



(43) International Publication Date
3 July 2014 (03.07.2014)

(10) International Publication Number
WO 2014/102715 A1

- (51) **International Patent Classification:**
A61K 9/54 (2006.01) *A61K 9/50* (2006.01)
- (21) **International Application Number:**
PCT/IB2013/061298
- (22) **International Filing Date:**
23 December 2013 (23.12.2013)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:**
3994/DEL/2012 24 December 2012 (24.12.2012) IN
- (71) **Applicant:** RANBAXY LABORATORIES LIMITED
[IN/IN]; Head Office: 12th Floor, Devika Tower, 06 Nehru
Place, New Delhi, Delhi 110019 (IN).
- (72) **Inventors:** VATS, Sandeep, Kumar; 1659/31, St. No. 3,
Shastri Colony, Gohana Road, Sonipat City, Haryana
131001 (IN). MONDAL, Balaram; Kharui, Purba, East
Midnapore, West Bengal 721134 (IN). RAMARAJU,
Kalaiselvan; s/o Ramaraju, Udayampatty, Kattukulam
Post, Thiruvellarai VIA, Tiruchirappalli, Tamil Nadu
621009 (IN). SINGH, Romi, Barat; A-14, Badshah Bagh,
Varanasi, Uttar Pradesh 221002 (IN). SINGLA, Ajay, Ku-
mar; A-50, FF, Executive Floors, South City - II, Gurgaon,
Haryana 122018 (IN).

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

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

Published:

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

(54) **Title:** PHARMACEUTICAL COMPOSITIONS COMPRISING A BIGUANIDE AND A LOW DOSE ANTIDIABETIC AGENT

(57) **Abstract:** The present invention relates to pharmaceutical compositions comprising a combination of a biguanide present in an extended-release form as well as an immediate-release form and a low dose antidiabetic agent present in an immediate-release form. It also relates to processes for preparing such compositions. Further, it relates to a method of treating diabetes using compositions of the present invention.



WO 2014/102715 A1

PHARMACEUTICAL COMPOSITIONS COMPRISING A BIGUANIDE AND A LOW DOSE ANTIDIABETIC AGENT

Field of the Invention

The present invention relates to pharmaceutical compositions comprising a
5 combination of a biguanide present in an extended-release form as well as an immediate-
release form and a low dose antidiabetic agent present in an immediate-release form. It
also relates to processes for preparing such compositions. Further, it relates to a method of
treating diabetes using compositions of the present invention.

Background of the Invention

10 Two major forms of diabetes mellitus are now recognized: Type I and Type II.
Type I diabetes, or insulin-dependent diabetes, is the result of an absolute deficiency of
insulin, the hormone that regulates glucose utilization; patients with Type I diabetes are
dependent on exogenous insulin for survival. Type II diabetes, or non-insulin-dependent
diabetes (NIDDM), often occurs concurrent with normal, or even elevated levels of insulin,
15 and appears to be the result of the inability of tissues to respond appropriately to insulin
(*i.e.*, insulin resistance). Insulin resistance is a major susceptibility trait of NIDDM and
also is a contributing factor in arteriosclerosis, hypertension, lipid disorders, and
polycystic ovarian syndrome.

Biguanides have been the most widely used class of antidiabetics. They act by
20 increasing insulin activity in the peripheral tissues, reducing hepatic glucose output due to
inhibition of gluconeogenesis, and reducing the absorption of glucose from the intestine.
Metformin, phenformin, buformin, etc., belong to this group. Metformin has been widely
prescribed for lowering blood glucose in patients with NIDDM and is marketed in 500 mg,
750 mg, 850 mg, and 1,000 mg strengths. However, because it is a short acting drug,
25 metformin requires twice-daily or three-times-daily dosing (500 mg to 850 mg tabs, 2 to 3
times per day or 1,000 mg tab twice per day with meals). Adverse events associated with
metformin include anorexia, nausea, vomiting, and diarrhea. The adverse events may be
partially avoided by either reducing the initial dose and/or the maintenance dose by taking
an extended-release dosage form rather than multiple daily doses. Besides reducing the
30 adverse events, administering an extended-release dosage form provides a reduction in the
frequency of administration. Further, the use of metformin therapy is limited by the

decline in the duration of its efficacy. This problem can be solved by using a biguanide in combination with other antidiabetic agents.

Since various antidiabetic agents act by different mechanisms, a combination therapy of a biguanide and an additional antidiabetic agent, therefore, would have a greater efficacy (an additive and/or synergistic effect) and there would be a possibility of reducing the adverse effects as a result of using lower doses.

There are many low dose antidiabetic agents which can be used in combination with a biguanide in an immediate-release form and enhance its efficacy and reduce the adverse events. The low dose antidiabetic agents include, but are not limited to, dipeptidyl peptidase-IV (DPP-IV) inhibitors such as sitagliptin, linagliptin, vildagliptin, saxagliptin, alogliptin, and dutogliptin; meglitinides such as mitiglinide, repaglinide, and nateglinide; second generation sulphonyl ureas such as glibenclamide, glipizide, gliclazide, and glimiperide; glucagon like peptide (GLP-1) analogues such as exenatide; and other hypoglycaemics which are used as an adjunct to metformin therapy.

The formulations comprising the combination of biguanide and a low dose antidiabetic agent are commercially available under the brand names Janumet[®] (sitagliptin + metformin HCl), Jentadueto[®] (linagliptin + metformin HCl), Kombiglyze XR[®] (saxagliptin + metformin HCl), Eucreas[®] (vildagliptin + metformin HCl), Avandamet (rosiglitazone maleate + metformin HCl), Glucovance[®] (glyburide + metformin HCl), Metaglip[®] (glipizide + metformin HCl), and Prandimet[®] (repaglinide + metformin HCl).

U.S. Patent Nos. 6,890,898; 6,803,357; 7,078,381; 7,157,429; 7,459,428; and 7,829,530 relate to the use of a combination of a DPP-IV inhibitor and metformin.

U.S. Publication No. 2009/0105265 and PCT Publication No. WO 2010/092163 cover compositions comprising combinations of DPP-IV inhibitors with metformin.

U.S. Patent No. 8,178,541; U.S. Publication No. 2011/0065731; and PCT Publication No. WO 2011/039367 cover pharmaceutical combinations and compositions comprising linagliptin and metformin.

U.S. Publication Nos. 2008/0076811; and 2011/0045062; and PCT Publication No. WO 2007/149797 cover combinations and compositions comprising vildagliptin and metformin.

U.S. Publication No. 2010/0074950 relates to a pharmaceutical composition for treating diabetes comprising a slow-release osmotic core comprising metformin and an immediate-release coating comprising a DPP-IV inhibitor.

U.S. Publication No. 2009/0221652 covers a combination of metformin and
5 meglitinide.

U.S. Patent No. 6,677,358 relates to a combination of a long-acting and a short-acting hypoglycemic agent. It covers a pharmaceutical composition comprising repaglinide and metformin together with a suitable carrier.

The combination formulations are of larger size, and hence result in reduced
10 patient compliance. In all the cited prior art, metformin is present in a high dose and hence a large amount of polymer would be required to control the release of metformin from the extended-release dosage form leading to a larger size formulation and hence decreased patient compliance. However, in the present invention, a portion of biguanide is present in an immediate-release form along with the low dose antidiabetic agent. The
15 addition of a portion of metformin in the immediate-release drug coat results in a reduction of the core size and hence leads to a composition having reduced size and improved patient compliance. Further, metformin acts as a water-soluble channeling agent and facilitates the dissolution of the poorly soluble drug.

Although the prior art teaches pharmaceutical compositions that contain both
20 biguanide and a low dose antidiabetic agent, there is a need in the art to develop drug formulations, in which biguanide is present in an extended-release form as well as an immediate-release form and a low dose antidiabetic agent is present in an immediate-release form, that are smaller in size, more patient compliant, involve a simple method of production, and are cost-effective.

25 Summary of the Invention

The present invention relates to a pharmaceutical composition comprising a biguanide in an extended-release form as well as an immediate-release form and a low dose antidiabetic agent in an immediate-release form. The present invention relates to a pharmaceutical composition of a biguanide and a low dose antidiabetic agent comprising:

- 5 (i) a biguanide core comprising a therapeutically effective amount of biguanide or its pharmaceutically effective salts and one or more pharmaceutically acceptable excipients;
- (ii) optionally a seal coat;
- 5 (iii) an extended-release coat comprising one or more rate-controlling materials, wherein there is at least one passageway;
- (iv) optionally a second seal coat;
- (v) an immediate-release drug coat comprising biguanide and a low dose antidiabetic agent or its pharmaceutically effective salt and one or more
- 10 pharmaceutically acceptable excipients; and
- (vi) optionally a film coat.

The present invention also includes processes for the preparation of said pharmaceutical composition and a method of treating diabetes by administering said pharmaceutical composition.

15 Detailed Description of the Invention

A first aspect of the present invention provides a pharmaceutical composition of a biguanide and a low dose antidiabetic agent comprising:

- 20 (i) a biguanide core comprising a therapeutically effective amount of biguanide or its pharmaceutically effective salts and one or more pharmaceutically acceptable excipients;
- (ii) optionally a seal coat;
- (iii) an extended-release coat comprising one or more rate-controlling materials, wherein there is at least one passageway;
- (iv) optionally a second seal coat;
- 25 (v) an immediate-release drug coat comprising biguanide and a low dose antidiabetic agent or its pharmaceutically effective salt and one or more pharmaceutically acceptable excipients; and
- (vi) optionally a film coat.

According to one embodiment of this aspect, the biguanide used in the composition is selected from one or more of metformin, phenformin, buformin, and pharmaceutically acceptable salts, solvates, polymorphs, enantiomers, isomers, or mixtures thereof.

Particularly, the biguanide is metformin or pharmaceutically acceptable salts, solvates, polymorphs, enantiomers, isomers, or mixtures thereof. The amount of biguanide in the present composition may range from 25 mg to 2000 mg.

According to another embodiment of this aspect, the low dose antidiabetic agent used in the composition is selected from one or more of DPP-IV inhibitors, meglitinides, second generation sulphonyl ureas, glucagon like peptide (GLP-1) analogues, other hypoglycaemics which are used as an adjunct to metformin therapy, or mixtures thereof. Particularly, the low dose antidiabetic agent is a DPP-IV inhibitor. More particularly, the low dose antidiabetic agent is a DPP-IV inhibitor, or pharmaceutically acceptable salts, solvates, polymorphs, enantiomers, isomers, or mixtures thereof.

According to another embodiment of this aspect, the biguanide is metformin and the low dose antidiabetic agent is a DPP-IV inhibitor.

According to another embodiment of this aspect, the ratio of biguanide in the core to that in the coat ranges from about 99:1 to about 60:40.

According to another embodiment of this aspect, the biguanide may be layered onto a pharmaceutically inert core or seed. The inert core or seed may be hydrosoluble or hydroinsoluble.

According to another embodiment of this aspect, the biguanide core of the present invention comprises one or more pharmaceutically acceptable excipients selected from one or more of fillers, binders, disintegrants, anti-adherents, lubricants, glidants, osmogents, coloring agents, and flavoring agents.

According to another embodiment of this aspect, the biguanide core may additionally contain one or more absorption enhancers.

According to another embodiment of this aspect, the biguanide core may additionally contain a swellable polymer.

According to another embodiment of this aspect, the biguanide core further comprises a low dose antidiabetic agent.

According to another embodiment of this aspect, the seal coat is applied over the biguanide core or over the extended-release coat.

According to another embodiment of this aspect, the rate-controlling material used in the composition is selected from one or more of hydrophilic polymers, hydrophobic
5 polymers, water-swallowable polymers, other hydrophobic materials, or mixtures thereof.

According to another embodiment of this aspect, the pharmaceutical composition of the present invention further comprises an additional antidiabetic agent.

A second aspect of the present invention provides a process for preparing a pharmaceutical composition comprising the steps of:

- 10 (i) preparing a core comprising biguanide or its pharmaceutically effective salts and one or more pharmaceutically acceptable excipients;
- (ii) optionally coating the core with a seal coat;
- (iii) coating the biguanide core of step (i) or the seal-coated core of step (ii) with
an extended-release coating composition comprising one or more rate-
15 controlling materials, wherein there is at least one passageway;
- (iv) optionally coating the core of step (iii) with a seal coat;
- (v) coating the extended-release core of step (iii) or the seal-coated core of step
(iv) with an immediate-release coating composition comprising a biguanide
and a low dose antidiabetic agent or its pharmaceutically effective salts and
20 one or more pharmaceutically acceptable excipients; and,
- (vi) optionally providing a film coat.

A third aspect of the present invention provides a method for treating diabetes by administering to a person in need thereof a pharmaceutical composition of a biguanide and a low dose antidiabetic agent comprising:

- 25 (i) a biguanide core comprising therapeutically effective amount of biguanide or its pharmaceutically effective salts and one or more pharmaceutically acceptable excipients;
- (ii) optionally a seal coat;

- (iii) an extended-release coat comprising one or more rate-controlling materials, wherein there is at least one passageway;
- (iv) optionally a second seal coat;
- (v) an immediate-release drug coat comprising biguanide and a low dose antidiabetic agent or its pharmaceutically effective salt and one or more pharmaceutically acceptable excipients; and
- (vi) optionally a film coat.

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

The term “passageway”, as used herein, includes an aperture, orifice, bore, hole, weakened area, or an erodible element such as a gelatin plug that erodes to form an osmotic passageway for the release of the biguanide from the tablet core. In the present invention, the hole can be drilled on either side or there can be two holes on one side.

The composition of the present invention may be in the form of tablets or capsules. The capsules may include one or more of aggregated particles, pellets, mini tablets, tablets, beads, or granules.

The biguanide core present in the composition of the present invention is an osmotic tablet core. The extended-release coat surrounding the core comprises a passageway that can allow for controlled-release of the drug from the core.

The extended-release biguanide core may be present as aggregated particles, pellets, mini tablets, tablets, beads, or granules.

Alternatively, the biguanide may be layered onto a pharmaceutically inert core or seed. The inert core or seed may be hydrosoluble or hydroinsoluble.

The hydrosoluble inert cores may include soluble cores, such as sugar spheres having sugars like dextrose, lactose, anhydrous lactose, spray-dried lactose, lactose monohydrate, mannitol, starches, sorbitol, sucrose, or mixtures thereof.

The hydroinsoluble cores may include one or more of glass particles/beads, silicon dioxide, calcium phosphate dihydrate, dicalcium phosphate, calcium sulfate dihydrate,

microcrystalline cellulose (*e.g.*, Avicel[®]), silicified microcrystalline cellulose (*e.g.*, Prosolv[®]), cellulose derivatives, powdered cellulose, or mixtures thereof.

The biguanide core of the present invention comprises one or more pharmaceutically acceptable excipients. The pharmaceutically acceptable excipients are those known to the skilled in the art and may be selected from one or more of fillers, binders, disintegrants, anti-adherents, lubricants, glidants, osmogents, coloring agents, and flavoring agents.

Suitable fillers or diluents are selected from the group comprising calcium phosphate dihydrate, calcium sulfate dehydrate; cellulose derivatives such as microcrystalline cellulose, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, methyl cellulose, carboxymethyl cellulose, sodium carboxymethyl cellulose, cellulose acetate butyrate, hydroxyethyl cellulose, and ethyl cellulose; dextrose; lactose such as anhydrous lactose, spray-dried lactose, and lactose monohydrate; sucrose; mannitol; sorbitol; starches; or mixtures thereof. Further examples of diluents include sodium chloride, polyvinylpyrrolidone, polyethylene glycol, polyvinyl alcohol, polyvinyl chloride, polyvinyl acetate, ethylene vinyl acetate, polypropylene, chitosan, copolymers of lactic and glycolic acid, lactic acid polymers, glycolic acid polymers, polyorthoesters, polyanhydrides, lectins, carbopols, silicon elastomers, polyacrylic polymers, maltodextrins, fructose, inositol, trehalose, maltose raffinose, dextrans, dextrans, alpha-, beta-, and gamma-cyclodextrins, hydroxypropyl-beta-cyclodextrin, or mixtures thereof.

Suitable binders are selected from the group comprising povidones, starches, corn starch, pregelatinized starch, microcrystalline celluloses (MCC), silicified MCC (*e.g.*, Prosolv[®] HD 90), microfine celluloses, lactose, calcium carbonate, calcium sulfate, sugar, mannitol, sorbitol, dextrans, dextrin, maltodextrin, dextrose, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, magnesium carbonate, magnesium oxide, stearic acid, gums, hydroxypropylmethyl celluloses or hypromelloses (*e.g.*, Klucel[®] EF, Methocel[®] E5 premium), or mixtures thereof.

Suitable disintegrants are selected from the group comprising starch, croscarmellose sodium, crospovidone, sodium starch glycolate, or mixtures thereof.

Suitable anti-adherents are selected from the group comprising magnesium stearate, talc, calcium stearate, glyceryl behenate, polyethylene glycols, hydrogenated vegetable oil, mineral oil, stearic acid, or mixtures thereof.

5 Suitable lubricants and glidants are selected from the group comprising colloidal anhydrous silica, stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated castor oil, sucrose esters of fatty acids, microcrystalline wax, yellow beeswax, white beeswax, sodium benzoate, sodium acetate, sodium chloride, or mixtures thereof.

10 Suitable osmogens that may be used as swelling agents in the upper compressed layer are selected from the group comprising sodium or potassium chloride; sodium or potassium hydrogen phosphate; sodium or potassium dihydrogen phosphate; salts of organic acids such as sodium or potassium acetate, magnesium succinate, sodium benzoate, sodium citrate and sodium ascorbate; carbohydrates such as mannitol, sorbitol, arabinose, ribose, xylose, glucose, fructose, mannose, galactose, sucrose, maltose, lactose, and raffinose; water-soluble amino acids such as glycine, leucine, alanine, and methionine; 15 urea and the like; a polymer consisting of acrylic acid lightly cross-linked with polyallylsucrose; or mixtures thereof. The active ingredient, for example, a biguanide, may itself act as an osmogen and facilitate the drug release.

The coloring agents and flavoring agents of the present invention may be selected from any FDA approved colors and flavors for oral use.

20 The biguanide core may additionally contain one or more absorption enhancers. Suitable absorption enhancers are selected from the group comprising surfactants (anionic, cationic, and amphoteric), bile salts, calcium chelating agents, fatty acids, cyclodextrins, chitosan, or mixtures thereof. Particularly, the absorption enhancer is a surfactant.

25 The biguanide core may additionally contain a swellable polymer. The term “swellable polymer” refers to polymers that gel, swell, or expand in the presence of water or biological fluids. Suitable swellable polymers are selected from the group comprising high molecular weight hydroxypropylmethyl cellulose, high molecular weight polyethylene oxides (such as POLYOX[®] WSR-301, WSR-303, or WSR Coagulant), hydroxypropyl cellulose, hydroxyethyl cellulose, sodium carboxymethyl cellulose, 30 xanthan gum, polyvinyl acetate, or mixtures thereof.

The biguanide core may be prepared by any pharmaceutically acceptable technique that achieves uniform blending, *e.g.*, dry blending, dry granulation, wet granulation, compaction, or fluidized bed granulation. Particularly, the core formulation of the present invention is fabricated by compression into tablets.

5 Suitable solvents are selected from the group comprising methylene chloride, isopropyl alcohol, acetone, methanol, ethanol, water, or mixtures thereof. Particularly, purified water is used as the solvent.

 Suitable rate-controlling materials used in the extended-release coat composition are selected from the group comprising one or more of hydrophilic polymers, hydrophobic
10 polymers, water-swellaable polymers, other hydrophobic materials, or mixtures thereof. The extended-release coat is permeable to the passage of water, biological fluids, and the active ingredient in the core. Further, the extended-release coat contains a passageway.

 Suitable hydrophilic polymers are selected from the group comprising cellulose derivatives such as hydroxypropylmethyl cellulose, hydroxypropyl cellulose, hydroxyethyl
15 cellulose, hydroxymethyl cellulose, methyl cellulose, carboxymethyl cellulose, sodium carboxymethyl cellulose, and carboxymethyl cellulose calcium; alginates such as alginic acid, ammonium alginate, sodium alginate, potassium alginate, calcium alginate, and propylene glycol alginate; gums such as xanthan gum, guar gum, and locust bean gum; polyvinyl alcohol; povidone; polyvinylpyrrolidone; carbomer; potassium pectate;
20 potassium pectinate; polysaccharide; polyalkylene oxides; polyalkyleneglycol such as PEG-400, PEG-3350, PEG-6000, or mixtures thereof. Particularly, hydrophilic polymers are selected from PEG-400, PEG-3350, starch and derivatives, or mixtures thereof.

 Suitable hydrophobic polymers are selected from the group comprising cellulose derivatives such as ethyl cellulose, hydroxyethyl cellulose, cellulose acetate, cellulose
25 acetate butyrate, cellulose acetate phthalate, cellulose acetate trimellitate, and hydroxypropylmethyl cellulose phthalate; poly (alkyl) methacrylate; copolymers of acrylic or methacrylic acid esters such as ammonio methacrylate copolymer (*e.g.*, Eudragit[®] RL or Eudragit[®] RS), methacrylic acid copolymers (*e.g.*, Eudragit[®] L, or Eudragit[®] S), methacrylic acid-acrylic acid ethyl ester copolymer (*e.g.*, Eudragit[®] L 100-5), methacrylic
30 acid esters neutral copolymer (*e.g.*, Eudragit[®] NE 30 D), dimethylaminoethyl-methacrylate-methacrylic acid esters copolymer (*e.g.*, Eudragit[®] E 100); vinyl methyl

ether/maleic anhydride copolymers (*e.g.*, Gantrez[®]), their salts and esters; polyvinyl acetate, or mixtures thereof.

Suitable water-swellaable polymers are selected from the group comprising polyethylene oxide having a molecular weight of from 100,000 to 8,000,000; 5 poly(hydroxy alkyl methacrylate) having a molecular weight of from 30,000 to 5,000,000; poly(vinyl) alcohol having a low acetal residue, which is cross-linked with glyoxal, formaldehyde, or glutaraldehyde and having a degree of polymerization of from 200 to 30,000; a mixture of methyl cellulose, cross-linked agar, and carboxymethyl cellulose; a water-insoluble, water-swellaable copolymer produced by forming a dispersion of a finely 10 divided copolymer of maleic anhydride with styrene, ethylene, propylene, butylene, or isobutylene cross-linked with from 0.001 moles to 0.5 moles of saturated cross-linking agent per mole of maleic anhydride in the copolymer; Carbopol[®] carbomer which is an acidic carboxy polymer having a molecular weight of from 450,000 to 4,000,000; Cyanamer[®] polyacrylamides; cross-linked water-swellaable indene-maleic anhydride 15 polymers; polyacrylic acid having a molecular weight of from 80,000 to 200,000; starch graft copolymers; acrylate polymer polysaccharides composed of condensed glucose units such as diester cross-linked polyglucan, and the like; Amberlite[®] ion exchange resins; Explotab[®] sodium starch glycolate; Ac-Di-Sol[®] croscarmellose sodium; or mixtures thereof.

20 Suitable hydrophobic materials are selected from the group comprising water-swellaable waxes such as beeswax, carnauba wax, microcrystalline wax, candelilla wax, spermaceti, montan wax, paraffin wax, shellac wax; hydrogenated vegetable oils such as hydrogenated cottonseed oil and hydrogenated castor oil; lecithin; hydrogenated tallow; petrolatum; ozokerite, and the like; synthetic waxes such as polyethylene, and the like; 25 fatty acids such as stearic acid, palmitic acid, lauric acid, eleostearic acids, and the like; fatty alcohols such as lauryl alcohol, cetostearyl alcohol, stearyl alcohol, cetyl alcohol, and myristyl alcohol; fatty acid esters such as glyceryl monostearate, glycerol monooleate, acetylated monoglycerides, tristearin, tripalmitin, cetyl esters wax, glyceryl palmitostearate, and glyceryl behenate; mineral oil, or mixtures thereof.

30 The extended-release coat composition may additionally include plasticizers selected from the group comprising propylene glycol, triethylene glycol, oleic acid,

ethylene glycol monoleate, triethyl citrate, triacetin, diethyl phthalate, glyceryl monostearate, dibutyl sebacate, acetyl triethyl citrate, acetyl tributyl citrate, castor oil, or mixtures thereof; and opacifiers selected from the group comprising titanium dioxide, talc, calcium carbonate, behenic acid, cetyl alcohol, or mixtures thereof.

5 The coating compositions may be coated onto the biguanide core by conventional methods such as drug layering, dry compression, deposition, and printing.

 The coating composition may be applied as a solution or dispersion of rate-controlling materials. Suitable solvents used for preparing a solution/dispersion of rate-controlling materials are selected from the group comprising methylene chloride,
10 isopropyl alcohol, acetone, methanol, ethanol, water, or mixtures thereof.

 A seal coating may be applied over the biguanide core or over the extended-release coat. The polymers used to provide the seal coating may include one or more of a hydrophilic polymer. Examples include, but are not limited to, hydroxypropyl cellulose, hydroxypropylisopropyl cellulose, methoxypropyl cellulose, hydroxypropylmethyl
15 cellulose, hydroxypropylpentyl cellulose, hydroxypropylhexyl cellulose, or mixtures thereof. The seal coating may optionally be opacified.

 The extended-release biguanide core is coated with an immediate-release drug layer. The immediate-release drug layer comprises a therapeutically effective amount of a low dose antidiabetic agent and a biguanide.

20 The low dose antidiabetic agents used in the composition include, but are not limited to, dipeptidyl peptidase-IV (DPP-IV) inhibitors such as sitagliptin, linagliptin, vildagliptin, saxagliptin, alogliptin, and dutogliptin; meglitinides such as mitiglinide, repaglinide, and nateglinide; second generation sulphonyl ureas such as glibenclamide, glipizide, gliclazide, and glimiperide; glucagon like peptide (GLP-1) analogues such as
25 exenatide; and other hypoglycaemics which are used as an adjunct to metformin therapy. The amount of the low dose antidiabetic agent used in the present composition may range from 1 mg to 200 mg.

 Further, a portion of biguanide is present in the immediate-release drug layer along with the low dose antidiabetic agent. The addition of a portion of biguanide in the coat
30 results in reduction of core size and hence leads to a composition having reduced size and

improved patient compliance. Further, a biguanide such as metformin acts as a water-soluble channeling agent and facilitates the dissolution of the poorly soluble drug.

The immediate-release drug layer further comprises one or more pharmaceutically acceptable excipients known to those skilled in the art which may be selected from one or
5 more of wicking agents, wetting agents, plasticizers, opacifiers, and colorants.

A wicking agent is defined as any material with the ability to draw water into the porous network of a delivery device. Suitable wicking agents are selected from the group comprising silicon dioxide (Syloid[®] 244 FP), kaolin, titanium dioxide, alumina, niacinamide, sodium lauryl sulfate, low molecular weight polyvinyl pyrrolidone, m-pyrol,
10 bentonite, magnesium aluminum silicate, polyester, polyethylene, or mixtures thereof. Particularly, the wicking agent is a non-swelling wicking agent, such as sodium lauryl sulfate, colloidal silicon dioxide, or low molecular weight polyvinylpyrrolidone.

Suitable wetting agents are selected from the group comprising hydrophilic surfactants, hydrophobic surfactants, or mixtures thereof. The hydrophilic surfactants may
15 be selected from one or more of non-ionic surfactants, ionic surfactants, or mixtures thereof.

Suitable hydrophobic surfactants are selected from the group comprising one or more of alcohols; polyoxyethylene alkylethers; fatty acids and fatty acid esters such as glycerol fatty acid monoesters, glycerol fatty acid diesters, acetylated glycerol fatty acid
20 monoesters, acetylated glycerol fatty acid diesters, lower alcohol fatty acid esters, polyethylene glycol fatty acid esters, polyethylene glycol glycerol fatty acid esters, polypropylene glycol fatty acid esters, and sorbitan fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene glycerides; lactic acid derivatives of monoglycerides; lactic acid derivatives of diglycerides; propylene glycol diglycerides;
25 polyoxyethylene-polyoxypropylene block copolymers; polyethyleneglycols as esters or ethers; polyethoxylated castor oil; polyethoxylated hydrogenated castor oil; polyethoxylated fatty acid from castor oil; polyethoxylated fatty acid from hydrogenated castor oil; or mixtures thereof.

Suitable non-ionic surfactants are selected from the group comprising
30 alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl macrogolglycerides; caprylocaproyl macrogolglycerides; polyoxyethylene alkyl ethers; polyoxyethylene

alkylphenols; polyethylene glycol fatty acid esters; polyethylene glycol glycerol fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; polyglycerol fatty acid esters; polyoxyethylene glycerides; polyoxyethylene sterols and derivatives and analogues thereof; polyoxyethylene vegetable
5 oils; polyoxyethylene hydrogenated vegetable oils; reaction products of polyols and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; sugar esters; sugar ethers; sucroglycerides; or mixtures thereof.

Suitable ionic surfactants are selected from the group comprising alkyl ammonium
10 salts; bile acids and salts, analogues, and derivatives thereof; fatty acid derivatives of amino acids, oligopeptides, and polypeptides; glyceride derivatives of amino acids, oligopeptides, and polypeptides; acyl lactylates; monoacetylated tartaric acid esters of monoglycerides; monoacetylated tartaric acid esters of diglycerides; diacetylated tartaric acid esters of monoglycerides; diacetylated tartaric acid esters of diglycerides;
15 succinylated monoglycerides; citric acid esters of monoglycerides; citric acid esters of diglycerides; alginate salts; propylene glycol alginate; lecithins and hydrogenated lecithins; lysolecithin and hydrogenated lysolecithins; lysophospholipids and derivatives thereof; phospholipids and derivatives thereof; salts of alkylsulfates; salts of fatty acids; sodium docusate; or mixtures thereof.

Suitable plasticizers are selected from the group comprising propylene glycol,
20 triethylene glycol, oleic acid, ethylene glycol monoleate, triethyl citrate, triacetin, diethyl phthalate, glyceryl monostearate, dibutyl sebacate, acetyl triethyl citrate, acetyl tributyl citrate, castor oil, or mixtures thereof.

Suitable opacifiers are selected from the group comprising titanium dioxide, talc,
25 calcium carbonate, behenic acid, cetyl alcohol, or mixtures thereof.

The immediate-release drug layer may further include one or more film-forming polymers. The film-forming polymers may be hydrophilic polymers.

The low dose antidiabetic agent coating composition may be applied as a solution or dispersion over the extended-release coat. Suitable solvents used for preparing a
30 solution or dispersion of the low dose antidiabetic agent are selected from the group

comprising methylene chloride, isopropyl alcohol, acetone, methanol, ethanol, water, or mixtures thereof.

5 The pharmaceutical composition may optionally be coated with one or more layers of a film-coat comprising film-forming agents and/or pharmaceutically acceptable excipients.

Examples of film-forming agents include, but are not limited to, ethyl cellulose, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, methyl cellulose, carboxymethyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropylmethyl phthalate, cellulose acetate, cellulose acetate trimellitate, cellulose acetate phthalate, 10 waxes such as polyethylene glycol, methacrylic acid polymers such as Eudragit[®] RL and Eudragit[®] RS, or mixtures thereof. Particularly, HPC-L is used as the film-forming agent. Alternatively, commercially available coating compositions comprising film-forming polymers marketed under various trade names, such as Opadry[®], may also be used for coating.

15 The film-forming agents may be applied as a solution or dispersion of coating ingredients. Examples of solvents used for preparing a solution or dispersion of the coating ingredients include methylene chloride, isopropyl alcohol, acetone, methanol, ethanol, water, or mixtures thereof.

The various coats of the composition may be coated using a conventional coating 20 pan, a spray coater, a rotating perforated pan, or an automated system, such as a centrifugal fluidizing (CF) granulator, a fluidized bed process, or any other suitable automated coating equipment.

The various compositions described above are used for treating diabetes.

The present invention is illustrated below by reference to the following examples. 25 However, one skilled in the art will appreciate that the specific methods and results discussed are merely illustrative of the invention, and not to be construed as limiting the invention, as many variations thereof are possible without departing from the spirit and scope of the invention.

EXAMPLES

Example 1:

Ingredients	Percent w/w of tablet
Core Tablet	
Metformin hydrochloride	73.33
Polyvinylpyrrolidone	6.03
Sodium lauryl sulphate	0.81
Hydroxypropylmethyl cellulose	0.81
Magnesium stearate	0.81
Purified water	q.s.
Seal Coating (2.0% weight build-up; range 1.5% to 2.5%)	
Hydroxypropylmethyl cellulose	1.64
Isopropyl alcohol (85 parts)	q.s.
Water (15 parts)	q.s.
Extended-Release Coating (2% to 10% weight build-up)	
Cellulose acetate	3.98
Polyethylene glycol	0.10
Triacetin	0.10
Acetone	q.s.
Purified water	q.s.
Drug Coating	
Linagliptin	0.41
Metformin hydrochloride	8.15
Hydroxypropyl cellulose	3.67
Poloxamer F-87	0.16
Purified water	q.s.
Ethanol	q.s.

Procedure:**Core Tablets:**

- 5 1. Metformin hydrochloride, hydroxypropylmethyl cellulose, and polyvinylpyrrolidone were mixed.
2. The dry mix of step 1 was granulated with water.
3. The granules of step 2 were dried to LOD <4.0% followed by the addition of sodium lauryl sulphate and magnesium stearate.
- 10 4. The blend of step 3 was compressed into core tablets.

Seal Coating:

5. The tablets of step 4 were coated with a hydro-alcoholic solution of hydroxypropylmethyl cellulose.

Extended-Release Coating:

- 5 6. A solution of cellulose acetate, polyethylene glycol, and triacetin was prepared in an acetone-water mixture.
7. The seal coated tablets of step 5 were coated with the solution of step 6.
8. The tablets of step 7 were dried at 45°C for 24 hours and drilled with two holes on both sides.

10 **Drug Layering:**

9. Metformin hydrochloride, poloxamer, and hydroxypropyl cellulose were dissolved in purified water.
10. Linagliptin was dispersed in ethanol.
11. The dispersion of step 10 was added to the solution of step 9.
- 15 12. The extended-release tablets of step 8 were coated with the dispersion of step 11 to obtain the final coated tablets.

Example 2:

Ingredients	Percent w/w of tablet
Core Tablet	
Metformin hydrochloride	70.15
Polyvinylpyrrolidone	5.46
Sodium lauryl sulphate	0.78
Hydroxypropylmethyl cellulose	0.78
Magnesium stearate	0.78
Purified water	q.s.
Seal Coating (2.0% weight build-up; range 1.5% to 2.5%)	
Hydroxypropylmethyl cellulose	1.56
Isopropyl alcohol (85 parts)	q.s.
Water (15 parts)	q.s.
Extended-Release Coating (2% to 10% weight build-up)	
Cellulose acetate	4.64
Polyethylene glycol/sorbitol	0.25
Triacetin	0.26
Acetone	q.s.
Purified water	q.s.
Seal coating (optional) (2.0% weight build-up; range 1.5 - 2.5%)	
Hydroxypropylmethyl cellulose	1.69
Isopropyl alcohol (85 parts)	q.s.
Water (15 parts)	q.s.
Drug Coating	
Linagliptin	0.39
Metformin hydrochloride	7.79
Hydroxypropyl cellulose	1.95
Poloxamer F-87	1.56
Purified water	q.s.
Film Coating (optional)	
Opadry [®] Clear	1.96
Purified water	q.s.

Procedure:**Core Tablets:**

1. Metformin hydrochloride, hydroxypropylmethyl cellulose, and sodium lauryl sulphate are loaded in a fluid bed granulator.
2. A binder solution of polyvinylpyrrolidone in purified water is prepared.
3. The dry mix of step 1 is granulated with the binder solution of step 2.
4. The granules of step 3 are dried to LOD <4.0% followed by lubrication with magnesium stearate.

5. The blend of step 4 is compressed into core tablets.

Seal Coating:

6. The tablets of step 5 are coated with a solution of hydroxypropylmethyl cellulose in an isopropyl alcohol-water mixture.

5 **Extended-Release Coating:**

7. A solution of cellulose acetate, polyethylene glycol/sorbitol, and triacetin is prepared in an acetone-water mixture.
8. The seal coated tablets of step 6 are coated with the solution of step 7.
9. The tablets of step 8 are dried in a tray drier at 40°C to 50°C for 24 hours and drilled
- 10 with two holes on both sides as appropriate.

Seal Coating:

10. The extended-release tablets of step 9 are coated with a solution of hydroxypropylmethyl cellulose in an isopropyl alcohol-water mixture.

Drug Layering:

- 15 11. Metformin hydrochloride and hydroxypropyl cellulose are dissolved in purified water.
12. Linagliptin is dispersed into the solution of step 11, followed by the addition of poloxamer.
13. The seal coated tablets of step 10 are coated with the dispersion of step 12.

20 **Film Coating:**

14. The drug layered tablets of step 13 are coated with an aqueous dispersion of Opadry[®] Clear to obtain the final coated tablets.

Example 3:

Ingredients	Percent w/w of tablet
Core Tablet	
Metformin hydrochloride	70.70
Polyvinylpyrrolidone	5.50
Sodium lauryl sulphate	0.79
Magnesium stearate	0.79
Isopropyl alcohol	q.s.
Purified water	q.s.
Seal Coating (2.0% weight build-up; range 1.5% to 2.5%)	
Hydroxypropylmethyl cellulose	1.56
Isopropyl alcohol (85 parts)	q.s.
Water (15 parts)	q.s.
Extended-Release Coating: (2% to 10% weight build-up)	
Cellulose acetate 398-10	4.72
Polyethylene glycol/sorbitol	0.25
Triacetin	0.26
Acetone	q.s.
Purified water	q.s.
Seal Coating (optional) (2.0% weight build-up; range 1.5% to 2.5%)	
Hydroxypropylmethyl cellulose	1.69
Isopropyl alcohol (85 parts)	q.s.
Water (15 parts)	q.s.
Drug Coating	
Linagliptin	0.39
Metformin hydrochloride	7.86
Hydroxypropyl cellulose	1.96
Poloxamer	1.57
Purified water	q.s.
Film Coating (optional)	
Opadry [®] Clear	1.96
Purified water	q.s.

Procedure:**Core Tablets:**

1. Metformin hydrochloride and sodium lauryl sulphate are sifted and loaded in a fluid
5 bed granulator.
2. A binder solution of polyvinylpyrrolidone in an isopropyl alcohol-water mixture is prepared.
3. The dry mix of step 1 is granulated with the binder solution of step 2.

4. The granules of step 3 are dried to LOD <4.0% followed by lubrication with magnesium stearate.
5. The blend of step 4 is compressed into core tablets.

Seal Coating:

- 5 6. The tablets of step 5 are coated with a solution of hydroxypropylmethyl cellulose in an isopropyl alcohol-water mixture.

Extended-Release Coating:

7. A solution of cellulose acetate-polyethylene glycol/sorbitol-triacetin is prepared in an acetone-water mixture.
- 10 8. The seal coated tablets of step 6 are coated with the solution of step 7.
9. The tablets of step 8 are dried in a tray drier at 40°C to 50°C for 24 hours and drilled with two holes on both sides as appropriate.

Seal Coating:

10. The extended release tablets of step 9 are coated with a solution of
- 15 hydroxypropylmethyl cellulose in an isopropyl alcohol-water mixture.

Drug Layering:

11. Metformin hydrochloride and hydroxypropyl cellulose are dissolved in purified water.
12. Linagliptin is dispersed into the solution of step 11 followed by the addition of
- 20 poloxamer.
13. The seal coated tablets of step 10 are coated with the dispersion of step 12.

Film Coating:

14. The drug layered tablets of step 13 are coated with an aqueous dispersion of Opadry[®] Clear to obtain the final coated tablets.

We Claim:

- 1 1. A pharmaceutical composition of a biguanide and a low dose antidiabetic agent
2 comprising:
 - 3 (i) a biguanide core comprising a therapeutically effective amount of biguanide
4 or its pharmaceutically effective salts and one or more pharmaceutically
5 acceptable excipients;
 - 6 (ii) optionally a seal coat;
 - 7 (iii) an extended-release coat comprising one or more rate-controlling materials,
8 wherein there is at least one-passageway;
 - 9 (iv) optionally a second seal coat;
 - 10 (v) an immediate-release drug coat comprising biguanide and a low dose
11 antidiabetic agent or its pharmaceutically effective salt and one or more
12 pharmaceutically acceptable excipients; and
 - 13 (vi) optionally a film coat.
- 1 2. The pharmaceutical composition according to claim 1, wherein the biguanide is
2 selected from metformin, phenformin, buformin, and pharmaceutically acceptable salts,
3 solvates, polymorphs, enantiomers, isomers, or mixtures thereof.
- 1 3. The pharmaceutical composition according to claim 1, wherein the low dose
2 antidiabetic agent is selected from DPP-IV inhibitors, meglitinides, second generation
3 sulphonylureas, glucagon like peptide (GLP-1) analogues, other hypoglycaemics which
4 are used as an adjunct to metformin therapy, or mixtures thereof.
- 1 4. The pharmaceutical composition according to claim 1, wherein the biguanide is
2 metformin and the low dose antidiabetic agent is a DPP-IV inhibitor.
- 1 5. The pharmaceutical composition according to claim 1, wherein the ratio of
2 biguanide in the core to that in the coat ranges from about 99:1 to about 60:40.
- 1 6. The pharmaceutical composition according to claim 1, wherein the biguanide is
2 layered onto a pharmaceutically inert core or seed.
- 1 7. The pharmaceutical composition according to claim 1, wherein the biguanide core
2 comprises one or more pharmaceutically acceptable excipients selected from one or more

3 of fillers, binders, disintegrants, anti-adherents, lubricants, glidants, osmogents, coloring
4 agents, and flavoring agents.

1 8. The pharmaceutical composition according to claim 1, wherein the biguanide core
2 additionally contains an absorption enhancer.

1 9. The pharmaceutical composition according to claim 1, wherein the biguanide core
2 additionally contains a swellable polymer.

1 10. The pharmaceutical composition according to claim 1, wherein the biguanide core
2 further comprises a low dose antidiabetic agent.

1 11. The pharmaceutical composition according to claim 1, wherein the seal coat is
2 applied over the biguanide core or over the extended-release coat.

1 12. The pharmaceutical composition according to claim 1, wherein the rate-controlling
2 material is selected from one or more of hydrophilic polymers, hydrophobic polymers,
3 water-swallowable polymers, other hydrophobic materials, or mixtures thereof.

1 13. A process for preparing a pharmaceutical composition comprising the steps of:

- 2 (i) preparing the core comprising biguanide or its pharmaceutically effective
3 salts and one or more pharmaceutically acceptable excipients;
- 4 (ii) optionally coating the core with a seal coat;
- 5 (iii) coating the biguanide core of step (ii) with an extended-release coating
6 composition comprising one or more rate-controlling materials, wherein there
7 is at least one passageway;
- 8 (iv) optionally coating the core of step (iii) with a seal coat;
- 9 (v) coating the extended-release core with an immediate-release coating
10 composition comprising a biguanide and a low dose antidiabetic agent or its
11 pharmaceutically effective salts and one or more pharmaceutically acceptable
12 excipients; and
- 13 (vi) optionally providing a film coat.

1 14. A method for treating diabetes by administering to a person in need thereof a
2 pharmaceutical composition of a biguanide and a low dose antidiabetic agent comprising:

- 3 (i) a biguanide core comprising therapeutically effective amount of biguanide or
4 its pharmaceutically effective salts and one or more pharmaceutically
5 acceptable excipients;
- 6 (ii) optionally a seal coat;
- 7 (iii) an extended-release coat comprising one or more rate-controlling materials,
8 wherein there is at least one passageway;
- 9 (iv) optionally a second seal coat;
- 10 (v) an immediate-release drug coat comprising biguanide and a low dose
11 antidiabetic agent or its pharmaceutically effective salt and one or more
12 pharmaceutically acceptable excipients; and
- 13 (vi) optionally a film coat.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2013/061298

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/54 A61K9/50
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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2010/074950 A1 (SESHA RAMESH [US]) 25 March 2010 (2010-03-25) paragraphs [0068], [0073], [0074], [0077] - [0081] -----	1-14
X	US 2007/172525 A1 (SESHA RAMESH [US]) 26 July 2007 (2007-07-26) paragraphs [0063] - [0065], [0073] - [0078]; example 1 -----	1-14
X	US 6 790 459 B1 (CHENG XIU XIU [US] ET AL) 14 September 2004 (2004-09-14) column 9, line 56 - column 11, line 67 -----	1-14



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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"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

24 April 2014

Date of mailing of the international search report

08/05/2014

Name and mailing address of the ISA/

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

Authorized officer

Uhl, Martin

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2013/061298

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2010074950	A1	25-03-2010	NONE
US 2007172525	A1	26-07-2007	NONE
US 6790459	B1	14-09-2004	NONE