(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 November 2005 (10.11.2005)

PCT

(10) International Publication Number
WO 2005/105044 A1

(51) International Patent Classification[7]: A61K 9/14, 47/48, 31/00

(21) International Application Number: PCT/IB2005/001163

(22) International Filing Date: 29 April 2005 (29.04.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
819/DEL/2004 30 April 2004 (30.04.2004) IN

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2005/105044 A1

(54) Title: PROCESS FOR MAKING INCLUSION COMPLEX OF SULFONYLUREAS HAVING IMPROVED AQUEOUS SOLUBILITY

(57) Abstract: The present invention relates to processes for improving the aqueous solubility of sulfonylureas by co-pulverization of sulphonyl urea and cyclodextrin. It also relates to pharmaceutical compositions exhibiting improved solubility, prepared using a co-pulverized mixture of sulfonyl urea and cyclodextrin.

PROCESS FOR MAKING INCLUSION COMPLEX OF SULFONYLUREAS HAVING IMPROVED AQUEOUS SOLUBILITY

Field of the Invention

The technical field of the invention relates to a process for improving the aqueous solubility of sulfonylureas by co-pulverization of sulfonyl urea and cyclodextrin. It also relates to pharmaceutical compositions exhibiting improved solubility, prepared using a co-pulverized mixture of a sulfonyl urea and a cyclodextrin.

Background of the Invention

Sulfonylureas are oral antidiabetic agents widely used for the treatment of type 2 diabetes. The sulfonylureas have poor aqueous solubility due to which their dissolution in the gastrointestinal fluids and subsequent absorption is slow. The oral antidiabetic must effectively control the plasma glucose levels especially after food intake when the glucose levels are higher than normal in a diabetic patient. This can be achieved by rapid absorption of the sulfonyl urea taken just before or immediately after food. Increasing the dissolution of the sulfonyl urea in the gastrointestinal fluids would help rapid absorption and faster onset of anti-diabetic action.

Attempts have been made to improve the aqueous solubility of sulfonylureas, for example, by increasing the surface area of sulfonyl urea by particle size reduction. U.S. Patent No. 4,060,634 discloses fine crystallizate of glyburide with a surface area of at least 3 to 10 m^2/g prepared by dissolving glyburide in a water soluble organic solvent and adding this solution to cold water or an acidic aqueous solution with stirring and collecting the precipitate of glyburide as fine particles. The reduction of particle size may increase the dissolution of sulfonyl urea to some extent but the inherent solubility remains the same.

U.S. Patent No. 3,883,648 describes preparing a solid dispersion of glyburide to improve its dissolution by dissolving glyburide in a polyglycol by heating, cooling and granulating the solid thus obtained.

U.S. Patent No. 4,696,815 discloses an oral antidiabetic formulation comprising a sulfonyl urea and a basic excipient and polyvinylpyrrolidone. In presence of basic

excipients such as sodium hydroxide or ammonium hydroxide, the solubility of the sulfonyl urea is improved. However, use of a basic excipient would require a special apparatus due to its corrosive nature.

U.S. Patent No. 6,464,988 discloses an inclusion complex of glipizide with a non-ionic surfactant and a cyclodextrin prepared by dissolving a nonionic surfactant in a solvent such as water and wetting cyclodextrin of particle size 10-250μm with the solution of nonionic surfactant to form a semi solid mixture, and mixing the semisolid mixture so formed with glipizide of particle size 1-40μm to form a mixed inclusion complex.

WO 03/043602A1 describes preparing a solid dispersion of drugs with poor solubility by dissolving the drug and a cyclodextrin in organic solvent, and removing the solvent by vacuum drying or spray drying to get the drug-cyclodextrin complex.

Most of these processes mentioned above involve the use of solvents. The use of organic solvents in particular, implicates additional precautions for safety considerations. Moreover, recovery of the complex from the solution would require additional processing steps.

U.S. Patent No. 5,007,966 discloses a method of forming a complex between a cyclodextrin and poorly soluble drug by forming a mixture of the poorly soluble drug and cyclodextrin with moisture content from about 25% to 65% by weight and further mixing in a ball mill charged with a plurality of balls. The patent exemplifies the process by preparing complexes of cyclodextrin with liquid guest molecules and does not disclose any process for improving the solubility of a solid guest molecule. Further, this process has a limitation of presence of moisture in the cyclodextrin for achieving good results.

European Patent No. EP 0 371 431 describes preparing supported drugs by a process which involves mixing the active substance and the support material like cyclodextrin, co-grounding the mixture in a mill in which the grinding chamber is saturated with one or more solvent vapors able to solubilize the active substance or to be absorbed on the surface of the support material.

The inventors have now discovered a process of improving the aqueous solubility of a sulfonyl urea which does not require use of solvents, basic excipients or high temperature. The process involves co-pulverizing a dry mixture of the sulfonyl urea and a

cyclodextrin. The process is simple and can be carried out easily with commonly available equipments. The co-pulverized mixture when dissolved in water gives a clear solution. The improved solubility of the sulfonyl urea may be due to a complex formation with cyclodextrin.

The present invention provides more flexibility and the co-pulverized mixture can be easily processed into solid dosage forms or liquid dosage forms as the pulverized mixture is completely water-soluble.

Summary of the Invention

In one general aspect there is provided a process of improving the aqueous solubility of sulfonyl urea. The process includes the steps of: (a) blending sulfonyl urea urea and cyclodextrin to form a dry mixture; (b) co-pulverizing the mixture; and (c) processing into a suitable dosage form.

Embodiments of the process may include one or more of the following features. For example, the sulfonyl urea and cyclodextrin may have a particle size of from about 0.1 microns to about 50 microns.

The mixture of sulfonyl urea and cycldextrin may be pulverized in a rotary mill, roller mill, mortar mill, or a ball mill. The sulfonyl urea and cyclodextrin may be mixed in a ratio of from about 1:1 to about 1:30 by weight.

The process may also include at least one other anti-diabetic compound. The antidiabetic compound may be glitazones and metformin, either in free form or in form of a pharmaceutically acceptable salt.

In another general aspect there is provided a pharmaceutical composition that includes a co-pulverized mixture of sulfonylurea and cyclodextrin.

Embodiments of the pharmaceutical composition may also include one or more pharmaceutically acceptable excipients. The one or more pharmaceutically acceptable excipients may include fillers, binders, disintegrants, lubricants, glidants, coloring agents, flavoring agents and coatings.

The pharmaceutical composition may also include at least one other anti-diabetic compound. The antidiabetic compound may be glitazones and metformin, either in free form or in form of a pharmaceutically acceptable salt.

The pharmaceutical composition may be in the form of one or more of a tablet, capsule, solution or suspension. The tablet composition may be coated with a functional and/or non-functional film forming polymer.

In yet another general aspect there is provided a method for the treatment of type 2 diabetes mellitus, or a disease or condition associated with diabetes mellitus. The method includes administering to a patient in need thereof a pharmaceutical composition that includes a co-pulverized mixture of sulfonylurea and cyclodextrin. The pharmaceutical composition may include an additional sulfonyl urea or cyclodextrins.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description and claims.

Detailed Description of the Invention

As described above, the inventors have developed dosage forms that contain sufonyl ureas and cyclodextrins that have been co-pulverized. Prior to co-pulverization, the particle size of sulfonyl urea may vary from about 0.1μm to about 500μm. Likewise, the cyclodextrin may also have a particle size of about 0.1μm to about 500μm. The initial smaller particle size of the materials prior to co-pulverization reduces the process duration. The ratio of sulfonyl urea to cyclodextrin may be from about 1:1 to about 1:30 by weight.

Suitable sulfonylureas include one or more of glyburide, glipizide, glimepiride, chlorpropamide and tolbutamide.

The cyclodextrtins are cyclic oligosaccharides consisting of multiple (α-1,4)-linked α-D-glucopyranose units that display amphoteric properties of a lipophilic central cavity and a hydrophilic outer surface. Depending upon the number of gluopyranose units, the cyclodextrins are classified as α, β and γ cyclodextrins. The synthetic derivatives of natural cyclodextrins are also available. Examples include hydroxypropyl-β-cyclodextrin, sulfobutylether-β-cyclodextrin, randomly methylated β-cyclodextrins, and the like. These synthetic derivatives have improved solubility over the natural cyclodextrins. The

cyclodextrins may include one or more of α-, β-, γ-cyclodextrin, and their derivatives. In particular, β-cyclodextrins include hydroxypropyl-β-cyclodextrin and sulfobutylether β-cyclodextrin.

The co-pulverized mixture obtained by the process described herein can be used in the preparation of various pharmaceutical dosage forms like tablets, capsules, oral solutions, suspensions etc. For inclusion in solid dosage forms, the co-pulverized mixture can be mixed with other commonly used excipients such as fillers, binders, disintegrants, glidants, lubricants and processed into a dosage form. The co-pulverized mixture can be dissolved in a pharmaceutically acceptable liquid along with other excipients to prepare a solution or suspension.

The pulverization may be carried out with commonly available equipments such as rotary mill, roller mill, mortar mill, ball mill. In particular, it may be carried out using a ball mill. The ball mill has a cylindrical shell which is rotated on a horizontal axis. In the shell, the balls are placed which can be of porcelain or stainless steel. The balls serve as a pulverizing medium. The shear forces are generated by the friction between the balls and between the walls of the shell and the balls. The size reduction and complex formation are due to these shear forces.

In general, the process comprises premixing sulfonyl urea and cyclodextrin in a blender. The blend is charged in a ball mill along with stainless steel balls and rotated at a speed sufficient to cause a sliding motion of the balls. The blend undergoes shearing forces of the balls and gets finely pulverized and mixed. During this process, the material sticking to the wall can be scraped. Generally, the ball mill can be operated from 1 hour to about 24 hours. The process can be followed in batches as well as continuously.

In one embodiment, the process comprises mixing sulfonyl urea and hydroxypropyl-β-cyclodextrin in a weight ratio of about 1: 20 and charging in a ball mill with stainless steel balls. The ball mill then is rotated for about 18 to 24 hours with intermittent scraping of the material adhered to the wall. The material is removed from the mill and sifted to remove any aggregates.

The present invention is further illustrated by the following examples which are provided merely to be exemplary of the invention and not to limit the scope of the

invention. Certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

Example 1:

Micronized glipizide and hydroxypropyl-β-cyclodextrin in a weight ratio of 1:20 were blended in a blender for 10 minutes. The blend was sifted and placed in a ball mill and the mill was rotated for 24 hours with intermittent scraping of the material adhered to the wall of the mill. The material was removed from the mill and sifted. Next, 105 mg of the mixture, which contains 5 mg unit dose of glipizide, was then dissolved in 30 mL water and gave a clear solution. This clear solution is believed to be indicative of complete or almost complete dissolution.

For comparison that the co-pulverizing leads to improvement in solubility of sulfonylureas, the following experiments were conducted.

Comparative Example 1:

Glipizide (2.5gm) and hydroxypropyl-β-cyclodextrin (50 gm) were blended in polythene bag and sifted through a 100# sieve. The sifted material was blended again in a polythene bag and sieved through the 100# sieve. The procedure was repeated three times. 105 mg of the physical mixture was dissolved in 30 mL of water. This gave a hazy solution. This hazy solution is believed to be indicative of incomplete or poor dissolution.

Comparative Example 2:

The above physical mixture of co-pulverized glipizide and hydroxypropyl-β-cyclodextrin was also stored at 60 °C in HDPE bottles to study the effect of temperature. Test samples of 105 mg of the physical mixture was withdrawn at 6, 12 and 24 hours and tested for solubility in 30 mL of water. The solution obtained in each of the cases was hazy. This hazy solution is believed to be indicative of incomplete or poor dissolution.

Comparative Example 3:

A few mL of water was added to the physical mixture of comparative example 1, worked into a paste and dried at 60°C. Next, 105 mg of this physical mixture of the dried

paste was dissolved in 30 mL of water which gave a hazy solution. This hazy solution is believed to be indicative of incomplete or poor dissolution.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are included within the scope of the present invention.

We claim:

1. A process for improving the aqueous solubility of sulfonylureas, the process comprising the steps of:

a) blending sulfonyl urea and cyclodextrin to form a dry mixture;

b) co-pulverizing the mixture; and

c) processing into a solid dosage form.

2. The process of claim 1, wherein the ratio of sulfonyl urea to cyclodextrin is from about 1: 1 to about 1:30 by weight.

3. The process of claim 1, wherein the co-pulverization is carried out for about 1 hour to about 24 hours.

4. The process of claim 3, wherein the co-pulverization is carried out for about 18 hours to about 24 hours.

5. The process of claim 1, wherein the sulfonyl urea comprises one or more of glyburide, glipizide, glimepiride, chlorpropamide and tolbutamide.

6. The process of claim 1, wherein the cyclodextrin comprises one or more of α-, β-, and γ-cyclodextrins.

7. The process of claim 6, wherein the cyclodextrin is β-cyclodextrin.

8. The process of claim 7, wherein the β-cyclodextrin comprises one or both of hydroxypropyl-β-cyclodextrin and sulfobutylether-β-cyclodextrin.

9. The process of claim 8, wherein the β-cyclodextrin is hydroxypropyl-β-cyclodextrin.

10. The process of claim 1, wherein the co-pulverizing is carried out in a rotary mill, roller mill, mortar mill or ball mill.

11. The process of claim 13, wherein the co-pulverizing is carried out in a ball mill.

12. The process of claim 1, further comprising mixing at least one other antidiabetic compound.

13. The process of claim 12, wherein the antidiabetic compound comprises one or more of glitazones and metformin, either in free form or in the form of a pharmaceutically acceptable salt.

14. The process of claim 1, wherein the dosage form comprises one or more of tablets, capsules, solutions and suspensions.

15. The process of claim 14, wherein the dosage form is a tablet.

16. The process of claim 15, wherein the tablet is coated with film-forming agents.

17. The process of claim 14, wherein the dosage form is a capsule.

18. A pharmaceutical composition comprising a co-pulverized mixture of sulfonyl urea and cyclodextrin.

19. The pharmaceutical composition of claim 18, wherein the composition further comprises one or more pharmaceutically acceptable excipients comprising fillers, binders, disintegrants, lubricants, glidants, coloring agents, flavoring agents, and coatings.

20. The pharmaceutical composition of claim 18, further comprising at least one other antidiabetic compound.

21. The pharmaceutical composition of claim 20, wherein the antidiabetic compound comprises one or more of glitazones and metformin, either in free form or in the form of a pharmaceutically acceptable salt.

22. The pharmaceutical composition of claim 18, wherein the composition comprises one or more of tablets, capsules, solutions and suspensions.

23. A method for the prevention or treatment of type 2 diabetes mellitus, or a disease or condition associated with diabetes mellitus, the method comprising administering to a patient in need thereof a pharmaceutical composition comprising a co-pulverized mixture of sulfonyl urea and cyclodextrin.

24. The method of claim 23, wherein the pharmaceutical composition further comprises at least one other antidiabetic compound.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2005/001163

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/14 A61K47/48 A61K31/00

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)
IPC 7 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 practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X, Y	MIRO A ET AL: "Improvement of gliquidone hypoglycaemic effect in rats by cyclodextrin formulations" EUROPEAN JOURNAL OF PHARMACEUTICAL SCIENCES, ELSEVIER, AMSTERDAM, NL, vol. 23, no. 1, September 2004 (2004-09), pages 57-64, XP004795882 ISSN: 0928-0987 the whole document abstract page 58, column 2, paragraph 2.3. page 63, columns 1-2, paragraph 4.CONCLUSIONS page 62; figure 4 ----- -/--	1-24

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in 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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Date of the actual completion of the international search	Date of mailing of the international search report
27 July 2005	05/08/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Luangkhot, N

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2005/001163

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	MITREVEJ A ET AL: "EFFECT OF GRINDING OF BETA-CYCLODEXTRIN AND GLIBENCLAMIDE ON TABLET PROPERTIES. PART I. IN VITRO" DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, NEW YORK, NY, US, vol. 22, no. 12, 1996, pages 1237-1241, XP009042109 ISSN: 0363-9045 the whole document abstract page 1238, column 2, paragraph 2-4 page 1241, column 1, paragraph 6 - column 2, paragraph 1	1-24
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INTERNATIONAL SEARCH REPORT

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Inter[redacted]nal Application No
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