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(54) Title: THE PROCESS FOR THE PREPARATION OF A FILM COATED TABLET COMPRISING LINAGLIPTIN AND METFORMIN

(57) Abstract: The present invention relates to a process for the preparation of a film coated tablet comprising linagliptin and metformin HCl, so the process provides the desired stability and dissolution profile of the tablet. The present invention also relates to a simple, rapid, cost effective, time-saving and industrially convenient process.

THE PROCESS FOR THE PREPARATION OF A FILM COATED TABLET COMPRISING LINAGLIPTIN AND METFORMIN

Field of the Invention

The present invention relates to a process for the preparation of a film coated tablet comprising linagliptin and metformin HCl, so the process provides the desired stability and dissolution profile of the tablet. The present invention also relates to a simple, rapid, cost effective, time-saving and industrially convenient process.

Background of the Invention

Diabetes mellitus is a group of disorders of carbohydrate metabolism in which the action of insulin is diminished or absent through altered secretion, decreased insulin activity or a combination of both factors. There are two main types of diabetes; Type 1 and Type 2:

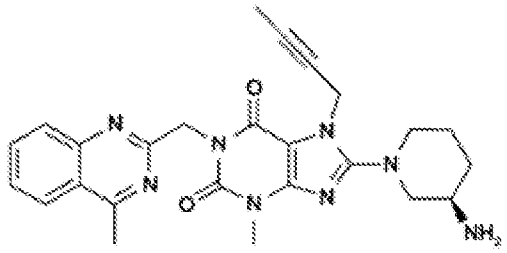
Type 1 diabetes occurs because the insulin-producing cells of the pancreas (beta cells) are damaged. In Type 1 diabetes, the pancreas makes little or no insulin, so sugar cannot get into the body's cells for use as energy. People with Type 1 diabetes must use insulin injections to control their blood glucose.

In Type 2 diabetes, the pancreas makes insulin, but it either doesn't produce enough, or the insulin does not work properly. This diabetes occurs most often in people who are over 40 years old and overweight. Type 2 diabetes may sometimes be controlled with a combination of diet, weight management, and exercise. However, treatment also may include oral glucose-lowering medications or insulin injections.

Linagliptin is used for type 2 or non-insulin dependent diabetes. It is a selective, orally administered, xanthine based dipeptidyl peptidase-4 (DPP-4) inhibitor used as an adjunct to diet and exercise to improve glycemic control. DPP-4 inhibitors work by blocking the action of DPP-4, an enzyme which destroys the hormone incretin. There are two types of incretin hormones found in the body, called glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). These hormones are naturally produced by the body in response to food intake. Their function is to help the body produce more insulin only when it is needed and reduce the amount of glucose being produced by the liver when it is not needed. Linagliptin works by binding to DPP-4 and preventing it from breaking down the

GLP-1 and GIP. This increases the levels of these hormones in the body and so increases their effect on controlling blood sugar.

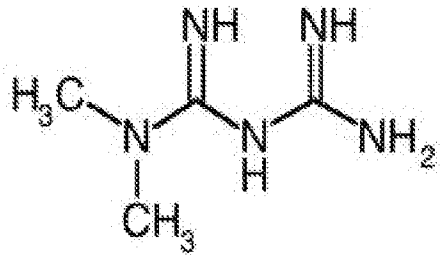
The chemical name of linagliptin is 8-[(3R)-3-aminopiperidin-1-yl]-7-but-2-yn-1-yl)-3-methyl-1-[(4-methylquinazolin-2-yl)methyl]-3,7-dihydro-1H-purine-2,6-dione and its chemical structure is shown in the Formula I.



Formula I

Metformin is antidiabetics having an orally-administrated biguanide structure. Metformin hydrochloride is a white to off-white crystalline compound and it is freely soluble in water and practically insoluble in acetone, ether and chloroform. Oral doses of metformin are generally recommended in the range of 500 to 2500 mg a day and a single dose may vary from 500 to 850 mg. It is used singly or in combination with sulfonylureas, alpha-glucosidase inhibitors, or insulin.

The chemical name of metformin hydrochloride is 1,1-dimethylbiguanide hydrochloride, has the following chemical structure of Formula II.



Formula II

A combination therapy of linagliptin with metformin HCl provides an even more effective treatment of type II diabetes. Linagliptin in combination with Metformin is marketed in the United States under the brand name Jentadueto® by Boehringer Ingelheim.

U.S. Patent Application No. US 20130122089 discloses a pharmaceutical composition comprising linagliptin with mannitol, pregelatinized starch, copovidone, cornstarch, and magnesium stearate.

Prior art teaches that linagliptin with a primary or secondary amino group are unstable and shows incompatibilities, degradation problems, or extraction problems.

The prior art references emphasize on using basic amino acid to overcome the problem of chemical degradation of free base of linagliptin when combined with metformin HCl.

US patent number 201 1206766 discloses pharmaceutical composition comprising linagliptin and metformin HCl and one or more pharmaceutical excipients, and a nucleophilic and/or basic agents for stabilizing said linagliptin against degradation. Furthermore, the patent discloses use of a basic amino acid L-arginine, which may be suitable for stabilizer.

The use of stabilizer does not only provide the desired stability but also isolates Linagliptin from the destabilizing matters which can be occurred during the preparation of the formulation.

Thus, still a need for a physically and chemically stable composition.

In the present invention, it has been found surprisingly a process for physically and chemically stable pharmaceutical composition comprising linagliptin and metformin that overcomes above mentioned problem.

Detailed Description of the Invention

The present invention is aimed to ensure a process for a film tablet comprising linagliptin and metformin HCl having good content uniformity and desired physically and chemically stability. The process is a simple, rapid, cost effective, time-saving and industrially convenient method.

Another object of the present invention is to eliminate problems and bringing additional advantages to the relevant prior art.

Another object of this present invention is to provide a process for a film tablet comprising linagliptin and metformin HCl having desired dissolution profiles.

The term "linagliptin" as used throughout the specification refers to not only linagliptin, but also its other pharmaceutically acceptable salt, pharmaceutically acceptable solvates, pharmaceutically acceptable hydrates, pharmaceutically acceptable enantiomers, pharmaceutically acceptable derivatives, pharmaceutically acceptable polymorphs or pharmaceutically acceptable prodrugs thereof.

Linagliptin is present as amorphous linagliptin, crystalline linagliptin having polymorphic form A, crystalline linagliptin having polymorphic form B and crystalline linagliptin having polymorphic form C, anhydrous form A, anhydrous form B or mixtures of thereof. Preferably, linagliptin is present as anhydrous form A and anhydrous form B. These forms of linagliptin are quite stable and stable compared to the amorphous form.

The process of preparing the formulation is important due to the very different regarding the amount of active ingredients in the formulation and the stability problems of linagliptin.

According to one embodiment of the present invention, a process for the preparation of a film coated tablet comprising linagliptin and metformin wherein the process comprises steps of:

a) Preparing a mixture called first mixture comprising metformin HCl and at least one pharmaceutically acceptable excipient,
b) Preparing a mixture called second mixture comprising linagliptin and meglumine,
c) Preparing a granulation solution.

When the film-coated tablet is prepared by the above-mentioned process it was seen that it does not lead to losses in the active agents or excipients during production and provides desired good content uniformity. It reflects that content uniformity play important role in the dissolution of the drug.

Meglumine belongs to the class of organic compounds known as hexoses. These are monosaccharides in which the sugar unit is a six-carbon containing moiety. Meglumine is soluble (in water) and is an organic base used as a pH-adjusting agent and solubilizing agent.

In general, linagliptin is not very stable when used with metformin HCl. the use of metformin HCl increases the acidic level of the medium, so linagliptin loses its stability. Especially, in solid dosage forms, amine group containing linagliptin may react with many excipients or impurities of excipients. In this invention, while a mixture called second mixture comprising linagliptin is preparing, it has been surprisingly found that using meglumine provides high

stability of linagliptin in a film coated tablet and thus desired level of dissolution rate is provided in the tablet. The second mixture does not comprise any excipient.

According to one embodiment of the present invention, first mixture comprises at least one pharmaceutically acceptable excipient which is a binder and a disintegrant.

According to one embodiment of the present invention, the granulation solution comprises a binder.

Since metformin HCl is used big proportion, the use of binder to prepare a homogeneous mixture provides the desired result.

Suitable binder is selected from the group comprising copovidone, povidone, hydroxylpropyl cellulose, hydroxypropyl methyl cellulose, methyl cellulose, carboxymethyl cellulose, polyethylene glycol, polyvinyl alcohol, polyvinyl acetate, alginate, sodium alginate, glycyrrhizin, polymetacrylates, poloxamer, polyacrylamide, aluminum hydroxide, benthonite, laponite, cetostearyl alcohol, polyoxyethylene-alkyl ethers, polydextrose, polyethylene oxide, xylitol, sucrose stearate or mixtures thereof.

According to one embodiment of the present invention, a binder is copovidone.

Metformin HCl is used big proportion that can lead to considerable problems during the preparation of formulation with regard to the uniformity of the content of active agent in the individual composition units. Because of problems uniformity of the content, the active substance may interact with several excipients. It reflects that content uniformity play important role in the dissolution of the drug. Using the right disintegrant helps to provide uniformity of the content and therefore it provides the desired dissolution profile

According to one embodiment of the present invention, a disintegrant is selected from the group comprising corn starch, sodium starch glycolate, carboxymethyl cellulose, carboxymethyl cellulose calcium, carboxymethyl cellulose sodium, hydroxypropyl cellulose, methyl cellulose, chitosan, starch, pregelatinized starch or mixtures thereof.

According to one embodiment of the present invention, a disintegrant is corn starch.

According to one embodiment of the present invention, the process for the preparation of a film coated tablet comprising linagliptin and metformin comprises steps of:

a) Preparing a mixture called first mixture comprising metformin HCl, copovidone and corn starch,

b) Preparing a mixture called second mixture comprising linagliptin and meglumine,
c) Preparing a granulation solution which comprising dissolving copovidone in water.

According to one embodiment of the present invention, the process for the preparation of a film coated tablet comprising linagliptin and metformin further comprises steps of:

d) Geometric dilution first mixture, second mixture with the granulation solution and obtained wet granule,
e) Wet sieving of the granule,
f) Drying and then sieving,

According to one embodiment of the present invention, geometric dilution and wet granulation prosses were used. the content uniformity is provided with geometric dilution and wet granulation. Improved content uniformity efficiently contributes to a marked increase in bioavailability. Improved content uniformity also favors to avoid toxicity in the otherwise possible event that the amount of drug substance would be too high.

Geometric dilution is a pharmaceutical process that thoroughly mixes a small amount of a drug with an appropriate amount of a diluent, an inert substance that thins or binds the drug. It ensures equal distribution of the drug throughout the resulting compound.

When mixing a small amount of a drug with a large amount of another ingredient or diluent, the process of geometric dilution is used. In this method the drug present in smaller quantity is placed in the mortar with an equal amount of the other ingredient. The two materials are triturated until they are well mixed.

According to one embodiment of the present invention, the process for the preparation of a film coated tablet comprising linagliptin and metformin further comprises steps of:

g) Adding a disintegrant at step (f) the mixture and mixing,
h) Sieving a glidant and adding at step (g) the mixture,
i) Adding a lubricant and mixing,
j) Pressing the mixture to form of tablet,
k) Coating tablets with coating agents.

The advantages of the present invention are even more significant especially thanks to step (g,h,i), as the problem of homogeneity, powder flowability and compressibility is even more

likely to occur when two active substances are incorporated in one final dosage form, especially when two actives are used very different regarding the amount.

Suitable glidant is selected from the group comprising colloidal silicon dioxide, talc or mixtures thereof.

According to one embodiment of the present invention, the glidant is colloidal silicon dioxide.

Suitable lubricant is selected from the group comprising magnesium stearate, sodium stearyl fumarate, polyethylene glycol, sodium lauryl sulphate, magnesium lauryl sulphate, fumaric acid, glyceryl palmitostearate, hydrogenated natural oils, zinc stearate, calcium stearate, silica, stearic acid, polyethylene glycol, paraffin or mixtures thereof.

According to one embodiment of the present invention, the lubricant is magnesium stearate.

According to one embodiment of the present invention, the disintegrant is corn starch, glidant is colloidal silicon dioxide, lubricant is magnesium stearate.

According to one embodiment of the present invention, the process for the preparation of a film coated tablet comprising linagliptin and metformin further comprises steps of:

g) Adding corn starch at step (f) the mixture and mixing,
h) Sieving colloidal silicon dioxide and adding at step (g) the mixture,
i) Adding magnesium stearate and mixing,
j) Pressing the mixture to form of tablet,
k) Coating tablets with coating agents.

According to one embodiment of the present invention, the half of used corn starch as disintegrant is added step (a) and the remaining half is added in step (g). It helps to provide the desired dissolution profile.

Suitable coating agents are selected from the group comprising polymethacrylates, hydroxypropyl methylcellulose, triacetin, glycerol triacetin, talc, red iron dioxide, yellow iron dioxide, propylene glycol, lactose monohydrate, hydroxypropyl cellulose, polyvinyl alcohol (PVA), polyethylene glycol (PEG), polyvinyl alcohol-polyethylene glycol copolymers (Kollicoat® IR), ethylcellulose dispersions (Surelease®), polyvinylprolidone, polyvinylprolidone-vinyl acetate copolymer (PVP-VA), all kinds of Opadry®, pigments, dyes, titanium dioxide, macrogol, coloring agent or mixtures thereof.

According to one embodiment of the present invention, the coating agents are hydroxypropyl methylcellulose, talc, red iron dioxide, yellow iron dioxide, titanium dioxide, propylene glycol or mixtures thereof.

According to one embodiment of the present invention, the hardness of a film coated tablet is important for mechanical stability of the formulation. The film coated tablet has a hardness of more than 150 N, preferably between 150 N – 400 N, more preferably between 200 N – 350 N, more preferably 300 N – 350 N.

Said process for preparing a film coated tablet comprising linagliptin and metformin HCl in this invention are stable. The combination does not show incompatibilities, degradation problems, or extraction problems with certain excipients such as meglumine, copovidone, corn starch, magnesium stearate, colloidal silicon dioxide.

In one embodiment of the invention, the film coated tablet obtained by the process described in the invention comprises;

- 0.05 - 10.0% by weight of linagliptin
- 70.0 - 90.0% by weight of metformin HCl
- 1.0 - 10.0% by weight of meglumin
- 2.0 - 8.0% by weight of corn starch
- 1.0 - 15.0% by weight of copovidone
- 0.1 - 3.0% by weight of colloidal silicon dioxide
- 0.1 – 3.0% by weight of magnesium stearate
- 0.1 – 4.0% by weight of coating of the total tablet.

In one embodiment of the invention, the film coated tablet obtained by the process described in the invention comprises;

- 0.1 - 1.0% by weight of linagliptin
- 80.0 - 85.0% by weight of metformin HCl
- 1.0 - 3.0% by weight of meglumin
- 3.0 - 4.0% by weight of corn starch
- 8.0 - 10.0% by weight of copovidone
- 0.2 - 1.0% by weight of colloidal silicon dioxide
- 0.2 – 1.0% by weight of magnesium stearate
- 1.0 – 3.0% by weight of coating of the total tablet.

Example 1: The film coated tablet formulation comprising linagliptin and metformin

	Ingredients	% by weight
First mixture	Metformin HCl	82.47
	Corn starch	3.22
	Copovidone	4.94
Second mixture	Linagliptin	0.41
	Meglumine	1.98
Granulation solution	Copovidone	4.12
	Water	8.24
	Magnesium stearate	0.82
	Colloidal silicon dioxide	0.37
	Coating	2.06
	TOTAL	**100**

Example 2: The film coated tablet formulation comprising linagliptin and metformin

	Ingredients	% by weight
First mixture	Metformin HCl	82.61
	Corn starch	3.22
	Copovidone	4.94
Second mixture	Linagliptin	0.21
	Meglumine	1.98
Granulation solution	Copovidone	4.12
	Water	8.24
	Magnesium stearate	0.82
	Colloidal silicon dioxide	0.37
	Coating	2.06
	TOTAL	**100**

Process for example 1 or 2;

a) Preparing a mixture called first mixture comprising metformin HCl, the half of copovidone and the half of corn starch,

b) Preparing a mixture called second mixture comprising linagliptin and meglumine,

c) Preparing a granulation solution which comprising dissolving the remaining half of copovidone in water.

d) Geometric dilution first mixture and second mixture with the granulation solution and obtained wet granule,

e) Wet sieving of the granule,

f) Drying and then sieving,

g) Adding the remaining half of corn starch at step (f) the mixture and mixing,

h) Sieving colloidal silicon dioxide and adding at step (g) the mixture,

i) Adding magnesium stearate and mixing,

j) Pressing the mixture to form of tablet,

k) Coating tablets with coating agents.

CLAIMS

1. A process for the preparation of a film coated tablet comprising linagliptin and metformin wherein the process comprises steps of:
    a) Preparing a mixture called first mixture comprising metformin HCl and at least one pharmaceutically acceptable excipient,
    b) Preparing a mixture called second mixture comprising linagliptin and meglumine,
    c) Preparing a granulation solution.

2. A process for the preparation of a film coated tablet according to claim 1, wherein first mixture comprising at least one pharmaceutically acceptable excipient which is a binder and a disintegrant.

3. A process for the preparation of a film coated tablet according to claim 1, wherein the granulation solution comprises dissolving a binder in water.

4. A process for the preparation of a film coated tablet according to claim 2 or 3, wherein a binder is selected from the group comprising copovidone, povidone, hydroxylpropyl cellulose, hydroxypropyl methyl cellulose, methyl cellulose, carboxymethyl cellulose, polyethylene glycol, polyvinyl alcohol, polyvinyl acetate, alginate, sodium alginate, glycyrrhizin, polymetacrylates, poloxamer, polyacrylamide, aluminum hydroxide, benthonite, laponite, cetostearyl alcohol, polyoxyethylene-alkyl ethers, polydextrose, polyethylene oxide, xylitol, sucrose stearate or mixtures thereof.

5. A process for the preparation of a film coated tablet according to claim 2 or 3, wherein a binder is copovidone.

6. A process for the preparation of a film coated tablet according to claim 2, wherein a disintegrant is selected from the group comprising corn starch, sodium starch glycolate, carboxymethyl cellulose, carboxymethyl cellulose calcium, carboxymethyl cellulose sodium, hydroxypropyl cellulose, methyl cellulose, chitosan, starch, pregelatinized starch or mixtures thereof.

7. A process for the preparation of a film coated tablet according to claim 2, wherein a disintegrant is corn starch.

8. A process for the preparation of a film coated tablet according to claim 1, wherein the process comprising steps of:

a) Preparing a mixture called first mixture comprising metformin HCl, copovidone and corn starch,
b) Preparing a mixture called second mixture comprising linagliptin and meglumine,
c) Preparing a granulation solution which comprising dissolving copovidone in water.

9. A process for the preparation of a film coated tablet according to claim 1 or 8, wherein the process further comprising steps of:

d) Geometric dilution of first mixture and second mixture with the granulation solution and obtained wet granule,
e) Wet sieving of the granule,
f) Drying and then sieving.

10. A process for the preparation of a film coated tablet according to claim 9, wherein the process further comprising steps of:

g) Adding a disintegrant at step (f) the mixture and mixing,
h) Sieving a glidant and adding at step (g) the mixture,
i) Adding a lubricant and mixing,
j) Pressing the mixture to form of tablet,
k) Coating tablets with coating agents.

11. A process for the preparation of a film coated tablet according to claim 10, wherein disintegrant is corn starch, glidant is colloidal silicon dioxide, lubricant is magnesium stearate.

12. A process for the preparation of a film coated tablet according to claim 1, wherein the tablet has a hardness of more than 150 N, preferably between 150 N – 400 N, more preferably between 200 N – 350 N, more preferably 300 N – 350 N.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/TR2021/050438

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/522 (2006.01)i; A61K 31/155 (2006.01)i; A61K 47/32 (2006.01)i; A61K 47/26 (2006.01)i; A61P 3/10 (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)

A61K; A61P

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)

EPODOC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2014080383 A1 (RANBAXY LAB LTD) 30 May 2014 (2014-05-30) Abstract; Examples 4 and 6	1-12
X	CN 104840960 A (GUANGDONG HEC PHARMACEUTICAL) 19 August 2015 (2015-08-19) Abstract; claims 1, 3, 5-8, 15, 18	1-12
X	WO 2015110962 A1 (WOCKHARDT LTD) 30 July 2015 (2015-07-30) Abstract; claims 1, 5-7, 13	1-12

☐ 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
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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
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA/TR	Authorized officer
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INTERNATIONAL SEARCH REPORT
Information on patent family members

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Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)	Publication date (day/month/year)
WO 2014080383 A1	30 May 2014	NONE	
CN 104840960 A	19 August 2015	NONE	
WO 2015110962 A1	30 July 2015	IN 187MUM2014 A	28 August 2015
		IN 186MUM2014 A	28 August 2015
		IN 185MUM2014 A	28 August 2015
		IN 184MUM2014 A	28 August 2015