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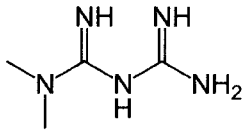
(54) **Title**: MICRONIZED METFORMIN

(57) **Abstract**: The present invention relates to pharmaceutical compositions comprising metformin that shall be used in the treatment of type 2 diabetes.

MICRONIZED METFORMIN

The present invention relates to pharmaceutical compositions comprising metformin that shall be used in the treatment of type 2 diabetes.

Metformin (Formula 1), chemical name of which is N,N-dimethylimidodicarbonimidic diamide, is a molecule belonging to biguanide class. Metformin was firstly disclosed in the application numbered US3174901. It is known that metformin is effective in the treatment of especially overweight and obese patients with type 2 diabetes who have healthy kidney functions. In different sources, it has been disclosed that said active agent can also be used in the treatment of polycystic ovary syndrome or different diseases caused by insulin resistance.



Formula 1

Metformin is available in metformin hydrochloride salt form as 500 mg, 750 mg and 1000 mg film coated tablet and prolonged release tablet forms on the market.

Bioavailability characteristics of products taken by the oral route are closely associated with dissolutions of the products. When the compositions having low dissolution are taken by patients, the active agent cannot reach therapeutically sufficient amounts in body resulting from insufficient dissolution of the active agent in body and this affects the treatment process negatively.

Furthermore, when the pharmaceutical compositions are formed into various dosage forms they are required to have content uniformity, in other words to comprise equal amount of active agent in unit dosage form. This depends on flow characteristics of the formulations prepared. Each unit dose of the formulations having desired flow characteristics comprises equal amount of the active agent.

As a result of the studies they conducted so as to improve dissolution profile and content uniformity characteristics of the formulations comprising metformin, the inventors have found that the pharmaceutical formulations wherein metformin having an average particle size (d_{50}) equal to or less than 15 μm is used have better dissolution and content uniformity of the

pharmaceutical compositions comprising metformin having an average particle size (d_{50}) equal to or less than 15 μm is ensured easily during preparation of the dosage forms.

In this respect, the present invention relates to pharmaceutical compositions comprising metformin having an average particle size (d_{50}) equal to or less than 15 μm.

In another aspect, the formulations of the present invention comprise metformin having an average particle size (d_{50}) preferably in the range of 1 μm to 15 μm, more preferably in the range of 3 μm to 12 μm.

The term ''average particle size'' refers to average particle size by volume and it is also shown with d_{50} in short. In this sense, the term d_{50} signifies that half of the said substance by volume has a particle size over the value stated with d_{50} and the other half of the substance by volume has a particle size below the value stated with d_{50}.

Metformin comprised in the pharmaceutical compositions of the present invention can be in the form of its pharmaceutically acceptable salts, hydrates, solvates, esters, enantiomers, diastereomers or combinations thereof. Metformin is preferably in the form of its salts, more preferably its hydrochloride salt.

D_{50} value can be measured with one of the known measuring devices, for instance with a device which measures particle distribution by laser diffraction (for instance, Malvern Mastersizer etc.).

Metformin of the present invention having a d_{50} value equal to or less than 15 μm can be bought and used as a product commercially provided in this manner. In addition, metformin having a d_{50} value equal to or less than 15 μm can also be obtained by pulverizing a product having coarser particle size singly or with an excipient (for instance microcrystalline cellulose etc.). At this point, pulverization can be performed by using the methods such as impact mill, jet mill, blade mill etc. Pulverization can be performed before preparation of the pharmaceutical composition comprising metformin as well as during preparation of the pharmaceutical composition of the present invention or before post-production storage of the pharmaceutical composition prepared.

In the case that blade mill is used, pulverization is performed by the effect of rotating blades in the device.

In the case that impact mill is used, pulverization is performed by the effect of rotating hammers in the device.

In the case that jet mill is used, pulverization is performed by providing collision of the particles with each other with the help of high-pressured and high-speed airstream.

The pharmaceutical compositions of the present invention comprising metformin having a d_{50} value equal to or less than 15 μm can be prepared in any dosage form such as tablet, effervescent tablet, effervescent granule, effervescent dry powder, film coated tablet, enteric-coated tablet, dry powder, granule, capsule, prolonged release tablet, modified release tablet, delayed release tablet.

The pharmaceutical compositions of the present invention comprising metformin having a d_{50} value equal to or less than 15 μm are preferably in tablet, prolonged release tablet, film coated tablet or effervescent tablet forms, more preferably in effervescent tablet form.

The pharmaceutical composition obtained can be formed into any dosage form stated above. In the case that the compositions are in tablet forms, the tablets obtained can be treated with film coating agents, for instance sugar based coating agents, water soluble film coating agents, enteric-coating agents, delayed release coating agents or coating compositions comprising any combination thereof.

Saccharose can be used singly or optionally with any of the agents such as talc, calcium, carbonate, calcium phosphate, calcium sulphate, gelatine, gum arabic, polyvinylpyrrolidone and pullulan or a combination thereof as sugar based coating agent.

The water soluble film coating agent can be selected from cellulose derivatives such as hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxyethyl cellulose, methyl hydroxyethyl cellulose and sodium carboxymethyl cellulose; synthetic polymers such as polyvinyl acetal diethyl aminoacetate, aminoalkyl methacrylate copolymers and polyvinylpyrrolidone and polysaccharides such as pullulan or combinations thereof.

The enteric-coating agents can be selected from cellulose derivatives such as hydroxypropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose acetate succinate, carboxymethyl ethyl cellulose, cellulose acetate phthalate, acrylic acid derivatives such as methacrylic acid copolymer L, methacrylic acid copolymer LD and methacrylic acid copolymer S and natural substances such as shellac or combinations thereof.

The delayed release coating agents can be selected from cellulose derivatives such as ethyl cellulose; acrylic acid derivatives such as aminoalkyl methacrylate copolymer RS, emulsion copolymer of ethyl acrylate-methyl methacrylate or combinations thereof.

In another aspect, the present invention relates to pharmaceutical compositions in effervescent tablet form comprising metformin having an average particle size (d_{50}) equal to or less than 15 μm.

The pharmaceutical compositions of the present invention comprising metformin having a d_{50} value equal to or less than 15 μm can comprise various excipients in addition to the active agent metformin.

The pharmaceutical compositions of the present invention comprising metformin having a d_{50} value equal to or less than 15 μm comprise at least one excipient selected from a group comprising disintegrant, diluent, lubricant, glidant, binder, effervescent couple comprising at least one acidic agent and at least one basic agent, colouring agent, pH regulating agent, surfactant, stabilizing agent, sweetener and/or taste regulating agent, flavouring agent in addition to the active agent metformin.

The disintegrant that can be used in the pharmaceutical compositions of the present invention comprising metformin having a d_{50} value equal to or less than 15 μm can be selected from a group comprising carboxymethyl cellulose, carboxymethyl cellulose calcium, carboxymethyl cellulose sodium, croscarmellose sodium, crospovidone, hydroxypropyl cellulose, microcrystalline cellulose, methyl cellulose, chitosan, starch, sodium starch glycolate.

The diluent that can be used in the pharmaceutical compositions of the present invention comprising metformin having a d_{50} value equal to or less than 15 μm can be selected from a group comprising calcium carbonate, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulphate, microcrystalline cellulose, dextrose, fructose, lactitol, lactose, magnesium carbonate, magnesium oxide, maltitol, maltodextrin, maltose, mannitol, simethicone, sorbitol, starch, sodium chloride, sucrose, talc, xylitol.

The lubricant that can be used in the pharmaceutical compositions of the present invention comprising metformin having a d_{50} value equal to or less than 15 μm can be selected from a group comprising calcium stearate, magnesium stearate, polyethylene glycol, sodium benzoate, potassium benzoate, sodium lauryl sulphate, talc, stearic acid, zinc stearate.

The glidant that can be used in the pharmaceutical compositions of the present invention comprising metformin having d_{50} value equal to or less than 15 μm can be selected from a group comprising tribasic calcium phosphate, colloidal silicone dioxide, magnesium silicate, magnesium trisilicate, talc.

The binder that can be used in the pharmaceutical compositions of the present invention comprising metformin having d_{50} value equal to or less than 15 μm can be selected from a group comprising carboxymethyl cellulose sodium, ethyl cellulose, gelatine, hydroxyethyl cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hypromellose, magnesium aluminium silicate, maltodextrin, methyl cellulose, povidone, starch.

The acidic agent composing the effervescent couple comprising at least one acidic agent and at least one basic agent that can be used in the pharmaceutical compositions of the present invention comprising metformin having a d_{50} value equal to or less than 15 μm can be selected from a group comprising organic acids such as malic acid, citric acid, tartaric acid, fumaric acid; and the basic agent can be selected from a group comprising agents such as sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogen carbonate.

The pH regulating agent that can be used in the pharmaceutical compositions of the present invention comprising metformin having a d_{50} value equal to or less than 15 μm can be selected from citrate, phosphate, carbonate, tartarate, fumarate, acetate and amino acid salts.

The surfactant that can be used in the pharmaceutical compositions of the present invention comprising metformin having a d_{50} value equal to or less than 15 μm can be selected from sodium lauryl sulphate, polysorbate, polyoxyethylene, polyoxypropylene glycol and similar agents.

The stabilizing agent that can be used in the pharmaceutical compositions of the present invention comprising metformin having a d_{50} value equal to or less than 15 μm can be selected from a group comprising tocopherol, tetrasodium edetate, nicotinamide, cyclodextrin.

The sweetener and/or taste regulating agent that can be used in the pharmaceutical compositions of the present invention comprising metformin having a d_{50} value equal to or less than 15 μm can be selected from a group comprising acesulfame, aspartame, dextrose, fructose, maltitol, maltose, mannitol, saccharine, saccharine sodium, sodium cyclamate, sorbitol, sucralose, sucrose, xylitol, sodium chloride.

The flavouring agent that can be used in the pharmaceutical compositions of the present invention comprising metformin having a d_{50} value equal to or less than 15 μm can be selected from a group comprising menthol, lemon, orange, vanilla, strawberry, raspberry, caramel and similar flavours.

The pharmaceutical compositions of the present invention comprising metformin having a d_{50} value equal to or less than 15 μm can comprise metformin in the range of 0.1 to 100% by weight, preferably in the range of 1 to 99% by weight, preferably in the range of 5 to 95% by weight and more preferably in the range of 10 to 50% by weight

In another aspect, the present invention relates to pharmaceutical compositions comprising metformin having a d_{90} value equal to or less than 50 μm. The inventors have observed that the active agent and the excipients are mixed homogeneously during preparation of the pharmaceutical compositions comprising metformin having a d_{90} value equal to or less than 50 μm and as a result of this, each unit dosage form prepared with the formulation comprises equal amount of active agent.

According to this, the present invention relates to pharmaceutical compositions comprising metformin having a d_{90} value equal to or less than 50 μm.

D_{90} value of metformin comprised in the pharmaceutical compositions of the present invention is equal to or less than 50 μm, preferably in the range of 1 to 50 μm, more preferably in the range of 5 to 45 μm.

In another aspect, the present invention relates to pharmaceutical compositions comprising metformin having a d_{50} value equal to or less than 15 μm and a d_{90} value equal to or less than 50 μm.

The term d_{90} signifies that 90% of the said substance by volume has a particle size below the stated value and 10% of the said substance by volume has a particle size over the stated value.

The pharmaceutical compositions of the present invention comprising metformin having a d_{50} value equal to or less than 15 μm can optionally comprise a second active agent in addition to metformin. The second active agent can be selected from antacid, anticholinergic, antispasmodic, antiemetic, antibiotic, antipropulsive, antiallergic, antidiarrheal, antiobesity, antithrombotic, antifibrinolytic, antianemic, antihypertensive, antifungal, antipruritic, antipsoriatic, antibiotic, antiseptic, antiacne, antibacterial, antimycotic, antiviral,

antineoplastic, antiarrhythmic, antiadrenergic, antiepileptic, anti-parkinson, antiprotozoal, anthelmintic, anti-inflammatory, diuretic, laxative, sulphonamide, imidazole, corticosteroid, thiazolidinedione, biguanide, immunostimulant, immunosuppressant, myorelaxant, analgesic, psycholeptic, psychoanaleptic peripheral vasodilator, beta blocker, calcium channel blocker and lipid modifying agents; alpha-glucosidase inhibitors, aldose reductase inhibitors, ACE inhibitors; multivitamin and minerals, vitamin A, vitamin D and its analogues, vitamin B_1, vitamin C, vitamin E, vitamin B_6, vitamin B_2, vitamin K, calcium, potassium, sodium, zinc, magnesium, fluoride, selenium.

The pharmaceutical compositions of the present invention comprising metformine having a d_{50} value equal to or less than 15 μm can optionally comprise a second active agent in addition to metformine. The second active agent can be selected from a group comprising meglitinides, alpha-glucosidase inhibitors, sulfonylureas, thiazolidinediones, biguanides, dipeptidyl peptidase-4 inhibitors.

In another aspect, said second active agent can be selected from a group comprising agents such as repaglinide, nateglinide belonging to meglitinide group; alpha-glucosidase inhibitor acarbose; acetohexamide, glindeklamid, glibornuride, gliclazide, gliquidone, glimepiride, glipizide, glibenclamide, chlorpropamide, tolbutamide belonging to sulfonylurea group; pioglitazone, rosiglitazone, rivoglitazone, rosiglitazone maleate, pioglitazone hydrochloride, troglitazone belonging to thiazolidinedione group; phenformin or a pharmaceutically acceptable salt thereof belonging to biguanide group; dipeptidyl peptidase-4 inhibitors sitagliptin, vildagliptin, saxagliptin, saxagliptin hydrochloride, sitagliptin phosphate, sitagliptin phosphate monohydrate.

Optionally, the pharmaceutical compositions of the present invention comprising metformin having a d_{50} value equal to or less than 15 μm can preferably comprise a second active agent belonging to meglitinide group, more preferably comprise nateglinide or rapeglinide as a second active agent in addition to metformin.

The pharmaceutical composition of the present invention can be obtained by

- mixing the active agent metformin and, if available, the second active agent homogeneously and adding at least one of the excipients stated above if required or
- mixing the active agent metformin and, if available, the second active agent homogeneously after granulated with at least one of the excipients or

- mixing the active agent metformin and, if available, the second active agent with at least one of the excipients and at least one of the excipients stated above and optionally granulating them with the granulation solution comprising excipient or,
- a method composed of using any method mentioned above separately for the active agent compositions and combining the formulations obtained in the case that two active agents are used.

The pharmaceutical composition of the present invention can be used in prevention and treatment of type 2 diabetes.

EXAMPLE 1: Tablet formulation comprising metformin

Metformin Tablet Formulation	
Active agent	% of amount (by weight)
Metformin hydrochloride (d_{50} = 9 μm)	15
Excipients	
Lubricant	2
Glidant	4
Organic base	15
Organic acid	5
Other excipients	59

Metformin hydrochloride, organic base, organic acid are mixed and granulated. The granules obtained are mixed with the excipients after dried. The glidant is added into the mixture obtained and mixed. The lubricant is added into the final mixture and the pharmaceutical composition obtained is compressed in tablet compression machine.

EXAMPLE 2: Tablet formulation comprising metformin

Metformin Tablet Formulation	
Active Agent	% of amount (by weight)
Metformin hydrochloride (d_{90} = 35 μm)	30
Excipients	

Lubricant	2
Glidant	3
Organic base	20
Organic acid	10
Other excipients	35

Metformin hydrochloride, organic base, organic acid are mixed. The excipients and the glidant are added into the mixture obtained. Then, the lubricant is added into the final mixture and the pharmaceutical composition obtained is compressed in tablet compression machine.

CLAIMS

1. A pharmaceutical composition comprising metformin, characterized in that the average particle size (d_{50}) of metformin is equal to or less than 15 μm.
2. The pharmaceutical composition comprising metformin according to claim 1, characterized in that the average particle size (d_{50}) of metformin is in the range of 1 μm to 15 μm.
3. The pharmaceutical composition comprising metformin according to claims 1 and 2, characterized in that the average particle size (d_{50}) of metformin is in the range of 3 μm and 12 μm.
4. The pharmaceutical composition comprising metformin according to any preceding claims, wherein said composition is prepared in any of the dosage forms of tablet, effervescent tablet, effervescent granule, effervescent dry powder, film coated tablet, enteric-coated tablet, dry powder, granule, capsule, prolonged release tablet, modified release tablet, delayed release tablet.
5. The pharmaceutical composition comprising metformin according to claim 4, wherein said formulation is in effervescent tablet, prolonged release tablet, film coated tablet forms.
6. The pharmaceutical composition comprising metformin according to any preceding claims, wherein metformin is in the form of its pharmaceutically acceptable salts, hydrates, solvates, esters, enantiomers, disastereomers or combinations thereof.
7. The pharmaceutical composition comprising metformin according to any preceding claims, wherein metformin is in the form of its pharmaceutically acceptable salt.
8. The pharmaceutical composition comprising metformin according to any preceding claims, wherein metformin is in metformin hydrchloride form.
9. The pharmaceutical composition comprising metformin according to any preceding claims, wherein said composition comprises pharmaceutically acceptable excipients along with metformin having an average particle size (d_{50}) equal to or less than 15 μm used as active agent.
10. The pharmaceutical composition comprising metformin according to claim 9, wherein said composition comprises at least one excipient selected from a group comprising disintegrant, diluent, lubricant, glidant, binder, effervescent couple comprising at least one acidic agent and at least one basic agent, colouring agent, pH regulating agent, surfactant, stabilizing agent, sweetener and/or taste regulating agent, flavouring agent along with

metformin having an average particle size (d_{50}) equal to or less than 15 μm used as active agent.

11. The pharmaceutical composition comprising metformin according to any preceding claims, wherein said composition comprises metformin having an average particle size (d_{50}) equal to or less than 15 μm in the range of 0.1 to 100% by weight used as active agent.

12. The pharmaceutical composition comprising metformin according to any preceding claims, wherein said composition comprises metformin having an average particle size (d_{50}) equal to or less than 15 μm in the range of 1 to 99% by weight used as active agent.

13. The pharmaceutical composition comprising metformin according to any preceding claims, wherein said composition comprises metformin having an average particle size (d_{50}) equal to or less than 15 μm in the range of 5 to 95% by weight used as active agent.

14. The pharmaceutical composition comprising metformin according to any preceding claims, wherein said composition comprises metformin having an average particle size (d_{50}) equal to or less than 15 μm in the range of 10 to 50% by weight used as active agent.

15. The pharmaceutical composition comprising metformin according to any preceding claims, wherein said composition comprises at least one second active agent selected from a group comprising antacid, anticholinergic, antispasmodic, antiemetic, antibiotic, antipropulsive, antiallergic, antidiarrheal, antiobesity, antithrombotic, antifibrinolytic, antianemic, antihypertensive, antifungal, antipruritic, antipsoriatic, antibiotic, antiseptic, antiacne, antibacterial, antimycotic, antiviral, antineoplastic, antiarrhythmic, antiadrenergic, antiepileptic, anti-parkinson, antiprotozoal, anthelmintic, anti-inflammatory, diuretic, laxative, sulphonamide, imidazole, corticosteroid, thiazolidinedione, biguanide, immunostimulant, immunosuppressant, myorelaxant, analgesic, psycholeptic, psychoanalytic peripheral vasodilator, beta blocker, calcium channel blocker and lipid modifying agents; alpha-glucosidase inhibitors, aldose reductase inhibitors, ACE inhibitors; multivitamin and minerals, vitamin A, vitamin D and its analogs, vitamin B_1, vitamin C, vitamin E, vitamin B_6, vitamin B_2, vitamin K, calcium, potassium, sodium, zinc, magnesium, fluoride, selenium in addition to metformin.

16. The pharmaceutical composition comprising metformin according to claim 15, wherein said composition comprises at least a second active agent selected from a group comprising meglitinides, alpha-glucosidase inhibitors, sulfonylureas, thiazolidinediones, biguanides, dipeptidyl peptidase-4 inhibitors in addition to metformin.

17. The pharmaceutical composition comprising metformin according to claim 16, wherein said composition comprises at least a second active agent selected from a group comprising the agents repaglinide, nateglinide belonging to meglitinide group; alpha-glucosidase inhibitor acarbose; acetohexamide, glindeklamid, glibornuride, gliclazide, gliquidone, glimepiride, glipizide, chlorpropamide, glibenclamide, tolbutamide belonging to sulfonylurea group; pioglitazone, rosiglitazone, rivoglitazone, rosiglitazone maleate, pioglitazone hydrochloride, troglitazone belonging to thiazolidinedione group; phenformin, metformin belonging to biguanide group; dipeptidyl peptidase-4 inhibitors sitagliptin, vildagliptin, saxagliptin, saxagliptin hydrochloride, sitagliptin phosphate, sitagliptin phosphate monohydrate in addition to metformin.

18. The pharmaceutical composition comprising metformin, characterized in that d_{90} value of metformin comprised in the composition is equal to or less than 50 μm.

19. The pharmaceutical composition comprising metformin according to claim 18, characterized in that d_{90} value of metformin comprised in the composition is in the range of 1 to 50 μm.

20. The pharmaceutical composition comprising metformin according to claim 19, characterized in that d_{90} value of metformin comprised in the composition is in the range of 5 to 45 μm.

INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2012/000153

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/14 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, BIOSIS, CHEM ABS Data, EMBASE, WPI 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 2007/131930 A1 (BOEHRINGER INGELHEIM INT [DE]; BOEHRINGER INGELHEIM PHARMA [DE]; WADA) 22 November 2007 (2007-11-22) page 2, lines 1-5 page 3, lines 19-21 page 6, line 20 - page 8, line 16; claims 1,4; examples -----	1-20
X	WO 2008/101943 A1 (GUIDOTTI & C SPA LABOR [IT]; VALLERI MAURIZIO [IT]) 28 August 2008 (2008-08-28) page 2, lines 2-13 page 4, line 7 - page 7, line 32; claims 1,3,11; examples ----- -/--	1-20

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

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 March 2013	11/03/2013

Name and mailing address of the ISA/	Authorized officer
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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2012/000153

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 738 754 A1 (TAKEDA PHARMACEUTICAL [JP]) 3 January 2007 (2007-01-03) paragraphs [0006], [0016], [0017], [0020], [0038] - [0039], [0047] - [0049]; claims 1,3,4,6 -----	1-11, 15-20

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/TR2012/000153

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007131930 A1	22-11-2007	EP 2026787 A1	25-02-2009
		JP 2009537478 A	29-10-2009
		US 2009252790 A1	08-10-2009
		US 2012012499 A1	19-01-2012
		WO 2007131930 A1	22-11-2007
WO 2008101943 A1	28-08-2008	NONE	
EP 1738754 A1	03-01-2007	CA 2562391 A1	27-10-2005
		EP 1738754 A1	03-01-2007
		JP 4739189 B2	03-08-2011
		US 2007166376 A1	19-07-2007
		WO 2005099760 A1	27-10-2005