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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
30 September 2004 (30.09.2004)

PCT

(10) International Publication Number
WO 2004/082664 A1

(51) International Patent Classification[7]: A61K 9/20

(21) International Application Number: PCT/IB2004/000821

(22) International Filing Date: 19 March 2004 (19.03.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
354/DEL/2003 21 March 2003 (21.03.2003) 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, 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, 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, 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, IT, 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*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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.

(54) Title: WATER-SOLUBLE TABLETS OF METFORMIN

(57) Abstract: The present invention relates to a water-soluble tablet that includes a pharmaceutically acceptable salt of metformin and dissolves to form a clear aqueous solution. It also relates to a process for the preparation of the tablet. The water-soluble tablet includes a pharmaceutically acceptable salt of metformin, one or more water-soluble sugar alcohols, and one or more other water-soluble excipient. The tablet dissolves in less than about three minutes in about 30 ml of water to give a clear solution.

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WATER-SOLUBLE TABLETS OF METFORMIN

Field of the Invention

The present invention relates to a water-soluble tablet that includes a pharmaceutically acceptable salt of metformin and dissolves to form a clear aqueous solution. It also relates to a process for the preparation of the tablet.

Background of the Invention

Diabetes Mellitus is characterized by an undesirable elevation of blood glucose levels and is one of the most common diseases affecting humans. The primary goal in the treatment of diabetes is to maintain blood glucose levels as close to normal as possible. Type I Diabetes Mellitus is caused by an absence of insulin in the individual and is treated with subcutaneous injections of insulin. Type II Diabetes Mellitus is caused by decreased circulating insulin, and is treated with oral hypoglycemic therapy. In some cases insulin therapy is required to control glucose levels and minimize complications related to the disease.

In oral hypoglycemic therapy, one of the compounds commonly used to treat diabetes is the biguanide derivative metformin. U.S. Patent No. 3,174,921 discloses various pharmaceutically acceptable salts of metformin, for example, phosphate, sulfate, hydrochloride, salicylate, maleate, benzoate, ethanedisulfonate, fumarate and glycolate. U.S. Patent No. 6,031,004 discloses metformin salts of dibasic acids, such as fumarate and succinate.

It has generally been observed that patient compliance in taking a medication is drastically reduced due to the inconvenience caused by swallowing tablets. The large sized tablets are not preferred by elderly or children due to their difficulty in swallowing. In fact, in many cases the patient's ability to swallow anything is compromised. Moreover, when a drug, such as metformin, has an unpleasant bitter taste, patient compliance is further reduced. Therefore, it is desirable to develop an oral dosage form, such as a water-soluble tablet of metformin, that is easy to consume and has a pleasant palatability.

CONFIRMATION COPY

Summary of the Invention

In one general aspect there is provided a water-soluble tablet that includes a pharmaceutically acceptable salt of metformin, one or more water-soluble sugar alcohols, and one or more other water-soluble excipient. The tablet dissolves in less than about three minutes in about 30 ml of water to give a clear solution.

Embodiments of the tablet may include one or more of the following features. For example, the tablet may dissolve in water in less than about one minute or in less than about two minutes to give a clear solution. The tablet may be dissolved in about 20 ml of water or about 15 ml of water.

The pharmaceutically acceptable salt of metformin may be one or more of phosphate, sulfate, hydrochloride, salicylate, maleate, benzoate, ethanedisulfonate, fumarate, glycolate, salts of dibasic acids, fumarate, and succinate. In particular, the pharmaceutically acceptable salt of metformin may be hydrochloride. The pharmaceutically acceptable salt of metformin may be up to about 95% weight by weight of the tablet.

The one or more water-soluble sugar alcohols may be one or more of sorbitol, mannitol, spray-dried mannitol, xylitol, erythritol, isomalt, hydrogenated starch hydrolysates, and combinations thereof. In particular, the water-soluble sugar alcohol may be xylitol, mannitol, or a mixture of xylitol and mannitol.

The other water-soluble excipients may be one or more of binders, lubricants, sweeteners, and flavoring agents. The binder may be one or more of soluble starch, polyvinylpyrrolidone, cellulose ethers, gums and carboxyvinyl polymer(s). In particular, the binder may be polyvinylpyrrolidone.

The lubricant may be one or more of polyethylene glycol, sodium propionate, sucrose, sodium chloride, silicon oil, simethicone, polyvinylpyrrolidone, DL-leucine, sodium benzoate, boric acid, sodium lauryl sulphate, and magnesium lauryl sulphate. In particular, the lubricant may be polyethylene glycol or sodium propionate. The polyethylene glycol may be pulverized/micronised. The polyethylene glycol may have a particle size of from about 90% less than 250μ. The polyethylene glycol may have a

molecular weight of from about 3500 to about 20,000, more particularly, from about 3500 to about 8000, and even more particularly of about 6000 or about 8000.

The sweetener may be one or more of aspartame, saccharine sodium, glycine, lactose, dextrose, fructose, maltose, sorbitol and sucrose and, in particular, the sweetener may be aspartame.

The one or more water-soluble sugar alcohols may be xylitol and spray-dried mannitol, the lubricant may be micronised polyethylene glycol, and the tablet may dissolve in about 15 ml of water in less than about one minute to give a clear solution.

The tablet may further include one or more additional antidiabetic agents selected from sulfonyl urea, glucosidase inhibitor and thiazolidinedione.

In another general aspect there is provided a process for the preparation of a water-soluble tablet. The process includes (a) mixing together a pharmaceutically acceptable salt of metformin, one or more water-soluble sugar alcohols, and one or more other water-soluble excipients to form a mixture, and (b) compressing the mixture to form a tablet. The tablet dissolves in less than about three minutes in about 30 ml of water to give a clear solution.

Embodiments of the process may include one or more of the following features. For example, the tablet may dissolve in water in less than about one minute or in less than about two minutes to give a clear solution. The tablet may be dissolved in about 10 ml or about 20 ml of water.

The mixture may be formulated into a tablet by direct compression. The mixture may be granulated prior to compression. The mixture may be wet granulated or dry granulated.

The pharmaceutically acceptable salt of metformin may be one or more of phosphate, sulfate, hydrochloride, salicylate, maleate, benzoate, ethanedisulfonate, fumarate, glycolate, salts of dibasic acids, fumarate, and succinate. The pharmaceutically acceptable salt of metformin may be up to about 95% weight by weight of the tablet.

The one or more water-soluble sugar alcohols may be one or more of sorbitol, mannitol, spray-dried mannitol, xylitol, erythritol, isomalt, hydrogenated starch hydrolysates, and combinations thereof.

The other water-soluble excipients may be one or more of binders, lubricants, sweeteners, and flavoring agents. The binder may be one or more of soluble starch, polyvinylpyrrolidone, cellulose ethers, gums and carboxyvinyl polymer(s).

The lubricant may be one or more of polyethylene glycol, sodium propionate, sucrose, sodium chloride, silicon oil, simethicone, polyvinylpyrrolidone, DL-leucine, sodium benzoate, boric acid, sodium lauryl sulphate, and magnesium lauryl sulphate. The polyethylene glycol may be pulverized/micronised. The polyethylene glycol may have a molecular weight of from about 3,500 to about 20,000.

The sweetener may be one or more of aspartame, saccharine sodium, glycine, lactose, dextrose, fructose, maltose, sorbitol and sucrose.

In the tablet, the one or more water-soluble sugar alcohols may be xylitol and spray-dried mannitol, the lubricant may be micronised polyethylene glycol, and the tablet may dissolves in about 15 ml of water within about one minute to give a clear solution.

The mixing may further include mixing one or more additional antidiabetic agents selected from sulfonyl urea, glucosidase inhibitor and thiazolidinedione

In another general aspect there is provided a method of treating diabetes mellitus. The method includes administering to a patient in need thereof a water soluble tablet that includes a pharmaceutically acceptable salt of metformin, one or more water-soluble sugar alcohols, and one or more other water-soluble excipients. The tablet dissolves in less than about three minutes in about 30 ml of water to give a clear solution.

Embodiments of the method of treatment may include one or more of the following features or any of the features described above. For example, the tablet may further include one or more additional antidiabetic agents selected from sulfonyl urea, glucosidase inhibitor and thiazolidinedione.

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.

Description of the Invention

It has now been discovered that metformin water-soluble tablets, having a pleasant taste and capable of dissolving within 3 minutes in water without residual particulate matter, can be easily prepared with water-soluble sugar alcohols and other water-soluble excipients. The water–soluble sugar alcohols, such as sorbitol, mannitol, xylitol, isomalt and hydrogenated starch hydrolysates, not only help in the quick disintegration of the tablet, but also provide compressible properties to the bulk. Therefore, metformin water-soluble tablets can be prepared by compressing a mixture of a pharmaceutically acceptable salt of metformin, water-soluble sugar alcohols and other water-soluble excipients.

Also discovered is a process which provides water-soluble tablets that include a pharmaceutically acceptable salt of metformin, are rapidly soluble in an aqueous media, and provide an easy mode of administration. As an alternative to dissolving in an aqueous solution, these tablets may instead be swallowed similar to conventional tablets.

The resulting tablet has the sufficient hardness and friability to withstand impacts during manufacturing, packaging and transport. For example, the tablet can have a hardness of about 2 kP to about 8 kP.

The inventors have developed various dosage forms of the water-soluble tablet of metformin and processes for their preparation. For example, the inventors have developed a water-soluble tablet that includes a pharmaceutically acceptable salt of metformin, one or more water-soluble sugar alcohols, and other water-soluble excipients. This dosage form dissolves in less than about three minutes in about 30 ml of water to give a clear solution.

The "water-soluble tablet" as used herein means an uncoated tablet that dissolves in water, as described in the British Pharmacopoeia 1988, Vol. II. The solution produced may be slightly opalescent due to added substances used in the manufacture of the tablets.

The term "clear aqueous solution" as used herein means that the solution formed after the tablet has completely dissolved should appear transparent to the naked eye. However, the solution produced may be slightly opalescent due to some water-insoluble impurities present in the excipients used to make the tablets.

Suitable pharmaceutically acceptable salts of metformin include one or more of phosphate, sulfate, hydrochloride, salicylate, maleate, benzoate, ethanedisulfonate, fumarate, glycolate, and salts of dibasic acids, such as fumarate and succinate. A particularly suitable salt of metformin is the hydrochloride salt. The pharmaceutically acceptable salt of metformin may be present up to about 95% weight by weight of the tablet.

Additionally, one or more antidiabetic agents, other than metformin, may also be incorporated in the tablet in a therapeutically effective amount. Suitable antidiabetic agents may include one or more of sulfonylurea, glucosidase inhibitor and thiazolidinedione. For example, a suitable sulfonylurea may be glyburide, glipizide, glimepiride, gliclazide and the like. A suitable glucosidase inhibitor may be acarbose and a suitable thiazolidinedione may be pioglitazone, rosiglitazone, troglitazone and the like.

Suitable water-soluble sugar alcohols may include one or more of sorbitol, mannitol, spray dried mannitol, xylitol, erythritol isomalt and hydrogenated starch hydrolysates and combinations thereof. Particularly suitable water-soluble sugar alcohols include xylitol and spray dried mannitol. Mannitol can be spray-dried mannitol, which is available under the trade name Pearlitol®. It is a free-flowing, directly compressible sugar that has a cooling taste due to the negative heat of solution. Spray dried mannitol gives tablets good hardness and also facilitates quick dissolution. The water-soluble sugar alcohol may be present at from about 10% to about 95% weight by weight of the tablet. In particular, it may be present at from about 30% to about 70% weight by weight of the tablet.

Besides a pharmaceutically acceptable salt of metformin and one or more water-soluble sugar alcohols, the tablet may include one or more water-soluble excipients. Suitable water-soluble excipients include one or more of water-soluble binders, lubricants, sweeteners and flavoring agents.

Suitable binders may include one or more of soluble starch, polyvinylpyrrolidone, cellulose ethers, gums, carboxyvinyl polymer(s) or combinations thereof.

Suitable lubricants include one or more of polyethylene glycol, sodium propionate, sucrose, sodium chloride, silicon oil, simethicone, polyvinylpyrrolidone, DL-leucine, sodium benzoate, boric acid sodium lauryl sulphate, magnesium lauryl sulphate and combinations thereof. For example, a particularly suitable lubricant is polyethylene glycol, and even more particularly suitable is pulverized or micronised polyethylene glycol having a particle size of about 90% less than 250μ. Polyethylene glycol may be selected from different molecular weight polyethylene glycols, such as those having molecular weights ranging from about 1,500 to about 20,000. Particularly suitable polyethylene glycols are those having molecular weights from about 3,500 to about 8,000. The polyethylene glycol may be present at from about 0.1% to about 10% weight by weight of the tablet, and particularly at from about 2% to about 10% weight by weight of the tablet.

Suitable sweeteners may include one or more of aspartame, saccharine sodium, glycine, lactose, dextrose, fructose, maltose, sorbitol and sucrose.

Suitable flavouring agents may include one or more of strawberry aroma, raspberry aroma, cherry flavour, lime flavour, fruit extracts, citrates and tartarates.

The tablet can be prepared by any conventional tableting method. In a direct compression method, a pharmaceutically acceptable salt of metformin, one or more water-soluble sugar alcohols, and one or more water-soluble excipients may be sifted through a mesh of suitable size. The sifted blend then may be mixed with lubricant and compressed using suitable tooling.

In a wet granulation method, a pharmaceutically acceptable salt of metformin may be mixed with a binder and granulated with purified water. Alternatively, a pharmaceutically acceptable salt of metformin may be mixed with one or more water-soluble sugar alcohols and granulated with a binder solution. The granules can be dried and mixed with other excipients and compressed using suitable tooling.

In a dry granulation, a blend of all the ingredients can be compacted to make granules of suitable size, which then are mixed with lubricant and compressed to form tablets.

While tablets in particular are the preferred final dosage form, granules made up of a pharmaceutically acceptable salt of metformin, one or more water-soluble sugar alcohols, and one or more water-soluble excipients can also be prepared and packed into sachets, bottles or other suitable packaging devices meant for unit/multiple dosage. These granules can be dissolved in water to give a clear solution that is consumed by the patient.

The following examples illustrate water-soluble tablets of metformin and processes of making the composition. The examples are merely provided to illustrate the compositions and processes for their preparation and are not intended to be limiting. The obvious variations of these compositions are contemplated to be within the scope of the present invention and the appended claims.

EXAMPLE 1

The tablets of Example 1 were formulated with metformin hydrochloride (500 mg), spray-dried mannitol (200 mg), xylitol (200 mg), aspartame (45 mg), monosodium citrate (20 mg), and micronised polyethylene glycol (25 mg). The metformin, spray-dried mannitol, xylitol, aspartame and monosodium citrate were sifted through a suitable mesh. The micronised polyethylene glycol was mixed with the above sifted blend and compressed into a tablet using appropriate tooling. These tablets, when dropped in 15 ml of water, dissolved quickly to give a clear solution.

EXAMPLE 2

The tablets of Example 2 were formulated with metformin hydrochloride (500 mg), polyvinyl pyrrolidone (10 mg), spray-dried mannitol (200 mg), xylitol (200 mg), aspartame (45 mg), monosodium citrate (20 mg), and micronised polyethylene glycol (25 mg). The pharmaceutically acceptable salt of metformin and polyvinyl pyrrolidone were mixed in a blender and granulated with purified water. The granules were dried and mixed with spray-dried mannitol, xylitol, aspartame and monosodium citrate. This blend was then mixed with micronised polyethylene glycol and compressed using appropriate

tooling. These tablets, when dropped in 15 ml of water, dissolved quickly to give a clear solution.

The compositions of Examples 1 and 2, prepared using metformin hydrochloride, are listed in Table 1.

TABLE 1

Composition	Example 1	Example 2
Metformin hydrochloride	500mg	500mg
Polyvinylpyrrolidone		10mg
Xylitol	200mg	200mg
Mannitol (spray-dried)	200mg	200mg
Aspartame	45mg	45mg
Monosodium citrate	20mg	20mg
Micronised polyethylene glycol	25mg	25mg
Purified water		q.s.
Total weight	990mg	1000mg

While this invention has been described with an emphasis upon preferred embodiments, it will be obvious to those of ordinary skill in the art that variations in the preferred methods of the present invention may be used and that it is intended that the invention may be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications encompassed within the spirit and scope of the invention as defined by the following claims.

WE CLAIM:

1. A water-soluble tablet comprising a pharmaceutically acceptable salt of metformin, one or more water-soluble sugar alcohols, and one or more other water-soluble excipients, wherein the tablet dissolves in less than about three minutes in about 30 ml of water to give a clear solution.

2. The water-soluble tablet according to claim 1, wherein the tablet dissolves in water in less than about two minutes to give a clear solution.

3. The water-soluble tablet according to claim 1, wherein the tablet dissolves in water in less than about one minute to give a clear solution.

4. The water-soluble tablet according to claim 1, wherein the tablet is dissolved in about 20 ml of water.

5. The water-soluble tablet according to claim 1, wherein the tablet is dissolved in about 15 ml of water.

6. The water-soluble tablet according to claim 1, wherein the pharmaceutically acceptable salt of metformin comprises one or more of phosphate, sulfate, hydrochloride, salicylate, maleate, benzoate, ethanedisulfonate, fumarate, glycolate, salts of dibasic acids, fumarate, and succinate.

7. The water-soluble tablet according to claim 6, wherein the pharmaceutically acceptable salt of metformin comprises hydrochloride.

8. The water-soluble tablet according to claim 1, wherein the pharmaceutically acceptable salt of metformin comprises up to about 95% weight by weight of the tablet.

9. The water-soluble tablet according to claim 1, wherein the one or more water-soluble sugar alcohols comprise one or more of sorbitol, mannitol, spray-dried mannitol, xylitol, erythritol, isomalt, hydrogenated starch hydrolysates, and combinations thereof.

10. The water-soluble tablet according to claim 9, wherein the water-soluble sugar alcohol comprises xylitol.

11. The water-soluble tablet according to claim 9, wherein the water-soluble sugar alcohol comprises mannitol.

12. The water-soluble tablet according to claim 9, wherein the water-soluble sugar alcohol comprises a mixture of xylitol and mannitol.

13. The water-soluble tablet according to claim 1, wherein the other water-soluble excipients comprise one or more of binders, lubricants, sweeteners, and flavoring agents.

14. The water-soluble tablet according to claim 13, wherein the binder comprises one or more of soluble starch, polyvinylpyrrolidone, cellulose ethers, gums and carboxyvinyl polymer(s).

15. The water-soluble tablet according to claim 14, wherein the binder comprises polyvinylpyrrolidone.

16. The water-soluble tablet according to claim 13, wherein the lubricant comprises one or more of polyethylene glycol, sodium propionate, sucrose, sodium chloride, silicon oil, simethicone, polyvinylpyrrolidone, DL-leucine, sodium benzoate, boric acid, sodium lauryl sulphate, and magnesium lauryl sulphate.

17. The water-soluble tablet according to claim 16, wherein the lubricant comprises polyethylene glycol.

18. The water-soluble tablet according to claim 17, wherein the polyethylene glycol is pulverized/micronised.

19. The water-soluble tablet according to claim 18, wherein the polyethylene glycol has a particle size of from about 90% less than 250μ.

20. The water-soluble tablet according to claim 17, wherein the polyethylene glycol has a molecular weight of from about 3500 to about 20,000.

21. The water-soluble tablet according to claim 20, wherein the polyethylene glycol has a molecular weight of from about 3500 to about 8000.

22. The water-soluble tablet according to claim 21, wherein the polyethylene glycol has a molecular weight of about 6000.

23. The water-soluble tablet according to claim 21, wherein the polyethylene glycol has a molecular weight of about 8000.

24. The water-soluble tablet according to claim 16, wherein the lubricant comprises sodium propionate.

25. The water-soluble tablet according to claim 13, wherein the sweetener comprises one or more of aspartame, saccharine sodium, glycine, lactose, dextrose, fructose, maltose, sorbitol and sucrose.

26. The water-soluble tablet according to claim 25, wherein the sweetener comprises aspartame.

27. The water-soluble tablet according to claim 1, wherein the one or more water-soluble sugar alcohols comprise xylitol and spray-dried mannitol, the lubricant comprises micronised polyethylene glycol, and the tablet dissolves in about 15ml of water in less than about one minute to give a clear solution.

28. The water-soluble tablet according to claim 1, wherein the tablet further comprises one or more additional antidiabetic agents selected from sulfonyl urea, glucosidase inhibitor and thiazolidinedione.

29. A process for the preparation of a water-soluble tablet, the process comprising:

(a) mixing together a pharmaceutically acceptable salt of metformin, one or more water-soluble sugar alcohols, and one or more other water-soluble excipients to form a mixture, and

(b) compressing the mixture to form a tablet,

wherein the tablet dissolves in less than about three minutes in about 30 ml of water to give a clear solution.

30. The process according to claim 29, wherein the tablet dissolves in water in less than about two minutes to give a clear solution.

31. The process according to claim 29, wherein the tablet dissolves in water in less than about one minute to give a clear solution.

32. The process according to claim 29, wherein the tablet is dissolved in about 20 ml of water.

33. The process according to claim 29, wherein the tablet is dissolved in about 15 ml of water.

34. The process according to claim 29, wherein the mixture is formulated into a tablet by direct compression.

35. The process according to claim 29, wherein the mixture is granulated prior to compression.

36. The process according to claim 35, wherein the mixture is wet granulated.

37. The process according to claim 35, wherein the mixture is dry granulated.

38. The process according to claim 29, wherein the pharmaceutically acceptable salt of metformin comprises one or more of phosphate, sulfate, hydrochloride, salicylate, maleate, benzoate, ethanedisulfonate, fumarate, glycolate, salts of dibasic acids, fumarate, and succinate.

39. The process according to claim 29, wherein the pharmaceutically acceptable salt of metformin comprises up to about 95% weight by weight of the tablet.

40. The process according to claim 28, wherein the one or more water-soluble sugar alcohols comprise one or more of sorbitol, mannitol, spray-dried mannitol, xylitol, erythritol, isomalt, hydrogenated starch hydrolysates, and combinations thereof.

41. The process according to claim 29, wherein the other water-soluble excipients comprise one or more of binders, lubricants, sweeteners, and flavoring agents.

42. The process according to claim 41, wherein the binder comprises one or more of soluble starch, polyvinylpyrrolidone, cellulose ethers, gums and carboxyvinyl polymer(s).

43. The process according to claim 41, wherein the lubricant comprises one or more of polyethylene glycol, sodium propionate, sucrose, sodium chloride, silicon oil, simethicone, polyvinylpyrrolidone, DL-leucine, sodium benzoate, boric acid, sodium lauryl sulphate, and magnesium lauryl sulphate.

44. The process according to claim 42, wherein the polyethylene glycol is pulverized/micronised.

45. The process according to claim 44, wherein the polyethylene glycol has a molecular weight of from about 3,500 to about 20,000.

46. The process according to claim 44, wherein the sweetener comprises one or more of aspartame, saccharine sodium, glycine, lactose, dextrose, fructose, maltose, sorbitol and sucrose.

47. The process according to claim 28, wherein the one or more water-soluble sugar alcohols comprise xylitol and spray-dried mannitol, the lubricant comprises micronised polyethylene glycol, and the tablet dissolves in about 15 ml of water within about one minute to give a clear solution.

48. The process of claim 29, wherein the mixing further comprises mixing one or more additional antidiabetic agents selected from sulfonyl urea, glucosidase inhibitor and thiazolidinedione.

49. A method of treating diabetes mellitus comprising administering to a patient in need thereof a water soluble tablet comprising a pharmaceutically acceptable salt of metformin, one or more water-soluble sugar alcohols, and one or more other water-soluble excipients, wherein the tablet dissolves in less than about three minutes in about 30 ml of water to give a clear solution.

50. The method of claim 49, wherein the tablet further comprises one or more additional antidiabetic agents selected from sulfonyl urea, glucosidase inhibitor and thiazolidinedione.

INTERNATIONAL SEARCH REPORT

In tional Application No
F .'IB2004/000821

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/20

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, EMBASE, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 031 004 A (BRETNALL ALISON E ET AL) 29 February 2000 (2000-02-29) column 2, line 26 - line 46	1-13, 28-41, 43,46, 48-50
Y	examples 9,10	16-23, 41-45

X	WO 01/39749 A (JAIN RAJESH ; SINGH AMARJIT (IN); PANACEA BIOTEC LTD (IN)) 7 June 2001 (2001-06-07) page 3, paragraph 4 - page 4, last paragraph page 24, paragraph 3 example 5	1-9, 11-16, 25,26

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

[X] Patent family members are listed in annex.

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Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International Application No
IB2004/000821

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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