



(43) International Publication Date
30 October 2014 (30.10.2014)

(10) International Publication Number
WO 2014/174469 A1

(51) International Patent Classification:

A61K 9/16 (2006.01) *A61K 31/00* (2006.01)
A61K 9/20 (2006.01)

(21) International Application Number:

PCT/IB2014/060953

(22) International Filing Date:

23 April 2014 (23.04.2014)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

1226/DEL/2013 25 April 2013 (25.04.2013) IN

(71) Applicant: **RANBAXY LABORATORIES LIMITED**
[IN/IN]; Head Office: 12th Floor, Devika Tower, 06 Nehru
Place, New Delhi, Delhi 110019 (IN).

(72) Inventors: **TIWARI, Ravindra**; House No. 1, Maruti
Colony, Behind Pankaj Hotel, Nayapura, Kota, Rajasthan
342002 (IN). **TIWARI, Kirpa Shankar**; 51-133 Nit,
Faridabad, Haryana 121001 (IN). **KOCHHAR, Ravi**; A-
118, Ground Floor, Greenwoods City, Opp. Sec - 45, Gur-
gaon, Haryana 122001 (IN).

(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,

AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY,
BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM,
DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,
HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR,
KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME,
MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ,
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SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM,
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM,
ZW.

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ,
UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ,
TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK,
EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV,
MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM,
TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
KM, ML, MR, NE, SN, TD, TG).

Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments (Rule 48.2(h))

(54) Title: PHARMACEUTICAL COMPOSITIONS COMPRISING A COMBINATION OF SITAGLIPTIN AND METFORMIN

(57) Abstract: The present invention relates to pharmaceutical compositions consisting essentially of sitagliptin, metformin, and a lubricant selected from the group consisting of glyceryl behenate, glyceryl palmitostearate, stearyl alcohol, cetostearyl alcohol, or mixtures thereof, wherein the pharmaceutical composition does not comprise a surfactant. The invention further relates to processes for the preparation of said pharmaceutical compositions.



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**PHARMACEUTICAL COMPOSITIONS COMPRISING A COMBINATION OF
SITAGLIPTIN AND METFORMIN**

Field of the Invention

The present invention relates to pharmaceutical compositions consisting essentially
5 of sitagliptin, metformin, and a lubricant selected from the group consisting of glyceryl
behenate, glyceryl palmitostearate, stearyl alcohol, cetostearyl alcohol, or mixtures
thereof, wherein the pharmaceutical composition does not comprise a surfactant. The
invention further relates to processes for the preparation of said pharmaceutical
compositions.

Background of the Invention

Sitagliptin is a dipeptidyl peptidase IV (DPP-IV) inhibitor used for the treatment of
type II diabetes mellitus. Metformin is a widely used biguanide that is also indicated for
the treatment of type II diabetes mellitus. A fixed-dose combination of sitagliptin and
metformin is indicated to improve glycemic control in adults with type II diabetes mellitus
15 when treatment with both sitagliptin and metformin is appropriate.

U.S. Publication No. 2009/0105265 discloses compositions comprising sitagliptin
and metformin. These compositions comprise sitagliptin and metformin in combination
with lubricants including magnesium stearate, calcium stearate, stearic acid, sodium
stearyl fumarate, hydrogenated castor oil, and mixtures thereof. The addition of lubricants
20 to these compositions resulted in a slow and inconsistent dissolution profile of sitagliptin.
This publication also discloses that the use of a surfactant, including anionic surfactants
such as sodium lauryl sulfate, sodium dodecanesulfonate, sodium oleyl sulfate, and
sodium laurate mixed with stearates and talc; cationic surfactants such as benzalkonium
chlorides and alkyltrimethylammonium bromides; neutral surfactants such as glyceryl
25 monooleate, polyoxyethylene sorbitan fatty acid esters, polyvinyl alcohol, and sorbitan
esters; and wetting agents such as poloxamer, polyoxyethylene castor oil derivatives, and
polyoxyethylene stearates.

U.S. Publication No. 2012/0202820 discloses pharmaceutical compositions
comprising sitagliptin and metformin in combination with a lubricant wherein the
30 lubricant is polyethylene glycol, or mixtures of polyethylene glycol with one or more other
lubricants, and comprises more than 10% by weight of the total weight of the composition.

Summary of the Invention

The present invention provides an alternate pharmaceutical composition of sitagliptin and metformin, wherein the pharmaceutical composition comprises a lubricant selected from the group consisting of glyceryl behenate, glyceryl palmitostearate, stearyl alcohol, cetostearyl alcohol, or mixtures thereof. The pharmaceutical compositions of the present invention were prepared without the use of a surfactant and were found to have a dissolution profile comparable to the marketed pharmaceutical composition of sitagliptin and metformin.

Detailed Description of the Invention

10 A first aspect of the present invention provides a pharmaceutical composition consisting essentially of sitagliptin, metformin, and a lubricant selected from the group consisting of glyceryl behenate, glyceryl palmitostearate, stearyl alcohol, cetostearyl alcohol, or mixtures thereof, wherein the pharmaceutical composition does not comprise a surfactant.

15 As used herein, the term "sitagliptin" includes sitagliptin and pharmaceutically acceptable salts thereof. The pharmaceutically acceptable salts include hydrochloride, hydrobromide, phosphate, sulphate, mesylate, besylate, tosylate, fumarate, malonate, malate, succinate, lactate, glycolate, maleate, citrate, and aspartate. The pharmaceutically acceptable salts of sitagliptin may be present in hydrate or anhydrate forms. The hydrate forms may be monohydrate or dihydrate forms. The pharmaceutically acceptable salts of sitagliptin may also be present in crystalline or amorphous forms. A particular example is sitagliptin phosphate, which may be present in a concentration of about 0.1% to about 30% by weight of the pharmaceutical composition. Sitagliptin phosphate may be used in the pharmaceutical composition in strengths of 25 mg, 50 mg, or 100 mg of sitagliptin.

25 As used herein, the term "metformin" includes metformin and pharmaceutically acceptable salts thereof. The pharmaceutically acceptable salts include hydrochloride, hydrobromide, fumarate, malonate, malate, succinate, lactate, glycolate, maleate, citrate, and aspartate. The pharmaceutically acceptable salts of sitagliptin may be present in hydrate or anhydrate forms. They may also be present in crystalline or amorphous forms.

30 A particular example is metformin hydrochloride, which may be present in a concentration of about 50% to about 90% by weight of the pharmaceutical composition. Metformin

hydrochloride may be used in strengths of 500 mg, 850 mg, or 1000 mg in the pharmaceutical composition.

Examples of lubricants include glyceryl behenate (*e.g.*, Compritol®), glyceryl palmitostearate (*e.g.*, Precirol®), stearyl alcohol, cetostearyl alcohol, or mixtures thereof.

- 5 The concentration of the lubricant may be about 0.01% to about 10% by weight of the pharmaceutical composition.

As used herein, the term “pharmaceutical composition” means compositions comprising sitagliptin and metformin. These compositions include tablets, capsules, pellets, pills, caplets, and granules. The pharmaceutical compositions may be prepared by
10 dry granulation, wet granulation, or direct compression. Wet granulation may include rapid mixer granulation or fluid bed granulation.

According to one embodiment of the present invention, there is provided a pharmaceutical composition consisting essentially of sitagliptin, metformin, and a lubricant selected from the group consisting of glyceryl behenate, glyceryl palmitostearate,
15 stearyl alcohol, cetostearyl alcohol, or mixtures thereof, wherein more than 80% of sitagliptin is released in 15 minutes when the dissolution is performed in 900 mL of 0.025M sodium chloride solution at 75 rpm using USP type II (paddle) apparatus.

According to one embodiment of the present invention, there is provided a pharmaceutical composition consisting essentially of sitagliptin phosphate, metformin
20 hydrochloride, and a lubricant selected from the group consisting of glyceryl behenate, glyceryl palmitostearate, stearyl alcohol, cetostearyl alcohol, or mixtures thereof, wherein the pharmaceutical composition does not comprise a surfactant.

According to another embodiment of the present invention, there is provided a pharmaceutical composition consisting essentially of sitagliptin phosphate, metformin
25 hydrochloride, and a lubricant selected from the group consisting of glyceryl behenate, glyceryl palmitostearate, stearyl alcohol, cetostearyl alcohol, or mixtures thereof, wherein the lubricant is present in an amount of about 0.01% to about 10% by weight of the pharmaceutical composition and the pharmaceutical composition does not comprise a surfactant.

30 A second aspect of the present invention provides a process for the preparation of a pharmaceutical composition consisting essentially of sitagliptin, metformin, and a lubricant selected from the group consisting of glyceryl behenate, glyceryl palmitostearate,

stearyl alcohol, cetostearyl alcohol, or mixtures thereof, wherein the pharmaceutical composition does not comprise a surfactant, the process comprising:

- a) blending sitagliptin and metformin;
- b) optionally, mixing the blend of step a) with one or more pharmaceutically acceptable excipients;
- c) dissolving or dispersing one or more pharmaceutically acceptable excipients in a suitable solvent;
- d) granulating the blend of step a) or step b) with the solution or dispersion of step c);
- e) blending the granules of step d) with a lubricant and optionally with one or more pharmaceutically acceptable excipients; and
- f) compressing the blend of step e) into suitable sized tablets or filling the blend of step e) into suitable sized capsules.

According to one embodiment of this aspect, the granulation is carried out in a rapid mixer granulator or a fluid bed granulator.

A third aspect of the present invention provides a process for the preparation of a pharmaceutical composition consisting essentially of sitagliptin, metformin and a lubricant selected from the group consisting of glyceryl behenate, glyceryl palmitostearate, stearyl alcohol, cetostearyl alcohol, or mixtures thereof, wherein the pharmaceutical composition does not comprise a surfactant, the process comprising:

- a) dissolving or dispersing sitagliptin and one or more pharmaceutically acceptable excipients in a suitable solvent;
- b) granulating metformin with the solution or dispersion from step a);
- c) blending the granules of step b) with a lubricant and optionally one or more pharmaceutically acceptable excipients; and
- d) compressing the blend of step c) into suitable sized tablets or filling the blend of step c) into suitable sized capsules.

According to one embodiment of this aspect, the granulation is carried out in a rapid mixer granulator or a fluid bed granulator.

Examples of suitable solvents that may be used for granulation include water, ethanol, methanol, isopropyl alcohol, dichloromethane, acetone, or mixtures thereof.

Pharmaceutically acceptable excipients include binders, disintegrants, diluents, and antioxidants. The excipients may be added intragranularly and/or extragranularly in the pharmaceutical compositions.

Examples of binders include cellulose or cellulose derivatives such as methylcellulose, hydroxy propyl methyl cellulose, hydroxy propyl cellulose, carboxy methyl cellulose sodium, polyvinyl pyrrolidone (*e.g.*, Kollidon® 30), copovidone, sodium alginate, microcrystalline cellulose, or mixtures thereof. The concentration of binders may be about 1% to about 50% by weight of the pharmaceutical composition.

Examples of disintegrants include sodium starch glycolate, croscarmellose, pregelatinized starch (*e.g.*, Starch 1500®), microcrystalline cellulose, calcium carboxy methyl cellulose, low substituted hydroxy propyl cellulose, magnesium silicate, aluminum silicate, or mixtures thereof. The concentration of disintegrants may be about 1% to about 50% by weight of the pharmaceutical composition.

Examples of diluents include lactose, sucrose, maltodextrin, microcrystalline cellulose, pregelatinized starch (*e.g.*, Starch 1500®), dextrose, mannitol, sorbitol, xylitol, isomalt, erythritol, or mixtures thereof. The concentration of diluents may be about 1% to about 50% by weight of the pharmaceutical composition.

Examples of antioxidants include ascorbic acid, butylated hydroxy anisole, butylated hydroxy toluene, or mixtures thereof. The concentration of antioxidants may be about 0% to about 2% by weight of the pharmaceutical composition.

The pharmaceutical composition may be further coated with a functional or non-functional coating. The coating composition may comprise pharmaceutically acceptable excipients such as binders, plasticizers, coloring agents, and opacifiers. The total weight gain after coating may be about 1% to about 10% by weight of uncoated composition.

Examples of binders for coating include cellulose or cellulose derivatives such as methyl cellulose, hydroxy propyl methyl cellulose, hydroxy propyl cellulose, and carboxy methyl cellulose sodium; alginic acid or sodium alginate; microcrystalline cellulose; gelatin; polyvinyl pyrrolidone; copovidone; starch; pregelatinized starch; or mixtures thereof.

Examples of plasticizers for coating include propylene glycol, triethyl citrate, tributyl citrate, dibutyl sebacate, triacetin, polyethylene glycol, diethyl phthalate, acetylated monoglycerides, or mixtures thereof.

5 Examples of opacifiers for coating include titanium dioxide, talc, calcium carbonate, behenic acid, and cetyl alcohol.

Examples of coloring agents for coating include FDA approved colorants such as iron oxide, Lake of Tartrazine, allura red, Lake of Quinoline Yellow, Lake of Erythrosine, or titanium dioxide.

10 Suitable solvents for coating include ethanol, methanol, isopropyl alcohol, dichloromethane, acetone, or mixtures thereof.

Alternatively, a premixed film-coating may be used. Suitable premixes include Opadry® coating dispersions.

The term “about”, as used herein, refers to any value which lies within the range defined by a variation of up to $\pm 10\%$ of the value.

15 The following examples illustrate the invention but are not to be construed as limiting the scope of the invention.

EXAMPLES

Example 1:

Ingredients	quantity/tablet (mg)
Sitagliptin phosphate monohydrate (equivalent to 50 mg of sitagliptin)	64.24
Metformin hydrochloride	500.00
Polyvinyl pyrrolidone (Kollidon® 30)	45.00
Purified water	q.s.
Pregelatinized starch (Starch 1500®)	72.76
Glyceryl behenate (Compritol®)	7.00
Total	689.00
Opadry® coating	20.67

Manufacturing Process:

- 20
1. Sitagliptin phosphate monohydrate and metformin hydrochloride were blended.
 2. Polyvinyl pyrrolidone was dissolved in purified water to obtain a solution.
 3. The blend of step 1 was granulated with the solution of step 2 in a rapid mixer

granulator to obtain granules.

4. The granules of step 3 were blended with glyceryl behenate and pregelatinized starch.
5. The blend of step 4 was compressed to obtain suitable sized tablets.
- 5 6. The tablets of step 5 were coated with Opadry® coating dispersion.

Example 2:

Ingredients	quantity/tablet (mg)
Sitagliptin phosphate monohydrate (equivalent to 50 mg of sitagliptin)	64.24
Metformin hydrochloride	500.00
Polyvinyl pyrrolidone (Kollidon® 30)	45.00
Purified water	q.s.
Pregelatinized starch (Starch 1500®)	72.76
Glyceryl palmitostearate (Precirol®)	7.00
Total	689.00
Opadry® coating	20.67

Manufacturing Process:

1. Sitagliptin phosphate monohydrate and polyvinyl pyrrolidone were dissolved in
10 purified water to obtain a solution.
2. Metformin hydrochloride was granulated with the solution of step 1 in a rapid mixer granulator.
3. The granules of step 2 were blended with glyceryl palmitostearate and pregelatinized starch.
- 15 4. The blend of step 3 was compressed to obtain suitable sized tablets.
5. The tablets of step 4 were coated with Opadry® coating.

Example 3:

Ingredients	quantity/tablet (mg)
Sitagliptin phosphate monohydrate (equivalent to 50 mg of sitagliptin)	64.24
Metformin hydrochloride	500.00
Polyvinyl pyrrolidone (Kollidon [®] 30)	45.00
Purified water	q.s.
Pregelatinized starch (Starch 1500 [®])	72.76
Stearyl alcohol	14.00
Total	696.00
Opadry [®] coating	20.67

Manufacturing Process:

1. Sitagliptin phosphate monohydrate and metformin hydrochloride were blended.
2. Polyvinyl pyrrolidone was dissolved in purified water to obtain a solution.
- 5 3. The blend of step 1 was granulated with the solution of step 2 in a rapid mixer granulator to obtain granules.
4. The granules of step 3 were blended with stearyl alcohol and pregelatinized starch.
5. The blend of step 4 was compressed to obtain suitable sized tablets.
6. The tablets of step 5 were coated with Opadry[®] coating.

10

Example 4:

Ingredients	quantity/tablet (mg)
Sitagliptin phosphate monohydrate (equivalent to 50 mg of sitagliptin)	64.24
Metformin hydrochloride	500.00
Polyvinyl pyrrolidone (Kollidon [®] 30)	45.00
Purified water	q.s.
Pregelatinized starch (Starch 1500 [®])	72.76
Cetostearyl alcohol	14.00
Total	696.00
Opadry [®] coating	20.67

Manufacturing Process:

1. Sitagliptin phosphate monohydrate and polyvinyl pyrrolidone were dissolved in purified water to obtain a solution.
2. Metformin hydrochloride was granulated with the solution of step 1 in a rapid mixer granulator.
3. The granules of step 2 were blended with cetostearyl alcohol and pregelatinized starch.
4. The blend of step 3 was compressed to obtain suitable sized tablets.
5. The tablets of step 4 were coated with Opadry[®] coating.

As a modification to the manufacturing process steps of Examples 1, 2, 3, and 4, the granulation step in all the examples was also carried out in a fluid bed granulator instead of a rapid mixer granulator.

15 Dissolution Study

Table 1 provides a comparison of the dissolution profile of sitagliptin in the pharmaceutical compositions of Examples 1, 2, 3, and 4 vis-à-vis Janumet[®] (sitagliptin 50 mg; metformin HCl 500 mg tablet). The dissolution was performed in 900 mL of 0.025M sodium chloride solution at 75 rpm using the USP type II (paddle) apparatus. The samples were analyzed by high performance liquid chromatography (HPLC) using an InertSustain[®] C18, 3 μ m, 150 mm x 4.6 mm, column and mobile phase having phosphate buffer pH 6.8 and acetonitrile in the ratio of 70:30. As seen from the results, the pharmaceutical compositions (Examples 1, 2, 3, and 4) prepared without the use of a surfactant and Janumet[®] tablets achieved the target dissolution profile of release of more than 85% of sitagliptin within 15 minutes, indicating that Janumet[®] tablets and the pharmaceutical compositions (Examples 1, 2, 3, and 4) have similar dissolution profiles.

Table 1: Percentage of sitagliptin released in the dissolution media (0.025 M sodium chloride solution).

Pharmaceutical Composition	Time point (in minutes)			
	10	15	20	30
Marketed tablet (Janumet [®])	74	90	96	98
Example 1	78	93	98	99
Example 2	72	90	97	99
Example 3	86	96	99	99
Example 4	85	96	98	98

We Claim:

- 1 1. A pharmaceutical composition consisting essentially of sitagliptin, metformin, and
2 a lubricant selected from the group consisting of glyceryl behenate, glyceryl
3 palmitostearate, stearyl alcohol, cetostearyl alcohol, or mixtures thereof, wherein
4 the pharmaceutical composition does not comprise a surfactant.
- 1 2. The pharmaceutical composition according to claim 1, wherein the sitagliptin is
2 sitagliptin phosphate and the metformin is metformin hydrochloride.
- 1 3. The pharmaceutical composition according to claim 1, wherein the lubricant is
2 present in an amount of about 0.01% to about 10% by weight of the
3 pharmaceutical composition.
- 1 4. A process for the preparation of a pharmaceutical composition according to claim
2 1, wherein the process comprises the steps of:
 - 3 a) blending sitagliptin and metformin;
 - 4 b) optionally mixing the blend of step a) with one or more pharmaceutically
5 acceptable excipients;
 - 6 c) dissolving or dispersing one or more pharmaceutically acceptable
7 excipients in a suitable solvent;
 - 8 d) granulating the blend of step a) or step b) with the solution or dispersion of
9 step c);
 - 10 e) blending the granules of step d) with a lubricant and optionally one or more
11 pharmaceutically acceptable excipients; and
 - 12 f) compressing the blend of step e) into suitable sized tablets or filling into
13 suitable sized capsules.
- 1 5. A process for the preparation of a pharmaceutical composition according to claim
2 1, wherein the process comprises:
 - 3 a) dissolving or dispersing sitagliptin and one or more pharmaceutically
4 acceptable excipients in a suitable solvent;
 - 5 b) granulating metformin with the solution or dispersion from step a);

- 6 c) blending the granules of step b) with a lubricant and optionally one or more
7 pharmaceutically acceptable excipients; and
- 8 d) compressing the blend of step c) into suitable sized tablets or filling into
9 suitable sized capsules.
- 1 6. The process for the preparation of a pharmaceutical composition according to
2 claim 4 or claim 5, wherein the granulation is carried out in a rapid mixer
3 granulator or a fluid bed granulator.
- 1 7. The pharmaceutical composition according to claim 1, wherein the pharmaceutical
2 composition is a tablet.
- 1 8. The pharmaceutical composition according to claim 1, wherein the pharmaceutical
2 composition is a film-coated tablet.
- 1 9. The pharmaceutical composition according to claim 1, wherein more than 80% of
2 sitagliptin is released in 15 minutes when the dissolution is performed in 900 mL
3 of 0.025M sodium chloride solution at 75 rpm using USP type II (paddle)
4 apparatus.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2014/060953

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K9/16 A61K9/20 A61K31/00
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, 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	WO 03/004009 A1 (GENEVA PHARMACEUTICALS INC [US]; MATHARU AMOL SINGH [US]; PATEL MAHEND) 16 January 2003 (2003-01-16)	1-9
Y	the whole document page 1, paragraph 1 page 7, lines 17-20 example 4 claims 1,2,6,7,10,18,28	1-9
Y	US 2012/202820 A1 (RIMKUS KATRIN [DE] ET AL) 9 August 2012 (2012-08-09) cited in the application the whole document example 3	1-9



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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Date of the actual completion of the international search

19 August 2014

Date of mailing of the international search report

27/08/2014

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Hilliers, Nathalie

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2014/060953

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2009/105265 A1 (KAMALI ASHKAN [US] ET AL) 23 April 2009 (2009-04-23) cited in the application claims 1,5; example 1 the whole document -----	1-9

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2014/060953

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