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(54) Title: MODIFIED RELEASE PHARMACEUTICAL TABLET FORMULATIONS

(57) Abstract: The present invention relates to pharmaceutical compositions produced so as to be used particularly in treatment of non-insulin dependent diabetes (NIDDM).

DESCRIPTION

MODIFIED RELEASE PHARMACEUTICAL TABLET FORMULATIONS

The present invention relates to pharmaceutical compositions produced so as to be used particularly in treatment of non-insulin dependent diabetes (NIDDM).

The Prior Art

Diabetes is generally described as a metabolic disorder usually occurring due to combination of genetic and environmental factors and resulting in extremely high blood glucose level (hyperglycemia).

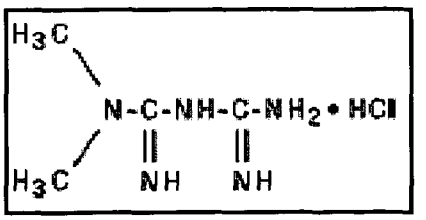
Diabetes occurs either due to reduce in insulin production (insulin dependent diabetes or Type 1 diabetes) or insulin resistance (Type 2 diabetes or non-insulin dependent diabetes (NIDDM)). Both situations cause high blood sugar level (hyperglycemia). Insulin came into use in 1921 and since then, all types of diabetes have been treated.

Type 2 diabetes or, in other terms, non-insulin-dependent diabetes is the most common form of diabetes and makes up about 90% of all diabetics. In this type of diabetes, there is insufficient insulin production together with insulin resistance in surrounding tissues. Pancreas should secrete more insulin in order to control the amount of glucose in blood effectively. However, as the disease progresses, insulin production lessens and the patient suffering from type 2 diabetes may need insulin injection.

Type 2 diabetes is controlled by antihyperglycemic (glucose lowering) drugs and insulin supplement or by using them together.

The drugs used by the oral route in treatment of Type 2 diabetes can be listed as sulfonylureas (glipizide, glimepiride), biguanides (metformin), alpha-glucosidase enzyme inhibitors (acarbose), glitazones (pioglitazone, rosiglitazone), glinides (nateglinide).

Metformin hydrochloride shown in formula (I) is an anti-diabetic active agent belonging to the class of biguanides.



Formula (I). Metformin Hydrochloride

The original product GLUCOPHAGE® is in tablet and prolonged release tablet forms comprising 1000 mg, 850 mg, 500 mg metformin hydrochloride.

Metformin hydrochloride is a highly water-soluble drug (more than 300 mg/ml at 25°C), it dissolves in gastro-intestinal juices quickly, and the active agent enters the blood quickly. Quick blood entrance of the active agent and instant increase in active agent plasma concentration cause some clinical difficulties such as increasing side effects, incorrect dosing.

Therefore, there is need for modified release dosage forms in order to enhance patient adherence to treatment and treatment efficiency in pharmaceutical technology.

Dosage forms with various release characteristics were designed in the prior art as a solution for these problems. The most commonly used one of these release types is prolonged release tablets usually composed of the osmotically active agents and a semi-permanent membrane. This semipermanent membrane allows gastric and intestinal juices to enter the dosage form and to dissolve the active agent. The active agent dissolved by the juices releases through a passageway on the semipermanent membrane.

In the case that the active agent to be used in production of such a tablet is not dissolved in gastric and intestinal juices, a substance expanding in the presence of a liquid, for instance a hydrogel is used and it expands and dispenses the active agent through a passageway. These osmotic tablet dosage forms are disclosed in the patents numbered US3845770, US3916899, US4034758 and US4783337 respectively.

Another release type is delayed release. The European Patent numbered EP1063971 relates to delayed release metformin hydrochloride formulations and production method thereof. The patent discloses a dosage form having a semipermeable membrane coating core comprising metformin hydrochloride in the range of 50 to 98%. Wet granulation is given as the production method of such dosage form throughout the document.

The application numbered WO2005123134 discloses a modified release dosage form comprising metformin as the active agent obtained by mixing metformin in a matrix comprising hydrophilic polymer, hydrophobic polymers and a lubricant homogeneously. The production method in the application is implemented by wet granulating metformin and polymers.

The application numbered WO9947128 discloses a system including two phases. The prolonged release system in the patent is composed of an inner solid phase comprising an active agent and a rate-controlling polymer and an outer phase comprising a rate-controlling polymer. However, high amount of polymer is required in order to control the release rate of a water-soluble active agent with a polymer. This high amount of polymer causes increase in size of the dosage form obtained with the active agent and other pharmaceutically acceptable excipients. A too large tablet cannot be swallowed by most patients and this reduces patient adherence to treatment.

Another problem related to metformin formulations occurs during production of a highly hygroscopic active agent metformin particularly in tablet dosage form. When highly hygroscopic metformin is desired to be produced in tablet dosage form, it requires high pressure due to low tablet compressibility. Tablet dosage form compressed under a high pressure cannot have sufficient hardness and corrosion robustness.

The patent numbered WO2006038226 discloses use of a binder in the range of 0.1 to 10% by weight in the modified release tablet formulations comprising metformin as a solution for said problem. According to the production method included in this patent,

1. Metformin is wet granulated with a granulation solution comprising a binder in the range of 0.1 to 10% by weight and the granules obtained are dried;
2. The dry metformin granules obtained in the first granulation are mixed with the rate-controlling polymer and other pharmaceutically acceptable excipients and wet granulated with the same granulation solution. The final granules obtained by this way are dried, treated with the lubricant and compressed in tablet form.

However, these alternative production methods and formulations in the prior art cannot be used effectively due to the fact that the rate-controlling polymer comprised in the modified release metformin tablets reacts with water and they turn to gel during granulation.

In addition, metformin formulations, which turn to gel, pose problem during tablet compression and the tablets produced with such formulation cannot provide sufficient physical conditions.

Therefore, there is need for a simple and easily practicable production method and new formulations for the formulations comprising metformin.

Detailed Description of the Invention

The present invention relates to new tablet formulations that can be produced without causing technical problems encountered in the prior art such as gelling, reduce in tablet hardness in production of the modified release tablet formulations comprising metformin and/or at least one pharmaceutically acceptable salt thereof.

These modified-release metformin tablet formulations of the present invention comprise metformin, at least one pharmaceutically acceptable rate controlling polymer, at least one pharmaceutically acceptable lubricant and optionally at least one other excipient.

Metformin comprised in the formulations of the present invention can be in the form of metformin or its pharmaceutically acceptable salt, racemate, solvate, hydrate, anhydrate, different polymorphic form and amorphous form or combinations thereof. The preferred active agent is metformin hydrochloride salt.

A characteristic feature of the modified release metformin tablet formulations of the present invention is that said formulations comprise metformin hydrochloride at least in the amount of 50% by weight.

A characteristic feature of the modified-release metformin tablet formulations of the present invention is that said formulations comprise metformin hydrochloride in the range of 55 to 80% by weight.

A characteristic feature of the modified-release metformin tablet formulations of the present invention is that said formulations comprise metformin hydrochloride in the range of 55 to 75% by weight.

The modified-release metformin tablet formulations of the present invention comprise at least one pharmaceutically acceptable rate-controlling polymer in order to provide the required release characteristics.

The rate-controlling polymer comprised in the modified release metformin tablet formulations of the present invention can be hydrophilic or hydrophobic. However, the preferred rate-controlling agent is a hydrophilic polymer in the formulations of the present invention.

In other words, a characteristic feature of the modified-release tablet formulations of the present invention is that said formulations comprise at least one hydrophilic polymer in order to control release rate of the formulations.

The modified-release metformin tablet formulations of the present invention comprise at least one pharmaceutically acceptable hydrophilic polymer in the range of 10% to 50% by weight.

The modified-release metformin tablet formulations of the present invention comprise at least one pharmaceutically acceptable hydrophilic polymer preferably in the range of 15% to 45% by weight.

The modified-release metformin tablet formulations of the present invention comprise at least one pharmaceutically acceptable hydrophilic polymer more preferably in the range of 15% to 40% by weight.

The hydrophilic polymers that can be comprised in the modified-release metformin tablet formulations of the present invention are selected from a group comprising hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyethylene oxide, carbomer, various metacrylic acid derivatives, sodium alginate or combinations thereof.

The polymers used in the scope of the present invention expand to form a hydrophilic matrix and they control metformin hydrochloride releasing in this way. After water enters into tablet, gel layer thickens and metformin hydrochloride is separated from this gel layer slowly. One of the important physicochemical characteristics of the polymer, viscosity of the polymer has a significant effect on the attainment of required release characteristics in the modified release pharmaceutical formulations.

According to this, the viscosity value of the hydrophilic polymer comprised in the formulations of the present invention is in the range of 3000 to 5000 cP.

The modified-release metformin tablet formulations of the present invention comprise at least one pharmaceutically acceptable lubricant and optionally at least one other excipient in addition to metformin and the rate-controlling polymer.

The lubricants that can be comprised in the modified-release metformin tablet formulations of the present invention can be selected from a group comprising talc, magnesium stearate, stearic acid, sodium stearyl fumarate, polyoxyethylene, glycol, leucine, alanine, glycine, sodium benzoate, sodium acetate, fumaric acid or a combination thereof.

The other excipients that can be comprised in the modified-release metformin tablet formulations of the present invention in addition to the active agent, the rate-controlling polymer and the lubricant can be selected from a group comprising binder, disintegrant, diluent, flavouring agent, sweetener, colouring agent, surfactant, anti-foaming agent, stabilizing agent, viscosity agent, film coating agents or a combination thereof.

The binder used herein can be selected from the starches such as potato starch, corn starch, wheat starch; sugars such as sucrose, glucose, dextrose, lactose, maltodextrin; natural and synthetic gums; gelatine; cellulose derivatives such as microcrystalline cellulose, HPC, HEC, HPMC, carboxymethyl cellulose, methyl cellulose, ethyl cellulose; polyvinylpyrrolidone (povidone); polyethylene glycol (PEG); waxes; calcium carbonate; calcium phosphate; alcohols such as sorbitol, xylitol, mannitol and water or a combination thereof.

The disintegrant used herein can be selected from the starches such as lactose, potato starch, corn starch, wheat starch, pregelatinized starch, sodium starch glycolate; cellulose derivatives such as croscarmellose sodium or microcrystalline cellulose; polyvinylpyrrolidone; crospovidone; alginic acid and its salts; chyles such as xhantan gum or veegum; ion-exchange resins or a combination thereof.

The diluent used herein can be selected from lactose or its derivatives (such as lactose anhydrate, lactose monohydrate), maltose, dextrin, maltodextrin, mannitol, sorbitol, starch or a combination thereof.

The flavouring agent used herein can be selected from natural aroma oils (such as peppermint oil, oil of wintergreen, clove bud oil, parsley oil, eucalyptus oil, lemon oil, orange oil), menthol, menthane, anethole, methyl salicylate, eucalyptol, cinnamon, 1- methyl acetate, sage, eugenol, oxanon, alpha-irisone, marjoram, lemon, orange, blackberry, propenyl guaetol acetyl, cinnamon, vanilla, timole, linalol, cinnamaldehyde glycerol acetal, N-substituted p-menthane-3-carboxamide, 3,1-methoxy propane 1.2-diol or a combination thereof.

The sweetener used herein can be selected from sucralose, sucrose, fructose, glucose, galactose, xylose, dextrose, laevulose, lactose, maltose, maltodextrin, mannitol, maltitol, maltol, sorbitol, xylitol, erythritol, lactitol, isomalt, corn syrup, saccharin, saccharin salts, acesulfame potassium, aspartame, D-tryptophan, monoammonium glycyrrhizinate, neohesperidin, dihydrochalcone, thaumatin, neotam, alitam, stevioside and cyclamates or a combination thereof.

The film coating agents used herein are composed of these components and/or combinations thereof: lactose, hydroxypropyl methylcellulose, triacetine, titanium dioxide, polyvinyl alcohol, talc, lecithin, sodium alginate, stearic acid, glyceride, oils and gelatines, sugar derivatives, polyethylene glycol.

The type and amount of the excipients comprised in the formulations have significant effect on the obtainment of required physical characteristics of the modified-release metformin tablet formulations of the present invention.

According to this, the tablet formulations have sufficient hardness value thanks to use of lactose in the range of 1 to 10% by weight as the diluent in the modified-release tablet formulations basically comprising metformin, the rate-controlling polymer and the lubricant. In other aspect, the formulations comprising lactose in the range of 1 to 10% by weight can be compressed easily without the need of high pressure and therefore the formulations can be produced easily.

In other words, a characteristic feature of the modified-release metformin tablet formulations of the present invention is that said formulations comprise metformin, the rate-controlling polymer, at least one pharmaceutically acceptable lubricant, lactose and optionally at least one other excipient.

The term "modified release" used throughout the text refers to prolonged release, delayed release, controlled release, fast release and/or slow release dosage forms. The modified release type used in the tablet formulations of the present invention is preferably prolonged release.

In the modified-release metformin tablet formulations of the present invention, 20-40% is dissolved at the end of the 1st hour, 45-65% is dissolved at the end of the 3rd hour, more than 85% is dissolved at the end of the 10th hour (pH: 6.8 phopshate buffer, USP II basket).

In other words, the present invention discloses the modified-release metformin tablet formulations wherein 20-40% of the active agent is dissolved at the end of the 1st hour, 45-65% of the active agent is dissolved at the end of the 3rd hour, more than 85% of the active agent is dissolved at the end of the 10th hour.

The present invention further submits a production method for the modified-release metformin tablet formulations.

According to this, the modified-release metformin tablet formulations of the present invention are produced by direct compression method. The formulations produced by direct compression method prevent the half reactions caused by the wet granulation method in the prior art and therefore the tablet dosage form produced have sufficient physical characteristics. In other aspect, direct compression method is advantageous since it can be performed more easily as compared to the other methods in the prior art.

The method to be used in production of the modified-release metformin tablet formulations of the present invention is composed of the following steps:

1. Metformin and at least one hydrophilic polymer are added and mixed,
2. Lactose is added into this mixture obtained and it is mixed again,
3. The lubricant is added into the mixture obtained in the second step and mixed,
4. The final mixture obtained is sent to the tablet compression machine and compressed in tablet form according to the suitable specifications,
5. The tablets compressed are preferably film coated.

Since this method used in obtainment of the modified-release metformin tablets of the present invention completely prevent the contact of the highly hygroscopic active agent metformin with water, it also prevents gelling of the rate controlling polymers and therefore degradation in the formulations. The modified-release metformin tablets produced by this method can be produced as having the sufficient physical robustness.

Another characteristic feature of this method of the present invention is mixing times between the steps. As it is known, the order of adding the components in the formulations and mixing times affect physical robustness of the final tablet.

According to this, the mixing time for the active agent and hydrophilic polymer is 10-20 minutes in the first step, for lactose is 10-20 minutes in the second step, for the lubricant is 1-10 minutes in the last step of the production method.

Mixing the abovementioned components in the times given provides an optimum physical robustness in the modified-release metformin tablets.

Said method is preferred because it is more effortless and economic as compared to the methods in the prior art.

The pharmaceutical formulations of the present invention are given below. The formulations of the present invention should not be limited to these examples.

EXAMPLES

Example 1. Modified-release Metformin Hydrochloride Tablet Formulation

Content	**Weight (%)**
Metformin Hydrochloride	67.50
Hydrophilic Polymer	25.00
Lactose	5.50
Lubricant	0.50
Coating agent	1.50
Total	**100**

The method for modified-release metformin tablet to be produced according to the formulation given above is as follows:

1. Sieving metformin hydrochloride and pharmaceutically acceptable hydrophilic polymer and mixing them for 15 minutes,
2. Sieving lactose into the mixture obtained and mixing them for 15 minutes,
3. Adding a pharmaceutically acceptable lubricant into the final mixture and mixing them for 3 minutes,
4. Sending the final mixture to tablet compression machine in order to compress in tablet form,
5. Coating the modified release tablets comprising metformin hydrochloride with the film coating solution.

CLAIMS

1. A modified-release tablet formulation comprising metformin as the active agent, at least one pharmaceutically acceptable rate controlling polymer, at least one pharmaceutically acceptable lubricant and optionally at least one other excipient.
2. The modified release tablet formulation according to claim 1, characterized in that the active agent comprised in the formulations is in the form of metformin or its pharmaceutically acceptable salt, racemate, solvate, hydrate, anhydrate, different polymorphic form and amorphous form or combinations thereof.
3. The modified release tablet formulation according to claim 2, characterized in that the active agent comprised in the formulations is metformin hydrochloride.
4. The modified release tablet formulation according to claim 3, characterized in that said formulations comprise metformin hydrochloride at least in the amount of 50% by weight.
5. The modified release tablet formulation according to claim 4, characterized in that said formulations comprise metformin hydrochloride in the range of 55 to 80% by weight.
6. The modified release tablet formulation according to claim 5, characterized in that said formulations comprise metformin hydrochloride in the range of 55 to 75% by weight.
7. The modified release tablet formulation according to claim 1, characterized in that said formulations comprise a hydrophilic polymer as the rate-controlling polymer.
8. The modified release tablet formulation according to claim 7, characterized in that said formulations comprise at least one pharmaceutically acceptable hydrophilic polymer in the range of 10% to 50% by weight.
9. The modified release tablet formulation according to claims 7-8, characterized in that said formulations comprise at least one pharmaceutically acceptable hydrophilic polymer in the range of 15% to 45% by weight.
10. The modified release tablet formulation according to claims 7-9, characterized in that said formulations comprise at least one pharmaceutically acceptable hydrophilic polymer in the range of 15% to 40% by weight.
11. The modified release tablet formulation according to claims 7-10, characterized in that hydrophilic polymers comprised in the formulations are selected from a group comprising hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyethylene oxide, carbomer, various metacrylic acid derivatives, sodium alginate or combinations thereof.

12. The modified release tablet formulation according to claims 7-11, characterized in that viscosity value of the hydrophilic polymer comprised in the formulations is in the range of 3000 to 5000 cP.
13. The modified-release tablet formulation according to claim 1, characterized in that the lubricant comprised in the formulations is selected from a group comprising talc, magnesium stearate, stearic acid, sodium stearyl fumarate, polyoxyethylene glycol, leucine, alanine, glycine, sodium benzoate, sodium acetate, fumaric acid or a combination thereof.
14. The modified-release tablet formulation according to claim 1, characterized in that the other excipients that can be comprised in the formulations are selected from a group comprising binder, disintegrant, diluent, flavouring agent, sweetener, colouring agent, surfactant, anti-foaming agent, stabilizing agent, viscosity agent, film coating agents or a combination thereof.
15. The modified release tablet formulation according to claim 14, characterized in that the diluent that can be comprised in the formulations is selected from lactose or its derivatives (such as lactose anhydrate, lactose monohydrate), maltose, dextrin, maltodextrin, mannitol, sorbitol, starch or a combination thereof.
16. The modified release tablet formulation according to claim 15, characterized in that said formulations comprise lactose in the range of 1 to 10% by weight as the diluent.
17. The modified release tablet formulation according to any preceding claims, characterized in that said formulations are prolonged release, delayed release, controlled release, fast release and/or slow release form.
18. The modified release tablet formulation according to claim 17, characterized in that said formulations are in prolonged release form.
19. The modified-release tablet formulation according to claim 18, characterized in that the formulations are dissolved in the range of 20-40% at the end of the 1st hour, 45-65% at the end of the 3rd hour, more than 85% at the end of the 10th hour in pH: 6.8 phosphate buffer.
20. A production method for the modified release tablet formulations according to claim 1, characterized in that said method is direct compression method.
21. The method according to claim 20, characterized in that said production method is composed of the following the steps:

I. Metformin and at least one hydrophilic polymer are added and mixed,
II. Lactose is added into this mixture and mixed again,
III. The lubricant is added into the mixture obtained in the second step and mixed,
IV. The final mixture obtained is sent to tablet compression machine and compressed in tablet form according to the suitable specifications,
V. The tablets compressed are preferably film coated.

22. The method according to claim 21, characterized in that the mixing time for the active agent and hydrophilic polymer is 10-20 minutes in the first step, the mixing time for lactose is 10-20 minutes in the second step, the mixing time for the lubricant is 1-10 minutes in the last step of the production method.

INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2013/000216

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20 A61K31/155
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 117 451 A (KUMAR VIJAI [US]) 12 September 2000 (2000-09-12) examples -----	1-22
X	R Narasimharao ET AL: "Design and Evaluation of Metformin Hydrochloride Extended Release Tablets by Direct Compression", International Journal of Research in Pharmaceutical and Biomedical Sciences, September 2011 (2011-09), XP055088175, Retrieved from the Internet: URL:http://www.ijrpbsonline.com/files/RS00025.pdf [retrieved on 2013-11-13] the whole document -----	1-22

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6117451 A	12-09-2000	NONE	