completion of the international search	Date of mailing of the international search report
02 March 2023	**02 March 2023**

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