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An agency of Industry Canada

CA 2801020 A1 2011/12/01

(21) 2 801 020

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(86) Date de dépôt PCT/PCT Filing Date: 2011/05/27
(87) Date publication PCT/PCT Publication Date: 2011/12/01
(85) Entrée phase nationale/National Entry: 2012/11/28
(86) N° demande PCT/PCT Application No.: CA 2011/000621
(87) N° publication PCT/PCT Publication No.: 2011/147026
(30) Priorité/Priority: 2010/05/28 (CA2,706,292)

(51) Cl.Int./Int.Cl. *A61K 31/4184* (2006.01), *A61K 31/549* (2006.01), *A61K 9/20* (2006.01), *A61P 9/12* (2006.01), *A61J 3/00* (2006.01)

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(54) Titre : PREPARATION PHARMACEUTIQUE STABLE CONTENANT DU TELMISARTAN ET DE L'HYDROCHLOROTHIAZIDE

(54) Title: A STABLE PHARMACEUTICAL FORMULATION COMPRISING TELMISARTAN AND HYDROCHLOROTHIAZIDE

(57) Abrégé/Abstract:
The present invention is directed to a stable pharmaceutical formulation comprising telmisartan, or a pharmaceutically acceptable salt thereof/ and a diuretic dispersed in a matrix. The matrix comprises at least one disinte grant in an amount ranging from 0.5 % to 20% by weight; a dissolution enhancing agent present in a molar ratio of dissolution enhancing agent to telmisartan of from 1:1 to 10:1; a water-insoluble diluent in an amount ranging from 15%-75% by weight and at least one other pharmaceutically acceptable excipient /or adjuvant in an amount ranging from 0 - 25% by weight,

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
1 December 2011 (01.12.2011)

PCT

(10) International Publication Number
WO 2011/147026 A3

(51) International Patent Classification:
*A61K 31/4184* (2006.01) *A61P 9/12* (2006.01)
*A61K 31/549* (2006.01) *A61J 3/00* (2006.01)
*A61K 9/20* (2006.01)

(21) International Application Number:
PCT/CA2011/000621

(22) International Filing Date:
27 May 2011 (27.05.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2,706,292 28 May 2010 (28.05.2010) CA

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(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, 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, IS, JP, KE, KG, KM, 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, PE, PG, PH, PL, PT, RO, RS, RU, 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, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, 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, ML, MR, NE, SN, TD, TG).

**Declarations under Rule 4.17**:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

**Published**:

— *with international search report (Art. 21(3))*

(88) Date of publication of the international search report:
26 January 2012

WO 2011/147026 A3

(54) Title: A STABLE PHARMACEUTICAL FORMULATION COMPRISING TELMISARTAN AND HYDROCHLOROTHIAZIDE

(57) Abstract: The present invention is directed to a stable pharmaceutical formulation comprising telmisartan, or a pharmaceutically acceptable salt thereof/ and a diuretic dispersed in a matrix. The matrix comprises at least one disinte grant in an amount ranging from 0.5 % to 20% by weight; a dissolution enhancing agent present in a molar ratio of dissolution enhancing agent to telmisartan of from 1:1 to 10:1; a water-insoluble diluent in an amount ranging from 15%-75% by weight and at least one other pharmaceutically acceptable excipient /or adjuvant in an amount ranging from 0 - 25% by weight,

# A STABLE PHARMACEUTICAL FORMULATION COMPRISING TELMISARTAN AND HYDROCHLOROTHIAZIDE

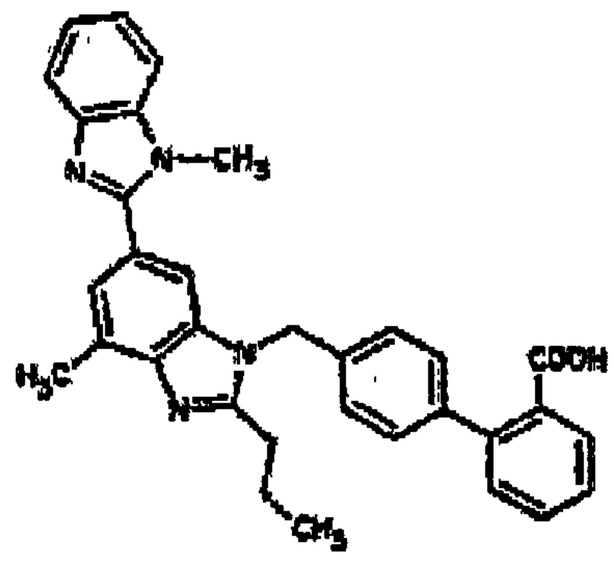
## FIELD OF THE INVENTION

The present invention relates to a pharmaceutical tablet formulation comprising two active ingredients. More specifically the present invention relates to a formulation comprising telmisartan, which is an angiotensin II receptor antagonist and hydrochlorothiazide, which is a diuretic, and methods of manufacturing thereof.

## BACKGROUND OF THE INVENTION

Telmisartan was first disclosed in European Patent No. 0,502,314 (issued on May 20, 1998 to Dr. Karl Thomae GmbH) as angiotensin II receptor antagonist and is indicated for treatment of mild to moderate essential hypertension in patients.

Its chemical name is 4'-[[4-methyl-6-(1-methyl-2-benzimidazolyl)-2-propyl-1-benzimidazolyl]methyl]-2-biphenylcarboxylic acid, with molecular formula $C_{33}H_{30}N_4O_2$, having following structure:



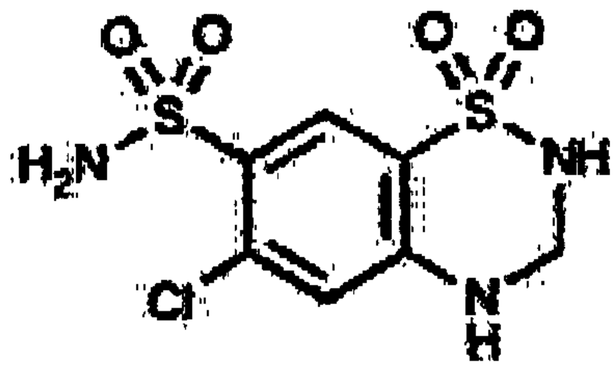

Telmisartan is a white to off-white, odorless crystalline powder. It is practically insoluble in water and in the pH range of 3 to 7, sparingly soluble in strong acid (except HCl) and soluble in strong base.

As disclosed in PCT Publication WO20000/43370 (corresponding to Canadian Patent No. 2,352,436, issued on March 23, 2010 to Boehringer Ingelheim Pharma KG) crystalline telmisartan exists in two polymorphic forms having different melting points. Under the influence of heat and humidity, the lower melting polymorph B transforms irreversibly into the higher melting polymorph A.

Telmisartan is an orally active, AT1 selective angiotensin II receptor antagonist. By selectively blocking the binding of angiotensin II to the AT1 receptors, telmisartan inhibits the vasoconstrictor and aldosterone-secreting effects of angiotensin II.

Telmisartan blocks AT1 receptors, and has essentially no affinity for the AT2 receptors. AT2 receptors have been found in many tissues; to date, they have not been found to be associated with cardiovascular homeostasis. Telmisartan does not inhibit angiotensin converting enzyme (ACE, also known as kininase II), the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin, nor does it affect renin or other hormone receptors or ion channels involved in cardiovascular regulation of blood pressure and sodium homeostasis. In hypertensive patients, antagonism of angiotensin II AT1 receptors results in two to three-fold increases in plasma renin and angiotensin II plasma concentrations. Long term effects of increased AT2 receptor stimulation by angiotensin II are unknown. Telmisartan is known on the market under the trade name Micardis ® by Boehringer Ingelheim Corporation.

Hydrochlorothiazide (HCTZ) is an orally administered thiazide diuretic which was first disclosed in United States Patent No. 3,163,645 (issued on December 29, 1964 to Ciba Corporation) and is indicated in the treatment of edema and hypertension. The chemical name for HCTZ is 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide, molecular formula is $C_7H_8ClN_3O_4S_2$ with following structure:



HCTZ is a white to practically white, crystalline powder which is slightly soluble in water and freely soluble in sodium hydroxide solution.

Combination of telmisartan and HCTZ is commercially available under the trade name Micardis Plus ® and is indicated for use in the treatment of hypertension.

However, particularly with a combination of telmisartan or a pharmaceutically acceptable salt thereof, and HCTZ, this approach was not feasible due to the incompatibility of HCTZ with basic compounds such as, e.g., meglumine (N-methyl-D-glucamine) which is a component of conventional telmisartan formulations and the reduced dissolution rate of HCTZ from the dissolving matrix as compared with dissolution from a disintegrating tablet.

Formulations using a combination of these two drugs are described in the following patents: WO2003/059327 (CA2472392), WO2004/096215 (CA2524091), WO2006063737 (CA2589493), WO2007/060170 (CA2625404), WO2007/144175 (CA2654890), WO2009/058950, and WO2009/115301.

PCT Publication No. WO2003/059327 (corresponds to Canadian Patent No. 2,472,392, issued to Boehringer Ingelheim Pharma on July 14, 2009) discloses a bilayer pharmaceutical tablet comprising a first layer containing telmisartan in substantially amorphous form in a dissolving tablet matrix and a second layer containing a diuretic in a disintegrating tablet matrix. This bilayer tablet structure overcomes the stability problem caused by the incompatibility of a diuretic like HCTZ with basic constituents of the telmisartan formulation. At the same time such a formulation provides for immediate release of the diuretic from the fast disintegrating matrix. However bilayer tablets as per PCT Publication No. WO2003/059327 tend to be slightly hygroscopic and,

therefore, need to be packaged using a moisture-proof packaging material such as aluminium foil blister packs, or polypropylene tubes and HDPE bottles which preferably contain a desiccant.

Several approaches to overcome the incompatibility problem have been reported in PCT Publication No. WO2003/059327. In one approach HCTZ particle was coated in a fluidized-bed granulator with a polymer solution containing water soluble polymers like hydroxypropylcellulose, hydroxypropylmethylcellulose or polyvinylpyrrolidone, thereby reducing the contact surface area of the HCTZ particles with the telmisartan formulation during mixing and compressing. However, by this means it was not possible to reduce the surface contact area of HCTZ with the telmisartan formulation in a compressed tablet to a degree sufficient to achieve the desired prolonged shelf life.

PCT Publication No. WO2004/096215 (corresponds to Canadian Patent Application No. 2,524,091, filed April 27, 2004 by Boehringer Ingelheim Pharma) relates to a medicament formulation of the crystalline sodium salt of 4'-[2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl) benzimidazol-1-ylmethyl]biphenyl-2-carboxylic acid (i.e., telmisartan) and methods for production thereof. The patent discloses pharmaceutical composition containing the telmisartan sodium salt and a diuretic.

PCT Publication No. WO2006/063737 (corresponds to Canadian Patent Application No. 2,589,493, filed December 9, 2005 by Boehringer Ingelheim Pharma) discloses a pharmaceutical composition comprising telmisartan and HCTZ for the treatment of hypertension in patients with an insufficient blood pressure reduction upon treatment either with an angiotensin II receptor antagonist, or a pharmaceutical composition of an angiotensin II receptor antagonist and a low dose of HCTZ, wherein the pharmaceutical composition contains the component telmisartan in a dissolving tablet matrix having instant release characteristics and wherein the diuretic HCTZ is in a separate layer in a disintegrating pharmaceutical matrix.

PCT Publication No. WO2007/144175 (corresponds to Canadian Patent Application No. 2,654,890, filed June 14, 2007 be Lek Pharmaceuticals D.D.) discloses a stable formulation

of telmisartan and HCTZ having both substances in separate units is prepared, exhibiting exceptional stability when subjecting to stress conditions.

PCT Publication No. WO2009/058950 (filed October 30, 2008 by Dr. Reddy's Laboratories Ltd.) discloses the pharmaceutical tablets comprising a first layer formulated for immediate release of telmisartan from a dissolving matrix and a second layer formulated for immediate release of HCTZ from a dissolving matrix, methods for producing tablets and methods of use for treating hypertension.

PCT Publication No. WO2009/115301 discloses a solid pharmaceutical composition comprising at least two layers, wherein the first layer contains a non-peptide angiotensin II receptor antagonist or a pharmaceutically acceptable salt thereof in a dissolving matrix and the second layer contains a diuretic or a pharmaceutically acceptable salt thereof, characterized in that the second layer contains the diuretic or the pharmaceutically acceptable salt thereof in a dissolving matrix and the pharmaceutical composition is substantially free of disintegrants.

It is often desirable to combine multiple active ingredients in a single pharmaceutical composition. Inclusion of multiple ingredients in a single composition generally reduces costs and provides the convenience of consuming a single medication rather than multiple medications for treating individual symptoms. However, a combination of ingredients might compromise the stability of a composition due to incompatibility between two active ingredients.

The solid pharmaceutical composition according to the present invention, preferably in the form of a tablet, provides an immediate release of the non-peptide angiotensin II receptor antagonist, in particular of the poorly water soluble telmisartan or pharmaceutically acceptable salts thereof, and also provides an immediate release of a diuretic from the tablet matrix. At the same time the tablet structure overcomes the stability problem caused by the incompatibility of diuretics, like HCTZ, with basic excipients of conventional telmisartan formulations, e.g. meglumine.

It is known from the literature that telmisartan has very poor aqueous solubility in the physiological pH range of the gastrointestinal tract between pH 1 and 7, and is soluble in strong base. On the other hand, HCTZ degrades in alkaline conditions i.e undergoes alkaline hydrolysis in the presence of heat and moisture. The major degradation product of HCTZ is 4-amino-6-chloro-1,3-benzenesulfonamide ("DSA") It is advantageous to administer both drugs concomitantly or even better to administer a composition comprising both, to treat hypertension.

Difficulty results from the fact that both active substances need to be released from the composition substantially simultaneously. Preparation of fixed dose combinations of telmisartan and HCTZ with adequate stability poses a challenge to formulators. Hence there is need for simple and stable fixed dose compositions containing telmisartan and HCTZ.

## SUMMARY OF THE INVENTION

The present invention provides a stable pharmaceutical formulation comprising telmisartan or a pharmaceutically acceptable salt and a diuretic dispersed in a matrix, said matrix comprising:

- at least one disintegrant in an amount ranging from about 0.5 % to about 20% by weight;
- a dissolution enhancing agent present in a molar ratio of dissolution enhancing agent to telmisartan of from about 1:1 to about 10:1;
- a water-insoluble diluent in an amount ranging from about 15% to about 75% by weight; and
- at least one other pharmaceutically acceptable excipient /or adjuvant in an amount ranging from about 0 to about 25% by weight.

The preferred diuretic of the present invention is HCTZ.

In a further aspect of the present invention, there is provided a stable pharmaceutical formulation wherein the in vitro dissolution rate of said formulation is at least about 80

% by weight of telmisartan dissolved within 30 minutes and at least about 80% of the diuretic dissolved within 30 minutes as measured by using USP type II apparatus at 75 rpm in 900ml of pH 7.5 phosphate buffer.

In a further aspect of the present invention, there is provided a process for the preparation of a stable pharmaceutical formulation comprising telmisartan or a pharmaceutically acceptable salt thereof, and a diuretic dispersed in a matrix, wherein said process comprises the following steps:

(1) - preparation of granulation solution;

(2) - dry mixing;

(3) - granulation;

(4) – lubrication; and

(5) – compression.

According to another aspect of the present invention, there is provided a use of a stable pharmaceutical formulation containing two active ingredients in a single layer, in an immediate release form, for the treatment or prevention of hypertension.

According to another aspect of the present invention further relates to stable formulations comprising telmisartan, or acceptable salts, and HCTZ, wherein the telmisartan or acceptable salt is in substantially amorphoous form.

## DETAILED DESCRIPTION OF THE INVENTION

In the present application, the terms or expressions "active agent", "active ingredient", "active pharmaceutical ingredient", "drug", "pharmacologically active agent", "pharmaceutically acceptable active agent" and/or "pharmaceutically acceptable active substance" are used interchangeably to refer to a chemical material, compound, agent or substance that has measurable specified or selected physiologic activity when administered to a subject in a pharmaceutically significant or effective amount. The active agent can be a therapeutic, a prophylactic, or a diagnostic agent. These terms of art are well-known in the pharmaceutical and medicinal arts.

The term "stability" refers to the extent to which a product retains, within specified limits and throughout its period of storage and use, the same properties and characteristics that it possessed at the time of its manufacture. There are five general types of stability defined by the United States Pharmacopoeia: chemical, physical, microbiological, therapeutic and toxicological.

The present invention discloses a pharmaceutical formulation comprising a combination of telmisartan and HCTZ in a single layer, preferably with magnesium oxide, that does not degrade or contribute to degradation of HCTZ, and a manufacturing process in order to get suitable stability properties without the need of expensive packing. For example, the active ingredients are present in a monolithic tablet or a single layer tablet.

In a preferred embodiment of the invention, there is provided bilayer pharmaceutical formulation comprising two active ingredients, wherein the first active ingredient is telmisartan or a pharmaceutically acceptable salt thereof, which is practically insoluble in water (pH 3- 9), though soluble in strong base. Preferably, according to the present invention the second active ingredient is HCTZ, which is slightly soluble in water, though soluble in sodium hydroxide solution. In the bilayer tablet, the first layer is a placebo layer and the second layer comprises telmisartan, or a pharmaceutically acceptable salt thereof, and the diuretic (e.g., HCTZ).

The formulation of the present invention further comprise pharmaceutically acceptable excipients. Such excipients are added to the formulations for a variety of purposes. One or more pharmaceutically acceptable excipients may be present in the composition of the present invention, such as for example diluents, binders, lubricants, disintegrants, glidants, and acidifying agents.

Some of the preferred pharmaceutically acceptable excipients of the formulations of the present invention include: povidone, sodium hydroxide, isopropyl alcohol, silicified MCC90 (Prosolv®), colloidal silicon dioxide (Aerosil ®), dibasic calcium phosphate hydrous, croscarmellose sodium, magnesium oxide heavy, magnesium stearate, microcrystalline cellulose and iron oxides.

Suitable diluents include for example pharmaceutically acceptable inert fillers such as microcrystalline cellulose, lactose, pregelatinized starch, dibasic calcium phosphate, saccharides, and/or mixtures of the foregoing.

Suitable binders include, for example, the following: povidone; copovidone; alginic acid; sodium alginate; cellulose derivatives such as hydroxypropyl methylcellulose, hydroxy propyl cellulose, hydroxy ethyl cellulose, methylcellulose and ethyl cellulose; gelatin; starch or starch derivatives; and mixtures thereof.

Suitable lubricants include, for example, the following: magnesium-, aluminum- or calcium-stearate, stearic acid, sodium stearyl fumarate, talc, sodium benzoate, glyceryl mono fatty acid, glyceryl monostearate hydrogenated vegetable oil, polyethylene glycol, and mixtures thereof.

Suitable disintegrants include, for example, the following: croscarmellose sodium, sodium starch glycolate, maize starch, CMC-Ca, CMC-Na, microcrystalline cellulose, cross-linked PVP, alginic acid, sodium alginate, pregelatinized starch and low-substituted hydroxy propyl cellulose.

Suitable anti-adherents include, for example, one or more compounds that are capable of preventing stickiness to surfaces of the punches. Examples of anti-adherents include silicon-containing compounds such as colloidal silicon dioxide, magnesium trisilicate and talc.

The stable pharmaceutical formulations of the present invention can be used to treat or prevent hypertension. For example, the pharmaceutical formulations of the present invention containing the two active ingredients in a single layer, in an immediate release form, can be used to treat or prevent hypertension.

<u>Illustrated Embodiments of the Formulations of the Present Invention</u>

According to an embodiment of the present invention, the stable pharmaceutical formulations comprise telmisartan, or a pharmaceutically acceptable salt, and a diuretic (preferably HCTZ), dispersed in a matrix. The matrix comprises:

- at least one disintegrant in an amount ranging from about 0.5% to about 20% by weight;
- a dissolution enhancing agent present in a molar ratio of dissolution enhancing agent to telmisartan of from about 1:1 to about 10:1;
- a water-insoluble diluent in an amount ranging from about 15% to about 75% by weight; and
- at least one other pharmaceutically acceptable excipient /or adjuvant in an amount ranging from about 0% to about 25% by weight.

The disintegrant in the formulations of the present invention include, for example, the following: crospovidone, croscarmellose sodium, sodium starch glycolate, starch, modified starch, maize starch, microcrystalline cellulose, cross-linked polyvinylpolypyrrolidone (PVP), alginic acid, sodium alginate, pregelatinized starch, carboxymethyl cellulose (CMC), CMC-calcium, CMC-sodium, low-substituted hydroxyl propyl cellulose, and combinations thereof. Preferably, the disintegrant is croscarmellose sodium.

The dissolution enhancing agent in the formulations of the present invention include, for example, the following: $NaHCO_3$, $KHCO_3$, $NA_2CO_3$, $Na_2HPO_4$, $K_2HPO_4$, tromethamine, triethanolamine, MgO, and $MgCO_3$. Preferably, the dissolution enhancing agent is MgO.

The water insoluble diluent in the formulations of the present inventions include, for example, the following: microcrystalline cellulose, di- or tri-basic calcium phosphate, crystalline cellulose, powdered cellulose, anhydrous silicic acid, calcium carbonate, calcium sulphate, magnesium silicate, magnesium trisilicate, magnesium aluminium metasilicate (Neusilin®), kaolin, starch, starch derivatives, and co-processed excipients. The co-processed excipient is preferably Ludipress(® (mixture of lactose and 3.2% Povidone K30), Cellactose® (mixture of lactose and cellulose), and Silicified MCC Prosolv® (mixture of microcrystalline cellulose and silicon dioxide). More preferably, the co-processed excipient is silicified microcrystalline cellulose Prosolv®.

Preferably, the formulation further comprises a solubilizing agent selected from the group consisting of: alkali metal hydroxide such as NaOH and KOH. More preferably, the solubilizing agent is NaOH.

Preferably, the formulation according to the present invention further comprises a surfactant or emulsifier present in an amount ranging from about 0.5% to about 10% by weight.

Preferably, the water insoluble diluent is selected from the group consisting of: microcrystalline cellulose, di- or tri-basic calcium phosphate, crystalline cellulose, powdered cellulose, anhydrous silicic acid, calcium carbonate, calcium sulphate, magnesium silicate, magnesium trisilicate, magnesium aluminium metasilicate (Neusilin), kaolin, starch, starch derivatives, and co-processed excipients. Also preferably, the co-processed excipient is selected from the group consisting of: Ludipress(® (mixture of lactose and 3.2% Povidone K30), Cellactose(® (mixture of lactose and cellulose), and Silicified MCC Prosolv® (mixture of microcrystalline cellulose and silicon dioxide). More preferably, the co-processed excipient is silicified microcrystalline cellulose Prosolv®.

In the preferred embodiments of the present invention, the *in vitro* dissolution rate of the formulation is at least 80% w/w of telmisartan dissolved within 30 minutes and at least 80% of the diuretic dissolved within 30 minutes as measured by using USP type II apparatus at 75 rpm in 900ml of pH 7.5 phosphate buffer.

More preferably, the *in vitro* dissolution rate of the formulations of the present invention is at least about 60% of telmisartan is dissolved within 5 minutes as measured by USP Paddle Method at 75 rpm at pH 7.5 dissolution phosphate buffer at 37°C; at least about 80% of telmisartan is dissolved within 10 minutes as measured by USP Paddle Method at 75 rpm at pH 7.5 dissolution phosphate buffer at 37°C; and at least about 90% of telmisartan is dissolved within 30 minutes as measured by USP Paddle Method at 75 rpm at pH 7.5 dissolution phosphate buffer at 37°C.

Furthermore, the *in vitro* dissolution rate of the HCTZ in the formulations of the present invention is at least about 55% dissolved within 5 minutes as measured by USP Paddle Method at 75 rpm at pH 7.5 dissolution phosphate buffer at 37°C; at least about 75%

dissolved within 10 minutes as measured by USP Paddle Method at 75 rpm at pH 7.5 dissolution phosphate buffer at 37°C; at least about 80% dissolved within 30 minutes as measured by USP Paddle Method at 75 rpm at pH 7.5 dissolution phosphate buffer at 37°C; and at least about 85% dissolved within 60 minutes as measured by USP Paddle Method at 75 rpm at pH 7.5 dissolution phosphate buffer at 37°C.

Preferably, the formulations of the present invention comprise less than about 0.5% by weight of 4–amino-6-chloro-1,3 benzenedisulfonamide (DSA) impurity in comparison to the initial HCTZ content when exposed to 40°C /75% RH conditions in Blister as well as HDPE pack. Also preferably, the *in vitro* dissolution rate remains similar to the initial value for telmisartan and for the diuretic on stabiliy as measured by using USP type II apparatus at 75 rpm in 900ml of pH 7, 5 phosphate buffer.

Illustrated Processes for Preparing the Formulations of the Present Invention

A wet granulation process, preferably a low shear granulation process, is preferred for preparing the stable pharmaceutical formulations of the present invention. When the process has for starting material a salt form of an angiotensin II receptor antagonist (i.e. telmisartan) the process comprises a dry mixing step and direct compression.

For example, the following process can be used to prepare a formulation of the present invention wherein the two active ingredients are in a single layer:

1) preparation of granulation solution;
2) dry mixing;
3) granulation;
4) lubrication; and
5) compression.

Preferably, the step of preparation of a granulation solution (step (1)) further comprises dissolving telmisartan under stirring in purified water with sodium hydroxide.
Preferably, step (1) further comprises dissolving povidone (K-30) in isopropyl alcohol.

Furthermore, the process preferably further comprises mixing the content of step (1) with the content of step (2) for 15 minutes.

Preferably, the step of dry mixing (step (2)) further comprises dry mixing silicified MCC 90 (Prosolv®), dibasic calcium phosphate hydrous, croscarmellose sodium and colloidal silicon dioxide in a ribbon blender for 5 min.

Preferably, step (2) further comprises screening the content obtained from step (2) through a comill equipped with 0.045R screen (1190 μm) and then mix for 5 minutes to yield a telmisartan blend.

Preferably, the step of granulation (step (3)) further comprises adding to the blend obtained from step (2) (the dry mixing step) the granulation solution. Preferably, step (3) further comprises drying the wet granules in a fluid bed drier at an inlet temperature of 50°C ± 5°C until a loss on drying value of 3.8%± 0.4% is obtained on a moisture analyzer set at 105°C for 10 minutes.

Preferably, the step (3) further comprises screening the dried granules through a comill equipped with 0.039R screen (1000 μm).

Preferably, the step of lubrication (step (4)) comprises mixing magnesium oxide heavy and the colloidal silicon dioxide (Aerosil®) and screening through #30 sieve (600μm). Preferably, step (4) further comprises screening HCTZ, microcrystalline cellulose PH102 (Avicel®) and croscarmellose sodium through #40 sieve (400μm) and adding to the granules of telmisartan and blending to yield a HCTZ blend.

Preferably, step (4) further comprises dispersing a portion of the HCTZ blend with magnesium stearate and screening the obtained content through #40 sieve (400μm) to yield a lubricated HCTZ blend.

Preferably, step (4) further comprises adding the lubricated HCTZ blend to the telmisartan granules and blending for 3 minutes to yield the actives blend.

Preferably, the process comprises a step of blending placebo involving screening microcrystalline cellulose, yellow or red iron oxide, colloidal silicon dioxide and croscarmellose sodium, through #40 sieve (400μm) and blending the content for 15 minutes to obtain an excipient placebo blend.

Preferably, the step of compression (step (5)) further comprises compressing the excipient blend and actives blend, to form a bilayer pharmaceutical formulation.

The present invention provides a process for the preparation of a pharmaceutical formulation containing two active ingredients in a monolithic tablet comprising the following steps:

1) dissolving telmisartan in purified water with sodium hydroxide;

2) dissolving a binder in isopropyl alcohol;

3) mixing the content of step (1) with the content of step (2);

4) blending pharmaceutical acceptable excipients;

5) granulating the blend of step (4) with the content of step (3);

6) drying the wet granules obtained from step (5);

7) screening the dried granules obtained from step (6);

8) mixing the granules of step (7) with additional pharmaceutically acceptable excipients;

9) preparing a mixture of the diuretic (HCTZ) and pharmaceutically acceptable excipients;

10) adding the content of step (9) to the content of step (8); and

11) compressing the blend of step (10).

The following process can be used to prepare a formulation of the present invention wherein the two active ingredients are in a single layer of a bi-layer tablet:

1) dissolving telmisartan in purified water with sodium hydroxide;

2) dissolving, povidone (K-30) in isopropyl alcohol;

3) mixing the solution of step (1) with the solution of step (2);

4) dry mixing the following pharmaceutical excipients: silicified MCC 90 (Prosolv®), dibasic calcium phosphate hydrous, croscarmellose sodium and colloidal silicon dioxide;

5) screening the content obtained from step (4) and then blending;

6) adding to the blend of step (5) to the granulation solution of step (3);

7) drying the wet granules in a fluid bed drier;

8) screening the dried granules obtained from step (7);

9) mixing the granules of step (8) with magnesium oxide heavy and the colloidal silicon dioxide (Aerosil® ) and screening the obtained mixture;

10) screening HCTZ, microcrystalline cellulose PH102 (Avicel®) and croscarmellose sodium, and blending with the granules of step (9);

11) dispersing a portion of blend with magnesium stearate and screening;

12) blending the content of step (11) together with the granules of step (9);

13) separately screening the microcrystalline cellulose, yellow iron oxide, colloidal silicon dioxide and croscarmellose sodium, through #40 sieve (400µm) and blending the content;

14) screening magnesium stearate and blending with the blend of step (12);

15) compressing the lubricated blend of step (14) and the blend of step (12), using a bilayer compression machine.

Preferably, the granulation solution is prepared by dissolving the telimisartan gradually by stirring in purified water with sodium hydroxide. The isopropyl alcohol and povidone (K-30) is dissolved in a separate vessel. Then, the content of solution of step (1) is mixed with the content of the solution of step (2).

Preferably, the obtained content is dry mixed and then screened with the following pharmaceutical excipients: silicified MCC 90 (Prosolv ®), dibasic calcium phosphate hydrous, croscarmellose sodium and colloidal silicon dioxide.

Preferably, the content of step (3) is added to the blend of step (5) and the granulation is carried out in a ribbon blender.

Preferably, the wet granules are dried in a fluid bed drier at inlet temperature of 50°C±5°C until a loss on drying value of 3.8%± 0.4% is obtained on a moisture analyzer set at 105°C for 10 minutes (step (7)).

Preferably, the dried granules obtained from step (7) are screened through a comill equipped with 0.039R screen (1000 µm) (step (8)).

Preferably, the granules of step (8) are mixed with magnesium oxide heavy and colloidal silicon dioxide (Aerosil®) and screened through #30 sieve (600µm) (step (9)).

Preferably, HCTZ, microcrystalline cellulose PH102 (Avicel®) and croscarmellose sodium are screened through #40 sieve (400µm), added to the granules of step (9) and blended for 20 minutes (step (10)).

Preferably, a portion of the blend obtained from step (10) is dispersed with magnesium stearate, and then screened manually through #40 sieve (400µm) and blended for 3 minutes (step (11)).

Preferably, microcrystalline cellulose PH102, yellow iron oxide, colloidal silicon dioxide and croscarmellose sodium are screened through #40 sieve (400µm) and blended for 15 minutes (step (13)).

Preferably, magnesium stearate is passed through a 40 (400µm) mesh screen, is introduced into the bin blender and blended for 3 minutes with mixture obtained from step (12), prior to compression (step (14)).

Preferably, the lubricated blend is compressed using capsule shaped tooling at average weight of 700 mg on a stokes bilayer compression machine (step (15)).

While several embodiments of the invention have been described ,it will be understood that the present invention is capable of further modifications and this application is intended to cover any variations uses or adaptations of the invention following in general the principles of the invention and including such departures from the present disclosure as to come within knowledge customary practices in the art to which the invention pertains, as may be applied to the essential features herein before set forth and falling within the scope of the invention.

**Examples**

The following examples illustrate the preferred embodiment and various aspects of the present invention.

Example 1

IMMEDIATE RELEASE DOSAGE FORM OF TELMISARTAN / HCTZ ACCORDING TO A PREFERRED EMBODIMENT OF THE PRESENT INVENTION

I. Preparation Of Granulating Solution:

1) In a vessel of purified water was added sodium hydroxide and dissolved under stirring. The required quantity of telmisartan was added gradually and dissolved under stirring.
2) In another vessel to isopropyl alcohol was added povidone (K-30) and dissolved under stirring.
3) The granulation solution is prepared by adding to the content of telmisartan solution (1) the Povidone K-30 solution (2) and mixing for 15 minutes.

Dry Mixing

4) Silicified MCC 90 (Prosolv®), dibasic calcium phosphate hydrous, Croscarmellose sodium and Colloidal Silicon Dioxide (Aerosil ®) was introduced into a ribbon blender and blended for 5 minutes. The blend was screened through a comill screen 0.045R (1190 µm). This blend was reintroduced into the ribbon blender and blended for 5 minutes.

Granulation

5) The blend of step 4 was granulated with solution of step 3 in a ribbon blender.
6) The wet granules were dried in a fluid bed drier at an inlet temperature of 50°C±5°C till a Loss on drying value of 3.8%± 0.4% is obtained on a moisture analyzer set at 105°C for 10 minutes.
7) The dried granules were screened through a co mill screen 0.039R screen (1000 µm) for further processing.

**Lubrication**

8) The dried screened granules of step 7 was added to a bin blender.

9) Magnesium oxide heavy and Colloidal Silicon Dioxide ( Aerosil ®) were dispersed and screened through #30 sieve (600µm).This sieved dispersion was added to the bin blender of step 8.

10) HCTZ, Microcrystalline Cellulose PH102 (Avicel®)and croscarmellose sodium was screened through #40 sieve (400µm).This sieved dispersion was introduced into the bin blender of step 8 and blended for 20 minutes.

11) Magnesium stearate was dispersed with a portion of the blend of step 10 in a polyethylene bag and screened manually through #40 sieve (400µm).This sieved dispersion was introduced into the bin blender of step 8 and blended for 3 minutes.

**II. Manufacturing of Yellow Placebo Blend**

12) Microcrystalline Cellulose PH 102 (Avicel®), Yellow oxide iron, Colloidal Silicon Dioxide (Aerosil ®) and croscarmellose sodium was screened through #40 sieve (400µm) and introduced into the bin blender and blended for 15 minutes.

13) Magnesium stearate was screened through #40 sieve (400µm) and introduced into the bin blender of step 12 and blended for 3 minutes.

**Compression**

14) The lubricated blend of step 11 and step 13 was compressed using capsule shaped tooling at an average weight of 700 mg on a stokes bilayer compression machine.

**Table I – Formulation of Example 1**

| No | Ingredient | mg/Tablet |
|---|---|---|
| | **(Telmisartan and HCTZ granules)** | |
| 1 | Telmisartan | 80 .0 |
| 2 | Sodium Hydroxide | 6.624 |
| 3 | Povidione (k30) | 4.80 |
| 4 | Purified water | 110.0* |
| 5 | Isopropyl Alcohol | 12.7** |
| 6 | Silicified MCC 90 ( Prosolv®) | 168.0 |
| 7 | Colloidal Silicon Dioxide ( Aerosil ®) | 4.8 |
| 8 | Dibasic Calcium phosphate Hydrous | 72.0 |
| 9 | Croscarmellose Sodium | 19.2 |
| 10 | Magnesium Oxide Heavy | 24.0 |
| 11 | Colloidal Silicon Dioxide ( Aerosil ®) | 2.4 |
| 12 | HCTZ | 25.0 |
| 13 | Microcrystalline Cellulose PH 102 (Avicel®) | 70.23 |
| 14 | Croscarmellose Sodium | 19.2 |
| 15 | Magnesium Stearate | 3.75 |
| | **Total** | **500.0** |
| | **Yellow Placebo granules** | |
| 16 | Microcrystalline Cellulose PH 102 (Avicel®) | 194.65 |
| 17 | Yellow oxide iron | 0.35 |
| 18 | Colloidal Silicon Dioxide (Aerosil ®) | 0.5 |
| 19 | Croscarmellose sodium | 4.0 |
| 20 | Magnesium Stearate | 0.5 |
| | **Total** | **200.0** |
| | **Total of both layers** | **700.0** |

* & **: Evaporates during processing. Does not appear in the final formulation.

**Dissolution**

The tablets obtained from Example 1 were subsequently tested for *in vitro* dissolution rate, measured by Apparatus II (USP Paddle Method), using the following parameters:

Speed: 75 rpm

Media: 900 ml, pH 7.5 Phosphate buffer

Temperature: 37°C.

The dissolution results are set out in Table 2 and 3 below.

Tables II and III compare the dissolution of Micardis Plus® 80/25 mg (telmisartan/HCTZ - telmisartan and HCTZ are dispersed in two separate layers) against the dissolution of Example 1 80/25 mg (telmisartan/HCTZ - telmisartan and hydrochlorothiazide are dispersed in a single layer)

**Table II**

| Media: 900 ml, 7.5 Phosphate buffer | | |
|---|---|---|
| Apparatus: USP Type II | | |
| RPM : 75 | | |
| | Micardis Plus® 80/25 mg | |
| Time | Lot no :810094 | Example 1 |
| minutes | % Telmisartan Dissolved | % Telmisartan Dissolved |
| 0 | 0 | 0 |
| 5 | 34 | 66 |
| 10 | 60 | 84 |
| 15 | 78 | 89 |
| 30 | 98 | 90 |
| 45 | 99 | 91 |
| 60 | 99 | 92 |
| ITP | 99 | 96 |

Table III

| Media: 900ml, 7.5 Phosphate buffer | | |
|---|---|---|
| Apparatus: USP Type II | | |
| RPM : 75 | | |
| | Micardis Plus® 80/25 mg | |
| Time | Lot No :810094 | Example 1 |
| min | % HCTZ Dissolved | % HCTZ Dissolved |
| 0 | 0 | 0 |
| 5 | 93 | 59 |
| 10 | 95 | 79 |
| 15 | 97 | 83 |
| 30 | 98 | 86 |
| 45 | 99 | 87 |
| 60 | 98 | 89 |
| ITP | 98 | 95 |

**Stability**

The stability of the illustrated embodiment of the formulation of present invention (Example1) was evaluated in two types of packaging at 40 °C /75% relative humidity conditions. The following parameters were evaluated,

1) Degradation of telmisartan and HCTZ in the formulation as per the present invention.
2) Dissolution of telmisartan and HCTZ in the formulation as per the present invention.
3) Moisture content of the formulation as per the present invention.

The results of degradation, dissolution and moisture content are set out in Tables IV, V, VI, VII, VIII and IX below

**Table IV: Degradation of formulation of Example I in HDPE bottles at 40°C/75% RH**

| **Pack I : HDPE pack with desiccant (Trisorb®)** | | | | | | |
|---|---|---|---|---|---|---|
| **Lot No: Formulation as per Example 1** | | | | | | |
| Parameter | **Initial (T=0)** | | **1 Month** | | **2 Months** | |
| Moisture content (%) | 3.71% | | 3.58% | | 3.34% | |
| **Degradation of Telmisartan** | | | | | | |
| **Known Impurities** | | | | | | |
| Comp 3 | - | | - | | - | |
| Comp 4 | - | | - | | - | |
| Comp 5 | - | | - | | - | |
| Comp 6 | 0.07% | | 0.07% | | 0.06% | |
| Comp 7 | - | | - | | - | |
| **Unknown Impurities** | **RRT** | **%** | **RRT** | **%** | **RRT** | **%** |
| | 0.87 | 0.03 | 0.87 | 0.03 | 1.40 | 0.03 |
| | 1.41 | 0.03 | 1.40 | 0.03 | 1.41 | 0.10 |
| | 1.42 | 0.07 | 1.41 | 0.09 | | |
| **Degradation of Hydrochlorothiazide** | | | | | | |
| **Known Impurities** | | | | | | |
| Comp 1* | 0.07% | | 0.07% | | 0.06% | |
| Comp 2 | 0.04% | | 0.04% | | 0.04% | |
| | | | | | | |
| Unknown Impurities | **RRT** | **%** | **RRT** | **%** | **RRT** | **%** |
| | 2.60 | 0.04 | 2.58 | 0.04 | 2.58 | 0.05 |

*** DSA Impurity**

**Table V: Dissolution of Telmisartan from formulation as per Example 1 in HDPE pack at 40°C/75% RH**

| Media: 900 ml, 7.5 Phosphate buffer | | | |
|---|---|---|---|
| Apparatus: USP Type II | | | |
| RPM : 75 | | | |
| | T=0 | 1 Month | 2 Months |
| Time in minutes | % Telmisartan Dissolved | % Telmisartan Dissolved | % Telmisartan Dissolved |
| 0 | 0 | 0 | 0 |
| 5 | 66 | 70 | 71 |
| 10 | 84 | 89 | 91 |
| 15 | 89 | 93 | 92 |
| 30 | 90 | 95 | 92 |
| 45 | 91 | 95 | 92 |
| 60 | 92 | 95 | 92 |

**Table VI: Dissolution of Hydrochlorothiazide from formulation as per example 1 in HDPE pack at 40°C/75% RH**

| Media: 900ml, 7.5 Phosphate buffer | | | |
|---|---|---|---|
| Apparatus: USP Type II | | | |
| RPM : 75 | | | |
| | T=0 | 1 Month | 2 Months |
| Time | % Hydrochlorothiazide Dissolved | % Hydrochlorothiazide Dissolved | % Hydrochlorothiazide Dissolved |
| 0 | 0 | 0 | 0 |
| 5 | 59 | 65 | 68 |
| 10 | 79 | 86 | 89 |
| 15 | 83 | 91 | 90 |
| 30 | 86 | 93 | 92 |
| 45 | 87 | 94 | 93 |
| 60 | 89 | 94 | 94 |

**Table VII: Comparative Degradation of Example I and Micardis plus® in ALU/ALU Blisters at 40°C/75% RH.**

| Pack II : ALU/ALU Blister pack | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Example 1 | | | | | | Micardis Plus 80/25 mg Lot No 810094 | | | |
| Parameter | Initial (T=0) | | 1 Month | | 2 Months | | Initial (T=0) | | 1Month | |
| Moisture content (%) | 3.71% | | 3.8% | | 3.5% | | 1.74% | | 1.71% | |
| Degradation of Telmisartan | | | | | | | | | | |
| Known Impurities | | | | | | | | | | |
| Comp 3 | - | | - | | - | | - | | - | |
| Comp 4 | - | | - | | - | | - | | - | |
| Comp 5 | - | | - | | - | | - | | - | |
| Comp 6 | 0.07% | | 0.07% | | 0.06% | | - | | - | |
| Comp 7 | - | | - | | - | | | | | |
| Unknown Impurities | RRT | % | RRT | % | RRT | % | RRT | % | RRT | % |
| | 0.87 | 0.03 | 0.87 | 0.03 | 0.87 | 0.03 | 1.46 | 0.03 | 1.46 | 0.03 |
| | 1.41 | 0.03 | 1.41 | 0.09 | 1.40 | 0.04 | 1.47 | 0.04 | 1.47 | 0.03 |
| | 1.42 | 0.07 | | | 1.41 | 0.10 | | | | |
| Degradation of Hydrochlorothiazide | | | | | | | | | | |
| Known Impurities | | | | | | | | | | |
| Comp 1 | 0.07% | | 0.06% | | 0.07% | | 0.10% | | 0.12% | |
| Comp 2 | 0.04% | | 0.04% | | 0.04% | | 0.03% | | 0.03% | |
| Unknown Impurities | RRT | % | RRT | % | RRT | % | RRT | % | RRT | % |
| | 2.60 | 0.04 | 2.58 | 0.04 | 2.60 | 0.05 | 2.58 | 0.05 | 2.58 | 0.05 |

**Table VIII: Dissolution of Telmisartan from formulation as per example 1 in ALU/ALU Blister pack at 40°C/75% RH**

| Media: 900ml, 7.5 Phosphate buffer | | | |
|---|---|---|---|
| Apparatus: USP Type II | | | |
| RPM : 75 | | | |
| | T=0 | 1 Month | 2 Months |
| Time in minutes | % Telmisartan Dissolved | % Telmisartan Dissolved | % Telmisartan Dissolved |
| 0 | 0 | 0 | 0 |
| 5 | 66 | 64 | 73 |
| 10 | 84 | 90 | 90 |
| 15 | 89 | 93 | 94 |
| 30 | 90 | 93 | 95 |
| 45 | 91 | 93 | 95 |
| 60 | 92 | 94 | 96 |

**Table IX: Dissolution of Hydrochlorothiazide from formulation as per example 1 in ALU/ALU Blister pack at 40°C/75% RH**

| Media: 900ml, 7.5 Phosphate buffer | | | |
|---|---|---|---|
| Apparatus: USP Type II | | | |
| RPM : 75 | | | |
| | T=0 | 1 Month | 2 Months |
| Time | % Hydrochlorothiazide Dissolved | % Hydrochlorothiazide Dissolved | % Hydrochlorothiazide Dissolved |
| 0 | 0 | 0 | 0 |
| 5 | 59 | 60 | 75 |
| 10 | 79 | 86 | 90 |
| 15 | 83 | 90 | 92 |
| 30 | 86 | 91 | 94 |
| 45 | 87 | 92 | 95 |
| 60 | 89 | 92 | 96 |

In light of the data presented in the tables set out above, the following can be concluded:

1) From Tables IV & VII the formulation according to present invention has comparable stability in both blister as well as HDPE pack with that of Micardis Plus® (80/25 mg).

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2) From Tables V, VI, VIII and IX the dissolution rate of HCTZ and telmisartan from formulations according to the present invention is not affected by the stability.

**CLAIMS:**

1. A stable pharmaceutical formulation comprising telmisartan, or a pharmaceutically acceptable salt thereof, and a diuretic dispersed in a matrix, said matrix comprising:

- at least one disintegrant in an amount ranging from about 0.5 % to about 20% by weight;
- a dissolution enhancing agent present in a molar ratio of dissolution enhancing agent to telmisartan of from about 1:1 to about 10:1;
- a water-insoluble diluent in an amount ranging from about 15% to about 75% by weight; and
- at least one other pharmaceutically acceptable excipient /or adjuvant in an amount ranging from about 0 to about 25% by weight.

2. The stable pharmaceutical formulation according to claim 1 wherein the diuretic is hydrochlorothiazide.

3. A stable pharmaceutical formulation according to claim 1 or 2, further comprising a surfactant or emulsifier present in an amount ranging from about 0.5% to about 10% by weight.

4. A stable pharmaceutical formulation according to any one of claims 1 to 3 wherein the *in vitro* dissolution rate of said formulation is at least about 80 % by weight of telmisartan dissolved within 30 minutes and at least about 80% of the diuretic dissolved within 30 minutes as measured by using USP type II apparatus at 75 rpm in 900ml of pH 7.5 phosphate buffer.

5. The formulation according to any one of claims 1 to 4, wherein the disintegrant is selected from the group consisting of: crospovidone, croscarmellose sodium, sodium starch glycolate, starch, modified starch, maize starch, microcrystalline cellulose, cross-linked polyvinylpolypyrrolidone (PVP), alginic acid, sodium alginate, pregelatinized

starch, carboxymethyl cellulose (CMC), CMC-calcium, CMC-sodium, low-substituted hydroxyl propyl cellulose, and combinations thereof.

6. The formulation according to claim 5 wherein the disintegrant is croscarmellose sodium.

7. The formulation according to any one of claims 1 to 6, wherein the dissolution enhancing agent is selected from the group consisting of: $NaHCO_3$, $KHCO_3$, $NA_2CO_3$, $Na_2HPO_4$, $K_2HPO_4$, tromethamine, triethanolamine, MgO, and $MgCO_3$.

8. The formulation according to claim 7, wherein the dissolution enhancing agent is MgO.

9. The formulation according to any one of claims 1 to 8, further comprising a solubilizing agent selected from the group consisting of alkali metal hydroxides such as NaOH and KOH.

10. The formulation according to claim 9, where the solubilizing agent is NaOH.

11. The formulation according to any one of claims 1 to 10, wherein the water insoluble diluent is selected from the group consisting of: microcrystalline cellulose, di- or tri-basic calcium phosphate, crystalline cellulose, powdered cellulose, anhydrous silicic acid, calcium carbonate, calcium sulphate, magnesium silicate, magnesium trisilicate, magnesium aluminium metasilicate, kaolin, starch, starch derivatives, and co-processed excipients.

12. The formulation according to claim 11, wherein the co-processed excipients is selected from the group consisting of: Ludipress® (mixture of lactose and 3.2% Povidone K30), Cellactose® (mixture of lactose and cellulose), and Silicified microcrystalline cellulose (Prosolv®), and combinations thereof.

13. The formulation according to claim 12 wherein the co-processed excipient is silicified microcrystalline cellulose (Prosolv®).

14. The formulation according to any one of claims 1 to 13, wherein the composition further comprises at least one pharmaceutically acceptable excipient selected from the group consisting of: binders, lubricants, flow agents, adsorbants, crystallization retarders, anti-adherents, pH modifiers and coloring agents.

15. The formulation according to any one of claims 1 to 14, further comprising less than 0.5% wt of 4-amino-6-chloro-1,3 benzenedisulfonamide (DSA) impurity in comparison to the initial hydrochlorothiazide content.

16. The formulation according to any one of claims claim 1 to 15, wherein the *in vitro* dissolution rate for telmisartan and the diuretic remains similar to the initial value for telmisartan and for the diuretic as measured by using USP type II apparatus at 75 rpm in 900ml of pH 7.5 phosphate buffer.

17. A low shear granulation process for preparing a stable pharmaceutical composition as per claim 1.

18. A process for the preparation of a stable pharmaceutical formulation according to claim 1, wherein said process comprises the following steps:

(1) - preparation of granulation solution;

(2) - dry mixing;

(3) - granulation;

(4) – lubrication; and

(5) – compression.

19. A process for the preparation of a stable pharmaceutical formulation containing a pharmaceutically acceptable salt form of an angiotensin II receptor antagonist, a

diuretic and a dissolution enhancing agent in a matrix, wherein said process comprises a step of dry blending and direct compression.

20. Use of a stable pharmaceutical formulation containing two active ingredients in a single layer, in an immediate release form, according to any one of claims 1 to 16 for the treatment or prevention of hypertension.

21. The formulation according to any one of claims 1 to 16, wherein the formulation is in the form of a monolithic tablet or a single layer tablet.

22. The formulation according to any one of claims 1 to 16, wherein the formulation is in the form of a bilayer tablet dosage form wherein a first layer is a placebo layer and the second layer comprises telmisartan, or a pharmaceutically acceptable salt thereof, and a diuretic.