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(54) Title: PHARMACEUTICAL COMPOSITIONS

(57) Abstract: The present invention relates to solid oral fixed dose compositions of metformin, atorvastatin, and valsartan, or their pharmaceutically accepted salts, processes for the preparation thereof, and the use of the compositions to treat certain diseases.

PHARMACEUTICAL COMPOSITIONS

The present invention relates to solid oral fixed dose compositions comprising metformin, atorvastatin, and valsartan; or the respective pharmaceutically acceptable salts, and processes for the preparation thereof. The solid oral compositions are useful in the treatment of a patient in need of treatment for Type 2 diabetes or pre-diabetes.

Type 2 diabetes is an increasingly prevalent disease that frequently leads to cardiovascular complications. Diabetes may be co-morbid with cardiovascular disease. The declining cardiovascular health of a patient with diabetes can be associated with increased medical expense and may result in death. There is desire for a single product oral treatment that can be used to treat or alleviate hyperglycemia associated with type 2 diabetes and alleviate or treat related co-morbidities such as hyperlipidemia, and/or hypertension. The literature demonstrates that early intensive control of blood glucose, blood pressure, and blood cholesterol reduces the risks of major clinical outcomes, including death, in diabetes. See, Chan, J.C.N., *Lancet Diabetes Endocrinol.* 2014; 2: 969–79.

A three component tablet comprising metformin, atorvastatin, and valsartan, is desired, however, the fixed dose combination presents several manufacturing and development challenges. There is a propensity for one or more of the components to react with each other during manufacturing, storage, distribution, and/or usage. In particular, the three component fixed dose tablet should be swallowed by the patient without crushing or splitting the tablet because premature contact between the components may result in undesirable impurities and undesirable physical form changes impacting drug product dissolution profiles. Pharmaceutical formulations containing two pharmaceutically active ingredients for use in treating Type 2 diabetes are known. Such formulations are commercially available. For example, Invokamet™ contains canagliflozin and metformin hydrochloride XR, Kombiglyze XR™ contains saxagliptin and metformin hydrochloride XR. There are additional known two component fixed dose compositions for use in treating Type 2 diabetes, each with metformin and either an SGLT2 inhibitor or a DPP4 inhibitor.

There continues to be a need for a single product to treat Type 2 diabetes by comprehensive management of blood sugar, lipid, and blood pressure. A fixed dose

combination offers the advantages of convenience to patients and improved adherence for taking the medication at appropriate dose and intervals as prescribed (see, for example, Pan et al., *J. Gen. Intern. Med. 23(5): 611-4, 2008*). In particular, there is a need for a single combination product which is small enough that it can be swallowed easily by an adult, whilst being stable and whilst retaining the dissolution characteristics of the active components as found in the respective commercially available monotherapy products.

Compositions of this invention provide a treatment that may improve the glycemic control in patients in need thereof, and further simultaneously treat hyperlipidemia and/or hypertension that may be related to or caused by increased blood glucose, in a patient in need thereof.

The present invention provides a single product oral composition comprising the three fixed dose pharmaceutically active ingredients metformin, atorvastatin, and valsartan, or their respective pharmaceutically acceptable salts, wherein the composition is a bilayer comprising a metformin layer and a co-mix valsartan and atorvastatin layer. In an embodiment, the co-mix layer is an immediate release layer. The present invention provides fixed dose compositions which are stable and which have desirable dissolution characteristics.

In particular, the present invention provides a solid oral fixed dose composition comprising:

a first layer which is an extended release layer comprising metformin, or a pharmaceutically acceptable salt thereof;

a second layer comprising valsartan, or a pharmaceutically acceptable salt thereof, and atorvastatin, or a pharmaceutically acceptable salt thereof;

and one or more excipients.

In an alternative embodiment, the present invention provides a solid oral fixed dose composition comprising:

a. an extended release layer comprising metformin hydrochloride XR or metformin hydrochloride;

b. a second layer comprising valsartan, or a pharmaceutically acceptable salt thereof, and atorvastatin, or a pharmaceutically acceptable salt thereof; and one or more excipients.

In one embodiment, the second layer is an immediate release layer. In one embodiment, the composition is a tablet, preferably a compressed tablet. In a further embodiment, the tablet is of a pharmaceutically acceptable size to be swallowed intact by an adult.

In one embodiment, the metformin or pharmaceutically acceptable salt thereof is metformin hydrochloride. In a further embodiment, the first layer comprises metformin hydrochloride, hypromellose and microcrystalline cellulose. Preferably, the first layer further comprises magnesium stearate and colloidal silicon dioxide.

In one embodiment, the metformin hydrochloride is present in the form of granules which additionally comprise povidone and magnesium stearate. In a further embodiment, the metformin containing extended release layer additionally comprises sodium stearyl fumarate or magnesium stearate; colloidal silicon dioxide; and microcrystalline cellulose.

In one embodiment, the metformin or pharmaceutically acceptable salt thereof is metformin hydrochloride and is present in a unit dose strength selected from the group consisting of about 250, about 500 and about 750 mg, preferably about 500 mg.

In one embodiment, the second layer comprises atorvastatin calcium trihydrate and valsartan.

In one embodiment, the atorvastatin or pharmaceutically acceptable salt thereof is atorvastatin calcium trihydrate and is present in a unit dose strength selected from the group consisting of about 5, about 10, about 15 and about 20 mg, preferably about 10 mg.

In one embodiment, the valsartan or pharmaceutically acceptable salt thereof is valsartan and is present in a unit dose strength of about 40, about 50, about 60, about 70 and about 80 mg, preferably about 80 mg.

In one embodiment, the second layer further comprises calcium carbonate and microcrystalline cellulose.

In an embodiment of the invention, the composition is a single product bilayer oral tablet formulation comprising a metformin layer and a co-mix layer comprising valsartan and atorvastatin. In an embodiment of the invention, the composition is a single product bilayer oral tablet formulation comprising an extended release metformin layer and a co-mix layer comprising valsartan and atorvastatin, or their respective

pharmaceutically acceptable salts. In an embodiment, the bilayer oral tablet is a compressed tablet with an intermediate layer between the tablet layers.

In an embodiment, the valsartan and atorvastatin calcium trihydrate co-mix layer further comprises a lubricant. In an embodiment, the lubricant is selected from the group consisting of magnesium stearate, stearic acid, and hydrogenated vegetable oil. In an embodiment, the lubricant is magnesium stearate.

In an embodiment, the valsartan, atorvastatin and metformin composition is pharmaceutically acceptable size to be swallowed intact by an adult.

An embodiment of this invention is a solid fixed dose composition comprising

a first layer which is an extended release layer comprising metformin, or a pharmaceutically acceptable salt thereof, wherein the metformin unit dose strength is about 500 mg;

a second layer comprising valsartan, or a pharmaceutically acceptable salt thereof, and atorvastatin, or a pharmaceutically acceptable salt thereof, wherein the valsartan unit dose strength is about 80 mg and the atorvastatin unit dose strength is about 10 mg;

and one or excipients.

In a further embodiment, the solid oral fixed dose composition comprises

a first layer which is an extended release layer comprising metformin hydrochloride in a unit dose strength of about 500 mg;

a second layer which is an immediate release layer comprising valsartan at a unit dose strength of about 80 mg and atorvastatin calcium trihydrate at a unit dose strength of about 10 mg;

and one or more excipients.

The present invention provides a process for preparing a solid fixed dose composition of the invention comprising forming a compressed tablet comprising:

a. an extended release layer comprising metformin, or a pharmaceutically acceptable salt thereof, and
b. a second layer comprising valsartan, or a pharmaceutically acceptable salt thereof, and atorvastatin, or a pharmaceutically acceptable salt thereof.

In an embodiment of the invention, the solid oral fixed dose composition is prepared using a process comprising

a. an extended release layer comprising metformin hydrochloride and

b. a second immediate release layer comprising valsartan, or a pharmaceutically acceptable salt thereof, and atorvastatin, or a pharmaceutically acceptable salt thereof; wherein the composition is prepared as a compressed tablet.

The fixed dose composition is advantageously useful for the treatment of a patient in need of treatment for Type 2 diabetes or a patient at risk for developing Type 2 diabetes. The fixed dose composition may be useful for treating a patient in need of treatment for pre-diabetes. The fixed dose combination is useful in the treatment of a patient in need of treatment for metabolic syndrome. The fixed dose composition can be useful for treating a patient in need of treatment for pre-diabetes and one or two conditions selected from the group consisting of hypertension and hyperlipidemia. The fixed dose composition can be useful for treating a patient in need of treatment for Type 2 diabetes and one or two conditions selected from the group consisting of hypertension and hyperlipidemia.

The present invention provides a method of treating Type 2 diabetes mellitus in a patient in need thereof comprising administering an effective amount of a composition of the invention. The present invention further provides a method of treating pre-diabetes in a patient in need thereof comprising administering an effective amount of a composition of the invention. The present invention further provides a method of treating metabolic syndrome in a patient in need thereof comprising administering an effective amount of a composition of the invention.

The present invention provides a composition of the invention for use in therapy. The present invention further provides a composition of the invention for use in the treatment of Type 2 diabetes mellitus. The present invention further provides a composition of the invention for use in the treatment of pre-diabetes. The present invention further provides a composition for use in the treatment of metabolic syndrome.

The present invention provides the use of a composition of the invention in the manufacture of a medicament for the treatment of Type 2 diabetes mellitus. The present invention further provides the use of a composition of the invention in the manufacture of a medicament for the treatment of pre-diabetes. The present invention further provides the use of a composition of the invention in the manufacture of a medicament for the treatment of metabolic syndrome.

In a particular embodiment, the patient being treated for Type 2 diabetes or pre-diabetes is also in need of treatment for hypertension and/or hyperlipidemia.

In a particular embodiment, the fixed dose composition of the invention is administered to the patient once per day.

Pharmaceutically acceptable salts and common methodology for preparing them are well known in the art. See, *e.g.*, P. Stahl, *et al.*, Handbook of Pharmaceutical Salts: Properties, Selection and Use, (VCHA/Wiley-VCH, 2002); S.M. Berge, *et al.*, "Pharmaceutical Salts," *Journal of Pharmaceutical Sciences*, Vol. 66, No. 1, January 1977.

In a preferred embodiment, the pharmacokinetic parameters of area under the curve (AUC) and maximum concentration (C_{max}) for each component are within a 90% confidence interval of 80–125% of the regulatory approved monotherapy.

As used herein, "about" means plus or minus 10%. Preferably, the term "about" means plus or minus 5%.

The term "tablet" as used herein means an oral pharmaceutical dosage formulation of all sizes and shapes. In an embodiment, the tablet is compressed. In an embodiment, the tablet may be swallowed intact by an adult without breaking or crushing the tablet.

The term "pre-diabetes" is a condition wherein the individual is pre-disposed to the development of Type 2 diabetes mellitus.

The term "treating" or "treatment" comprise therapeutic treatment of a patient diagnosed with a condition. Therapeutic treatment may be symptomatic treatment in order to relieve the symptoms of a condition or may stop or slow the progression of the condition.

As used herein, the term "hypromellose" means hydroxypropyl methylcellulose (HPMC). An example of a commercially available hypromellose is Methocel ™ K100M.

The term "metformin" as used herein refers to metformin or a pharmaceutically acceptable salt thereof. Metformin is chemically described as 1,1-dimethylbiguanide. Metformin is a well-known, commercially available pharmaceutical for use in treating type 2 diabetes. Such pharmaceutically acceptable salts of metformin include for example, metformin hydrochloride, metformin fumarate salt, metformin succinate salt, metformin hydrobromide salt, metformin p-chlorophenoxy acetate salt, and metformin

embonate, and other known metformin salts of mono and dibasic carboxylic acids. Metformin hydrochloride salt is a preferred pharmaceutically acceptable salt.

Metformin is preferably administered as an extended release formulation, also known as XR or ER, of metformin hydrochloride. Exemplary metformin extended release formulations are known, for example, US 6,723,340, US 6,340,475, and US 6,660,300.

It is preferred that the metformin or pharmaceutically acceptable salt thereof is present in an extended release formulation comprising a diffusion rate controlling polymer such as, but not limited to, hypromellose, diluents such as microcrystalline cellulose, magnesium stearate, and colloidal silicon dioxide. A further preferred metformin layer comprises a granulation of metformin hydrochloride with povidone, and magnesium stearate, wherein the metformin granulation is mixed with hypromellose, and microcrystalline cellulose, silicon dioxide, and magnesium stearate. A further preferred metformin layer comprises a granulation of metformin hydrochloride about 95% by weight, povidone about 4.5% by weight, and magnesium stearate about 0.5% by weight. In a further embodiment, the metformin granulation is combined with hypromellose, microcrystalline cellulose, magnesium stearate, and colloidal silicon dioxide.

In an embodiment, the metformin, or pharmaceutically acceptable salt thereof, is present in the form of granules. In a further embodiment, the metformin granules additionally comprise a binder, for example povidone and sodium carboxymethylcellulose, and optionally, a lubricant, for example magnesium stearate, sodium stearyl fumarate and stearic acid. The preferred binder in the granules is povidone. Povidone may be present in an amount of up to 5% by weight of the granules, preferably about 4.5%. The preferred lubricant in the granules is magnesium stearate. Magnesium stearate may be present in an amount of up to 1% by weight of the granules, preferably about 0.5%.

The preferred dissolution control polymer in the first layer comprising metformin, or a pharmaceutically acceptable salt thereof, is hypromellose. Hypromellose K200M and Hypromellose K15M are preferred. Hypromellose K100M is particularly preferred. The hypromellose may be present in an amount of 20 to 45% by weight of this first layer, preferably 33 to 42% by weight and more preferably 35 to 39% by weight.

Preferably, the hypromellose has a viscosity from about 4,000 mPa.s to about 200,000 mPa.s, more preferably from about 50,000 to about 200,000 mPa.s, and more preferably 80,000 mPa.s to 120,000 mPa.s, measured as a 2% solution in water. A viscosity of about 100,000 mPa.s (K100M) may be preferred.

In an embodiment, the first layer comprising metformin, or a pharmaceutically acceptable salt thereof, comprises, in addition to the metformin granules, microcrystalline cellulose. Microcrystalline cellulose may be present in an amount of 0.5 to 15% by weight of the first layer, more preferably 5 to 10% by weight.

In a further embodiment, the first layer comprising metformin, or a pharmaceutically acceptable salt thereof, comprises, in addition to the metformin granules, colloidal silicon dioxide. Colloidal silicon dioxide may be present in an amount of up to 1% by weight of the metformin layer.

In a further embodiment, the first layer comprising metformin, or a pharmaceutically acceptable salt thereof, comprises in addition to the metformin granules a lubricant, for example sodium stearyl fumarate, magnesium stearate or stearic acid. The preferred lubricants are sodium stearyl fumarate and magnesium stearate. The lubricant may be present in an amount of up to 1% by weight of the first layer.

The first layer of the composition can be prepared using common tableting methods that involve mixing, comminution, and fabrication steps commonly practiced and well known to those skilled in the art. It may be preferred that the metformin, or pharmaceutically acceptable salt thereof, is dry mixed.

The first layer comprising metformin, or a pharmaceutically acceptable salt thereof, preferably has a total weight of no more than 1000 mg. More preferably, it has a total weight of 900 mg to 1000 mg. In a particular embodiment, this layer has a total weight which is less than the total tablet weight of the regulatory approved monotherapy product Glucophage® XR (1025 mg).

Valsartan is a well-known commercially available pharmaceutical for use in treating hypertension. Valsartan is chemically described as N-(1-oxopentyl)-N-[[2'-(1H-tetrazol-5-yl)[1,1-biphenyl]-4-yl]methyl]-L-valine. Valsartan is a free acid with pKas of 3.9 and 4.7. The most common solid form of commercially available valsartan is the semi-crystalline form possessing a melting endotherm, T_m of about 100°C.

Atorvastatin, or atorvastatin calcium trihydrate, is a well-known commercially available pharmaceutical for use in treating hyperlipidemia. Atorvastatin calcium trihydrate ([R-(R*,R*)]-2-(4-fluorophenyl)-β,δ--dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate) is the most common solid form of commercial atorvastatin drug substance and possesses known pH dependent chemical instability. At pH < 6, atorvastatin degrades to an undesired byproduct, a lactone. The acid-sensitivity of atorvastatin raises a potential problem when formulating with the active valsartan, a free acid. Many common tableting excipients have a surface pH < 6, that can lead to atorvastatin lactone formation when mixed and during storage. Thus, a straightforward combination of atorvastatin with many common tableting excipients produces an unstable product under typical ICH storage conditions. Atorvastatin is therefore often wet granulated with a basic agent, e.g. calcium carbonate, to raise the local pH to prevent lactone formation.

Atorvastatin is often granulated with basic excipients, such as the alkaline metal salts calcium carbonate or sodium bicarbonate, to decrease lactone formation. Valsartan, a free acid, has been shown to form salts with alkaline metals. It is challenging to formulate valsartan in the fixed dose composition in the presence of stabilizing alkaline metal salt excipients to avoid physical conversion of the valsartan to a salt form that may have different dissolution properties thereby impacting *in-vivo* dissolution and absorption.

In an embodiment, the second layer comprises calcium carbonate.

In a further embodiment, the second layer comprises microcrystalline cellulose.

In a further embodiment, the second layer comprises a disintegrant, for example, croscarmellose sodium or crospovidone. The preferred disintegrant is croscarmellose sodium.

In a further embodiment, the second layer comprises iron oxide red.

In a further embodiment, the second layer comprises a lubricant, for example sodium stearyl fumarate, magnesium stearate or stearic acid. Sodium stearyl fumarate or magnesium stearate are preferred.

In a further embodiment, the second layer comprises colloidal silicon dioxide.

The unit dose strength of metformin, or pharmaceutically acceptable salt thereof, in particular metformin hydrochloride, for incorporation into the fixed-dose composition is preferably 250 to 1000 mg. A preferred unit dose strength of metformin or

pharmaceutically acceptable salt thereof, in particular metformin hydrochloride, is about 250, about 500, about 750, about 850, or about 1000 mg. A further preferred unit dose strength of metformin or pharmaceutically acceptable salt thereof, in particular metformin hydrochloride, is selected from the group consisting of about 250, about 500 and about 750 mg. A preferred unit dose strength of metformin or pharmaceutically acceptable salt thereof, in particular metformin hydrochloride, in the fixed dose composition is about 500 mg.

The unit dose of atorvastatin, or pharmaceutically acceptable salt thereof, in particular atorvastatin calcium trihydrate, for incorporation into the fixed dose composition is preferably 5 to 20 mg. A preferred unit dose strength of atorvastatin, or pharmaceutically acceptable salt thereof, in particular atorvastatin calcium trihydrate, is about 5, about 10, about 15, or about 20 mg. A preferred unit dose strength of atorvastatin, or pharmaceutically acceptable salt thereof, in particular atorvastatin calcium trihydrate, is about 10 mg.

The unit dose of valsartan, or pharmaceutically acceptable salt thereof, in particular valsartan, for incorporation into the fixed dose composition is preferably 40 to 80 mg. A preferred unit dose strength of valsartan, or pharmaceutically acceptable salt thereof, in particular valsartan, is about 40, about 50, about 60, about 70, or about 80 mg. A further preferred unit dose strength of valsartan or pharmaceutically acceptable salt thereof, in particular valsartan, is about 80 milligrams.

As used herein "coating" and "coat" means a layer added to the bilayer composition. The skilled artisan will recognize that a coating may be added to enhance the pharmaceutical elegance, taste mask, enhance stability, coloring, ease of swallowing, and the like.

A layer may be provided between pharmaceutically active layers or as a coat to enhance stability, pharmaceutical elegance, and/or lamination of the active layer(s).

As used herein "top coat" means the outer most layer of the composition. The top coat can be colored, opaque or clear.

As used herein "pharmaceutically acceptable size" means a size that is generally suitable for swallowing intact by an adult without fracture, breaking, or crushing. Generally, the largest dimension of the tablet should not exceed about 22 mm. As used herein, the largest cross sectional area means the largest cross sectional area of the tablet

that lies in a plane perpendicular to the longest axis of the tablet. If the shape is non-conventional, such as a pentagon, triangle, diamond, and the like, then the largest cross sectional area will be the area of the smallest circle, oval, or ellipse that would completely enclose the cross sectional shape. It may be preferred that the pharmaceutically acceptable size is an oval shape of less than or equal to about 20mm by 10mm, preferably about 14 mm by 9 mm. In an embodiment, the fixed dose composition is oval in shape with dimensions of less than 22 mm by 11 mm, preferably less than 20mm by 11mm. It may be preferred that the pharmaceutically acceptable size is a round shape less than about 11mm diameter. The thickness of the fixed dose composition may vary but preferably it is in the range of 7 mm to 9 mm.

As used herein, the term "extended release" means that the active is gradually released from the composition. Generally, the active is released over a period of up to 12 hours from administration. Preferably, the active, in particular metformin or a pharmaceutically acceptable salt thereof, is released over a period of between 10 and 12 hours. The release of the active from the composition (the dissolution) is measured in pH 6.8 buffer using conventional dissolution testing.

As used herein, the term "immediate release" means that the majority of the active is released quickly from the composition. Preferably, at least 80% of the active is released within 30 minutes from administration, preferably within 15 minutes. The release of the active from the composition (the dissolution) is measured in pH 6.8 buffer using conventional dissolution testing.

Tablets may be prepared by direct compression or other commonly used processes as wet granulation or dry granulation (roller compaction). The addition of lubricants may be helpful and are known in the art. Typical lubricants are for example, magnesium stearate, stearic acid, and hydrogenated vegetable oil.

Additional excipients may be added, provided that the overall size of the tablet is minimized. For example, granulating aids, binders, and additives to enhance powder flowability, tablet hardness, and tablet friability.

The skilled person will readily appreciate that the fixed dose composition of the present invention may be prepared using various techniques known in the art. This section provides examples of techniques and conditions which may be used but is in no way limiting.

Atorvastatin calcium trihydrate is pre-mixed with calcium carbonate, co-mixed with valsartan, a cellulosic excipient, and other appropriate tableting excipients. This layer is compressed (as layer 2) onto a hypromellose matrix tablet of metformin (layer 1), to form a bilayer tablet. To minimize tablet size, the metformin matrix layer is reduced to the smallest feasible size of 700 to not more than 1000 mg, preferably 800 to 1000 mg, more preferably 900 mg to 1000 mg, that maintains a dissolution profile similar to that of the approved metformin XR product (Glucophage ® XR). The tablet is processed and packaged under controlled temperature and humidity conditions to control water activity to defined ranges to minimize lactone formation.

1) Atorvastatin calcium trihydrate is pre-blended (dry) with a stabilizing excipient, preferably calcium carbonate, using suitable pharmaceutical blending equipment. This blend may also be dry granulated using suitable granulation equipment. Extra-granular excipients may also be added per conventional granulation practice.
2) The atorvastatin pre-blend (or granulation), valsartan, and appropriate tableting excipients are then blended together using suitable pharmaceutical blending equipment. This blend is then lubricated with an appropriate excipient using suitable pharmaceutical blending equipment.
3) Metformin, hypromellose, and other appropriate tableting excipients are blended together using suitable pharmaceutical blending equipment. Metformin may be granulated or milled using conventional processes to improve process.
4) The two blends are then compressed sequentially at the desired ratios to produce a bilayer tablet using suitable pharmaceutical bi-layer tablet compression equipment.
5) An intermediate layer may be optionally applied between the two layers to increase bonding strength and prevent layer separations or delamination.
6) The final fixed dose combination tablet may or may not be film coated with a final film over-coat, such as with a mixture of hydroxypropyl cellulose and hydroxypropyl methyl cellulose, or other suitable film forming polymers, containing titanium dioxide or other coloring agents such as iron oxides, dyes, and the like, to improve tablet strength and handling, ability to be swallowed, stability, taste masking and pharmaceutical elegance.

7) A top coat may or may not be applied.

The fixed dose compositions may also contain one or more additional formulation ingredients selected from a wide variety of excipients known in the pharmaceutical arts. Such ingredients may include, but are not limited to, diluents, compression aids, binders, glidants, disintegrants, lubricants, flavors, colors, flavor enhancers, sweeteners and preservatives.

In an embodiment, the fixed dose composition may be swallowed by an adult without crushing or breaking the tablet. The oral composition may be administered once per day or twice per day, as determined by a physician. It is especially preferred that the oral composition may be administered once per day.

Appropriate process and packaging controls to ensure control of water activity to levels may be beneficial in preparation of a pharmaceutically acceptable stable product.

Specific tablet shape (e.g. modified oval or capsule shape), and design, (e.g. two color tablet) may be incorporated to reduce visual bulkiness, facilitate swallowing, and maintain tablet strengths.

Example 1

A fixed dose combination tablet comprising 500 mg metformin HCl, 80 mg valsartan, 10 mg atorvastatin calcium trihydrate

The composition is prepared using the components set forth in Table A, below. Hypromellose, colloidal silicon dioxide, metformin HCl granules (95%), and microcrystalline cellulose are pre-blended for 1 to 2 minutes, de-lumped and blended again in a V-blender for 10 minutes. After sieving, magnesium stearate is charged to the same V-blender and the mixture is blended for 3 minutes.

The blend for the valsartan/atorvastatin calcium trihydrate layer (layer-2) is prepared. Atorvastatin calcium trihydrate and calcium carbonate are first pre-blended in a granulator for 2 minutes. The blend is mixed using a blade speed of 110 rpm and cross screw speed of 250 RPM. This pre-blend is discharged into a bag.

Valsartan, microcrystalline cellulose, colloidal silicon dioxide, iron oxide red, and croscarmellose sodium are added to the same bag and pre-blended in the bag for 1 to 2

minutes. The blend is then de-lumped, and blended in a V-blender for 10 minutes. After sieving, magnesium stearate is charged to the same V-blender and the mixture is blended for 3 minutes.

The blends are loaded into separate hoppers in a bilayer tablet press. Using modified oval tooling (0.4528 x 0.7480 inch), bilayer tablets are prepared targeting a 900 mg metformin layer weight and a 260 mg valsartan/atorvastatin calcium layer weight.

During processing and packaging of the product, it is preferred that the room humidity is controlled to less than 50% at room temperature, about 20°C. It is further preferred that room humidity is controlled to less than 20% at room temperature, about 20°C.

Table A

Component	Amount (mg)
Metformin HCl– Layer-1	
Metformin HCl granules	526.32
Metformin HCl	500
Povidone	23.68
Magnesium stearate	2.64
Hypromellose 2208, 100,000 mPa.s viscosity	315.00
Microcrystalline cellulose, silicified	45.18
Magnesium stearate	9.00
Colloidal silicon dioxide	4.5
Total Layer 1	900
Valsartan/Atorvastatin Calcium – Layer-2	
Atorvastatin Calcium	10.85
Calcium carbonate light	50.00
Valsartan	80.00
Microcrystalline cellulose, silicified	99.96
Croscarmellose sodium	13.00
Iron oxide red	0.21
Magnesium stearate	3.59
Colloidal silicon dioxide	2.39

Total Layer 2	260
Total tablet weight	1160

The tablet size and weight are desired to be acceptable to the patient for oral consumption without fracturing the tablet. The formulation comprising fixed dose combination of Example 1 is consistent with pharmaceutically elegant formulations that may be swallowed intact, without fracture of the tablet.

Alternate Preparation
Wet Granulation

For comparison, a bilayer tablet is prepared using a wet granulation formulation.

1) Atorvastatin calcium trihydrate is wet granulated with calcium carbonate and the granulating excipients: hydroxypropyl cellulose, polysorbate 80, microcrystalline cellulose, lactose, and croscarmellose sodium, using water as the granulating liquid.
2) This wet granulation is thoroughly dried and sized using appropriate pharmaceutical equipment.
3) Valsartan and appropriate tableting excipients are pre-blended together using suitable pharmaceutical blending equipment.
4) The dried and sized atorvastatin granules are then combined with the valsartan pre-blend and blended together using suitable pharmaceutical blending equipment. This blend is then lubricated with an appropriate excipient using suitable pharmaceutical blending equipment.
5) Metformin, hypromellose and other appropriate tableting excipients are blended together using suitable pharmaceutical blending equipment.
6) The two blends are then combined at the desired ratios, using suitable pharmaceutical tablet compression equipment, to produce a bilayer tablet of equivalent dose as the fixed dose combination of Example 1.

Tablets are placed on an accelerated stability study and the primary degradant, the atorvastatin lactone, is monitored to gauge the effectiveness of the stabilization of atorvastatin in the dosage form. Samples are stored in open containers at elevated

controlled temperature and humidity. Samples are tested for the lactone impurity using HPLC with UV detection. The data provided in Table B, demonstrate desired stability of the Example 1 formulation. The data provided in Table C and Table D suggest that the composition of Example 1 provides dissolution profiles that are comparable to the respective regulatory agency approved mono-product.

Atorvastatin Stability

Unexpectedly, the stability of the fixed dose composition prepared using the dry mix of Example 1 performed better than the Wet Granulation preparation.

Table B

Presentation	% atorvastatin lactone measured on stability: 40°C/50% RH			
	Initial	1 week	2 weeks	4 weeks
Example 1	0.36	0.40	0.45	0.44
Wet Granulation	0.38	0.62	0.79	0.93

Valsartan Stability

The physical stability of valsartan in a composition prepared using sodium bicarbonate as the stabilizing excipient for atorvastatin is compared to a composition using calcium carbonate. X-ray powder diffraction data show that upon open dish storage at 40°C/75% RH for 8 days valsartan interacts with sodium bicarbonate and the sodium salt of valsartan is the likely product. Surprisingly, no interaction of valsartan with calcium carbonate is observed using the composition of Example 1 that would suggest formation of the calcium salt of valsartan, despite this salt being reported in the art. The composition of Example 1 minimizes the undesired calcium salt.

Dissolution

Dissolution of the atorvastatin and valsartan is measured in 50 mM pH 6.8 phosphate buffer at 37°C using a USP apparatus II with HPLC and UV detection. The percent release of the IR components in the Example 1 composition compare favorably to the regulatory agency approved mono products). The regulatory approved atorvastatin product is Lipitor® and the regulatory approved valsartan product is Diovan®.

Table C

Presentation	Average (n=6) % release at 30 minutes	
	Atorvastatin	Valsartan
Mono Product	98	100
Example 1	92	103

Dissolution of metformin is measured in 50 mM pH 6.8 phosphate buffer at 37°C using a USP apparatus II with HPLC and UV detection. The percent release of metformin in the Example 1 composition compares favorably to the regulatory agency approved mono product (Glucophage ® XR) over 10 hours.

Table D

Time (hr)	Average (n=6) % release metformin HCl	
	Example 1	Mono Product
1	27	26
3	51	48
6	73	68
10	91	85

Size of Metformin Layer and Dissolution Rate

The dissolution rate of metformin hydrochloride in two metformin-valsartan bilayer tablets in which the total weight of metformin layer was reduced relative to the commercially available metformin product Glucophage®XR was measured and compared to the dissolution rate in Glucophage®XR.

The composition of the bilayer tablet is set out below in Table E.

Table E

Component	Amount mg	% wt of layer
Metformin HCl granules (95%)*	526	56.9
HPMC	343	37.1
Microcrystalline Cellulose	47	5.1
Sodium stearyl fumarate	9	1.0
TOTAL layer	**925**	**100.0**
Valsartan	80	38.1
Microcrystalline cellulose	92	43.8
Croscarmellose sodium	31.5	15.0
Silicon dioxide	2.1	1.0
Iron oxide red	0.2	0.1

Sodium stearyl fumarate	4.2	2.0
TOTAL layer	**210**	**100.0**

Metformin HCl granules (95%)*	526	53.9
HPMC	363.2	37.2
Microcrystalline cellulose	76.1	7.8
Sodium stearyl fumarate	9.8	1.0
TOTAL layer	**975.1**	**100.0**
Valsartan	80	27.2
Microcrystalline cellulose	154.9	52.7
Croscarmellose sodium	44.1	15.0
Silicon dioxide	7.4	2.5
Iron oxide red	0.3	0.1
Sodium stearyl fumarate	7.4	2.5
TOTAL layer	**294.1**	**100.0**

*Granules composed of: 95% wt metformin HCl, 0.5% wt magnesium stearate and 4.5% wt povidone.

Dissolution of metformin hydrochloride is measured in 50mM pH 6.8 phosphate buffer at 37°C using a USP apparatus I. The results are set out below in Table F.

Table F

	% metformin HCl released					
	60 min	120 min	180 min	360 min	600 min	720 min
Glucophage®XR 1025 mg tablet	31.2	45.4	56.1	77.6	95.5	100
Bilayer tablet with 925 mg metformin layer total wt	31.9	46.8	58.7	80.3	96.7	100
Bilayer tablet with 975 mg metformin layer total wt	30.2	45.3	56.7	78.6	96.3	100

It is well known that the surface area to volume ratio (SA/Vol) of a matrix XR tablet impacts the release rate of the drug, with a higher SA/Vol resulting in a faster

release. As the Glucophage®XR tablet is oval (unit dose of metformin HCl is 500 mg) in shape and weighs about 1025 mg, it would be expected that a tablet of similar composition and shape, only smaller in mass, should have a faster dissolution rate. However, these data surprisingly show that the size of the metformin layer can be reduced without resulting in a measurable difference in dissolution rate.

WE CLAIM:

1. A solid oral fixed dose composition comprising

a first layer which is an extended release layer comprising metformin, or a pharmaceutically acceptable salt thereof;

a second layer comprising valsartan, or a pharmaceutically acceptable salt thereof, and atorvastatin, or a pharmaceutically acceptable salt thereof;

and one or more excipients.

2. The composition according to claim 1 wherein the second layer is an immediate release layer.

3. The composition according to claim 1 or claim 2 wherein the composition is a tablet.

4. The composition according to claim 3 wherein the tablet is a compressed tablet.

5. The composition according to claim 3 or claim 4 wherein the tablet is of pharmaceutically acceptable size to be swallowed intact by an adult.

6. The composition according to any one of claims 1 to 5 wherein the metformin or a pharmaceutically acceptable salt thereof is metformin hydrochloride.

7. The composition according to claim 6 wherein the metformin hydrochloride is present in the form of granules which additionally comprise povidone and magnesium stearate.

8. The composition according to claim 7 wherein the first layer further comprises sodium stearyl fumarate or magnesium stearate; colloidal silicon dioxide; and microcrystalline cellulose.

9. The composition according to any one of claims 6 to 8 wherein the metformin hydrochloride is present in a unit dose strength selected from the group consisting of about 250, about 500, and about 750 mg.

10. The composition according to claim 9 wherein the metformin hydrochloride is present in a unit dose strength of about 500 mg.

11. The composition according to any one of claims 1 to 10 wherein the second layer comprises atorvastatin calcium trihydrate and valsartan.

12. The composition according to claim 11 wherein the atorvastatin calcium trihydrate is present in a unit dose strength selected from the group consisting of about 5, about 10, about 15, and about 20 mg.

13. The composition according to claim 12 wherein the atorvastatin calcium trihydrate is present in a unit dose strength of about 10 mg.

14. The composition according to any one of claims 11 to 13 wherein the valsartan is present in a unit dose strength selected from the group consisting of about 40, about 50, about 60, about 70, and about 80 mg.

15. The composition according to claim 14 wherein the valsartan is present in a unit dose strength of about 80 mg.

16. The composition according to any one of claims 1 to 15 wherein the second layer further comprises calcium carbonate and microcrystalline cellulose.

17. A solid oral fixed dose composition comprising

a first layer which is an extended release layer comprising metformin hydrochloride in a unit dose strength of about 500 mg;

a second layer which is an immediate release layer comprising valsartan at a unit dose strength of about 80 mg and atorvastatin calcium trihydrate at a unit dose strength of about 10 mg;

and one or more excipients.

18. A process for preparing a solid oral fixed dose composition according to any one of claims 1 to 17 comprising forming a compressed tablet comprising

a. an extended release layer comprising metformin, or a pharmaceutically acceptable salt thereof, and
b. a second layer comprising valsartan, or a pharmaceutically acceptable salt thereof, and atorvastatin, or a pharmaceutically acceptable salt thereof.

19. A process according to claim 18 wherein the process temperature is maintained to room temperature (about 20°C) and humidity controlled to less than about 50% room humidity.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2018/041433

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/24 A61K31/00
ADD.

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	NISHARANI NISHARANI RANPISE ET AL: "Formulation and Development of Fixed Dose Combination of Antihypertensive and Antidiabetic Agent for treatment of Co-existent Type Two Diabetes Mellitus and Hypertension", INDIAN JOURNAL OF PHARMACEUTICAL EDUCATION AND RESEARCH, vol. 48, no. supplementary, 1 December 2014 (2014-12-01), pages 10-117, XP55502436, IN ISSN: 0019-5464, DOI: 10.5530/ijper.48.4s.14 the whole document ----- -/--	1-19

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
6 September 2018	19/09/2018

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2018/041433

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	I. Nishanth ET AL: "Formulation Development and Evaluation of Bilayer Tablets of Telmisartan for Immediate Release and Metformin Hydrochloride for Sustained Release", Research J. Pharma. Dosage Forms and Tech., 1 January 2013 (2013-01-01), pages 139-144, XP55502769, Retrieved from the Internet: URL:http://rjpdft.com/HTMLPaper.aspx?Journal=Research+Journal+of+Pharmaceutical+Dosage+Forms+and+Technology%3bPID%3d2013-5-3-5 [retrieved on 2018-08-28] the whole document -----	1-19

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