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(54) Title: A NOVEL MODIFIED RELEASE PHARMACEUTICAL COMPOSITION OF SITAGLIPTIN OR PHARMACEUTICALLY ACCEPTABLE SALT THEREOF

(57) Abstract: The present invention relates to a novel modified release pharmaceutical composition of sitagliptin or pharmaceutically acceptable salt thereof. In particular the present invention relates to a novel modified release composition of sitagliptin or pharmaceutically acceptable salt thereof that achieves desired minimum effective plasma concentration of the sitagliptin sufficient for effective glycemic control in patients with type 2 diabetes mellitus. A method of improving glycemic control in adults with type 2 diabetes mellitus and reducing or eliminating fluctuations in plasma concentration of sitagliptin is also provided by the present invention.

A NOVEL MODIFIED RELEASE PHARMACEUTICAL COMPOSITION OF SITAGLIPTIN OR PHARMACEUTICALLY ACCEPTABLE SALT THEREOF

This patent application claims priority to Indian Provisional Patent Application number 2421/MUM/2014 (filed on Jul 26, 2014), the contents of which are incorporated by reference herein.

Field Of The Invention

The present invention relates to a novel modified release pharmaceutical composition comprising sitagliptin or pharmaceutically acceptable salt thereof. By providing a novel modified release composition of sitagliptin or pharmaceutically acceptable salt thereof, it is possible to achieve desired minimum effective plasma concentration of sitagliptin that is sufficient for effective glycemic control in patients with type 2 diabetes mellitus. The invention further provides a method of improving glycemic control in adults with type 2 diabetes mellitus and reducing or eliminating fluctuations in plasma concentration of sitagliptin by using such composition. A method for the preparation of such composition is also described.

Background Of The Invention

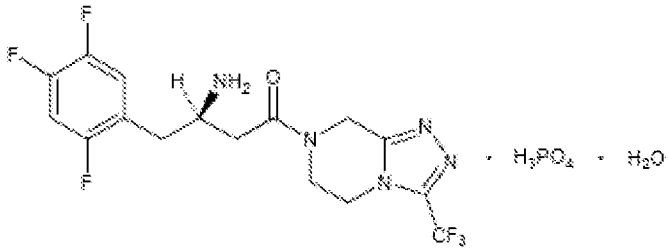
Type 2 diabetes is the most common form of diabetes and it is one of the most prevalent chronic diseases. Treatment of type 2 diabetes mellitus (T2DM) initially starts with diet and exercise, followed by oral antidiabetic monotherapy. During long-term treatment these regimens do not sufficiently control hyperglycemia in many patients, leading to a requirement for combination therapy within several years following diagnosis.

Drugs of choice for combination therapy include biguanides, DPP-IV inhibitors, sulfonylurea, thiazolidinedione, alphaglucosidase inhibitor, amylin analog, glucagon-like peptide-1 (GLP-1) or incretin mimetic, meglitinide and insulin. Out

of these classes of drugs, biguanides and DPP-IV inhibitors are preferred choices for management of type 2 diabetes in the recent past. As the DPP-IV inhibitors are specific to reduction of post-prandial elevated glucose level as opposed to the lack of effect on the resting glucose level, combining them with biguanide is preferred.

Dipeptidyl peptidase IV (DPP-IV) inhibitors act by inhibiting dipeptidyl peptidase IV (DPP-IV) enzyme, a multifunctional transmembrane glycoprotein enzyme that cleaves N-terminal dipeptides from polypeptides with L-proline or L-alanine at the penultimate position. The selectivity of DPP-IV inhibitors against other closely-related proline-specific dipeptidyl peptidases, particularly DPP-8 and DPP-9, has been a potential for adverse events associated with non-selective DPP-IV inhibitors. The inhibition of DPP-8 and DPP-9 has been found to be associated with toxicities in rat and dog (Lankas, G. R., et al. Diabetes, 2005; 54:2988-2994). Therefore, it is important to demonstrate that DPP-IV inhibitors do not appreciably inhibit these closely related enzymes.

Sitagliptin is an orally-active DPP-IV enzyme inhibitor, available as monohydrate of its phosphate salt. Chemically, monohydrate of sitagliptin phosphate is 7-[(3R)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8tetrahydro-3- (trifluoromethyl) -1,2,4-triazolo [4,3-α] pyrazine phosphate (1:1) monohydrate with the following structure:



It is marketed in United States in the form of tablets under brand name Januvia®. Fixed dose combination of sitagliptin phosphate with metformin is also available under the brand name Janumet® which exhibits immediate release of both sitagliptin and metformin.

There are several drug combinations commercially available for management of T2DM.

U.S. Patent number US 6,099,862 discloses controlled release tablet containing metformin and glipizide.

U.S. Patent RE44,186 discloses a method of treatment for T2DM using DPP-IV inhibitor and one or more other antidiabetic agents such as metformin, glyburide, troglitazone, pioglitazone and rosiglitazone.

U.S. Patent 8,414,921 discloses pharmaceutical compositions comprising fixed-dose combinations of a DPP-IV inhibitor and metformin.

U.S. Publication number 20070172525 and 20080064701 discloses pharmaceutical compositions comprising an immediate-release DPP-IV inhibitor and a slow-release form of metformin.

U.S. Patent 8,329,217 discloses a controlled release osmotic device containing a bi-layered core of at least two different active agents which provides therapeutically effective levels of both the actives for an extended period of time following oral administration.

U.S. Publication number 20130059002 discloses a pharmaceutical composition comprising metformin and sitagliptin or pharmaceutically acceptable salt thereof in two separate compartments. The document also discloses a combination composition comprising an extended release metformin HCl and an extended release sitagliptin.

European patent publication number EP 1,537,880 A1 relates to a sustained release formulation of DPP-IV inhibitor comprising a hydrophilic polymer.

Even though antidiabetic combinations have been proven effective for diabetes management, existing once daily formulations still may fall short by exhibiting sub-therapeutic plasma concentrations or expose to undesired higher plasma concentrations of antidiabetic agents than that required for safe glycemic control and may ultimately failing to provide round the clock diabetes management. This variation in plasma levels of the antidiabetic agents may be attributed to their varying solubilities, different physiological targets and pharmacokinetic (PK) profiles.

Despite of its therapeutic benefits, strong inhibition of DPP-IV activity by DPP-IV inhibitors in living organisms potentiates the vasodilating action of substance P. Moreover, DPP-IV activity of nasal mucosa and the density of inflammatory cells in nasal mucosa of patients with chronic rhinosinusitis are in a reverse correlation and DPP-IV activity increases when chronic rhinosinusitis was cured (FASEB, 2002; 16:1132-1134). Therefore, strong inhibition of DPP-IV activity in diabetic patients with concurrent chronic inflammation is not considered preferable as it may cause aggravation of the inflammation. It was also reported that an interferon-α treatment of patients with hepatitis C is characterized by decrease in serum DPP-IV activity and the treatment is associated with side effects such as depression and anxiety. Therefore, the severity of depression and anxiety can be correlated with decreased serum DPP-IV activity (Mol. Psychiatry, 2001, 6:475-480) and which may be aggravated further by strong DPP-IV inhibition.

The developmental report of Januvia® 100 mg submitted to EMEA demonstrates relation between plasma concentration of sitagliptin and its pharmacokinetic or pharmacodynamic profile. In report, a single dose study of sitagliptin in T2DM patients suggested that near-maximal reduction of post-challenge glucose excursion was associated with three factors, viz. sitagliptin plasma concentrations of approximately 100 nM or higher, plasma DPP-IV inhibition of 80% or higher, and augmentation of post-challenge active GLP-1 levels of 2-fold

or higher. It was further reasoned that for optimal chronic glucose lowering in T2DM patients, plasma DPP-IV inhibition should be 80% or greater at steady state trough. According to the report, once daily single dose administration of immediate release sitagliptin phosphate 100mg (Januvia®) tablet provides a maximum plasma concentration (C_{max}) of 950 nM within 1.3 hours that decreases to less than 100 nM by 24 hours post administration which leads to the following two issues.

Firstly, as the EC_{80} for sitagliptin is 100 nM, the plasma concentration of below 100 nM achieved by 24 hours post administration of 100 mg dose of Januvia® is sub-therapeutic, which may lead to loss of glycemic control for about last 4 hours with current once daily dosage regimen. Such inadequate glycemic control of about 4 hours after each dose administration may be seen until the steady state plasma concentration is achieved on 10^{th} day of the once daily dosage regimen. Such inadequate glycemic control should be avoided for effective management of T2DM.

Secondly, the 100 mg immediate release dosage form leads to essentially non required maximum plasma concentration of about 950 nM within 1.3 hours post administration, since the maximal DPP-IV inhibition occurs at about 125 nM. Such higher plasma concentration achieved by the 100 mg immediate release dosage may aggravate inflammation or lead to depression and anxiety which are not desirable for the diabetic patient as mentioned above.

Sitagliptin has average renal clearance of 350 ml/min and volume of distribution of about 198 liters. As sitagliptin is cleared off body mainly through kidney, its dose adjustment prior to initiation of therapy and periodically thereafter is essential in renal function compromised patients and becomes even more essential due to role of renal function in diabetic patients. Specifically patient with renal insufficiency is prescribed lesser dose of sitagliptin than that to normal patient.

Thus, as a result, the existing sitagliptin products may suffer from three issues, firstly causing hyperglycemia in last few hours (e.g. last eight hours) of the day post administration causing hyperglycemia, secondly exposing the patient for several initial hours to essentially non required maximum plasma concentration following administration, and thirdly require renal function monitoring before and during treatment.

None of the currently available therapies, however, address the requirement of providing better glycemic control for 24 hours after single dose administration and reducing the side-effects due to undesirably higher C_{max} of sitagliptin achieved by the current marketed dosage form. Hence, there still exists an enduring need for alternate and improved compositions of sitagliptin which may address aforesaid objectives for effective T2DM management.

Summary Of The Invention

In one general aspect, there is provided a modified release composition comprising sitagliptin or pharmaceutically acceptable salt thereof and optionally, at least one antidiabetic agent, wherein sitagliptin in the composition inhibits activity of DPP-IV enzyme by 80% or more over a period of at least 24 hours after oral administration of single dose of the composition to a subject.

In another general aspect, there is provided a modified release composition comprising sitagliptin or pharmaceutically acceptable salt thereof; one or more rate controlling excipients and optionally, at least one antidiabetic agent, wherein sitagliptin in the composition inhibits activity of DPP-IV enzyme by 80% or more over a period of at least 24 hours after oral administration of single dose of the composition to a subject.

In another general aspect, there is provided a modified release composition comprising sitagliptin or pharmaceutically acceptable salt thereof and optionally, at least one antidiabetic agent, wherein once daily administration of said composition to a subject achieves mean steady state plasma concentration (C_{ss}) of sitagliptin on or before 7 days.

In another general aspect, sitagliptin in the composition exhibit modified release so as to inhibit activity of DPP-IV enzyme by 80% or more over a period of at least 24 hours after oral administration of single dose of the composition to a subject.

In another general aspect, there is provided a modified release composition comprising about 25mg to about 100mg sitagliptin or pharmaceutically acceptable salt thereof and optionally, at least one antidiabetic agents, wherein once daily administration of said composition to a subject inhibit activity of DPP-IV enzyme by 80% or more over a period of at least 24 hours.

In another general aspect, there is provided a modified release composition comprising sitagliptin or pharmaceutically acceptable salt thereof and optionally, at least one antidiabetic agent wherein a substantial dose of sitagliptin in the composition exhibit zero order release over a period of at least 24 hours after oral administration of single dose of the composition.

In another general aspect, antidiabetic agent in the modified release composition exhibit immediate and/or extended release from said composition.

In another general aspect, total dose of the sitagliptin in modified release composition is divided into an immediate release part and an extended release part.

In another general aspect, the extended release part of sitagliptin in the modified release composition exhibits zero order release.

In another general aspect, the modified release composition of sitagliptin further comprises two antidiabetic agents.

In another general aspect, there is provided a modified release composition comprising:
(a) sitagliptin or pharmaceutically acceptable salt thereof,
(b) at least one biguanide or pharmaceutically acceptable salt thereof, and
(c) optionally one or more α-glucosidase inhibitors or pharmaceutically acceptable salt thereof;
wherein a substantial dose of sitagliptin in the composition exhibit zero order release over at least 24 hours after oral administration of single dose of the composition to a subject.

In another general aspect, there is provided a modified release composition comprising:
(a) sitagliptin or pharmaceutically acceptable salt thereof,
(b) at least one biguanide or pharmaceutically acceptable salt thereof; and
(c) optionally one or more α-glucosidase inhibitors or pharmaceutically acceptable salt thereof;
wherein once daily administration of the composition achieves mean steady state plasma concentration (C_{ss}) of sitagliptin on or before 7 days.

Additional antidiabetic agents may be selected from DPP-IV inhibitors, insulin sensitizers, α-glucosidase inhibitors, biguanides, insulin secretagogues, sodium-glucose co-transporter-2 (SGLT-2) inhibitors, β3 agonists, GPR40 agonists, GLP-1 receptor agonists, amylin agonists, phosphotyrosine phosphatase inhibitors, gluconeogenesis inhibitors, 11 β -hydroxysteroid dehydrogenase inhibitors,

adiponectin or agonist thereof, IKK inhibitors, leptin resistance improving drugs, somatostatin receptor agonists, and glucokinase activators.

Suitable biguanides may be selected from metformin, buformin, phenformin or pharmaceutically acceptable salt thereof.

Suitable insulin secretagogues may be selected from acetohexamide, chlorpropamide, tolbutamide, tolazamide, glipizide, glybuzole, gliclazide, glibenclamide, gliquidone, glyclopyramide, glimepiride, neteglinide, repaglinide, mitiglinide or pharmaceutically acceptable salt thereof.

Suitable sodium-glucose co-transporter-2 (SGLT-2) inhibitors may be selected from dapagliflozin, canagliflozin, ipragliflozin, tofogliflozin, empagliflozin, sergliflozin, remogliflozin, ertugliflozin, luseogliflozin, atigliflozin or pharmaceutically acceptable salt thereof.

Suitable α-glucosidase inhibitors may be selected from voglibose, acarbose, miglitol, emiglitate or pharmaceutically acceptable salt thereof.

Suitable GPR40 agonists may be selected from AMG 837, TAK-875 or pharmaceutically acceptable salt thereof.

Suitable GLP-1 receptor agonists may be selected from AMG 837, TAK-875, NN-2211, exendin-4, BIM-51077, CJC-1131 or pharmaceutically acceptable salt thereof.

Suitable gluconeogenesis inhibitors may be selected from glycogen phosphorylase inhibitor, glucose-6-phosphatase inhibitor, glucagon antagonist or pharmaceutically acceptable salt thereof.

In another general aspect, amylin agonist is pramlintide, phosphotyrosine phosphatase inhibitor is sodium vanadate, 11 β -hydroxysteroid dehydrogenase inhibitor is BVT-3498 and glucokinase activators is Ro-28-1675 or pharmaceutically acceptable salt thereof.

In another general aspect, there is provided a modified release composition comprising sitagliptin or pharmaceutically acceptable salt thereof and optionally, at least one antidiabetic agents, wherein the composition maintains mean plasma concentration of sitagliptin in the range of about 100 nM to about 850 nM over a period of at least 24 hours after oral administration of single dose of the composition to a subject.

In another general aspect, there is provided a modified release composition comprising sitagliptin or pharmaceutically acceptable salt thereof and optionally, at least one antidiabetic agents, wherein the composition provides mean plasma concentration of sitagliptin in the range of about 100 nM to about 850 nM over a period of at least 24 hours after oral administration of single dose of the composition to a subject.

In another general aspect, there is provided a modified release composition comprising:

(a) sitagliptin or pharmaceutically acceptable salt thereof, and

(b) optionally at least one antidiabetic agent or pharmaceutically acceptable salt thereof;

wherein the composition provides mean plasma concentration of sitagliptin or pharmaceutically acceptable salt thereof in the range of about 100 nM to about 850 nM over a period of at least 24 hours after oral administration of single dose of the composition.

In another general aspect, there is provided a modified release composition comprising:

(a) sitagliptin or pharmaceutically acceptable salt thereof;

(b) one or more rate controlling excipients and
(c) optionally at least one antidiabetic agent or pharmaceutically acceptable salt thereof;
wherein the composition provides mean plasma concentration of sitagliptin or pharmaceutically acceptable salt thereof in the range of about 100 nM to about 850 nM over a period of at least 24 hours after oral administration of single dose of the composition.

In another general aspect, there is provided a modified release composition comprising:
(a) sitagliptin or pharmaceutically acceptable salt thereof,
(b) metformin or pharmaceutically acceptable salt thereof, and
(c) voglibose or pharmaceutically acceptable salt thereof;
wherein the composition provides mean plasma concentration of sitagliptin or pharmaceutically acceptable salt thereof in the range of about 100 nM to about 850 nM over a period of at least 24 hours after oral administration of single dose of the composition to a subject.

In another general aspect, the modified release composition comprises about 25mg to about 100mg sitagliptin or equivalent amount of its pharmaceutically acceptable salt.

In another general aspect, the dose of sitagliptin or equivalent amount of its pharmaceutically acceptable salt administered through the modified release composition for treatment of type 2 diabetes mellitus in the renal function compromised patient is about 25 mg or 50 mg. The individual dose can be adjusted based on the renal function assessment.

In another general aspect, there is provided a modified release composition comprising about 25mg to about 100mg sitagliptin or pharmaceutically acceptable salt thereof and optionally, at least one antidiabetic agents, wherein

once daily administration of said composition to a subject provides a mean steady state maximum plasma concentration ($C_{ss(max)}$) of sitagliptin in the range of about 350 nM to about 750 nM after oral administration of single dose of the composition to a subject.

In another general aspect, there is provided a modified release composition comprising 100 mg sitagliptin or pharmaceutically acceptable salt thereof and optionally, at least one antidiabetic agents, wherein the composition exhibit a mean steady state minimum plasma concentration ($C_{ss\ (min)}$) of sitagliptin in the range of about 200 nM to about 500 nM after oral administration of single dose of the composition to a subject.

In another general aspect, there is provided a modified release composition comprising sitagliptin or pharmaceutically acceptable salt thereof and optionally, at least one antidiabetic agent, wherein said composition exhibit an in vitro release profile such that about 30% to about 70% of sitagliptin is dissolved within 8 hour and/or about 50% to about 90% of sitagliptin is dissolved within 16 hour after placement of the composition in a dissolution test conducted according to USP, using USP Apparatus I at 100 rpm and a dissolution medium of water at about 37°C.

In a further general aspect, the modified release composition comprises 100 mg sitagliptin or pharmaceutically acceptable salt thereof wherein the composition comprises 10mg to 50mg of sitagliptin in immediate release part and 50 mg to 90 mg of sitagliptin in extended release part.

In another general aspect, the modified release composition comprises 100 mg sitagliptin or pharmaceutically acceptable salt thereof and provides mean plasma concentration in the range of about 100 nM to about 400 nM, after 4 hours of oral administration of single-dose of the composition to a subject.

In another general aspect, the modified release composition comprises 100 mg sitagliptin or pharmaceutically acceptable salt thereof and provides a mean plasma concentration of sitagliptin or pharmaceutically acceptable salt thereof in the range of about 150 nM to about 350 nM after 8 hours of single dose administration of said composition to a subject.

In another general aspect, the modified release composition comprises 100 mg sitagliptin or pharmaceutically acceptable salt thereof and provides a mean plasma concentration of sitagliptin or pharmaceutically acceptable salt thereof in the range of about 200 nM to about 320 nM after 12 hours of single dose administration of said composition to a subject.

In another general aspect, the modified release composition comprises 100 mg sitagliptin or pharmaceutically acceptable salt thereof and provides a mean plasma concentration of sitagliptin or pharmaceutically acceptable salt thereof in the range of about 180 nM to about 370 nM after 20 hours of single dose administration of said composition to a subject.

In another general aspect, there is provided a modified release composition comprising:
(a) at least one component exhibiting extended release of sitagliptin or pharmaceutically acceptable salt thereof;
(b) at least one component exhibiting extended release of metformin or pharmaceutically acceptable salt thereof, and optionally
(c) at least one component exhibiting immediate release of metformin and/or sitagliptin or salt thereof;
wherein the composition maintains mean plasma concentration of sitagliptin or pharmaceutically acceptable salt thereof in the range of about 100 nM to about 850 nM over a period of at least 24 hours after oral administration of single dose of said composition to a subject.

In another general aspect, the minimum therapeutically effective plasma concentration of sitagliptin and optionally, at least one antidiabetic agent in the modified release composition is achieved by their osmotically controlled release from the composition.

In another general aspect, the modified release composition is in the form of an osmotic dosage form.

In another general aspect, the modified release composition comprises: (i) a semipermeable wall provided around an osmotic formulation comprising sitagliptin or pharmaceutically acceptable salt thereof, optionally at least one antidiabetic agent or pharmaceutically acceptable salt thereof, an osmotic agent, and an osmopolymer; and (ii) a passageway.

In another general aspect, there is provided a method of reducing side effects associated with increased plasma concentration of sitagliptin in a patient undergoing T2DM treatment, which method comprises of orally administering single dose of a modified release composition comprising sitagliptin or pharmaceutically acceptable salt thereof and optionally, at least one antidiabetic agent or pharmaceutically acceptable salt thereof, wherein a substantial dose of sitagliptin in the composition exhibit zero order release over a period of at least 24 hours.

In another general aspect, there is provided a method of treating type 2 diabetes mellitus comprising administration of the modified release composition to a subject in need thereof as substantially described herein before.

BRIEF DESCRIPTION OF THE FIGURES

FIGURE 1 is a graph showing plasma concentration profile of Januvia®, 100 mg tablet in fasting conditions.

FIGURE 2 is a graph showing plasma concentration profile of Januvia®, 100 mg tablet in fed conditions.

FIGURE 3 is a graph showing comparative plasma concentration profile of Januvia®, 100 mg tablet (Innovator) and 3 different modified release compositions of the invention (Test, viz. 10 mg + 90 mg ER, 25 mg + 75 mg ER and 50 mg IR + 50 mg ER).

FIGURE 4 is a graph showing simulated plasma concentration profile of modified release 100 mg sitagliptin composition with 10 mg of immediate release part and 90 mg of extended release part.

FIGURE 5 is a graph showing simulated plasma concentration profile of modified release 100 mg sitagliptin composition with 25 mg of immediate release part and 75 mg of extended release part.

FIGURE 6 is a graph showing simulated plasma concentration profile of modified release 100 mg sitagliptin composition with 50 mg of immediate release part and 50 mg of extended release part.

Detailed Description Of The Invention

The inventors of the present invention have surprisingly found that optimum therapeutic plasma concentration of sitagliptin can be maintained in order to provide optimal glycemic control over 24 hours by administering a novel modified release composition of sitagliptin. Novel modified release composition of the present invention maintains the therapeutically effective plasma concentration of sitagliptin and does not allow it to surpass the optimal level, therefore avoids side effects or problems associated with administration of sitagliptin. The novel modified release composition according to the present invention provides

sufficient plasma concentration of sitagliptin over 24 hours after single dose oral administration. Additionally, such compositions achieve steady state concentration of sitagliptin relatively earlier than that achieved by conventional dosage forms.

The inventors have surprisingly found that the desired DPP-IV inhibition can be achieved with a once daily dose of sitagliptin using the novel modified release composition. Particularly, the composition achieves more than 80% of DPP-IV enzyme inhibition over a period of over at least 24 hours after single dose oral administration. Further, the novel modified release composition of sitagliptin in accordance with the present invention achieves optimal plasma concentration, thus avoiding undesirable side effects such as aggravation of inflammation in diabetic patients with concurrent inflammation and depression/anxiety.

The management of T2DM can be done by providing modified release composition comprising sitagliptin. For providing better glycemic control over at least 24 hours after single dose administration and reducing the side-effects due to undesirably higher C_{max} and strong inhibition of DPP-IV activity by sitagliptin is, however, not always required for effective type 2 diabetes therapy.

The novel modified release composition of the present invention is capable of appropriately inhibiting DPP-IV activity and that can be administered once daily. It is also possible to achieve a desired effect by maintaining a minimum effective plasma concentration of sitagliptin by administering the composition of the present invention. Particularly, the modified release composition avoids peaks and valleys (fluctuations) in plasma concentration of sitagliptin alone or in combination with other antidiabetic agent. Figure 3 shows the comparative plasma concentration profile of Januvia® tablet and modified release composition of the present invention containing equal doses of sitagliptin.

The term "pharmaceutically acceptable salt" are meant those salts in which the anion does not contribute significantly to the toxicity or pharmacological activity of the salt, and, as such, they are the pharmacological equivalents of the bases of the drug compound.

The term “DPP-IV inhibitor” refers to compounds that are intended to potentiate the endogenous incretin response by preventing the proteolysis of GLP 1 or GIP through the inhibition of one or more of the DPP-IV isoforms in the body (McIntosh, C. H. S., et al., Regulatory Peptides, 2005; 128:159-65). A number of such agents have been approved, under review at the FDA or in clinical development (Hunziker, D., et al., Curr. Top. Med. Chem., 2005; 5:1623-37; Kim, D., et al., J. Med. Chem., 2005; 48:141-51).

The term "modified release" as used herein in relation to the composition according to the invention or used in any other context means release, which is not completely immediate release and is taken to encompass controlled release, sustained release, prolonged release, timed release, retarded release, extended release and delayed release. The term "modified release composition" as used herein can be described as compositions whose drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as a solution or an immediate release dosage form. The modified release composition may exhibit combination of at least two types of releases of the drug. For example, the composition comprising an immediate release part and an extended release part of sitagliptin may, overall, exhibit modified release of sitagliptin from such dosage form.

The term "extended release" is used in its conventional sense to refer to a composition that makes the drug available over an extended period after ingestion, and preferably, although not necessarily, results in substantially constant blood levels of the drug over an extended time period. The term

extended release used in context of the present invention includes, but not limited to, zero order release of the drug.

The term “rate controlling excipients” is used to refer to excipients which modify release of active agent from compositions whose drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as a solution or an immediate release dosage form.

The term “zero order release” includes a zero order release as well as pseudo-zero order release profiles of the drug. A zero order release profile characterizes the release profile of a dosage form that releases a constant amount of drug per unit time. A pseudo-zero order release profile is one that approximates a zero-order release profile.

By "steady state" or ‘C_{ss}’ is meant a pattern of plasma concentration versus time following continuous administration of a constant dose, where the plasma concentration peaks and plasma concentration troughs are essentially identical within each dosing interval. The upper (peak) and lower (trough) values of the steady state concentration are termed as ‘steady state maximum concentration’ or ‘$C_{ss\,(max)}$’ and ‘steady state minimum concentration’ or ‘$C_{ss\,(min)}$’ respectively.

The term “subject” or alternatively "individual" includes mammals. Non-limiting examples of mammals include humans, preferably human suffering from diabetes and particularly type 2 diabetes.

The term “substantial amount of sitagliptin” refers to at least 5% and more preferably at least 10% of the total amount of sitagliptin in the composition or any amount of sitagliptin that is released at least 1 hour post oral administration of the composition. Substantial release of sitagliptin from the composition may be achieved, for example, by providing a composition releasing sitagliptin in at least

two separate pulses. Such formulation includes a composition with an immediate release part and an extended release part of sitagliptin.

As to the release profiles of the modified release compositions containing sitagliptin have several potential advantages over its conventional immediate release (IR) formulations. Mainly the gradual release of sitagliptin into the gastrointestinal (GI) tract provides lower maximum effective concentrations, thus reducing or avoiding unwanted side effects.

The novel modified release composition of the present invention exhibits release of sitagliptin in such a way that it achieves and maintains minimum effective concentration of sitagliptin for at least 24 hours after oral administration. Preferably, the composition maintains about 80% or more inhibition of sitagliptin for at least 24 hours after oral administration of single dose of the composition.

The DPP-IV enzyme activity in plasma can be measured by, for example, a method utilizing the "method of Raymond et al., Diabetes, vol. 47, pp. 1253-1258 (1998)". The decrease rate of the DPP-IV enzyme activity in plasma may be different from the determined values as long as it is within the general error range. Moreover, depending on the measurement method of the DPP-IV enzyme activity in plasma, the decrease rate of the DPP-IV enzyme activity in plasma may be different from the determined values. For example, when, of the measurement conditions of the DPP-IV enzyme activity in plasma, the kind of substrate, substrate concentration, reaction time, dilution fold of the plasma and the like are different from the method described in the above-mentioned reference, the decrease rate of the DPP-IV enzyme activity in plasma may be greater than the determined values and, for example, 90% may be a value not less than 95%. Several methods of determining serum DPP-IV enzyme activity are also known in the art. For example, a bioluminescent assay for determining DPP-IV enzyme activity by means of detecting the Gly-Pro cleaving activity is provided by Martha O'Brien et al. (Cell Notes, Issue-16, 2006).

Other antidiabetic agents may be selected from the group comprising insulin sensitizers (e.g. pioglitazone, rosiglitazone, tesaglitazar, ragaglitazar, muraglitazar, edaglitazone, metaglidasen, naveglitazar), α-glucosidase inhibitors (e.g., voglibose, acarbose, miglitol, emiglitate), biguanides (e.g., metformin, buformin), insulin secretagogues [sulfonylurea e.g., tolbutamide, glibenclamide, gliclazide, chlorpropamide, tolazamide, acetohexamide, glyclopyramide, glimepiride, glipizide, glybuzole;, repaglinide, nateglinide, mitiglinide), sodium-glucose co-transporter-2 (SGLT-2) inhibitors (e.g. Dapagliflozin, Canagliflozin, Ipragliflozin, Tofogliflozin Empagliflozin, Serglflozin, Remogliflozin, Ertugliflozin, Luseogliflozin, Atigliflozin), β3 agonists (e.g., AJ-9677), GPR40 agonists, GLP-1 receptor agonists (e.g., GLP-1, GLP-1MR agent, N,N-2211, AC-2993 (exendin-4), BIM-51077, CJC-1131), amylin agonists (e.g., pramlintide), phosphotyrosine phosphatase inhibitors (e.g. sodium vanadate), gluconeogenesis inhibitors (e.g., glycogen phosphorylase inhibitor, glucose-6-phosphatase inhibitor, glucagon antagonist), sodium-glucose cotransporter (SGLUT) inhibitors (e.g., T-1095), 11 β -hydroxysteroid dehydrogenase inhibitors (e.g., BVT-3498), adiponectin or agonist thereof, IKK inhibitors (e.g., AS-2868), leptin resistance improving drugs, somatostatin receptor agonists, glucokinase activators (e.g., Ro-28-1675), GIP (Glucose-dependent insulinotropic peptide) and the like or one or more pharmaceutically acceptable salt, ester, solvates and derivatives thereof.

DPP-IV inhibitors may be selected from the group comprising alogliptin, linagliptin, vildagliptin, saxagliptin, dutogliptin, gemigliptin, denagliptin, evogliptin, gosogliptin, omarigliptin, teneligliptin, trelagliptin and melogliptin or pharmaceutically acceptable salt thereof. A preferred salt of sitagliptin is the phosphate salt, most preferably in the form of its monohydrate. A preferred salt of saxagliptin is the hydrochloride salt. A preferred salt of alogliptin is the benzoate salt.

It is preferred to use a pharmaceutically acceptable salt of sitagliptin and/or antidiabetic agents, especially a salt exhibiting moderate to high solubility in water. Illustrative salts include those prepared using the following acids: hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, methanesulfonic acid, ethanesulfonic, 2-hydroxyethanesulfonic, benzenesulfonic, p-hydroxybenzoic, toluenesulfonic, formic, acetic, propionic, benzoic, anthranilic, tartaric, maleic, malic, citric, isocitric, succinic, ascorbic, lactic, glycolic, gluconic, glucuronic, pyruvic, oxaloacetic, fumaric, aspartic, glutamic, stearic, salicylic, phenylacetic, mandelic, pamoic, pantothenic, sulfanilic, cyclohexylaminosulfonic, algenic, β-hydroxybutyric, galactaric and galacturonic acids.

Rate controlling excipients are chosen to modify release of active agent from compositions and may be selected from but not limited to osmopolymers, hydrogels, osmogents, hydrophilic, hydrophobic, amphiphilic polymers or copolymers or inert materials or derivatives and or combinations thereof.

Various methods known in the art can be used to determine plasma concentration or in-vitro profile of the novel modified release composition in accordance with present invention.

It is preferred that mean steady state plasma concentration (C_{ss}) of sitagliptin is achieved on or before 7 days on once daily administration of the modified release composition in accordance with the present invention.

In an embodiment, the modified release composition comprising sitagliptin or pharmaceutically acceptable salt thereof and optionally maintains mean plasma concentration of sitagliptin in the range of about 100 nM to about 850 nM after oral administration of single dose of said composition.

In an embodiment, the modified release composition comprising sitagliptin or pharmaceutically acceptable salt thereof and optionally provides mean plasma

concentration of sitagliptin in the range of about 100 nM to about 850 nM after oral administration of single dose of said composition to a subject.

In a further embodiment, the modified release composition maintains mean plasma concentration of sitagliptin in the range of about 100 nM to about 700 nM and more preferably in the range of 100 nM to about 500 nM after oral administration of single dose of the said composition to a subject.

It is further preferred that the modified release composition comprising sitagliptin or pharmaceutically acceptable salt thereof exhibits a mean steady state maximum plasma concentration ($C_{ss(max)}$) of sitagliptin in the range of about 350 nM to about 750 nM after oral administration of single dose of the said composition to a subject.

In an embodiment, the modified release composition comprising sitagliptin or pharmaceutically acceptable salt thereof provides a mean steady state minimum plasma concentration ($C_{ss\ (min)}$) of sitagliptin in the range of about 200 nM to about 500 nM after oral administration of single dose of the composition to a subject.

In an embodiment, the modified release composition comprising sitagliptin or pharmaceutically acceptable salt thereof have maximum plasma concentration (Cmax) and exhibits a mean steady state minimum plasma concentration ($C_{ss\ (min)}$) of sitagliptin in the range given below after oral administration of single dose of said composition to a subject.

Time (Hrs)	IR/ER dose (mg)		
	10/90	25/75	50/50
	Plasma Concentration (Cmax in nM)		
24h	250-400	225-375	300-500
Day 2	300-500	400-600	600-800
Day 3	300-500	450-650	600-800

	Day 4 (Steady State achieved by Day 3)		
Css (max)	419	522	699
Css (min)	361	314	242

The amount of sitagliptin present in modified release composition is sufficient to provide a daily dose in one to a small plurality, for example one to about 4, of dosage units to be administered at one time. Preferably the full daily dose is delivered in a single dosage unit. An amount of about 1mg to about 500 mg per dosage unit, or about 0.05% to about 80% by weight of the composition, will generally be suitable. The amount of sitagliptin may be calculated on the basis of its base or salt.

Preferably an amount of about 25 mg to about 100 mg sitagliptin per dosage unit is present. Specific amounts per tablet contemplated herein include 25, 50, and 100 mg sitagliptin base, however overages may be added as and when required according to composition and release profile requirements.

It is preferred that total dose of sitagliptin in the composition is divided in to an immediate release part and an extended release part.

In an embodiment, the extended release part in the composition exhibits zero order release of sitagliptin.

In a further embodiment, the antidiabetic agent in the composition exhibits immediate and/or extended release.

The particular release and/or PK profile as defined herein can be achieved using one or more release-modifying means, for example, providing the composition in the form of matrix or sitagliptin with various rate controlling substances known in the art or by providing coating of rate controlling substances over the sitagliptin containing core.

It would be appreciated to the person skilled in the art that dose of sitagliptin can be adjusted considering progression of disease and patient's physiology. For example, dose of sitagliptin in the modified release composition can be adjusted (from 100 mg to 50 mg or 25 mg) in case of renal function compromised patients.

In an embodiment, the modified release composition comprises 100mg sitagliptin or pharmaceutically acceptable salt thereof in which total dose of sitagliptin or pharmaceutically acceptable salt thereof is divided in to about 10 mg to about 50 mg of immediate release part and about 50 mg to about 90 mg of extended release part. Figure 4 to 6 shows the plasma concentration profile of sitagliptin 100 mg composition with immediate and extended release parts in said ranges.

The modified release composition may take any form suitable for oral administration, but is typically formulated as a discrete solid dosage unit such as a tablet or capsule, wherein sitagliptin or pharmaceutically acceptable salt thereof is present as solid particles, and is formulated together with one or more pharmaceutically acceptable excipients. The excipients are selected in part to provide a release profile and/or PK profile consistent with those defined above.

The modified release composition in the form of a tablet can be of any suitable size and shape, for example round, oval, polygonal or pillow-shaped, and optionally bear nonfunctional surface markings. Especially in the case of coated tablets they are preferably designed to be swallowed whole and are therefore typically not provided with a breaking score. Dosage unit compositions of the invention can be packaged in a container, accompanied by a package insert providing pertinent information such as, for example, dosage and administration information, contraindications, precautions, drug interactions and adverse reactions.

In an embodiment, the modified release composition may comprises an active core comprised of one or more inert particles, each in the form of a bead, pellet, pill, granular particle, microcapsule, microsphere, microgranule, nanocapsule, or nanosphere coated on its surfaces with sitagliptin in the form of e.g., a sitagliptin -containing coating or film-forming composition using, for example, fluid bed techniques or other methodologies known to those of skill in the art. The inert particle can be of various sizes, so long as it is large enough to remain poorly dissolved. Alternatively, the active core may be prepared by granulating and milling and/or by extrusion and spheronization of a polymer composition containing sitagliptin.

Illustratively, release-modifying means suitable for use in a composition of the invention include a polymer matrix wherein the sitagliptin is dispersed; a release-controlling layer or coating surrounding the whole dosage unit or sitagliptin-containing particles, granules, beads or zones within the dosage unit; and an osmotic pump. In a preferred embodiment, the modified release composition is provided in the form of an osmotic pump.

In an embodiment, the hydrophilic polymer matrix may further include an ionic polymer, a non-ionic polymer, or water-insoluble hydrophobic polymer to provide a stronger gel layer and/or reduce pore quantity and dimensions in the matrix so as to slow diffusion and erosion rates and concomitant release of sitagliptin. This may additionally produce a more steady, zero order release of the sitagliptin. Various ionic polymer, a non-ionic polymer, or water-insoluble hydrophobic polymer known in the art may be used.

In an embodiment, the modified release composition comprises-
(a) at least one component exhibiting extended release of sitagliptin or pharmaceutically acceptable salt thereof;
(b) at least one component exhibiting extended release of metformin or pharmaceutically acceptable salt thereof, and optionally

(c) at least one component exhibiting immediate release of metformin and/or sitagliptin or pharmaceutically acceptable salt thereof.

It is preferred that a substantial dose of sitagliptin in the composition exhibits zero order release over a period of at least 24 hours after oral administration of single dose of the composition.

In an embodiment, the modified release composition comprising sitagliptin or pharmaceutically acceptable salt thereof and optionally, at least one antidiabetic agent, exhibit an in vitro release profile such that about 30% to about 70% of sitagliptin is dissolved within 8 hour and/or about 50% to about 90% of sitagliptin is dissolved within 16 hour after placement of the composition in a dissolution test conducted according to USP, using USP Apparatus I at 100 rpm and a dissolution medium of water at about 37°C.

In an embodiment, the modified release composition may comprise pH modifying agent and or suitable pharmaceutically acceptable buffer.

In an embodiment, both the antidiabetic agent and a substantial dose of sitagliptin in the composition exhibit zero order release from said composition.

In a further embodiment, a substantial dose of sitagliptin in the modified release composition exhibits zero order release over at least 24 hours after oral administration of single dose of the composition.

In a further embodiment, the minimum therapeutically effective plasma concentration of sitagliptin and optionally, at least one antidiabetic agent from the modified release composition is achieved by their osmotically controlled release from the composition.

In an embodiment, the osmotic dosage form comprises: (i) a semipermeable wall provided around an osmotic formulation comprising sitagliptin or pharmaceutically acceptable salt thereof, an osmotic agent, and an osmopolymer; and (ii) a passageway.

By way of example, a capsule based on osmotic release mechanism may be formulated with a single osmotic unit or it may incorporate 2, 3, 4, 5, or 6 push-pull units encapsulated within a hard gelatin capsule, whereby each bilayer push pull unit contains an osmotic push layer and sitagliptin layer, both surrounded by a semi-permeable membrane. One or more orifices are drilled through the membrane next to the sitagliptin layer. This membrane may be additionally covered with a ph-dependent enteric coating to prevent release until after gastric emptying. The gelatin capsule dissolves immediately after ingestion. As the push pull unit(s) enter the small intestine, the enteric coating breaks down, which then allows fluid to flow through the semi-permeable membrane, swelling the osmotic push compartment to force sitagliptin out through the orifice(s) at a rate precisely controlled by the rate of water transport through the semi-permeable membrane. Release of sitagliptin can occur over a constant rate for at least up to 24 hours.

The osmotic push layer comprises one or more osmotic agents creating the driving force for transport of water through the semi-permeable membrane into the core of the delivery vehicle. One class of osmotic agents includes water-swellable hydrophilic polymers, also referred to as "osmopolymers" and "hydrogels," including, but not limited to, hydrophilic vinyl and acrylic polymers, polysaccharides such as calcium alginate, polyethylene oxide (PEO), polyethylene glycol (PEG), polypropylene glycol (PPG), poly(2-hydroxyethyl methacrylate), poly(acrylic) acid, poly(methacrylic) acid, polyvinylpyrrolidone (PVP), crosslinked PVP, polyvinyl alcohol (PVA), PVA/PVP copolymers, PVA/PVP copolymers with hydrophobic monomers such as methyl methacrylate and vinyl acetate, hydrophilic polyurethanes containing large PEO blocks, sodium croscarmellose, carrageenan, hydroxyethyl cellulose (HEC),

hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), carboxymethyl cellulose (CMC) and carboxyethyl, cellulose (CEC), sodium alginate, polycarbophil, gelatin, xanthan gum, and sodium starch glycolate.

Another class of osmotic agents includes osmogents, which are capable of imbiging water to affect an osmotic pressure gradient across the semi-permeable membrane. Exemplary osmogens include, but are not limited to, inorganic salts, such as magnesium sulfate, magnesium chloride, calcium chloride, sodium chloride, lithium chloride, potassium sulfate, potassium phosphates, sodium carbonate, sodium sulfite, lithium sulfate, potassium chloride, and sodium sulfate; sugars, such as dextrose, fructose, glucose, inositol, lactose, maltose, mannitol, raffinose, sorbitol, sucrose, trehalose, and xylitol; organic acids, such as ascorbic acid, benzoic acid, fumaric acid, citric acid, maleic acid, sebacic acid, sorbic acid, adipic acid, edetic acid, glutamic acid, p-toluenesulfonic acid, succinic acid, and tartaric acid; urea; and mixtures thereof.

Materials useful in forming the semipermeable membrane include various grades of acrylics, vinyls, ethers, polyamides, polyesters, and cellulosic derivatives that are water-permeable and water-insoluble at physiologically relevant pHs, or are susceptible to being rendered water-insoluble by chemical alteration, such as crosslinking.

Suitable osmotic dosage form may be provided in the form of a mono-layer, bi-layer or tri-layer dosage form. In an embodiment, the bi-layer oral osmotic dosage forms include a first component layer, comprising at least one drug, one of which is sitagliptin and excipients for forming a deliverable drug composition when hydrated, and a second push layer, comprising a fluid-expandable osmopolymer and excipients, contained within a compartment formed by a semipermeable membrane and having exit means for drug release from the compartment. The two layers are compressed into bi-layer tablet cores before the semipermeable membrane is applied and a suitable orifice for drug release

there through is formed. Alternatively, the bi-layer tablet cores are formed when two component layers are compressed together to provide a longitudinally compressed tablet core having a 'capsule-shaped' configuration with a different layer at each narrow end.

Bi-layer oral osmotic dosage forms and methods of making and using such dosage forms are known in the art, for example, as described and claimed in the following US Patents, owned by Alza Corporation: U.S. Pat. Nos. 4,327,725; 4,612,008; 4,783,337; and 5,082,668, each of which is incorporated in its entirety by reference herein.

The suitable pH modifying agent include malic acid, fumaric acid, adipic acid, succinic acid, lactic acid, acetic acid, oxalic acid, maleic acid, ammonium chloride, preferably tartaric acid, and more preferably citric acid, or a combination of such acids. The skilled person will appreciate that, when weak acids are employed which are not solids (and therefore not particulate) at or around room temperature and atmospheric pressure, they may be adsorbed into a particulate carrier material (such as colloidal silica) in order to provide particles comprising the weakly acidic material.

The suitable buffer system include materials that, when provided in a composition of the invention, provide a weakly acidic buffer system and are present in a sufficient amount to enable the maintenance of pH buffer forming materials thus include combinations of weak acid and salt of weak acid, such as combinations of the aforementioned acids with alkaline salts of those acids, including sodium citrate, potassium citrate, sodium tartrate, potassium tartrate and the like. Preferred buffer forming materials are citric acid and sodium citrate. The skilled person will appreciate that, when materials are employed which are not solids (and therefore not particulate) at or around room temperature and atmospheric pressure, they may be adsorbed into a particulate carrier material

(such as colloidal silica) in order to provide particles comprising the weakly-acidic buffer forming materials.

The combination of features including the osmotic properties of the component layers, the fluid flux properties of the semipermeable membrane and the configuration of the tablet core ensures that sitagliptin is released at a desired rate over an extended time period, preferably over at least 24 hours.

The tri-layer oral osmotic dosage forms include a novel tri-layer tablet core surrounded by a semipermeable membrane and having suitable exit means for releasing at least one drug, one of which is sitagliptin through the semipermeable membrane. In an embodiment, the tri-layer tablet core has a first drug-containing layer, a second drug-containing layer and a third push layer. In operation, through the cooperation of the dosage form components, drug is successively released from the first drug-containing layer and then from the second drug-containing layer. Excipients in the drug-containing layers may be varied and adjusted for other purposes such as manufacturing convenience and pharmaceutical elegance. In this manner, dosage forms that exhibit reliable drug release having the desired profile over an extended time period, preferably over at least 24 hours, can be reliably and efficiently manufactured.

There is also provided a method of reducing side effects associated with increased plasma concentration of sitagliptin in a patient undergoing T2DM treatment, which method comprises of orally administering single dose of a modified release composition comprising sitagliptin or pharmaceutically acceptable salt thereof and optionally, at least one antidiabetic agent or pharmaceutically acceptable salt thereof, wherein a substantial dose of sitagliptin in the composition exhibits zero order release over a period of at least 24 hours.

There is also provided a method of treatment of a subject having a condition or disorder for which sitagliptin is indicated, the method comprising orally

administering to the subject, not more than once daily, a modified release composition as substantially described herein before throughout the specification.

Examples

Example 1: Modified release tablet containing 25, 50 and 100mg Sitagliptin or pharmaceutically acceptable salt thereof

Table 1

Sr. No.	Ingredients	Qty/tablet (mg)		
		A	B	C
1	Sitagliptin Phosphate Anhydrous	31.015	62.031	124.062
2	Lactose	42.000	42.000	42.000
3	Microcrystalline cellulose	41.985	41.969	42.938
4	Hypromellose (HPMC K4M)	32.000	36.000	42.000
5	Hypromellose (HPMC K100M)	115.000	110.000	105.000
6	Magnesium Stearate	3.000	3.000	4.000
Total Weight		**265.000**	**295.000**	**360.000**

Process:

Sitagliptin phosphate anhydrous, Lactose, Microcrystalline cellulose, Hypromellose (HPMC K4M) and Hypromellose (HPMC K100M) were co-sifted together using vibro-sifter fitted with 40# ASTM sieve. The mixture was granulated in a rapid mixer granulator for 5-10 min by spraying aqueous/hydro-alcoholic medium. Wet granules were dried in fluidized bed dryer at 60±5°C. The dried granules were then screened through #30 mesh and milled using a multimill. Dried granules were blended in a double cone blender for 3 min with colloidal silicon dioxide and magnesium stearate, both previously sifted through #60 mesh. Finally, the lubricated blend was compressed using a rotary compress tablet machine.

Example 2: Modified release tablet containing 25, 50 and 100mg Sitagliptin or pharmaceutically acceptable salt thereof

Table 2

Sr. No.	Ingredients	Qty/Tablet (mg)		
Core Tablet		**A**	**B**	**C**
1	Sitagliptin Phosphate Anhydrous	27.914	55.828	111.656
2	Microcrystalline cellulose	42.812	32.225	64.450
3	Hypromellose (HPMC K4M)	35.000	35.000	70.000
4	Hypromellose (HPMC K100M)	55.000	55.000	110.000
5	Magnesium Stearate	1.600	1.600	3.200
Core Tablets Wt (mg)		162.326	179.653	359.306
Extended Release Coating Composition				
6	Polymethyl acrylic acid polymer (Eudragit)	11.2	12.25	19.6
7	Triethyl citrate	1.92	2.1	2.8
8	Silicon dioxide	3.84	4.2	5.6
Total Coated Tablet Wt (mg)		179.286	198.203	387.306
Immediate Release Part Coating Composition				
9	Sitagliptin Phosphate	3.102	6.203	12.406
10	Opadry Clear	3.420	4.629	8.529
Coated Tablet Wt (mg)		185.808	209.035	408.240
Film Coating				
11	Opadry II Biege	5.574	6.271	12.247
Total Film Coated Tablet Wt (mg)		**191.382**	**215.305**	**420.487**

Process:

(I) Core Tablets Preparation:

Sitagliptin phosphate anhydrous, Microcrystalline cellulose, Hypromellose (HPMC K4M) and Hypromellose (HPMC K100M) were co-sifted together using vibro-sifter fitted with 40# ASTM sieve. The mixture was granulated in a rapid mixer granulator for 5-10 min by spraying aqueous/hydro-alcoholic medium. Wet granules were dried in fluidized bed dryer at 60±5°C. The dried granules were then screened through #30 mesh and milled using a multimill. Dried granules were blended in a double cone blender for 3 min with colloidal silicon dioxide and

magnesium stearate, both previously sifted through #60 mesh. The lubricated blend then compressed using a rotary compress tablet machine.

(II) Extended Release Coating:

Aqueous dispersion of Eudragit with Triethyl citrate and Silicon dioxide was prepared and coated on the tablets in a perforated pan coater while keeping the temperature between 50-60° C. The extended release coated tablet was dried in coating pan at 45±5° C to remove coating solvent.

(III) Immediate Release Part Coating:

Aqueous solution of Sitagliptin phosphate anhydrous and Opadry clear in purified water was then sprayed over previously drilled tablets in coater till the desired drug is loaded.

(IV) Film Coating:

Finally, the tablets were coated with Opadry system for aesthetic purpose.

Example 3: Modified release tablet containing 25, 50 and 100mg Sitagliptin or pharmaceutically acceptable salt thereof

Table 3

Sr. No.	Ingredients	Qty/Tablet (mg)		
Core tablet		**A**	**B**	**C**
1	Sitagliptin Phosphate Anhydrous	31.015	62.031	124.062
2	Microcrystalline cellulose	37.385	26.369	52.738
3	Hypromellose (HPMC K4M)	35.000	35.000	70.000
4	Hypromellose (HPMC K100M)	55.000	55.000	110.000
5	Magnesium Stearate	1.600	1.600	3.200
Core Tablets Wt (mg)		160.000	180.000	360.000
Extended Release Coating Composition				
6	Polymethyl acrylic acid polymer	9.60	10.80	17.28
7	Triethyl citrate	1.92	2.16	2.88
8	HPMC E5/Povidone K30	3.84	4.32	5.76
9	Silicon dioxide	1.92	2.16	2.88
Total Coated Tablet Wt (mg)		**173.440**	**195.120**	**383.040**

Process:

(I) Core Tablets Preparation:

Sitagliptin phosphate anhydrous, Microcrystalline cellulose, Hypromellose (HPMC K4M) and Hypromellose (HPMC K100M) were co-sifted together using vibro-sifter fitted with 40# ASTM sieve. The mixture was granulated in a rapid mixer granulator for 5-10 min by spraying aqueous/hydro-alcoholic medium. Wet granules were dried in fluidized bed dryer at 60±5°C. The dried granules were then screened through #30 mesh and milled using a multimill. Dried granules were blended in a double cone blender for 3 min with colloidal silicon dioxide and magnesium stearate, both previously sifted through #60 mesh. The lubricated blend then compressed using a rotary compress tablet machine.

(II) Extended Release Coating:

Aqueous dispersion of Polymethyl acrylic acid polymer with Triethyl citrate, HPMC E5/Povidone K30 and Silicon dioxide was prepared and coated on the tablets in a perforated pan coater while keeping the temperature between 50-60° C. The extended release coated tablet was dried in coating pan at 45±5° C to remove coating solvent.

Example 4: Modified release tablet containing 25, 50 and 100mg Sitagliptin or pharmaceutically acceptable salt thereof

Table 4

Sr. No.	Ingredients	Qty/Tablet (mg)		
		A	B	C
1	Sitagliptin Phosphate Anhydrous	31.015	62.031	124.062
2	Microcrystalline Cellulose	59.985	28.969	57.938
3	Hydroxy propyl cellulose	3.000	3.000	6.000
4	Povidone	2.000	2.000	4.000
5	Glyceryl Behenate	2.000	2.000	4.000
6	Colloidal silicon Dioxide	1.000	1.000	2.000

7	Magnesium Stearate	1.000	1.000	2.000
Core Tablet Wt (mg)		100.000	100.000	200.000
Extended Release Coating I Composition				
8	Ethyl cellulose 100cps	7.20	7.20	11.20
9	Polyethylene glycol	2.40	2.40	2.40
10	Povidone K30	2.40	2.40	2.40
	Coated Tablet Wt (mg)	112.000	112.000	216.000
Extended Release Coating II Composition				
11	Eudragit L30D55	5.824	5.824	11.232
12	Triethyl Citrate	0.896	0.896	1.728
13	Polyethylene glycol	0.896	0.896	1.728
14	Silicon Dioxide	1.344	1.344	2.592
Coated Tablet Wt (mg)		**120.960**	**120.960**	**233.280**

Process:

(I) Core Tablets Preparation:

Sitagliptin phosphate anhydrous, Microcrystalline cellulose, Hypromellose (HPMC K4M) and Hypromellose (HPMC K100M) were co-sifted together using vibro-sifter fitted with 40# ASTM sieve. The mixture was granulated in a rapid mixer granulator for 5-10 min by spraying aqueous/hydro-alcoholic solution of Povidone. Wet granules were dried in fluidized bed dryer at 60±5°C. The dried granules were then screened through #30 mesh and milled using a multimill. Dried granules were blended in a double cone blender for 3 min with Glyceryl Behenate, colloidal silicon dioxide and magnesium stearate, both previously sifted through #60 mesh. The lubricated blend then compressed using a rotary compress tablet machine.

(II) Extended Release Coating I:

Organic dispersion of ethylcellulose with PEG and Poviodne was prepared using methylene chloride and iso-propyl alcohol or ethanol and iso-propyl alcohol and

coated on the tablets in a perforated pan coater while keeping the temperature between 50±5° C. The extended release coated tablet was dried in coating pan at 45±5° C to remove coating solvent.

(II) Extended Release Coating II:

Aqueous dispersion of Eudragit with Triethyl citrate, Polyethylene glycol and Silicon dioxide was prepared and coated on the tablets in a perforated pan coater while keeping the temperature between 50-60° C. The extended release coated tablet was dried in coating pan at 45±5° C to remove coating solvent.

Example 5: Modified release tablet containing 25, 50 and 100mg Sitagliptin or pharmaceutically acceptable salt thereof

Table 5

Sr. No.	Ingredients	Qty/Tablet (mg)		
		A	B	C
Core Tablet				
1	Sitagliptin Phosphate Anhydrous	27.914	55.828	111.656
2	Mannitol (Pearlitol SD200)	40.000	40.000	80.000
3	Povidone K 90	12.000	12.000	24.000
4	Microcrystalline cellulose PH 102	87.286	59.372	118.744
5	Polyethylene Glycol (PEG 6000)	10.000	10.000	20.000
6	Colloidal silicon dioxide	1.000	1.000	2.000
7	Magnesium stearate	1.800	1.800	3.600
Core Tablet Wt (mg)		180.000	180.000	360.000
Extended Release Coating				
8	Cellulose Acetate (CA-320S)	6.47	6.65	13.67
9	Cellulose Acetate (CA-398-10)	10.80	10.80	14.40
10	Polyethylene Glycol 400	0.90	0.90	1.44
Total ER Coated Tab wt (mg)		198.00	198.00	388.80
Immediate Release Part				
11	Sitagliptin Phosphate Anhydrous	3.102	6.203	12.406

12	Hypromellose E3	6.798	3.697	7.034
IR Part Coated Tablets		207.900	207.900	408.240
Film Coating				
13	Opadry Biege (mg)	12.474	12.474	24.494
Total Film Coated tab wt (mg)		**220.374**	**220.374**	**432.734**

Process:

(I) Core Tablets Preparation:

Sitagliptin phosphate anhydrous, Mannitol, Povidone K 90 and Microcrystalline cellulose were co-sifted using vibro-sifter fitted with 40# ASTM sieve. The mixture was again mixed in a rapid mixer granulator for 5 minutes and then granulated using aqueous/hydro-alcoholic solution of polyethylene glycol 6000. Wet granules were then dried in fluidized bed dryer at about 40-55°C. Dried granules were then screened through #20 mesh sieve and the retained granules were milled in a multimill. The milled granules were then blended in a double cone blender for 3 min with a previously sifted [through #60 mesh] mixture of colloidal silicon dioxide and magnesium stearate. The lubricated blend was then compressed using rotary compress tablet machine.

(II) Extended Release Coating:

Aqueous solution of Polyethylene Glycol (PEG) 400 was prepared in purified water. Cellulose acetate (CA-320S) followed by cellulose acetate (CA-398-10) were added in acetone slowly under continuous stirring. Aqueous solution of PEG 400 was then added in the cellulose acetate-acetone mixture. The solution was then stirred at slow speed for about 1 h to get a clear/transparent solution.

The core tablets as obtained above were coated with extended release coating solution using a perforated pan coater while keeping the temperature between 30-45°C. The extended release coated tablets were dried in coating pan at 45±5°C to remove coating solvent.

The extended release coated tablets were drilled mechanically or by means of laser drilling system with orifice size of about 0.5-0.8 mm.

(III) Immediate Release Part Coating:

Aqueous solution of sitagliptin phosphate anhydrous in hypromellose E3 and purified water was prepared. The solution was sprayed over previously drilled tablets in pan coater till the desired drug is loaded.

(IV) Film Coating:

Finally, the tablets were coated with Opadry system for aesthetic purpose.

Example 6: Modified release tablet containing 25, 50 and 100mg Sitagliptin or pharmaceutically acceptable salt thereof

Table 6

Sr. No.	Ingredients	Qty/Tablet (mg)		
		A	B	C
Drug Layer Composition				
1	Sitagliptin Phosphate Anhydrous	23.262	46.523	93.046
2	Polyethylene oxide (Sentry Polyox WSR N80)	69.738	139.477	92.954
3	Iron oxide Red	--	--	0.010
4	Hypromellose (HPMC 5cps)	6.500	13.000	13.000
5	Magnesium Stearate	0.500	1.000	1.000
6	Isopropyl alcohol	q.s.	q.s.	q.s.
Drug Layer Weight (mg)		100.000	200.000	200.000
Push Layer Composition				
7	Polyethylene Oxide (Polyox Coagulant)	45.650	91.300	91.300
8	Iron oxide Red	0.500	1.000	1.000
9	Hypromellose (HPMC 5cps)	3.500	7.000	7.000
10	Sodium Chloride	20.000	40.000	40.000
11	Magnesium Stearate	0.350	0.700	0.700
12	Isopropyl alcohol	q.s.	q.s.	q.s.
Core Tablet Wt (mg)		170.000	340.000	340.000
Extended Release Coating Composition				
13	Cellulose Acetate (CA-398-10)	19.788	25.840	25.840
14	Polyethylene Glycol 3350	0.816	1.360	1.360

Extended Release Tablet Weight (mg)		197.200	374.000	367.200
Immediate Release Part Coating Composition				
15	Sitagliptin Phosphate Anhydrous	7.754	15.508	31.015
16	Opadry II Biege	7.494	13.868	13.049
IR Coated Tablet Weight (mg)		205.852	396.576	411.265
Film Coating				
17	Opadry Clear	6.176	11.897	12.338
Film Coated Tablet Weight (mg)		**212.027**	**408.473**	**423.602**

Process:

(I) Preparation of Drug Layer:

Sitagliptin phosphate Anhydrous was mixed with Polyethylene oxide (Sentry Polyox WSR N80) and then and sifted through #20 ASTM. Hypromellose 2910 (METHOCEL™ E5 Premium LV) was and sifted through #30 ASTM. Pre-sifted iron oxide red was added to the drug layer composition for identification.

The above mixture was granulated for 10 minutes using isopropyl alcohol. Wet granules were dried in fluidized bed dryer and sifted through #20ASTM followed by blending with pre-sifted magnesium stearate [through #60 ASTM] for 3 min in double cone blender.

(II) Push Layer Preparation:

Polyethylene oxide (Sentry Polyox WSR N80), Hypromellose and sodium chloride were sifted through #20 ASTM. Pre-sifted iron oxide red [through #60ASTM] was added to the push layer composition.

The above mixture was granulated in rapid mixer granulator for 5 min using isopropyl alcohol. Wet granules then dried in fluidised bed dryer and sifted through #20ASTM followed by blending with pre-sifted magnesium stearate [through #60 ASTM] for 3 min in double cone blender.

The blend of drug layer and push layer was compressed to form bi-layer tablets using a bi-layer tabletting machine.

(III) Extended Release Coating:

Aqueous solution of Polyethylene Glycol (PEG) 3350 was prepared in purified water. Separately cellulose acetate was dissolved in require quantity of acetone and the aqueous solution of PEG 3350 was added into it under stirring. The solution was then stirred at slow speed for about 1 h to get a clear/transparent solution.

The core tablets as prepared above were coated with extended release coating solution of cellulose acetate and polyethylene glycol 3350 in perforated pan coater. The drug layer side of extended release coated tablets were then drilled by using tablet drilling laser system with one preformed passageway (orifice) of 0.7±0.1 mm diameter.

(IV) Immediate Release Part Coating:

Aqueous solution of sitagliptin phosphate anhydrous and Opadry system in purified water was prepared. The solution was sprayed over previously drilled tablets in pan coater till the desired drug is loaded.

(V) Film Coating:

Finally, the tablets were coated with Opadry system for aesthetic purpose.

Example 7: Modified release tablet containing 25, 50 and 100mg Sitagliptin or pharmaceutically acceptable salt thereof

Table 7

Sr. No.	Ingredients	Qty/Tablet (mg)		
		A	B	C
Core Tablet				
1	Sitagliptin Phosphate Anhydrous	15.508	31.015	62.030
2	Mannitol (Pearlitol SD200)	20.000	20.000	40.000
3	Lactose Anhydrous	56.000	56.000	112.000
4	Microcrystalline cellulose PH 102	93.692	78.185	156.370
5	Povidone K 30	12.000	12.000	24.000
6	Colloidal silicon dioxide	1.000	1.000	2.000
7	Magnesium stearate	1.800	1.800	3.600

Core Tablet Wt (mg)		200.000	200.000	400.000
Extended Release Coating Composition				
8	Cellulose Acetate-320S	8.40	8.40	12.00
9	Cellulose Acetate -398-10	14.00	14.00	20.00
10	Polyethylene Glycol 400 /6000	5.60	5.60	8.00
ER Coated Tab wt (mg)		228.00	228.00	440.00
Immediate Release Part Coat				
11	Sitagliptin Phosphate Anhydrous	15.508	31.015	62.031
12	Hypromellose	7.292	14.585	25.969
IR Part Coated Tablets		250.800	273.601	528.000
Film Coating				
13	Opadry Biege (mg)	10.032	10.944	21.120
Total Film Coated tab wt (mg)		**260.832**	**284.545**	**549.120**

Process:

(I) Core Tablets Preparation:

Sitagliptin phosphate anhydrous, Lactose and Microcrystalline cellulose were co-sifted using vibro-sifter fitted with 40# ASTM sieve. The mixture was again mixed in a rapid mixer granulator for 5 minutes and then granulated using aqueous/hydro-alcoholic solution of povidone K30. Wet granules were then dried in fluidized bed dryer at about 50-60°C. Dried granules were then screened through #20 mesh sieve and the retained granules were milled in a multimill. The milled granules were then blended in a double cone blender for 3 min with a previously sifted [through #60 mesh] mixture of colloidal silicon dioxide and magnesium stearate. The lubricated blend was then compressed using rotary compress tablet machine.

(II) Extended Release Coating:

Aqueous solution of Polyethylene Glycol (PEG) 400 was prepared in purified water. Cellulose acetate (CA-320S) followed by cellulose acetate (CA-398-10) were added in acetone slowly under continuous stirring. Aqueous solution of PEG 400 was then added in the cellulose acetate-acetone mixture. The solution was then stirred at slow speed for about 1 h to get a clear/transparent solution.

The core tablets as obtained above were coated with extended release coating solution using a perforated pan coater while keeping the temperature between 30-45°C. The extended release coated tablets were dried in coating pan at 45±5°C to remove coating solvent.

(III) Immediate Release Part Coating:

Aqueous solution of sitagliptin phosphate anhydrous in hypromellose E3 and purified water was prepared. The solution was sprayed over previously coated tablets in pan coater till the desired drug is loaded.

(IV) Film Coating:

Finally, the tablets were coated with Opadry system for aesthetic purpose.

Example 8: Modified release tablet containing 25, 50 and 100mg Sitagliptin or pharmaceutically acceptable salt thereof

Table 8

Sr. No.	Ingredients	Qty/Tablet (mg)		
		A	B	C
Core Tablet				
1	Sitagliptin Phosphate Anhydrous	27.914	55.828	111.655
2	Mannitol (Pearlitol SD200)	20.000	20.000	40.000
3	Lactose Anhydrous	56.000	56.000	112.000
4	Microcrystalline cellulose PH 102	83.612	58.025	116.050
5	Povidone K 30	12.000	12.000	24.000
6	Colloidal silicon dioxide	1.000	1.000	2.000
7	Magnesium stearate	1.800	1.800	3.600
Core Tablet Wt (mg)		202.326	204.653	409.305
Extended Release Coating Composition				
8	Polyacrylic resin (Eudragit)	8.50	8.60	12.28
9	Ethylcellulose	14.16	14.33	20.47
10	Hydroxylpropyl cellulose	4.25	4.30	6.14
11	Triethyl citrate	1.42	1.43	2.87
ER Coated Tab wt (mg)		**229.24**	**231.87**	**448.19**

Immediate Release Part Coat				
12	Sitagliptin Phosphate Anhydrous	3.102	6.203	12.406
13	Hypromellose	6.034	12.332	23.108
IR Part Coated Tablets		238.376	250.405	483.704
Film Coating				
14	Opadry Biege (mg)	14.442	15.304	29.580
Total Film Coated tab wt (mg)		**252.818**	**265.709**	**513.284**

Process: The tablets were prepared according to Example 3 in which the extended release coating composition was prepared by making a solution of polyacrylic resin, Ethyl cellulose, Hydroxylpropyl cellulose and tri-ethyl citrate in alcohol. The solution was then applied on to core tablets as per Example 3.

Example 9: Modified release tablet containing Sitagliptin or Pharmaceutically acceptable salt thereof

Table 9

No.	Ingredients	Qty/Tablet (mg)		
Batch No		**A**	**B**	**C**
Core Tablet				
1	Sitagliptin Phosphate Anhydrous	100-115		
2	Mannitol (Pearlitol SD200)	70-90	70-90	70-90
3	Povidone K 90	20-28	20-28	10-14
4	HEC 250H	-	8-12	6-9
5	Microcrystalline cellulose PH 102	140-155	140-155	145-160
6	Polyethylene Glycol (PEG 6000)	15-25	8-12	8-12
7	Colloidal silicon dioxide	1.5-3.0	-	-
8	Sodium Stearyl Fumarate	-	1-3	1-3
9	Magnesium stearate	3-4	3-4	3-4
Core Tablet Wt (mg)		**360-400**	**360-400**	**360-400**
Extended Release Coating				
10	Cellulose Acetate (CA-320S)	12-16	10-16	10-16
11	Cellulose Acetate (CA-398-10)	6-10	5-10	5-10
12	Polyethylene Glycol 400	1-2	2-4	2-4
Total ER Coated Tab wt (mg)		380-420	380-420	380-420
Immediate Release Part				
13	Sitagliptin Phosphate Anhydrous	15-25	15-25	15-25
14	Opadry YS-IR-7006 Clear#	15-25	15-25	15-25
IR Part Coated Tablets		420-460	420-460	420-460
Film Coating				
15	Opadry Pink 20H540007	15-25	10-16	10-18
Total Film Coated tab wt (mg)		445-485	445-470	445-470

Process: The tablets were prepared according to Example 5

Example 10: Modified release tablet containing Sitagliptin or Pharmaceutically acceptable salt thereof

Table 10

No.	Ingredients	Qty/Tablet (mg)		
Batch Number		**A**	**B**	**C**
Core Tablet				
1	Sitagliptin Phosphate Anhydrous	100-115		
2	Polyethylene oxide (Polyox N80)	110-130	105-125	100-120
3	Hypromellose (HPMC) 6cps	10-20	8-16	10-20
4	Citric acid	-	-	3-8
5	Magnesium stearate	0.5-2.0	0.5-2.0	0.5-2.0
Core Tablet Wt (mg)		**220-260**	**220-260**	**220-260**
Push layer				
6	Polyox WSR 303	80-90	115-140	115-140
7	Sodium Chloride	25-35	35-45	35-45
8	Hypromellose (HPMC 6 cps)	4-8	7-12	7-12
9	Iron Oxide Red	0.5-0.9	0.5-1.5	0.5-1.5
10	Magnesium stearate	0.4-0.8	0.7-1.2	0.7-1.2
Total Push layer weight (mg)		110-130	170-190	170-190
Bilayer Tablet weight (mg)		340-380	400-440	400-440
Seal coating				
11	HPC SSL	8-12	10-14	10-14
12	PEG 400	0.4-0.7	0.4-0.7	0.4-0.7
Seal coated tablet weight (mg)		360-380	420-450	420-450
ER Coating				
13	Cellulose Acetate (CA-98-10)	20-35	25-40	25-40
14	PEG 3350	2-4	1.5-4.0	1.5-4.0
ER coated tablet weight (mg)		380-420	440-480	440-480
Drug Layering				
15	Sitagliptin Phosphate Anhydrous	15-25	15-25	15-25
16	Opadry YS-IR-7006 Clear#	15-25	15-25	15-25
Drug layered Tablet weight		420-460	480-520	480-520
Film Coating				
17	Opadry Pink 20H540007	15-30	10-20	10-20
Total Film Coated tab wt (mg)		440-480	490-540	490-540

Process: The tablets were prepared according to Example 6

Tablets obtained from example 9 and 10 were subjected to dissolution studies. The results of dissolution studies performed are provided in Table 11 and 12 respectively.

Table 11: Dissolution profile

Time (h)	A			B			C		
	% Drug dissolved (Water, 900 ml, USP Type-1, 100 rpm)								
	Mean	SD	RSD	Mean	SD	RSD	Mean	SD	RSD
1	17	1	5.88	15	0.5	3.33	17	1.7	10
2	22	1	4.55	18	0.8	4.44	19	1.4	7.37
4	32	2	6.25	33	4.5	13.64	26	1.3	5
8	48	2	4.17	64	6	9.38	47	2.5	5.32
12	59	3	5.08	83	5.5	6.63	64	3.8	5.94
16	68	3	4.41	89	2.9	3.26	78	4.5	5.77
20	75	2	2.67	92	1.7	1.85	88	4.8	5.45
24	81	3	3.7	93	1.4	1.51	96	4.1	4.27

Table 12: Dissolution profile

Time (h)	A			B			C		
	% Drug dissolved (Water, 900 ml, USP Type-1, 100 rpm)								
	Mean	SD	RSD	Mean	SD	RSD	Mean	SD	RSD
1	16	1.0	6.25	18	0.8	4.44	17	1.1	6.47
2	21	1.0	4.76	19	0.8	4.21	18	0.9	5.00
4	38	4.0	10.53	26	1.5	5.77	23	0.9	3.91
8	70	2.0	2.86	45	4.1	9.11	51	4.0	7.84
12	83	2.0	2.35	61	3.9	6.39	79	4.2	5.32
16	86	2.0	2.33	72	4.3	5.97	92	2.0	2.17
20	89	2.0	2.25	82	4.5	5.49	96	1.0	1.04
24	89	2.0	2.25	88	4.1	4.66	97	1.0	1.03

Example 11: Modified release tablet containing Sitagliptin or pharmaceutically acceptable salt thereof

Table 13

No.	Ingredients	Qty/Tablet (mg)		
Batch No		**A**	**B**	**C**
Core Tablet				
1	Sitagliptin Phosphate Anhydrous	100-115		
2	Mannitol (Pearlitol SD200)	70-90	70-90	70-90
3	Povidone K 90	20-30	20-30	10-16
4	HEC 250H	-	8-12	6-9
5	Citric acid	6-9	6-9	6-9
6	Microcrystalline cellulose PH 102	130-150	130-150	140-160
7	Polyethylene Glycol (PEG 6000)	15-25	8-12	8-12
8	Colloidal silicon dioxide	1-3	-	-
9	Sodium Stearyl Fumarate	-	1-3	1-3
10	Magnesium stearate	3-4	3-4	3-4
Core Tablet Wt (mg)		**360-400**	**360-400**	**360-400**
Extended Release Coating				
11	Cellulose Acetate (CA-320S)	10-16	10-16	10-16
12	Cellulose Acetate (CA-398-10)	6-10	6-10	6-10
13	Polyethylene Glycol 400	1-2	3-5	3-5
Total ER Coated Tab wt (mg)		380-420	380-420	380-420
Immediate Release Part				
14	Sitagliptin Phosphate Anhydrous	15-25	15-25	15-25
15	Opadry YS-IR-7006 Clear#	15-25	15-25	15-25
IR Part Coated Tablets		430-460	430-460	430-460
Film Coating				
16	Opadry Pink 20H540007	15-25	10-20	10-20
Total Film Coated tab wt (mg)		450-475	450-470	450-470

Process: The tablets were prepared according to Example 5

Example 12: Modified release tablet containing Sitagliptin or pharmaceutically acceptable salt thereof

Table 14

No.	Ingredients	Qty/Tablet (mg)		
	Batch Number	**A**	**B**	**C**
	Core Tablet			
1	Sitagliptin Phosphate Anhydrous		100-115	
2	Polyethylene oxide (Polyox N80)	100-120	100-120	90-110
3	Hypromellose (HPMC) 6cps	10-20	8-15	12-18
4	Citric acid	-	-	3-6
5	Magnesium stearate	1-2	1-2	1-2
6	HEC 250H	6-10	-	-
	Core Tablet Wt (mg)	**230-250**	**230-250**	**230-250**
	Push layer			
7	Polyox WSR 303	75-95	120-140	120-140
8	Sodium Chloride	25-35	35-45	35-45
9	Hypromellose (HPMC 6 cps)	4-8	6-12	6-12
10	Iron Oxide Red	0.5-1.0	1-2.0	1-2.0
11	HEC 250H	-	6-8	-
12	Magnesium stearate	0.4-0.8	0.75-1.50	0.75-1.50
	Total Push layer weight (mg)	110-130	170-190	170-190
	Bilayer Tablet weight (mg)	350-370	400-440	400-440
	Seal coating			
13	HPC SSL	8-12	10-14	10-14
14	PEG 400	0.4-0.75	0.5-1.50	0.50-1.50
	Seal coated tablet weight (mg)	360-380	420-440	420-440
	ER Coating			
15	Cellulose Acetate (CA-98-10)	20-30	25-35	25-35
16	PEG 3350	2-4	1.5-3.0	1.5-3.0
	ER coated tablet weight (mg)	380-420	450-470	450-470
	Drug Layering			
17	Sitagliptin Phosphate Anhydrous	15-25	15-25	15-25
18	Opadry YS-IR-7006 Clear#	15-25	15-25	15-25
	Drug layered Tablet weight	420-460	480-520	480-520
	Film Coating			
19	Opadry Pink 20H540007	15-25	15-25	15-25
	Total Film Coated tab wt (mg)	440-480	500-540	500-540

Process: The tablets were prepared according to Example 6

Claims

We claim:

1. A modified release composition comprising: a) sitagliptin or pharmaceutically acceptable salt thereof; and b) one or more rate controlling excipients, wherein the composition provides mean plasma concentration of sitagliptin or pharmaceutically acceptable salt thereof in the range of about 100 nM to about 850 nM over a period of at least 24 hours after once daily oral administration to a subject.

2. A modified release composition comprising: a) about 25mg to about 100mg of sitagliptin or pharmaceutically acceptable salt thereof; and b) one or more rate controlling excipients, wherein the sitagliptin or pharmaceutically acceptable salt thereof in the composition inhibits activity of DPP-IV enzyme by 80% or more over a period of at least 24 hours after oral administration to a subject.

3. A modified release composition comprising: a) sitagliptin or pharmaceutically acceptable salt thereof; and b) one or more rate controlling excipients, wherein once daily administration of said composition to a subject provides mean steady state plasma concentration (C_{ss}) of sitagliptin or pharmaceutically acceptable salt thereof on or before 7 days.

4. A modified release composition comprising: a) about 100 mg sitagliptin or pharmaceutically acceptable salt thereof; and b) one or more rate controlling excipients, wherein the composition provides a mean steady state maximum plasma concentration ($C_{ss(max)}$) of sitagliptin or pharmaceutically acceptable salt thereof in the range of about 350 nM to

about 750 nM after oral administration of single dose of the composition to a subject.

5. A modified release composition comprising: a) 100 mg sitagliptin or pharmaceutically acceptable salt thereof; and b) one or more rate controlling excipients, wherein the composition provides a mean steady state minimum plasma concentration ($C_{ss\ (min)}$) of sitagliptin or pharmaceutically acceptable salt thereof in the range of about 200 nM to about 500 nM after oral administration of single dose of the composition to a subject.

6. A modified release composition comprising: a) 100 mg sitagliptin or pharmaceutically acceptable salt thereof; and b) one or more rate controlling excipients, wherein the composition provides a mean plasma concentration of sitagliptin or pharmaceutically acceptable salt thereof in the range of about 180 nM to about 370 nM after 20 hours of single dose administration of said composition to a subject.

7. The modified release composition of any of the preceding claim, wherein the composition provides extended release of sitagliptin or pharmaceutically acceptable salt thereof over a period of at least 24 hours after oral administration of single dose of the said composition to a subject.

8. The modified release composition of any of the preceding claim, wherein total dose of sitagliptin or pharmaceutically acceptable salt thereof in the composition comprises an immediate release part and an extended release part.

9. The modified release composition of claim 8, wherein the immediate release part of the composition comprises about 10mg to about 50mg of sitagliptin or pharmaceutically acceptable salt thereof.

10. The modified release composition of claim 8, wherein the extended release part of the composition comprises about 50 mg to about 90 mg of sitagliptin or pharmaceutically acceptable salt thereof.

11. The modified release composition of any of the preceding claim, wherein said composition exhibit an in vitro dissolution profile such that about 30% to about 70% of sitagliptin is dissolved within 8 hour and/or about 50% to about 90% of sitagliptin is dissolved within 16 hour after placement of the composition in a dissolution test conducted according to USP using Apparatus I at 100 rpm and a dissolution medium of water at about 37°C.

12. The modified release composition of any of the preceding claim, wherein said composition further comprises another antidiabetic agent.

13. The modified release composition of claim 12, wherein sitagliptin or pharmaceutically acceptable salt thereof and the other antidiabetic agent in the composition exhibit extended release over a period of at least 24 hours after oral administration of single dose of the said composition to a subject.

14. The modified release composition of claim 12 or 13, wherein said other antidiabetic agent is selected from insulin sensitizers, α-glucosidase inhibitors, biguanides, insulin secretagogues, sodium-glucose co-transporter-2 (SGLT-2) inhibitors, β3 agonists, GPR40 agonists, GLP-1 receptor agonists, amylin agonists, phosphotyrosine phosphatase inhibitors, gluconeogenesis inhibitors, sodium-glucose cotransporter (SGLUT) inhibitors, 11 β -hydroxysteroid dehydrogenase inhibitors,

adiponectin or agonist thereof, IKK inhibitors, leptin resistance improving drugs, somatostatin receptor agonists, and glucokinase activators.

15. The modified release composition of claim 14 wherein said other antidiabetic agent is selected from a biguanides, an α-glucosidase inhibitor or combinations thereof.

16. The modified release composition of claim 15, wherein said biguanide is metformin or pharmaceutically acceptable salt thereof.

17. The modified release composition of claim 15, wherein said α-glucosidase inhibitor is voglibose or pharmaceutically acceptable salt thereof.

18. The modified release composition of claim 16, wherein the composition comprises:
(a) at least one component exhibiting extended release of sitagliptin or pharmaceutically acceptable salt thereof;
(b) at least one component exhibiting extended release of metformin or pharmaceutically acceptable salt thereof, and optionally
(c) at least one component exhibiting immediate release of metformin and/or sitagliptin or salt thereof.

19. The modified release composition of any of the preceding claim, wherein said composition is in the form of an osmotic dosage form.

20. The modified release composition of claim 19, wherein said osmotic dosage form comprises:
(i) a semipermeable wall provided around an osmotic formulation comprising sitagliptin or pharmaceutically acceptable salt thereof, an osmotic agent, and an osmopolymer; and
(ii) a passageway.

21. A method of treating type 2 diabetes mellitus in a subject in need thereof, said method comprising administration of the modified release composition of any of the preceding claim to the subject.

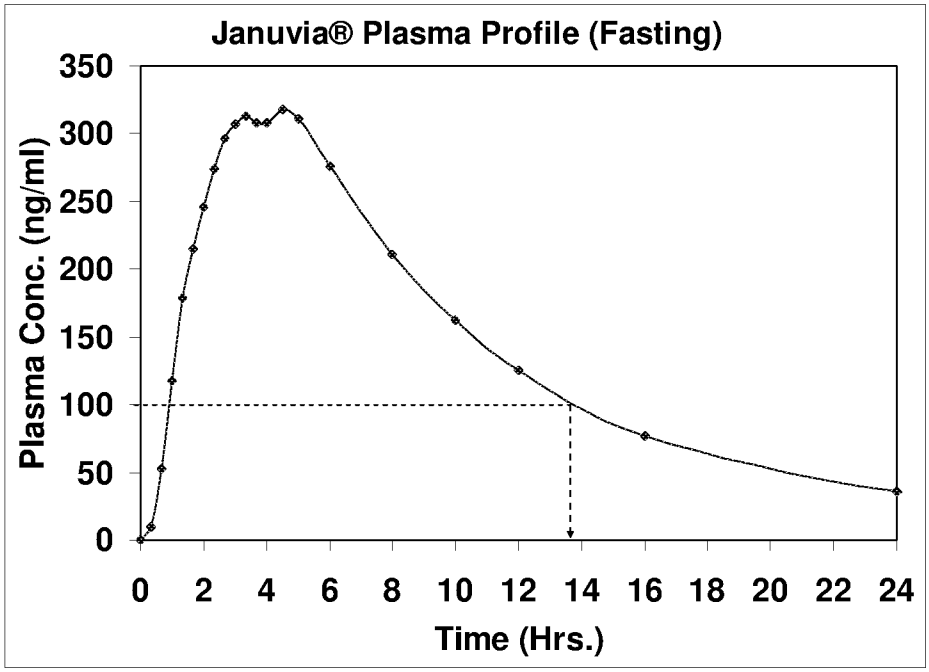

Januvia® Plasma Profile (Fasting)
Plasma Conc. (ng/ml)
350
300
250
200
150
100
50
0
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (Hrs.)

FIGURE 1

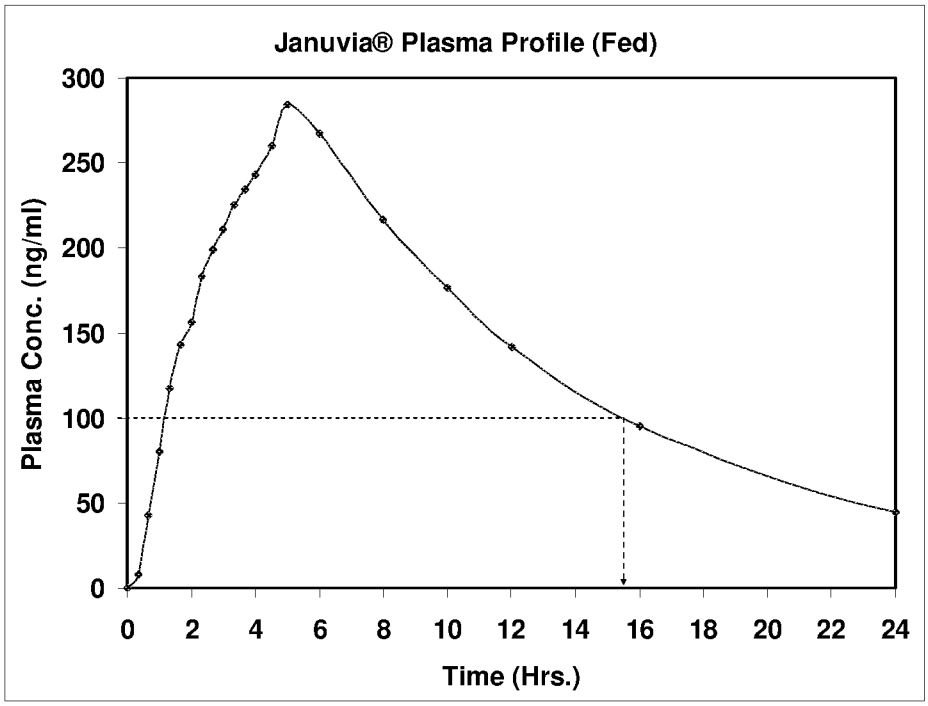

Januvia® Plasma Profile (Fed)
Plasma Conc. (ng/ml)
300
250
200
150
100
50
0
0
2
4
6
8
10
12
14
16
18
20
22
24
Time (Hrs.)

FIGURE 2

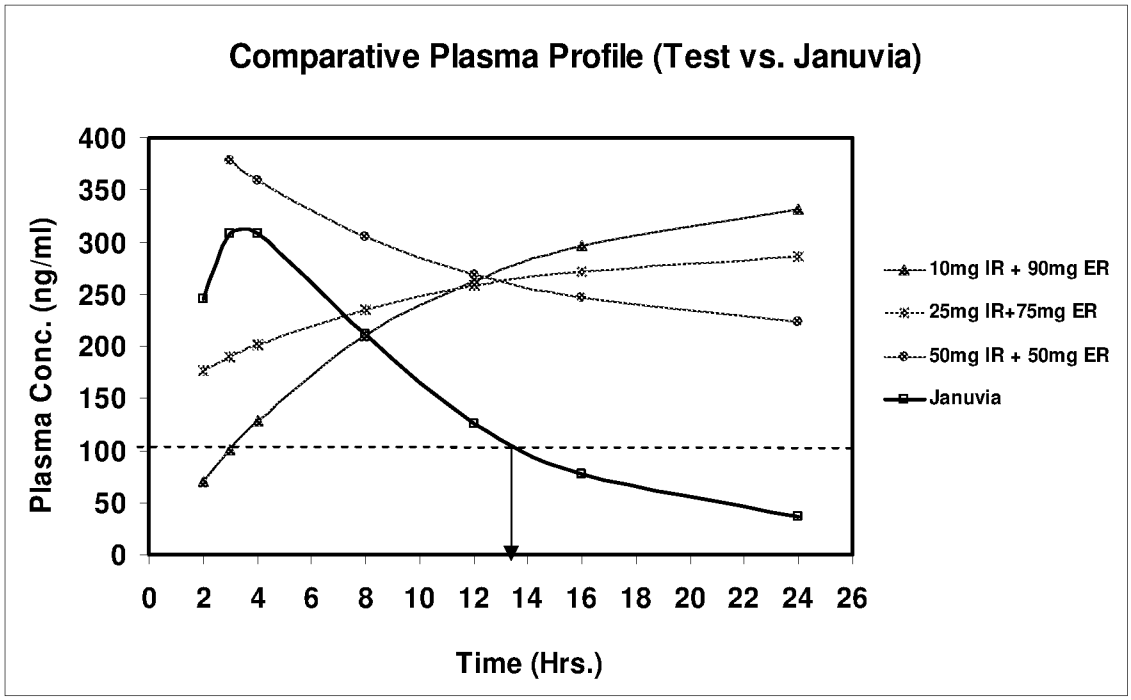

Comparative Plasma Profile (Test vs. Januvia)
Plasma Conc. (ng/ml)
400
350
300
250
200
150
100
50
0
0 2 4 6 8 10 12 14 16 18 20 22 24 26
Time (Hrs.)
10mg IR + 90mg ER
25mg IR+75mg ER
50mg IR + 50mg ER
Januvia

FIGURE 3

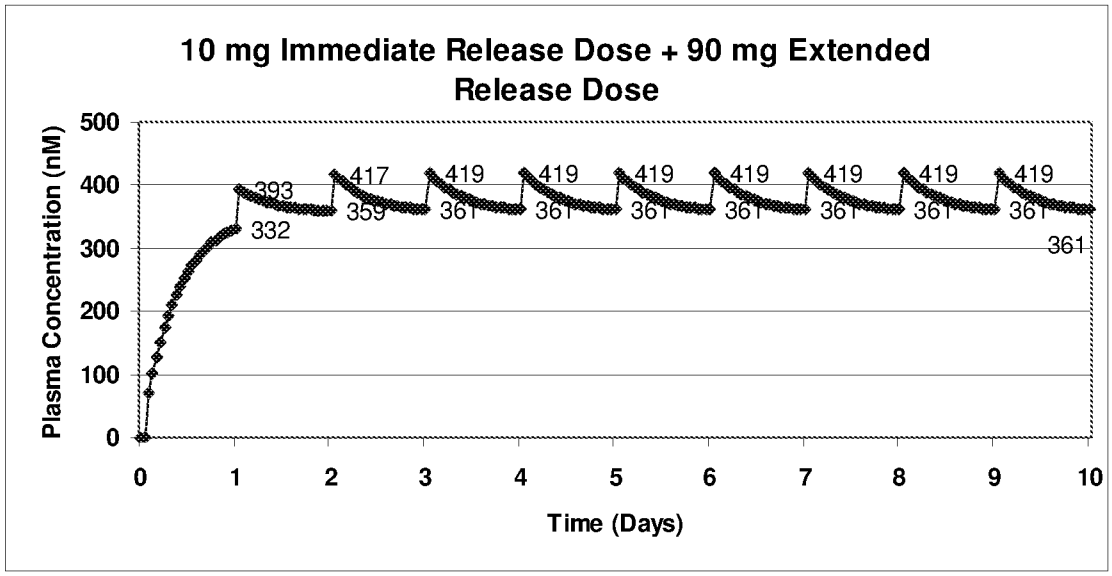

10 mg Immediate Release Dose + 90 mg Extended Release Dose
Plasma Concentration (nM)
500
400
300
200
100
0
0
1
2
3
4
5
6
7
8
9
10
Time (Days)
393
332
417
359
419
361
419
361
419
361
419
361
419
361
419
361
419
361
361

FIGURE 4

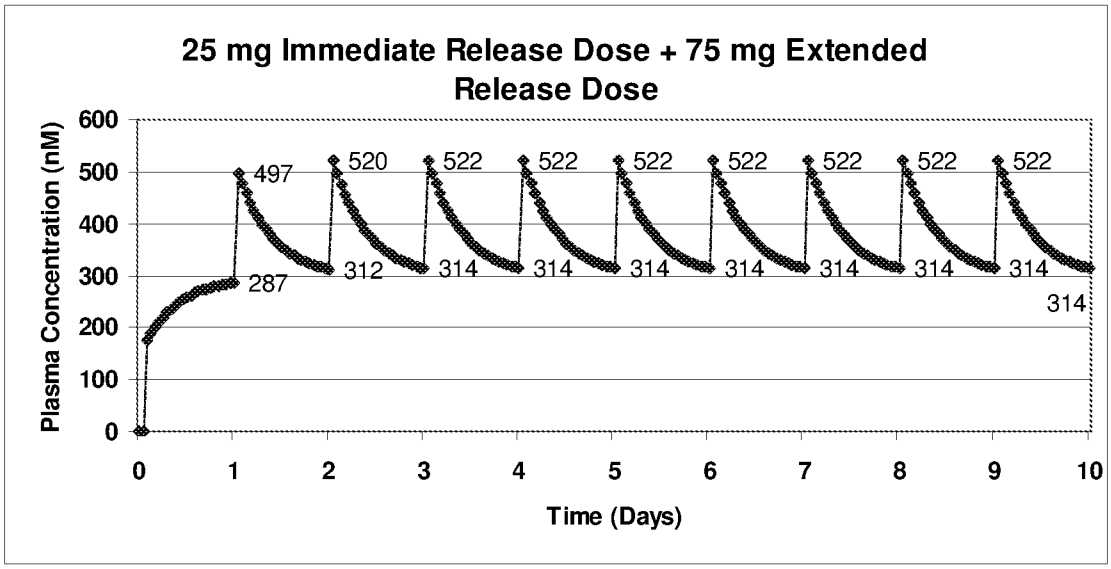

25 mg Immediate Release Dose + 75 mg Extended Release Dose
Plasma Concentration (nM)
600
500
400
300
200
100
0
497
520
522
522
522
522
522
522
522
287
312
314
314
314
314
314
314
314
314
0
1
2
3
4
5
6
7
8
9
10
Time (Days)

FIGURE 5

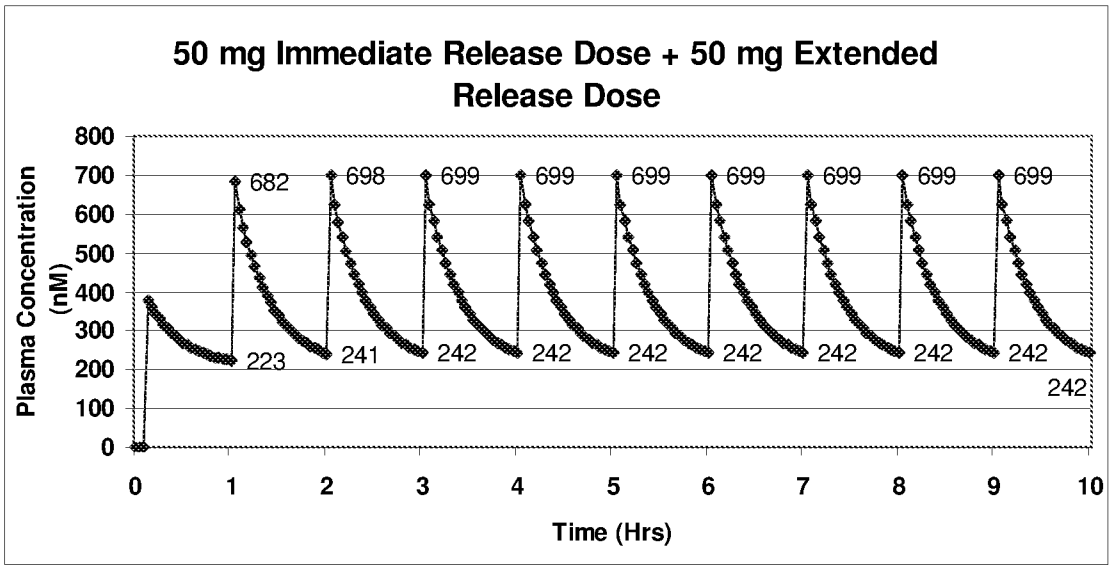

50 mg Immediate Release Dose + 50 mg Extended Release Dose
Plasma Concentration (nM)
800
700
600
500
400
300
200
100
0
682
698
699
699
699
699
699
699
699
223
241
242
242
242
242
242
242
242
0
1
2
3
4
5
6
7
8
9
10
Time (Hrs)

FIGURE 6

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2015/055554

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K9/20 A61K9/24 A61K9/28
ADD.

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN 103 027 898 A (SHENZHEN HYBIO PHARMACEUTICAL) 10 April 2013 (2013-04-10) the whole document -----	1-21
X	US 2013/059002 A1 (SMRDEL POLONA [SI] ET AL) 7 March 2013 (2013-03-07) cited in the application examples 2-4, 10-20 -----	1-21
X	US 2008/064701 A1 (SESHA RAMESH [US]) 13 March 2008 (2008-03-13) cited in the application paragraph [0039] - paragraph [0042] paragraph [0076] examples 1,2 -----	1-21

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

☒ 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

"E" earlier application or patent but published on or after the international filing date

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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

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 October 2015	27/10/2015

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2015/055554

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
CN 103027898 A	10-04-2013	NONE	
US 2013059002 A1	07-03-2013	EP 2356985 A1	17-08-2011
		EP 2533767 A1	19-12-2012
		US 2013059002 A1	07-03-2013
		WO 2011098483 A1	18-08-2011
US 2008064701 A1	13-03-2008	NONE	